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PERSONALIZED MEDICINE: LEGAL AND ETHICAL CHALLENGES

Edited by Juli Mansnérus, Raimo Lahti and Amanda Blick

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Preface

This anthology deals with the legal and ethical challenges regarding personalized (precision) medicine and healthcare. It can also be regarded as the final report of a research project on the legal and ethical aspects of personalized medicine. It complements the reported results of the consortium ‘Personalised medicine to predict and prevent Type 1 Diabetes (P4 Diabetes)’ which were briefly presented in the booklet entitled ‘Better, Smarter, Now: Personalised Health – From Genes to Society (pHealth)’, Academy of Finland, Helsinki 2019.

That consortium was funded by the Academy of Finland in 2015–2019; the research project on the legal and ethical issues of personalized medicine by its Research Council for Culture and Society (Decision No. 29259, Announcement on 4 June 2015). The consortium has had the following responsible researchers and sites of research: as chairholder Academy Professor Riitta Lahesmaa, M.D., Ph.D. (Turku Centre for Biotechnology); as members Professor Mikael Knip, M.D., Ph.D. (University of Helsinki, Faculty of Medicine), Professor Harri Lähdesmäki, Dr. Sc. (Tech.) (Aalto University and Turku Centre for Biotechnology), Professor Matej Orešič, Ph.D. (Turku Centre for Biotechnology and Steno Diabetes Center, Denmark), Professor Jorma Toppari, M.D., Ph.D. (University of Turku, Faculty of Medicine), and the undersigned Professor Raimo Lahti, LL.D., M.Soc.Sc. (University of Helsinki, Faculty of Law).

The articles of this anthology are not limited to the aspects of predicting and preventing Type 1 Diabetes only, as the name of the consortium would suggest. The list of participating researchers indicates that many-sided medical expertise was represented in the consortium and, in addition, computational data analysis as well as legal and ethical issues were covered by the participating sites of research. A comprehensive examination of the issues of personalized medicine requires multidisciplinary approaches. In this anthology, the legally and ethically oriented mainstream of writings has been complemented with an article of a computer scientist in order to recognize the possibilities and challenges of machine learning when interpreting the patient’s need for help.

The central team of authors regarding legal and ethical issues of personalized medicine has consisted of Sandra Liede, Juli Mansnérus, and Amanda Blick, who have enjoyed one or more shorter research periods funded by the Academy of Finland. In addition, the Academy-funding has supported Céline Dujardin’s, Merike Helander’s, and the signatory’s research travels. Other contributing authors are Walter Roslin, Liisa Vaaraniemi, and Lauri Lahti.

On behalf of all authors, I express our sincere thanks to the Academy of Finland, to the responsible researchers of the whole consortium, to the Faculty of Law, University of Helsinki, as well as to the peer reviewer of this anthology's manuscript Professor Veikko Launis. It is our hope that this anthology would be useful both for the academic community and for the decision-makers in the fields of healthcare and (personalized) medicine. It is also advisable that the anthology would give an impetus for further research activity in these new spheres of medical law and biolaw.

Helsinki, in December 2020

Raimo Lahti

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1

Introduction

LL.D. Juli Mansnéerus, Professor (Emeritus) Raimo Lahti
and LL.M. Amanda Blick

The regulatory schemes of healthcare and biomedicine are in a constant state of flux. In particular, the paradigm of personalized medicine is an emerging topic, triggering some specific legal and ethical challenges as regards to data collection, sharing and use, informed consent, privacy and public trust, and the changing status of patients and social equality. In Chapter 2, Professor (Emeritus) Raimo Lahti addresses these legislative developments and challenges on the basis of Finnish and common-European experience. The benefits and drawbacks of different regulatory schemes will be discussed. For instance, do we need different types of means ranging from ‘soft’ professional guidelines in order to maintain a high medical-ethical standard to legal rules with diverse enforcement models and sanctioning methods? Do we need a strategy that integrates private law damages schemes with administrative measures and – as a last resort (*ultima ratio*) – criminal sanctions?

In Chapter 3, LL.D. Candidate Sandra Liede discusses Finnish legislative processes aiming to draft ‘innovation-friendly’ legislation for scientific research purposes (the Biobank Act) as well as integrating genomic research results into the clinical setting (the draft Genome Act), which have been heavily challenged by rapid developments in technology and medicine, as well as by confrontations regarding finding the right balance between scientific and commercial interests, public health and individual rights. This Chapter also aims to provide insights on the legislative processes surrounding personalized medicine with a special focus on how the freedom of science, equitable access to healthcare, public health, and commercial issues have been balanced in practice with individual rights as expressed in the EU Charter and the Council of Europe’s Oviedo Convention. Finally, suggestions are made for finding a way forward towards a more balanced communication of the rights and responsibilities of the State while aiming to provide equitable access to personalized health solutions.

While in Chapter 4, LL.D. Candidate Céline Dujardin presents some critical perspectives on Europe’s latest healthcare paradigm, which is grounded on the

pooling of healthcare data, comprising of human genetic information as well as lifestyle patterns. First, the author sketches the contours of current scientific knowledge in the field of genetics and reviews precision medicine as a healthcare model. Thereafter she explores the whys and wherefores of the research benefit, token which is held as a core argument to support the collection of healthcare data, and finally, she tests whether this initiative bears the potential of a biopower.

In Chapter 5, LL.D. Candidate Merike Helander reviews the Finnish and international legislation of genome testing in terms of consent on behalf of a young child. Medical treatment, research based on the patient's autonomy, and the requirement for informed consent as a prerequisite for treatment and research are discussed from the perspective of a child.

In Chapter 6, LL.M. Amanda Blick discusses the legal and ethical aspects of CRISPR/Cas9 and prime editing, the disruptive gene-editing technologies that have been described to substantially expand the scope and capabilities of gene therapy. Special attention is paid to the ethical aspects of such applications that have opened new debates within the scientific community. In particular, the author focuses on the questions of how we should interpret the concept of human dignity in the bioethical discussion surrounding germline editing; and whether the child's right to the highest attainable standard of health and the parents' right to bring a child into the world who is not affected by the illness that they carry could, in some cases, balance out the child's right to inherit a genetic pattern which has not been artificially changed.

In Chapter 7, LL.D. Juli Mansnéus provides an overview of ongoing initiatives to accelerate the market-entry of advanced therapy medicinal products ('ATMPs') that are a heterogeneous class of modern biotechnology medicines encompassing medicinal products based on genes, cells, and tissues. In particular, the joint action plan issued by the European Medicines Agency (the 'EMA') and the European Commission in late 2017 will be discussed. The plan aims at improving the regulatory environment for ATMPs to facilitate the research, development, and approval of these products in the European Union. Regulators are now taking measures to create a facilitative regulatory environment that encourages innovation, protects public health, and enables timely patient access to innovative, new therapies whilst ensuring patient safety. In Europe, the role of risk-proportionate adaptations to clinical trials and GMP manufacture along with the EMA's early-access incentives and initiatives are presented as potential facilitators of market entry will be discussed.

In Chapter 8, LL.M. Waltter Roslin explores risk-sharing agreements and the conditional reimbursement of pharmaceuticals in Finland. These are agreements between payers and providers to mitigate the risk of uncertainty sometimes found

in novel pharmaceutical products. Conditional reimbursement was introduced through a legislative experiment that first ran between 2017–2019 and now continued for another six years from 2020–2025. The author provides an overview of risk-sharing in general in relation to pharmaceuticals, the relevant Finnish legislation, and legislative experiments. Also future challenges are identified in relation to the transparency of the risk-sharing agreements and challenges with increasing the variety of the existing agreement types. Some European experiences and general trends are also discussed.

In Chapter 9, LL.D. Juli Mansnérus and LL.M. Liisa Vaaraniemi investigate the patentability of CRISPR/Cas9 technology in Europe and the United States. Special attention is paid to the recent legal dispute over a patent concerning the use of the CRISPR/Cas9 system in eukaryotic cells. The parties involved in the dispute are two academic institutions, the University of California and the Broad Institute of MIT and Harvard, which have been investigating the system and its potential use as a genome-editing tool. Interestingly, the United States Patent and Trademark Office and the European Patent Office have granted the patent to both of the parties of the legal dispute. In particular, the two patent offices have adopted a very different approach to the concepts of innovative step and obviousness in inventions. This dispute influences the scientific community and those who wish to use this technology commercially. This Chapter will look into the implications of this legal dispute as well as some lessons learned.

The final Chapter 10 by Dr. Sc. (Tech.) Lauri Lahti goes beyond legal or ethical considerations of personalised medicine, discussing how machine learning can be used to enable identification of dependencies in the knowledge processes of healthcare and thus to support providing personalized care that addresses the patient's needs. Machine learning experiments have been carried out to find out what kind of results can be gained when training a convolutional neural network model based on the 'need for help' ratings to classify persons into groups relying on the background information. Lahti reports preliminary results of his experiments showing that it is possible to categorize and distinguish respondent groups based on the patterns of their answer distributions.

2

Regulatory Schemes in Innovative Healthcare and Biomedicine

by Professor (Emeritus) Raimo Lahti

Abstract

There are discernible divergent developments in the regulatory schemes of healthcare and biomedicine as well as in the role of various legal sanctions in the regulation of medical law and biolaw.

In the Nordic welfare states, a new regulatory approach to medical malpractice and treatment injuries was introduced in the 1980s: the statutory, mandatory patient insurance (no-fault) scheme. The role of normal indemnity or criminal liability based on the individual's fault was radically diminished as a result of this new regulatory scheme.

Another tendency can be seen in the strengthening of the legal rights of patients as well as in the increase of the protection of human rights and dignity of the human being with regard to the application of biology and medicine. A typical and perhaps the most influential example of the last-mentioned development is the adoption of the special international legal instrument, Convention on Human Rights and Biomedicine (ETS No. 164, The Oviedo Convention) in 1997 and its later additional protocols.

The newest trend is to examine the legislative schemes addressing the mechanisms of personalized medicine and its challenges in such issues as (big) data collection and sharing, informed consent, privacy and public trust, and the changing status of patients and social equality.

In my paper, these legislative developments will be analyzed on the basis of Finnish and common-European experience. The benefits and drawbacks of different regulatory schemes will be discussed. For instance, do we need differentiated means ranging from 'soft' professional guidelines in order to maintain a high medical-ethical standard to legal rules with diverse enforcement models and sanctioning methods, and do we need a strategy that integrates private law damages schemes with administrative measures and – as a last resort (*ultima ratio*) – criminal sanctions?

2.1 Introduction

In the Nordic welfare states, a new regulatory approach to medical malpractice and treatment injuries was introduced since the 1980s: statutory, mandatory, patient insurance (no-fault) scheme. The role of normal indemnity or criminal liability based on the individual's fault was radically diminished as a result of this new regulatory scheme.

Another tendency can be seen in the strengthening of the legal rights of patients as well as in the increase of the protection of human rights and dignity of the human being with regard to the application of biology and medicine. A typical and perhaps the most influential example of the last-mentioned development is the adoption of the special international legal instrument, Convention on Human Rights and Biomedicine in 1997, and its later additional protocols¹.

The newest trend is to examine the phenomena and mechanisms of personalized (precision) medicine and health care² and its regulatory challenges in such issues as data collection and sharing, informed consent, privacy and public trust, and the changing status of patients and social equality. In a recent research document, personalized health is defined in the following way: '[p]ersonal health care approaches are tailored based on specific information on your genes, your body and your lifestyle, to be as effective as possible and to comprehend disease treatment, prevention, diagnostics, and rehabilitation'. The trend towards personalized health has been accelerated by recent developments in molecular sciences, major advances in information technology, and a favorable regulatory environment.³ The International Consortium for Personalized Medicine (ICPerMed) has outlined a vision of how personalized medicine will lead to the next generation of healthcare by 2030.⁴

1 Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine, ETS No. 164). See Biomedicine and human rights. The Oviedo Convention and its additional protocols. Council of Europe Publishing, Strasbourg 2009.

2 See, e.g., Barbara Prainsack, *Personalized Medicine. Empowered Patients in the 21st Century?* New York University Press, New York 2017.

3 Better, Smarter, Now: Personalised Health. Results of the Academy Programme Personalised Health. Results of the Academy Programme Personalised Health – From Genes to Society (pHealth). Academy of Finland, Helsinki 2019 [www.aka.fi/phealth], Preface. – The author of this paper has been the responsible researcher in the partial project (concerning legal and ethical issues) of the consortium within that Academy Programme Personalised Health, under the chair of Academy Professor Riitta Lahesmaa (University of Turku), on 'Personalised medicine to predict and prevent type 1 diabetes'.

4 The ICPerMed vision for 2030 (September 2019): How can personalised approaches pave the way to Next-Generation Medicine?

In this paper, these legislative developments will be analyzed on the basis of Finnish, common-European, and partly global experience. The benefits and drawbacks of different regulatory schemes will be discussed. For instance, do we need differentiated means ranging from ‘soft’ professional guidelines in order to maintain a high medical-ethical standard to legal rules with diverse enforcement models and sanctioning methods, and do we need a strategy that integrates private law damages schemes with administrative measures and – as the last resort (*ultima ratio*) – criminal sanctions?

2.2 Medical Law and Biolaw and Their Relation to Bioethics – Parallel Regulatory Schemes

The boundaries of the two new sectors of law, medical law and biolaw, are fluid. Medical law conventionally comprises legal issues relating to healthcare personnel, medicine, and healthcare, especially insofar as these have to do with the relationship between patient and doctor (or other healthcare professional). When health law is addressed instead of or complementary to medical law, the former typically covers legal issues relating to the healthcare system as a part of public law. Health law is integrally linked with social welfare law, which conventionally comprises sets of legal norms concerning social security.

Biolaw is the most recent of the sectors of law enumerated here. Its emergence has to do with advances made in biology and medicine, in particular with regard to the applications of biomedicine and biotechnology, and with the enhanced understanding of bioethics. Bioethics had already earlier become the established umbrella term covering the ethical dimensions of medical treatment and care, healthcare, biological and medical research, and environmental issues. Developments in medical reproductive technologies and genetic engineering in particular have given rise to wholly new ethical and legal dilemmas. Bioethical questions do not merely restrict the applications of biology or medicine in relation to human beings but cover the biotechnology in general.⁵ Biolaw, as a new field of law and legal science, covers the same fields of biomedicine and biotechnology as bioethics but concentrates on judicial issues.

5 See, e.g., Cosimo Marco Mazzoni (ed.), *A Legal Framework for Bioethics*. Kluwer Law International, The Hague 1998. The term ‘bioethics’ originates from the work of Van Rensselaer Rotter (1971); see Helga Kuhse – Peter Singer (eds.), *Bioethics. An Anthology*. Blackwell Publishing, Oxford 1999, Introduction.

The legal speciality of medical law and biolaw focuses on the legal issues of healthcare and those involving medical technology and other applications in an integrative way. Within such a new legal discipline, the general principles and concepts contained in the legal regulation of healthcare and medicine can be structured and systematised into more consistent and coherent general doctrines of law than in case of the traditional division of subjects. This goal of creating coherence into legal science is challenging at the present time when the fragmentation and pluralism of legal orders and the ‘polycentricity’ of legal sources are characteristic features of modern legal development.⁶

2.3 The Increase of Legal Regulatory Schemes in Healthcare and Biomedicine

The need for a cohesive body of research in medical law and biolaw has been boosted by the rapid development of legislation in this field over the past few decades. And given that (bio)medicine has traditionally been considered to be an area of social life that should be subject to as little legal regulation as possible, this change in perspective is a marked one. Mutual trust is required in the relationship between patient and doctor, and the principles guiding such relationships are traditionally deemed to be drawn from medicine and medical ethics rather than from law. Professional codes of conduct have played an important role here. Such codes are usually international in nature, being approved either by international official organisations or professional societies.

The principle of a patient’s right to self-determination only gained a foothold in medical ethics after World War II, in connection with the Nuremberg trials. The decision by the military tribunal led to the creation of the Nuremberg Code (1947) on the performance of medical trials on human subjects.

M. Cherif Bassiouni has differentiated between five stages through which human rights evolve in accordance with the degree to which the right has attained international acceptance: he lists the enunciative, declarative, prescriptive,

6 See, generally, Erick Valdés – Juan Alberto Lecaros (eds.), *Biolaw and Policy in the Twenty-First Century. Building Answers for New Questions*. (Springer Nature International, 2019). See also Sirpa Soini, *Geenitetaus ja lakien henki. Tutkimus geenitestien sääntelystä [Genetic testing and the spirit of laws. A study on the regulation of genetic testing]*. Doctoral thesis. Unigrafia, Helsinki 2020. Soini prefers the term ‘biomedical law’ instead of ‘biolaw’.

enforcement, and criminalization stages.⁷ Accordingly, criminalization is the ultimate framework in the regulation of modern biomedical techniques (see later). Linda Nielsen reminds us that regulation in the area of biotechnology is a particularly scrupulous endeavor for several reasons, and legislation and regulation in the area is a means, not a goal. It is important to protect human dignity, integrity, privacy, and non-discrimination, but the forms of protection may vary considerably, and she analyses in detail different models of protection and regulation.⁸ Inger-Johanne Sand has based her theoretical scenario on the philosophical works of Michel Foucault and has sketched a comprehensive conceptual framework for governing, law, and politics in the EU law as to modern biotechnologies.⁹

In a Nordic welfare state such as Finland, public healthcare services account for a considerable part of the total healthcare sector. This gives additional importance to questions concerning the position and duties of the public authorities (the State and local government).¹⁰ For example, what is the legal position of the individual, and what are the legal remedies available to him against a healthcare sector authority or official exercising public power or deciding on health services? Or what means are employed to steer and supervise healthcare staff and the healthcare system as a whole?

In the early 1990s, municipalities and municipal federations were saddled with the responsibility of arranging public healthcare and were given increased independence in its implementation. The same time period saw a transition in healthcare administration from administrative supervision and guidance to the less regulated performance guidance and information steering. Administrative supervision and guidance have been reorganised in the reforms of recent years. The use of administrative coercive measures has been streamlined and extended to apply equally to healthcare units.

The expansion of legislation governing healthcare in Finland is explained in part by the increased regulation of the sector's organisation, resources, and steering, which is typical of welfare states. In addition, particular emphasis was

7 M. Cherif Bassiouni, *The Proscribing Function of International Criminal Law in the Processes of International Protection of Human Rights*, in Theo Vogler (Hrsg.) *Festschrift für Hans-Heinrich Jescheck zum 70. Geburtstag*, II. Duncker & Humblot, Berlin 1985, pp. 1453–1475, 1455.

8 Linda Nielsen, *From Bioethics to Biolaw*, in *A Legal Framework for Bioethics*, supra note 5, pp. 39–52.

9 Inger-Johanne Sand, *Governmentality, Biopolitics and the EU*, in Kimmo Nuotio (ed.), *Europe in Search of 'Meaning and Purpose'*. Forum Iuris, Helsinki 2004, pp. 149–170.

10 As for the following explanation, see Raimo Lahti, *Medical law and biolaw*, in Kimmo Nuotio et al. (eds.), *Introduction to Finnish Law and Legal Culture*. Forum Iuris, Helsinki 2012, pp. 249–260, 251.

placed at the initial stages on rectifying defects of a fundamental nature having to do with the rights and freedoms of patients (examples include the elimination of forced castration and the revised regulation of the involuntary treatment of psychiatric patients). With the 1980s came preparations for measures to improve the legal position of 'ordinary', somatic patients as well. This work resulted in the enactment of the Patient Injuries Act (585/1986)¹¹ and the Act on the Status and Rights of Patients (785/1992)¹². Underlying these reforms was the rise of fair trial philosophy, in consequence of which the human and fundamental rights of the individual as well as the rights of consumers are strengthened in the legal system.

As Francesco Francioni points out, the development of modern technologies has influenced on the elaboration of many treaties and soft-law instruments in order to establish standards and supervision procedures in relation to biotechnology risks. According to him, the following human rights are most directly affected by biotechnologies: (1) human dignity, (2) non-discrimination, (3) self-determination, (4) rights pertaining to the human body, such as life, integrity, and health, (5) economic and social rights, including intellectual property rights and sustainable development.¹³

In his introduction to the anthology on European Law and New Health Technologies, Roger Brownswood sees that collection of articles as a search for an establishment whether there is a distinctively European way of regulating new health technologies. According to him, the contributors of the book analyse the ways in which so much of European regulatory thinking (within both the EU and the Council of Europe) is oriented towards the regional market (for health technologies) qualified by considerations of risk (where both prospective costs and benefits attract attention), human rights, and ethics. Difficult balances must be made in relation to the leading considerations, in particular between regulatory restriction for the sake of safety and human rights and regulatory support for the sake of innovation and the market.¹⁴

11 This Act will be from 1 January 2021 replaced by the Patient Insurance Act (948/2019). However, the basic structure and main contents of the Act of 1986 are retained.

12 Hereinafter the 'Patient Rights Act'.

13 Francesco Francioni, Genetic Resources, Biotechnology and Human Rights: the International Legal Framework, in Francesco Francioni (ed.), *Biotechnologies and International Human Rights*. Hart Publishing, Oxford 2007, pp. 3–32, 4, 18.

14 Roger Brownswood, Foreword, in Mark L. Flear – Anne-Maree Farrell – Tamara K. Hervey – Thérèse Murphy (eds.), *European Law and New Health Technologies*. Oxford University Press, Oxford 2013, vii–ix. See also, i.a., Sigmund Simonsen, *European Integration – a Case Example from European Biomedical Research Law*, in Elisabeth Rynning – Mette Hartlev (eds.), *Nordic Health Law in a European Context – Welfare State Perspectives on Patients' Rights and Biomedicine*. Martinus Nijhoff Publishers / Brill, Leiden 2012, pp. 255–266.

These references emphasize the significance of human rights as the main regulatory restriction. The UN's Universal Declaration of Human Rights (UDHR, 1948), European Convention on Human Rights (ECHR, 1950), and the UN's Convention on Civil and Political Rights (CCPR, 1966) originate their legacy from the experience of the Second World War. Article 7 of CCPR prescribes that nobody shall be without his or her free consent to be subjected to medical or scientific experiments.

The role of the case-law of the European Court of Human Rights (ECtHR) has been important also in the field of bioethics.¹⁵ The adoption of the Council of Europe's Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine (Biomedicine Convention, 1997) and the proclamation of the Charter of Fundamental Rights of the EU (2000) have strengthened the normative governance of biomedicine in Europe.¹⁶

The rise of human and fundamental rights thinking since the early 1990s has in Finland increased the necessity for legal regulation by statutory acts in many fields while at the same time clarifying the characteristics of such need and the manner of its implementation.¹⁷ Finland's accession to the European Union (EU) in 1995, in turn, obliged it as a new member-state to implement Community legislation to a part of the national legal order and, after that, to recognise where the Community legislation affects the application of national law. The implementation of human rights binding on Finland, as well as of EU law (as it stands after the Lisbon Treaty) must be safeguarded through statutory legal remedies.

The prerequisites for restricting human and fundamental rights are precisely defined in the relevant legislation. Section 21 of the Finnish Constitution (731/1999)¹⁸ concerning protection under the law gives everyone the right to have his or her case dealt with by a legally competent court of law or other authority, as well as to have a decision pertaining to his or her rights or obligations reviewed by a court of law or other independent organ for the administration of justice. The guarantees of a fair trial and good governance shall be laid down by an Act. Section 80(1) of the Constitution further requires that the principles governing

15 See, e.g., Research report. Bioethics and the case-law of the Court. ECtHR 2012 (available at www.echr.coe.int: Case-law – Case-Law Analysis – Research Reports).

16 See, e.g., Richard Ashcroft, Novel Rights-Based Approaches to Health Technologies, in *European Law and New Health Technologies*, *supra* note 14, pp. 309–322.

17 As for the following account, see in general Introduction to Finnish Law and Legal Culture, *supra* note. 10, *passim*.

18 An unofficial translation into English with the amendments up to 817/2018 included is available from the website of the Ministry of Justice: <https://www.finlex.fi/fi/laki/kaannokset/1999/en19990731.pdf>.

the rights and obligations of private individuals and the other matters that under this Constitution are of a legislative nature shall be governed by Acts, i.e. instruments passed by Parliament. EU law imposes requirements having to do with the efficiency, proportionality, and effectiveness of national legal remedies in its implementation.

Based on the above, it would not be overstating the case to say that human and fundamental rights have created a new value foundation for our legal system, and one which introduces a greater degree of coherence. The trend in law otherwise is one of differentiation and fragmentation, as indicated by the emergence of medical law and biolaw as a distinct sector of law. The strengthening of human and fundamental rights has a positive, cohering effect on this new sector of law too.

A need for new kinds of legal regulation has arisen from the rapid advances seen in recent years in methods of artificial human reproduction (assisted fertility treatments) and medical genetics. The development of biomedicine has made topical, for example, the protection of unborn life (the human embryo)¹⁹. Advances in biomedical methods, genetic engineering in particular, has focused awareness on a new value to be afforded legal protection, the inviolability of the human genome. Equally, the concept of human dignity – counted already earlier among human rights of a fundamental nature and principles of medical law alike – has assumed new dimensions and gained in scope²⁰.

2.4 Finnish Examples of Legal Regulation of Healthcare: Patient Acts

The enactment of the Patient Rights Act of 1986 and the Patient Injuries Act of 1992 had the aim of enhancing the legal protection of both patients and staff in

19 See, e.g., Juli Mansnérus – Céline Dujardin – Raimo Lahti, Forms and levels of legal protection of the human embryo in biomedical research in Finland and France, in Emil W. Pływaczewski – Ewa M. Guzik-Makaruk (eds.) *Current Problems of the Penal Law and Criminology*. C.H. Beck, Warszawa 2019, 199–224; Laura Walin, Ambiguity of the embryo protection in the Human Rights and Biomedicine Convention: Experiences from the Nordic countries. *European Journal of Health Law*, Vol. 14, 2007, pp. 130–148.

20 See, e.g., the critical analysis of Laura Walin, Human Dignity as a Legal Argument in the Era of Modern Biomedicine, in *Nordic Health Law in a European Context*, *supra* note 14, pp. 243–254.

healthcare and medical treatment.²¹ In keeping with its title, the Patient Rights Act expressly lays down provisions on the legal rights of patients. This Act was intended to clarify, harmonise, and strengthen the principles to be observed in the care and treatment of patients. Structural changes in the healthcare system – the increasing degree of technicality and specialisation in healthcare, and the growing size of healthcare units – served to underscore the aim of legal protection underlying the Acts.

To the best of my knowledge, these Acts, which improved the legal position of patients, were the first of their kind in the world, although a similar development of legislation and professional standards occurred in several other countries as well, usually as a part of an overall strengthening of human and fundamental rights thinking. In Finnish legal culture, human and fundamental rights clearly gained in status in the 1990s, with the ratification of the ECHR in 1990 and the entry into force of the basic rights reform in the Finnish Constitution in 1995. As a result of this development, patient rights too have been given increasing weight. Under the Finnish Constitution (Section 19), the public authorities are obligated to guarantee everyone adequate social, health, and medical services and to promote the health of the population.

The Patient Rights Act and the Patient Injuries Act may today be considered to constitute the core statutes of medical law. Follow-up data on the application of both Acts has been systematically compiled in order to evaluate the achievement of the aims set for the Acts and to determine the needs for their reform.

These Acts are of particular significance when determining the basic legal concepts and general legal principles belonging to the general doctrines of medical law. The general doctrines of the sector of law itself, meanwhile, provide the key justification for its independent position.

The Patient Injuries Act introduced a mandatory liability insurance scheme to improve patients' access to compensation. The scheme was thought in most cases to replace in practice the enforcement of ordinary tort liability and penal liability and by such means to avoid the conventional court proceedings by a simplified dispute settlement. The principles of general tort law are observed in the determination of the amount of compensation but the preconditions for the right to compensation differ from general tort law in that malpractice or negligence on the

21 As for the following review, see in more detail Raimo Lahti, *Towards a Comprehensive Legislation Governing the Rights of Patients: The Finnish Experience*, in Lotta Westerhäll – Charles Phillips (eds.): *Patient's Rights – Informed Consent, Access and Equality*. Nerenius & Santérus, Stockholm 1994, pp. 207–221; idem, *The Finnish Patient Injury Compensation System*, in Sheila A.M. McLean (ed.): *Law Reform and Medical Injury Litigation*. Dartmouth, Aldershot 1995, pp. 147–162.

part of any individual need not be established. Patient injury within the meaning of the Act, i.e. a bodily injury to a patient in connection with healthcare or medical treatment, is defined in the initial sections of the Act, and it thus constitutes a special type of injury. For example, compensation shall be paid for bodily injuries if it is probable that these injuries result from examination or treatment taken or neglected, providing that an experienced healthcare professional would have examined or treated the patient in a different manner and would thereby probably have avoided the injury.

The Patient Rights Act lays down coherent provisions to govern the status and rights of patients, whether in receipt of in public or private healthcare. In a way, the Act unifies features of law concerning persons, falling within the scope of private law, and social welfare law, falling within the scope of public law. This manner of regulation – taking into account the relevance of the Patient Injuries Act – has an impact on the understanding of the legal relationship between patient and healthcare professional, and on the formation of the principles which guide that relationship. The emphasis in the Act is on the determination at the level of law of the principles defining the status of the patient, and the Act lacks, for example, its own sanction provisions.

The Patient Injuries Act and Patient Rights Act are also significant with regard to the guidance, supervision and sanctions system in healthcare. The Patient Injuries Act underscores the meaning of damages as a restorative sanction, whereas the Patient Rights Act introduced certain new means for guidance and supervision: the position of Patient Ombudsman and the objections procedure. The supervision of healthcare professionals in Finland has traditionally taken place by administrative means, i.e. through administrative sanctions as well as disciplinary procedures and the control of the rights to practice medicine. Criminal penalties are of little significance in the field of healthcare.

The aim of strengthening certain legal principles comes across clearly in a reading of the Patient Rights Act. These principles are also constitutive as to the basic concepts of modern medical ethics and bioethics: respect for human dignity, integrity, right of self-determination, and the privacy of the patient. Furthermore, the values reflected in these principles occupy centre stage in our fundamental rights provisions of the Constitution laid down in 1995.

The Patient Rights Act upholds and specifies the substance of this right of self-determination and the related right of access to information, as well as the status of minor patients. At the same time, the principle concerning the binding nature of a patient's advance directive, relevant to both terminal treatment and living wills, was also recorded in law.

For a long time, the weight of these basic principles of medical law was not sufficiently acknowledged in legal thinking or practice. For example, in connection with the drafting of the provisions of the Criminal Code in its Chapter 21 concerning homicide and bodily assault (578/1995), there was reason to clarify to the Legal Affairs Committee of Parliament the following: when a patient's right to self-determination has been confirmed by a statutory act, the provisions of the Criminal Code cannot impose on physicians a duty to sustain the life of terminally ill patients through extraordinary measures contrary to the wishes duly expressed by the patient.

2.5 Biomedicine and Fundamental and Human Rights

The rise of human and fundamental rights thinking since the early 1990s has in Finland increased the necessity for legal regulation by statutory acts in many fields while at the same time clarifying the characteristics of such need and the manner of its implementation.²²

In a recent collection of articles, the US editors view technological change through the lens of human rights and emphasize as the fundamental values of their human rights-based approach following ones: universality/inalienability, indivisibility, interdependence/interrelatedness, equality and non-discrimination, participation/inclusion, and accountability/rule of law. The writings of the book highlight three common themes associated with interactions between human rights and technology: the relationship between technology and power, the effect of technological innovation on accountability, and the shifting boundary between public and private.²³

It would not be overstating the case to say that human and fundamental rights have created a new value foundation for our legal system, and one which introduces a greater degree of coherence. The trend in law otherwise is one of differentiation and fragmentation, as indicated by the emergence of medical law and biolaw as a distinct sector of law. The strengthening of human and fundamental rights has a positive, coherence creating effect on this new sector of law, too. Human rights

22 As for the Scandinavian discussion, see Henriette Sinding Aasen – Rune Halvorsen – António Barbosa da Silva (eds.), *Human Rights, Dignity and Autonomy in Health Care and Social Services: Nordic Perspectives*. Intersentia, Antwerp 2009, *passim*. An examination of medical law from a human rights perspective is Elizabeth Wicks, *Human Rights in Healthcare*. Hart Publishing, Oxford 2007.

23 Molly K. Land – Jay D. Aronson (eds.), *New Technologies for Human Rights Law and Practice*. Cambridge University Press, Cambridge 2018, esp. ch. 1 (DOI: 10.1017/9781316838952).

arguments may also be used as the basis for the critical assessment of certain activities in health care and biomedicine²⁴.

The Convention on Human Rights and Biomedicine was adopted in Oviedo on 4 April 1997 and it took international effect in 1999. This Biomedicine Convention and its Additional Protocols on the Prohibition of Cloning Human Beings (ETS No. 168, 1998) and on Transplantation of Organs and Tissues of Human Origin (ETS No. 186, 2002) were ratified by Finland in 2009. The substantive provisions of these European legal instruments were implemented to Finnish legal order on 1 March 2010, and after that the provisions have the status of statutory law equal to those of Parliamentary Acts.

The Biomedicine Convention serves to supplement or specify the European Convention on Human Rights in the field of biomedicine. The case law of the European Court of Human Rights in application of the Convention has occasionally made references to the standards of the Biomedicine Convention even when the allegedly infringing State has not even ratified it. One may conclude from this that the provisions of the Biomedicine Convention may in effect guide the evolutionary interpretation of the European Convention on Human Rights²⁵.

As its full name suggests, the Biomedicine Convention seeks to protect human rights and human dignity with regard to the application of biology and medicine. Its provisions define general principles (such as consent, private life and the right to information) as well as special standards as for human genome, biological and medical research on persons and human embryos, and organ and tissue transplants. The Biomedicine Convention and its Additional Protocols afford a minimum level of protection which does not prevent wider protection from being afforded in the application of biological and medical knowledge, respectively.

Of particular importance is Article 1 of the Biomedicine Convention, according to which the purpose of the Convention is to protect the dignity and identity of all human beings. The Biomedicine Convention and its Protocols are of significance, not only for the sake of formulating human rights principles and standards to be applied in the field of biomedicine, but also for providing guidance for priority-setting and balancing these divergent principles and standards. No conflict between the ratified Convention or its Protocols and the Constitution of Finland could be demonstrated, even though Article 1 of the Convention – when emphasising the protection of human *beings* – represents a certain change in the

24 Cf. the theory of critical legal positivism, developed by Kaarlo Tuori, *Ratio and voluntas: the tension between reason and will in law*. Ashgate, Burlington VT 2010, *passim*.

25 See examples of cases where the Oviedo Convention has been cited in the ECtHR, Research report. Bioethics and the case-law of the Court, *supra* note 15, p. 52.

protected values, because it may be understood as a reason for increased legal protection of the human embryo.

From Finland's point of view, the Convention and its Protocols reinforce and specify already-existing and applied constitution and human rights provisions in the field of biomedicine. The ratified Convention and its Protocols have affected the relevant legal regulation in Finland even before ratification. Following the ratification, the public authorities shall, under Section 22 of the Finnish Constitution, guarantee the observance of basic rights and liberties and human rights. Consequently, norms equivalent by their nature to human rights are given a special position, as are basic rights and liberties. The said effect extends to both the legislator and to those who apply the law, including the professional in the field of healthcare and biomedical activities.

There is a keen interaction between ethical and legal regulation. Martin Scheinin has regarded the codes of professional and research ethic as relevant standards in the application of legal norms ²⁶. In a recent anthology Cesare P. R. Romano *et alia* make a distinction between the international human rights law (basic notions of international law) and international bioethics law (which consist of such soft-law instruments as 1997 UNESCO Universal Declaration on Human Genome and Human Rights), They regard the last-mentioned documents as customary international law in the making, because soft law is a good tool to find out what the prevailing practice and *opinio juris* are. They also advocate that the instruments of international bioethics law should be integrated with the broader human rights law corpus.²⁷

A norm (either a rule or principle) is legally relevant, i.e. it has legal implications (such as legal sanctioning) when it has an institutional support, in other words a support in legal sources (legislation or legal practice). However, there are borderline areas which is reflected by the distinction between hard and soft law. An example of such an institutional support is Article 4 of the Biomedicine Convention, which prescribes that any intervention in the health field, including research, must be carried out in accordance with relevant professional obligations and standards.

26 Martin Scheinin, Ihmisoikeudet ja tutkimusetiikka [Human rights and research ethics], in Paavo Löppönen et al. (eds.), Tiede ja etiikka [Science and ethics]. WSOY, Porvoo 1991, pp. 85–103, 91.

27 Cesare P. R. Romano, The Governance of Human (Germline) Genome Modification at the International and Transnational Level, in Andrea Boggio – Cesare P.R. Romano – Jessica Almqvist (eds.), Human Germline Genome Modification and the Right to Science. A Comparative Study of National Laws and Policies. Cambridge University Press, Cambridge 2020, pp. 22–79, 26, 78.

It must also be noted that it is typical for the argumentation in medical law and biolaw that it reconciles and balances divergent legal-ethical values, interests and principles. In like manner, a key aspect of the legal argumentation here, instead of the ordinary interpretation of the law under legal rules, is the weighing against each other of mutually divergent legal principles of different strengths.²⁸

A convergence of legal and ethical argumentation implicates problems for instance, how to interpret such vague concepts as human dignity and human being. There is no consensus in legal doctrines about the contents of these concepts, although they are key concepts in the implementation of the Biomedicine Convention. The same is true in relation to the legal position of human stem cells and human embryos. Neither exists any established legal practice how to balance (weight) conflicting or colliding principles (values) with each other – except the basic priority setting in the Biomedicine Convention, Article 2: The interests and welfare of the human being shall prevail over the sole interest of society or science.²⁹ The doctrine of the margin of appreciation dominates in ECtHR consideration of modern health technologies, but ECHR requires respect for a minimum core of rights: autonomy-type rights (consent, privacy) and to some extent equality and the right to health.³⁰

As for the activities of health care and biomedicine, which in essence are governed by morals and professional standards, there is reason to keep in mind the idea of so-called reflexive law as a third form of law (in addition to formal and substantive law). Accordingly, in a pluralistic society the legislator's role should be restricted to imposing only boundary conditions and flexible procedures, offering a framework within which individuals and groups may then exercise their moral autonomy.³¹ Debate of this kind has focused on the principles for regulating medical research, to take just one example. Although the Finnish Medical Research Act (488/1999) imposes limits on the permissibility and conditions of such research, no attempt is even made to exhaustively regulate the grounds employed by the

28 See also Soini, *Geenitestausta ja lakien henki* (*supra* note 6), p. 126, according to whom biomedical regulation represents theoretically a sort of legal pluralism and transnationalism; it includes such a sort of pluralism in which values and morals are reflected in judicial practices.

29 Cf., e.g., Mansnérus et al., *supra* note 19 and Laura Walin, *supra* notes 19, 20.

30 See Rory O'Connell – Sjef Gevers, *Fixed Points in a Changing Age? The Council of Europe, Human Rights, and the Regulation of New Health Technologies*, in *European Law and New Health Technologies* (*supra* note 14), pp. 46–69, 57, 67.

31 See my earlier analysis Raimo Lahti, *Life's Beginnings: Law and Moral Dilemmas. The Finnish Yearbook of International Law*, Vol. II, 1991, 438–468, p. 445, where I refer to David Jabbari, *The role of Law in reproductive medicine: a new approach*. *Journal of medical ethics*, Vol. 16, 1990, pp. 35–40. The distinction between formal, substantive and reflexive law is based on Gunther Teubner, *Substantive and reflexive elements in modern law. Law and society review*, Vol 17, 1983, pp. 239–286.

ethics committees provided for in law as they go about their task of evaluating the ethicality of research projects.

Finnish legislation has for the most part been amended to comply with the requirements under the Biomedicine Convention and its ratified Protocols. In certain respects, the regulations enforced become directly applicable in the absence of specific legislation. Examples of such regulations would be Articles 12 and 13 of the Biomedicine Convention (predictive genetic tests and interventions on the human genome). However, it would be highly desirable for national legislation to implement such Articles by specifying legal provisions.

With respect to the impact on the legislator and the ones applying the norms it has been valuable to investigate how an important possibility considered by the Finnish research community, somatic cell nuclear transfer technique utilized in therapeutic cloning is preserved subsequent to the ratification of the Biomedicine Convention without reservation as stipulated in the sub-paragraph 2 of the Article 18. According to this perception, only reproductive cloning would be prohibited. In this very question clarification of the national legislation would be desirable on accordance with the Swedish example. To be noted that Sweden has in a similar situation deemed necessary to make a reservation in the said article upon the ratification of the Biomedicine Convention.

The interpretative effect of the Biomedicine Convention and its ratified Protocols shall also be taken into consideration. I mention as an example infant male circumcision, on which the Finnish Supreme Court issued a precedent in its decision *KKO 2008:93*. The Supreme Court held that the conduct of a mother who had a Muslim son of 4 years circumcised for religious reason was not to be deemed illegal and punishable as an offence of assault. In its argumentation, the Supreme Court made no reference to the Biomedicine Convention – which admittedly at the time had yet to be ratified. Subsequent to the ratification of the Convention, the effect of Article 6(1) must – to my mind – be considered; accordingly, an intervention in the health field may only be carried out on a person who does not have the capacity to consent, for his or her direct benefit.³²

In its precedents *KKO 2016:24-25*, the Supreme Court confirmed its earlier ruling with some specifications: the minor intervention in a male child's physical integrity with his guardians' consent, taking the form of a medically appropriate circumcision conducted on religious or cultural grounds should be regarded as a justifiable measure (and not punishable as an assault) with regard to the

³² See my critical analysis about the case Raimo Lahti, Infant Male Circumcision – Finnish Supreme Court Ruling on a Multicultural Legal Protection, in *Nordic Health Law in a European Context*, *supra* note 14, pp. 216–227.

child's overall interests, irrespective the child's own will. In the precedent KKO 2016:24, the Supreme Court also dealt with the effect of Article 6(1) of the Biomedicine Convention. According to its reasoning, the child's direct benefit could be interpreted as covering cultural or social benefit (especially for the child's attachment to his religious and social community) and not only medical benefit to the child. This argument represents to my mind more a collective interest than an individual interest (as the individual right to corporal integrity), and this individual interest should prevail over the collective interests of the society or certain community (minority) groups, thereby better reflecting the basic values of the Finnish Constitution and Biomedicine Convention.

2.6 What Kind of Legal Regulatory Scheme for the Activities in Healthcare and Biomedicine?

As explained in section 2.4 above, Patient Acts represent in Finland a new regulatory approach to medical practice and treatment of injuries since 1980s. The statutory, mandatory patient insurance (no-fault) scheme reduced the role of penal and administrative sanctioning.

An influential example of the international legal instruments for strengthening the protection of human rights with regard to the application of biology and medicine is Biomedicine Convention. Its Article 25 stipulates that Parties shall provide for appropriate sanctions to be applied in the event of an infringement of provisions contained in the Convention. Criminal sanctions are not preferred.

I remind you about a resolution of a non-governmental organization on the subject. In an international colloquium in 1988 and a congress in 1989 of the International Association of Penal Law (AIDP), the topic 'Criminal law and modern bio-medical techniques' has been deliberated.³³ The Vienna Congress (1989) concluded to a resolution on the subject³⁴, and it emphasizes, *i.a.*,

‘1.5. In balancing these colliding interests, different points of view and results are to be expected due to the influence of different religious, ethical, and political convictions of different legal cultures and social structures.

33 See especially the general report of Raimo Lahti, Criminal Law and Modern Bio-Medical Techniques. *Revue Internationale de Droit Pénal*, Vol. 59, 1988, pp. 603–628.

34 Resolutions of the Congresses of the International Association of Penal Law (1926–2014), *Revue Internationale de Droit Pénal*, Vol. 86, 2015, pp. 353–363.

In view of the frontier crossing character of these problems and increasing interdependence among the various countries, internationally uniform standards and rules should be achieved [and] if possible binding laws are to be introduced on an international level.’

Taking care of those various interests requires differentiated means ranging from professional guidelines in order to reach or maintain a high medical-ethical standard to legal rules with diverse enforcement models and sanctioning methods. A strategy that integrates private law damages schemes with administrative measures and criminal sanctions was in the resolution regarded as most adequate. Criminalization of medical activity as well as the threatening of penalties should remain as a means of last resort (*ultima ratio*). The first precondition has to be the worthiness of the endangering good and the blameworthiness of the endangering action (*Strafwürdigkeit*). Furthermore, on the basis of a cost-efficiency comparison of different means, the employment of criminal punishment should prove both as necessary (*Strafbedürftigkeit*) and suitable (*Straftauglichkeit*).³⁵

Twenty-two years later, Carlos Maria Romeo-Casabona deals with the same subject³⁶ and concludes:

‘The difficulties presented by new crimes in the biotechnology sector, demand the legislator to proceed with the utmost scrupulousness. The effectiveness of a preventive answer regarding these crimes, their political-legal justification and the fact that they may or may not be disregarded due to their merely symbolic effect will ultimately depend on whether or not legislative technical premises have been properly managed for description and punishment of these kinds of offences.’

Criminal law provisions on modern biotechnology should be critically assessed on wider bases to address properly the new dangers and risks to more complex activities in a society. In this kind of risk society, there is a tendency to use criminal law for a solely symbolic-expressive purpose as a *prima* and not as an *ultima ratio* as well as a tendency to loosen the requirements of traditional criminalization principles, such as the clear identification of the protected legal interests and the strict definition of the constituent elements of the crime.³⁷

The questions revolving around the legal status of the embryo or materials of embryonic origin should not be disconnected from their cultural context. That

35 *Ibid.* pp. 354–355.

36 Carlos Maria Romeo-Casabona, Criminal Policy and Legislative Techniques in Criminal Law on Biotechnology. *Revue Internationale de Droit Pénal*, Vol. 82, 2011, pp. 83–108, 108.

37 Cf., generally, Raimo Lahti, Towards a principled European criminal policy: some lessons from the Nordic countries, in Joanna Beata Banach-Gutierrez and Christopher Harding (eds.), *EU Criminal Law and Policy. Values, Principles and Methods*. Routledge: London 2017, pp. 56–69.

might explain the differences in punishment regarding acts somehow threatening genetic inheritance. The international community has already set boundaries for the protection of genetic inheritance. When looking at national legislation, we find that there are differences in wording for the same type of misconduct. For instance, this specific wording can be seen in the Finnish in Section 4 of Chapter 22 (373/2009) of the Finnish Criminal Code entitled ‘Unlawful manipulation of genetic inheritance’:

‘A person who undertakes research involving the manipulation of the integrity of a human or a human embryo or a human foetus and that is intended to make possible

(1) the cloning of a human,

(2) the generation of a human by combining embryos or

(3) the generation of a human by combining human germ cells and animal genetic material,

shall be sentenced for unlawful manipulation of genetic inheritance to a fine or to imprisonment for at most two years.’

This penal scale for the manipulation of genetic inheritance is much lower than in France, where it has been regarded as comparative with a crime against humanity³⁸. As to the level of punitiveness in the Finnish penal scales, it should be noticed the starting point of Finnish criminal policy: from all the different mechanisms through which the general preventive effect of the punishment should be reached, deterrence is not the most important; it is the socio-ethical disapproval which affects the sense of morality and justice – general prevention instead of general deterrence – without a need for a severe penal system.³⁹ Even the Finnish provision has been criticized for the relatively heavy sanctions, although their *travaux préparatoire* do not go any deeper into the reasons why these specific acts – and nothing else – are against human dignity⁴⁰.

38 See Mansnérus et al., *supra* note 19, p. 211.

39 See, generally, Raimo Lahti, Towards a More Efficient, Fair and Humane Criminal Justice System. *Cogent Social Sciences* (2017), 3: 1303910. <http://dx.doi.org/10.1080/23311886.2017.1303910>. Accessed 24 July 2020.

40 See Walin, *supra* note 20, p. 253.

In a comprehensive comparative study on human germline modification, the editors plead in their recommendations for a human rights framework for such regulation of human germline genome modification that acknowledges the necessary restrictions on freedom of research and benefit-sharing but primarily emphasizes the rights to science and the right of science.⁴¹

2.7 Special Challenges of Personalized (Precision) Medicine to Its Regulation

Personalized medicine has a great potential for producing powerful new discoveries; it has been assessed that many key insights require the integration of an enormous scale of genetic and medical information. At the same time, there are regulatory concerns around issues such as data collection and sharing, informed consent, privacy and public trust, the changing status of patients, and social equality.

In a partial project of the Academy Programme Personalized Medicine mentioned at the beginning of this paper, the utilization and management of digital samples, patient data, clinical practices, and business activities advancing personalized medicine were studied. The main findings of that project show that the promotion of personalized health care takes predominantly place in the framework of innovation policy and is mainly concerned with economic expectations and commercialization.⁴² The researchers of that project identified two rhetoric framings within which the expectations, pursuits, plans, and activities for advancing personalized medicine are connected into a reasonable and justifiable endeavor: innovation policy and data-driven medicine.⁴³ One researcher of that project has noticed how the argumentation for data-driven medicine relies on the moral principle of health (such as common good, public

41 Boggio et al., *Toward a Human Rights Framework for the Regulation of Human Germline Genome Modification*, in *Human Germline Genome Modification and the Right to Science*, *supra* note 27, pp. 585–617, 614, 616.

42 Ilpo Helén – Hanna Lehtimäki – Karoliina Snell, *Good(s) for health: Personalized health services and flexible appropriation of bioinformation*, in *Better, Smarter, Now: Personalised Health*, *supra* note 3, pp. 14–15.

43 Heta Tarkkala – Ilpo Helén – Karoliina Snell, *From health to wealth: The future of personalized medicine in the making*. *Futures*, Vol. 109, 2019, pp. 142–152 (<https://doi.org/10.1016/j.futures.2018.06.004>).

health or national competitiveness) and tends to undermine the arguments related to autonomy and privacy.⁴⁴

The trend towards more personalized medicine will in many ways affect the patient-physician relationship: the physician has much more digital data which can be analyzed by using algorithms for clinical purposes; patients become more activated, and they are more often research contributors, but there is also the darker side of data-driven medicine (digital surveillance); borderline between research and care becomes flexible (for example, experimental treatments become prevalent); it furthers a shift from reactive and symptomatic medicine toward continuous and pre-symptomatic medicine.⁴⁵

In the literature, there is increasingly deliberation about the proper balance between patient privacy and autonomy rights and the public interest in research. For instance, in a recent anthology, the editors remind that the traditional ethical codes and regulations do not necessarily concern health Big Data activities. Therefore, legal and regulatory challenges relate, *inter alia*, to the requirement of informed consent, accountability schemes for (re)using health data, and intellectual property rights in the field.⁴⁶

In Finland, attention has recently been paid to developing innovation-friendly regulatory approaches and practices as part of the Government's Analysis, Assessment and Research Activities in 2020.⁴⁷ As one legislative example of this kind of regulation has been analyzed the Act on the Secondary Use of Health and Social Data (552/2019), which was enacted in order to facilitate research with health data in various registers and their reuse in business. This Act should be seen in connection with the strategical totality of legislation, i.e. the earlier Biobank Act (688/2012)⁴⁸ and its pending reform after the implementation of the EU's General Data Protection Regulation (GDPR) 679/2016 (which came into effect on 25 May 2018) and the national Data Protection Act (1050/2018), as well as the proposed implementation of the EU's Clinical Trial Regulation 536/2014

44 Karoliina Snell, Health as the Moral Principle of Post-Genomic Society: Data-Driven Arguments Against Privacy and Autonomy. Cambridge Quarterly of Healthcare Ethics, Vol. 28, 2019, pp. 201–214. (DOI:10.1017/S0963180119000057).

45 See, generally, Prainsack, Personalized Medicine, *supra* note 2, passim.

46 Glenn Cohen – Holly Fernandez Lynch – Effy Vayena – Urs Gasser (eds.), Big Data, Health Law, and Bioethics. Cambridge University Press, Cambridge 2018, Introduction, pp. 1–13, 5. See also, generally, Jochen Vollmann – Verena Sandow – Sebastian Wäscher – Jan Schildmann (eds.), The Ethics of Personalized Medicine. Critical Perspectives. Routledge, London 2020 (orig. 2015).

47 Vesa Salminen – Kimmo Halme (eds.), Innovation-friendly regulation: Current state and good practices. Publications of the Prime Minister's Office, Helsinki 2020:27.

48 An unofficial translation into English is available from the website of the Ministry of Justice: https://www.finlex.fi/fi/laki/kaannokset/2012/en20120688_20120688.pdf.

(Government Bill 18/2020) and the draft Act on National Genome Centre and on the Use of Genetic Data (2019).

In the totality of that new legislation, a balance between patients' individual rights (autonomy, privacy and data protection) and the public interest (including innovation policy and national competitiveness) in research should be sought. Certain provisions and procedures according to the Finnish Constitution provide safeguards for taking individual rights seriously, in particular Section 80(1) requiring legal acts of the Parliament for the regulation of the rights and obligations of private individuals and the Parliamentary review of Government Bills by the Constitutional Law Committee⁴⁹.

In a study commissioned by the European Parliament (2019) it is anticipated that the General Data Protection Regulation (GDPR) will enhance scientific research, *inter alia*, in respect of data security, regulatory clarity regarding processor responsibilities and the transfer of data, research collaborations within the EU, and the autonomy and trust of data subjects. The study also proposed normative options to help resolve potential ambiguities and promptly address procedural concerns.⁵⁰

Finland already has the experience from the application of the Biobank Act of 2012. While protecting individual data, the Act facilitates responsible and approved medical research in academia and industry. Firstly, a 'broad consent' for medical research was adopted. Secondly, previously collected samples can be transferred to the national biobank framework and used in future studies. Thirdly, individuals may remove their consent at any time and request any data generated on their samples or data.⁵¹ A 'dynamic concept' is also preferred in the study for the European Parliament.⁵²

49 See Juha Lavapuro, Constitutional review in Finland, in Introduction to Finnish Law and Legal Culture, *supra* note 10, pp. 127–140. For instance, as for the Government Bill of the Act on the Secondary Use of Health and Social Data, Constitutional Law Committee of the Parliament required in its Statement 1/2018 that Committee's constitutional comments on the GDPR, autonomy and privacy shall be taken into account in the final drafting of the law text.

50 How the General Data Protection Regulation changes the rules for scientific research. Study. Panel for the Future Science and Technology. European Parliamentary Research Service, July 2019, esp. Executive summary.

51 These merits are listed by Mark Daly, Director of the Institute for Molecular Medicine Finland (FIMM), in Open Access Government, Research & Innovation, 9 July 2019.

52 How the General Data Protection regulation changes the rules for scientific research, *supra* note 50, p. 62. Similarly, see Timothy Caulfield – Blake Murdoch, Biobanking and the consent problem, in Timo Minssen, Janne Rothmar Herrmann – Jens Schovsbo (eds.), Global Genes, Local Concerns. Legal, Ethical, and Scientific Challenges in International Biobanking. Edward Elgar, Cheltenham, UK 2019, pp. 173–184.

A new example of regulation in Finland is the draft Act on National Genome Centre and on the Use of Genetic Data (2019). This new Act would deal with recording genetic data for a national registry and the safe storing and handling of that data. The preconditions for its use would be drafted so that the rights of the individuals (privacy and equality, non-discrimination) could be secured. In all, the new Act would aim at the building of genetic databases and data storage as well as at regulating the availability of genetic data and the governance issues. The data protection and accountability for data interpretation, validation, errors, and possible consequences would be important principles in the regulation. As already mentioned above (ch. 5), national legislation is needed for implementing and specifying Articles 12 and 13 of the Biomedicine Convention.

A recent doctoral thesis by the Norwegian scholar Anne Kjersti Befring, entitled 'Personalized medicine – Legal perspectives' (2019), proves the importance of basic research on the subject. She also makes concrete proposals for amendments of health legislation, for instance, for the treatment of genetic data, for the control of genetic variations, and for the use of artificial intelligence and algorithms in big data analytics.⁵³

In her recent doctoral thesis, entitled 'Genetic testing and the spirit of laws' (2020), the Finnish scholar Sirpa Soini regards the regulatory scene in the biomedical field as a complex one with transnational laws, ethical codes, guidelines, and other policy papers. Because the biomedical field is dynamic and evolving in science, 'regulatory approaches need careful assessment in terms of need and accuracy, so that basic research and adoption of new applications are not unnecessarily hindered'.⁵⁴

53 Anne Kjersti Befring, *Persontilpasset medicin. Rettslige perspektiver*. Gyldendal, Oslo 2019, esp. ch. 14.

54 Soini, *Geenitestit ja lakien henki*, *supra* note 6, esp. p. viii (English abstract).

2.8 Conclusions

I have analyzed legislative developments on the basis of Finnish, common-European, and partly global experience. The benefits and drawbacks of different regulatory schemes were discussed. When summarizing the results, the following trend is discernible: the differentiation and fragmentation of legal order, as indicated by the emergence of medical law and biolaw as a distinct sector of law. At the same time, the strengthening of human and fundamental rights has a positive, coherence-creating effect on this new sector of law, too. Human rights arguments may also be used as the basis for the critical assessment of certain activities in health care and biomedicine.

It is typical for the argumentation in medical law and biolaw that it reconciles and balances divergent legal-ethical values, interests, and principles. In like manner, a key aspect of the legal argumentation here, instead of the ordinary interpretation of the law under legal rules, is the weighing against each other of mutually divergent legal principles of different strengths. Taking care of those various interests requires differentiated means ranging from professional guidelines in order to reach or maintain a high medical-ethical standard to legal rules with diverse enforcement models and sanctioning methods. A strategy which integrates private law damages schemes with administrative measures and criminal sanctions was in the resolution regarded as most adequate. Criminalization of medical activity as well as the threat of penalties should remain as a means of last resort (*ultima ratio*).

When developing innovation-friendly regulatory approaches and practices in relation to personalized medicine, which is the newest trend in health care and biomedicine, a proper balance between patients' individual rights (autonomy, privacy and data protection) and the public interest (including innovation policy and national competitiveness) in research should be sought. The recent incentive to research activity, ICPeMed vision for 2030 in line with the 3rd Sustainable Development Goal of the United Nations 2030 Agenda, sets out a vision for personalized medicine in the following sub-areas: data and technology, intersectoral synergies, healthcare system reforms, and education and literacy.⁵⁵

55 The ICPeMed vision for 2030, *supra* note 4, p. 11.

3

Building the Regulatory Framework for Personalized Medicine: Case Finland

by LL.D. Candidate Sandra Liede

Abstract

Government legislative actions have been considered necessary in Finland in order to establish principles and rules for responsible, equal and secure processing of human biological materials as well as genomic and health data, which are all sources for delivering personalized medical solutions. When it's done right, legislation can secure socially just and sustainable procedures as well as provide an enabling and secure legal environment for research, innovations and economic growth in the health sector.

However, even well-designed e.g. flexible, enabling legislation can contain pitfalls and result in adverse unintended effects, if the purpose as to the justifications and reasoning for such legislation is not communicated accordingly. This is especially relevant when legislation is designed to be applied in rapidly developing fields such as personalized medicine, which blurs the lines between research and the clinic, and challenges fundamental bioethical principles. In Finland, the legislative processes aiming to draft 'innovation-friendly' legislation for scientific research purposes (the Biobank Act) as well as integrating genomic research results into the clinical setting (the draft Genome Act) have been heavily challenged by rapid developments in technology and medicine, as well as by confrontations regarding finding the right balance between scientific and commercial interests, public health and individual rights.

This article aims to provide insights on the legislative processes surrounding personalized medicine. Special focus is on how the freedom of science, equitable access to healthcare, public health and commercial issues have been balanced in practice with individual rights as expressed in the EU Charter and the Council of Europe's Oviedo Convention, the ethical backboard of all biomedical issues. Distinctively, how the principle of primacy of the human being in Article 2 in the Oviedo Convention is reflected in the Finnish legislation. Further analysis is performed by providing examples of how challenges have been managed and how the related legal solutions reflect necessity and proportionality in terms of the legitimate

aims pursued by the legislation. Finally, suggestions are made for finding a way forward towards a more balanced communication of the rights and responsibilities of the state while aiming to provide equitable access to personalized health solution for all people of the nation.

3.1 The Promise and Challenges of Personalized Medicine

Personalized medicine is based roughly on the analysis and application of genomic and associated health data for the purposes of prediction, prevention, diagnosis, treatment and monitoring of human diseases. Many associate personalized medicine with the abbreviation P4, which stands for predictive, preventive, personalized and participatory medicine.¹ Personalized medicine is also known as genomic medicine or precision medicine.

The systematic storage of genomic data has substantially increased during the past decade, and currently small and large-scale genomic databases exist all over the globe. Many countries have established national strategies for personalized medicine (most recently the UK in 2020²), but beyond the strategies only few are in the process of implementing those visions and integrating genomic data into the healthcare system at a national level.³ Finland is one of the few, with a very ambitious executive objective of providing personalized medical opportunities for the whole population of the nation.⁴ Genomic data is envisioned to serve as

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- 1 Leroy Hood. Systems Biology and P4 Medicine: Past, Present, and Future. *Rambam Maimonides Med J*. 2013 Apr; 4(2), p. e0012. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3678833/> The Finnish Institute for Welfare and Health has taken P4 medicine a few steps forward by adding population health (P5) and translating genomics to healthcare (P6) as priority settings for successful implementation of personalized medicine. See <https://blogi.thl.fi/lets-measure-your-blood-pressure-cholesterol-waist-circumference-and-then-the-impact-of-the-genome/> and <https://thl.fi/en/web/thlfi-en/research-and-expertwork/projects-and-programmes/p6-genomics-to-healthcare>.
 - 2 Genome UK: The future of healthcare. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/920378/Genome_UK_-_the_future_of_healthcare.pdf.
 - 3 Dornitza Stark – Lena Dolman – Teri A. Manolio – Brad Ozenberger – Sue L. Hill –Mark J. Caulfield, Yves Levy – David Glazer – Julia Wilson – Mark Lawler –Tiffany Boughtwood – Jeffrey Braithwaite – Peter Goodhand – Ewan Birney – Kathryn N. North. Integrating Genomics into Healthcare: A Global Responsibility. *Am J Hum Genet*. 2019 Jan 3, 104(1), pp. 13–20. doi: 10.1016/j.ajhg.2018.11.014. PMID: 30609404; PMCID: PMC6323624.
 - 4 Improving health through the use of genomic data. Finland's Genome Strategy Working Group Proposal Reports and memorandums of the Ministry of Social Affairs and Health 2015:34.

a valuable, but optional, data type to be combined with other health data sets for accomplishing this objective, in cases where it is clinically and scientifically justified. The government's strategic vision is in the process of being implemented by drafting legislation for the responsible, equal and secure use of genomic data (draft Genome Act).⁵ The new legislation aims to establish a new public authority, the Genome Center⁶, which would take leadership of guiding the implementation of legislation by giving guidelines targeted for public and private healthcare providers, the biobanking field and commercial players collectively. In addition, establishing a national centralized genomic database and developing necessary IT structure and decision-making tools for clinicians are part of the national initiative and aim to support integrating evidence-based genomic data and applications into the healthcare system. Establishing a Genome Center as a public authority is based on the proposition that the Center would be exercising public authority as the controller of the centralized national genomic database.

Implementation of the Finnish strategy has been delayed as it has encountered numerous obstacles and challenges during the past five years. These challenges vary from regulatory (leadership)⁷, practical (funding) and scientific⁸ to ethical and legal issues. In principle, many support the government's efforts to align collective principles for the secure processing of genomic data. Even legal provisions have been considered acceptable to the extent that they're intended for securing the rights of present and future generations. For example, many agree that people's right to an open future, and the right to know or not to know about their genetic character, should not be sacrificed. This in turn has led to challenging fundamental concepts such as self-determination and questioning the validity of present consent mechanisms and the justifications of ordering genetic test kits online if the rights of other people cannot concurrently be respected. Added training for genetic counselling has also been warranted. Guidance and leadership in these areas is much needed, yet there is wide disagreement of who should have the mandate to guide the entire field in these issues. Some consider this to be a prerogative of specialized medical professionals. The government proposed to place leadership

5 STM071:00/2018. Draft government bill on the Genome Center and the conditions for processing genomic data.

6 Genomikeskus. Available at: <http://www.genomikeskus.fi/en/frontpage.html>. Accessed 19.11.2020.

7 Mikko Wennberg, 'Lainvalmistelu kaipa pikaista uudistamista'. Available at: <https://puheenvuoro.uusisuomi.fi/wennberg/lainvalmistelu-kaipa-pikaista-uudistamista/>. Accessed 19.11.2020.

8 Juhani Knuuti, 'Monigeeniset riskimittarit eivät ratkaise sepelvaltimotaudin seulontaa'. Available at: <https://blogit.ts.fi/terveys-tiede/monigeeniset-riskimittarit-eivat-ratkaise-sepelvaltimotaudin-seulontaa/>. Accessed 19.11.2020.

at the Genome Center, as no currently existing profession or entity has the legal powers to give guidance on all of the topics associated with personalized medicine.

Many have opposed any additional legislation for genomics, as the European Union's (EU) general data protection regulation (GDPR)⁹ is considered to provide adequate risk-based protection for data subjects in addition to providing an innovation-friendly regulatory environment for data processing. Correspondingly, the EU In Vitro Diagnostic Regulation (IVDR)¹⁰ provides strict legal requirements and liabilities in the context of genetic testing for a medical purpose, as the manufacturer must thoroughly substantiate that the test is safe, performs as intended, and delivers a clinical benefit. Adding technical safeguards and guidelines for genetic counselling could provide sufficient support for securing the rights and freedoms of all the people concerned. As a response, the government offered to establish a centralized national secure processing environment (which will concurrently be established following the 2019 enactment of the Act 552/2019¹¹ for Secondary Use of Health and Social data). However, in the case of genomic data and as apart from other health data, the government proposed that security measures should be elevated (due to the nature of genomic data and the interests of others in need of securing) and that biobanks and the healthcare sector should be obligated to store all deriving genomic data in a centralized national database to minimize the risks of keeping multiple copies in allocated databases.

Highlighting the distinctive nature of genomic data wasn't received well during the public consultations and was considered a threat to scientific research. As for centralized storage (which was backed by cybersecurity experts) and the aim to prevent storing multiple copies of genomic data in various databases, commercial interests formed a barrier for implementation. Presence of the government was viewed as interference in the market economy. However, the scientific community was more open to the idea provided that the government would financially support the storage of all of the data and access could be guaranteed. Some health care providers in turn viewed that the government was interfering with the medical profession and endangered patient safety by proposing to add technical layers

9 Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation).

10 Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU.

11 English translation for the Act on the Secondary Use of Health and Social Data is available at [https://stm.fi/documents/1271139/1365571/The+Act+on+the+Secondary+Use+of+Health+and+Social+Data/a2bca08c-d067-3e54-45d1-18096de0ed76/The+Act+on+the+Secondary+U](https://stm.fi/documents/1271139/1365571/The+Act+on+the+Secondary+Use+of+Health+and+Social+Data/a2bca08c-d067-3e54-45d1-18096de0ed76/The+Act+on+the+Secondary+Use+of+Health+and+Social+Data.pdf) se+of+Health+and+Social+Data.pdf. Accessed 19.11.2020.

in between clinicians and patients. As to the overall value and the purposeful use of genomic data in the clinic, scientific debate has torn the medical field into two different camps causing determined polarization of communication. All mentioned views have been expressed in the documents¹² or discussions¹³ related to the legislative process of the draft Genome Act and highlight the complexities surrounding personalized medicine and balancing competing interests.

In the current health care regime of Finland, genomic data – or rather targeted panel and whole exome sequencing – is mainly used for diagnosing and treating patients with rare diseases or cancer, or for individually tailoring pharmaceutical therapies.¹⁴ Clinical applications based on whole genome data have been mainly used at the experimental or design stage, and only few physicians process patients' actual genomic data in their day to day working life. However, the Helsinki University Hospital (HUS) – representing a majority of the largest university hospital district of Finland – has recently invested in new technology and introduced genome sequencing in the clinic, at the request of its patients.¹⁵ Public healthcare investing in genomic sequencing equipment clearly indicates that the healthcare system is taking a turn towards personalized genomics based diagnosis and treatments. Beyond the health care setting, genomic data is produced in Finland mostly within the biobanking sector.

In the future, and especially as sequencing technology becomes more common, increasing understanding of disease development mechanisms and the genetic background of diseases is expected to translate into the clinic as higher knowledge, new therapies and improved opportunities for planning personalized care and health promotion. For example, research shows that in children with type 1 diabetes, certain genes activate long before the antibodies associated with the disease are detected in the blood circulation.¹⁶ Such results may help to identify children who develop diabetes in the future. The Global Alliance of Genomics and Health (GA4GH) has predicted that by 2025 up to 60 million genome sequences

12 STM071:00/2018.

13 STM086:00/2016.

14 Improving health through the use of genomic data. Finland's Genome Strategy Working Group Proposal Reports and memorandums of the Ministry of Social Affairs and Health 2015:34.

15 Minutes of the meeting of the HYKS hospital area board. June 12, 2018. HUS/1802/2018. Available at: <http://husd36ofi.oncloudos.com/kokous/2018296669-3.PDF> Accessed 19.11.2020.

16 Henna Kallionpää – Juhi Somani – Soile Tuomela – Ubaid Ullah, Rafael de Albuquerque – Tapio Lönnberg – Elina Komsii – Heli Siljander – Jarno Honkanen – Taina Härkönen – Aleksandr Peet – Vallo Tillmann – Vikash Chandra – Mahesh Kumar Anagandula – Gun Frisk – Timo Otonkoski – Omid Rasool – Riikka Lund – Harri Lähdesmäki – Mikael Knip – Riitta Lahesmaa. Early Detection of Peripheral Blood Cell Signature in Children Developing Beta-Cell Autoimmunity at a Young Age. American Diabetes Association. Available at: <https://diabetes.diabetesjournals.org/content/68/10/2024>. Accessed 19.11.2020.

could be carried out in the clinical setting.¹⁷ This would effectively mean that the sequences produced by health care would outnumber the sequencing activities carried out for research purposes and replace the current, older analysis methods used in the clinic.

Yet, the increasing amount of clinical genomic data doesn't mean that all patients will de facto be sequenced as the clinical need for genomic analyses should always be medically and scientifically assessed on an individual and case-by case basis. The primary benefits of using genomic data have so far been demonstrated within diagnosis of hereditary and rare diseases. The use of genomic data has for example made it possible to significantly reduce the time taken to reach a diagnosis for the patient. In the area of cancer diseases, genomic data can also be used in the selection and monitoring of treatment. These are the low hanging fruits that many global personalized medicine initiatives attach to. In terms of public communication, they are also the easiest projects to convey to the larger audiences, because they produce impact in the present timeframe.

As for improving population health by preventing multifactorial common diseases such as coronary diseases, type 2 diabetes and common cancers – the scientific evidence is pending, and wider public health impacts are expected in the longer future. There are hopeful expectations that genomic data could help identify genetic variants that are associated with common diseases, which in turn could lead to stratifying populations and initiating active intervention planning for early treatment, additional tests or lifestyle changes. Prevention programs could be targeted or tailored to those at higher risk. Even so, the scientific debate is still ongoing – both on the value of unique risk data for the prevention of chronic diseases and how such data could instigate healthier behavior patterns and eventually impact public health. There is a growing body of scientific literature backing the potential of genomic data for prevention and public health purposes. Scientists in Finland are also working hard to produce much needed evidence for fully integrating genomics into the clinic.

The globally unique Finnish P6 project (Genomics to Healthcare) is a large-scale national initiative aiming to prepare the Finnish health care system for the clinical utilization of genetic risk information and is very essential for future hopes to integrate genomics into the clinic around this area. The objectives of the project include providing scientific evidence for the utility of genetic risk information in healthcare by carrying out randomized disease-specific intervention trials, evaluating and building competence and genomic literacy skills, evaluating the

17 Ewan Birney – Jessica Vamathevan – Peter Goodhand. Genomics in healthcare: GA4GH looks to 2022. bioRxiv 203554; doi: <https://doi.org/10.1101/203554>.

health-economic impact of genetic risk-information in healthcare and achieving a level of consensus among various stakeholders for translating genomics into the clinic.¹⁸

In addition to the many legislative, clinical and scientific hurdles to widespread clinical implementation, personalized medicine in Finland is also heavily challenged by various concerns spanning from critique towards the government for lack of funding¹⁹ and establishing a very complex legal framework²⁰ to ethical and legal aspects concerning for example the right to know²¹ and not to know, incidental and secondary findings²², privacy²³ as well as consent and opt-out procedures²⁴. However, some of the highlighted concerns require further studies and structured debate to confirm their existence and actual impacts. On a positive note and beyond the concerns expressed, a forward-looking spirit still prevails among the different actors within the personalized medicine framework - which gives hope that a common path to consensus can be found.

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- 18 P6 – Genomics to Healthcare. Available at: <https://thl.fi/en/web/thlfi-en/research-and-expertwork/projects-and-programmes/p6-genomics-to-healthcare>. Accessed 19.11.2020.
- 19 Olli Carpén – Marco Hautalahti. Puheenvuoro: Suomalainen potilas ansaitsee yksilöllisen hoidon. *Turun Sanomat*, 1.3.2019.
- 20 Tom Southerington – Seppo Vainio – Anne Pitkäranta. Biopankkilainsäädännön muuttuva kenttä: uhkat ja mahdollisuudet. *Lääketieteellinen aikakauskirja Duodecim* 2019;135(10):973–4.
- 21 Aaro Tupasela – Sandra Liede. (2016) State Responsibility and Accountability in Managing Big Data in Biobank Research: Tensions and Challenges in the Right of Access to Data. In: Brent Mittelstadt – Luciano Floridi (eds.), *The Ethics of Biomedical Big Data*. Law, Governance and Technology Series, vol 29. Springer, Cham. https://doi.org/10.1007/978-3-319-33525-4_12.
- 22 Toni Lehtinen, Haluaisitko tietää riskisi sairastua verenpainetautiin tai Alzheimeriin? Suomeen suunnitellaan biopankkitietojen verkkopalvelua. Available at: <https://www.hs.fi/paivanlehti/05022020/art-2000006396045.html>. Accessed on 19.11.2020.
- 23 Sirpa Soini, Biobanks as a central Part of the Finnish Growth and Genomic Strategies: How to Balance Privacy in an Innovation Ecosystem? *The Journal of Law, Medicine and Ethics*. Volume: 44 issue: 1, page(s):24–34.
- 24 Joanna Forsberg – Sirpa Soini, A big step for Finnish biobanking. *Nat Rev Genet* 15, 6 (2014). <https://doi.org/10.1038/nrg3646>; Karoliina Snell – Heta Tarkkala. Questioning the rhetoric of ‘a willing population’ in Finnish biobanking. *Life Sci Soc Policy*. 2019 Dec; 15: 4; and Marjut Salokannel – Heta Tarkkala – Karoliina Snell, Legacy samples in Finnish biobanks: social and legal issues related to the transfer of old sample collections into biobanks. *Hum Genet* 138, 1287–1299 (2019). <https://doi.org/10.1007/s00439-019-02070-0>.

3.2 Legislation as a Tool for Leading Innovation

Personalized medicine is in nature characterized by a ‘commercial ethos’ and the increasing presence of commercial actors in producing personalized healthcare services and products. Concurrently, genomic and biomedical research is increasingly commercialized.²⁵ Nevertheless, business-driven innovation activities are commonly viewed as an effective way of reforming, reviving and supporting healthcare services and the entire health innovation ecosystem. Socially responsible corporate actors and a responsible market economy support building and maintaining the welfare society.

In situations of social crisis, such as the prevailing Covid-19 pandemic, the importance of commercial collaborative activities is further emphasized. For example, commercially produced patient monitors, respirators, intensive care equipment, diagnostics, hygiene solutions and products and services related to remote digital care are in high demand. International public-private collaborative efforts have resulted in establishing digital solutions to enable health workers in battling the virus. These include cost-effective technologies, which can reduce costs, duplication and waste. The use of digital technologies can additionally prevent the occurrence of false-negative results and eliminate inconclusive diagnostics by pooling the results into a cloud and using artificial intelligence to analyze the data. Correspondingly, in the research environment commercial collaborations have sped up the development of pharmaceuticals and vaccines. This is also reflected as rapid reviews and publications of Covid-19 papers and results from ongoing vaccine trials.

Commercial players are an integral part of the healthcare system and the government’s role is to support them to enhance innovation activities for the benefit of patients and public health. Securing innovation and competitiveness in the health sector is a cross-industry and societal concern. In order to support innovation, decision makers strive to create favorable operating environments for the development of personalized medicine. Such environments can be created for example by drafting and enacting innovation-friendly legislation - also described as ‘enabling’ or ‘flexible’ legislation.²⁶ Legislation, as opposed to industry-driven

25 Timothy Caulfield – Ubaga Ogbogu. The commercialization of university-based research: Balancing risks and benefits. *BMC Med Ethics* 16, 70 (2015). <https://doi.org/10.1186/s12910-015-0064-2>.

26 Vesa Salminen – Kimmo Halme. Policy Brief: ‘Framework for innovation-friendly regulation’. Available at: <http://julkaisut.valtioneuvosto.fi/bitstream/handle/10024/162229/22-2019-Framework%20for%20innovatio.n-friendly%20regulation.pdf> Other means include for example creating common European health data space. Accessed 19 November 2020.

guidelines, is generally required to guarantee that all commercial actors assume their social responsibility consistently by following the rules of law. Maintaining and supporting responsible social actions is one of the most important functions of the government.

The development of personalized medicine requires flexible laws so that the law doesn't end up becoming a barrier to medical development. Such flexibility was provided with the Finnish Biobank Act (688/2012).²⁷ Flexibility in this context means technology-neutral outcome-based law, which leaves room for interpretation. The desired outcome is improved public health – by supporting research and eventually integrating the results into the healthcare system and society. Research activities are supported, provided that the actors follow the strict rules of the Biobank Act which have been established to protect sample and data donors. Operating within the legal regime of biobanking is an indication and guarantee that biobanks and researchers are supervised and guided by official authorities and thus act responsibly according to law.

Filling the legal gaps with interpretation is left at the responsibility of legal practitioners and supervisory authorities. Leaving room for interpretation is a key element of innovation-friendly legislation in fast-developing areas. The law is not intended to solve all possible challenges and preferably aims to guarantee minimum standards for responsible activity. Support for challenging questions can be found elsewhere – primarily from the legally binding sources of justice, such as human and basic rights documents, legal principles, and court cases. From this point of view, unstructured random public debate or assertive views expressed in social media should not be dogmatized as a source for interpretation. They are preferably isolated opinions, which do not reflect the majority of the public or the wider public morality. However, as with well-designed legislation, carefully structured public debate can at best call attention to public moral and indicate how society views social responsibilities as well as the necessity and proportionality of legislation. The tricky part is to pick the clues and identify the questions in need of immediate legislative attention – and to specify what should be left to be solved yet by interpretation or by added efforts of clearer communication by the government.

A recently published article and the following public discourse in Finland provide an excellent example of the complexities of opinions a legislator may have to balance with when working with enabling legislation. In an article published

27 The Biobank Act (688/2012) in English. Available at: https://www.finlex.fi/fi/laki/kaannokset/2012/en20120688_20120688.pdf.

in Helsingin Sanomat,²⁸ a journalist criticized Finngen, which is Finland's largest public-private genomic research project. The core of the critic highlighted conflicts of interest, collaborations with commercial pharma partners, and the importance of being open about these two central topics. Finngen represents early-stage basic research, the results of which are returned to Finnish biobanks for further use by the entire scientific community. The journalist's critique was aimed at what he perceived as unrealistic promises given to the public and implied that the project would mainly benefit the pharma industry and the main investigators of Finngen. This claim was enforced by shining light on the industry ties of one of the main investigators and highlighted the problem of patenting. Although Finngen itself doesn't aim to produce any patents, findings from possible separate 'bespoke analyses' could be potentially patented by pharma companies. Benefits of the project for patients and society went largely unnoticed (which was criticized by patient advocacies²⁹) and the journalist implied that the interests of the research subjects were not sufficiently respected and that in a worst-case scenario the masses of Finnish genomic data would end up in the hands of U.S. intelligence authorities following concerns raised in the recent *Schrems II*-judgement³⁰. The journalist duly and fairly called for the main investigator's responsibility. However, one could only guess the motivation and driving forces behind the article, as it was also quite transparent that there had been intense lobbying behind the scenes.

The article received fairly wide coverage as it spread in different social media outlets. In the end, the main achievement of the episode was reflected as echo chambers where the different parties only interacted with people they agreed with and essentially reinforced polarization, rather than deliberation.³¹ There was no substantial increase in withdrawals of consents or distrust towards the project or the scientific community in general. Neither did the media coverage reflect wider public moral. However, the public discussion did leave open a very central question as to how decision makers should react to the unstructured but

28 Marko Junkkari – Boris Stefanov. Kauppaa kansan verellä. Helsingin Sanomat. Available at: <https://www.hs.fi/sunnuntai/art-2000006623764.html> Accessed 19 November 2020.

29 Minna Anttonen – Mirjami Tran Minh. Syöpään sairastuneille geenitutkimus tuo toivoa. Available at: <https://www.hs.fi/mielipide/art-2000006630043.html?share=ee15aa931bf7c7b bd4767c7adoafi799>. Accessed 19 November 2020.

30 CJEU case C-311/18 Data Protection Commissioner v Facebook Ireland and Maximilian Schrems. Available at: <https://curia.europa.eu/jcms/upload/docs/application/pdf/2020-07/cp200091en.pdf> Accessed 19 November 2020.

31 More on how social media works: Naomi Barnes. Navigating algorithms and affective communities in the quest for altmetric stardom. September 9th, 2020. Available at: <https://blogs.lse.ac.uk/impactofsocialsciences/2020/09/09/navigating-algorithms-and-affective-communities-in-the-quest-for-altmetric-stardom/>. Accessed 19 November 2020.

increasing public debate. For example, should a more structured public debate be proposed, or should there be a more detailed legal examination of the minimum standards of law, and balancing of competing interests and distribution of benefits within society?

3.2.1 The Oviedo Convention as an Ethical Backdrop for Enabling National Legislation

The Council of Europe's Convention (ETS No. 164) for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine from 1997 (the Oviedo Convention)³² and its Additional Protocols³³ aim to promote human rights, democracy and the rule of law in relation to biomedical science and the practice of medicine. There is a strong relationship between the Oviedo Convention and the 1950 European Convention on Human Rights (ECHR)³⁴ as both aim to defend human beings by using the same basic set of accepted principles.³⁵

Regardless of many of the similarities of the two conventions, there still remain some differences in their applicability and enforcement.³⁶ For example, contrary to the ECHR, the Oviedo Convention provides a set of flexible rules, which aim to ensure possible protection, and not *due* protection of human dignity and bio-rights. The Oviedo Convention is a dynamic living instrument which means that the interpretation and application of the Convention's provisions adapt to situations that possibly did not exist when the Convention was originally approved. The role of national governments is to uphold and elevate what is considered as the minimum standards of the Oviedo Convention.

The two agreements differ also as to the control mechanisms regarding violations of their provisions. The Oviedo Convention has no mechanism to investigate and take decisions on violations, but a breach of the Oviedo Convention

32 Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine. Available at: <https://www.coe.int/en/web/conventions/full-list/-/conventions/rms/090000168007cf98>. Accessed 19 November 2020.

33 The Additional Protocols for human cloning (1998), organ transplantation (2002), biomedical research (2004) and genetic testing for health purposes (2008).

34 European Convention on Human Rights. Available at: https://www.echr.coe.int/documents/convention_eng.pdf. Accessed 19 November 2020.

35 Francesco Seatzu – Simona Fanni. Correction: The Experience of the European Court of Human Rights with the European Convention on Human Rights and Biomedicine. *Utrecht Journal of International and European Law* 31(81), pp. 112–113. DOI: <http://doi.org/10.5334/ujiel.dk>.

36 *Ibid.*

can be analyzed and the provisions enforced by the contributing case law of the European Court of Human Rights (ECtHR) – as long as the breaches are in the scope of the ECHR.³⁷ Biomedical issues featured prominently in the case law of the ECtHR relate mostly to questions regarding the beginning and end of life.³⁸ In its conclusions the ECtHR has reflected research-related bioethical issues, such as privacy, self-determination, informed consent, protection of genetic and other clinical data and the right to know, especially upon Article 8³⁹ of the ECHR, which not only aims to defend individuals against arbitrary actions of the State, but to also guarantee personal autonomy and the right to self-determination.⁴⁰

The bioethical court cases, in which Article 8 was invoked, the Court performed balancing between individual rights and public interest and examined, whether an interference with the individual right had emerged. The Court also assessed whether there had been a legitimate aim for the interference and if the limitations had been lawful and necessary in a democratic society (See *Dubská and Krejzová v. the Czech Republic*).⁴¹ Lawfulness refers to provisions based on domestic law and which are in force at the relevant time and which a person is able – if need be with appropriate advice – to foresee to a degree that is reasonable in the circumstances.

In the assessment of necessity, the ECtHR has concluded that a 'pressing social need' should be identified and reflected in context of proportionality as to the legitimate aim pursued. The test of necessity assesses whether an interference with individual rights advances a pursued 'social need', such as social interests and rights and freedoms of others, and reaches no further than necessary to meet the said 'social need' (*Mouvement Raëlien Suisse v. Switzerland*).⁴² In the case of *Refah Partisi (The Welfare Party) and others v. Turkey*, the Court concentrated

37 Article 32 of the ECHR.

38 Council of Europe: 20th anniversary of the Oviedo Convention (2017). Available at: <https://rm.coe.int/oviedo-convention-conference-final-report-e/1680796fc5>. Accessed 19 November 2020.

39 Article 8 of the Convention – Right to respect for private and family life '1. Everyone has the right to respect for his private and family life, his home and his correspondence. 2. There shall be no interference by a public authority with the exercise of this right except such as is in accordance with the law and is necessary in a democratic society in the interests of national security, public safety or the economic wellbeing of the country, for the prevention of disorder or crime, for the protection of health or morals, or for the protection of the rights and freedoms of others.'

40 Francesco Seatzu, 'The Experience of the European Court of Human Rights with the European Convention on Human Rights and Biomedicine' (2015) 31(81) *Utrecht Journal of International and European Law* 5, DOI: <http://dx.doi.org/10.5334/ujiel.da>. Accessed 19 November 2020.

41 ECHR no 28859/11 and 28473/12.

42 ECHR no 16354/06.

on assessing ‘social need’ as in whether there was plausible evidence that the risk to democracy was sufficiently imminent.⁴³

The test of proportionality on the other hand evaluates if a fair balance between competing interests has been achieved and the essence and minimum core of the right in question has been respected. Additionally, the ‘relevant and sufficient’ reasons set forth by national authorities should be assessed. In the context of the necessity and proportionality test, the Court has reiterated the fundamentally subsidiary role of the Convention system and recognizes that the national authorities have direct democratic legitimation in so far as the protection of human rights is concerned. It is therefore primarily the responsibility of the national authorities to assess whether fair balance between public interest and individual rights, is achieved. States are additionally allowed to determine the means which they consider most proportionate for achieving the aim of balancing competing rights. A wide margin of appreciation is usually provided to States when they are required to strike a balance between competing private and public interests or different Convention rights. However, the scope of the margin will depend on the seriousness of the interest at stake and the gravity of interference (See *Dubská and Krejzová v. the Czech Republic*, *Fernández Martínez v. Spain*⁴⁴, *Odièvre v. France*⁴⁵, *Van der Heijden v. the Netherlands*⁴⁶ and *Z v. Finland*⁴⁷).

One of the very basic principles of medical and bio law is documented in Article 2 of the Oviedo Convention - primacy of the human being: ‘*The interests and welfare of the human being shall prevail over the sole interest of society or science*’. The principle of primacy of the human being has inspired the entire Convention and is also one of the key principles for governments to follow when drafting legislation in the area of personalized medicine. The origin of the principle is further elaborated in the Explanatory Report, which specifies that the interests and welfare of the human being must *in principle* take precedence over the sole interests of society or science in the event of a conflict between them.⁴⁸ How this is interpreted is reflected in the case law of the ECtHR.

43 ECHR no 41340/98, 41342/98, 41343/98 et al.

44 ECHR no 56030/07.

45 ECHR no 42326/98.

46 ECHR no 42857/05.

47 ECHR no 22009/93.

48 The Explanatory Report: Available at: <https://rm.coe.int/CoERMPublicCommonSearchServices/DisplayDCTMContent?documentId=09000016800ccde5> The explanatory Report does not constitute a binding part of the Oviedo Convention. However, it is commonly referred to in interpreting the Convention. Accessed 19 November 2020.

Another fundamental principle for personalized medicine, equitable access to health care, is expressed in Article 3 of the Oviedo Convention. According to the provision, Parties shall take appropriate measures for providing equitable access to health care of appropriate quality. Health care in this context means offering diagnostics, prevention, therapy and rehabilitation (*Explanatory Report*)⁴⁹. The standard of care must be assessed in light of scientific progress. Access to health care must be equitable, meaning first and foremost the absence of unjustified discrimination. The aim of the provision is to prompt States to adopt the requisite measures as part of its social policy in order to ensure equitable access to health care. These measures may take many different forms and a wide variety of methods. The Article can be interpreted to mean that governments can adopt for example the principles of personalized medicine as policy measures and provide personalized solutions equitably for the people of its nation.

Simultaneous protection of primacy of the human being, the interests of society, the progress of science and research, as well as commercial interests has caused a need to develop principles and rules to resolve conflicts potentially arising between these interests. Generally, the protection of the human means that human dignity is protected from scientific and societal actions which instrumentalize dignity. For example, creating human embryos for research is prohibited in article 18 of the Oviedo Convention. Article 21 prohibits financial gain of the human body and its parts. However, research on human embryos and the human body or its parts lie outside of the scope of prohibitions and are allowed when certain preconditions are followed. Article 15 is a general rule with reference to scientific research. According to the Article scientific research in the field of biology and medicine shall be carried out freely, subject to the provisions of the Convention and other legal provisions ensuring the protection of the human being. The Article represents a shift towards a level of pragmatism and allows States flexibility as to balancing different interests in national legislation. According to the case *Z v. Finland*, even a requirement in the public interest can justify overriding an individual right such as the one expressed in Article 8, if the legal prerequisites are fulfilled and safeguards are designed to secure an effective protection.

49 Explanatory Report to the Convention for the protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine.

3.2.1.1 *Margin of Appreciation in Biomedical Research in Light of the Oviedo Convention and ECtHR Case Law*

Basic conditions for biomedical (incl. genomic) research are expressed in the articles of the Oviedo Convention. As a general rule, Article 16 requires that necessary consent as provided for under Article 5 is given expressly, specifically and is documented. Article 5 is a standard recognized by the majority of the Parties to the Convention. However, the Convention also reflects consensus in Article 22 as to that human body parts may be removed in the course of an intervention (clinical or research based), and consequently stored and used for a purpose other than that for which it was removed – given that this is done in conformity with ‘appropriate’ information and consent procedures. The aim of Article 22, like Article 5, is to ensure the protection of individuals and together they reflect *the minimum standards* set by the Oviedo Convention. Governments must uphold and elevate them in compliance with Article 27⁵⁰ of the Oviedo Convention.

According to the Explanatory Report to the Oviedo Convention, information and consent arrangements may vary according to the circumstances, thus allowing for flexibility since the express consent of an individual to the use of parts of his body is not systematically needed. As a conclusion, an argument can be made that Article 22 cannot be interpreted as conferring an absolute obligation to always obtain consent before processing stored samples for secondary purposes. Nevertheless, individuals must be protected. The application of Article 22 may be apt, especially if it is impossible (the deceased) or highly difficult (current residency not known or the multitude of people concerned) in practice to reach those people. In these cases, the right to respect of private life and accordingly Article 8 of the ECHR may be best secured by adding safeguards, namely legislating the use of those samples and adding information procedures and other protective safeguards while allowing the use for legitimate, e.g. scientific purposes as established in Article 22.

The central legal issue then from a legislative point of view while balancing competing interests is whether a government has a negative obligation to abstain from legislative actions and leave it to be decided by controllers if and when the appropriate information and consent procedures have been fulfilled, or whether there is a positive obligation of the government to provide an appropriate regulatory framework securing the rights of people while concurrently supporting research. In the case *Mouvement Raëlien Suisse v. Switzerland*, the Court asserted a double

⁵⁰ Article 27 – Wider protection: ‘None of the provisions of this Convention shall be interpreted as limiting or otherwise affecting the possibility for a Party to grant a wider measure of protection with regard to the application of biology and medicine than is stipulated in this Convention’.

logic test for solving whether a case concerns negative or positive obligations. If the absence of any (e.g. legislative) action by the national authorities would not have resulted in a violation of the Convention, there would be no case at all. This might be the case if furthering of science relied on consent alone. On the other hand, if the authorities failed to take action relating to the second option, using stored samples, it could be argued that there may be a case of a violation of the Convention, as positive actions are needed to specify what the ‘appropriate’ procedures are. If a finding of a violation implies the need for additional restorative action by the government that indicates a positive obligation. The ECtHR has concluded that the margin of appreciation is broader in the case of positive obligations arising from the Convention.⁵¹

Among other safeguards, appropriate information procedures may be added as positive actions, but there is no legal basis for requiring full coverage as to the number of people being actually reached by the procedures as privacy can be respected also in other ways, which complement the said procedures. As for realizing the right to self-determination, judging by the case law of the ECtHR, one of the prerequisites for justified procedures seems to be that they are based on national law and are foreseeable either per se or with the support of appropriate advice. Emphasis is placed on the adequate accessibility and sufficiently precise formulation of the national provisions so that an individual ‘is able’ to foresee the regulatory landscape of the relevant country in question (See *Dubská and Krejzová v. the Czech Republic*).

A wide margin of appreciation has also been afforded in cases of the ECtHR where the issues have been controversial in nature or when the State is required to balance different interests or rights of the Convention. Controversial implies to situations where there is no consensus within the member States of the Council of Europe, either as to the relative importance of the interest at stake or as to the best means of protecting it, particularly where the case raises sensitive moral or ethical issues (See *Dubská and Krejzová v. the Czech Republic*, *Van der Heijden* and *Parrillo v. Italy*). In the case of consent versus allowing the use of stored samples for secondary purposes, it can be reasonably argued that there is consensus as to the possibility of using stored samples (supported with information practices)

⁵¹ ECHR no 16354/06.

as an alternative to obtaining informed consent although there is no common agreement on the right balance between these two.⁵²

While balancing competing interests the margin of appreciation doctrine allows governments to take into account, for example, the characteristic traditions of the state. Hence, the ways in which different countries protect the minimum standards of the Oviedo Convention may reflect national traditions and legal culture. Conclusively, the Court cannot demand uniform implementation or balancing of the provisions of the Oviedo Convention in all Signatory States as such a command could be perceived as an intervention on national constitutional values and policy choices. In principle, national authorities are the most rationally placed operators to assess the necessity and appropriateness of any local restrictions or limitations.⁵³ The ECtHR has to date accepted the reasons and arguments of governments relatively easily, although it works toward setting clear, uniform and well-defined criteria for defining the minimum standards of human rights.⁵⁴

3.2.1.2 Balancing National Legislation in Light of the EU Charter

In addition to the minimum standards set by the Oviedo Convention for balancing competing interests, the EU Charter of Fundamental Rights of the European Union (EU Charter) has since its enforcement in 2009 added a strong legal framework to the discussion of balancing interests in the health field. The Oviedo Convention has not been signed by the EU, neither are bioethical questions per se in the legislative scope or competence area of the EU, but EU impact can be achieved by legislative measures which have direct influence on national debates.⁵⁵ A direct reference to the Oviedo Convention was established in the Charter's Explanatory notice, which elucidated the explanation of Article 3 in the Charter (the integrity of the person). According to Article 3, in the fields of medicine

52 For example: Salla Silvola. Biobank Regulation in Finland and the Nordic Countries. In Elisabeth Rynning – Mette Hartlev. Nordic Health Law in a European Context. Welfare State Perspectives on Patient's Rights and Biomedicine. Brill / Nijhoff 2011. https://doi.org/10.1163/9789004223813_020 and Marjut Salokannel – Heta Tarkkala – Karoliina Snell. Legacy samples in Finnish biobanks: social and legal issues related to the transfer of old sample collections into biobanks. Hum Genet 138 2019, pp. 1287–1299. <https://doi.org/10.1007/s00439-019-02070-0>. And Marjut Salokannel. Ethical review, data protection and biomedical research in the Nordic countries: A legal perspective. Policy paper 1/2017. NordForsk.

53 Janneke. Gerards. Margin of Appreciation and Incrementalism in the Case Law of the European Court of Human Rights. Human Rights Law Review, 2018, 18, pp. 495–515 doi: 10.1093/hrlr/ngy017.

54 *Ibid.*

55 An overview report on bioethics in the European Union. Secretariat of the Commission of the Bishops' Conferences of the European Community. 2009. Available at: http://www.comece.eu/dl/KlMkJKJOllkJqx4KJK/20091029PUBIO_EN.pdf. Accessed 19 November 2020.

and biology the free and informed consent of the person concerned must be respected according to the procedures laid down by law. The Explanatory notice makes particular reference to the Additional Protocol (ETS 168) to the Oviedo Convention concerning the prohibition of cloning human beings and expressly states that the principles of Article 3 of the Charter reflect those principles of the said protocol. What is noteworthy is that the Explanatory notice makes no reference to the Additional Protocol concerning biomedical research (ETS 195). Consequently, Article 3 leaves a margin of interpretation as to the precise scope of the provision and applicability to biomedical research using human biological samples. However, the topic of research can be approached by applying Article 1 (human dignity), which constitutes the real basis of fundamental rights, or Article 7 (respect for private life).

After the entry into force of the Lisbon Treaty, the EU Charter became the main reference for assessing compliance of national legislation with fundamental rights, which has since been illustrated especially in the landmark cases *Digital Rights Ireland*⁵⁶ and *Schrems*⁵⁷ of the European Court of Justice (CJEU). Additionally, the CJEU has affirmed in recent case law that validity of national legislation must be reflected solely in the light of the fundamental rights guaranteed by the Charter, and not the ECHR.⁵⁸ However, the CJEU has also concluded that specific provisions of the ECHR must be ‘taken into consideration’ for the purpose of interpreting the parallel provisions of the Charter (*J.N. v Staatssecretaris van Veiligheid en Justitie*).⁵⁹ According to Article 52(3) of the EU Charter the meaning and scope of the Charter rights shall be the same as laid down by the ECHR.

As the primary reasoning for collecting, storing and processing biological samples is to derive genetic information from the samples, the EU rules for privacy and data protection are central for addressing governments’ legislative scope of margin of appreciation. The right to ‘respect for private life’ (also the right to privacy) is addressed by Article 7 of the Charter and directly corresponds to Article 8 of the ECHR. Article 8 of the EU Charter provides specific ‘protection for personal data’ and does not correspond to a directly comparable right protected by the ECHR. However, Article 8 of the ECHR is relevant for interpreting the

⁵⁶ CJEU C-293/12 and C-594/12.

⁵⁷ CJEU C-362/14.

⁵⁸ European Data Protection Supervisor. Assessing the necessity of measures that limit the fundamental right to the protection of personal data: A Toolkit. 11 April 2017. Available at: https://edps.europa.eu/sites/edp/files/publication/17-04-11_necessity_toolkit_en_o.pdf. Accessed 19 November 2020.

⁵⁹ CJEU C-601/15 PPU.

provision as according to the Explanatory note of the EU Charter, Article 8 of the Charter is amongst others based also on Article 8 ECHR.

Following Article 8 of the Charter personal data must be processed fairly for specified purposes and on the basis of the consent of the person concerned *or some other legitimate basis* laid down by law. In line with Article 6 of the GDPR, apart from consent, also other lawful bases for processing data (for example which are laid down by law) are available as long as appropriate safeguards are in place and processing is fair, lawful, transparent and accords with data minimization standards and individual rights.⁶⁰ When processing involves genetic or health data, the provisions of Article 9 are to be additionally followed. However, according to the case law of the CJEU, any data processing operation laid down by legislation is legally considered a limitation on the right to the protection of personal data, regardless of whether that limitation may be justified.⁶¹

As legislation in the context of personalized medicine aims to balance various interests, the provisions of Article 23 relating to restrictions, are central for assessing the margin of appreciation provided for governments. The Article allows legislative measures that may restrict individual rights, when such restrictions respect the essence of fundamental rights and freedoms and are necessary and proportionate in a democratic society to safeguard for example public health. Article 168 in the Treaty on the Functioning of the European Union reflects what are considered public health interests that are worthy of a high level of protection in all Union policies and activities. These are, for example, public health improvement, preventing diseases, obviating sources of danger to health, fighting against major health scourges and promoting research in their causes, their transmission and their prevention. EU countries are primarily responsible for organizing and delivering public health measures and the EU health policy serves to compliment the national policies. For example, the EU has given several recommendations to Member States for the purpose of Article 168. In the case of rare diseases (including genetic diseases), the EU has recommended for governments to identify research resources and needs and priorities for basic, clinical, translational and social research as well as modes of fostering them.⁶²

60 European Data Protection Board. Guidelines 05/2020 on consent under Regulation 2016/679. Available at: https://edpb.europa.eu/sites/edpb/files/files/file1/edpb_guidelines_202005_consent_en.pdf. Accessed 19 November 2020.

61 European Data Protection Board. Guidelines 05/2020 on consent under Regulation 2016/679. Available at: https://edpb.europa.eu/sites/edpb/files/files/file1/edpb_guidelines_202005_consent_en.pdf. Accessed 19 November 2020.

62 Council recommendation of 8 June 2009 on an action in the field of rare diseases (2009/C151/02.)

Article 52 of the EU Charter defines the conditions under which rights may be limited. According to the provision, any limitations on the rights and freedoms recognized by the Charter must be provided for by law and respect the essence of those rights and freedoms. Limitations are accepted only if they are necessary and are subject to the principle of proportionality. The principle of proportionality plays a central role in the case law of the CJEU and has deeply affected EU law since the judgement in the *Internationale Handelsgesellschaft* case in 1970.⁶³ According to the judgement, a public authority may not impose obligations on a citizen except to the extent to which they are strictly necessary in the public interest to attain the purpose of the measure. The case law of the CJEU has ever since reflected a strict necessity test for any limitations and applies especially to the rights to personal data protection and respect for private life with regard to the processing of personal data. Proportionality and necessity in the EU law differ from the respective principle reflected in the ECHR. In the case law of the CJEU, necessity is considered as a case- and facts-based concept, which requires assessment by the EU legislator and consideration in the light of the specific circumstances surrounding the case as well as the provisions of the measure and the concrete purpose it aims to achieve. In the context of EU law, national legislative actions should be supported by evidence describing the problem, how it will be addressed and why existing or less intrusive measures cannot sufficiently address it. It can be fairly argued that for example Horizon 2020, the biggest EU Research and Innovation program ever, describes in its essence the problems governments are facing and how they will be addressed and why previous measures have not been enough for promoting research in public health matters.

In conclusion, balancing individual rights with scientific and commercial interests or public health interests, holds possibilities for interpretation and national solutions within the margin of appreciation as provided for in the Oviedo Convention and the EU Charter and the subsequent case-law of the ECtHR and CJEU. However, limitations of individual rights will have to pass the necessity and proportionality tests. Thus, the spotlight will next be turned on national legislation and the examples of how the margin of appreciation has been employed and justified in Finland.

⁶³ Judgment of the Court of 17 December 1970. Case 11–70.

3.2.2 The Finnish Biobank Act as an Example of Innovation-friendly Legislation

According to article 3 of the Oviedo Convention '*parties shall take appropriate measures to provide equitable access to health care of appropriate quality*'. How healthcare is provided, is left for the parties to decide nationally. The EU Charter Article 35 specifies that everyone has the right of access to preventive health care and the right to benefit from medical treatment under the conditions established by national laws and practices. A high level of human health protection shall be ensured. The health interests which require high level of protection were assessed in the previous chapter of this article and include, in order to be protected, policies and activities for e.g. promoting research in the causes, transmission and prevention of diseases.

Sometimes addressing complex societal challenges such as equitable access to health care requires visionary and brave decisions by the legislator. An example of visionary legislation within the field of personalized medicine is the Finnish Biobank Act, which was approved in 2012 after the Constitutional Law Committee of the Finnish Parliament had assessed its compliance with the constitution, Finland's international commitments, especially the Oviedo Convention, and the balance between primacy of the human being and public interests, freedom of science and the constitutional obligation to promote public health.⁶⁴

The Biobank Act was globally unique as its objective was to support research activities for the purposes of promoting health, understanding the mechanisms of disease or developing the products and treatment practices used in health care and medical care, and to balance it with principles of openness and individual rights such as privacy and self-determination. The act was one of Finland's first of several attempts at leading innovation with bold legislation. Due to the efforts to legislate a dynamic, fast moving area of biomedical research, a multidisciplinary steering group was established to monitor and assess the deployment and effects of the Act, development of the research infrastructure, international research

64 According to Section 19 in the Constitution (731/1999), public authorities must ensure adequate social and health services for everyone and promote the health of the population. The Constitutional Law Committee, statement 10/2012, p. 1 '*The task of the biobank is to serve researchers and research groups by storing and collecting samples and by giving them to those who do biobank research. This task has a close connection to freedom of science, as secured in the Finnish Constitution and indirectly also to the constitutional obligation of public sector to promote health of the people*'.

The GDPR also emphasizes the proper balance of rights: 'The right to the protection of personal data is not an absolute right; it must be considered in relation to its function in society and be balanced against other fundamental rights, in accordance with the principle of proportionality.' Recital 4, GDPR.

collaboration and the effective realization of individual rights of the sample donors, as well as public attitudes towards research.⁶⁵

Research on human biological samples and clinical data and other health-related data has been performed throughout the history of Finland, as the country has a long tradition in genetic research. Non-profit clinical sample and data repositories have previously represented the same objectives as larger repositories known as biobanks do today, but at a much smaller scale. The Biobank Act enabled to scale up research activities and simultaneously made the wide-ranging use of samples and associated data transparent. Governmental oversight and supervision, unified handling, access and registration requirements as well as vetting of biobanks were only a few of the novel proactive measures presented by the Finnish Biobank Act for the purpose of protecting individual rights.

Prohibition of financial gain (Article 21 in the Oviedo Convention) is respected in the Act, as in Finland biobanking is, by nature, considered to represent public interest in the form of scientific research and promoting public health. The infrastructure can be established only to support scientific research, and not for commercial purposes. Private actors may establish biobanks, but in the name of public interest all stored samples and data must be open for the use of the entire scientific community accordingly with the provisions of the Biobank Act. Charges may be collected but they must correspond to the costs incurred in the processing (incl. storage) of the samples. A research project utilizing the samples may be a public/private collaborative project and the legislation does not differ between the two. In the course of processing samples and associated data, biobank operators exercise public authority and their decisions are subject to an appeal, which effectively makes them administrative decisions by nature.

Broad consent was, at the time of enacting the Biobank Act, introduced as a new concept and tool for indicating the donor's will to participate in biobanking research. With the entry into force of the GDPR, the possibility to use broad consent for research purposes beyond biobanking was further confirmed (Recital 33). According to Section 11 of the Biobank Act the right to process samples in a biobank is based on consent, unless otherwise is regulated in the Act (e.g as in the case of legacy samples). The structure and the content of the Section corresponds to what has been described previously on the minimum standards of the Oviedo Convention relating to sample processing and the legal conditions for processing

⁶⁵ STM065:00/2012. The steering group issued an interim report in 2015: Sosiaali- ja terveysministeriön raportteja ja muistiota 2015:26. Available at: <https://stm.fi/hanke?tunnus=STM065:00/2012>. Accessed 19 November 2020.

of personal data in accordance with EU law. Of the 44 sections of the Biobank Act, roughly half provide legal safeguards for the protection of personal data.

The Act also provided sample and data donors new rights, which added to the rights provided by the GDPR and cannot be deviated from. For example, people have a right to be informed of the significance of any health-related data produced from their samples stored in a biobank.⁶⁶ Legal possibilities to monitor and control the use of their samples and associated data were significantly increased with transparency requirements in the Act. Currently donors can influence the partial or entire use of their samples and associated data either by giving active consent or by opting out of the use of legacy samples. Opting out refers to the process indicated in Article 22 of the Oviedo Convention. In light of EU law, opting out indicates processing personal data based on legislative actions in accordance with Articles 23 of the GDPR and 52 of the EU Charter.

3.2.2.1 Necessity and Proportionality in the Biobank Act

In the context of necessity and proportionality assessment, the ongoing national public debate regarding legacy samples⁶⁷ cannot be ignored. The Finnish Biobank Act introduced personal and public opt-out notification procedures (alternatives for each other) for transferring legacy samples into biobanks and making them available for scientific research purposes. These purposes are understood broadly and correspond with the wording of the GDPR, which recognizes technical development and demonstration, fundamental research, applied research, and privately funded research as scientific research (Recital 159). Projects focusing purely on product development without the purpose of increasing scientific knowledge are outside of the scope of the Biobank Act and accordingly samples and data cannot be waived for these purposes exclusively. However, outcomes resulting from biobank projects can be used for further product development.

The public opt-out procedure has been a particular point of frustration, as it has not been commonly understood that the opt-out model is one of the minimum standard options provided for in the Oviedo Convention for the purpose of processing stored samples for secondary use. As for the use of associated personal data, the opt-out system is also allowed in EU law for the necessary protection of public health. Necessity in the case of biobanking in Finland can be argued to emerge from the fact that e.g. rare (genetic) diseases, cancer diseases, and chronic

⁶⁶ This right has however led to novel challenges, which are addressed in the draft Genome Act.

⁶⁷ Salokannel et al. in *supra* note 52. Legacy samples in Finnish biobanks: social and legal issues related to the transfer of old sample collections into biobanks. *Human Genetics* 138, pp. 1287–1299 (2019). <https://doi.org/10.1007/s00439-019-02070-0>.

diseases are an imminent threat to public health and the use of legacy samples in supporting research, new discoveries, and innovations in these areas comprehend a 'pressing social need' in order to find innovative medical solutions. Had the said legacy samples not been used in the strictly regulated realm of biobanking, the scientifically valuable samples would have been inaccessible to the scientific community at large. Finland has not created the possibility and is by no means the only country using the option provided for in the Convention. However, Finland is one of the few countries, which has used the margin of appreciation in order to add layers of protection to complement the broad use of legacy samples. These protective layers form the basis for assessing proportionality.

For example, an ethics committee pre-evaluation of legacy sample transfers into a biobank - including an assessment of prior consents related to the original collection of those samples - has been incorporated into the process. Secondly, an authoritative⁶⁸ decision is required on the admissibility of adopting the public notification procedure and thus the final decisive vote lies at the supervisory authority, not at the biobank. In addition, the Finnish biobanks have incorporated added routines of checking national registries if and which sample donors are still alive and are competent for giving active consent. After these checks, the biobanks have begun to send personal notifications to sample and data donors, informing them of sample and data transfers. Biobanks have also provided individuals an opportunity to opt-out or give active consent for the future use of the samples and data. There are thus multiple layers of independent and objective assessments and a variety of steps to consider rights and freedoms of the data donors. It can be fairly argued that the essence of fundamental rights and freedoms have been duly respected. Nevertheless, the main critical claim remains and asserts that the competing interests have not been proportionately balanced.

Consequently, the public notification procedure has not been perceived by decision makers as a legal issue in need of urgent correction. Both methods (consent and opt-out as well as the procedures of personal and public notification) have been considered legally acceptable within the frameworks of the Oviedo Convention and EU law. It has from the very beginning been clear that a public notification will not in practice reach sample donors as efficiently as a personal notification would. This became evident while passing the law in Parliament. However, in light of the case law of the ECtHR it can be argued that the procedure is justified as it has a legitimate aim, is necessary for imminent public health reasons and is based on national law which is adequately accessible and is thus

68 The National Supervisory Authority for Welfare and Health, Valvira, assesses whether the sample donors should, in each individual case, be contacted personally, or not.

foreseeable so that an individual is able to understand the legislative framework either alone or with the support of appropriate advice.

The public notification process regarding both legacy samples and associated data was beforehand approved by the Constitutional Law Committee of Finland. According to the Committee statement 12/2012, p. 4: *'...associating sensitive data with the samples requires express consent. This principle can be deviated from for legacy samples only.'* Thus, the constitutional assessment clearly identified the optional minimum standards offered by the Oviedo Convention and accepted the use of the margin of appreciation in national biobanking legislation. However, contrary to prevailing critique, the acceptance did not open a door for unlimited processing of personal data. Processing of data is accepted only to the extent that is justified by the GDPR and corresponding case law and is necessary and proportionate in terms of the intended use.

The purpose limitation and minimization principles required by the GDPR are addressed widely in the Biobank Act. Section 28 of the Biobank Act regulates access conditions and requires that linking the data and sample sets is justified for the purpose of a specific research project and that the access request otherwise fulfils the additional conditions declared in Section 26, which specifies access principles in detail. These include requirements that the intended use corresponds to the research area defined for the biobank and the criteria and conditions established for processing samples. Such conditions may be set, for example, during ethical preview or authoritative decisions relating to transfers of legacy samples (as was officially required by the Data Protection Authority and Valvira) regarding the Maternity Cohort). Further, terms and restrictions provided by law must be observed in the relevant research project and the person granted access must hold an appropriate professional and academic qualification for processing samples and data. All samples and data are pseudonymized prior to granting access to them, unless there is a specific reason not to do so, as has been the case when research was focused on rare diseases concerning relatively small groups of people. In these cases, the researcher usually already has obtained the consent of the people concerned for processing their personal data.

The Biobank Act sets down the principles for access but does not specify the actual legal premises for a national health register to disclose the data. A legal premise is currently provided for by the Secondary Use Act, which came into force in Finland in 2019. The Act enabled to establish a new authority, Findata⁶⁹, for administering and authorizing data access centrally. Within the framework, data access to pseudonymized data is provided only in a secure processing environment,

69 Findata. Available at: <https://www.findata.fi/en/>. Accessed 19.11.2020.

effectively giving high protection of privacy for data subjects and the secure use of personal data. The Secondary Use Act specifies the general conditions for access, and the criteria of the Biobank Act add to these conditions. In conclusion, the protection of individuals and personal data is multilayered. The legal framework does not allow the establishment of unlimited data resources and preferably respects the minimization principle – even in projects at the scale of Finnngen.

The principle of data minimization is also supported by Section 14 of the Biobank Act, which applies to data associated and stored with the samples in a biobank. According to the provision, a sample may be stored with associated data containing information on the data subject and the subject's health status as well as information on lifestyle and environmental factors affecting the subject's health and which have consensually been obtained from the subject. In the case of legacy samples, data may be associated with the samples based on an opt-out procedure, as has been described previously in this article. An essential objective to recognize is that Finnish biobanks are not comprehensive health data registers and are also not authorized to become one by storing extensive copies of health register data for all possible future uses. Access to extensive health register data for specific research purposes is always regulated via the Secondary Use Act. For the sake of clarity, Section 14 applies to associated data stored in a biobank as a distinction from Section 28, which applies to combining different data sets for the purpose of research utilizing samples and associated data obtained from a biobank. The two Sections of the Biobank Act together with the Secondary Use Act form a comprehensive framework of legal safeguards.

How the opportunities to consent or opt-out are realized in practice depends on a large extent on the information provided to and received by people.⁷⁰ One of the main purposes of the entire Finnish Biobank Act is to promote openness as to the use of samples and data (Section 1) and thereby maintaining trust in the system. This requirement of openness is not an empty definition, as it is further elaborated in the provisions of the Biobank Act and even to an extent that is not typical for the scientific culture. Active communication is key for successful biobanking and personalized medicine. Currently, the biobanks notify people of, for example, the different sample collections, processing of samples and data as

70 Sandra Liede, Biopankkilaki määrittää säännöt – ja sen ansiosta saamme uusia hoitoja ja lääkkeitä. Available at: <https://healthtech.teknologiateollisuus.fi/fi/ajankohtaista/biopankkilaki-maarittaa-saannot-ja-sen-ansiosta-saamme-uusia-hoitoja-ja-laakkeita> (7.9.2020). Accessed 19.11.2020.

well as of ongoing research projects and results thereof.⁷¹ Different media outlets are utilized and additionally technical solutions for enabling dynamic consent procedures are being developed in the biobanks and the government level. In the future, openness and transparency are intended to be increased by integrating the information, consent, and opt-out procedures into a national information management service called Kanta. However, there is still much to improve to enhance openness and transparency. The examples from the Finnish biobanking field can hopefully provide a very valuable lesson for other personalized medicine projects in Finland and globally.

From a historical perspective, biobanking has always been criticized globally due to the commercial elements involved. Correspondingly, commercially favorable laws tend to trigger opposition and critique from many directions. If legislation is too flexible or too open to conflicting interpretations, it may result in adverse effects such as confrontations between legislators, decision-makers, supervisory authorities, and various other actors in the field of health. In Finland, the conflicting views regarding the proper application and interpretation of the Biobank Act have been recorded in the interim report published by the Finnish Ministry of Social Affairs and Health. The report is a collection of views and concerns presented by different actors in the biobanking field touching upon the finesses and details of the Act and how it should be reformed in the future. The report provides a valuable insight into prevailing social perceptions surrounding specific scientifically and commercially beneficial legislation which has expressly been created to support research activities for the benefit of science, society, individual people, and public health. The previous pages have hopefully elucidated how balance has been sought and proportionality accomplished and how the challenges can be met in future projects.

3.2.3 The Draft Genome Act

As sample and data collections have amplified and new technologies have developed, the speed of generating genomic data has skyrocketed in biobanking, the clinical setting, and the commercial market. This in turn has resulted in various new challenges, which are not specific to any one of the mentioned areas but

71 Internet search for 'biopankki' (the word for biobank in Finnish) gives 66,500 results. Search for 'transfer of samples to biobank' produces 6,090 results. Biobanks have presence at least in facebook, twitter and instagram. Sandra Liede – Sirpa Soini – Tom Southerington: Comment on 'Salokannel et al., Legacy samples in Finnish biobanks: social and legal issues related to the transfer of old sample collections into biobanks'. *Hum Genet* 139, pp. 675–677 (2020). <https://doi.org/10.1007/s00439-020-02133-7>, Accessed 18.12.2020.

rather are collective and concern all of them. These challenges relate to collective issues and impact individual people's lives and the broader societal context. To a great extent, the characteristics and very nature of genomic data is the central denominator for the various implications. Within the GDPR genetic data is placed in the special categories of data and is considered 'sensitive' in nature. Processing of genetic data is prohibited unless section 2 of Article 9 in the GDPR provides a legal basis for it. In Finland, the legislator proposed, after consulting the national data protection authority, that processing would be based on 'public interest' due to public health issues, equitable access to healthcare, and for the purpose of securing rights and freedom of others. Using public interest as a legal basis for processing genetic data indicates a positive obligation for the government to take legislative actions in order to secure the rights and freedoms of data subjects. For this reason, the draft Genome Act aims to not only establish a Genome Center for leading balanced discussion in the area but also to lay down provisions for the responsible use of genomic data. Still, the reasoning for legislating 'genome-specific' issues is not, per se, grounded in the stigmatization of genomic data as opposed to other sensitive medical data, but rather in the need to secure individual and collective rights.

Specific risks associated with the nature of genomic data have been assessed in the opinion of the Article 29 Data Protection Working Party (WP29), which was established under Article 29 of Directive 95/46/EC⁷². According to the opinion, genetic information is unique by nature and enables differentiating people from one another. Genetic information can also provide information about relatives of a person, or about the ethnicity of entire communities. It can additionally be used for making reproductive choices. According to the WP29 opinion, strong protection of genetic data is a prerequisite for respecting collective rights such as equality and the right to health.

By the time the decision-makers in Finland received a signal indicating that government backing in the form of a national genome strategy was urgently needed, the technologies and applications had already begun to translate fast into the clinic and into the laptops, mobile phones, and smart wearable devices of the informed consumers. The work to draft a national genome strategy was launched in 2014 and finalized in 2015, but unfortunately still in the year 2020, the implementation of the strategy (which remains a working group proposal) is still lacking. The slow pace of the legislator has been highly criticized, as the proposal

72 ARTICLE 29 Data Protection Working Party. Working Document on Genetic Data. Available at: https://ec.europa.eu/justice/article-29/documentation/opinion-recommendation/files/2004/wp91_en.pdf. Accessed on 19.11.2020.

for a national genome strategy originally contained many good feasible objectives and solutions. As always, where there's a gap, there's also opportunity – thus many solutions for pressing needs are already being addressed by various actors in the health field. For example, possibilities for providing services for returning clinically relevant results from biobanking projects and Direct to Consumer (DTC) genetic tests and services for genetic counselling are actively explored. Many consider that there is no need to establish a Genome Center for the purpose of answering these needs.

Even so, government actions are still considered necessary because of the collective nature of the social needs and concerns related to them. Government activities are especially needed to reach sustainable, socially just and inclusive goals. Radical innovations have the potential of bringing rapid benefits and solutions to pressing social needs but rarely do they cater to the entire population without backing from the government. As slow as the process has been, the emphasized role of the government is to try and foresee an optimal legal framework, which leaves space for innovation and encourages new solutions and ensures safe conditions and fair benefits for everyone.⁷³

Returning of results provides a feasible example of a challenge that is collective in nature. In the likely event that genomic testing has been carried out in biobanking or commercial genetic testing, and the results are predictive of genetic disease or they identify the person as a carrier or point to predisposition or susceptibility to a disease, the person will have to be referred to appropriate genetic counselling. Normally in a research context, incidental or secondary findings are not returned to research subjects. However, Section 39 in the Finnish Biobank Act expressly affirms that sample donors have the right to receive, upon request, information derived from the sample (e.g. genomic data) concerning the donor's health.⁷⁴

According to article 12 of the Oviedo Convention, such tests may be performed only for health purposes or for scientific research linked to health purposes and are subject to appropriate genetic counselling. The Convention leaves a wide margin of appreciation for governments to assess first, the scope of health purposes and secondly, the appropriateness of genetic counselling. Distinct guidance and legislation on the topic are currently lacking in Finland. The interpretation of what 'health purpose' indicates can be complex. For example, distinctions between perceiving health as catering to symptoms by providing a diagnosis or clinical care or considering health as the absence of a disease are extremely relevant for

73 Vesa Salminen – Kimmo Halme, *supra* note 29.

74 Tupasela et al. in *supra* note 21.

legally defining the scope of application of international documents. The paradigm shift from care to prevention is also very distinctive for personalized medicine.

Generally, if a genetic analysis is carried out within the public healthcare sector in Finland, the person would be referred to a specialist doctor of hereditary diseases. Since these kinds of consultations are expected to increase in the future and the total of give or take 50 specialists in the said professional area won't have the resources to cater to all requests, there would have to be a common protocol on how to proceed, whom to consult and where to find additional support. After costs, volumes, and available expertise have been thoroughly assessed, a chain of responsibility ought to be established. Specializing doctors and specialist nurses could be educated by the hereditary diseases specialists for giving counselling as to the impacts related to findings of monogenic and rare diseases as well as cancer diseases. An unresolved question is how and with which legal mandate could the protocol be established if it were to extend beyond the clinic and into the biobanking and commercial field. One option would be to legislate and draw a red line at monogenic, rare, and cancer diseases and require the presence of a hereditary diseases professional in all activities, which may produce the indicated results.

The Finnish government has also proposed that the implied mandate would be given to the future Genome Center, which could – with the help of hereditary diseases specialists – give collective guidance to the entire field surrounding personalized medicine. The Genome Center would be an added resource to be utilized by the specific medical profession and would enable giving guidance collectively to all actors in the field, without having to give separate legislation each time a need for guidance occurs. Unfortunately, the medical profession is yet to be open to accepting this proposition as there is still ongoing debate surrounding polarized isolated issues, which relate mostly to common diseases, risk calculations, and prevention strategies. However, as the amount of genomic data is gradually expanding due to the activities of biobanks, research projects, and commercial actors, there is a genuine need for guidance as to how to communicate the results to individual people. The key question for legislators is how to provide safe, sustainable, and socially just solutions in order to secure equal rights and health for the whole population?

The weakness of the Finnish genome project seems to be that too many complex questions are being solved at the same time. The overabundance of unresolved questions has resulted in a standstill in the legislative work. Many of the issues could however be solved with less laborious mechanisms such as guidance. Which makes it even more important that legislative efforts should be focused on establishing the Genome Center, which could then take lead and

ownership of the complex issues at stake. Due to the mentioned reasons, this article proposes that the provisions for establishing a Genome Center be separated from the legislative process of designating legal prerequisites for processing genomic data. It may very well be possible and even likely in the near future that the EU, namely the European Data Processing Board, will take lead in introducing new guidelines for processing genetic data.

3.3 The Way Forward – Bridging the Gap

As important as media coverage has been for challenging the justifications of the complex legislative framework, it has also shed light on the conflicting or even distorted understandings of how legislation should be established or amended. Legal theory emphasizes the importance of distinguishing the legally binding elements of law from the reflections of social perceptions and atmosphere. Public perceptions may guide the legislative process and even impact legal interpretations by pointing out the areas in need of increased social responsibility, but attaching to said views by dogmatizing them is not generally considered legally justified and should not be documented as legally binding. Embracing a historical perspective makes it even more evident that social reflections are triumphantly one-sided and time-related.

However, in the complex area of personalized medicine, finding an optimal path forward towards a consensus will require bridging the gap between legislators, the public, and the different actors in the field of genomics and personalized medicine by enhanced communication. Well-structured and methodically designed public debate can be a much more powerful source of public morality than unconstructive disputes supported by random media outlets. High-quality debate can be especially valuable for setting the appropriate level of protection. Well-grounded public debate is also more apt to increasing the public's trust in the government as well as research and commercial actors. Furthermore, public debate can increase legitimacy and support for ethically complex legislation.

Article 28 in the Oviedo Convention requires Member States to engage in a public debate with society in the field of biomedicine. According to the provision, fundamental questions raised by the developments of biology and medicine should be addressed by State parties to the Convention and subjected to appropriate public discussion and consultation. The Council of Europe Committee on Bioethics (DH-BIO) has produced a guide to assist in initiating or supporting public

debate and responding to it through public policy.⁷⁵ According to the guidance, understanding which approaches are most appropriate and effective is one of the most fundamental challenges. In this context, four key considerations are proposed in the document: establishing the timing, objectives, and reasons for initiating public debate and defining who should be involved. Public debate should never be used for furthering private interests. From a legislative point of view, public debate needs to have an actual and functional connection to the legislative process to be effective so that the different participants truly feel empowered to influence the conditions of their collective future.

Defining and understanding the critical roles of different participants is key to agreement and unity. Each should ultimately recognize that they have been given an opportunity to be heard even if the end conclusion isn't favorable for them. In the case of scientists and commercial actors, finding a common language with the legislator is important in order to understand one another. For example, scientists and commercial actors commonly envision new solutions for unsolved problems or unmet needs. Some of the solutions may be scalable, some may tend to the needs of only a single person or a small group of people. Usually, a thorough risk assessment is mandatory and technical security measures are adapted to correspond to the assessed risk. What is not required is a thorough risk assessment and evaluation of all unknown consequences and risks in possible future uses and edge cases beyond the use of what the actor originally intended. Rather, one might hope that maybe others can figure out new and innovative ways to extend what the primary innovators already created. Legislative work runs contrary to the role of science and private organizations. Legislators have a duty to assess all the expected and unexpected consequences and risks – especially if it is attempting to legislate the use of genomic data.

3.4 Conclusions

Governments have a statutory duty, democratic responsibility, and political mandate to deliver public services in consistent and equal ways.⁷⁶ The risk of not acting may be far greater than the risk of maintaining the status quo. The draft government proposal for the Genome Act states in its first sentences of the

⁷⁵ DH-BIO/INF(2018)11 FINAL.

⁷⁶ OECD. Fostering innovation in the public sector. Available at: <https://oecd-opsi.org/wp-content/uploads/2018/07/Fostering-Innovation-in-the-Public-Sector-254-pages.pdf>. Accessed 19.11.2020.

introductory chapter that *'Everyone has been guaranteed the right to enjoy the highest accessible physical and mental health. This right to health, as guaranteed by article 12 of the 1966 International UN Covenant on Economic, Social and Cultural Rights is often interpreted as a right to require positive actions by the state to actively promote health.'* By understanding and embracing this duty of the government, it may become easier to accept that the objective has all along been to promote health responsibly and equally for all.

4

‘Precision Medicine’: Critical Reflections on Europe’s Latest Healthcare Paradigm

by LL.D. Candidate Céline E. Dujardin

Abstract

Precision medicine is the healthcare model chosen by the European Union to tackle healthcare costs and improve research outcomes. This new paradigm is grounded on the pooling of healthcare data, which comprises human genetic information as well as lifestyle patterns. On a regional level, the Union has prompted a series of initiatives aiming at the mutualisation of healthcare information, with the collaboration of dedicated national bodies. The International Consortium for Personalized Medicine (ICPerMed), the ‘1+Million Genomes Initiative,’ for instance, comes along with the facilitation of exchange of healthcare data amongst European and international medical consortia. The current craze surrounding precision medicine is not without raising legitimate concerns as to the results, methods and aims of this new healthcare policy, which substitutes the circulation of patients to that of their personal medical data across the Union. The creation of such medical data flows posits the question of its authentic rationale. While economic arguments are heralded as an end, one is to ask whether precision medicine does not pave the way for a more prescriptive and controlling regional healthcare policy, tightening its mesh on both societal and personal levels. Several hypotheses are examined in this paper: I first sketch the contours of current scientific knowledge in the field of genetics, and review precision medicine as a healthcare model. I then explore the whys and wherefores of the research benefit token which is held as a core argument to support the collection of healthcare data. Furthermore, such argument is not foreign to a technocratic worldview, whereby policies are led by experts. I finally test whether this initiative bears the potential of a biopower.

* * *

‘The problem is an empirical one [...] it’s what I choose to call ‘decisional distance.’ In other words, it is a question of measuring the optimal distance between a decision made and the individual it concerns, in such a way that the individual has a say in what is done and in such a way that this decision is intelligible to him, while at the same time being geared to his situation, without having to go through an inextricable maze of regulations.’¹

Michel Foucault, Philosopher, 1983.

‘Europeanisation has opened a constantly increasing gap between decision makers and those who are affected by decision making.’²

Christian Joerges, Professor of Law, 2014.

The process of integration of the Union has been an empirical one. A difficult identification of EU citizens to the Union’s institutions and policies is a common argument against it. More specifically, health has always been a challenging political issue. It touches upon the antagonising forces of life and death, which are the typical powers of the suzerain.³ Modern-day politics has divested the thaumaturge of their healing power, to the benefit of dedicated institutions. Liberated from magical thinking, contemporary medicine is precise, rational or ‘disenchanted,’ according to Max Weber’s expression. The discovery of the human genome has brought medicine to a new dimension, involving sophisticated biotechnologies, with an unprecedented hope of curing diseases at root level. The technocratic turn that healthcare has operated in Europe entails a widening of the patient-doctor relationship, to that of translational medicine. Genetic information is to be scrutinised by funded research groups to tackle identified diseases at regional level, and prompt updated Union healthcare orientations. From a societal viewpoint, such a change is not without raising interrogations as to the way patients will appraise this new medical paradigm, and how it will affect their self-perception, as citizens, and as patients. Both a philosopher – Foucault – and a jurist – Joerges, share the same concern regarding this growing ‘decisional distance.’ The genomic rationalised and regionalised medicine will as well affect

1 Michel Foucault and CFTD, Alan Sheridan, trans., “Sécurité sociale: l’enjeu,” in Lawrence D. Krizman, Michel Foucault, Politics, Philosophy, Culture, Interviews and Other Writings 1977–1984, (New York and London: Routledge, 1983), 168–169.

2 Christian Joerges, “Legitimacy Without Democracy in the EU? Perspectives on the Constitutionalisation of Europe through Law,” in Miguel Maduro, Kaarlo Tuori and Suvi Sankari, eds., *Rethinking European Law and Legal Thinking*, 248–268, 265.

3 Larry Dossey, ‘The Royal Touch: A Look at Healing in Time Past,’ *EXPLORE* 9, no. 3, (May-June 2013).

the spiritual dimensions of care and with the risk of increasing patients' feeling of solitude and powerlessness, somewhat reduced to their genetic ontology.

What is today's state of knowledge in the field of genetics? The deciphering of the human genome through the Human Genome Project⁴ (HGP) achieved in 2003 unraveled about 20 500 human genes, conceived of as the 'history book – a narrative journey of our species through time'⁵ by Francis Collins in 2001, the then director of the National Human Genome Institute (NHGI). The turn of the 21st century hallmarked the incursion of quasi- 'disruptive'⁶ biotechnologies into the allopathic realm. During the last two decades, the deciphering project of the human genetic codex shifted towards a narrower scope: the decoding of *the* 'human genome' has been followed by the ongoing collection of 'human genomes' or 'human genetic information,' thanks to the drastic multiplication of public-private genetic databases consortia, a soaring global phenomenon. Lately, the American ENCODE project offered to create 'an encyclopedia detailing inner workings of human and mouse genomes'⁷ to identify functional areas in the genome i.e. protein-coding genes.⁸ Comparative approaches with different species are in trend.⁹ The genetic *codex* is envisaged as a vast library, whereby scientists infer the root cause of diseases, and tailor a pharmaceutical response. This is a crude description of the current scientific gist as I draft the present contribution. Changes in scientific paradigms are tested by history, and I would say, *captatio benevolentiae*, that one cannot wage on their effective success. In the Biolegal realm, positive law is geared to march in lockstep with the evolution of medicine, and the incessant renewal of its societal and ethical challenges.

4 Human Genome Project <https://www.genome.gov/human-genome-project/What>.

5 *Ibid.* The full sentence attributed to Francis Collins is: 'It's a history book - a narrative of the journey of our species through time. It's a shop manual, with an incredibly detailed blueprint for building every human cell. And it's a transformative textbook of medicine, with insights that will give health care providers immense new powers to treat, prevent and cure disease'.

6 See Clayton M. Christensen, *The Innovator's Dilemma: When New Technologies Cause Great Firms to Fail*, (Boston, Massachusetts: Harvard Business Review Press, 2016).

7 Prabarna Gangluy, 'NHGRI-funded project creates encyclopedia detailing inner workings of human and mouse genomes,' 29 July 2020, <https://www.genome.gov/news/news-release/NHGRI-funded-project-creates-encyclopedia-detailing-inner-workings-of-human-and-mouse-genomes>.

8 *Ibid.*

9 See, for instance, Prabarna Ganguly, 'Comparing epigenetic differences between humans and domestic dogs provides an emerging model of aging,' 9 July 2020, <https://www.genome.gov/news/news-release/NHGRI-researchers-reframe-dog-to-human-aging-comparisons>.

The 21st century medical zeitgeist is thus genetic data,¹⁰ prolonging the incursion of rational discourses within the doctor-patient relationship.¹¹ This steady ‘disenchantment’ of the *ars medicinae*,¹² in line with the technologisation of medical practices, is not without raising concerns as to the very use of its paradigmatic mutations. Such research endeavors require the collection of ‘data,’ a critical objective upon which genetic research depends. The ensuing uses of genetic human research findings are called into question, especially when research projects pursue a wider economical interest through biotechnological application. In this perspective, cooperation between political organs and research instances is key to the scaffolding of sustainable policies for precision medicine in Europe. This dynamic between rationality and political decisions reveals a continual imbalance, to the benefit of a technocratic orientation of healthcare and research policies in the Union, hence the division of its dedicated bodies¹³ and a symptomatic weakness of harmonisation, diagnosed as ‘constitutional asymmetry.’¹⁴ As Habermas observes, the political has become the organ of execution of a ‘scientific intelligentsia.’¹⁵ Scientists advocating for a philanthropic view of a better world is but nothing new.¹⁶ The normative power of human genomics on society remains hard to assess, though Jennifer Doudna’s presentation during the 2017 South by Southwest (SXSW) technological fest in Texas displayed a vast range of applications in the field of germline editing, as presented in the daily newspaper *Le Monde* by Bernard Monasterolo.¹⁷ Assuredly, biomedical science, and more specifically genetics, is

10 Dean Southwood, ‘In Genes We Trust: Genetic Privacy in the Age of Precision Medicine,’ in *Personhood in the Age of Biolegality*, Brave *New Law*, eds. Marc de Leeuw and Sonja van Wichelen, (Switzerland: Springer Nature/Palgrave Macmillan, 2020), 167.

11 Michel Foucault, A.M. Sheridan, trans., *The Birth of the Clinic*, (London: Routledge, 1973), xv.

12 Alexandre Abensour, ‘L’éthique en médecine: une nouvelle compassion face à l’indifférence modern?’ in *Traité de bioéthique I- Fondements, principes, repères*, Emmanuel Hirsch, ed., (Toulouse: Érès, 2010), 73.

13 Scott L. Greer, Nick Fahy, Heather A. Elliott, Matthias Wismar, Holly Jarman and Willy Palm, *Everything You Always Wanted to Know About European Union Health Policies but Were Afraid to Ask*, European Observatory on Health Systems and Policies, (London, UK: WHO, 2014), 4–5.

https://www.euro.who.int/__data/assets/pdf_file/0008/259955/Everything-you-always-wanted-to-know-about-European-Union-health-policies-but-were-afraid-to-ask.pdf?ua=1.

14 Govin Permanand and Elias Mossialos, ‘Constitutional Asymmetry and Pharmaceutical Policy Making in the European Union,’ *Journal of European Public Policy* 12, no. 4 (2015): 687–709.

15 Jürgen Habermas, René Ladmiraal (trans.), *La technique et la science comme « idéologie »*, (Paris: Gallimard, 1973), 100.

16 André Pichot, *L’Eugénisme ou les généticiens saisis par la philanthropie*, (Paris: Hatier, 1995), 4.

17 Bernard Monasterolo, ‘L’édition du génome fait le show au SXSW,’ *Le Monde*, (17 March 2017) : https://www.lemonde.fr/pixels/article/2017/03/17/l-edition-du-genome-fait-le-show-au-festival-sxsw_5096510_4408996.html.

reshaping Western society through the unfolding of a new set of norms: typical items, usually that of aging and healthcare costs, are to be radically tackled. In this context, what we often label as 'Law' or 'Biolaw' is reduced to its strictly instrumental function. It is within a regulatory framework that research based upon genetic databases is conducted, with a topical emphasis on the protection of the fundamental rights of data donors, and more specifically, due respect for data privacy within data sharing schemes. Two antagonising targets must be enforced: the respect of each donor's privacy, and the pooling of an increasing amount of genetic information. The anonymity or pseudonymisation of human genetic data stocks are therefore the legal keystone from which research is deemed to conform to ethical methods; yet, in the meantime, 'precision medicine' entails a profiling of each donor's genetic code. Within the allopathic context, genetic information is made available to dedicated professionals as a diagnostic tool for inheritable diseases (such as type I diabetes), orphan diseases, and other ailments (in the field of oncology, cardiology, *inter alia*). As a healthcare policy, precision medicine may unlock the exclusive and confidential relationship between the patient and the medical practitioner, bound by the Hippocratic Oath, nowadays enshrined in the WMA Declaration of Geneva.¹⁸ Human genetic heritage fulfills a manifold function: it is part of a person's biological conformation, but also serves as raw material for public health projects. The genetic diagnosis concerns both the individual and the population, both on macro and micro levels.¹⁹ Regulatory frames upon which medical professionals are to contribute to 'precision medicine' policies lay bare a *terra incognita*: since both phenotypic and genotypic information across Members States shall be collected,²⁰ will citizens have the right to refuse to contribute to the collective 'genetic effort'²¹ in the future? To what extent will the 'common weal' argument be exercised upon them? Does the present-day legal framework act as an efficient protective screen, or does it play the role of the 'legality token' of a multi-leveled data-driven Biopower?

18 World Medical Association, Declaration of Geneva, 'The Physician's Pledge,' 9 July 2018. <https://www.wma.net/policies-post/wma-declaration-of-geneva/>.

19 Bob Jessop, 'From Macro-Powers to Governmentality: Foucault's Work on Statehood, State Formation, Statecraft and Statepower,' *Political Geography*, 26, no. 1 (January 2007): 6. 'The study of power should begin from below, in the heterogeneous and dispersed microphysics of power, explore specific forms of its exercise in different institutional sites, and consider how, if at all, these were linked to produce broader and more persistent societal configurations. One should study power where it is exercised over individuals rather than legitimated at the centre; explore the actual practices of subjugation rather than legitimated at the center [...].'

20 Euan A. Ashley, 'Towards precision medicine,' *Nature Reviews Genetics*, no. 17, (2007): 507–522. <https://doi.org/10.1038/nrg.2016.86>

21 This very expression can be found, for instance, in the late 'Covid Human Genetic Effort' initiative: <https://www.covidhge.com>.

In this paper, I try to unravel the Union's 'precision medicine' rationale from two vantage points, which Axel Honneth has identified as competing critiques of power²²: Habermas's anthropological delineation of knowledge and interest, and Foucault's biopolitical model of normalisation. I first explain that 'precision medicine' is a multi-faceted concept, at the crux of various Union instruments (1). I contend that the 'research benefit token' argument is far from anodyne, given the Member States' constitutional traditions and the bioethical review of the ECtHR (2). I then explain how Union healthcare follows a liberal and technocratic line (3), as described by Jürgen Habermas. I finally test if Union genetic data sharing initiative bears the potential of becoming a polity akin to that of Michel Foucault's biopower (4).

4.1 'Precision Medicine'

It took more than a decade for Europe to catch up with the lead of the American 'genetic revolution.' On the international scene, the Global Alliance for Genomics and Health claims the analysis of not less than 50 million genomes and exomes by 2021.²³ The late European '1+ Million Genomes Initiative'²⁴ mimics this policy, aiming at the mutualisation of regional genetic databases. Its proclaimed objective is to enhance the 'effectiveness, accessibility, sustainability and resilience of health systems in the European Union'²⁵. Indeed, '[i]nterpreting people's health characteristics- including their genomes- is key to delivering effective health and care.'²⁶ Prolific scientific literature confirms that symptomatic medicine made a huge leap forward in terms of 'precision,' for genetic information allows a deeper understanding of the causes of ailments, and therefore helps in tailoring the pharmaceutical responses to each genetic makeup. Yet, discourses surrounding 'precision medicine' qua policy correspond to a rather prospective spirit, meant to bear fruitful results: 'a game changer for European health research and clinical

22 Axel Honneth, Dautrey Marianne and Olivier Voirol, trans., *Critique du pouvoir*, (Paris: La Découverte, 2016), p. 281.

23 Fruzsina Molnár-Gábor and Jan O Korberl, 'Genomic Data Sharing in Europe is Stumbling – Could a Code of Conduct Prevent its Fall?' *EMBO Molecular Medicine* 12, no. e11421, (2020): 1.

24 European Union '1+ Million Genomes Initiative' <https://ec.europa.eu/digital-single-market/en/european-1-million-genomes-initiative>.

25 *Ibid.*

26 European Commission, DG Connect, '1+Million Genome Roadmap 2020-2022, Summary of a Document Adopted on 4 February 2020 by the Signatories of the Declaration' <https://ec.europa.eu/digital-single-market/en/european-1-million-genomes-initiative>.

practices: sharing more genomic data will improve understanding and prevention of disease, allowing for more personalized treatments (and targeted drug prescription), particularly for rare diseases, cancer, and brain-related diseases.²⁷

Biolaw's human rights consistence is chiefly represented by the case-law of the European Court of Human Rights (ECtHR) on a regional level- coined as its bioethical facet²⁸- confirming the Europeanness of medical rights. Potential data donors are thus at the crossroads of a heterogeneous normative nexus. On Union level, healthcare is a relatively recent object, yet the rise of data circulation has yielded new prospects for cross-border healthcare possibilities,²⁹ and pooling of medical information within the Digital Single Market³⁰. The flow of health data is meant to have a leveraging effect to the scaffolding of an integrative Union healthcare program.

The basis for the Union's precision medicine project is article 168 TFEU, under the aegis of the Commission (article 114. 3 TFEU),³¹ the EU regulatory framework for pharmaceuticals, the 'GDPR'³² and other EU instruments.³³ This block is the skeleton upon which personalized medicine, as a healthcare policy, is to be attained as a core objective of the Union, 'a high level of health protection,'

27 Digibyte, 'EU countries will cooperate in linking genomic databases across borders', 10 April 2018 <https://ec.europa.eu/digital-single-market/en/news/eu-countries-will-cooperate-linking-genomic-databases-across-borders>.

28 Council of Europe, Court of Human Rights, Research Report. Bioethics and the case-law of the Court, 20 October 2016, 3. 'For the purposes of this report the term "*bioethics*" has been understood to encompass the protection of the human being (his/her human rights and in particular human dignity) in the context of the development of biomedical sciences.'

29 Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare.

30 European Commission, 'EU countries will cooperate in linking genomic databases across borders,' 10 April 2018. <https://ec.europa.eu/digital-single-market/en/news/eu-countries-will-cooperate-linking-genomic-databases-across-borders>.

31 Article 114. 3 TFEU. 'The Commission, in its proposals envisaged in paragraph 1 concerning health, safety, environmental protection and consumer protection, will take as a base a high level of protection, taking account in particular of any new development based on scientific facts. Within their respective powers, the European Parliament and the Council will also seek to achieve this objective.'

32 Regulation (EU) 2016/679 of the European Parliament and the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation).

33 Chiefly, the *in vitro* diagnostics and medical device legislation, and clinical trials regulation.

complementing national policies.³⁴ In this respect, the enhancement of digital platforms constitutes a significant ally to the Union's integration prospects, yet grounded on the circulation of data rather than patients, despite the cross-border care directive.³⁵ The cooperation between health systems has been supported by the Council,³⁶ to 'improve the availability of skills and resources across the European Union,'³⁷ eased by Electronic Health Records (ERH).

Precision medicine, also labelled as 'personalized medicine,' is medicine's new international Copernican revolution. To the European Commission: 'common medicines' are deemed to be 'no longer effective in treating large numbers of patients'³⁸ due to the rise of healthcare costs caused by population aging.³⁹ This observation is in line with that of the American Food and Drug Administration (FDA) portal, which conveys an equivalent message: the imperative need to prompt a tailored disease prevention, and thus leave behind the one-size-fits-all paradigm.⁴⁰ 'Precision medicine' does not correspond to any specific medical or scientific cure per se, but rather designates a certain healthcare policy or 'model,'⁴¹ based upon the mutualisation of human genetic information, on both national

34 Article 168, 1, § 2. 'Union action, which shall complement national policies, shall be directed towards improving public health, preventing physical and mental illness and diseases, and obviating sources of danger to physical and mental health. Such action shall cover the fight against the major health scourges, by promoting research into their causes, their transmission and their prevention, as well as health information and education, and monitoring, early warning of and combating serious cross-border threats to health.'

35 European Commission, Study on cross-border health services: enhancing information provision to patients, (June 2018), 125–126. https://ec.europa.eu/health/sites/health/files/cross_border_care/docs/2018_crossborder_frep_en.pdf.

Thus far, the cross-border care directive has not been a success: '[...] the literature showed that a limited number of patients exercise their right to treatment in another MS. [...] Specific barriers that prevent patients from seeking treatment abroad include the financial burden of upfront payment under Directive 2011/24/EU and obtaining reimbursement after having travelled abroad to receive treatment.'

36 Council of the European Union, Council Conclusions on Encouraging Member States-driven Voluntary Cooperation Between Health Systems, (16 June 2017). <http://data.consilium.europa.eu/doc/document/ST-10381-2017-INIT/en/pdf>.

37 *Ibid.*, 4.

38 European Commission, Personalized medicine. Background, conference reports, publications and links related to personalized medicine: <https://ec.europa.eu/info/research-and-innovation/research-area/health-research-and-innovation/personalized-medicine_en> accessed 29 February 2020.

39 *Ibid.*

40 US Food and Drug Administration, Personalized medicine. <https://www.fda.gov/medical-devices/vitro-diagnostics/precision-medicine> accessed 29 February 2020.

41 European Commission, Personalized Medicine. https://ec.europa.eu/health/human-use/personalized-medicine_en.

and regional levels. In the 2015 Council conclusions on personalized medicine for patients, it is defined as:

'A medical model using characterization of individuals' phenotypes and genotypes (e.g. molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention.'⁴²

Easing 'data sharing'⁴³ within the digital single market has thus become a crucial issue. The European Commission communication released in April 2018⁴⁴ confirms that 'Data is a key enabler for health transformation'⁴⁵ though the report emphasises the need to harmonise data mutualisation among member States.⁴⁶ The use of A.I. and data-analytics are meant to optimise the use of healthcare digital market similarly.⁴⁷ The sensitive character of medical information is not emphasised in this definition of personalized medicine, worded as follows:

'Personalized medicine is an emerging approach that uses data generated by new technologies to better understand the characteristics of an individual and deliver the right care to the right person at the right time. New technologies enable a wider use of genomic and other information (such as molecular profiling, diagnostic imaging, environmental lifestyle data) to help doctors and scientists better understand diseases and how to better predict, prevent, diagnose, and treat.'⁴⁸

Precision medicine is in fact medicine that analyses genetic information which is said to enhance both the physicians' diagnoses and research outcomes. This medical approach entails mass genetic sequencing and does not necessarily serve a

42 Council conclusions on personalized medicine for patients, (2015/C, 421/03). <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:C:2015:421:FULL&from=EN>.

43 European Commission, Personalized medicine.

44 Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee of the Regions on enabling the digital transformation of health and care in the Digital Single Market; empowering citizens and building a healthier society, Brussels 25 April 2018, COM (2018) 233 final. <https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:52018DC0233&from=EN>.

45 *Ibid.*, 1.

46 *Ibid.*, 2.

47 *Ibid.*

48 *Ibid.*

strictly curative purpose, since it includes preventive or predictive aims. Evidently, this endeavour yields interrogations as to the protection of citizens' privacy, and how damageable the release of sensitive information – in spite of the boundaries set by the GDPR⁴⁹ – could drastically alter peoples' freedoms. The proclaimed aims constitute the leap of faith to which European patients will most certainly have to abide by, at least from the Commission's prospective vision in the 'Bohemia project'.⁵⁰

Understood *lato sensu*, norms involved in this healthcare data policy are twofold: on the one hand, Union-law-stamped norms which aim at easing the implementation of the precision medicine policy, and, on the other hand, rationalised norms emanating from medical spheres *per se*, corresponding to Biomedical expert jurisdictions, inferred from probabilistic categorisations used in omics.⁵¹ Emphasis is indeed made on the use of omics and 'biomarkers',⁵² which relate to a rationalised medical gaze via 'quantifiable characteristics of medical processes'.⁵³ This quantification of health sketches a blueprint of medical normality, which belongs to the scientists' jurisdiction.⁵⁴ One is to ask if, perhaps, such aims of rationalisation⁵⁵ and normalisation via medical diagnoses do not

49 Regulation (EU) 2016/79 of the European Parliament and the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation), § (34), (35), (53).

50 European Commission, Directorate-General for Research and Innovation, Precision Medicine – Targeted Scenario N°1, (Luxembourg: Publications Office of the European Union, 2018). <https://ec.europa.eu/info/sites/info/files/precision-medicine-targeted-scenario-14_2018_en.pdf>

Its prospective summary is worth a read: 'It is 2040. Individualized precision medicine combining mass data analyses, genetic engineering, epigenetics, and knowledge about the personal microbiome and the biotic environment helps anticipate and cure illnesses. Human enhancement is an issue of ethical and regulatory concern.'

51 See European Commission, Commission Staff Working Document, Use of '-omics' technologies in the use of personalized medicine, Brussels, 25 October 2013. http://ec.europa.eu/research/health/pdf/2013-10_personalized_medicine_en.pdf.

52 Kyle Strimbu and Jorge A. Tavel. 'What are Biomarkers?' *Current opinion in HIV and AIDS* 5, no. 6, (2010): 463–466. <https://doi.org/10.1097/COH.0b013e32833ed177>.

53 *Ibid.*, 2.

54 *Ibid.*, 5. 'Understanding the relationship between measurable biological processes and clinical outcomes is vital to expanding our arsenal of treatments for all diseases, and for deepening our understanding of *normal*, healthy physiology. [emphasis added]'

55 Alexandre Abensour, 'L'Éthique en médecine: une nouvelle compassion face à l'indifférence modern?' in Emmanuel Hirsch (ed.), *Traité de bioéthique I- Fondements, principes, repères*, (Toulouse: Érès, 2010), pp. 70–94, 73.

unravel a Bachelardian 'epistemological obstacle',⁵⁶ preventing other medical approaches to swerve from the current healthcare doxa⁵⁷ and the 'redefinition of disease taxonomy'.⁵⁸ The use of biomarkers circumvents clinical endpoints i.e. 'the subject's health and well-being from the subject's perspective'.⁵⁹

The 'precision medicine' approach seems to be mostly holistic in numbers. This rationalised 'bench to bedside' policy circumvents the emotional management of illness, the alleviation of pain and the patient's well-being which are critical deontological duties.⁶⁰ Once consent is given, patients are empowered by the sole possibility of revoking it. As attainable as it may be, one is to question the true cost of this programme, in terms of respect for private life and other civil liberties, since precision medicine also comprises the analysis of lifestyle data,⁶¹ known as 'lifestyle medicine'.⁶² Volens nolens, the destiny of one's genetic and healthcare information is far from secured, regardless of the promises and vows of international research consortia, waging on 'codes of conduct'⁶³ and self-regulatory frameworks, rather than that of a genuine legal and ethical control. Bearing in mind the Modern origins of Bioethics, free rein for science has objectively shown to be a dramatically naïve mindset.

56 Gaston Bachelard, *La Formation de l'Esprit Scientifique, Contribution à un Psychanalyse de la Connaissance* (Paris: Vrin, 2011), 67. 'Nous allons nous efforcer de montrer que cette science du général est toujours un arrêt de l'expérience, un échec de l'empirisme inventif. [...] Il y a en effet une jouissance intellectuelle dangereuse dans une généralisation hâtive et facile'. Author's translation: 'We will strive proving that this science of the general is always an interruption of experience, a defeat of inventive empiricism. [...] There is indeed a dangerous intellectual enjoyment in a hasty and easy generalisation.'

57 European Commission, *Commission Staff Working Document*, 7. The Commission Staff working document on personalized medicine clearly evokes a change of paradigm: 'Current health care models are organ-, system- or disease-oriented. Personalized medicine is expected to bring about a *change of paradigm* by integrating large-scale molecular data with clinical data.' [emphasis added], 7.

58 *Ibid.*

59 *Ibid.*

60 WMA, Declaration of Geneva. 'The health and well-being of my patient will be my first consideration.'

61 See, for instance, Yalan Chen, Xingyun Liu, Yijun Yu, Chunjiang Yu, Lan Yang, Yuxin Lin, Ting Xi, Ziyun Ye, Zhe Feng, Bairong Shen, 'PCaLiStDB: a lifestyle database for precision prevention of prostate cancer,' Database, Volume 2020, 2020, bazi154. <https://doi.org/10.1093/database/bazi154>.

62 European Commission, *Commission Staff Working Document*, 5–6. '[...] therapies have been developed, and prescribed, using 'average patient' approach that does not take into account patients' 'molecular makeup', a factor that, together with environmental and *lifestyle factors*, determines susceptibility to disease, the course of disease, and response to treatment.' [emphasis added]

63 Molnár-Gábor and Korbel, 'Genetic Data in Europe is Stumbling,' 5.

4.2 The ‘Research Benefit’ Token

Precision medicine, as such, evolves with a continuous flow of information which could, depending on the feasibility of its expansion, involve hundreds of millions of citizens.⁶⁴ The Union framework is of regional and international scale,⁶⁵ with the aim of accruing genetic data flow in the context of a healthcare policy. Yet its ambit remains an open book, given the vagueness of the research schemes aims: the exploratory character of Biomedical research somewhat prevents researchers from guaranteeing a precise picture of their research outcomes: a plethora of research discoveries occur spontaneously, it is called serendipity. In Union Law, medical research is not the only sector where the protection of genetic data requires scrutiny.⁶⁶ The use of biological information within a transnational and judicial cooperation scheme enlightens the importance of biological (and medical) information, for their identificatory function in law enforcement procedures. The ‘Police Directive’ 2016/680⁶⁷ confirms the existence of discrepancies between Member States as to the management of such information, since: ‘[t]he *approximation* of Member States’ laws should not result in any lessening of the personal data protection [emphasis added]’ (Preamble, (15) *in fine*), a bad omen in terms of legal certainty and, hence a noteworthy caveat:

‘Considering the complexity and sensitivity of genetic information, *there is a great risk of misuse* and re-use for various purposes *by the controller*. Any discrimination based on genetic features should in principle be prohibited.’ [emphasis added]⁶⁸

64 Approximately 448 million. See Eurostat, Communiqué de Presse 111/2020, 10 July 2020. <<https://ec.europa.eu/eurostat/documents/2995521/11081101/3-10072020-AP-FR.pdf/15ed8ebe-82de-05bc-36e9-fef0faae1e33>>. See, as well, Regulation 2016/679, (6), <https://eur-lex.europa.eu/eli/reg/2016/679/oj>.

‘The scale of the collection and sharing of personal data has increased significantly.’

65 Molnár-Gábor and Korbel, ‘Genetic Data in Europe is Stumbling,’ 7.
DOI: 10.15252/emmm.201911421.

66 Agence des droits fondamentaux de l’Union européenne et Conseil de l’Europe, Manuel de droit européen en matière de protection des données, 2018, 17.

67 DIRECTIVE (EU) 2016/680 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 27 April 2016 on the protection of natural persons with regard to the processing of personal data by competent authorities for the purposes of the prevention, investigation, detection or prosecution of criminal offences or the execution of criminal penalties, and on the free movement of such data, and repealing Council Framework Decision 2008/977/JHA.

68 *Ibid.*, Preamble (23).

The data controller – an institution processing personal data, for instance - is not given *carte blanche* to use genetic information, because of the exigency of a 'legitimate interest'.⁶⁹ The manifold relevance of genetic data, as an identificatory element or as research material, entails a clear delineation of limits as to the legitimacy of their use by both public and private bodies. It is important to note that racial or ethnic characteristics are 'particularly sensitive in relation to fundamental rights and freedoms'.⁷⁰ There lies a clear prohibition of the categorisation of personal data which would support 'theories which attempt to determine the existence of separate human races'.⁷¹ Yet, special categories of personal data may also be processed for 'health purposes, including public health and the management of health-care services, especially in order to ensure the quality and cost-effectiveness of the procedures used for settling claims for benefits and services in the health insurance system, or for archiving purposes in the public interest, scientific or historical research purposes or statistical purposes'.⁷² This is perhaps the most telling example of the 'research benefit token.' The prospective character of the precision medicine initiative leaves the door open for important discussions, especially that which concerns the efficacy of patients' rights within the Union. Given the nature of its legislative basis, mostly composed of secondary legislation, the margin of action of citizens against excessive usage of their medical information by research groups shall be further specified. The universal character of the sensitiveness of human genetic information is a compelling urgency for intellectual and normative alignment.

Whilst the precision medicine initiative is to ease the flow of medical information across the Union, numerous cases of the ECtHR concern medical (genetic) data used for their probative or preemptive value, by or against individuals, and are subject to a tight regimentation. One is to ask whether this double-standard⁷³ upon medical secrecy unveils a discrepancy regarding the protection of freedoms. In the case of the precision medicine programme, exchange facilitation via digital technologies is justified by the attainment of common weal (art. 168 TFEU), substantiated by economic benefits. This, again, highlights the very power of the research benefit argument. This economic rationale appears in plain light, once again, concerning the management of human genetic information. If resources

69 GDPR, Recital 47.

70 GDPR, Recital 51.

71 *Ibid.*

72 GDPR, Recital 52.

73 Kathrin Kuhnert, 'Bosphorus – Double standards in European human rights protection?' in *Utrecht Law Review*, Volume 2, Issue 2, (December 2006).

have changed in nature, the rationale remains the same. ‘Data’ is the latest flowing layer of a mercantile exchange, amidst a vast nexus of products and services. Yet, genetic and healthcare data are a challenge to an unabashed liberal management, because of bioethical barriers. It seems difficult to envisage genetic and medical data as an anodyne resource, since it is a constitutional and bioethical imperative to secure the consent of their respective holders.

4.3 The Technocratic Line

Research benefits constitute a philanthropic argument favouring the ushering of sensitive medical information. Moreover, the medical token is unquestionably powerful. Indeed, who would not incline, *prima facie*, to contribute to the common healthcare effort ‘for the benefit of patients and society.’⁷⁴ Our intuitive perception of medical and research professionals is generally positive. Scientists are the heroes of today, and, to keep up to a totemic-religious role⁷⁵ - and maintain consensus with the public- enhance their communication abilities to democratise their knowledge.⁷⁶ Communication is key, and the discursive facet of science is critical in many aspects, let alone fundraising. Research impregnates the societal realm by reshaping social interactions, be it in shifting forms of individuation (genetic information is topical in this respect), or, from a societal vantage point, by prompting new forms of rational legitimation. Habermas indeed contends that classical theories of statecraft and power are becoming irrelevant because of their lack of social embedment.⁷⁷ His reappraisal of knowledge blurs the lines as to the determination of interests and influence of research groups onto the political realm.⁷⁸ Research findings do serve a political purpose, and may no longer be envisaged as the purport of scientists locked up in their ivory tower. Between medical norms and legally stamped norms lies a gateway which circumvents former forms of power legitimation, hallmarked by a strong token of scientificity.

74 Molnár-Gábor and Korbel, ‘Genetic Data in Europe is Stumbling,’ 1.

75 Jürgen Habermas, Thomas McCarthy, trans., *The Theory of Communicative Action Volume 2: Lifeworld and System: A Critique of Functionalist Reason*, (Boston: Beacon Press, 1987), 52–53.

76 See Dennis Meredith, *Explaining Research, How to Reach Key Audiences to Advance Your Work*, (Oxford: OUP, 2010).

77 Axel Honneth, Dautrey Marianne and Olivier Voirol, trans., *Critique du pouvoir: Michel Foucault et l’École de Francfort, élaborations d’une théorie critique de la société*, (Paris: La Découverte, 2016), 240.

78 Jürgen Habermas, René Ladmiraal, trans., *La technique et la science comme « idéologie »*, (Paris: Gallimard, 1973), 101.

Tight regimentation somewhat reflects the invasive character of science-laden norms in many sectors of civil life, and this strongly applies to healthcare as well.

The technocratic line henceforth consists in finding justifications which are not necessarily tied to classical political worldviews. Science, through experimentation and exploration, has widened the scope of the technically feasible. Therefore, scientific projects are geared to fulfilling practical outcomes, with the promise of a return on investment. Ignoring this facet of Biomedical research would be, again, naïve. If one adds to this rationale a liberal framework, then the research ethics argument reveals a certain weakness. Given its procedural position, the ethical review of the ECtHR slackens the feedback reaction on potential abuses of genetic data management. As to the Court of Justice, its control is exercised upon an economic regulatory basis, which tinges its cases' motives. In the Union paradigm, health as such is concretely envisaged as a 'service' or 'data,' despite the ethical guarantees of its dispersed constitutional kernel.⁷⁹ In fact, the ambit of the GDPR, concerning research, seals the impossibility of exercising tight control over the uses of data in research projects, since 'it is often not possible to fully identify the purpose of personal data processing for scientific purposes at the time of data collection.'⁸⁰ While a separate consent of the subject should be gathered by the controller for further processing, one might question the existence of absolute control of such ethical observance. This reveals an uncanny *légèreté* as to the objective control over the use of genetic information, to the benefit of research groups. Yet white blouse misconduct exists: the extent of settlements in the field of pharmaceuticals proves the importance of setting clear boundaries within the field of drug development, in terms of fair use of patients' medical information and pricing.⁸¹ Since research on genetic data aims at tailoring medication uptake upon patients' genetic makeup, the imperative clarification of the Union's integrative pricing policy continues to lag whilst '[m]edicines, particularly the research-segment, are an extremely profitable industry', worthy of governments' 'safeguarding,'⁸² to the dismay of international competitors.⁸³ Personalized medicine is to tackle upstream costs

79 See *infra* note 87.

80 GDPR, Recital 33. See as well, Recital 43 *in fine*.

81 Ellen 't Hoen, 'Time to put a stop to the abuse of orphan drug regulation- the latest scandal,' *Medicines Law & Policy*, (January 9 2019).

<https://medicineslawandpolicy.org/2019/01/time-to-put-a-stop-to-the-abuse-of-orphan-drug-regulation-the-latest-scandal/>.

82 Permanand and Mossialos, 'Constitutional Asymetry,' 688.

83 Joseph H. Golec and John A. 'Vernon, European Pharmaceutical Price Regulation, Firm Profitability, and R&D Spending, Working Paper 12676,' National Bureau of Economic Research, Massachusetts, (November 2006).

<https://www.nber.org/papers/w12676.pdf>.

incurred by the inadequate uptake of medicines, and ensuing adverse reactions, which represents an important expenditure item (6% of hospital admissions.)⁸⁴ The rationale is, again, an economic one:

‘Significant upfront investment may be needed for technological upgrades, structural changes, and education and training efforts for staff in health care systems. Such investment may however be offset by savings in *unnecessary costs* due to inadequate treatment for a patient. The *economic* impact of personalized medicine therefore needs to be considered from an overarching level, the so-called ‘societal’ cost perspective encompassing the complete health care system as well as patient benefits in terms of reduced days of incapacity, days of hospitalisation, etc.’ [emphasis added]⁸⁵

Curbing ‘unnecessary costs’ is indeed a crucial objective yet requiring tight cooperation between a web of juxtaposed healthcare and social systems. To be truly effective, such objective calls for a genuine reform of healthcare systems, with unavoidable political meddling. In recent decades, the shift towards a managerial model (*governance*) of public hospitals has not been positively received on national levels.⁸⁶ On a tangential point, the health services market displays a similar field of inconsistency. The Court’s cases⁸⁷ unfold the difficult equalisation of health costs incurred by between Member States, conundrums which their ex-post codification in the cross-border care Directive has timidly succeeded in tackling, by loosening authorisation requirements and reinforcing legal certainty. Regarding the harmonisation of pricing, the ‘Transparency Directive’⁸⁸ was meant to ease import and export of medicine and prevent national policies from

84 European Commission, Commission Staff Working Document: Use of ‘-omics’ Technologies in the Development of Personalized Medicine, Brussels, 25 October 2013, 4.
http://ec.europa.eu/research/health/pdf/2013-10_personalized_medicine_en.pdf.

85 *Ibid.*, 6.

86 A striking example is the recent reforms of French healthcare system. See Jean-Pierre Claveranne, Christophe Pascal and David Piovesan, ‘La gouvernance hospitalière à la croisée des chemins,’ in Bras, Pierre Louis and Gérard de Pouvourville, eds., *Traité d’économie et de gestion de la santé*, (Paris: Sciences Po, 2009).

87 See for instance *Luisi and Carbone*, joined cases 286/82 and 26/83 [1984] ECR 377; *SPUC v. Grogan*, C-159/90 [1991] ECR I-4685; *Vanbraeckel*, C-368/98 [2001] ECR I-5363; *Geraets-Smiths and Peerbooms*, C-157/99 [2001] ECR I-5473; *Müller-Fauré*, C-385/99 [2003] ECR I-4509.

88 Council Directive of 21 December 1988 relating to the transparency of measures regulating the pricing of medicinal products for human use and their inclusion in the scope of national health insurance systems.

imposing financial restrictions, yet with mitigated success.⁸⁹ Healthcare remains a rather national matter, since scientific requirements for treatments may vary from a country to another, hampering the flow of health services. Citing James Wilson,⁹⁰ Govin Permanand and Elias Mossialos demonstrate that the Union's pharmaceutical policy resolutely serves the industry's interests.⁹¹ If one acquiesces to the technocratic hypothesis, its political importance remains undefined since the Union is practically prevented from scaffolding a purely liberal healthcare market by weighty national particularisms. Habermas explains that the technocratic model is insufficient⁹²: knowledge production does not necessarily coalesce with technological applications. Technical and practical questions do not follow an identical line: healthcare reality does not necessarily correspond to industrial (medical) productions. While recital 157 of the GDPR clearly states that research results are to ground a 'knowledge-based policy',⁹³ one may sensibly question biotechnological and digital applications resulting from such endeavour. Clear decisions – emanating from political organs- must be taken for such a technocratic system to remain dynamic. This dialectic should involve the public as well, given the importance that genetic research holds for future generations. Institutions and research groups must organise prescientific discussions,⁹⁴ to find an agreement on the expected pragmatic outcomes,⁹⁵ and act in unison with political stakeholders.

89 Permanand and Mossialos, 'Constitutional Asymetry,' 701.

90 James Q. Wilson, 'The Politics of Regulation,' in James Q. Wilson, ed., *The Politics of Regulation*, (New York: Basic Book Inc, 1980).

91 *Ibid.*, 694.

92 Jürgen Habermas, René Ladmiral, trans., *La technique et la science comme idéologie*, (Paris: Gallimard, 1973), 101.

93 'Research results obtained through registries provide solid, high-quality knowledge which can provide the basis for the formulation and implementation of *knowledge-based policy*, improve the quality of life for a number of people and improve the efficiency of social services [emphasis added]', (Recital 157, GDPR).

94 Habermas, *La technique*, 110.

95 *Ibid.*, 114.

4.4 A Biopolitical Future?

What could be the ultimate outcome of such ‘knowledge-based policy’? Politics and knowledge do not always pursue the same objective. Biomedicine, as a source of moral norms (*primum non nocere*) and medical norms (*ars medicinae*), challenges the cohesiveness of our classical understanding of law from the usual positivist lens. The legal anointing follows a manifold purpose: first, the enshrinement of moral conduct which is specifically intended for medical practitioners, in their contractual relationship with the patient at micro-level; second, the regulatory anointing of public health policies on a macro-level. Laws tend to balance between rationality and morals, yet for European Biolaw, moral thresholds vary geographically. Thus, one is to conceive of Biolaw as an instrument rather than a cohesive normative source. Current trends confine Biolegal scholarship into a positivistic vault, despite a recent attempt to theorise it.⁹⁶ Consequently, one is led to turn to other intellectual models, which do not necessarily match classical legal analysis. To Foucault, the law and its representative instances, such as the Judge, are only a mere representation of a ‘king.’⁹⁷ His ‘anti-juridism,’⁹⁸ inferred from his analysis of Boulainvilliers’ theory on the downfall of French nobility,⁹⁹ reflects the frailty of the juridical institution in Foucault’s own sight. Like Habermas, Foucault observes that old constitutional models have become maladjusted to the technologisation of modern society. Therefore, research and bio-technological consortia need to be considered as part of a recent diversification and deployment of normative instances. Conversely, their growing importance in decision-making require a certain distancing with scientific knowledge, for its normative charge constitutes a strong source of power legitimation. In this respect, Foucault’s distancing from the ‘medical gaze’ started with the ‘Birth of the Clinic’ (1963) where he analyses the evolution of the patient’s existence as a subject, via a critical analysis of medical discourses. Embedded in its historical segment, the medical sight appears to evolve together with medical knowledge. Medicine is thus no absolute truth, but rather a given discourse, embedded in an identified epistemological layer. Foucault’s initial stance on medical norms in ‘Birth of the Clinic’ will evolve in his ensuing opuses. Locating the genuine roots of the ‘Birth

96 Roman Andrzej Tokarczyk, *Biojurisprudence: Foundations of Law for the Twenty-First Century*, (Lublin: Maria Curie-Skłodowska University Press, 2008).

97 See Institut National de l’Audiovisuel, Foucault et la justice, 25 April 1977: <https://www.ina.fr/video/I06277667/michel-foucault-et-la-justice-video.html>.

98 Op. Cit., Foucault, *Il faut défendre la société*, 173.

99 Henri Comte de Boulainvilliers, *Essais sur la noblesse de France contenant une dissertation sur son origine et abaissement*, (Amsterdam: S.n., 1732).

of Biopolitics' (1979) within Foucault's numerous lectures is a delicate question. Foucault introduces the concept in his 'History of Sexuality,' and more specifically at the end of the first part, in *The Will to Knowledge*:¹⁰⁰

'It was life more than the law that became the issue of political struggles, even if the latter were formulated through affirmations concerning rights. The 'right' to life, to one's body, to health, to happiness, to the satisfaction of needs, and beyond all the oppressions or 'alienations,' the 'right' to rediscover what one is and all that one can be, this 'right' - which the classical juridical system was utterly incapable of comprehending - was the political response to all these new procedures of power which did not derive, either, from the traditional right of sovereignty.'¹⁰¹

One can conceive of this passage as the roadmap of 'Society must be defended' (1975–1976), and further lectures on biological governmentality. Foucault displaces the object of political dominion from the legal realm, to technologies of power exercised over the living. The exercise of this 'right of death and power over life'¹⁰² connects us with the crucible of both Biolaw and Bioethics. In 'Society must be defended,' Foucault sketches out the contours of the government of the living, the right to 'make live' ('faire vivre') or 'let die' ('laisser mourir.')103 In Foucault's Biopolitics, power through control is exercised over a given population using non-disciplinary¹⁰⁴ instances of 'normalisation' unto people,¹⁰⁵ whereby diseases become a 'population phenomenon.'¹⁰⁶ In such a setting, the question remains whether the State will exercise a *disciplinary* or a *regulatory* bio-power¹⁰⁷ over its population. As this stage, ascribing a disciplinary function to the human genome per se seems hard to fathom, yet the normalising effect of healthcare policies is, on the contrary, salient, since it entails the classification of patients according to their

100 Michel Foucault, *Histoire de la sexualité I. La volonté de savoir*, (Paris: Gallimard, 1976). 'S'ouvre ainsi l'ère du biopouvoir', 184.

101 Robert Hurley (trans.), Michel Foucault, *The History of Sexuality. An introduction*, (New York: Peregrine Books, 1984), 145.

102 *Op.cit.*, *History of sexuality*, 133.

103 Michel Foucault, *Il faut défendre la société*, Cours au Collège de France, 1976, (Paris: Seuil, 1997), 214.

104 Disciplinary power corresponds to a more tailored response to certain types of persons labelled as abnormal; this concept relates to Foucault's *Discipline and Punish* (1975) and *Abnormal* (1974–1975).

105 Foucault, *Il faut défendre la société*, 216.

106 *Ibid.*, 217.

107 *Ibid.*, 226.

genetic disease. This trait is reinforced by the normal-pathological threshold,¹⁰⁸ which proved having found a fertile ground in medicine, and more so, genetic medicine. The fragmentation of the executive power into various expert bodies in capitalist societies entails a tendency to normalisation, since norms are to frame, convey or facilitate information flows. Foucault conceives of Biopolitics as a bottom-up system,¹⁰⁹ whereby control is exercised in all sectors of biological life, via a strong monitoring of healthcare and other disciplinary instances. His model addresses a given population rather than economic agents. Power and control are exercised through all capillaries of power, in line with his 'panoptic' concept of surveillance. Yet, the 'Biopolitical hypothesis' is questionable as a coherent model to explain the Union's orientations in terms management of genetic data. There is no clear indication of a direct and vertical power or urge applied upon citizens, or that which would coerce them in changing their lifestyle, in function of their genetic makeup- thus far. Foucault, as a 'genealogist of statecraft',¹¹⁰ aimed at scaffolding and explaining new models of government in relation a state's biological substrate, namely the population. There is no, need for the EU to abide by any genetic hygienism, but rather an encouragement, upon lawfully gathered consent, to provide national repositories with valuable information for research groups and bolster economic growth within the digital market. In this respect, Habermas' analysis matches the technocratic orientation of such healthcare policy. Foucault's model, however, sketches out a darker scenario for future 'knowledge-based' policies, questioning the ultimate aims of scientific legitimization.

4.5 Conclusions

Precision medicine, like other expert domains, is the late modern result of a slow process of knowledge division and scientification. The flow of healthcare information is meant to ease the work of research groups and bolster the production of pharmaceutical treatments. In such paradigm, genetic information holds a pivotal role: it is the codex from which diseases are to be inferred, and tackled. Yet, such a vision of medicine works in well-defined cases, while numerous diseases have an environmental cause, or are due to certain lifestyle patterns. In terms of freedoms, the ushering of such information is compelling, especially if it is to

108 See Georges Canguilhem, *Le normal et le pathologique*, (Paris: PUF, 1966).

109 Bob Jessop, 'From Micro-Power to Governmentality: Foucault's Work on Statehood, State Formation, Statecraft and Statepower,' *Political Geography* 26, (2007): 24–40, 34.

110 *Ibid.*, 36.

be controlled under the guise of medical reason. There is no absolute guarantee as to the ethical use of such information by research groups or other dedicated bodies. The consent revocability alone does not seem to counteract the potential use or abuse of data, be it for research purposes. The results of such studies on healthcare and genetic information may affect a higher number of European citizens than that of the donors alone. In fact, 'knowledge-based' policies might as well be based on research results which initially concerned a certain number of subjects, rather than the entirety of a given population. This might create a feeling of 'decisional distance,' reinforced by a certain fear of reification. In this perspective, the medicine precision initiative is built on a fragile ground in terms of respect for fundamental rights and health democracy. Its economic rationale requires a solid protection of patients, not only as potential holders of a genetic risk, but primarily as persons.

5

Genomic Testing and Giving Consent on Behalf of a Child¹

by LL.D. Candidate Merike Helander

Abstract

Genetic research is increasingly being performed both in clinical medicine and in medical research. There is a high interest in the field and the vision is that in the future health promotion and treatment of diseases would be individually designed based on genomic information. It is also necessary to conduct genome research involving children because children have the right to the best possible treatment and medication. Legal questions concerning genome research involving children are particularly interesting when a child's participation in early childhood is based on the proxy-consent and the data is possibly stored for future research purposes. The genomic data of the child always provides data about both parents and other close relatives. Some research findings may be relevant to the child only in adulthood. Samples and the data can be stored for decades in biobanks. In this chapter, I review relevant regulation in the Finnish legislation of genome testing in terms of consent on behalf of a young child. In Finland, in the absence of specific legislation of genomic testing, regulation on healthcare, medical research, and biobanking remains applicable. The parents' right to act on behalf of the child are regulated to some extent differently in these situations.

5.1 Introduction

Genetic research is increasingly being performed both in clinical medicine and in medical research. There is a high interest in the field and the vision is that in the future health promotion and treatment of diseases would be individually designed based on genomic information. For some diseases, such as certain cancers,

¹ My warmest thanks to LL.M. Amanda Blick for her great help with the translation this article from Finnish to English.

individualised treatments are already a reality.² Diagnostic pre-symptomatic genetic tests in children are mainly carried out as part of the child's treatment. Large-scale genomic tests are especially used to diagnose rare diseases, which are often examined in a newborn or a young child.³ Genomic information is also examined in medical research, in which children may participate under certain legal conditions. Biobanks play a key role in utilising genomic information in medical research. Children's samples are also stored in biobanks. Through research into the genetic factors that influence the health and diseases of children of different ages, even children can benefit from the advances made in the field of medicine.⁴

In this paper, I will review the legislation of genome testing in terms of consent on behalf of a young child. Medical treatment and research are based on the patient's autonomy and the requirement for informed consent as a prerequisite for treatment and research. The starting point for international and national regulation is that the consent of the child is given by his or her custodian until the child is able to decide for himself or herself on the basis of his or her age and maturity. The right of the custodian to give consent on behalf of the child is based on his or her status as the child's legal representative.

Genomic tests are often performed on newborns or very young children, so consent to the test is given by the custodian. Consent on behalf of a child requires careful consideration as to whether consenting is in the best interests of the child as a patient or as a research subject. When giving consent on behalf of another person, there is also always a strong connection to the question of who is entitled to access the research results and other patient information. In Finland, in the absence of specific legislation, regulation on healthcare and medical research remains

2 Parempaa terveyttä genomitiedon avulla. The National Genome Strategy. Proposals for action by the working group. Ministry of Social Affairs and Health. Reports and Memorandums 2015:24, pp. 8 and 28. The term genome refers to the entire human genetic material which consists of DNA (deoxyribonucleic acid). A gene is a piece of DNA that causes a cell to produce a specific product such as a protein. See more specifically, Maarit Jokela: DNA perimän välittäjänä, pp. 9–14 in Maarit Jokela – Mirkka Oja-Leikas – Meri Rova (ed.): Kiehtovat geenit. Mihin geenitietoa käytetään? Duodecim 2017, and in the same publication Johannes Kettunen: Geeneistä genomiin, pp. 15–21.

3 Helena Kääriäinen: Geenitestaus. Lääkärikirja Duodecim 2 May 2015, available online at www.terveyskirjasto.fi/terveyskirjasto. See also Carla G Van El – Martina C Cornel – Pascal Borry – Ros J Hastings – Folrence Fellmann – Shirley V Hodgson – Heidi C Howard – Anne Cambon-Thomsen – Bartha M Knoppers – Hanne Meijers-Heijboer – Hans Scheffer – Lisbeth Tranebjaerg – Wybo Dondorp – Guido M W R De Wert: The whole-genome sequencing in health care. Recommendations of the European Society of Human Genetics. European Journal of Human Genetics 2013, Vol. 21(6), pp. 580–584.

4 Government proposal 229/1998 on the Medical Research Act, p. 15. See also Näkökulmia lääketieteellisestä tutkimuksesta lapsilla. Valtakunnallisen terveydenhuollon eettisen neuvottelukunnan asettaman työryhmän loppuraportti 2003, pp. 4–5; Kouvalainen, Kauko: Lasten lääkeshoidon historiasta. Tabu 6/2005, Lääkelaitos, pp. 8–12.

applicable.⁵ Genomic testing is conducted as part of a treatment or research, therefore requiring informed consent.⁶ This generally applies to biobanking as well. The parent's right and duty to act on behalf of the child are regulated to some extent differently in these situations.

My intention is therefore to examine *how giving consent on behalf of the child is regulated in different situations where genomic research is carried out and how legislation safeguards the rights of the child*. To illustrate the topic, I will first describe how genomic information is utilised in children and I will reflect on the specificity of genomic data over other patient data. The nature of genomic data contributes to whether consent to genomic research should be evaluated differently than consent to other medical research or treatment. Then, in accordance with the research questions mentioned above, I will look at the regulation of consent on behalf of the child and assess how it contributes to the realisation of the rights of the child.

5.2 Genome Research and Children

5.2.1 Genomic Information as the Basis for Personalized Medicine

Today, health promotion, disease prevention, and treatment are increasingly based on genetic data derived from the patient's genome, as well as other information from clinical research and lifestyle and environments, which can be combined and analysed using effective digital methods. This relates to *personalized medicine*

5 Specific legislation is currently under preparation, see the draft Government proposal on the Genome Centre and the conditions for processing genomic data (hereinafter draft Genome Act) of 9 May 2019 prepared by the Ministry of Social Affairs and Health, available online at <<https://stm.fi/hanke?tunnus=STM071:00/2018>> as well as the draft Government proposal for the Biobank Act, repealing the Biobank Act (688/2012) and amending the Act on the Medical Use of Human Organs, Tissues and Cells (101/2001) and the Act on the Status and Rights of the Patient (785/1992) (the draft Biobank Act) 28 March 2018, available online at <<https://stm.fi/hanke?tunnus=STM110:00/2015>>. The reforms will have an impact on, e.g. how samples and related information can be used for research, development, and innovation purposes in addition to therapeutic purposes, and how the privacy and autonomy of the registered individuals can be protected in different situations.

6 Commercial genetic tests are excluded from this study, for an outlook on the subject see e.g. Marja Pirttivaara: Kuluttajille suunnatut genomitietopalvelut, pp. 175–184 in Jokela et al. 2017. See also Kavot Zillén – Jameson Garland – Santa Slokenberga: The Rights of Children in Biomedicine. Challenges posed by scientific advances and uncertainties. The Council of Europe's Committee on Bioethics 2017, pp. 29–31. On problems with commercial genetic tests, see e.g. Nina Meincke: Geenitestit. Oikeudellisia kysymyksiä. Lakimiesliiton kustannus, Helsinki 2001, pp. 31–34.

that seeks targeted treatment, i.e. the most effective and safe treatment selected for each patient based on his or her individual characteristics and symptoms.⁷

Gene and genome research are utilised in patient care to diagnose diseases and developmental disorders and to find, among other things, the most effective medication with the least side-effects. In addition to clinical work, tests are performed in medical research and clinical trials.⁸ Various tests are used to analyse varying fractions of the genome. A gene test analyses the structure of DNA at the level of one or a few genes. Gene panels are used to diagnose a particular disease or symptom, where dozens or hundreds of genes are studied simultaneously. Genome-wide sequencing is utilised in research and, for example, in the diagnosis of rare diseases and in the treatment of cancer. In clinical settings its use in patient care is not yet very common. Exome sequencing, the determination of the region coding the protein of the genome, is utilised in both research and patient care, particularly in the diagnosis of rare hereditary diseases, congenital malformations and cancer.⁹ Genetic counselling is central to gene and genome research.

In paediatric patients, genetic testing is usually used when the child has symptoms but the diagnosis is otherwise unclear. Targeted gene panel tests are used when a child has a clearly rare condition, but the test is needed to make a diagnosis. Genome-wide screening or exome sequencing is utilised in situations where the symptoms are vague and no suitable gene panel is used. In particular large-scale tests include the difficulty of result interpretation and may, for example, reveal genetic defects of unknown significance or those that will cause an untreatable disease. The results of the test may also be relevant to the parents, siblings, possible future siblings, and other close biological relatives of the child.¹⁰

7 See Helena Kääriäinen: *Geeni- ja genomitutkimuksia terveille ja sairaille*, pp. 79–87 in Jokela et al. 2017; Palotie – Samuli Ripatti: *Suomi luomassa genomiikan ja terveystiedon internetiä* [Finland establishing the internet of genomics and health data]. *Duodecim* 2017;133:771–5; Sakari Jokiranta – Kristiina Hotakainen – Iris Salonen – Pasi Pöllänen – Kai-Petri Hänninen – Jari Forsström – Ilkka Kunnamo: *Genomitieto käytännön lääkärin arkipäivään – päätöksenteon digitaaliset työkalut* [Genomic data into everyday work of a medical practitioner - digital tools for decision-making]. *Duodecim* 2017;133:791–800.

8 Kääriäinen 2017, pp. 81–84. Predictive genetic testing to determine the risk of developing a particular disease is performed on children only when the disease should be prevented or treated in childhood. Tests that predict the later disease of the unborn child can be done at the request of the parents in the embryonic and foetal stages.

9 See e.g. Kääriäinen 2015; Jonna Saarela – Kaisa Kettunen: *Kenelle eksomisekvensointi?* [Who would benefit from exome sequencing?] *Duodecim* 2017;133(5):481–8.

10 Kääriäinen 2015. See also Samuel Myllykangas – Juha W Koskenvuo – Tero-Pekka Alastalo: *Uuden polven sekvensointimenetelmät geenidiagnostiikassa* [Novel high-throughput sequencing strategies in genetic diagnostics]. *Duodecim* 2013;129(2):141–8.

The exploitation of genomic data in all its aspects, such as its importance for improving public health, is not without criticism.¹¹ At the same time, many of the various threats associated with genomic information are also being considered. Possible security breaches and disclosure of data for commercial purposes are seen as challenges in data privacy. The use of genomic information, for example, in the field of genetic profiling in insurance or working life, and the potential for increased discrimination against sick or disabled people is a cause for concern.¹² The various treatments based on genomic information, gene therapies, and genetic engineering, in turn, raise questions about their safety and, for example, whether the development will lead to eugenics.¹³ The development of gene therapies and drugs is expensive, so their equitable availability is a concern for many.¹⁴ Another challenge may be the availability of sufficiently comprehensive genetic counselling. Gene tests on children also include questions about how far parents have access to their child's information and whether they deprive the child of the right not to know when giving consent on behalf of the child.

Although genomic information can already be used today to diagnose and treat many diseases, from many aspects these are still in the early phases. Much more research is also needed before genetic treatments, such as gene therapies

11 Juhani Kere: Hyödyttääkö genomitieto kansanterveyttä? *Duodecim* 2019;135(22):2147–8. See also the interview of Professor of Pharmacogenetics Mikko Niemi 'Geenitestit ovat vain yksi työkalu', *Suomen Lääkärilehti* 22/2018 vsk 73, p. 1411.

12 The risk of genomic information falling into the wrong hands can also be made more proportionate by stating that every blood sample or hair follicle contains all the human genetic information and can therefore, in theory, lead to misuse (Kääriäinen 2015). See also, e.g. *Lääkärin etiikka*, 7. painos, *Suomen Lääkäriliitto* 2013, pp. 90–92; Many threats and ethical issues have already been addressed at the legislative level.

13 See e.g. Alisa Opar: CRISPR-edited babies arrived, and regulators are still racing to catch up. *Nature Medicine* 2019, Vol.25(11), p. 1634(3); Petter Portin: Ihmisen geeniterapiassa avautuu uusia mahdollisuuksia. *Duodecim* 2016;132(1):26–32; Seppo Ylä-Herttua: Geenihoidot: haasteita ja lupauksia. pp. 88–94 in Jokela et al. 2017. On the ethics of the consequences of gene therapies, see Matti Häyry: Ihminen 2.0. Geneettisen valikoinnin ja parantelun eettiset kysymykset. *Gaudeamus* 2012, pp. 187–208.

14 An example of this is the situation that has arisen in the public debate in Finland. Pediatric patients with severe and rare neurological SMA muscle disease caused by a genetic mutation did not receive the specific nusinersen medication intended for treatment due to its high cost. A similar debate has taken place in several European countries. Since then, the Council for Choices in Health Care in Finland (COHERE Finland) has outlined that patients who become ill as a child can receive this medication. See Palveluvalikoimaneuvoston perustelumuistio ja perusteet neuvostolle suosituksen antamiseksi. Aihe: Nusinersen SMA-taudin hoidossa. Justification memorandum of 15 March 2018. STMo38:00/2017. On February 21, 2019, COHERE Finland has also announced that it has begun preparing criteria for the continued treatment of the nusinersen medication.

and gene editing, are so advanced and safe that they can be used extensively.¹⁵ The development of personalized medicine based on genomic data requires the availability of extensive sample data and other health data from a sufficiently large population.¹⁶ Finland has particular strengths to become a leading international actor in genome research. These include, for example, our demographic population being established by a small founding population, comprehensive health records and the use of a personal identification number, a tradition of epidemiological research, large sample collections of population data, and a favourable attitude of citizens towards research.¹⁷

A genomic centre is currently being set up in Finland, with the task of developing, among other things, a nationwide genomic data register.¹⁸ The establishment of the genome centre is included in the proposal of the Ministry of Social Affairs and Health Task Force for a National Genome Strategy for 2015–2020. Under this strategy, a new law will regulate the operation of the genome centre, including the conditions for carrying out genetic analyses, the protection of genome data and its responsible and appropriate use. The purpose of a genomic data register would be to support health and medical care, disease prevention and scientific research. It could be used both in the treatment of individual patients and in medical research. The use of the register is therefore linked to health purposes. The genomic data register would consist of lawfully stored genomic data and related metadata generated by biobanks and health care providers.¹⁹

15 See e.g. Portin 2016; Seppo Ylä-Herttua: Geeniterapialääkkeet tekevät tuloaan. *Duodecim* 2013;129:788–9. The first gene therapies were administered to humans in 1989. Only a few gene therapy drugs have been approved in Europe. About 3,000 clinical trials have been performed by the end of 2018 (interview of Kirmo Wartiovaara in the podcast *Terveysteksti-Geenit*, *Duodecim* 2019). See also Josephine Johnston – John D Lantos – Aaron Goldenberg – Flavia Chen – Erik Parens – Barbara A Koenig: Sequencing Newborns: A Call for Nuanced Use of Genomic Technologies. *Hastings Center Report* July 2018, Vol. 48, p. 5.

16 See e.g. Palotie – Ripatti 2017; Jokiranta et al. 2017. An example of genetic research based on genetic information is the FinnGen research project that aims to better understand the mechanisms of diseases and develop new therapies by combining genomic and health information., available online at <www.finnngen.fi>.

17 Palotie – Ripatti 2017, p. 772.

18 STM 2015:24, p. 33. For information of the genome centre, see also <www.genomikeskus.fi>.

19 For the aim, data content and purpose of the genomic data register, see the draft Genome Act, pp. 138–140. The recording obligation would mean that the register would contain genomic data on patients regardless of whether they have refused to the processing of their genomic data for non-therapeutic purposes, as well as on samples analysed in biobanks with active consent or old samples transferred to a biobank. The aim is to create a register of variations and reference data from the genomic data received or produced by the genome centre for health and medical care, disease prevention, and scientific research. The disclosure of data for these purposes would be provided for in the same act.

The upcoming new legislation would cover genetic testing, defined as all genetic laboratory tests that can be used to infer a person's health or genetic status, predict disease risk or side effects of treatment, diagnose or confirm disease or illness, or determine and assess treatment and its effects.²⁰ Health-related analyses for the purpose of scientific research would fall outside of the scope of the act. If research results from which conclusions on health status can be drawn are utilised in the treatment of individual patients or the results obtained are disclosed to the research subject, however, this would be considered an interpretation of the results that would be subject to the regulatory rules on genetic analyses included in the new act.²¹ The legislation has been under preparation for a long time and it is included controversial issues. At this stage, it is still difficult to predict what will happen to the upcoming proposal of legislation. In accordance with the current plan, the government proposal will be submitted to Parliament in March 2021.

5.2.2 Is Genomic Data More Special Than Other Health Data?

When considering whether consent to genomic research should be evaluated differently than other health or medical research, the key question is whether genomic information should be considered special when compared to other health data.²² Privacy and sensitivity of health data are the starting point for international regulation, such as the General Data Protection Regulation (Regulation (2016/679) of the European Parliament and of the Council on the protection of natural persons with regard to the processing of personal data and on the free movement of such data and repealing Directive 94/46/EC). Similarly, national legislation, such as the Data Protection Act (1050/2018) and legislation on patient data in health care,

20 Draft Genome Act, pp. 165–166. According to the draft for the act, a person's health status means a physiological or pathological function or condition. If genetic analysis makes it possible to draw conclusions about these, they fall within the scope of the act. The scope of the draft for the act includes predictive analyses as well as disease risk and disease prevention analyses. The draft for the act also covers genetic tests to diagnose and confirm a disease or illness. In addition, pharmacogenetic analyses, i.e. analyses that predict a drug response or reaction, fall within the definition of treatment within the meaning of the act.

21 Draft Genome Act, p. 166 (direct translation): If, for example, a scientific study shows that a particular marker measured in a blood sample may help in diagnosing a disease or illness before symptoms begin, such a result would not be considered a health-related genetic analysis or health service. Instead, confirming the finding with additional tests to support an individual diagnosis and interpreting the result or data to determine a health condition or disease or to determine treatment or preventive measures is considered a health-related genetic analysis and health service within the meaning of the draft for the act to which health services apply.

22 The term 'health data' is usually used as a synonym for patient data, although it can also be understood more broadly to include e.g. information on lifestyle and living conditions. In personalized medicine, it is natural to speak of health information precisely in its broadest sense.

considers that health data enjoy privacy protection, and, as a rule, may only be processed by a limited number of healthcare professionals involved in client or patient care. Genomic data is considered personal data and health data.²³

However, genomic data has also been given a special status to a certain extent. In particular, the United Nations Educational, Scientific and Cultural Organization (UNESCO) and the Council of Europe have been active players. UNESCO has adopted, *inter alia*, the Universal Declaration on Human Genome and Human Rights (1997) and the International Declaration on Human Genetic Data (2003). The Council of Europe Convention for the Protection of Human Rights and Human Dignity in the Field of Biology and Medicine (Finnish Treaty Series 23-24/2010, the Biomedicine Convention), with its additional protocols, is a key legal instrument in this field at the European level.²⁴ In addition, various recommendations have been issued within the Council of Europe.²⁵ These instruments establish principles that enable genetic testing, but also limit research and genetic interventions. The fundamental principles of the documents are respect for human dignity, self-determination, protection of privacy, and genetic nondiscrimination.

There is a broad consensus on the privacy and sensitivity of health data. It is also generally accepted that genomic data is part of health data. According to Launis, a *strong interpretation* of the special position of genomic data over other health data is based on the notion that genetic data is more accurate and predictable than other health data, that it also tells more about other individuals, mainly close relatives than other health data, and that it is also permanent, more fundamental and more personal. Under a *weak interpretation*, genetic data is exceptional in some uses or applications and requires special protection in certain situations, such as in the insurance business or recruitment. A weak interpretation

23 Article 4(13) of the General Data Protection Regulation: ‘genetic data’ means personal data relating to the inherited or acquired genetic characteristics of a natural person which give unique information about the physiology or the health of that natural person and which result, in particular, from an analysis of a biological sample from the natural person in question. See also recitals 34–35 and 51–54 in the preamble to the General Data Protection Regulation.

24 There are four additional protocols to the Biomedicine Convention: the Additional Protocol on the Prohibition of Cloning Human Beings (CETS 168), the Additional Protocol concerning Transplantation of Organs and Tissues of Human Origin (CETS 186), the Additional Protocol on Biomedical Research (CETS 195) and the Additional Protocol concerning Genetic Testing for Health Purposes (CETS 203). Finland has ratified the first two in connection with the ratification of the Biomedicine Convention. Finland has also signed the Additional Protocol concerning Genetic Testing for Health Purposes and its ratification is related to the preparation of the Genome Act. Finland has not yet signed the Additional Protocol on Medical Research.

25 See, *inter alia*, the Recommendation CM/Rec(2016)6 on research on biological materials of human origin, the Recommendation CM/Rec(2016)8 on the processing of personal health-related data for insurance purposes, including data resulting from genetic tests, and the Statement on genome editing technologies, 2015.

also highlights the fact that obtaining informed consent is more challenging in genetic research. Explaining and understanding the details of genetic research when giving consent is complex and obscure, so it is not always clear whether the conditions for informed consent are met as required.²⁶

On the other hand, issuing a special status for genomic data in relation to other health data has also been criticised. It is argued, *inter alia*, that genomic information determines only a part of human characteristics and that lifestyle and environmental factors, for example, have a major impact on health. By conventional diagnostic means, as many conclusions can be drawn from on a person's health status based on a person's symptoms and other external signs or behaviours as a genetic test would tell. Anyone familiar with the family's medical history may also determine the person's risk of becoming ill later. Disclosure of other health data can sometimes violate a person's privacy much more severely than genomic information falling into the wrong hands.²⁷ One view has been that genetic health data can only be considered as more fundamental than other health data in the subjective sense, resting on a person's own perceptions and beliefs.²⁸ The question is, then, how a person himself or herself views the health data, whether he or she considers the results of a genetic test to be more specific and reliable than other test results, and how he or she will act on the information he or she receives.

Regardless of which interpretation is chosen, to me, it seems justified that at least like other health data, genomic information is treated as sensitive personal data. The uncertainties, but also the possibilities, of genomic data go far into the future. Thus, especially from the perspective of the best interest of the child, it is justified to view genomic data as sensitive data. When a child is not yet in a position to influence the processing of his or her genome data, it would be necessary to consider it even as highly sensitive data. Parents' decisions in favour

26 Veikko Launis: *Geeniteknologia, arvot ja vastuu*. Gaudeamus 2003, pp. 58–61. See also Kirsi Vähäkangas – Esko Länsimies: *Suostumuskäytäntö ja henkilöllisyyden suoja geenipankkitutkimuksessa*, *Suomen Lääkärilehti* 14/2004 vsk 59, pp. 1552–1555; Meincke 2001, pp. 22–24.

27 On the conversation, see e.g. Aarno Palotie – Mari Kaunisto – Helena Kääriäinen – Markus Perola – Kimmo Pitkänen – Samuli Ripatti – Sirpa Soini – Elisabeth Widén: *Genomitiedon arkaluonteisuus on tiukassa elävä myytti*. *Lääkärilehti* 15/2018 vsk 73, pp. 916–917 and response Lasse Lehtonen – Heikki Saxén: *Geenitieto on salassapidettävää terveydentilätietoa*. *Lääkärilehti* 17/2018 vsk, 73 pp. 1044–1045.

28 Veikko Launis: *Ihmisarvo*. Vastapaino, Tampere 2018, pp. 276–284. Launis discusses the conceptual question of whether it is philosophically meaningful to consider genetic health data to be more fundamental to other individual health data in the sense that it embodies an individual's permanent and unchanging nature or identity. He has also stated that almost any health data can, in a subjective sense, be a feature that defines a person's essence or identity, respectively (Launis 2003, p. 60).

of the child in early childhood should not jeopardize the best interests of the child now or in the future.

5.3 Consent Given on Behalf of a Child

5.3.1 Informed Consent as a Prerequisite for Genomic Research

Self-determination and the right to the integrity of the individual are fundamental principles of medical ethics and medical law and biolaw. It follows from these principles that treatment procedures and medical research will generally require the consent of the patient or research subject.²⁹ The rapid development of biomedicine is a constant challenge to ethical and legal thinking and thus requires a review of legislation in a changing regulatory environment. This also applies to the evaluation of regulation around consent, for example in the context of genome research.

The basic principles of informed consent are permanent. Legally valid consent requires that the consenting party has the necessary capacity to make the decision, has sufficient knowledge to do so, has the opportunity to consider the matter before making his or her decision, and voluntarily makes the decision without coercion or pressure. It must be also possible to withdraw consent. The principles apply equally to children when they are able to give their consent and to custodians when they give consent on behalf of the child.³⁰

Giving informed consent to genome testing requires an understanding of the rather complex and difficult issues involved, including heredity, and therefore high

29 The doctrine of informed consent which embodies the autonomy and the right to the integrity of the patient or subject has evolved over the decades as a dialogue between medical ethics and medical and biolaw since the 1940s. The starting point for regulation in the field of biolaw is considered to be the adoption of the Nuremberg code in 1947. For an outlook on the development of the doctrine of informed consent, see e.g. Irma Pahlman: *Potilaan itsemäärämis-oikeus*. 2. ed. Edita, Helsinki 2006, pp. 121–140.

30 On the child's right to self-determination, see Kirsi Pollari: *Lapsipotilaan päätöksentekokyky ja sen arviointi*. *Acta Universitatis Lapponiensis* 387, 2019, pp. 145–171. On the consent of the child to health care research, see e.g. Priscilla Alderson: *Children's Consent and 'Assent' to Healthcare Research*, pp. 174–189 in Michael Freeman (ed.): *Law and Childhood Studies*, Oxford University Press 2012; Liisa Nieminen: *Lapsi tutkimuskohteena: Kuka päättää lapsen osallistumisesta tutkimukseen?* *Lakimies* 2/2009 pp. 226–253. On the consent of the child and biobanks, see Liisa Nieminen: *Biopankkitoiminta lasten terveyden ja hyvinvoinnin edistäjänä: oikeudellinen tarkastelu*, pp. 58–85 in Niina Rutanen – Kaisa Vehkalahti (ed.): *Tutkimuseettisistä sääntelystä elettyyn kohtaamiseen. Lasten ja nuorten tutkimuksen etiikka II. Nuorisotutkimusverkosto/ Nuorisotutkimusseura* 2019.

requirements are placed on pre-consent information.³¹ When a custodian gives consent on behalf of a child, he or she must consider his or her grounds for the consent specifically from the perspective of the child. It is understandable that the decision of a custodian may also be influenced by his or her own personal wishes and views, but that consent should nevertheless be primarily in the best interests of the child. The difficulty might be also that there is still a great deal of uncertainty and unawareness about genome testing. So, is it even possible at all to provide the necessary information needed for informed consent? In this context, specific questions arise, such as how to deal with secondary research findings that may emerge in the research that will only be relevant much later and to whom the results should be shared. Or how to prepare for the fact that something significant to the health of the child can be interpreted from the once analysed genomic data later on? If the testing reveals, now or later, that the child is at risk of developing a serious disease at some point in his or her life, what impact will that knowledge have on the child's future life? Knowledge can influence how parents provide care for the child and whether, for example, they start to unnecessarily protect the child, leading to a restriction of the child's normal life. It also affects the child's right not to be aware of the disease risk. The genetic risk factors that have emerged from genomic testing may be of wider significance, at least to the parents themselves, to the siblings of the child tested, and to any possible future siblings.³²

5.3.2 International Regulation on Consent Given on Behalf of the Child

In all cases where the rights of the child are concerned, the regulation must be in conformity with the United Nations Convention on the Rights of the Child (Finnish Treaty Series 59-60/1991).³³ The Convention on the Rights of the Child does not

31 The custodian giving consent on behalf of the child should also, e.g. to some extent understand and consider the fact that in biobanking, samples and related information may be disclosed not only to research but also to development and innovation activities.

32 About the challenges, see e.g. Kenneth Boyd: The impossibility of informed consent? *Journal of Medical Ethics* 2015;41:44–47. Especially in relation to genomic tests in children Katherine Burke – Angus Clarke: The challenge of consent in clinical genome-wide testing. *Archives of Disease in Childhood* 2016;101:1048–1052.

33 The importance of the human right treaties to health care regulation generally, see e.g. Lisa Forman – Sivan Bomze: International Human Rights Law and the Right to Health: An Overview of Legal Standards and Accountability Mechanisms, pp. 33–71 in Gunilla Backman (ed.): *The Right to Health. Theory and practice*. Studentlitteratur Ab. Lund 2012; Birgit Toebes: Introduction: Health and Human Rights in Europe, pp. 1–19 in Birgit Toebes – Mette Hartlev – Aart Hendriks – Janne Rothmar Herrman (ed.): *Health and Human Rights in Europe*. Intersentia 2011.

contain an explicit article on consent to health interventions or medical research, but confirms the right of the child to influence decision-making in relation to himself or herself in accordance with his or her age and maturity (article 12)³⁴ and that the custodians have the right and duty to protect the child and to act in the best interests of the child (articles 3(2) and 18). Every child has the inherent right to life and to the survival and development to the maximum extent possible (article 6), and to the closely related right to the enjoyment of the highest attainable standard of health (article 24).³⁵ The healthy development of a child and the best health care available to him or her can be promoted, for example, by allowing children to participate in medical research. Any research, however, must be safe and in the best interests of the child.³⁶ It should also be borne in mind that a child, like adults, has the right to privacy (article 16) and to physical and mental integrity (article 19).

In particular, the Charter of Fundamental Rights of the European Union requires compliance with, *inter alia*, the requirement for the informed consent of the person concerned, obtained in accordance with the procedures laid down by law (Article 3(2)(a)).³⁷ In addition, numerous international agreements and recommendations on biomedicine provide, in principle, for the required consent in a very uniform manner and in line with the requirements for informed consent

34 Opinions of the United Nations Committee on the Rights of the Child on the involvement of the child in health in General Comment No. 12 on the right of the child to be heard (CRC/C/GC/12), paras. 98–104. The Committee emphasises the provision of information for children in connection with treatment and participation in research. The Committee also recalls that the child has the right to counselling, which does not equal the right to medical consent and should therefore not be subject to any age limit.

35 On the interpretation of articles 6 and 24, see Noam Peleg: *The Child's Right to Development*. Cambridge University Press 2019, pp. 120–126.

36 The United Nations Committee on the Rights of the Child emphasises the responsibility of institutions, researchers, private companies, and others involved in research on children to respect the principles and provisions of the Convention and the International Ethical Guidelines for Biomedical Research Involving Human Subjects. The Committee also points out that, in research, the best interests of the child must always prevail over the general or scientific progress of the community. See General Comment No. 15 (2013) on the right of the child to the enjoyment of the highest attainable standard of health (art. 24 (CRC/C/GC/15), para. 85. For more details on the best interests of the child, see General Comment No. 14 (2013) on the right of the child to have his or her best interests taken as a primary consideration (art. 3, para. 1) (CRC/C/GC/14). See also General Comment No. 3 on HIV/AIDS and the rights of the child (CRC/GC/2003/3), para. 29.

37 The Charter also enshrines the child's right to protection and care, as well as the right to express his or her views and to have them taken into account in accordance with age and maturity (Article 24). Everyone has the right of access to preventive health care and the right to benefit from medical treatment under the conditions established by national laws and practices (Article 35).

already stated above.³⁸ As a general rule, in the case of a small child, consent is given by the parent or custodian until the child is able to give his or her consent. For example, the Biomedicine Convention (Article 6) and its Additional Protocol on Genetic Testing (Article 12) require that consent to a health measure or research be given by the legal representative of the child or by an authority or a person or body provided for by law. The Explanatory Report to the Biomedicine Convention uses the plural form of ‘parents who have custody of the minor’, but does not otherwise state whether the consent of both parents is always or in some cases required or only the consent of the other parent is sometimes sufficient.³⁹

In addition to these general consent requirements that apply to genomic research, international standards restrict the child’s participation in research in various ways. Of course, limitations must be taken into account when assessing consent on behalf of the child. Under the Biomedicine Convention, a child who is unable to give his or her consent may participate in research if the results have the potential to produce real and direct benefit to his or her health and the child does not object (Article 17). Where a study is not expected to be of immediate benefit to the subject, it may only be undertaken if the research entails only minimal risk and burden for the individual and the research has the aim of contributing to the ultimate attainment of results capable of conferring benefit to the person concerned or to other persons in the same age category or afflicted with the same disease or disorder or having the same condition. With regard to genomic research, it should also be noted that under the Biomedicine Convention, predictive genetic testing may only be carried out for health purposes or health-related scientific research and must be accompanied by appropriate genetic counselling (Article 12). In the case of minors, the provision is further specified in the Additional Protocol concerning Genetic Testing for Health Purposes, which requires that a genetic test may only be carried out for the child’s direct benefit. As a general rule, testing of a child should be withheld until the child can give his or her own consent. However, if abstaining from testing has a negative effect on the health or well-being of the child, testing is possible earlier. This includes, for example, a situation where preventive measures may be taken in the event of a disease that

38 Also pursuant to Article 7 of the General Data Protection Regulation, when the processing of personal data is based on the consent of the data subject, it shall be explicit, and the controller must be able to prove its existence. It must be also possible to withdraw consent. See also recital 32 in the preamble to the General Data Protection Regulation. The draft Genome Act (pp. 63–87) contains a fairly comprehensive summary of international regulatory developments as well as foreign and EU legislation.

39 Explanatory Report to the Convention for the protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine (CETS 164), para. 45.

may occur before the child is able to decide on testing.⁴⁰ Finland has not yet been ratified the Additional Protocol, but has already signed it in 2008. The Additional Protocol does not apply to genetic tests carried out for research purposes or to tests carried out on the human embryo or foetus.

International regulation of consent also leaves room for national discretion which has also been applied.⁴¹ For example, regulations and practices regarding the consent of a child to clinical trials vary considerably within the European Economic Area. The age at which a child can give his or her consent ranges from 14 to 18, and in some countries, there is no specific age limit at all. There are also differences in who can give consent on behalf of the child: one parent, both parents, or the legal custodian.⁴²

5.3.3 National Legislation on Consent Given on Behalf of the Child

National regulations follow the principles of international regulation. The basis for this regulation is the Constitution of Finland (731/1999), which guarantees everyone the right to privacy and personal integrity (section 7). This is also considered to guarantee the individual's right to self-determination.⁴³ Children must be treated as equal individuals and have the right to influence matters concerning themselves to a degree corresponding to their level of development (section 6(3)). The responsibility of parents for the protection and well-being of children is, in turn, expressed as the responsibility of the public authorities to support the family and other persons responsible for the care of the child in this task (section 19(3)).

40 Explanatory Report to the Additional Protocol to the Convention on Human Rights and Biomedicine concerning Genetic Testing for Health Purposes CETS 203, para. 91. Testing may be also allowed, for example, on the grounds that a predictive test performed without delay and producing a negative result might spare the subject highly invasive regular examinations (para. 92).

41 E.g., the Explanatory Report for the Biomedicine Convention (CETS 164, para. 42) states the following: 'Since the purpose of the Convention is not to introduce a single system for the whole of Europe but to protect persons who are not able to give their consent, the reference in the text to domestic law seems necessary: it is for domestic law in each country to determine, in its own way, whether or not persons are capable of consenting to an intervention and taking account of the need to deprive persons of their capacity for autonomy only where it is necessary in their best interests'.

42 See Pirkko Lepola – Allison Needham – Jo Mendum – Peter Sallabnak – David Neubauer – Saskia de Wildt: Informed consent for paediatric clinical trials in Europe. *Archives of Disease in Childhood (ADC)* 2016;101:1017–1025.

43 Government proposal 309/1993 on amending the fundamental rights provisions of the Constitution, p. 46.

National legislation protects the specificity of genetic data in many ways, but as it has already been shown, in Finland, specific legislation for gene tests or genomic research is yet to exist.⁴⁴ Currently, genomic research and consent to research will thus rely on legislation relating to health and medical research. Patient status is regulated by the Act on the Status and Rights of Patients (785/1992, the Patient Act), which applies as a general law when it comes to the organization of health and medical care (section 1). In the case of a minor, the starting point is that the child is cared for in agreement with him or her if the child is able to decide on his or her age and level of development; otherwise, the care is decided in agreement with the custodian or other legal representative (section 7).⁴⁵ When a child participates in a medical examination, the consent provisions can be found in the Medical Research Act (488/1999, the Research Act). The Act of the Medical Use of Human Organs and Tissues (101/2001, the Human Tissue Act) regulates the collection of specimens taken for therapeutic or diagnostic purposes for medical or research purposes. The Biobank Act (688/2012) applies when a sample is given for and stored in a biobank.⁴⁶

The above-mentioned legal acts follow the principle of the Patient Act on the right of the custodian or other legal representative to give consent on behalf of the child. The Research Act also provides for more detailed conditions for the participation of a child in research (section 6). A minor may only be examined if the same scientific results cannot be obtained by other subjects and if the research presents only a minor risk of injury or burden to the minor. In addition, it is expected that the research is expected to have a direct benefit to his or her health or a particular benefit to the same age group or state of health. The child's own consent is bound to reaching the age of 15 and to the child's maturity and

44 Chapter 22 of the Criminal Code of Finland (373/2009) contains penal provisions for violation of a foetus, embryo, and genetic inheritance. In addition, the prohibition of genetic modification is laid down in the Act on Assisted Fertility Treatments (1237/2006, sections 4 and 5). Section 15 of the Medical Research Act stipulates that Research on embryos and gametes for the purpose of developing procedures for modifying hereditary properties shall be prohibited, unless the research is for the purpose of curing or preventing a serious hereditary disease. Under the Act on the Protection of Privacy in Working Life (759/2004, section 15), the employer is not permitted to require the employee to take part in genetic testing during recruitment or during the employment relationship, and has no right to know whether or not the employee has ever taken part in such testing.

45 Consent is usually given by the child's parents. However, the parent/custodian does not have the right to refuse treatment that is necessary to prevent a danger to the child's life or health. The right of a parent to decide on the care of his or her child is also limited by the fact that the parent does not have the right to demand any treatment, but the treatment must always be medically acceptable.

46 The Biobank Act has allowed the collection of children's samples from the outset, but only now have some biobanks started collecting children's samples. It is not possible to retrieve genomic data from all samples stored in the biobank.

understanding of the research or the research procedure in question (section 8). A further condition is that the research is expected to directly benefit the child. In the Human Tissue Act, the child's own consent is tied to his or her ability to understand the situation (section 7). Under section 12(3) of the Biobank Act, the custodian gives consent on behalf of the minor. In addition, if a minor is able to understand the significance and nature of biobank research, given his or her age and level of development, his or her written consent is also required.⁴⁷

When evaluating consent regulation, it is important to consider the difference between medical research and biobank research. In medical research, consent is given to a particular pre-planned trial and its primary purpose is to protect the subject's autonomy and personal integrity. Consent covers sampling and use of the sample for research. The subject shall receive the necessary information about the trial before consent is given. In biobank research where, at the time of consent or at the time of sampling, not all the studies in which the sample or the analysed data is intended to be used are known. Under the current Biobank Act, only one 'broad consent' is given. With the consent of the subject, the subject authorises the storage of the sample in a biobank and the consent will subsequently cover the processing of the samples and other sensitive personal data in research activities. According to the Government proposal for the Biobank Act, informed consent requires that the person giving consent must be provided with sufficient information of the nature of biobank research, including the use of any genetic and other data. Consent is based on the knowledge of the purpose of the biobank

47 A person may also later refuse the processing samples and data stored in the biobank. This also applies to the so-called old samples that have been transferred to the biobank by operation of law. The rights contained in the Biobank Act to revoke or amend the consent given and to prohibit or restrict the use of old samples have been granted only to the data subject. However, consent and withdrawal of consent have been considered as comparable legal acts. Thus, the custodian would have the right to withdraw the consent and apparently also to prohibit or restrict the use of the child's samples under the same conditions as he has the right to give consent on behalf of the child. See e.g. the decision of the Parliamentary Ombudsman 'Lääketieteellisessä tutkimuksessa voi käsitellä henkilötietoja vain suostumuksensa perusteella', diary number 3107/4/12, 19 December 2013. Biobanks apparently do not yet have the capacity to handle limited consents or prohibitions (e.g. Kimmo Kääriä – Sirpa Soini – Suvi Kouki – Jari Suhonen: Biopankkisuostumusten hallinta Kanta-palvelujen avulla, toiminnallinen määrittely. Terveysten ja hyvinvoinnin laitos - Ohjaus 1/2016, p. 10). See also a summary of the guidelines for the consent of minors in biobanks in Nieminen 2019.

and the nature of the operations of the biobank, not on individual trials for which samples may be used in the future.⁴⁸

It is noteworthy that the above-mentioned legal acts do not require the consent of the child to be in the best interests of the child. In this context, the requirement of the Convention on the Rights of the Child to give priority to the best interests of the child in all decisions concerning the child implies that consent for genomic research on behalf of the child should also be in the best interests of the child. The assessment of the best interests of the child entails, *inter alia*, that the custodian should consider the long-term effects of the decision on the child.⁴⁹ This is a consequence of the persistent nature of genomic information, but also of the fact that child health decisions often have a long-lasting effect, even up to adulthood. This is particularly important when it comes to participating in biobank research, where samples and data are stored for a long period of time and when consent is given it is not known for what they will be used in the future. With the consent of a young child, research can be carried out even before the child is able to understand the meaning of the matter and to influence decision-making concerning himself or herself. Biobank research may reveal findings that are not relevant until after the child has grown up. It is therefore a question of protecting the privacy of the child and of the right of the child to know and not to know during childhood, but also as he or she grows up. Of course, it is also a question of the extent to which parents are entitled to know about the findings of the child's samples.⁵⁰

In the next section, I will discuss issues related to consent on behalf of the child, which in themselves concern other treatment or research, but which in my view should be considered separately for genomic research. They relate to the custodian's consent to consent, the requirement in the Research Act and

48 Government proposal 86/2011 for the Biobank Act and amending the Act on the Medical Use of Human Organs, Tissues and Cells and the Act on the Status and Rights of the Patient, p. 50. See also Matteo Macilotti: Reshaping Informed Consent in the Biobanking context. *European Journal of Health Law* 19 (2012) pp. 271–288. The content of the consent, however, may remain unclear to the consenting person, see Yle Uutiset 8 December 2019 'Suomalaiset antaneet yli 400 000 suostumusta biopankkeihin – Ylen kysely vahvistaa, että monelle on epäselvää, mihin he ovat suostuneet', available online at <<https://yle.fi/uutiset/3-11103007>>.

49 The time dimension of the assessment of the best interests of the child has been considered, among other things, from the perspective of child protection. Although the decision on custody is based on an assessment of the current situation, child protection is in fact a matter of making a prediction of how the authority's decisions will in reality affect the best interests of the child now and in the future. See e.g. Tapio Rätty: *Lastensuojelulaki*. Edita, Helsinki 2015, p. 13.

50 See e.g. Josephine Johnston – Eric Juengst: Are Parents Really Obligated to Learn as Much as Possible about Their Children's Genomes? *Hastings Center Report* July 2018, Vol. 48, pp. 14–15. Parents may have the need to find out everything possible about the child's health, which may be due, for example, to the fact that they want to prepare for the child's possible special needs. On the other hand, they may even feel obligated to consent to any medical procedure that could benefit the child.

the Biobank Act that the consent given should be in accordance with the child's presumed will, and how the consent on behalf of the child affects the child's privacy and the right to know and be ignorant. It should be noted that a person other than the child's biological parent may be the custodian of the child. However, in the following review, I will not address this point of view, but assume that the custodian is the biological parent of the child. Also, I will not address the challenges that may arise if consent is separated from one of the parents.

5.3.4 Challenges Related to Giving Consent on Behalf of the Child

5.3.4.1 *Who Gives Consent: A Parent Alone or Both Parents Together?*

As a general rule, parents or other legal custodians of a child have the right to decide on behalf of the child until the child is sufficiently mature in age and level of development to decide for themselves or once the child reaches the age of 18. The Act on Child Custody and Right of Access (361/1983, the Child Custody Act) contains the basic provisions governing the legal relationship between the child and the custodian. The purpose of child custody is to ensure the well-being and balanced development of the child in accordance with the child's individual needs and wishes (section 1). Custody is primarily the responsibility of the child's parents or other legal custodians who must act in accordance with section 1. The custodians have the right to decide on the care, upbringing, residence and other personal matters of the child (section 4) and the custodian represents the child in his or her personal affairs unless otherwise provided by law. Parents cannot, therefore, make decisions on behalf of the child for any given reason.⁵¹

Unless otherwise provided or prescribed, the custodians of a child are jointly responsible for the duties inherent in custody and make the decisions concerning the child together (section 5 of the Child Custody Act).⁵² By way of exception to this general rule, if one of the parents cannot participate in the decision-making concerning the child due to travel, illness or any other reason, and a delay in the decision-making would be detrimental, the consent of his or her is not necessary.

51 See e.g. Urpo Kangas: *Perhe- ja jäämistöoikeuden perusteet*. Alma Talent 2013, p. 98. Kangas states that all the decisions relating to the child's care are closely connected to the child's personal life and life choices.

52 The provisions refer to the right of the court to issue orders on the division of responsibilities between custodians (9.4). Parents can also agree on the division of responsibilities between custodians (section 7, revised on 1 December 2019). See Government proposal 88/2018 on the Act amending the Act on Child Custody and Right of Access and other related acts, pp. 44–45.

The right of the custodian alone to decide on the child in the event of the other custodian being prevented from participating in the decision-making process applies only to minor matters. However, if the child's best interests do not seem to require otherwise, on the matter of great significance for the future of the child parents may only make a joint decision. According to the legislative documents, a matter of major importance to the future of the child is, *inter alia*, the decision on the child's medical care, such as surgery or medical treatment in the event of a serious disease. In such cases, the consent of both custodians is always required. The fact that the other custodian is not present or that failure to perform the treatment measure could cause harm would in principle not be sufficient reason to deviate from the obligation to cooperate. However, the best interests of the child must always be considered. Thus, for example, in situations where the health or life of the child is at risk or the health of the child would be endangered if medical procedures were not performed, the consent of a single parent may be sufficient.⁵³ From the point of view of the Child Custody Act, it is clear that the obligation to cooperate is intended to be quite strong and should only be derogated from for specific reasons.

In practice, health care is conducted with the consent of a single custodian in usual, routine situations and minor interventions.⁵⁴ In these situations, it is often possible to assume the existence of an authorisation from another custodian. For example, if another custodian regularly brings the child alone to the clinic or to the doctor's office, the professional may assume that an authorisation exists.⁵⁵ It is somewhat problematic that the issue remains to be solved in individual

53 Government proposal 224/1982 for the Act on Child Custody and Right of Access and amending the Guardianship Act and other related acts, p. 14. The exceptions to the joint responsibility provided in the Child Custody Act exist mainly due to practical reasons. As an additional condition, the 'harm caused by delay' defined in section 5 of the Child Custody Act may be something other than harm caused to the child alone. The preparatory works did not, however, specify what is meant by this or to whom the inconvenience to others could only justify the decision of the custodian alone.

54 Kurki-Suonio, Kirsi: Kuka saa päättää lapsen asioista? *Lakimies* 7–8/2010 pp. 1183–1203, and for situations in health care in particular pp. 1189–1192. See also Salla Lötjönen: The Regulation of Neonatal Research in Finland, pp. 123–135 in Su Mason – Christopher Megone (eds.): *European Neonatal Research: Consent, Ethics Committees and Law*. Ashgate, Aldershot 2001, p. 123.

55 This can be a status-based, situational or authorization-based authorization. In fact, for each procedure performed at the reception, the professional has to assess separately whether only one of the custodians can decide on it alone. On the division of parental responsibility, see Hakalehto, Suianna: *Lapsioikeuden perusteet*. Alma Talent 2018, pp. 187–189 and in health care in particular, Pollari 2019, pp. 95–98.

situations, although accepted practices per se have been formed.⁵⁶ In health care, cooperation between parents and health care professionals is, as a rule, a day-to-day activity. However, there are also challenging situations the resolution of which could be facilitated with clear regulation.

For example, the Supreme Court of Finland has stated that non-medical circumcision of boys must be regarded as a significant matter within the meaning of Article 5(2) of the Child Custody Act, which can be decided only jointly by the custodians.⁵⁷ The Parliamentary Ombudsman, for his part, has taken a stand on the joint responsibility of custodians in his decisions concerning both medical research and vaccination. The Ombudsman is of the opinion that, as a rule, the participation of a child in medical research can only be decided by both parents together. On the other hand, the consent of one parent has been considered sufficient for routine healthcare measures. The consent of one parent may also be considered sufficient for medical research if the required intervention is minor, such as blood sampling.⁵⁸ In the decisions on swine flu vaccination and HPV vaccination, the Ombudsman, referring to the provisions of the Child Custody Act on the obligation of custody to cooperate, states that vaccination requires, in principle, the consent of both custodians. The above-mentioned vaccinations are not routine procedures for which only the consent of one of the custodians would be sufficient.⁵⁹

Therefore, even in the light of the above-mentioned solutions, the joint responsibility of the custodians can be considered as the general rule. In addition, it should be noted that the Child Custody Act requires that derogations be provided

56 In the view of the Ministry of Social Affairs and Health, the consent of one parent is sufficient for vaccinations under the national childhood vaccination program, but confirmation of refusal to be vaccinated is required from both custodians (decision of the Parliamentary Ombudsman of 17 June 2011, diary number 4640/4/409, paragraph 3.3.). See also Merike Helander: *Rokottaako vai ei?* pp. 59–95 in Suvianne Hakalehto – Irma Pahlman (eds.): *Lapsen oikeudet terveydenhuollossa*. Kauppakamari 2018, pp. 84–88.

57 KKO 2016:25, paragraphs 21–28. The Supreme Court also ruled that the custodians have no right to even collectively decide on measures against the child which, objectively assessed, would violate the child's fundamental rights and would be contrary to his or her best interests.

58 Decision of the Parliamentary Ombudsman 25 October 2006, diary number 1016/4/04, 'Menettely lääketieteellisessä tutkimuksessa', paragraph 3.4.3. In his decision, the Ombudsman referred to both section 5 of the Child Custody Act and the final report of the ETENE working group on research on children.

59 Decision of the Parliamentary Ombudsman of 17 June 2011, diary number 4640/4/09, 'Parents' permission to vaccinate a child against swine flu' and decision of the Parliamentary Ombudsman 11 June 2015, diary number 5294/2/13, 'Implementation of the HPV vaccination campaign'.

or prescribed separately.⁶⁰ However, at least for the time being, the Patient Act, the Research Act or the Biobank Act have not done so.⁶¹ Nor have these acts or their working documents specifically addressed the issue of genome research. A provision is required in the forthcoming Genome Act requiring the consent of both custodians to carry out high-risk genetic analyses. Genome-wide analyses are considered high-risk analyses in the legislative proposal.⁶² In contrast, for low-risk, routine analyses, only the consent of the other custodian would be enough. This is justified by the fact that the threshold for carrying out health-related genetic tests should not be set too high. The Ombudsman's view has been stricter: the obligation of custody cooperation should not be tied to the risk classification of genetic tests. Cooperation of the custodians should therefore in principle be required for all genetic analyses.⁶³

The letter of reference to minors for biobanks recognizes the need for cooperation, at least in some situations. This is justified, *inter alia*, by the special status of children as data subjects.⁶⁴ The letter advises that, depending on the circumstances, it might be reasonable to seek the consent of both custodians, which is supported by the fact that biobank research may target genetic data that may concern both parents. Particularly in the case of joint custody, it would be advisable to seek the opinion of both custodians. In case of disagreement between custodians, refusal to seek consent should be considered. Ultimately, this should be decided on a case-by-case basis in the best interests of the child. Genome

60 The joint responsibility of custodians is provided, for example, in section 3 of the Freedom of Religion Act (453/2003), under which the religion of a child is decided jointly by the custodians. In case law, the Supreme Administrative Court, for example, concluded in its decision KHO:2004:99 that if the another custodian objects, the other custodian alone cannot validly declare a non-religious child to religious education with reference to the relevant provision of the Freedom of Religion Act and section 5 of the Child Custody Act.

61 Section 7 of the Patient Act does not take a position on joint responsibility or on how to proceed if the custodians disagree. Nor do the drafting documents specify the co-operation of custodians, but merely refer only to the Child Custody Act (Government proposal 185/1991 on the Act on the Status and Rights of the Patient, p. 17). The Government proposal for the Biobank Act (Government proposal 86/2011, pp. 49–50), on the other hand, states that giving consent for the storage of a sample in a biobank does not include a decision that is significant for the minor, so the consent of one custodian would be sufficient. The definition for a significant decision is not provided in the Government proposal. The reform of the Biobank Act also does not require the consent of both custodians, but it is especially recommended in situations of joint custody (draft Biobank Act, p. 42).

62 Draft Genome Act, p. 223.

63 Opinion of the Ombudsman on the draft Genome Act of 12 July 2019, EOAK/2777/2019.

64 The National Supervisory Authority for Welfare and Health letter of reference to biobanks on the basics of processing samples and data from minors of 27 April 2016, pp. 2–3. Today, the responsible authority for the guidance and supervision of biobanking and maintains a public register of biobanks in order to perform its tasks is Finnish Medicines Agency Fimea. See more at <<https://www.fimea.fi/valvonta/biopankit>>.

research also reveals information about other close relatives of the subject. In addition to the fact that consenting to research may easily become challenging, if custodians disagree or the consent of only one parent has been obtained, it can have an impact on how information about the research results can be given to any relatives of the unknowing parent.⁶⁵

In the legislative reform of the Biobank Act, specific provisions on biobank samples in newborns are proposed.⁶⁶ Newborn sampling would be restricted by the ban on taking extra samples for biobanks. In addition, the need to comment on the point at which biobank consent could be sought has been identified. For the purpose of participating in a medical study, consent for the collection of umbilical cord blood samples has been sought during pregnancy, as consent required during childbirth has been considered ethically questionable. If this were to be the case for biobank samples, it would be clear that prior consent on behalf of the newborn would be provided for separately. In my view, there is also the specific question of whether a pregnant woman can give her consent alone or whether the consent of both biological parents is required. The general rule in other legislation is that decision-making during pregnancy is restricted to the mother's right. However, if at any point biobank samples are used to determine a child's genomic information, it is possible that it will also provide information relevant to the health of the child's father or close relatives. Thus, it would be important that consent be sought from both parents of the child.

While it is not possible and appropriate to define all situations that arise in health care and medical research, it would be much clearer for the joint responsibility of custodians that the law would provide guidelines on how to proceed in the event of disagreement between the custodians. The Parliamentary Ombudsman has also noted a lack of legislation in this respect in at least two of its decisions on child vaccination. In the Ombudsman's view, the Patient Act should be clarified, with reference to the legislation regarding adults with disabilities. In

65 Probably the most ethically challenging situations are those in which one parent or other relatives are unknowingly at risk and the parent who consented on behalf of the child being examined is unable or unwilling to pass the information on to the other parent or relatives. Although the right to data protection must be respected, the right of another person to know, for example, about a life-threatening illness, could justifiably be considered more important (Lääkärin etiikka 2013, p. 87).

66 This is justified by the fact that the collection of samples from newborns raises strong ethical issues, which means that the provisions of the current Biobank Act are not sufficient to ensure the legal protection of newborns. However, these issues are not specified. The samples collected in the biobank could in practice be umbilical cord blood samples as well as heel samples. An umbilical cord blood sample would be obtained from a non-invasive blood sample taken after delivery after umbilical cord dissection and a heel sample from the sampling of newborns for statutory metabolic diseases (Draft Biobank Act, p. 45).

the case of adults with disabilities, when their representatives disagree, the matter must be resolved in a way that can be considered to be in the patient's personal interest.⁶⁷ In the case of a minor, a similar requirement could be written in the form 'in the best interests of the child'. In addition, at least the detailed rationale of the act should guide how the best interests of the child should be assessed.⁶⁸

5.3.4.2 *Presumed Will or the Best Interest of the Child*

The Research Act and the Biobank Act provide that consent on behalf of a child must be in accordance with the child's presumed will. This provision (section 15(3)) was added to the Research Act in connection with the national implementation of the European Parliament and Council Directive on clinical trials on medicinal products (2001/20/EC) in 2004. No further justification for the addition was provided back then.⁶⁹ In the preparatory works of the Biobank Act, the presumed will of a minor is linked to the determination of the child's opinion: the person giving consent on behalf of the child should as far as possible clarify the child's opinion and act accordingly. The consent would then be in accordance with the child's presumed will.⁷⁰ A similar concept of presumed will is not expressed, for example, in the Biomedicine Convention. Instead, it only requires that the views of the child be taken into account according to age and maturity.

The above-mentioned regulation is problematic for two reasons. First, the concept of 'presumed will' is used in a way that does not take into account children of different ages. The newborn or young child who has not yet been able to form his or her views on the research or any research procedures probably has not been able to express anything that another person could base an assumption on in terms of his or her will. In these situations, it may not even be possible to think that the child's opposition might be taken into account. Usually, the concept of 'presumed will' is used to regulate health care, for example in situations where the patient

67 Decision of the Parliamentary Ombudsman of 17 June 2011, diary number 4640/4/409, and decision of the Parliamentary Ombudsman of 11 June 2015, diary number 5249/2/13.

68 On factors to be taken into account in assessing the best interests of the child, see CRC/C/GC/14, in particular paras. 46–99.

69 Government proposal 20/2004 on amending the Medical Research Act and the Medicines Act. The Directive (Article 4) states the following: '... consent must represent the minor's presumed will'. Regulation 536/2014/EU of the European Parliament and of the Council on clinical trials on medicinal products no longer mentions the concept of presumed will. The amendments to the law related to the implementation of the decree are to be submitted to Parliament at the end of 2019. According to the Government proposal for the Act on Clinical Trials and certain related laws (11 April 2018), the presumed will requirement is no longer proposed. The rationale is that the legislation explicitly obliges the child to be consulted and involved in the decision-making process, even if he or she is not yet able to give his or her consent.

70 Government proposal 86/2011, p. 49.

cannot give consent, but the initiation of treatment cannot be postponed. This may be an unconscious or demented patient whose decision is made by their legal representative and must be in accordance with the person's presumed will. Thus, the concept of 'presumed will' generally refers to the past, a person's previously expressed view of the present matter. The intention may have been expressed explicitly in writing or communicated verbally to another person.⁷¹ The person's view can be ascertained from the family members or other close relatives.

Another problem with the 'presumed will' construction is that it does not oblige the child's best interests to be taken fully into account but is based on the (presumed) opinion of the child, as expressed e.g. in the preparatory documents to the Biobank Act.⁷² Section 7 of the Patient Act provides for consent on behalf of a minor patient but does not stipulate that treatment should be in the best interests of the child, who is not self-determined. Instead, the previously expressed will of the disabled adult must be taken into account when consent is given and, if this is not clear, the patient must be treated in a way that can be considered to be in his or her personal interest (section 6(3)).⁷³ The presumed will for a disabled adult has been discussed, for example, in an emergency care setting. The stable and healthy will previously expressed by an adult supersedes objective criteria for care. In the case of a child, his or her previously expressed will, which differs from objective criteria of care, could be followed only exceptionally. This is true even if it is a child who is mature enough to consent. The reason for this is that the child with a shorter life experience than adults may not be able to understand the consequences of his or her decision.⁷⁴

Instead of following the doctrine of presumed will in the Research Act and the Biobank Act, it would be more reasonable to require consent in the best interest

71 Sections 6(2) and 6(3) of the Patient Act. The concept of presumed will can also be used in a situation where the person is dead (sections 9(1) and 12(2) of the Human Tissue Act). According to the view of The Committee on Constitutional Affairs, the presumption of a person's consent to the removal of his or her organs and tissues after his or her death cannot be based on how other people, for example, according to opinion polls, react to the matter. Instead, efforts should be made to clear out the previously expressed opinion of the deceased (Statement of the Committee on Constitutional Affairs 24/2010 – Government proposal 276/2009, p. 3). In the context of a gene bank discussion, it has been proposed to use, instead of or in addition to informed consent, e.g. presumed consent based on the presumption that people will consent to research that is presumed to be harmless. It has, however, been considered a problematic option. See Vähäkangas – Länsimies 2004, p. 1554.

72 Government proposal 86/2011, p. 49. See also government proposal 18/2020, p. 149.

73 Government proposal 185/1991, p. 17. The treatment of a disabled patient shall consider his or her personal views and the factors he or she would give priority to.

74 Markku Helin: Lapsi ja vajaakykyinen potilaana. Suomen Lääkärilehti 40/2003 vsk 58, pp. 4025–4028. In this context, Helin also raises the question of how the custodians' right to parenthood is respected in these situations.

of the child. Similarly, the requirement of consent in favour of the best interests of the child should be added to the Patient Act and should also be included in the new Genome Act. Such legislation could clarify and harmonise the existing practices. It would also take into account children of all ages. When assessing the best interests of the child, the rights of the child shall be taken into account holistically and on a case by case basis. Thus, it also includes examining the child's opinion in accordance with the child's evolving capacity.⁷⁵ The assessment may therefore also take into account the 'presumed will' formed on the basis of the child's opinions when it comes to an older child who is able to express or has previously expressed his or her views on the subject.

5.3.4.3 A Child's Right to Privacy or a Parent's Right to the Child's Genomic Data?

A parent's right to a child's health data is based on the parent's responsibility to take care of the child's growth and development in the best interests of the child. At the same time, the parent should respect the child's privacy and self-determination in accordance with the child's evolving capabilities and should also seek to safeguard the child's fundamental and human rights in advance. When it comes to genomic information, the precautionary protection of the rights of the child could mean, for example, that the parent would not have the right to know all the results of the genome research at a stage when the child is not yet able to consent to the research. It is possible that at some point the genomic information of each child would be determined early, possibly immediately upon birth.⁷⁶ The earlier the genome information is explored, the more attention should be paid to

⁷⁵ CRC/C/GC/14, para. 43. The obligation to find out the opinion of the child applies to children of all ages. See e.g. Priscilla Alderson – Joanna Hawthorne – Margaret Killen: The Participation Rights of Premature babies. *The International Journal of Children's Rights* 2005, Vol. 13(1–2), p. 31–50.

⁷⁶ This conclusion is supported by, e.g. the reflections on collecting samples from newborns presented in the reform of the Biobank Act (draft Biobank Act, pp. 44–45).

the protection of the child's privacy and the child's right to know or not to know at a later stage.⁷⁷

The right of access to patient and health records is an integral part of consent and everyone is naturally entitled to their own information. Under Article 10 of the Biomedicine Convention, everyone has the right of access to information concerning their state of health, but if they do not wish to have such information, their wishes must be taken into account.⁷⁸ Similarly, at the national level, section 5 of the Patient Act confirms the right of the patient to know and not to know. The patient shall be given information about his or her state of health, the significance of the treatment, various alternative forms of treatment and their effects and other factors related to his or her treatment that are significant when decisions are made on the treatment given to him or her. However, the information should not be given against the will of the patient or when it is obvious that giving the information would seriously endanger the patient's life or health. In the case of a minor who is not yet able to make independent decisions regarding his or her treatment, the information should be given to the person making the decision on behalf of the child, i.e. usually the parent of the child.⁷⁹

When genomic research is performed in the context of a child's clinical care, the analysed information comprises part of the child's patient information. The

77 Johnston – Juengst 2018. The studies mentioned in the article have examined the willingness of parents to find out a child's genomic information. Willingness has been found especially on the part of parents of sick children. Parents of healthy children are more reserved. As for the justifications, e.g. a desire to prepare for any possible special needs of the child or an obligation to allow any medical procedure that may be beneficial to their child. In Finland, the willingness of parents to participate in voluntary screenings during pregnancy has been studied. 90% of pregnant women planned to participate in chromosome aberration screening in combination screening, more than 80% in structural screening at weeks 18–21 of pregnancy, and less than a tenth in structural screening after week 24 of pregnancy. The most common reasons were ensuring the child's state of health, finding diseases and abnormalities, confirming the pregnancy, seeing the child, getting all possible information, and ensuring the number of fetuses (Maarit Nykänen – Siiri Nelimarkka – Anna Turunen – Reija Klemetti: Vanhempien odotuksia ja kokemuksia sikiöseulonnoista Suomessa 2015. The expectations and experiences of pregnant women and their partners concerning foetal screening in Finland 2015]. National Institute for Health and Welfare (THL). Discussionpaper 6/2018. Helsinki, Finland 2018 (abstract in english), pp. 16–18).

78 According to the Explanatory Report to the Biomedicine Convention, a person's will not to know himself or herself may in certain situations be waived or the information could be provided to a third party, e.g. if the provision of the information is likely to prevent the spread of a contagious disease. Exceptions may also be provided in national law. For more details, see CETS 164, paras. 63–70.

79 The provision should be interpreted narrowly, i.e. the mere suspicion of danger or harm would not be sufficient (Government proposal 185/1991, p. 15). Valvira's guidance letter of 2016 states (p. 5) that the regulation in the Patient Act should be duly taken into account in connection with sampling when it comes to treatment or diagnostics and, where applicable, also when samples are collected with consent only for biobanking.

processing of patient data is primarily governed by the provisions of Chapter 4 of the Patient Act on patient records and other materials related to treatment.⁸⁰ The basic premise is that the parent has a right to the child's patient records, which of course is also a prerequisite for the parent's involvement in the decision to care for the child. The legislation does not comment on the extent or accuracy with which the results of (genetic) research should be communicated to parents, so it is up to the attending physician to decide. The reporting of results may involve ethically problematic situations. Not all findings can be interpreted yet. Genome-wide research may also find incidental findings, for example, about a disease that is currently untreatable, or which may not manifest until adulthood.⁸¹ Should these be told to the parents of a young child? The research results of a child always reveal information about both biological parents, so are parents entitled to be informed of the results that are relevant to them? Genetic counselling should be given in connection with the reporting of results but may not always be sufficiently available.⁸²

When a custodian exercises his or her right to view a child's medical records, he or she always interferes with the child's privacy to some extent. This relates to a restriction of a right recognised as a fundamental and human right, thereby requiring that such a restriction regulated with sufficient precision and legitimacy.⁸³ The same applies to information given to a custodian from a biobank. In my view, the existing legislation does not fully meet these requirements. For example, the Biobank Act only provides for the right of the custodian to give biobank consent on behalf of the child but does not explicitly state with whom, in these situations,

80 Among other legislation, e.g. the Act on the Electronic Processing of Client Data in Healthcare and Social Welfare (159/2007).

81 Myllykangas et al. 2013, p. 143. Targeted methods can be used to study genetic areas relevant to patient care in large clinical populations. Genome and exome sequencing provide information that is not directly related to clinical questions but may be relevant to the patient's health and future. Ethical issues related to targeted methods can be reduced by limiting analytics to subjects relevant to the clinical problem.

82 See e.g. Kääriäinen 2017, pp. 84–85. On the challenges in dealing with diagnoses based on genetic testing, especially within families, see Meincke 2001, pp. 72–75; Line Bune Juhl: Genetic Privacy: Autonomy or Solidarity? pp. 292–303 in Elisabeth Rynning – Mette Hartlev (eds.): *Nordic Health Law in a European Context*. Martinus Nijhoff Publishers, 2012.

83 Article 16 of the Convention on the Rights of the Child reaffirms the child's right to privacy, which must not be infringed arbitrarily or unlawfully. On the conditions for the restriction of fundamental rights, see the Report of the Committee on Constitutional Affairs 25/1994 – Government proposal 309/1993, p. 5.

any research findings will be shared.⁸⁴ The provision on the right of access of registered individuals (section 39) does not specifically regulate the situation of acting on behalf of the child. Although there is no explicit legislation, it is clear that the findings must be communicated to the caregiver when it is relevant to the child's care and the child is not yet able to take responsibility for his or her care.⁸⁵ In this respect, the previously mentioned guidance letter for biobanks refers to the Data Protection Ombudsman's statement that, in principle, the rights of the data subject belong to everyone, regardless of age or disability, and that a third party cannot exercise the data subject's rights. The rights of the data subject include the right to access the data stored in the register. Under certain conditions, another person may also be authorised by the data subject in exercising his or her rights. Such legal representatives include, for example, custodians of a minor child or other legal guardians. The guidance letter does not elaborate on how a young child should be dealt with or, for example, whether information should always be given to the requesting custodian or both.

The disclosure of information concerning a young child should be decided in the best interests of the child and the starting point should be that only the information necessary to ensure the good care of the child is provided to the parents. Information relating, for example, to a disease that appears at the earliest in adulthood and which cannot be prevented by any measures, should not be provided. At the same time, however, it must be ensured that the child himself or herself receives the desired data when being able to understand their meaning and when being able to take responsibility for his or her own health. This is the

84 The Government Decree on the Consent Form for Biobanks (643/2013) stipulates that the consent document also records the possible consent of the sample donor as to whether the biobank may report a clinically significant finding, but does not specifically comment on who will be informed if another person has given consent on behalf of the sample donor.

85 Valvira's guidance letter of 2016. The guidance states, among other things, that as with consent, the minor should also be consulted and his or her opinion taken into account when he or she is judged to be sufficiently mature, considering his or her age and developmental stage. Pursuant to section 9(2) of the Patient Act, a minor should also have the right to prohibit the provision of information related to a sample from a biobank to a custodian or other legal representative. Ultimately, the matter should be resolved in the best interests of the child. For example, if the clinical finding is a serious illness, it would most likely be in the best interests of the child to inform the custodian or other legal representative. In situations where the child has himself refused to provide information to the custodian, the matter should ultimately be resolved in the best interests of the child.

position taken in the forthcoming Genome Act.⁸⁶ This approach, however, also has its own challenges. Once the child's genomic information has been determined by the consent of the custodian, the child will no longer have the opportunity to make his or her own decision on the sequencing of the genome or whether to allow the use of the genome data in research. The right to refuse to receive information and the right to subsequently prohibit the use of the data for research purposes later as a teenager or adult does not fully guarantee the child's right to an open future.

5.4 Conclusions

In considering the issues of regulating consent on behalf of the child, it has been assumed above that sensitive health data is created in the process of genomic research, especially when conducted in early childhood and with extensive genetic testing. The protection of the rights of the child must therefore be a paramount consideration in the processing of such data. In addition to safeguarding the right of the child to influence decision-making in relation to himself or herself in accordance with his or her developing capacities, care must be taken in the best interests of the child when giving consent on behalf of the child. The Convention on the Rights of the Child confirms the independent status of the child as the subject of his or her rights and the special protection of the child's right. The custodians should find a balance between these two rights when acting on behalf of the child. My views above (section 3.4) on how the law on the consent of the child should be developed would help to achieve this balance.

Existing legislation does not explicitly address informed consent from the perspective of genome research. Thus, at least for the time being, regulation leaves a great deal of room for interpretation to the enforcer. Genomic data is, at the very least, sensitive personal data comparable to other health data, so it would be important to explicitly regulate its processing. The Genome Act that is currently under preparation and the reformed Biobank Act will play a key role in this respect.

86 The draft Genome Act (p. 227) proposes that a minor whose health-related genetic analysis has been performed with the consent of a custodian be informed of the storing of genomic information as he or she grows up. It also states the following (direct translation): the custodians in the position of decision-maker should not take a decision which is contrary to the best interests of the child, for example by requiring them to be informed of any diseases that may arise in adulthood that the child, especially when older, may not want to know. In these situations, the doctor should act in the best interests of the minor and in such a way that the right not to know and the right to an open future are actualized. The child may be informed at the time of the genetic analysis of matters relevant to the current treatment or other situation or circumstance.

6

Germline Gene Therapy: Safeguarding the Best Interests of the Child

by LL.M. Amanda Blick

Abstract

New gene-editing technologies such as CRISPR/Cas9 and prime editing have been described as having the potential to substantially expand the scope and capabilities of gene therapy. Such previously unimaginable treatment possibilities provide different applications in healthcare, including correcting disease-causing genetic mutations in children entirely through germline cells or embryos. The risks relating to the use of these techniques as well as the question of whether such use offends against human dignity have since been debated in the scientific community. Notably, the Nuffield Council on Bioethics has in its recent report placed higher focus on the welfare of the future person, deviating from the more traditional human rights argument where the integrity of the human genome is understood as an extension of safeguarding human dignity. Through balancing the legal-ethical principles around the ongoing discussion, this article argues that the current human rights perspective should place more focus on parents' reproductive rights as well as the child's right to the highest attainable standard of health, thereby considering the best interests of the unborn individual as a whole.

6.1 CRISPR/Cas9 and Prime Editing: A World of Possibilities

The previous years have marked the discovery of disruptive gene-editing technologies that have been described to substantially expand the scope and capabilities of gene therapy. These include technologies like CRISPR ('Clustered, Regularly Interspaced, Short Palindromic Repeats') and prime editing, which have been referred to as one of the most promising and even the most important

developments in the field of gene editing to date.¹ Compared to the cost-efficiency and ease of use of earlier technologies, such technologies can also offer previously unimaginable treatment possibilities through their applications in healthcare.² Not only are they useful in somatic therapies for the prevention and cure of genetic diseases, but they have potential in correcting disease-causing genetic mutations in children entirely through germline cells or embryos, thereby even altering the genome that can be passed onto any future generations.³

The ethical aspects of such applications have also opened new debates within the scientific community. Commentators have pointed out the risks relating to the use of these techniques as well as considered inheritable genome editing to constitute a violation of human dignity in itself. Among these voices, the Committee on Social Affairs, Health and Sustainable Development of the Council of Europe recently reiterated the call for a ban on using germline cells or human embryos which have undergone intentional germline editing by declaring that such use crosses a line viewed as ethically inviolable.⁴ This area of research is particularly highlighted by ethical concerns surrounding human dignity, both relating to the inviolability of the human genome and the best interests of the child in terms of the child's right to the highest attainable standard of health. The article focuses

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- 1 The CRISPR system that relies on the Cas9 enzyme functions together with a small RNA molecule. On the principle of base-pair complementarity, the RNA molecule recognises the region of the target DNA, which is then cleaved by the Cas9 enzyme. For a more detailed explanation of the technology's working mechanism, see Jennifer A Doudna – Emmanuelle Charpentier, *The New Frontier of Genome Engineering with CRISPR-Cas9*. *Science* 346(6213) 2014, pp. 1258096-1–1258096-9. The article provides an in-depth analysis of the functioning system of CRISPR-Cas9 and further explains its ability to potentially correct genetic mutations that cause inherited disorders. Similarly, prime editing is described to have the ability to correct about 89% of known pathogenic variants. See Andrew V Anzalone – Peyton B Randolph – Jessie R Davis – Alexander A Sousa – Luke W Koblan – Jonathan M Levy – Peter J Chen – Christopher Wilson – Gregory A Newby – Aditya Raguram – David R Liu, *Search-and-replace genome editing without double-strand breaks or donor DNA*. *Nature* 576(7785) 2019, pp. 149–157.
 - 2 See Tracey Tomlinson, *A CRISPR Future for Gene-Editing Regulation: a Proposal for an Updated Biotechnology Regulatory System in an Era of Human Genomic Editing*. *Fordham Law Review* 87(1), pp. 437–483, 482, Joanna Smolenski, *CRISPR/Cas9 and Germline Modification: New Difficulties in Obtaining Informed Consent*. *Am J Bioeth* 15(12) 2015, pp. 35–68, 35, and Heidi Ledford, *CRISPR, the disruptor*. *Nature* 522(7554) 2015, pp. 520–524, 520.
 - 3 See John EJ Rasko – Gabrielle M O'Sullivan – Rachel A Ankeny, *Is inheritable genetic modification the new dividing line?*, pp. 1–15 in John Rasko – Gabrielle O'Sullivan – Rachel Ankeny (eds.), *The Ethics of Inheritable Genetic Modification: A Dividing Line?* Cambridge University Press 2006, p. 6, where germline editing is defined as any biomedical intervention altering the set of genes with transgenerational effects, including all interventions performed at an early enough stage to have inheritable effects. In somatic gene therapy, respectively, the functioning gene is introduced into the already differentiated non-germ cells from the human body, replacing the defective one, but without the aim to induce mutations in the germline.
 - 4 Committee on Social Affairs, Health and Sustainable Development. *Germline genome editing in human beings*, Declaration adopted by the Committee on 4 December 2018.

on these questions of how we should interpret the concept of human dignity in the bioethical discussion surrounding germline editing; and whether the child's right to the highest attainable standard of health and the parents' right to bring a child into the world who is not affected by the illness that they carry could, in some cases, balance out the child's right to inherit a genetic pattern which has not been artificially changed.

6.2 Review of the Fundamental Rights Associated with Germline Gene Therapy

6.2.1 Grounds for Excluding Germline Gene Therapy: Respecting the Physical Integrity of Descendants

Various direct and indirect regulation mechanisms surrounding germline gene therapy exist in both national legislation as well as international instruments, including human rights conventions and primary and secondary law of the European Union.⁵ On the national level, the prohibitions of undertaking germline gene therapy are laid down in sections 4 and 5 of the Act on Assisted Fertility Treatments (1237/2006) as well as Chapter 22, sections 3 and 5 of the Criminal Code of Finland (39/1889).⁶ These prohibitions follow from various human rights instruments and most notably the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine ('the Biomedicine Convention'), Article 13 of which provides that and intentional human germline modification shall be prohibited in all cases, even for health-related reasons.⁷

5 The process leading to the development and eventual commercialisation of gene therapy medicines has areas been largely harmonised in the Union in areas such as clinical trials and obtaining marketing authorisation for advanced therapy medicinal products. Article 3(2)(c) of the Charter of Fundamental Rights of the European Union further provides that the prohibition of 'eugenic practices, in particular those aiming at the selection of persons, must be respected in the fields of medicine and biology'.

6 Section 15 of the Medical Research Act (488/1999) further stipulates that research on embryos and gametes for the purpose of developing procedures for modifying hereditary properties shall be prohibited, but this prohibition does not apply if the research is carried out for the purpose of curing or preventing a serious hereditary disease.

7 Notably, on p. 27, the Government proposal 3/2006 to Parliament for the Act on Assisted Fertility Treatments and amending the Paternity Act makes a reference to Article 13 to the Biomedicine Convention, although the Biomedicine Convention was only ratified a few years after on 13 November 2009 and entered into force on 1 March 2010.

Indirect control mechanisms discouraging the development of germline gene therapy are further contained in relevant Community law. These include inter alia the harmonised legislation around advanced therapy medicinal products and the provision of economic incentives for research through patenting.⁸ Another example is Article 90(2) of the Regulation 536/2014 of the European Parliament and of the Council on clinical trials on medicinal products for human use which provides that ‘no gene therapy trials may be carried out which result in modification to the subject’s germline genetic identity’. A similar view is further reflected in Article 6(2) of the Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions which considers the commercial exploitation of processes for modifying the germline genetic identity of human beings as contrary to *ordre public* and morality, thereby limiting the economic incentives for research of CRISPR/Cas9 and prime editing in human applications.⁹ The Commission’s report on the Development and Implications of Patent Law in the Field of Biotechnology and Genetic Engineering explains that this exclusion of germline gene therapy exists in particular in order to respect the ‘physical integrity of descendants’ – simultaneously, however, the Commission recognises somatic gene therapy as ‘very valuable for the treatment of genetic diseases’.¹⁰

The regulatory mechanisms surrounding germline gene therapy are unequivocal even where commentators describe that interpreting the exclusion as intending to

8 Following what is stated in recital 40 in the preamble to the Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions, the decision to unequivocally exclude germline therapy from patentability was based on the ‘consensus within the Community’ that interventions in the human germline offend against *ordre public* and morality. The earlier proposal for the directive further stated that unequivocally excluding from patentability any such methods of treatment was ‘important’ in view of the ‘importance and the controversial nature of the unprecedented questions’ See recital 24 in the preamble to the proposal for a European Parliament and Council Directive on the legal protection of biotechnological inventions, COM/95/0661 final.

9 Article 6(1) of the directive states that inventions shall be considered unpatentable where their commercial exploitation would be contrary to *ordre public* or morality. With reference to Article 6(1), Article 6(2) specifies that inter alia processes for modifying the germline genetic identity of human beings and uses of human embryos for industrial or commercial purposes are excluded from patentability.

10 Report from the Commission to the European Parliament and the Council - Development and implications of patent law in the field of biotechnology and genetic engineering, COM/2002/0545 final, point 5.2.3. The connection between physical integrity and human dignity is understood to rely on both the Charter of Fundamental Rights of the European Union as part of the primary law that is applicable for directive as well as the reference to recital 16 of the preamble to the directive which states that the the European Convention on Human Rights forms part of the general principles of Community law, further providing that patent law must be applied so as to protect the dignity and integrity of the person. See Oliver Mills, *Biotechnological Inventions: Moral Restraints and Patent Law*. Routledge 2010, p. 146.

deny the incentive for research on the prevention of severe hereditary diseases is in itself ‘controversial’.¹¹ This controversial nature of such exclusions is apparent from the further issues that have been raised during the implementation of Community legislation. For example, upon implementing the relevant provisions of the Directive 98/44 into the Patents Act (550/1967), the Environmental Committee commented that modifying the genetic identity of human germ cells so that alleles causing hereditary diseases are corrected cannot be considered contrary to *ordre public* or morality and such methods should be patentable.¹² It was explained that the examples listed should be read in conjunction with the general provision – this, however, is in great contrast with the wording of Article 6(2)(c) of Directive 98/44, which explicitly states that such methods are considered unpatentable, thus leaving no room for such interpretation.

In my opinion, the above contrasting views show that while germline gene therapy is discouraged in many instances, the issue appears to be more complex than the current legislative position sets it out to be. I wish to argue that the basic values enshrined in European human rights instruments around human dignity and integrity form a common ground for exploring further the concept of human dignity in the field of biolaw.¹³ Next, I will investigate whether any applications for germline gene therapy exist that are acceptable in light of human dignity after the concept first defined through the contents of human rights conventions and other legislation.

6.2.2 Interpretations of the Concept of Human Dignity

The concept of human dignity is reflected upon several human rights conventions – and they are also where human dignity derives its legislative force on the

11 Ana Nordberg, Patentability of human enhancement: from ethical dilemmas to legal (un) certainty, pp. 54–92 in Tana Pistorius (ed.), *Intellectual Property Perspectives on the Regulation of New Technologies*. Edward Elgar 2018, p. 77.

12 Statement of the Environmental Committee 3/2000 – Government proposal 21/2000, p. 2.

13 The following bioethical principles are identified in conjunction with international human rights standards: freedom of research; benefit sharing; solidarity; respect for dignity; and the obligation to respect and to protect the rights and individual freedoms of others. See Andrea Boggio – Cesare P R Romano – Jessica Almqvist, *Toward a Human Rights Framework for the Regulation of Human Germline Genome Modification*, pp. 585–617 in Andrea Boggio – Cesare P R Romano – Jessica Almqvist (eds.), *Human Germline Genome Modification and the Right to Science: A Comparative Study of National Laws and Policies*. Cambridge University Press 2020, pp. 585–588.

supranational level.¹⁴ While the European Convention on Human Rights refers to human dignity only implicitly, it is still understood as the supporting principle behind all the more practical embodiments that human rights instruments provide.¹⁵ As the primary international instrument aiming to protect human dignity by prohibiting the misuse of innovations in biomedicine, the Biomedicine Convention underlines securing human dignity as its leading purpose.¹⁶ According to its Explanatory Report, the concept of human dignity ‘constitutes the essential value to be upheld’ and it is understood to form the basis of most of the values emphasised in the Convention.¹⁷

The Convention, however, provides no further definition or explanation as to what human dignity actually comprises, and this type of ambiguity is also the reason why the concept of human dignity has also faced criticism.¹⁸ Without a more structured basis in argumentation, the concept of human dignity is argued to risk becoming a void mantra for expressing distrust towards any new technology.¹⁹ Since the concept of human dignity is so difficult to define – not to mention unlikely to face opposition – it is for this reason that using it as an argument would require specifying more precisely what human dignity means in any given context and why the proposed or existing policy decisions are necessary

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- 14 In addition to these international human rights instruments, human dignity is also reflected upon national legislation, including section 1(1) of the Constitution of Finland (731/1999) which provides that the constitution shall guarantee the inviolability of human dignity and the freedom and rights of the individual and promote justice in society.
 - 15 Protocol No. 13 to the Convention for the Protection of Human Rights and Fundamental Freedoms concerning the abolition of the death penalty in all circumstances, Vilnius, 3 May 2002, which refers to ‘the full recognition of the inherent dignity of all human beings’. The concept is often traced to originate from Immanuel Kant putting forward the idea of human dignity as the superiority of man over other animals by the merits of his personality and ability to act freely in accordance with the universal moral laws. According to Foster, however, it was only after the Second World War and the atrocities of the Holocaust that human dignity established its position as a very significant, if not the most important principle in human rights. See Charles Foster, *Human Dignity in Bioethics and Law*. Hart 2011, p. 40.
 - 16 Article 1(1) of the Biomedicine Convention obliges all Member States to the Convention to ‘protect the dignity and identity of all human beings and guarantee everyone, without discrimination, respect for their integrity and other rights and fundamental freedoms with regard to the application of biology and medicine’.
 - 17 Explanatory Report to the Convention for the protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine, para. 9.
 - 18 This criticism is not new, as leaders of philosophical thought from both the left and right such as Schopenhauer, Marx, and Nietzsche condemned the term as contentless and without reference to any concrete basis. See Christopher McCrudden, *Human dignity and judicial interpretation of human rights*. *European Journal of International Law* 19(4) 2008, pp. 655–724, 661.
 - 19 Laura Walin, *Alkio- ja kantasolututkimuksen sääntely bio-oikeudellisena mallina*. *Forum Iuris* 2010, pp. 38–39.

to safeguard its inviolability.²⁰ I have to agree with this view, as many of the human rights conventions as well as their explanatory reports inevitably fail to address the concept of human dignity, and it is indeed a difficult one to define. Understanding the political atmosphere behind these developments, securing its formal importance by including the concept in the human rights instruments is argued to have been prioritised over fighting over exact definitions.²¹ Indeed, despite the issues relating to the concept's ambiguity, it is still viewed to play an important role in contributing to particular methods of human rights interpretation and adjudication.²²

In determining physical integrity, further problems arise with the definition of the human being, as an unborn child is not yet a legal person who could be a direct subject of protectable rights.²³ When the International Bioethics Committee working for UNESCO issued a document titled Report of the IBC on updating its reflection on the human genome and human rights, it declared that when it comes to the question of physical integrity and human life, a consensus is 'impossible to attain'.²⁴ While some contend that the threshold of the right to life is reached only at some point of the development of human life, others believe that unconditional respect is due from the very beginning, presupposing a strong notion of the sanctity of life, to which understanding embryogenesis as an ongoing process is connected.²⁵ The legal ambiguity of the unborn individual's status and rights – or the lack of them – leaves room for arguments on both sides: on the one hand, it makes it possible to ignore the question of the welfare of the unborn individual, since one could argue that there is no legal person that could be seen as the subject of any such rights; on the other hand, those with an antagonistic

20 *Ibid.*

21 Foster 2011, p. 94.

22 McCrudden 2008, pp. 655–724.

23 This is the view adopted in the Finnish legal system as recognised by Walin 2010, pp. 101–102. See also Douglas Walton, The slippery slope argument in the ethical debate on genetic engineering of humans. *Sci Eng Ethics* 23(6) 2017, pp. 1507–1528, 1527, where he states that one could 'say that germline modification is done on a patient that does not exist yet'.

24 The intention of this updated report was reportedly to address some of the ethical issues raised by the Chinese experiment that edited germline of non-viable human tripronuclear zygotes. See Puping Liang – Yanwen Xu – Xiya Zhang – Chenhui Ding – Rui Huang – Zhen Zhang – Jie Lv – Xiaowei Xie – Yuxi Chen – Yujing Li – Ying Sun – Yaofu Bai – Zhou Songyang – Wenbin Ma – Canquan Zhou – Junjiu Huang, CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes. *Protein Cell* 6(5) 2015, pp. 363–372.

25 UNESCO International Bioethics Committee, Report of the IBC on updating its reflection on the Human Genome and Human Rights. SHS/YES/IBC-22/15/2REV.2. UNESCO 2015, pp. 25–26, where it is further noted that even the most widespread religions do not seem to agree on this question.

approach towards restrictions on germline editing can claim that there is no human whose physical integrity could be violated.²⁶

The definition of the human being was reflected in the decision on *Vo v. France* of 8 July 2004.²⁷ Raising the question of whether an unborn child is considered to have a right to life under Article 2 of the ECHR, the Court commented on this issue by stating that while no European consensus exists on the nature and status of the embryo or foetus as regards being a person with the right to life for the purposes of Article 2, even the fact that the embryo or a foetus has the potential and capacity to become a person means that it requires some level of protection in the name of human dignity. The Court concluded that as a common ground between States, it may be only regarded that the unborn humans, at the stage of embryo or foetus, belong to the human race, without offering a clear answer to the question of whether an unborn child is a person or not.²⁸

As demonstrated by the decision *Vo v. France* of 8 July 2004, the fact that an unborn human is not considered a legal person does not mean that the unborn human would be completely devoid of protection under the ECHR. The biggest problem here still seems to be that many varying definitions of these concepts exist with no exact meaning to build their core. Thus, the legal use of the term appears to occur in cases where it is not possible to provide clear rational justifications for the arguments supporting the claims; this, in turn, leads to further ambiguity, as European states with varying legal cultures share different ideas on the concept of dignity. Deviating from this thought, I believe that it is the systematisation of such concepts that truly empowers their use, and acknowledging that nations place different emphasis on the basic principles that are understood to define the concept of human dignity in European bioethics and biolaw is a good place to

26 See, e.g. Foster 2011, pp. 58–60, where he explains that this ambiguity is also why the concept is subject to constant interpretation. See also Juli Mansnérus – Céline Dujardin – Raimo Lahti, *Forms and levels of legal protection of the human embryo in biomedical research in Finland and France*, pp. 199–224 in Ewa M Guzik-Makaruk – Emil W Plywaczewski (eds.), *Current Problems of the Penal Law and Criminology: Aktuelle Probleme des Strafrechts und der Kriminologie*. Wydawnictwo C.H Beck 2019.

27 In the case of *Vo v. France*, Mrs Vo claimed compensation for the loss of her six-month-old foetus as the pregnancy was accidentally terminated in a hospital after a misunderstanding.

28 *Vo v. France*, paras 84 and 85.

start.²⁹ Without clear legal rules or guiding principles to which we can adhere, we risk facing arbitrary use of power in important bioethical issues – or, as I argue later to be the case with Community law – with conservative views overriding European pluralism.

6.2.2.1 Reviewing the Human Genome as an Extension of Human Dignity

To better understand the concept of human dignity, it is worth reviewing its definition in human rights instruments and the relevant bioethics commentaries further explaining its content. Justifying the necessity of prohibiting germline gene therapy to respect the physical integrity of descendants implies that future individuals, although yet unborn, are recognised as entities to which human rights argumentation to some extent applies.³⁰ As pointed above, the concept of human dignity is an abstract one and does not necessarily have to relate to an individual in order to be violated. Instead, it is the human genome that is in many sources reviewed as an extension of human dignity.

Referring to Articles 2 and 3 of the ECHR, in its recommendation on Genetic Engineering in 1982, the Council of Europe emphasised how the rights to life and human dignity imply the ‘right to inherit a genetic pattern which has not been artificially changed’.³¹ Building upon this, Article 1 of the UNESCO’s Universal Declaration on the Human Genome and Human Rights explains how the human genome is ‘the heritage of humanity’ in a symbolic sense, underlying ‘the fundamental unity of all members of the human family, as well as the recognition of their inherent dignity and diversity’.³² In the same recommendation, germline interventions were identified as an example of practices that could be contrary to human dignity.³³ Still relying on the notion of Article 1 of the UDHR, the

29 On these basic ethical principles – autonomy, dignity, integrity and vulnerability – see Jacob Dahl Rendtorff, ‘Basic ethical principles in European bioethics and biolaw: Autonomy, dignity, integrity and vulnerability – Towards a foundation of bioethics and biolaw. *Medicine, Health Care and Philosophy* 5(3) 2002, pp. 235–244.

30 In the same recommendation, the Council of Europe further recognized the great potential of gene therapy, stating at para. 4. d. that ‘the explicit recognition of this right must not impede development of the therapeutic applications of genetic engineering (gene therapy), which holds great promise for the treatment and eradication of certain diseases which are genetically transmitted’.

31 Recommendation 932 (1982) on Genetic Engineering. Text adopted by the Assembly on 26 January 1982 (22nd Sitting).

32 As a soft-law instrument, the Universal Declaration on the Human Genome and Human Rights acts as a framework around which the details and refinements of the actual binding national and international legislation may later have been developed.

33 Article 24 of the Universal Declaration on the Human Genome and Human Rights, 1997.

UNESCO International Bioethics confirmed its view that even for therapeutic purposes, any alternatives to this interpretation ‘would be to jeopardise the inherent and therefore equal dignity of all human beings and renew eugenics, disguised as the fulfilment of the wish for a better, improved life’.³⁴

The Biomedicine Convention further signifies the impermissible nature of germline modifications due to human dignity. It is understood that the Convention was mostly designed to address developments in gene therapy, and it does indeed take a stance on the subject.³⁵ For other than preventative, diagnostic, or therapeutic purposes, any interventions seeking to modify the human genome are generally prohibited under Article 13 of the Convention, and intentional human germline modification is prohibited in all cases, even for health-related reasons.³⁶ The explanatory report clarifies that the article does not rule out somatic interventions that affect the germline through unwanted side effects, for example, in certain cancer treatments by radiotherapy or chemotherapy possibly affecting the reproductive system of the person undergoing the treatment.³⁷ Therefore, it seems that any modifications of the human germline violate human dignity only through their deliberative nature.³⁸

34 Report of the IBC on updating its reflection on the Human Genome and Human Rights, 26.

35 Jeff Kipling, *The European Landscape for Human Genome Editing: A review of the current state of the regulations and ongoing debates in the EU*. Academy of Medical Sciences 2016, p. 12.

36 This is apparent from the wording of the Article 13, where it is stipulated that an intervention seeking to modify the human genome may only be undertaken ‘only if its aim is not to introduce any modification the genome of any descendants’.

37 See the Explanatory Report to the Convention for the protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine (CETS 164), para. 92, stating this ‘may be the case, for example, for certain treatments of cancer by radiotherapy or chemotherapy, which may affect the reproductive system of the person undergoing the treatment’. The issues that relate to these ‘incidental enhancements’ are the same that are raised outside preventive medicine. Taking the example of gene therapy that has had unexpected side effects in mice, should these have similar effects in humans, they would not only prevent early-onset Alzheimer’s disease, but also improve the treated individuals’ cognitive capacities and extend their lifespans. This further raises the question of whether such interventions fall outside the limits of responsible gene-editing or are they just acceptable side effects of successful disease prevention. Eric T Juengst – Gail E Henderson – Rebecca L Walker – John M Conley – Douglas MacKay – Karen M Meagher – Katherine Saylor – Margaret Waltz – Kristine J Kuczynski – R Jean Cadigan, *Is Enhancement the Price of Prevention in Human Gene Editing?* *CRISPR J* 1(6) 2018, pp. 351–354, 353.

38 Ana Nordberg elaborates on whether the provision may interpreted as only prohibiting non-therapeutic germline interventions, arguing that ‘genetic therapy, even if it affects future generations, does not have the aim of introducing a modification since its objective is to cure or prevent a medical condition’. Nordberg 2018, p. 77. The UNESCO International Bioethics Committee, however, confirms that such an interpretation is not exactly in line with the aim of the Convention. See the Report of the IBC on updating its reflection on the Human Genome and Human Rights, p. 26. For further discussion on this idea of intentionality, see Rasko – O’Sullivan – Ankeny 2006, p. 5.

The Biomedicine Convention has been described as ‘important’ and ‘unique’ as it is the first – and only – international legally binding instrument fully devoted to biomedical issues.³⁹ However, even on a European level, the Convention is not exactly universal, since as a regional instrument, the Convention has limited geographic scope and application.⁴⁰ While it has been presented that the ratification of the Biomedicine Convention and its Protocols would indicate that a growing European consensus has been built around its provisions, agreeing with such perspectives is noted to be difficult since the Convention has only been ratified at a varying rate.⁴¹ Out of 47 Member States, 35 have signed the Convention, but only 29 of these have also ratified it and implemented the principles into their national laws, with six of those ratifying Member States having reservations limiting the extent to which they are bound to certain provisions.⁴²

Despite the various opinions surrounding this question, the Council of Europe nevertheless views the human genome as an extension of human dignity, without offering many answers as to why this is. This view has since been challenged by various commentators assessing the question of whether editing the genome of one’s descendants could truly amount to an infringement of human dignity. One notable example is the recent report by the Nuffield Council on Bioethics which states that the concept of human dignity is not helpful in this context and that the moral importance of human beings is not dependent on the possession of a particular set of genomic variations.⁴³ Even the Finnish Medical Association has stated in its ethical guidelines that the integrity of the genome should not be considered an intrinsic value, viewing the modification of the disease-causing gene so that a healthy one would be transmitted to future generations as desirable.⁴⁴

Although all European bioethics commentators appear to share the commitment to human dignity, some argue that using the human dignity argument against

39 Henriette Roscam Abbing, *The Convention on Human Rights and Biomedicine. An Appraisal of the Council of Europe Convention*. *European Journal of Health Law* 5(4) 1998, pp. 377–387, 379. In her appraisal, Henriette Roscam Abbing states that it is, in essence, a Health Law Convention ‘pur sang’.

40 Francesco Francioni, *Genetic Resources, Biotechnology and Human Rights: The International Legal Framework*, pp. 3–32 in *Biotechnologies and International Human Rights*. Hart 2007, p. 27.

41 Juli Mansnéus, *Commercialisation of Advanced Therapies: A Study of the EU Regulation on Advanced Therapy Medical Products*. Unigrafia 2016, p. 80.

42 These states include Croatia, Denmark, France, Norway, Switzerland and Turkey.

43 Nuffield Council on Bioethics, *Genome Editing and Human Reproduction: social and ethical issues*. Nuffield Council on Bioethics 2018, p. 158.

44 Finnish Medical Association, *Lääkärin etiikka*. Suomen Lääkäriliitto 2013, p. 92. In Finnish, they provide that ‘on toivottavaa, että sairauden geeni voitaisiin korvata normaalilla ja terve geeni siirtyisi jälkeläisiinkin. Genomin koskemattomuudesta ei pidä tehdä itseisarvoa’.

modifying the human germline is a ‘logical fallacy’.⁴⁵ Reviewing the human genome as an extension of human dignity can even give rise to arguments that would support the thought of the right to being born with a ‘core genetic identity’, without certain diseases.⁴⁶ Some authors further challenge the concept of the human genome by stating that the term lacks coherence in any case: as the human genome should be understood as ever-changing living material that does not remain static in human individuals, it remains unclear how the inviolability of the genome is compromised through germline editing.⁴⁷ I agree this to be a valid point to the extent of how trillions of mutations have been estimated to take place inside of our bodies every day; but I do not believe that we should completely ignore the concept of human dignity relating to the human genome when considering, for example, the production of chimeras consisting of human and animal DNA. The truth is perhaps found somewhere in between these extremities, with the principles of the welfare of the future person and social justice and solidarity guiding such moral evaluation.

6.2.2.2 *Safeguarding the Best Interests of the Unborn Individual*

‘Would it be unethical not to fix something if you could? If it were very safe, wouldn’t it be wrong not to?’⁴⁸

Alongside human dignity, the quest for harmonisation and European constitutional pluralism has resulted in another core value that is reflected in the Biomedicine Convention, namely the value of protecting fundamental rights.⁴⁹ I want to approach this question from a human rights perspective that notes the various implications relating to gene therapy, both when it comes to the human dignity aspect of individual rights as well as the societal implications on human dignity

45 Iñigo de Miguel Beriain, Human dignity and gene editing. *EMBO Rep* 19(10) 2018, e46789.

46 Martin Gunderson, Human Rights, Dignity, and the Science of Genetic Engineering. *Social Philosophy Today* 22/2006, pp. 43–57, 46.

47 Walin 2010, p. 80.

48 These are the exact words of Nobel laureate Craig Mello as presented in Cormac Sheridan, CRISPR germline editing reverberates through biotech industry. *Nature Biotechnology* 33(5) 2015, p. 432.

49 Susan Millns, Consolidating Bio-rights in Europe, pp. 71–84 in Francioni 2007, pp. 71–72. Recalling the history of the instrument, one of the members of the drafting group recognizes that ‘it was soon decided that the concept of dignity, identity and integrity of human beings/ individuals should be both the basis and the umbrella for all other principles and notions that were to be included in the Convention’.

– and I will start systematically from the individual aspects first, later following up on the solidarity aspects on a societal level.

6.2.2.3 The Right to the Highest Attainable Standard of Health

The World Health Organisation was the first to formulate the right to the highest attainable standard of health in the level of human rights instruments by declaring it in its 1946 Constitution as a ‘right of every human being without distinction of race, religion, political belief, economic or social condition’.⁵⁰ Shortly afterwards in 1948, the United Nations was then also inspired to recognise the right to health as a human right and laid down in Article 25 of the Universal Declaration of Human Rights which provides the right to a standard of living adequate for the health and well-being of each individual themselves as well as their family.⁵¹

Among the human rights instruments recognising the right to the highest attainable standard of health is also the Oviedo Convention, Article 3 of which requires member states, taking into account health needs and available resources, to take ‘appropriate measures with a view to providing, within their jurisdiction, equitable access to health care of appropriate quality’. For children in particular, Article 24 of the Convention on the Rights of the Child guarantees every child the right to the enjoyment of the highest attainable standard of health and to facilities for the treatment of illness and rehabilitation of health.⁵² Article 12 of the International Covenant on Economic, Social and Cultural Rights further provides that the ‘right of everyone to the enjoyment of the highest attainable standard of physical and mental health’ requires active steps from the Member States. This, as clarified by the guidance on the full realisation of the right to health in the General Comment No. 14, results in the right to health providing not only the freedom to control one’s health and body but also entitlements to health services.⁵³

50 The Constitution was described as revolutionary at the time of its adoption. See Maite San Giorgi, *The Human Right to Equal Access to Health Care*. Intersentia 2012, p. 10.

51 For a commentary, see Yuval Noah Harari, *Homo Deus: A Brief History of Tomorrow*. Signal Books 2016, p. 30, where he states that ‘the Universal Declaration of Human Rights does not say that humans have ‘the right to life until the age of ninety’. It says that every human has a right to life, period. That right isn’t limited by any expiry date’.

52 Toebeles elaborates further on the concept of health, stating that to some it is a physical condition marked by the absence of disease or infirmity, while to others it represents a state without harm. See Birgit Toebeles, *Health and Human Rights: In Search of the Legal Dimension*. *Human Rights & International Legal Discourse* 9(2) 2015, p. 212–224.

53 These health services include preventive, curative, primary, and rehabilitative care as well as treatment relating to reproductive health and mental health, provision of essential drugs, and treatment of epidemic diseases. See San Giorgi 2012, pp. 11–12.

On the basis of these human rights instruments, the right to health is understood to confer the right to the underlying determinants of health, including healthcare.⁵⁴ After the adoption of the above-described human rights instruments, the advancements in healthcare have then expanded the contents of the right to health extending to the individual also being able to access preventive medicine.⁵⁵ The UNESCO International Bioethics Committee also recognises this development, stating that the benefits resulting from advancements in human genetics having an impact on health protection and healthcare should be considered a part of the fundamental right of every human being to enjoy the highest attainable standard of health.⁵⁶

As preventive medicine is thus understood to be included in the right to the highest attainable standard of health, preventing severe hereditary illnesses through gene therapy also falls into this category – after all, in individual cases, it is indisputable that a child born with a severe hereditary illness will face suffering from its symptoms and, as a result, experience a lower quality of life.⁵⁷ Based on this conclusion, some authors have even described the assertion that germline interventions would offend human dignity as ‘highly debatable’ when its aim is to protect future generations from severe inheritable diseases.⁵⁸ This view is shared by those who on these same grounds go as far as describing the incentives to continue gene editing research as ‘a moral imperative’.⁵⁹ I believe that it is therefore relevant to further investigate the question of whether applications for germline modifications exist that would rather safeguard human dignity instead of violating it. Rather than focusing on the abstract concept of protecting human dignity, I hold that these aspects appear to place greater emphasis on the more practical interests and welfare of the individual affected by his or her condition.

54 San Giorgi 2012, at p. 19, provides further examples of the core content of these determinants, including nutrition, housing, access to safe and potable water, adequate sanitation and safe and healthy occupational conditions.

55 Ana Nordberg – Timo Minssen – Sune Holm – Maja Horst – Kell Mortensen – Birger Lindberg Møller, Cutting edges and weaving threads in the gene editing (Я)evolution: reconciling scientific progress with legal, ethical, and social concerns. *Journal of Law and the Biosciences* 5(1) 2018, pp. 35–83, 63–64.

56 The IBC mentions personalized medicine and precision as concrete examples in the advancements that can have an impact on health protection and healthcare. See the Report of the IBC on updating its reflection on the Human Genome and Human Rights, p. 28.

57 Deryck Beylveveld – Roger Brownsword, *Human Dignity in Bioethics and Biolaw*. Oxford University Press 2001, p. 145.

58 Nordberg – Minssen – Holm – Horst – Mortensen – Lindberg Møller 2018, pp. 63–64.

59 Julian Savulescu – Jonathan Pugh – Thomas Douglas – and Christopher Gyngell, The moral imperative to continue gene editing research on human embryos. *Protein & Cell* 6(7) 2015, pp. 476–479.

This is not to say, however, that germline gene therapy is without concerns, both those relating to the human dignity of the unborn individual as well as the wider societal effects. These deserve their own review that I will conduct later in this article by focusing both on the aspects relating to the individual and the aspects that have a clear connection to society as a whole.

6.2.2.4 Risk-to-Benefit Ratio: When Are Therapies Sufficiently Safe and Effective?

The UNESCO International Bioethics Committee has recently stated that the current restrictive approach to germline editing exists due to the uncertainties on the effect that germline modification could have on future generations.⁶⁰ Similar to any therapy, overcoming safety concerns remains a prerequisite for human applications – and at the present stage of research, safety and efficacy for CRISPR/Cas9 and prime editing are still not sufficiently demonstrated to ensure that germline gene therapy would only affect the targeted genes.⁶¹ It is argued that for germline gene therapy, these safety concerns are highlighted when considering how significantly the intervention is likely to affect the lives of individuals who could be considered ‘designed on demand’ and transmit their genome to future generations without consent.⁶² If the therapy ends up being unsuccessful, it is not only the future person that will be affected – as the effects of germline editing are hereditary, the next generations will also face the consequences, and the effects of any off-target mutations will not always be benign or predictable nor readily reversible.⁶³ Considering further how some mutations resulting from unsuccessful gene therapy might not be detected until only later in life, proceeding

60 Report of the IBC on Updating Its Reflection on the Human Genome and Human Rights, p. 14.

61 Although the accuracy of gene editing has significantly improved with CRISPR-Cas9 and prime editing when compared to previous methods, there have been implications that even the most accurate technology developed so far has not yet worked with sufficient accuracy. As of the current situation, there is a prevailing risk that the Cas9 enzyme alters other parts of the genome than what has been intended, causing unwanted changes in the DNA. Moreover, the CRISPR-Cas9 technology has been shown to work most efficiently in cells that lack a functional p53 protein, a phenotype common to cancer cells, leaving cells vulnerable to tumorigenic mutations and thus possibly resulting in increased cancer risk. See Emma Haapaniemi – Sandeep Botla – Jenna Persson – Bernhard Schmierer – Jussi Taipale, CRISPR–Cas9 genome editing induces a p53-mediated DNA damage response- *Nature Medicine* 24(7) 2018, pp. 927–930.

62 Report of the IBC on updating its reflection on the Human Genome and Human Rights, p. 25.

63 Marcelo de Araujo, Editing the Genome of Human Beings: CRISPR-Cas9 and the Ethics of Genetic Enhancement. *Journal of Evolution and Technology* 27(1) 2017, pp. 24–42.

with caution is argued to be all the more justified to ensure that human dignity is not compromised.⁶⁴

At present, due to our lack of knowledge of these potentially detrimental effects, the risks of irreversible damage relating to germline interventions are therefore described to be disproportionate in comparison with its potential benefits, and in view of these concerns, there is widespread agreement that germline gene therapy should not be encouraged.⁶⁵ The European Group of Ethics in Science and New Technologies ('EGE') shares this view by stating that a moratorium should prevail on such genetic modification on human embryos or gametes which would result in the modification of the human genome.⁶⁶

In the clinical context, some authors argue that for germline editing to become a viable option from the perspective of human dignity, precision should be unbending and no errors should be tolerated to avoid transgenerational harm.⁶⁷ On a more general level, such an approach appears to be not very widely adopted in medicine – medical procedures completely free from the risk of adverse effects seem to be more the exception than the rule. Instead, it is the balance between the impact of the risks and the benefits that should form the dividing line.⁶⁸ Both the UNESCO International Bioethics Committee as well as the Nuffield Council on Bioethics have recommended that applications in gene therapy should be proven to be 'acceptably safe and effective' before considering them for treatment of human beings – this does not necessarily equal 'free from any risk'.⁶⁹

Even this above approach, however, would require reaching an agreement on the threshold of what we consider as 'acceptably safe and effective'. I agree safety risks to be a valid concern for the time being – it is, however, expected that at some point, the risk-to-benefit ratio will reach a favourable limit where the benefits could outweigh the risks on certain therapies targeting the germline for curing severe hereditary illnesses. It is central to here understand the balancing

64 Dana Carroll, *Genome Editing: Past, Present, and Future*. *Yale J Biol Med* 90(4) 2017, pp. 653–659, 655.

65 Donald B Kohn – Matthew H Porteus – Andrew M Scharenberg, *Ethical and regulatory aspects of genome editing*. *Blood* 127(21) 2016, pp. 2553–2560, 2556.

66 The EGE has not, however, introduced any similar objections to somatic therapy. See European Group on Ethics in Science and New Technologies, *Statement on gene editing*, 2015, pp. 1–2.

67 Eli Y Adashi – I Glenn Cohen, *Therapeutic Germline Editing: Sense and Sensibility*. *Trends in Genetics* 36(5) 2020, pp. 315–317, 315.

68 For discussion of the complexity of the risk-to-benefit ratio, see Janet Malek, *Understanding Risks and Benefits in Research on Reproductive Genetic Technologies*. *J Med Philos* 32(4) 2007, pp. 339–358.

69 Report of the IBC on Updating Its Reflection on the Human Genome and Human Rights, p. 28, and the Nuffield Council on Bioethics 2018, p. 156.

of the great benefits achieved from preventing potentially severe – possibly even lethal – effects of hereditary illnesses versus the risks associated with the therapy itself. At the point where the risk falls below these benefits, germline gene therapy could start to appear more favourable in clinical settings. Correspondingly, for issues where safer and more effective alternatives exist, there are no sufficient grounds for pursuing germline editing in terms of the risk-to-benefit ratio. Further contributing to this view, Lasse Lehtonen has argued that the more severe the effects of inherited disease are, the more justified it seems to treat the carrier of the gene that causes the disease.⁷⁰ I consider that this can be alternatively formulated as to say that the more gene therapy intends to secure the welfare of the future person, the more favourable gene therapy appears – and the fewer benefits we can expect from therapy, the less viable it seems to accept its risks from the perspective of human dignity.

It is therefore relevant to discuss whether there are justifiable grounds for germline modification or whether the unborn individual's right to health could be secured through alternative approaches such as somatic interventions or embryo selection. At least in some cases, germline gene therapy does seem more viable than somatic interventions. When corrected at the earliest stages of human development, all of the differentiating cells inherit the added gene during cell division, including both somatic and germ cells, this alone promising a clear benefit for the treatment of genetic diseases affecting a variety of cell types.⁷¹ Somatic gene therapy, respectively, would possibly require a combination of several procedures to accomplish delivery to the many different organs and their disparate cell types. Not only does germline gene therapy allow editing all the affected cells at once, it also presents a potential treatment for diseases in non-dividing cells to which somatic cell gene therapy might not apply.⁷² Additionally, while somatic gene therapy cannot alleviate the symptoms caused by irreversible damage during foetal development attributable to defective genes, germline gene therapy potentially prevents such damage, correcting these before embryogenesis proceeds to further stages.⁷³ Somatic gene therapy, although widely used in the

70 Lasse Lehtonen, Ihmisen geeniterapia, pp. 25–36 in Lasse Lehtonen (ed.), *Bio-oikeus lääketieteessä*. Edita 2006, pp. 35–36.

71 Cystic fibrosis is provided as an example. See LeRoy Walters – Julie Gage Palmer, *The Ethics of Human Gene Therapy*. Oxford University Press 1997, pp. 62–63.

72 Among such diseases, Lesch-Nyhan syndrome is named as an example, expressing itself in the nervous system, the cells of which are both non-removable and non-dividing. Correspondingly, many of the diseases prevalent in the Finnish genetic heritage are often caused by mutations in a single-nucleotide polymorphism (SNP). These are among the diseases that could be potentially corrected by germline gene editing.

73 Walters – Palmer 1997, *The Ethics of Human Gene Therapy*, 63.

management of severe hereditary diseases, further has no use as a treatment for mitochondrial diseases as it is not possible to repair or alter the mutations occurring in mitochondrial genes by using somatic interventions. Because of the way that mutations in mitochondrial DNA occur, the health of the affected unborn individuals is more or less at stake, with comparisons such as ‘each pregnancy would be like playing a game of reproductive roulette, the variable being how severely affected the baby would be’.⁷⁴

Some authors still question the necessity of germline editing on the grounds that if we want to prevent hereditary illnesses, it can be already achieved with the use of preimplantation genetic diagnosis (‘PGD’). In this method, after several viable embryos are produced via successful in vitro fertilisation (‘IVF’), the technology works by simply selecting the embryo without the disease-causing allele.⁷⁵ PGD lacks the risks of germline editing because no DNA is altered in the process, and given that PGD is indeed useful in many circumstances, it is argued that germline intervention is not needed because the theoretical possibility of not transmitting specific identifiable genes applies to ‘virtually all interested couples’ through the methods already available.⁷⁶ However, when looking deeper into the circumstances in which prospective parents find themselves, I find it difficult to agree with this statement. Several reasons can exist as to why such selection is not always possible; for example, the number of viable embryos might be reduced due to advanced maternal age or due to prior failures to reach the embryo transfer stage. It is argued that germline editing proves indispensable in these and related contexts.⁷⁷

Further human dignity aspects relate to whether the whole process of embryo selection apart from germline editing presents itself as a eugenic practice as it includes selecting out individuals who have done nothing wrong but to inherit genes causing disability and disease.⁷⁸ This is a mindset that the report of the UNESCO International Bioethics Committee to some extent appears to agree on, stating how gene therapy could also be a way to eliminate the need for such

74 Alice Park, The next frontier in fertility treatments. *Time* 193(1) 2019, p. 32. The article also discusses a promising innovation in fertility treatments, mitochondrial replacement therapy (MRT), which involves replacing the mutated mitochondrial DNA with healthy mitochondrial DNA from a donor, essentially resulting in the child having three biological parents by introducing a small amount of DNA from a donor.

75 On the clinical use of the technology and a further description of its working mechanism, see Harvey J Stern, Preimplantation genetic diagnosis: prenatal testing for embryos finally achieving its potential. *J Clin Med* 3(1) 2014, pp. 280–309.

76 Paul R Billings – Ruth Hubbard – Stuart A Newman, Human germline gene modification: a dissent. *Lancet* 353(9167) 1999, pp. 1873–1875, 1874.

77 Adashi – Cohen 2020, pp. 315–317.

78 Stephen Wilkinson, *Choosing Tomorrow’s Children: The Ethics of Selective Reproduction*. Oxford University Press 2010, p. 149.

selection without raising the issue of deciding on the life itself.⁷⁹ It is then presented that germline editing, as it allows all children to be born while safeguarding their right to the highest attainable standard of health, could present itself as just as acceptable or even more acceptable option – only that embryo selection is morally accepted in several European states for the prevention of serious illnesses while germline editing is not.⁸⁰ These issues with discrimination along with societal implications and effects on social sustainability will be further discussed in the later sections of this article.

6.2.2.5 The Question of Autonomy and Reproductive Rights

Autonomy is one of the further consequences deriving from human dignity.⁸¹ To better explain this link between human dignity and autonomy, it can be understood in the sense that the right to self-determination also underpins respect for the integrity of the individual.⁸² Respecting the principle of human dignity is thus assumed to require taking the person into account as an autonomous individual who chooses their own destiny.⁸³ Following up on this thought, one of the reasons why somatic gene therapy is considered much less problematic in this sense is that its direct effects are only limited to the treated child but not his or her possible future descendants.⁸⁴ Thus, upon closer investigation, one of the issues with germline editing appears to stem from how it fails to respect the autonomy of the yet-unborn individuals that are inevitably affected by the parental decision. This viewpoint is particularly challenging when considering that the effects of germline

79 Report of the IBC on updating its reflection on the Human Genome and Human Rights, p. 26, where it is stated that this could further help reduce the controversies around respecting the right to life.

80 On further discussion on the ethics of selection, see Alix Lenia Hammerstein – Matthias Eggel – Nikola Biller-Andorno, Is selecting better than modifying? An investigation of arguments against germline gene editing as compared to preimplantation genetic diagnosis. *BMC Medical Ethics* 20:83 2019.

81 This, as argued by Nordberg et al., is apparent from Article 6 of the Universal Declaration on the Human Genome and Human Right as well as Article 11 of the Universal Declaration on Bioethics and Human Rights, adopted by the UNESCO General Conference on 19 October 2005. See Nordberg – Minssen – Holm – Horst – Mortensen – Lindberg Møller 2018, p. 52.

82 Mansnérus 2016, p. 32. Interestingly, as noted by Mansnérus, the individual right to self-determination has not been mentioned in the Biomedicine Convention nor in the Explanatory Report.

83 On respect of autonomy among the principles of medical ethics, see Raanan Gillon, Ethics needs principles—four can encompass the rest—and respect for autonomy should be ‘first among equals’. *J Med Ethics*, 2003;29(5):307–12.

84 Roberto Andorno, The Oviedo Convention: A European Legal Framework at the Intersection of Human Rights and Health Law, 140, *Journal of International Biotechnology Law*, 2005, 02 I: 133–143.

therapy are understood to be irreversible as the autonomy of the future individual is compromised without the ability to ever decide otherwise.⁸⁵

In addition to the above-described safety issues, dissenting opinions often refer to this lack of autonomy, describing the legal permission to specifically alter the lives of unborn individuals ‘unprecedented and unjustified’.⁸⁶ Some even go as far as stating that germline editing would result in ‘generations of nonconsent’ as the inheritable alterations would first present themselves in the genome of the child and then in the subsequent generations.⁸⁷ As legislation otherwise allows parents to make medical decisions on behalf of their children given that such decisions are in the best interest of the child, some authors hold that the consent would not be required for the first edited generation or even for the generations that follow as ‘non-existent beings’ cannot be subjects of such rights.⁸⁸ From the human rights perspective, the Council of Europe does appear to be in line with this principle in its Recommendation on Genetic Engineering, stating that in cases of experiment with embryos, gene therapy must not be used ‘except with the free and informed consent of the parents or legal guardians’.⁸⁹ This refers to the possibility of gene therapy being undertaken with the consent of parents, thereby neglecting the idea of the autonomy of future generations.

Clinical applications of germline modification also involve the question of the prospective parents’ reproductive rights. The strengthened understanding of what the right to privacy and family life should contain has gradually extended to rights relating to reproductive health – albeit historically, reproductive rights have not always extended to the prospective parents’ right to become parents let alone to choose what characteristics their child will have in terms of health and well-being.⁹⁰ For one example, the number of parents driven to undergo reproductive screening shows a continually increasing trend: undergoing these screenings has

85 This argument, however, applies to all other conditions that the child inherits even without modifications on the germline.

86 Paul R Billings – Ruth Hubbard – Stuart A. Newman, Human germline gene modification: a dissent, *Lancet* 1999; 353: 1873–1875.

87 Niklaus H Evitt – Shamik Mascharak – Russ B Altman, Human Germline CRISPR-Cas Modification: Toward a Regulatory Framework. *Am J Bioeth* 15(12) 2015, pp. 25–29, 27.

88 *Ibid.*

89 The Council of Europe, Committee of Ministers, Recommendation 934 (1982) on Genetic Engineering, paragraph 4. c.

90 Another example of how reproductive rights have formed positive obligations for the state is the provision of infertility treatments to single women. Here, the right to have a family is considered more important than the child’s right to be born into a family of two parents. See Sakari Salminen – Riitta Burrell – Lasse Lehtonen: *Hedelmöityshoidot, lisääntymisvapaus ja lapsen etu. Oikeustiede-Jurisprudentia* 2007:XL, pp. 303–404, 333.

not only become the norm, but it is now common to terminate the pregnancies where the child is suspected of having severe developmental defects.⁹¹

It is also worth noting that in other medical matters, parents also make decisions on behalf of their child – although the legal status of the unborn child makes a similar assessment difficult. The future legal entity does not have a real separate right to self-determination, while parents have the right to prenatal autonomy, which grants them the right to decide the fate of their yet-unborn children. By analogy, I consider this to take place in the form of expectant mothers with substance abuse problems who are granted autonomy in terms of their decisions despite any detrimental effects they may have on the future individual.⁹² The judgment of the European Court of Human Rights below highlights how far the limits of parental autonomy can truly extend, the case concerning an action in favour of the condemnation of Italy for violating the ECHR as Italian legislation did not allow couples to resort to PGD while simultaneously allowing selective abortions.

In the judgment *Costa and Pavan v. Italy* of 28th August 2012, No. 54270/10, the Court interpreted the concept of parental autonomy against human dignity. The applicants in this case were an Italian couple who had learned that they were carriers of cystic fibrosis as their first child was born with the condition. In the quest to avoid their other children to also suffer from the effects of the disease, they wanted to use preimplantation genetic diagnosis which would allow the genetic selection of an embryo free from cystic fibrosis.⁹³ The Italian Government justified the ban on their recourse to PGD inter alia due to the interest in precluding the risk

91 Hannah Lou, *Eugenics Then and Now: Constitutional Limits on the Use of Reproductive Screening Technologies*, *Hastings Constitutional Law Quarterly* 42(2) 2015, pp. 393–414. This ‘modern culture of pregnancy’ is characterized to reflect what the author calls an ‘unspoken discomfort with human disabilities and imperfections’ that, coupled with a bias towards termination when abnormalities are found, creates justifications and attitudes for interference with nature. As a personal thought, it is possible that a great variable in what the term ‘reproductive rights’ has comprised of over time has been the simple fact that the inherited conditions of an unborn child could not have been previously affected at all – many children, as they have traditionally been brought into this world, have been born without the parents setting too many expectations on the possibility to affect the health status of their child. With the availability of new diagnostics and therapies, this paradigm is now shifting.

92 See Merike Helander, *Päihdeongelmaisen odottavan äidin itsemääräämisoikeus vai lapsen etu?*, pp. 61–100 in Raimo Lahti (ed.), *Biolääketiede, tutkimus ja oikeus*. *Forum Iuris* 2012, pp. 87–88. On the feminist aspects of this discussion, see Riitta Burrell, *Naisia ja sikiöitä: Avustetusta lisääntymisestä ja sikiön oikeuksista*. *Forum Iuris* 2003, pp. 22–23.

93 *Costa and Pavan v. Italy* of 28th August 2012, No. 54270/10, para. 3.

of eugenic selection.⁹⁴ The Court, however, concluded that where Italy, on the one hand, banned the use of PGD, but on the other hand, allowed the applicants to abort a foetus affected by the disease, this inconsistency in Italian legislation violated Article 8 of the Convention guaranteeing the right to the respect of private and family life.⁹⁵

This decision is argued to constitute an important step in the recognition of prospective parents' right, as phrased by the Court, 'to bring a child into the world who is not affected by the illness that they carry'.⁹⁶ In a commentary for the case, it was argued that the right to a genetically healthy child in fact equals the 'right to eugenics', further envisaging the 'improvement of the human condition by a greater technological mastery of individual and collective existence'.⁹⁷ It is noteworthy that in the preparatory works of the Finnish Fertility Treatments Act, instead of referring to any types of eugenic practices, the prohibition on germline modification was justified only generally on the grounds of protecting the interests and dignity of the child.⁹⁸

On the national level, the Supreme Court of Finland has assessed how to balance the question of parental autonomy and best interests of the child in cases of elective surgery performed on children for religious or cultural reasons. In its conclusions, the Supreme Court stated that when exercising parental rights, account must be taken of any restrictions arising from fundamental rights, and in the event of any conflict, the guardians should seek to find solutions that are in the best interests of the child.⁹⁹

On the basis of the above, parents may, therefore, have the right to decide on behalf of their child on measures that interfere with the child's physical integrity, given that such measures intend to promote the child's welfare and development.

94 *Costa and Pavan v. Italy*, para. 46.

95 *Costa and Pavan v. Italy*, paras 64 and 71.

96 *Costa and Pavan v. Italy*, para. 65.

97 Gregor Puppink, *The Case of Costa and Pavan v. Italy and the Convergence between Human Rights and Biotechnologies. Commentary on the ECHR Ruling in Costa and Pavan v. Italy*, No. 54270/10, 28th August 2012 (July 1, 2013). *Quaderni di Diritto Mercato Tecnologia* - N°3, Anno III, pp. 152–177, 171.

98 Government proposal 3/2006, pp. 27–28. As noted by Salminen et al., historically, the same grounds of protecting the interests of the child also worked to justify forced sterilisations or abortions, but these would now be considered obvious violations of human dignity and of fundamental rights. See Salminen – Burrell – Lehtonen 2007, p. 348.

99 KKO 2008:93, para. 23.

In particular, when this concerns the child's health status on which in the most serious of cases even the child's right to life might be dependent on, this question should be balanced to secure the welfare of the future person rather than just noting on the physical integrity of descendants. I am inclined to challenge the worth of respecting the physical integrity of descendants if those descendants' quality of life is greatly reduced as a result – if they are even capable of living at all. This is also why I propose looking at an alternative approach toward securing human dignity in this field.

6.3 Doctrinal Reassessment: Blurring the Lines between Somatic and Germline Interventions

The ethical and legal issues raised by genome editing might differ according to their field of application. While proponents for drawing these distinctions state that they help clarify the typical ethical and legal distinction between acceptability and unacceptability, the line between somatic and germline cells is argued not to be '100% impermeable in principle'.¹⁰⁰ Similarly, others have raised the question of whether this differentiation between somatic and germline interventions should be upheld, particularly when considering that somatic gene therapy can also have side effects on the human germline.¹⁰¹ Further blurring the artificial distinction of drawing the line between somatic and germline interventions, the Nuffield Council on Bioethics suggests assessing the acceptability of such therapies on two leading principles: the welfare of the future person and social justice and solidarity.

6.3.1 Protecting the Welfare of the Future Person

From the perspective of human dignity, drawing the distinction between therapeutic interventions versus enhancement as well as the distinction between somatic and germline interventions shown to be more difficult in practice than it seems on paper. The Nuffield Council on Bioethics has recognised this difficulty of

100 Hermann Garden – David Winickoff, *Gene editing for advanced therapies: Governance, policy and society*, OECD Science, Technology and Industry Working Papers. OECD Publishing 2018, No. 2018/12.

101 Jens Reich – Heiner Fangerau – Boris Fehse – Jürgen Hampel – Ferdinand Hucho – Kristian Köchy – Martin Korte – Bernd Müller-Röber – Jochen Taupitz – Jörn Walter – Martin Zenke, *Human Genome Surgery – Towards a responsible evaluation of a new technology*. Analysis by the Interdisciplinary Research Group Gene Technology Report. Berlin-Brandenburg Academy of Sciences and Humanities 2015, p. 14.

drawing a clear distinction between different types of human applications for gene therapy and instead suggests that the primary focus should rely on the welfare of the future person by formulating the principle as follows:

‘Gametes or embryos that have been subject to genome editing procedures (or that are derived from cells that have been subject to such procedures) should be used only where the procedure is carried out in a manner and for a purpose that is intended to secure the welfare of and is consistent with the welfare of a person who may be born as a consequence of treatment using those cells.’¹⁰²

The above represents a very different mindset from the interpretation of the central human rights around this issue than those presented the interpretations of human rights instruments and Community law. It deviates away from the traditional understanding of the concept of human dignity, rather focusing more on the potential benefits of the technology, stating that it could potentially reduce unnecessary human suffering and untimely death from diseases that could be prevented with its therapeutic applications. Further, it even suggests that the principle of protecting the welfare of the future person respects human dignity rather than violates it.

6.3.1.1 Procreative Beneficence and the Risk of Instrumentalisation

The concept of human dignity is further argued to be inseparably linked to the prohibition of human instrumentalisation.¹⁰³ This principle is widely recognised by European bioethics legislation along with the UNESCO International Bioethics Committee which in its report provides how human dignity entails the duty to refrain from reducing anyone to a ‘mere instrument for the fulfilment of the wishes and preferences of others’.¹⁰⁴ The origins of this principle are understood to derive from the second formulation of Kant’s universal moral law, the categorical imperative, which reads as follows:

¹⁰² Nuffield Council on Bioethics 2018, p. 75.

¹⁰³ Foster 2011, pp. 43–57.

¹⁰⁴ Report of the IBC on updating its reflection on the Human Genome and Human Rights, p. 11, where the Report of the IBC states that ‘the responsibility to future generations is important because it respects the rights of those coming into life later on. It is also important for our social relationships, for a society in solidarity and for justice between all peoples to keep in mind that the respect for the dignity of every human being entails the duty to refrain from making her or him a mere instrument for the fulfilment of the wishes and preferences of others’.

‘Handle so, dass du die Menschheit sowohl in deiner Person, als in der Person eines jeden anderen jederzeit zugleich als Zweck, niemals bloß als Mittel brauchst.’¹⁰⁵

The risk of instrumentalisation is recognised as one of the concerns relating to germline editing. This is due to the fact that through germline editing, coming into existence is argued to be no longer left to chance but depends on certain genetic preconditions.¹⁰⁶ This, in turn, risks undermining the right to self-determination as the child is treated as a means of fulfilling parental or societal expectations.¹⁰⁷ Indicating respect for individuals as ends-in-themselves is well recognised in the European legal culture even on the level of the basic ethical principles in bioethics and biolaw, although arguably understood through the lenses of cultural differences and local variations.¹⁰⁸ As an opponent to this thought widely accepted and manifested in European bioethics and human rights tradition, Julian Savulescu has put forward the idea of procreative beneficence, essentially stating that it is instead a moral imperative for us to create the ‘best’ individuals possible.¹⁰⁹ This putative obligation to produce the ‘best’ child appears to be internal to the parents’ own desire to be motivated by concern for the wellbeing of their future child in selecting against genetic illnesses.¹¹⁰

Other views have posed a critical review towards the concept of instrumentalisation, pointing out that referring to human dignity to prohibit germline is more or less pretentious, as to some it seems ‘obvious’ that choosing not to edit the genome of this embryo would imply treating the embryo as a mere means and not as an end in itself.¹¹¹ I still must add to this discussion that various other reproductive technologies apply the concept of genetic selection to screen out severe genetic illnesses. As provided in the judgment of *Costa and Pavan v. Italy*,

105 ‘Act so that you treat humanity, whether in your own person or in the person of any other, always at the same time as an end, never merely as a means to an end.’ Immanuel Kant, *Grundlegung zur Metaphysik der Sitten*. Johann Friedrich Hartknoch 1785, p. 429.

106 On the discussion around genetic preconditioning, see also Alix Lenia Hammerstein – Matthias Eggel – and Nikola Biller-Andorno, Is selecting better than modifying? An investigation of arguments against germline gene editing as compared to preimplantation genetic diagnosis, *BMC Medical Ethics* 20(83) 2019, p. 3.

107 *Ibid.*

108 Jacob Dahl Rendtorff, Basic ethical principles in European bioethics and biolaw: Autonomy, dignity, integrity and vulnerability – Towards a foundation of bioethics and biolaw. *Medicine, Health Care and Philosophy* 5/2002, 235–244, 235.

109 Julian Savulescu, Procreative Beneficence: Why We Should Select the Best Children, *Bioethics* 15(5) 2001, pp. 413–426, 413.

110 Savulescu 2011, 416–417.

111 de Miguel Beriain 2018.

this is not viewed as such to constitute a problem from the perspective of human rights, although the same arguments that apply to the risk of instrumentalisation of the unborn human by means of germline editing apply to PGD and other prenatal screening technologies as well. This is not to say that these could not be problematic from other perspectives such as health inequities on a societal level, but in terms of instrumentalisation, this does not seem to pose a convincing argument for these technologies to violate human dignity.

6.3.1.2 *'Slippery Slope' Arguments*

Some authors have based their opposition on permitting any types of therapeutic interventions for the human germline on the argument that even unambiguous cases of curing severe hereditary illnesses could eventually become a step on a path towards non-therapeutic genetic enhancement.¹¹² These researchers in the field share the concerns that if therapeutic interventions on the human germline were permitted, it would start a path towards non-therapeutic enhancement.¹¹³ One of the aspects relating to this criticism is that even if editing the human germline for therapeutic purposes were considered acceptable, such editing would also inevitably lead to non-therapeutic applications.¹¹⁴ These 'slippery slope' arguments essentially state that while all gene editing is based on the initial justification of curing severe illnesses, the line between therapy and enhancement will inevitably become more blurred, slowly leading up to dystopian scenarios.¹¹⁵ This thought discourages germline editing even in cases where germline editing would benefit

112 Douglas Walton, The slippery slope argument in the ethical debate on genetic engineering of humans, *Sci Eng Ethics* 23(6) 2017, pp. 1507–1528.

113 Edward Lanphier – Fyodor Urnov – Sarah Ehlen Haecker – Michael Werner – Joanna Smolenski, Don't edit the human germ line, *Nature* 519(7544) 2015, pp. 410–411, 411. Harari even carefully describes how such development could take place: 'The same might happen with genetic engineering. If a billionaire openly stated that he intended to engineer super-smart offspring, imagine the public outcry. But it won't happen like that. We are more likely to slide down a slippery slope. It begins with parents whose genetic profile puts their children at high risk of deadly genetic diseases.' Harari 2016, p. 52–53.

114 Matti Häyry, *Rationality and the Genetic Challenge: Making People Better?* Cambridge University Press 2012, p. 193 and Lehtonen 2006, p. 36.

115 Wibren van der Burg, Slippery Slope Arguments, pp. 129–142 in Ruth Chadwick (ed.): *Encyclopedia of Applied Ethics*, Vol. 4. Academic Press 1998, p. 129. As noted by de Araujo 2017, p. 28, these dystopian futures are depicted in popular culture in films like *Gattaca* (1997) and novels such as Aldous Huxley, *Brave New World*. Chatto & Windus 1932.

the welfare of the future individual since it would also eventually lead to pursuing genetic human enhancement, which the authors consider morally wrong in itself.¹¹⁶

In addition to the hopes of curing genetic illnesses that have been difficult to treat up to now – and the occasional reference to the possibility of human enhancement – the main response relates to fear and concern about the possible abuse of the technology.¹¹⁷ Honnefelder describes this fear as an expression of fundamental moral intuitions, further asserting that such intuitions are very important and, in accordance with the ‘heuristics of fear’, should not be ignored.¹¹⁸ As Honnefelder insightfully points out, however, like slippery slope arguments, these moral intuitions still cannot substitute for a thorough examination and judgment based on moral and legal principles.¹¹⁹ Honnefelder continues to argue that such legal and ethical discussions still face certain difficulties, including the fact that the suggested procedures are new and therefore they first need to be identified and accurately described. After achieving this, the consequent step of applying our moral and legal standards and principles requires that we classify the new procedures based on our experiences – and the difficulty is that because these procedures are new, our experiences are not always applicable. Still, since ethics and legislation refer to actions, these actions must be identified and described accurately and in accordance with the general consensus.¹²⁰

116 Douglas Walton, *The slippery slope argument in the ethical debate on genetic engineering of humans*. *Sci Eng Ethics* 23(6) 2017 pp. 1507–1528, 1527, where he systematises this concept by stating that it actually divides into two main different slippery slope arguments: first one argues that current developments will blur the boundary between somatic and germline interventions; this argument more specifically presumes that the acceptance of germline gene therapy ‘is a catastrophic outcome in its own right’; the second one argues that once germline gene therapy is established as an acceptable medical procedure, it will inevitably be used for genetic enhancement as well – the latter argument is not, however, against the acceptance of germline gene therapy per se.

117 Ludger Honnefelder, *Human Rights and Democracy in the Face of Scientific and Medical Developments – Defending Scientific, Medical and Technological Ethics*, *Nordic Journal of Human Rights* 1(22) 2004, pp. 36–37.

118 Honnefelder 2004, pp. 17–18. On the concept of heuristic of fear, see Hans Jonas, *The Heuristics of Fear*, pp. 213–221 in Melvin Kranzberg (ed.), *Ethics in an Age of Pervasive Technology*. Westview Press 1980.

119 Ludger Honnefelder, *Science, Law and Ethics: The Biomedicine Convention as an Ethico-legal Response to Current Scientific Challenges*, pp. 13–22 in J.K.M. Gevers – E.H. Hondius – J.H. Hubben (eds.), *Health Law, Human Rights and the Biomedicine Convention: Essays in Honour of Henriette Roscam Abbing*. Martinus Nijhoff 2005.

120 Honnefelder 2005, p. 18.

6.3.2 Social Justice and Solidarity

While conforming to the principle of protecting the welfare of the future individual is in all instances necessary, it is not alone sufficient to make such edits morally permissible.¹²¹ Based on this conclusion, the Nuffield Council forms the second leading principle of germline editing on social justice and solidarity:

‘The use of gametes or embryos that have been subject to genome editing procedures (or that are derived from cells that have been subject to such procedures) should be permitted only in circumstances in which it cannot reasonably be expected to produce or exacerbate social division or the unmitigated marginalisation or disadvantage of groups within society.’¹²²

The UNESCO International Bioethics Committee also notes that respect for the dignity of every human being is important for not only our social relationships but ‘a society in solidarity and for justice between all peoples’.¹²³ This concept of solidarity, broadly understood as a mutual obligation to assist one another, is listed among the principles that bioethics commentators have traditionally placed value on in the European context, also justifying a strong involvement of state authorities in public healthcare.¹²⁴ European bioethics have indeed argued to be characterised by the principle of solidarity, which results in human dignity further expressing the intrinsic value of the human being in a community or society.¹²⁵

6.3.2.1 *The Concern of Widening Societal Divisions*

When considering the acceptability of germline editing from the perspective of human dignity, it is to be understood that the concept also touches upon broader societal issues – respect for human dignity also consequently requires respect for diversity, non-discrimination, and non-stigmatisation.¹²⁶ This understanding of ‘human dignity as a constraint’ essentially states that human dignity may also pose restraints to individuals despite autonomy comprising part of human

¹²¹ Nuffield Council on Bioethics 2018, p. 75.

¹²² Nuffield Council on Bioethics 2018, p. 87.

¹²³ Report of the IBC on updating its reflection on the Human Genome and Human Rights, p. 33.

¹²⁴ See Amir Muzur – Iva Rinčić, The Oviedo Convention and (European) bioethics: how much do they really have in common? *Jahr* 8(16) 2017, p. 248, and Prainsack, Barbara – Alena Buyx, Solidarity: Reflections on an emerging concept in bioethics. Nuffield Council on Bioethics 2011, p. 22.

¹²⁵ Jacob Dahl Rendtorff, Basic ethical principles in European bioethics and biolaw: Autonomy, dignity, integrity and vulnerability – Towards a foundation of bioethics and biolaw, *Medicine, Health Care and Philosophy* 5/2002, pp. 235–244, 237.

¹²⁶ Nordberg – Minssen – Holm – Horst – Mortensen – Lindberg Møller 2018, p. 52.

dignity.¹²⁷ While the UNESCO International Bioethics Committee also recognises that the benefits resulting from advancements in human genetics having an impact on health protection and health care should be considered as content of the fundamental right of every human being to enjoy the highest attainable standard of health, scientific progress should not deepen inequalities within and among countries nor be used for discriminating against individuals or groups.¹²⁸ Some populations or individuals having a genetic advantage over others is thus understood to represent a social problem that relates not only to the inequity itself but also to the social and health inequality regarding access.¹²⁹

Regarding the societal connection on human dignity and human rights, Article 3 of the Biomedicine Convention further underlines how ‘the interests and welfare of the individual should prevail over the sole interests of science or society’.¹³⁰ I believe that this principle also leads to the conclusion that while we should carefully consider these wider societal concerns presented above, when the welfare of a child is truly at stake – as is the case with severe hereditary illnesses – these sole societal interests cannot override the interests and welfare of the future individual. Simultaneously, however, this Article should not be misunderstood in the sense of only focusing attention on individuals and removing society from its responsibilities and requirements of social solidarity. As emphasised by the UNESCO International Bioethics Committee, genetic profile and other factors of individual biology are not the only factors dictating rules for individual adaptability to social conditions and the environment.¹³¹ This further allows room for us to

¹²⁷ Beylerveld – Brownsword 2011, pp. 29–47.

¹²⁸ Report of the IBC on updating its reflection on the Human Genome and Human Rights, p. 9. The IBC notes the following: ‘Effects of discrimination and stigmatization can also occur with regard to prenatal and preimplantation genetic testing. The consequence of detecting a genetic abnormality is very often not a therapeutic intervention for the unborn child, which may be simply impossible. Even though some diagnoses have led to treatment in utero, the more likely consequence is resorting to abortion or discarding the embryo. Erroneous or misinterpreted results could lead to the destruction of healthy and normal embryos or fetuses. The introduction of non-invasive prenatal diagnosis is being increasingly implemented as a routine measure during early stages of pregnancy, especially in countries with an established system of technique-based pregnancy care. This could have a major impact not only on reproductive freedom, but also on the perception of disability and on societal solidarity with disabled people and women who give birth to them.’

¹²⁹ Eduardo Rodriguez Yunta, Ethical Issues in Genome Editing using Crispr/Cas9 System, *J Clin Res Bioeth* 7(2) 2016, 1000266.

¹³⁰ On the contrary, commentators have noted that the Biomedicine Convention has through this approach diminished the importance of the society and thus taken a step towards denying the typically European principle of solidarity. See Muzur – Rinčić 2017, p. 248.

¹³¹ Report of the IBC on updating its reflection on the Human Genome and Human Rights, p. 11.

consider the societal aspects of germline editing, to which also the issues around selection and discrimination are closely connected.

6.3.2.2 *The Issues Around Selection and Discrimination*

The assessment of whether human germline editing could be contrary to human dignity is similar to the question of procreative rights, especially relating to the use of IVF procedures.¹³² Both allow selecting for avoiding severe genetic conditions, and since PGD also includes selecting out disability and disease, it too can be considered a form of eugenics.¹³³ These practices have also been said to increase social pressure upon parents, as opting out of such practices could be perceived as prospective parents ignoring the health status of their future child.¹³⁴ This, according to Sandel, could represent a detrimental level of ‘hyperagency’ to mastering every aspect of life, in particular the aspect of reproduction.¹³⁵ Germline editing could thus have collateral and indirect effects on other people in society as well through the widening of existing differences between people due to access.¹³⁶ This is also why the Nuffield report also faced critical reviews arguing that germline editing would be socially dangerous owing to the disparity that would result from allowing those who can afford such procedures to edit the genomes of their own children. Without access to germline gene therapy for prospective parents who do not possess the financial means required, the pre-existing differences between those of a different socio-economical standing would widen as long-term effects of such interventions.¹³⁷

Voices of marginalised groups have further issued their concerns relating to the selective reproductive technologies communicating something about the society perceiving the lesser status or value of disabled people. This is not only argued to cause psychological damage but also wider harm through the effects on broader social attitudes towards disabled people.¹³⁸ Under this ‘expressivist objection’, selecting against the birth of those suffering from genetic illnesses expresses a discriminatory attitude and sends a harmful message about disabled

¹³² De Araujo 2017, pp. 24–42.

¹³³ Wilkinson 2010, p. 149.

¹³⁴ Michael J Sandel, *The case against perfection: ethics in the age of genetic engineering*. Harvard University Press 2007, p. 62.

¹³⁵ *Ibid.*

¹³⁶ Nuffield Council on Bioethics 2018, pp. 79–80 and Emmanuelle Tuerlings, *Background Paper Governance 1 Human Genome Editing*. WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing 2019.

¹³⁷ Walters – Palmer 1997, p. 83.

¹³⁸ Bjørn Hofmann, ‘You are inferior!’ Revisiting the expressivist argument. *Bioethics* 31(7) 2017, pp. 505–514.

people also to wider society through the health policies that promote such actions through allowing, funding, or recommending its use.¹³⁹ When there is a shift in expectations, the social acceptance of those conditions may decrease. I not only share these concerns but consider the possibility of discrimination to be two-sided – in addition to those facing challenges with the issue today, I see here the theoretical possibility a new group of genetically edited children being discriminated against due to being viewed as ‘less human’ and individuals with an unedited genome presented as more ‘pure-blood’ humans.¹⁴⁰

Referring back to the judgment *Costa and Pavan v. Italy* of 28th August 2012, No. 54270/10, it is still significant to note how despite Italy arguing that respecting the prohibition of discrimination for genetic reasons would have required stepping away from any practices where the selection of embryos was necessary, the Court did not accept this reasoning due to the inconsistency of practices around PGD and selective abortions.¹⁴¹ Thus, based on this conclusion, in cases where other forms of selective reproduction technologies are available, even if they exist only to prevent a serious genetic illness, germline editing cannot be denied on the grounds of wanting to avoid genetic discrimination. Still, if such practices were to become commercialised and further normalised, this could lead to a shift in norms relating to the expectations of its use.¹⁴² While it might be difficult to predict the exact consequences that these technologies could have on a wider societal level, all of these factors require evaluation before moving forward with clinical applications – and bear directly on the risk-benefit analysis and the assessment of the justification for any given use.¹⁴³

Referring to the reasoning above, however, the effort to cure and prevent severe genetic illnesses and the premature death that follows seems to be of overriding importance, and arguably, for therapeutic applications, the assessment of human dignity does not provide a clear justification for the prohibition of germline gene therapy in clinical settings – in my view, the arguments in favour of therapeutic use

139 Nuffield Council on Bioethics 2018, p. 83.

140 I believe this example is even comparable to the discrimination that Muggle-born wizards face in Harry Potter, a series of fantasy novels written by British author JK Rowling, where they are being called ‘mudbloods’ solely because of their background while wizards with no Muggles or Muggle-borns on their family tree receive the title of ‘pure-bloods’.

141 *Costa and Pavan v. Italy* of 28th August 2012, No. 54270/10, paras 64 and 71.

142 On this idea of shifting social norms and ‘progress’, see the Nuffield Council on Bioethics 2018, p. 78–79.

143 Sarah Chan – Peter J Donovan – Thomas Douglas – Christopher Gyngell – John Harris – Robin Lovell-Badge – Debra J. H. Mathews – Alan Regenberg, Genome editing technologies and human germline genetic modification: The Hinxton group consensus statement. *Am J Bioeth* 15(12) 2015, pp. 45–46.

seem to supersede those opposing it on the grounds of human dignity. I am aware, however, that this might not be the conclusion of some Member States where their national identity and own human rights tradition place more importance on other basic principles on European bioethics; but given the value that these technologies could have in terms of safeguarding the best interests of the child, I believe it is worth discussing whether we can find a balance with these values through embracing the doctrine of European pluralism.

6.3.3 Balancing European Pluralism with Religion in Bioethical Discussion

Along with the above-discussed principles, the human rights tradition that is reflected in European bioethics also includes the tradition of pluralism. European pluralism essentially refers to accepting the various moral codes and their differences between states, allowing them to decide on ethically sensitive matters where no clear consensus exists. Simultaneously, the principle of pluralism promotes states to adhere to the agreed human rights principles, including that of pluralism.¹⁴⁴ The adopted ‘united in diversity’ approach to ethics can be respected to allow European states to freely select and decide on the level of protection of the accepted values.¹⁴⁵

While inevitably influenced by the historical events that have shaped the European culture to what it is today, the concept of human dignity in the context of the integrity of the human genome is understood to also strongly rely on the Judeo-Christian roots.¹⁴⁶ Due to the later attempts to avoid reference to religion, the concept of human dignity in legal texts has reached a level of self-evidency – and once detached from this theological framework, the pragmatic considerations reflected in human rights conventions are described to have turned into a ‘semi-

¹⁴⁴ This ‘cultural regionalism’ is built on the idea of subsidiarity under which European states interpret these principles according to the particularity of their specific convictions. See Dahl Rendtorff 2002, p. 235. This principle of subsidiarity is also referred to in Article 5(3) of the Treaty on European Union, which provides that in areas which do not fall within its exclusive competence, the Union shall act only if and in so far as the objectives of the proposed action cannot be sufficiently achieved by the Member States, either at central level or at regional and local level, but can rather, by reason of the scale or effects of the proposed action, be better achieved at Union level.

¹⁴⁵ Markus Frischhut, *The Ethical Spirit of EU Law*. Springer 2019, p. 231.

¹⁴⁶ Yechiel Michael Barilan, *Human Dignity, Human Rights, and Responsibility. The New Language of Global Bioethics and Biolaw*. MIT Press, 2014.

fictional, semi-real status “ascribed” to the person as such’.¹⁴⁷ Community law is understood to also have been shaped by religion, but it is also argued that the relationship between religion and the Union law operates in both directions: while the Union recognises the promotion of *ordre public* and morality as a valid basis of law and thus enables religious norms to influence the content of Community law, the Union is argued to have the power to also impact the role that religion has in Europe as of today.¹⁴⁸ For germline gene therapy, the sanctity of the human genome relies in particular on Catholic views where the man is seen as *Imago Dei*, the ‘image of God’, which also influences how the meaning and importance of human dignity and its implications in bioethics are understood to vary even between European countries.¹⁴⁹ The different approaches that Member States have adopted on this issue highlights the fact that no European consensus exists on balancing bioethical principles with religious views, including the relationship between religion and human dignity.¹⁵⁰

Through strict regulation on research leading up to the advanced therapy medicinal products associated with germline therapy as well as assisted reproduction services, the use of medical applications of gene editing is already carefully controlled in European countries.¹⁵¹ Indeed, I believe that not only should be up to the national legislator to decide how to regulate the advances that gene-editing technologies offer in human applications – further requiring flexibility in

147 Aurel Kolnai, Dignity. *Philosophy* 51(197) 1976, pp. 251–271, 259. On contrasting thoughts, see Lisa Sowle Cahill, Germline genetics, human nature, and social ethics, pp. 145–166 in Ronald Cole-Turner (ed.), *Design and Destiny: Jewish and Christian Perspectives on Human Germline Modification*. MIT Press 2008. Cahill reports from the Jewish and Christian perspective that germline modification could be acceptable for therapeutic, although not for enhancement purposes.

148 Ronan McCrea, *Religion and the Public Order of the European Union*. Oxford University Press 2010, p. 2.

149 Rendtorff – Kemp 2000, p. 143.

150 For example, the Irish constitution strongly respects human dignity described to derive from the Catholic doctrine of the sanctity of life, which is reflected in particular in the protection of the life of the unborn individual as essential to the idea of human dignity. The debate between Catholic and secular bioethics highlights the Italian discussion around these basic principles. The Netherlands, by contrast, exercises the principles of tolerance, autonomy, and pluralism, also visible in the liberal views on other bioethical issues like euthanasia. For further examples, see Rendtorff – Kemp 2000 p. 195.

151 As provided by Article 9(1) of the Additional Protocol to the Convention on Human Rights and Biomedicine concerning Biomedical Research (CETS No. 195), every research project shall be submitted for independent examination of its ethical acceptability to an ethics committee. Along with these ethical reviews preceding clinical trials, data protection legislation, funding policies, and applying for marketing authorisation, obtaining reimbursement from public healthcare systems further remains an imperative for commercial success in the Union and thus presents itself as an effective mechanism in regulating these technologies. On further control mechanisms, see Mansnérus 2016, pp. 93–99.

the other regulatory areas where this issue is harmonised in the Union – but that the time might be right for reassessment on the national level as well.¹⁵²

6.4 Conclusions

This article has provided an insight into the complex relationship between the currently existing direct and indirect regulation mechanisms surrounding germline editing and the safeguarding of the best interests of the child. First, it has highlighted the connection on how any prohibitions against germline gene therapy are understood to mainly rely on the concept of human dignity where they are argued to respect the physical integrity of descendants as well as the integrity of the genome. After reviewing the human dignity aspects in terms of uses for germline gene therapy, I have questioned whether a consensus truly exists on therapeutic applications offending against human dignity once the safety issues around these technologies are adequately resolved. Balancing the legal-ethical principles on the child's right to enjoy the highest attainable standard of health along with the parents' reproductive rights might just as well as work to justify clinical applications in this field – this all relies on how each state balances these basic European bioethical principles touching upon human dignity in their own legal culture. It is also worth arguing that the emphasis we put on each of these values can change – and has changed – over the years among nations. Understanding this development, a less restrictive approach would better reflect the pluralistic views around human dignity. For the view that the Finnish legal culture shares based on the basic principles of bioethics, the position on whether therapeutic applications of human germline editing offend human dignity seems to be dissenting – but for other legal cultures with different emphasis on these values, this might be different.¹⁵³ We should accept these differences as a reflection

¹⁵² The UNESCO International Bioethics Committee also appears to note this possibility and elaborates on how germline editing without any sound medical reason should be discouraged through legislation, further suggesting removal of public resources and in some cases also using prohibitions as examples. See the Report of the IBC on updating its reflection on the Human Genome and Human Rights, p. 26.

¹⁵³ Referring to what has been stated above, see, e.g. Finnish Medical Association 2013, p. 92, where it is stated that passing on the normally-functioning copy of gene be to offspring would be a desirable outcome, and that integrity of the genome should not be considered an intrinsic value.

of European pluralism, understanding how ethics are culturally embedded and thus regional.¹⁵⁴

I have therefore argued that the current human rights perspective should place more focus on the right to the highest attainable standard of health, here considering the best interests of the unborn individual. As the arising gene-editing technologies like CRISPR/Cas9 and prime editing could soon be closing a gap between possibility and reality, the UNESCO International Bioethics Committee has noted that such rapid developments in the field will require continuous reflection and re-interpretation of the principles touching upon human dignity.¹⁵⁵ In efforts to respond to this development, the WHO has recently formed the Human Genome Editing Expert Advisory Committee, advising and making recommendations on global standards for governance and oversight of human genome editing. The European Commission is also in dialogue with the WHO, other international organisations, and Member States on approaches for a global governance framework. The EGE is also currently developing its opinion on gene editing, comprising an analysis of the ethical, societal, and fundamental rights implications of genome editing as well as a set of policy recommendations. These upcoming opinions, reports, and statements will inevitably influence the developments around germline gene editing in Europe, with hopes that when reviewing the issue around human dignity, the best interests of the child will also be considered as a whole.

¹⁵⁴ Inger-Johanne Sand, *Governmentality, Biopolitics and the EU*, pp. 149–170 in Kimmo Nuotio (ed.), *Europe in Search of 'Meaning and Purpose'*. Forum Iuris 2004, p. 169.

¹⁵⁵ Report of the IBC on updating its reflection on the Human Genome and Human Rights, pp. 127–8.

7

Over Ten Years Since the Adoption of the EU Regulation on Advanced Therapy Medical Products — Lessons Learned Thus Far

by LL.D. Juli Mansnérus

Abstract

Advanced therapy medicinal products ('ATMPs') are a heterogeneous class of modern biotechnology medicines encompassing medicinal products based on genes, cells, and tissues. The European Medicines Agency (the 'EMA') and the European Commission issued a joint action plan in late 2017 with the goal of improving the regulatory environment for ATMPs to facilitate the research, development, and approval of these products in the European Union. Regulators around the world are taking measures to create a facilitative regulatory environment that encourages innovation, protects public health, and enables timely patient access to innovative, new therapies whilst ensuring patient safety. In Europe, the role of risk-proportionate adaptations to clinical trials and GMP manufacture along with the EMA's early-access incentives and initiatives are presented as potential facilitators of market entry.

7.1 Introduction

Advanced therapy medicinal products ('ATMPs') are a very heterogeneous class of modern biotechnology medicines encompassing medicinal products based on genes, cells, and tissues. They provide new therapeutic opportunities for many diseases and debilitating injuries to the human body, particularly in disease areas

of unmet medical need.¹ ATMPs were introduced into the EU legislation with the adoption of Regulation (EC) 1394/2007 (Regulation (EC) No. 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No. 726/2004, 2007, hereinafter the ‘ATMP Regulation’). The primary consequence is that all ATMPs in the EU are centrally authorized by the European Commission. In parallel, the Committee for Advanced Therapies (the ‘CAT’), which is the primary scientific committee of the EMA that scientifically evaluates ATMPs, was also established.

The ATMP Regulation amended Directive 2001/83/EC (Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, 2001), which is the overarching directive for medicinal products for human use.² The ATMP Regulation includes several incentives to develop ATMPs: fee reductions for scientific advice, a classification system to determine if investigational products adhere to the definition of ATMPs, and a certification procedure for quality and non-clinical data for small and medium-sized enterprises.³ These two classification procedures are performed by the CAT, and they provide two means of engaging with the European regulators before the marketing authorization process. Overall, similar requirements are in place for ATMPs compared to other medicinal products, including compliance with Good Clinical Practice (‘GCP’) and Good Manufacturing Practices (‘GMP’) during the course of all clinical trials and compliance with post-marketing requirements.⁴

1 Christian K. Schneider – Jilma Paula – Flamion Bernd – Todorova Bruno – Racheva Lyubina – Anna Paphitou – Ivana Haunerova – Toivo Maimets – Jean-Hugues Trouvin – Egbert Flory – Asterios Tsiftoglou – Balázs Sarkadi – Kolbeinn Gudmundsson – Maura O’Donovan – Giovanni Migliaccio – Jānis Ancāns – Maciulaitis, Romaldas – Robert, Jean-Louis – Samuel, Anthony – Ovelgönne, Johannes H – Hystad, Marit – Andrzej Mariusz Fal – Beatriz Silva Lima – Anca Stela Moraru – Peter Turcáni – Robert Zorec – Sol Ruiz – Åkerblom, Lennart – Narayanan, Gopalan – Kent, Alastair – Bignami, Fabrizia – Dickson, J George – Dietger Niederwieser – Maria-Angeles Figuerola-Santos – Ilona G. Reischl – Claire Beuneu – Rosen Georgiev – Maria Vassiliou – Alena Pychova – Mette Clausen – Taina Methuen – Sophie Lucas – Martina Schüssler-Lenz – Vasilios Kokkas – Zsuzsanna Buzás – Niall MacAleenan – Maria Cristina Galli – Aija Linē – Jolanta Gulbinovic – Guy Berchem – Committee for Advanced Therapies (CAT). *Nature Reviews. Drug Discovery*, Vol. 9, No. 3, 2010, pp. 195–201.

2 Paula Salmikangas – Sol Ruiz – Martina Schuessler-Lenz – Patrick Celis – Ilona Reischl – Margarida Menezes-Ferreira – Egbert Flory – Mathias Renner – Nicholas Ferry. *Marketing Regulatory Oversight of Advanced Therapy Medicinal Products (ATMPs) in Europe: The EMA/CAT Perspective*, in: Maria C. Galli – Mercedes Serabian (eds.), *Regulatory Aspects of Gene Therapy and Cell Therapy Products*, *Advances in Experimental Medicine and Biology*. Springer International Publishing 2015, pp. 103–130. https://doi.org/10.1007/978-3-319-18618-4_6.

3 *Ibid.*

4 *Ibid.*

It has been argued that the rigorous regulatory requirements stemming from the ATMP Regulation as well as the high cost of GMP compliance impede the market entry of new advanced therapies. Since the adoption of the ATMP Regulation in late 2008, a small number of ATMPs⁵ has been granted a marketing authorization in the European Union. Yet, it should be noted that the reality is much more complicated. The reasons for the small number of ATMPs in the European market are only partly attributable to the rigorous regulatory requirements. Generally speaking, there are a number of aspects that may constitute obstacles for the market entry of new advanced therapies. Such aspects include, but are not limited to, availability of research funding and capital investments to fund high development costs; uncertainties in intellectual property protection; privacy protection and ethical aspects affecting access to primary materials; disharmonized classification of ATMPs; difficulties in the accommodation of personalized, niche production with industry-scale standards on GMP; difficulties in obtaining pre-clinical and clinical research authorizations as well as the burdensome marketing authorization procedure. Furthermore, the high cost of ATMPs and difficulties in obtaining reimbursement are often mentioned as obstacles for the market access of ATMPs.⁶ However, it should be noted that some ATMPs are granted a hospital exemption at the Member State level. The exemption enables ATMP manufacturing outside of commercialization pathways on a non-routine basis for ATMPs that are custom-made for individual patients. The requirements are not as rigorous as for clinical trials but should include, for example, central manufacturing standards (Article 28 of the ATMP Regulation).

5 As of 26 November 2020 15, to be exact of which 3 have been withdrawn.

6 Juli Mansnérus, *Commercialisation of Advanced Therapies. A Study of the EU Regulation on Advanced Therapy Medical Products*. LL.D. University of Helsinki, Faculty of Law 2016, p. 104.

Table 1. Overview of ATMPs in the European Union

Product	Year of approval	Approval pathway	Product description	Indication ^a	Orphan drug	Validity
Chondro-Celect	2009	Standard	Autologous cartilage cells	Cartilage defects of the knee	N	N
Glybera	2012	Approval under exceptional circumstances	Adeno-associated viral vector for gene delivery	Familial lipoprotein lipase deficiency	Y	Y
MACI	2013	Standard	Matrix applied characterized autologous cultured chondrocytes	Cartilage defects of the knee	N	Y
Provenge	2013	Standard	Autologous peripheral blood mononuclear cells	Prostate cancer	N	N
Imlygic	2015	Standard	Genetically modified oncolytic viral therapy	Melanoma	N	Y
Holoclar	2015	Conditional	Autologous human corneal epithelial cells containing stem cells	Corneal lesions	Y	Y
Strimvelis	2016	Standard	Autologous CD34+ transduced cells with retroviral vector	Adenosine deaminase deficiency (ADA-SCID)	Y	Y
Zalmoxis	2016	Conditional	Allogeneic T cells genetically modified with retroviral vector	Adjunctive treatment in haploidentical hematopoietic stem cell transplantation of adult patients with high-risk hematological malignancies	Y	N
Spherox	2017	Standard	Spheroids of human autologous matrix-associated chondrocytes	Cartilage defects of the knee	N	Y
Alofisel	2018	Standard	Allogeneic mesenchymal stem cells	Complex perianal fistula(s) in adult patients with Crohn's disease	Y	Y
Kymriah	2018	Standard (PRIME)	Genetically modified autologous T cell immunotherapy	Pediatric B-cell acute lymphoblastic leukemia (ALL); Relapsed or refractory diffuse large B-cell lymphoma	Y	Y
Yescarta	2018	Standard (PRIME)	Genetically modified autologous T cell immunotherapy	Relapsed or refractory large B-cell lymphoma	Y	Y
Luxturna	2018	Standard (PRIME)	Voretigene neparvovec	Leber Congenital Amaurosis; Retinitis Pigmentosa,	Y	Y
Zynteglo	2019	Standard (PRIME)	Stem cells taken from the patients that have been genetically modified to contain a working gene for beta-globin	beta thalassaemia	Y	Y
Zolgensma	2020	Standard (PRIME)	Onasemnogene asepavovec	Spinal muscular atrophy	Y	Y

NB: Table lists marketing authorizations until 26 November 2020.

The ATMP field is quite new. Due to the immaturity of technologies and the associated scientific uncertainties, it may be too early to expect results. Many of the current technologies in development are novel, and decade-old inventions are just now reaching the European market. Indeed, ATMPs' road to the market is rather long and requires long-term investment. For instance, the development of *Strimvelis* took more than 20 years of intense research.⁷ In the beginning, *Holoclax* seemed an exceptional case, as research and development started around 1996 and first clinical results were published just a year later. However, in reality, the product was under development for 25 years.⁸ When it comes to the ATMP pipeline and novel emerging technologies, such as CRISPR (which was discovered in 2012), it is likely that we still need to wait before seeing products enter the market, as there is still a number of safety considerations that need to be addressed.⁹ Yet, the marketing authorization of two genetically modified T cell immunotherapies shows that new technologies are slowly reaching the market (*Kymriah*, *Yescarta*).

Even though market entry appears quite a complicating and resource-consuming process, the challenges do not end there. The EMA may withdraw products due to safety reasons or because of a company's failure to ensure the manufacturing of the product. The marketing authorization holder can also request the revocation of the license when it can no longer deliver the ATMP or purely for commercial reasons. Currently, most ATMPs target (ultra) orphan diseases and small patient populations, which makes it often impossible to benefit economics of scale and difficult to make reasonable profits to cover substantial development and GMP-compliant manufacture costs. Hence, such niche markets become vulnerable to the withdrawal of ATMPs. Indeed, the majority of the withdrawals of ATMPs have been made for commercial reasons, not due to safety considerations.¹⁰

An ATMP must also be commercially successful in order for it to stay on the market, as the marketing authorization and GMP-compliant facilities are

7 GSK, StrimvelisTM receives European marketing authorisation to treat very rare disease, ADA-SCID, 2016. Available at: <https://www.gsk.com/en-gb/media/press-releases/strimvelistm-receives-european-marketing-authorisation-to-treat-very-rare-disease-ada-scid/>. Accessed 13 September 2020.

8 Alison Abbott, Behind the scenes of the world's first commercial stem-cell therapy, Nature News Q&A. Available at: http://www.nature.com/news/behind-the-scenes-of-the-world-s-first-commercial-stem-cell-therapy-1.17022?WT.mc_id=TWT_NatureNews. Accessed 13 September 2020.

9 Michael Kosicki – Kärt Tomberg – Allan Bradley, Repair of double-strand breaks induced by CRISPR–Cas9 leads to large deletions and complex rearrangements. *Nature Biotechnology* 36 2018, pp. 765–771.

10 Mansnérus 2016, *supra* note 6, p. 12.

costly to maintain. At one extreme, *Glybera*, uniQure's world's most expensive gene therapy to treat an ultra-orphan disease lipoprotein lipase deficiency, was only used once in the EU and subsequently withdrawn due to its commercial failure in the EU and difficulties reaching the US market.¹¹ Another example of an orphan product is *Strimvelis*, which is designated for a very rare disease affecting approximately 15 people in the EU on a yearly basis.¹² A limited patient population results in a very high cost of a product. *Holoclax* is targeting a bigger, but still a rather limited patient group, only 1,000 European patients per year.¹³ However, some ATMPs, such as *Imlygic*, indicated for late-stage melanoma reach a larger market, as approximately 19,250 metastatic melanoma patients are treated in Europe every year.¹⁴

Costs associated with GMP compliance constitute one of the major bottlenecks for the efficient translation of research into commercialized advanced therapies. Since the adaptation of the ATMP Regulation, all developers of advanced therapies have been required to comply with industry-level standards on quality, safety, and efficacy. However, many ATMPs are developed by academia and SMEs who struggle with stringent regulations for medicinal products.¹⁵ Thus, the EMA has been facing a difficult task: fostering research on ATMPs to expand patient access whilst ensuring the safety of the patients. To meet these objectives, the EMA has actively organized stakeholder consultations. After a series of multi-stakeholder meetings, the EMA released new GMP guidelines specific for ATMPs in November 2017 to allow risk-based flexibilities to these rigorous requirements.¹⁶ To further foster research on ATMPs, the EMA and the European Commission issued a joint

11 uniQure, uniQure Announces It Will Not Seek Marketing Authorization Renewal for Glybera in Europe, 2017. Available at: http://www.uniqure.com/GL_PR_Glybera%20withdrawal_FINAL_PDF.pdf. Accessed 29 October 2018.

12 GSK 2016.

13 Giovanni Milazzo – Michele De Luca – Graziaella Pellegrini, *Holoclax*: first of its kind in more ways than one. *Cell and Gene Therapy Insights* 2 2016, pp. 183–197.

14 ESMO, Press Release: Thousands of Melanoma Patients in Europe Have no Access to New Life Saving Drugs, 2016. Available at: <https://www.esmo.org/Conferences/Past-Conferences/ESMO-2016-Congress/Press-Media/Thousands-of-Melanoma-Patients-in-Europe-Have-no-Access-to-New-Life-Saving-Drugs>. Accessed 29 October 2018.

15 Tomáš Borán – Margarida Menezes-Ferreira – Ilona Reischl – Patrick Celis – Nicolas Ferry – Bernd Gänsbacher – Hartmut Krafft – Michele Lipucci di Paol – Dariusz Sladowski – Paula Salmikangas, Clinical Development and Commercialization of Advanced Therapy Medicinal Products (ATMPs) in the EU: how are the product pipeline and regulatory framework evolving? *Hum. Gene Ther. Clin. Dev.* 28 2017, pp. 126–135. <https://doi.org/10.1089/humc.2016.193>.

16 European Commission, Guidelines on Good Manufacturing practice specific to Advanced Therapy Medicinal Products 2017a, adopted on 22 November 2017. Available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2017_11_22_guidelines_gmp_for_atmps.pdf. Accessed 13 September 2020.

action plan in late 2017 with the goal of improving the regulatory environment for advanced therapies to facilitate the research, development, and approval of these products in the EU.¹⁷ Regulators are now taking measures to create a facilitative regulatory environment that encourages innovation, protects public health, and, finally, enables timely patient access to innovative, new therapies whilst ensuring the safety of the patients. In particular, the role of risk-proportionate adaptations to clinical trials and GMP manufacture along with the EMA's early-access incentives and initiatives are presented as potential facilitators of market entry. This chapter analyses and presents the latest changes and events in the ATMP space in Europe.

Table 2. Eligibility of Adaptive and Expedited Regulatory Pathways in the European Union

Regulatory pathway	Pathway type	Eligibility	Key characteristics
Accelerated Assessment	E	<ul style="list-style-type: none"> • Great interest to public health with respect to therapeutic innovation • Preliminary clinical evidence of substantial benefits 	<ul style="list-style-type: none"> • Reduced regulatory evaluation period
PRIME	E	<ul style="list-style-type: none"> • Potential to benefit patients with unmet medical needs based on early clinical data 	<ul style="list-style-type: none"> • Intensive regulatory engagement • Eligible for accelerated assessment
Conditional Approval	A	<ul style="list-style-type: none"> • Serious condition with unmet medical needs • Use in emergency situations • Orphan designation 	<ul style="list-style-type: none"> • Approval based on non-confirmatory data • Eligible for accelerated assessment
Approval under Exceptional Circumstances	A	<ul style="list-style-type: none"> • Ultra-rare conditions • Lacking state of scientific knowledge blocks comprehensive studies • Comprehensive studies are unethical 	<ul style="list-style-type: none"> • Approval based on non-confirmatory data

A=adaptive regulatory pathway, E=expedited regulatory pathway

17 European Commission, European Commission-DG Food Health and Safety and European Medicines Agency Action Plan on ATMPs, 2017b. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/10/WC500237029.pdf. Accessed 13 September 2020.

7.2 The EU Regulation on ATMPs Affecting the Commercialization Landscape

7.2.1 Background of the ATMP Regulation

The emergence of human tissue engineering technologies in the late nineties triggered concerns about inadequate regulatory governance in this field. The need for harmonized EU-wide legislation was evident.¹⁸ Ever since, the need for establishing a more favorable regulatory atmosphere to support and facilitate the development of a strong internal market for ATMPs has been urging. Initially, the EU-wide *lex specialis* on ATMPs was deemed necessary for the purpose of safeguarding public health (even though healthcare as a public service does not, as such, subordinate to the internal EU market). Yet, under proportionality and subsidiarity principles, ‘*common safety concerns in public health in an area in which application of existing EU legislation and additional national measures have proven insufficient*’ were the only route for the European Commission to enact EU-wide legislation in the ATMP field.¹⁹

The industry raised the concern that the lack of EU-wide legislation on ATMPs would harm patients since they are denied the potential benefits of these therapies. In addition, legal harmonization of the European ATMP field was assumed to improve predictability and, consequently, potentially facilitate decision-making in investments in R&D of ATMPs. It was also predicted to cut the expenses of meeting different quality, safety, efficacy, and marketing standards in the different EU Member States.²⁰ The impact of the industry lobbying was significant, while other stakeholders (such as academia and public tissue establishments) had a minor influence in the final scope and contents of the legislation in the field, which can be seen in the following aftermath:

- i. *Ethically neutral and quite a technical approach.* The EU’s limited mandate to harmonize the ethical aspects of ATMPs resulted in an ethically neutral, rather technical legislative approach. Some disputed that ethical aspects were avoided (such as the commercialization of altruistically donated material of human origin). The industry’s lobbying blurred the differences between non-profit and profitmaking activities

¹⁸ Mansn erus 2016, *supra* note 6, p. 172.

¹⁹ *Ibid.*

²⁰ *Ibid.*

of tissue establishments.²¹ Ethical issues were left to be dealt with by the Member State, as far as possible. This has resulted in disharmonized approaches to the availability of certain types of raw materials or products based on such materials. Also, the current wording of Article 4 Directive 2001/83/EC is drafted so ambiguously that the Member States may deny access to products based on cells or tissues on many possible grounds.²²

- ii. *Commercial actors are now allowed to perform cell and tissue banking activities.* However, in some Member States, it is still very difficult for SMEs and other commercial actors to carry out comprehensive activities despite the EUCTDs framework (The framework Directive 2004/23/EC and two technical directives, 2006/17/EC and 2006/86/EC) allowing them to procure, store, and process cells and tissues and to be qualified as tissue establishments.²³
- iii. *Widening the scope of the EUCTDs to cover autologous cells to be used for medicinal products.* The distinction between the regulation applicable to autologous and allogeneic tissue- and cell-based products was avoided.²⁴ However, small-scale production of autologous products often takes place in hospitals. For such tailor-made production, the expensive industrial GMP manufacture model is not well suited.²⁵ To mitigate these issues, the European Commission has launched ATMP-specific GMP guidelines also addressing some particularities of autologous products.²⁶
- iv. *Inclusion of ATMPs as a subcategory of cell- and tissue-based products within the medicinal products regulatory regime.* ATMPs must now be compliant with the requirements for conventional pharmaceuticals. Even though GMP standards play an important role in the quality

21 Jean-Paul Pirnay – Alain Vanderkelen – Daniel De Vos – Jean-Pierre Draye – Thomas Rose – Carl Ceulemans – Nadine Ectors – Isabelle Huys – Serge Jennes – Gilbert Verbeke. Business oriented EU human cell and tissue product legislation will adversely impact MS' health care systems. *Cell Tissue Bank*. Dec;14(4) 2013, pp. 525–60.

22 *Ibid.* Mansnérus 2016, *supra* note 6, p. 173.

23 Pirnay et al. 2013, *supra* note 21. See also Mansnérus 2016, *supra* note 6, pp. 173–174.

24 Pirnay et al. 2013, *supra* note 21.

25 Mansnérus 2016, *supra* note 6, pp. 173–174.

26 European Commission 2017a.

management of ATMPs and the protection of public health²⁷, such requirements risk becoming disproportionately costly for SMEs, research units in the academia, and public tissue establishments, and, consequently, impeding innovation.²⁸ Recently, some risk-based flexibilities have been allowed in the ATMP-specific GMP guidelines.²⁹

- v. *Conditions for applying for a hospital exemption are kept as narrow as possible.* Consequently, some valuable established therapies are risking becoming unavailable.³⁰ To avoid negative incentives, the hospital exemption should be kept narrow³¹ and other risk-proportionate flexibilities should be applied to facilitate the manufacturing of ATMPs.³²
- vi. *Creating an incentive system for SMEs.* These incentives focus on the main financial and administrative entry obstacles for SMEs in pre-marketing authorization procedures. Some of the incentives have been extended to cover the academia and non-profit organizations. Despite these incentives, other obstacles (especially GMP compliance-related financial hurdles) make it hard for SMEs to enter the EU market.³³

27 Mansn erus 2016, *supra* note 6, p. 174.

28 Pirnay et al. 2013, *supra* note 21.

29 European Commission 2017a.

30 Pirnay et al. 2013, *supra* note 21..

31 Kim F Pearce – Martin Hildebrandt – Hildegard Greinix – Stefan Scheduling – Ulrike Koehl – Nina Worel – Jane Apperley – Matthius Edinger – Andrea Hauser – Eva Mischak-Weissinger – Anne M Dickinson – Mark W Lowdell. Regulation of advanced therapy medicinal products in Europe and the role of academia. *Cytotherapy* 2014 Mar;16(3), pp. 289–97.

32 Mansn erus 2016, *supra* note 6, p. 174.

33 *Ibid.*

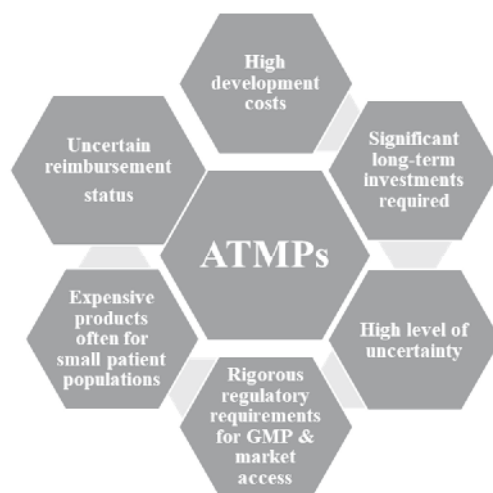


Figure 1. Major Challenges in the ATMP Development and Commercialization Pathway

7.3 Benefits and Shortcomings of the ATMP Regulation

On the one hand, the ATMP Regulation was initially motivated by internal market objectives — the need to ensure the free movement of ATMPs within the EU to facilitate their access to the internal market and to foster the competitiveness of European pharmaceutical companies. On the other hand, however, the need to guarantee the highest level of health protection for patients was strongly emphasized.³⁴ Both industry and patients alike anticipated to benefit from a facilitated access to the EU market via the centralized procedure.³⁵ Manufacturers were expected to benefit from improved regulatory certainty for the development of ATMPs and the free movement of those products within the EU as well. It was also assumed that patients and healthcare professionals would benefit from a timely access to innovative treatments.³⁶

Yet, a few years after the adoption of the ATMP Regulation, it appeared evident that the ATMP Regulation in its actual form failed to meet some of its above-mentioned primary objectives, as few new products entered the EU

³⁴ Mansnérus 2016, *supra* note 6, p. 175.

³⁵ Bettina Klug – Patrick Celis – Melanie Carr – Jens Reinhardt, Regulatory structures for gene therapy medicinal products in the European Union. *Methods Enzymol* 507 2012, pp. 337–54.

³⁶ *Ibid.*

market. However, the reasons for the low number of ATMPs are only partly attributable to the ATMP Regulation.³⁷ The European Commission organized a public consultation regarding the experience gained from the application of the ATMP Regulation³⁸ and released, together with the EMA, a joint action plan to address shortcomings of the ATMP Regulation and related processes.³⁹

³⁷ Mansn  rus 2006, *supra* note 6, p. 175.

³⁸ Klaus-Dieter Sohn, Centrum f  r Europ  ische Politik EU Report: ‘Experience with the ATMP Regulation’, cepPolicyBrief No. 2014–34 2014. Available at: http://www.cep.eu/Analysen/COM_2014_188_ATMP/cepPolicyBrief_COM_2014_188_ATMP_Regulation.pdf. Accessed 14 September 2020.

³⁹ European Commission 2017b, *supra* note 17.

Table 3. Benefits and Shortcomings of the ATMP Regulation

Benefits	Shortcomings
<p>+ increased regulatory and administrative assistance from the EMA's SME Office</p> <p>+ significant 90 percent fee reductions for scientific advice and inspections for SMEs (65 percent fee reduction for others)</p> <p>+ significant fee reductions for the marketing authorization application for SMEs developing ATMPs or orphan medicinal products</p> <p>+ fee reductions on the EMA's scientific advice have been recently extended to cover academia and non-profit organizations if the applicant qualifies for the PRIME scheme</p> <p>+ postponement of the fee payable for marketing authorization application or related inspection until after the grant of the marketing authorization for SMEs</p> <p>+ conditional fee exemption where scientific advice is followed and the marketing authorization is unsuccessful for SMEs</p> <p>+ certification of quality/nonclinical data for ATMPs for SMEs</p> <p>+ providers of equipment or GMP grade ancillary reagents potentially benefit from the ATMP Regulation, as their short term sales may increase when ATMP suppliers are adapting to meet the standards</p>	<p>– the number of licensed ATMPs in the internal market remains low and many licenses have been withdrawn (<i>However, reasons for this can be only partly attributed to the ATMP Regulation.</i>)</p> <p>– the interest of big pharma in the development of ATMPs still remains limited and pharmaceutical industry standards constitute significant financial impediments for developers of ATMPs (i.e. usually SMEs, academia, and hospitals) providing tailor-made or niche advanced therapies</p> <p>– the introduction of pharmaceutical industry standards (such as GMP and marketing authorization requirements) to cover ATMPs resulting in a predominantly risk-averse regulatory environment (<i>However, it is positive that recently issued new GMP and CLP Guidelines include ATMP-specific adaptations and risk-proportionate flexibilities, and ATMP-specific GCP Guidelines are soon to be launched.</i>)</p> <p>– inconsistencies in the application of the hospital exemption is conducive to creating uncertainty amongst national competent authorities and developers of ATMPs, as it does not promote the harmonization of practices</p> <p>– the significant administrative burden and high cost of GMP compliance has been underestimated by research funding bodies</p> <p>– inconsistencies in the implementation of the ATMP Regulation, in particular the lack of harmonized ATMP classifications constitute a barrier to the development of ATMPs across the EU, as national competent authorities cannot use the classification procedure when they face difficulties with the classification of ATMPs</p> <p>– the certification procedure is used very seldom, it needs to be linked to the marketing authorization procedure, and fee reductions should be extended to cover non-profit organizations (i.e. academia)</p>

Source: Adapted from Mansnérus with updates *supra* note 6, p. 180

7.4 New Measures to Accelerate the Market Entry of ATMPs in the EU

At first glance, one could find that the actual benefits of the ATMP Regulation appear quite limited, as the rigorous GMP and marketing authorization requirements seem to have hampered the market entry of new ATMPs. Yet, it can also be assumed that the ATMP Regulation has protected patients from unsound treatments. It is clear that policymakers and regulators alike are facing a very difficult task; they need to find the appropriate approach to deal with uncertainties and potential risks to public health whilst balancing between conflicting interests, such as innovation, safety, and the free movement of goods. In 2014, the European Commission identified five concrete amendment proposals to accelerate the translation of research into authorized ATMPs: (1) improving the conditions for non-profit organizations; (2) extending the certification procedure to cover non-commercial organizations and ensuring a better link with the marketing authorization procedure; (3) streamlining the current definitions of ATMPs to cover all ATMPs to prevent disparities in national classifications; (4) adapting the marketing authorization requirements for special products (particularly autologous ATMPs); and (5) harmonizing the hospital exemption to avoid negative incentives.

More recently, the European Commission and the EMA have, pursuant to their joint action plan, taken a number of measures to improve the conditions for the market entry of ATMPs. These measures include, but are not limited to, revising standards and launching risk-based adaptations, streamlining different procedures, improving stakeholder interaction and training as well as initiating discussions for the further harmonization of discrepancies in national approaches.

7.4.1 Revising Standards and Streamlining Procedures to Address Particularities of ATMPs

GMP compliance-related costs have been reported to constitute a major bottleneck for the translation of research into advanced therapies. It has been argued that rigorous technical requirements (which are not negative as such) risk becoming disproportionately costly for SMEs and, consequently, impeding innovation. Recent ATMP-specific adaptations to GMP requirements have been welcomed by developers of ATMPs, as the specific characteristics of ATMPs are now better taken into consideration. These flexibilities are anticipated to decrease the costs related to compliance with GMP guidelines.

It appears that along with the EMA, some regulatory authorities in the Member States seem to have adopted a pragmatic approach already, allowing for a risk-based assessment of manufacturing procedures. The most recent adaptations to the ATMP-specific GMP requirements together with the risk-proportionate adaptations to clinical trials represent positive developments that may facilitate the market entry of ATMPs. Among other things, a number of changes in applicable guidelines and standards are hoped to facilitate the development and manufacturing of ATMPs in the foreseeable future: ATMP-specific GMP standards, Q&A document on the risk-based approach to non-substantially manipulated ATMPs, guidelines on GLP for ATMPs (all above published 2017), guidelines on GCP for ATMPs led by the European Commission (published 2019), guidelines on investigational ATMPs (consultation closed), scientific guidelines on ATMPs (a number of guidelines have been adopted lately or are being revised), scientific considerations on gene editing technologies (under preparation) as well as guidelines on safety, efficacy, and RMPs for ATMPs and the revision of the EMA's procedural guidance on the evaluation of ATMPs (both revised in 2018). The introduction of the supplementary GMP requirements for ATMPs is not only necessary to facilitate the market entry of new ATMPs but also to protect public health. However, it should be noted that without efficient enforcement in the form of inspections and effectiveness measures, EU directives and regulations as such are inadequate to protect patients from unsafe medicinal products. Therefore, increasing the training of inspectors and other relevant stakeholders is of paramount importance.

7.4.2 Increased Stakeholder Interaction and Training

Under Article 78 of the Clinical Trials Regulation, the Member States of the EU shall appoint inspectors to supervise compliance with said regulation. Moreover, it is the Member States' responsibility to ensure that the inspectors are adequately qualified and trained. No unified ATMP inspection training or assessment criteria have been set thus far. It is clear that GMP compliance as such does not automatically guarantee the quality, safety, and efficacy of a medicinal product. For this reason, inspections and unified assessment criteria should be in place when similar quality and safety standards for ATMPs are being pursued in the Member States.

There is also a concern that the current risk-based approach puts major pressure on qualified persons, as they may release products according to different interpretations in different Member States. In this respect, the EMA has acknowledged that qualified persons would benefit from more guidance and

training in risk-proportionate approaches. More recently, the EMA has taken several measures to mitigate this problem. It has committed to providing enhanced scientific support and possibilities for early dialogue with multidisciplinary expert teams as part of the PRIME scheme, and the CAT is organizing awareness sessions with ATMP related topics. The EMA has also committed to providing increased stakeholder support for SMEs and academia and increasing awareness of regulatory processes and framework as well as increasing interaction between EMA and health technology assessment bodies.

7.4.3 Harmonization of Discrepancies in National Approaches

The hospital exemption, which is applied very inconsistently across the EU Member States, is conducive to create uncertainty amongst national competent authorities and developers of ATMPs. To mitigate this problem, the EMA has initiated discussions with national competent authorities in order to harmonize practices.

Beyond the ATMP Regulation as such, there are also other areas affecting the ATMP field that would benefit from a greater EU-wide harmonization. For instance, the GMO Directive (Directive 2001/18/EC) is not particularly designed for medicinal products. Thus, a number of shortcomings appear in its disharmonized implementation across the EU. Establishing a central repository listing the requirements and timelines for GMO assessment in every Member State could possibly be the first step towards greater harmonization. The European Commission is initiating a dialogue with national competent authorities to reduce discrepancies in GMO legislation applicable to ATMPs.

7.4.4 Potential of the EU Regulation on Clinical Trials for ATMPs

The new Clinical Trials Regulation (Regulation 536/2014) entered into force on 16 June 2014. From the perspective of developers of ATMPs, the Clinical Trial Regulation allows for a streamlined application procedure via a single entry point-EU portal, more harmonized review of clinical trial applications, and possibly faster approval times. The EMA has paid attention to the differing requirements across the EU Member States. In particular, the integration of assessment in clinical trial authorizations poses a challenge in the context of multicenter clinical trials on ATMPs. The timelines of such assessment should be aligned with those of a clinical trial authorization.

Regardless of the harmonization of the application process, it should be noted that ethical approvals of clinical trials remain within the competence of

the Member States. Consequently, the endorsement of a trial depends on the ethical position adopted by the ethical boards of the Member States. As long as different national competent authorities apply the classification of medicines as ATMPs differently, this will also constitute an impediment for ATMP development. Developers of orphan drugs face difficulties in this respect, as research must be conducted across many jurisdictions to obtain adequate recruitment rates. On a more general note, concerns have been voiced that the benefit-risk balance of products in development focuses mostly on risks. Some stakeholders argue that greater emphasis should be put on expected but realistic benefits, especially in the case of unmet medical needs.

7.5 Conclusions

The ATMP Regulation aims to harmonize the legislative landscape for ATMPs throughout the EU, with the EMA offering regulatory support to developers. The near future will reveal how widely the reformed risk-based approach in GMP manufacture and clinical trials gains wider general acceptance among the national regulatory authorities and ATMP developers in Europe. It also remains to be seen whether these adaptations are sufficient to nurture the ATMP meadow and ameliorate the availability and accessibility of valuable treatments. Furthermore, a careful assessment of benefit-risk balances should constitute a part of the development strategy early on. These aspects should be discussed early with regulators and health technology assessment bodies alike to allow the adaptation of GMP and marketing authorization requirements. Future development and authorization is likely to occur under accelerated access pathways, which need to be duly aligned with payment and reimbursement structures to ensure and facilitate global patient access to new technologies.

8

On the Lookout for Experience: The Legislative Experiment of Conditional Pharmaceutical Reimbursement in Finland

by LL.M. Waltter Roslin

Abstract

This chapter explores risk-sharing agreements and the conditional reimbursement of pharmaceuticals in Finland. These are agreements between payers and providers to mitigate the risk of uncertainty sometimes found in novel pharmaceutical products. Introduced through a legislative experiment that first ran between 2017–2019 and now continued for another six years from 2020–2025. Overall, the first experiment delivered positive results, however, the consensus was that more experiences from all aspects of risk-sharing were needed and further data collection is required to fully grasp how conditional reimbursements should be legislated in Finland. Conditional risk-sharing has the potential to increase access to treatment, which can have human rights implications as states are often mandated to provide a certain level of healthcare to their citizens, this general relation to fundamental human rights is analysed in this chapter. An overview will be provided of risk-sharing in general in relation to pharmaceuticals, the relevant Finnish legislation, and legislative experiments. Issues within the legislation and the experiments will be expanded upon, and future challenges identified, namely in relation to the transparency of the risk-sharing agreements and challenges with increasing the variety of the agreement types utilised. European experiences and general trends are also presented to give a short overview and contrast. This chapter intends to be a descriptive exercise in forming a ground basis for understanding the current national system of conditional reimbursements and provide few closer insights into the potential future after the current experiment.

8.1 Introduction: Risk-Sharing Agreements in Pharmaceuticals and the Finnish Experiment

Healthcare is one of the cornerstones of modern welfare society, representing a promise from the state to provide and enable a healthy life, but it is also an ever-increasing expenditure.¹ A vast number of actors and organisations are working to maintain the access to treatment, both public and private, either financed based on a private insurance model or a national insurance model. However, irrespective of how the access to a doctor is provided, treatment also requires medicine, and the development of pharmaceuticals has long been a partner in the societal equation of maintaining health. As a naturally occurring *panacea* has not yet been discovered, there is an interest in developing new medicines. However, as the development of pharmaceuticals can be a costly endeavour, with long development processes, vigorous testing phases, and competition, the manufacturing of a new drug requires a vast amount of faith, deep pockets and a projection of profit. Whilst research occurs in universities and hospitals around the world, manufacturing and development are mainly conducted by pharmaceutical companies. Nonetheless, the question of profit is a central factor with private companies, and the societal sphere in which the industry operates is layered. As there is a societal interest in the attainment of pharmaceuticals and the continuation of their development, the state also has its role to play in incentivising them.

To mitigate the risks posed by the development of novel medicine, risk-sharing agreements (RSA) are utilised.² In particular, their benefits are the increase mitigation of uncertainty about clinical outcomes and cost-effectiveness of medicines for the state by allowing conditional reimbursement of the drug, enabling early access to treatment for patients with more experimental and innovative medicine, easing national budgets, and promoting more focused

1 Data from the Finnish institute for health and welfare show that there has been a steady increase in expenditure between 2000-2018, especially expenditures on outpatient care rose 8,6% between 2017-2018, for more information: Terveysten ja hyvinvoinnin laitos, Tilastoraportti 23/2020, Terveystenhuollon menot ja rahoitus 2018. 06/2020.

2 RSA's are agreements between payers and producers aimed at mitigating the risk caused by the uncertainty of the curative value of new and existing medicines. A more in-depth definition is given in chapter 2.

utilisation of a medicine on a subgroup of patients.³ Risk sharing is especially beneficial for orphan diseases, as their profitability is often perceived as low, and the limited patient-base can pose difficulties in attaining enough real-world data.⁴ However, similar uncertainties can still exist in other products, if they have been recently developed and lack the necessary ‘real-world data’ to satisfy the state’s reimbursement board. Thus, risk-sharing can enable a novel product’s potential reimbursement and hasten its entry to the market.

In 2017, Finland joined the trend carried by many EEA countries by introducing a conditional reimbursement scheme with Chapter 6, section 6a of the Finnish Health Insurance Act (*Sairausvakuutuslaki*).⁵ However, instead of permanent legislation, the government used experimental legislation to implement the new scheme.⁶ Introduced in Government Bill 184/2016,⁷ the duration of the trial was set for three years; however, not enough conclusive evidence was generated to decide the future of conditional reimbursement in Finland, and the experiment was continued for another six years with the following legislative trial.⁸ Based on the past and the current experiments there is room to analyse the general impact of conditional reimbursement on the Finnish health care sector, its actors, patients, and the general legislative framework. There are currently 37 products with a risk-sharing agreement with the Finnish Pharmaceutical Pricing Board

3 Francisco R. Gonçalves – Susana Santos – Catarina Silva – Gabriela Sousa, Risk-sharing agreements, present and future. *Ecancermedalscience* 2018 pp. 2–3; Martin Wenzel – Suzannah Chapman, Performance-based managed entry agreements for new medicines in OECD countries and EU member states: How they work and possible improvements going forward. *OECD working papers* No. 115 02/2020, pp. 12–14; Louis P. Garrison & others, Performance-Based Risk-Sharing Arrangement – Good Practices for Design, Implementation, and Evaluation: Report of the ISPOR Good Practices for Performance-Based Risk-Sharing Arrangements Task Force. *Value in Health* 16(5) pp. 703–719, 704–710.

4 For more see: Wouter Boon – Luis Martins – Marc Koopmanschap, Governance of conditional reimbursement practices in the Netherlands. *Health Policy* 119(2), pp. 180–185.

5 The Health Insurance Act (in Finnish: *Sairausvakuutuslaki*, Act of 1224/2004, as amended).

6 Experimental legislation is a governance tool, where the state introduces an act that is made valid only for a specified duration, used to search and test alternative ways to solve societal issues.

7 Hallituksen esitys eduskunnalle laiksi sairausvakuutuslain muuttamisesta ja väliaikaisesta muuttamisesta sekä laeiksi lääkelain 57 b ja 2013 §:n ja terveydenhuollon ammattihenkilöistä annetun lain 22 ja 23 §:n muuttamisesta HE 184/2016 VP (Government Bill 184/2016). In the Finnish legal order, the intention of the legislator, often perceived through the government bills, is used as a weakly binding source of law and thus given more attention to than in some other jurisdictions. See more: Aulis Aarnio, *The Sources of Law in Aulis Aarnio (ed.), Essays on the Doctrinal Study of Law*. Springer 2011 pp. 147–163.

8 Hallituksen esitys eduskunnalle laiksi sairausvakuutuslain muuttamisesta ja väliaikaisesta muuttamisesta HE 40/2019 VP (Government Bill 40/2019).

(FPPB); all are financial-based agreements.⁹ This means that the conditionality of the reimbursement is tied to a performance of a financial factor, the amount of units sold, patients treated, or the volume of product used. However, instead of focusing on financial aspects, performance-based agreements are also possible, focusing on the quality of treatment and patients' response to it.¹⁰ As focusing on the outcome of treatment would potentially increase the quality of treatment and the overall betterment of society, there could be a potential benefit in increasing performance-based agreements in conditional reimbursement decisions.

8.1.1 The Structural Overview of Conditional Reimbursements in Finland; Government Bills 184/2016 and 40/2019 as Well as the Functioning of the Pharmaceutical Pricing Board

Conditional reimbursement in Finland was introduced in 2017 to utilise new drugs in a controlled manner and increase patient access to treatment. In addition, the goal was to supplement Prime Minister Juha Sipilä's government's program to cut EUR 150 million from pharmaceutical reimbursements. The plan was to increase competition, reduce drug waste, promote rational treatment and the configuration of the special reimbursement. Conditional reimbursement was then proposed as a new risk-sharing mechanism to control the introduction of new products.¹¹ In a Conditional Reimbursement Agreement (CRA), the provider, in this case the pharmaceutical company, enters into an agreement with the payer (the government) operated by FPPB, to mitigate the potential risk a new pharmaceutical product may have. Through guaranteeing a reachable endpoint with the agreement, the provider guarantees a particular outcome with the product having the risk in case of non-fulfilment, to trigger a duty to return the reimbursed portion of the price to the government. The government will then grant a reimbursement decision to a product that might not have been reimbursable in the past due to lack in some parts of its 'real-world data', providing patients with access to novel products. The nature of these agreements is often financial, as

9 FPPB, Conditional Reimbursement. 08/2020 Available online at: https://www.FPPB.fi/content/uploads/2020/01/Ehdollinen-korvattavuus_010820.pdf.

10 For a good overview of the two types of risk-sharing agreements see: Jacqueline C Bouvy – Claudine Sapède – Sarah Garner, Managed Entry Agreements for Pharmaceuticals in the Context of Adaptive Pathways in Europe. *Front Pharmacol* 2018; Martin Wenzel – Suzannah Chapman pp. 12–16.

11 Government Bill 184/2016 p. 1.

also seen in Finland's case, mostly due to the ease of using volume/price related endpoints, which is also echoed by the general risk-sharing trends in Europe.¹²

The responsibility to manage and approve the new conditional agreements was delegated to the FPPB, the pharmaceutical pricing board functioning within the Ministry of Health and Social Affairs as it already had the oversight of the general reimbursement application proceedings. The mandate of FPPB is based on the Health Insurance Act.¹³ Its task, under Chapter 6, section 1 of the Act, is to validate reimbursement, validate a reasonable wholesale price for the purpose of reimbursement, and to make decisions to increase the reasonable wholesale price and the termination of reimbursement and reasonable wholesale price. The board consists of the main body, as well as an expert group all appointed by the Ministry of Health and Social Affairs for a three-year period.¹⁴ FPPB is a separate entity from the Finnish Medicines Agency (Fimea), which is the Finnish national body within larger EU-wide pharmacovigilance and manages the market authorisation process for Finland under the European Medicines Agency (EMA). Fimea oversees and supports pharmaceutical development and has since 2015 gathered the performance and economic value-based evaluations of pharmaceutical products and coordinated the related cooperation. The goal of Fimea is to evaluate all new hospital medicines and major product expansions¹⁵. Under the current structure, reimbursement application requires the market authorisation of the pharmaceutical.¹⁶ Hence, with both agencies conducting analysis into the reimbursability of a product, whilst remaining interconnected, the agencies' mandate does not overlap.

Despite its few visible shortcomings, the 2017–2019 experiment produced 33 financial-based CRAs. It was generally viewed positively by stakeholders: when asked during the public consultation from the Ministry of Social Affairs and Health whether the experiment should be discontinued, made permanent or continued, the continuation was sought by all parties present.¹⁷ Hence, a new experimental

12 Bouvy – Sapede – Garner 2018 p. 3; see also Wenzel – Chapman 2020, pp. 17–27.

13 Health Insurance Act Chapter 6, section 1–3.

14 Health Insurance Act Chapter 6, section 2.

15 Heikki Ruskoaho, *Lääkekorvausjärjestelmän kehittäminen: Selvityshenkilön loppuraportti. Sosiaali- ja terveysministeriö 06/2018* p. 39.

16 Health Insurance Act Chapter 6, section 4, subsection 1.

17 *Sosiaali- ja terveysministeriö, Lausuntopyyntö luonnoksesta hallituksen esitykseksi sairausvakuutuslain muuttamisesta ja väliaikaisesta muuttamisesta. 08/2019*. The responses can be found at <https://stm.fi/hanke?tunnus=STM060:00/2019>; unfortunately, they are only available in Finnish.

legislation was initiated with Government Bill 40/2019 to address and continue the previous experiment.

The wording of the act remains rather similar as it was during the old experiment, apart from a few changes made to further clarify for both FPPB and contracting pharmaceutical companies to conduct the agreements better. Most notably, there was the decision to keep the wholesale price of a product engaged in a CRA confidential and not to include the agreed price in the determination of a reasonable wholesale price of another product.¹⁸ However, the real potential impact of the continuation of the experiment can be seen as a possibility to increase the portion of performance-based agreements in Finland. Performance-based agreements are heavily reliant in the collection and accumulation of data by healthcare professionals.¹⁹ The previous experiment's three-year duration was very little time to achieve any substantial information. This possibility for an increase in performance-based agreements was also noted down in the deliberations of the legislator.²⁰

8.1.2 How Are Conditional Reimbursement Agreements Regulated Under the Finnish Health Insurance Act?

Under Chapter 6, section 6a of the Finnish Health Insurance Act, a novel pharmaceutical product can be granted conditional reimbursement, proven if there is a special unmet medical need, and there is substantial uncertainty with the cost of treatment, the effectiveness of the product, cost-effectiveness, or other substantial uncertainty related to the reimbursement of a product or the evaluation of the reasonable wholesale price. FPPB then, based on the application, decides whether to initiate the negotiations with the pharmaceutical company. If the negotiation stage is reached, an agreement can be made between FPPB and the company on the reimbursement. Reimbursement can be valid for a maximum duration of five years, consisting of a single decision or continuous fixed-term decisions.²¹

In the CRA, the category of reimbursement is also agreed upon. This can be one of the following: basic reimbursement, lower special reimbursement, and higher special reimbursement, this type of a direct price reduction is rather

18 Health Insurance Act Chapter 6, section 7, subsection 4.

19 Garrison and others, pp. 708–713.

20 Government Bill 40/2019.

21 Health Insurance Act Chapter 6, section 6 a, subsection 3; section 12 subsection 2.

commonly used, especially in oncological drugs.²² The Health Insurance Act does not stipulate using other forms of risk-sharing, yet price reduction has been used in Finland by Kela prior and is thus the most prominent type. Nonetheless, as the law does not stipulate a preference over the reimbursement type and with the potential increase in performance-based agreements, more intricate options, such as outcome guarantees for the population or money back guarantees for individuals, are possible.²³

Reimbursement can be sought for the general use of the product, unless the product fulfils one of the four requirements under Chapter 6, section 5, Subsection 2: 1) the drug is used to treat a disease of a temporary nature or with mild symptoms; 2) the therapeutic value of the treatment is low; 3) the product is used for another purpose than treatment of a disease; or 4) the drug is a traditional herbal product or homeopathic.²⁴ In the case usage of the product might fall under the aforementioned categories, a limited reimbursement can be agreed upon for a specific use of a product.²⁵

The agreements themselves, as well as the negotiations, are kept confidential due to the sensitive commercial data within them. This most often refers to the agreed wholesale price of the drug. The reason for such confidentiality may be because a Member State's pricing board can, in practice, apply the wholesale price of a product in a foreign country to determine the reasonable price in its home territory. The final price of a drug in one EU Member State can impact the price of the same or similar drug in another.²⁶ However, there is a clash with the principles of transparency by the Finnish Act on the Openness of Governmental Activities. Naturally, an exception exists in case of commercially sensitive data, where confidentiality can be claimed.²⁷ However, especially as discovered during the previous experiment, when a product subject to an agreement is used as

22 Kim Pauwels et al. Managed Entry Agreements for Oncology Drugs: Lessons from the European Experience to Inform the Future. *Frontiers in Pharmacology* 2017, p. 5.

23 Garrison et al, 2013 p. 707.

24 Health Insurance Act Chapter 6, section 5, subsection 2.

25 Health Insurance Act Chapter 6, section 6; Meaning if product X, would be a more expensive product to treat an illness A than its current competitor, yet it would have a secondary use as a treatment for illness B, it could be granted limited reimbursement under the Health Care Act to treat B if it has proven value. This limitation was introduced in Government Bill 97/2005 to partially limit the exceeding costs of reimbursements and to clarify under what circumstances reimbursement can be given.

26 This practice is known as external price referencing; for more information, see: Cécile Rémuzat and others, Overview of external reference pricing system in Europe. *Journal of Market Access & Health Policy* 2015.

27 Act on Openness of Governmental Activities (in Finnish: *Laki viranomaisten toiminnan julkisuudesta* act of 621/1999, as amended) Chapter 6 Section 24, subsection 1(20).

a comparator for the appraisal of another product, to what extent should the confidentiality be lifted to ensure there are no artificial veils barring cost-effective agreements? This utilisation of confidential data was, in practice, prohibited during the first experiment. It would appear that with added subsection 4 to Chapter, section 7 of the Health Insurance Act,²⁸ the utilisation of a product under agreement as a comparator when determining a reasonable wholesale price is barred. However, now that part of the product should be used as a comparator, to what extent is confidentiality in the agreements beneficial?

As seen in the earlier subsection, the requirements for conditional reimbursement are threefold: the product must be novel, there is an unmet medical need, and the product has some flaws barring it from the general reimbursement scheme. Novelty is often mentioned in intellectual property related matters, implying something as being recent and different; however, this naturally excludes already available remedies that might currently struggle with reimbursement applications, namely orphan diseases.²⁹ There appears to be a lack of discussion into the potential conditional reimbursement of older products; should such agreements be facilitated to better cover the treatment of diseases that have very low patient numbers? Additionally, with the potential increase of personalized medicine in the future,³⁰ the way pharmaceuticals are used could develop into more individual-based dosages, instead of the bulk production currently used to supply patients.

8.2 Risk-Sharing

8.2.1 Risk-Sharing Agreements and Managed Entry Agreements: Similar Definitions, Different Focus?

After a review of the recent academic publications, there have been a plethora of definitions given to RSAs, which are also referred to as Managed Entry Agreement (MEA), Patient Access Schemes, or Special Pricing Agreements, each with slightly differing emphasis.

²⁸ Health Insurance Act Chapter 6, section 7, subsection 4.

²⁹ Hallituksen esitys eduskunnalle laiksi sairausvakuutuslain muuttamisesta ja väliaikaisesta muuttamisesta HE 97/2005 VP (Government Bill 97/2005), p. 8.

³⁰ See more: Janet Mifsud – Marcel Maliepaard, Pharmacokinetics and Pharmacogenetics: Bringing the Magic Bullet Closer to Reality, pp. 91–107 in G. Grech – I. Grossman (eds) *Preventive and Predictive Genetics: Towards Personalized Medicine*. Advances in Predictive, Preventive and Personalized Medicine. Springer 2015.

Authors appear to use the definitions of MEAs and RSAs interchangeably. The difference in whether the term MEA is utilised over RSA appears to be related to the specificity and the policy objective the author wishes to convey.³¹ When aimed to specify the relation between the state and the pharmaceutical company in the introduction of new products, MEA seems to be more favoured. There also seems to be an underlying focus on affordability and access with MEAs rather than the more overall risk coverage with RSA. This was also promoted by Ferrairo and others when observing that within eastern Europe, in the available agreements, only some of them had any true risk-sharing components, and the legislator has not given any definition of the risk or risk-sharing in question. However, as also pointed out in the study, risk-sharing can also be implicit.³² This is also because these agreements cover products that have limited evidence coverage. Due to this implicit risk, even if the agreement does not have any true risk-sharing elements, it should still be a practice of risk-sharing. In Finland, the legislator refers to the general sphere of conditional reimbursement as an application of risk-sharing models,³³ without there being a distinction between RSAs or MEAs. MEAs are in general risk-sharing measures and thus irrespective of which term is applied, the matter is still related to the general subject of risk-sharing. However, by focusing on calling it a risk-sharing agreement, the term has a more general approach on the subject despite their definition being the same. Naturally, with further development of novel risk-sharing measures, it may become important to distinguish between the terms; however, they still appear to be used rather interchangeably.

When searching for a general definition of RSAs, inspiration can also be sought from MEAs. There is a generalised definition of ‘managed entry agreement as any arrangement between a manufacturer and payer/provider that enables access to a health technology subject to certain conditions’.³⁴ Another definition gives more emphasis on the risk inherent to the agreement: ‘Agreements concluded by payers and pharmaceutical companies to diminish the impact on the payer’s budget of new and existing medicines brought about by either the uncertainty of the value of the medicine and/or the need to work within finite budgets.’³⁵ A third definition would be ‘Market access agreements between payer/provider

31 Wenzel – Chapman 2020, p. 12.

32 Alessandra Ferrairo et al., *The Implementation of Managed Entry Agreements in Central and Eastern Europe: Findings and Implications*. *PharmacoEconomics* 35 2017, pp. 1271–1285, 1280.

33 Government Bill 40/2019, Government Bill 184/2016.

34 Jacoline C. Bouvy – Claudine Sapède – Sarah Garner 2018 p. 3.

35 Adamski and others, *Risk sharing arrangements for pharmaceuticals: potential considerations and recommendations for European payers*. *BMC Health Services Research* 2010, pp. 2– 3.

and pharmaceutical companies utilize various pricing mechanisms that attempt to manage the degree of risk and uncertainty presented at the time of pricing and reimbursement application.³⁶

It becomes evident by comparing these provided definitions that RSAs identify as its core the contact between producer and payer as well as the facilitated increased access to treatment. Taking into account a conditional element, the presence of risk inherent to the real-life behaviour of a medicine that may negatively impact the payer, and the risk of ‘decision uncertainty’, the possibility for the product not to be effective or cost-efficient. There is clash between how the producer and payer may have a different view of the potential value of the product, and only by agreeing to a shared risk taking can both parties be assured.³⁷

However, by taking the risk and providing the manufacturer the reimbursement there is further facilitation of pharmaceutical development and access to treatment. Hence a more compact version of the definition of an RSA would be that RSAs are agreements between payers and producers aimed at mitigating the risk caused by the uncertainty of the curative value of new and existing medicines.

8.2.2 Financial-Based and Performance-Based Agreements: A Short Overview

RSAs have been divided into two categories, financial agreements, and performance-based agreements. Financial-based agreements, also currently the preferred form of RSAs within Europe are categorised by an observable financial performance.³⁸ Price/volume arrangements and budget impact schemes, focusing on the financial control of expenditures, where the manufacturer might pay to the payer a rebate of a portion exceeding an agreed threshold, or if a certain threshold is not reached, a duty to refund the reimbursement may trigger. This is the form of the agreement currently utilised by FPPB with its CRAs. Alternative to this is a patient access scheme, where free products or discounts are often agreed for a specific period to improve the value of the new medicine and accumulate further real-life data for future reimbursement. Patient access schemes also cover a price-capping scheme, where an individual patient’s expenses are capped.³⁹ Whilst not being a producer/payer agreement, Kela uses a patient access-based system with the general cap

36 Faulkner et al. Pricing and Reimbursement Experiences and Insights in the European Union and the United States: Lessons Learned to Approach Adaptive Payer Pathways, Clinical pharmacology and therapeutics 2016, pp. 730–742, 731.

37 Garrison et al., 2013 p. 706.

38 Wenzel – Chapman 2020, p. 13.

39 Adamski et al, 2010 pp. 3–4.

an individual must pay for medicine in Finland. Performance-based agreements can be generally observed to contain an added level of data collection, where the price/reimbursement and/or revenue of the product is connected to the outcome of the collected data either explicitly by a specific agreement, or implicitly, through a possibility to renegotiate coverage. The data collection can either be related to the performance of the product within the whole patient base or the functioning of treatment in individual cases. Two models of performance-based agreements can be identified, a performance-linked real-world arrangement, where the utility and outcome of the treatment is the priority, or a research-orientated arrangement, where the focus is on the attainment of further evidence to reduce uncertainty and provide data for further reimbursement decisions.⁴⁰ Naturally, a performance-based CRA can contain elements of both.

8.2.3 European Trends with Risk-Sharing: There Is a Clear Preference for Financial-Based Agreements

With the numbers of RSAs increasing globally, the general trend in Europe has been to favour financial-based agreements over performance based, with England and Italy being the notable exceptions.⁴¹ This can potentially be attributed to the stark contrast between the two agreement types, with financial-based agreements generally viewed as less cumbersome for the parties.⁴² The general drawbacks of performance-based agreements are identified as the difficulty in evidence gathering, lack of good endpoints, and general complexity for patients.⁴³ Risk-sharing seems to imply a more cumbersome process for states and pharmaceutical companies to undergo, and for them to succeed, critical data infrastructure is required.

A recent study from Sweden reviewed all RSAs made by the Swedish Authority between January 2015 to August 2019 compiling agreements made for 56 products, highlighting that the focus of the Swedish national reimbursement agency was said to be cost-sharing rather than risk-sharing.⁴⁴ Seeing as there are less performance based agreements made than financial ones in general, this might be the focus

40 Garrison et al. 2013 p. 705; Pauwels et al. 2017, pp. 4–5, Bouvy – Sapede – Garner 2018, pp. 3–6.

41 Wenzel – Chapman 2020, pp. 17, 25.

42 Wenzel – Chapman 2020, p. 25.

43 Bouvy – Sapede – Garner 2018, p. 5.

44 Emelie Andersson – Johanna Svensson – Ulf Persson – Peter Lindgren, Risk sharing in managed entry agreements – A review of the Swedish experience. *Health Policy* 124(4) 2020 pp. 404–410, 409.

in many other countries as well.⁴⁵ Cost-sharing is still an integral part of RSAs; however, its impact on the development of pharmaceuticals and the lack of risk-sharing should be further researched. This ideology has most likely had an impact on the number of performance-based agreements, as cost-sharing would appear to be more easily managed and require less generated evidence than risk-sharing.

8.2.4 Human Rights and Risk Sharing: Interplay Between Increased Access and Right to Receive Treatment?

There is a multitude of economic and political reasons for Finland to utilise risk sharing; however, there are also human rights obligations from the Finnish Constitution as well as the European Charter of Fundamental Rights to consider when utilising RSAs. Through increases in the availability of pharmaceuticals for a wider patient base in both novel medicines but also lowered prices, there is potential higher access to treatment, which contributes to the ideals of the general welfare state, but also directly promotes the abstract goals of sections 6 and 19 of the Constitution.⁴⁶

Section 19 Subsection 3 of the Constitution tasks the government and municipalities to ensure that everyone has access to an adequate level of healthcare, and the general promotion of health. This agency does not set a subjective right about the received care, but rather requires a general possibility for access, whether public or private.⁴⁷ The general discussion tends to gravitate more towards providing hospital services, but access to pharmacy bought prescriptions is also a crucial part of the overall picture of healthcare services. Discussion can easily gravitate towards the general ‘which particular medicine should be reimbursed’ instead of the current focus on the overall functioning of the CRAs. It is clear that with limited resources not everything can be reimbursed, however through designing and utilising RSAs more products can become available to patients,⁴⁸ hence improving access to treatment provided by the social welfare system, better fulfilling the objects set in section 19. This also promotes the right to equality enshrined in section 6, if through CRAs, products with fewer patients can be

45 The observation made by Ferrario and others was that from the countries they researched had no definition of risk or risk-sharing, and the policymakers did not address these agreements as RSAs, stating that the introduction of ‘risk’ came from academic literature instead. Hence the focus on cost-sharing might be rooted in this contrast; Ferrario et al. 2017, p. 1283.

46 Finnish Constitution (in Finnish *Suomen Perustuslaki* Act of 731/1990, as amended) Chapter 2, Section, 6 Equality Principle; Chapter 2, Section 19, Right to Social Security.

47 Kaarlo Tuori – Toomas Kotkas, *Sosiaalioikeus*. Talentum 2016 p. 237.

48 Faulkner et al. 2016, p. 730; Adamski and others 2010 p. 2.

gradually introduced into the general reimbursement scheme, patients suffering from far rarer illnesses could be granted increased access for reimbursements, not originally possible due to the high risk that would befall the government without risk-sharing or vice-versa can promote the creation of novel treatments that previously might have been deemed financially over costly to produce.

The Finnish Constitution echoes the rights of European citizens under Article 35 of the European Charter, where '[e]veryone has the right of access to preventive health care and the right to benefit from medical treatment under the conditions established by national laws and practices.'⁴⁹ Akin to the section 19 of the Finnish Constitution, the obligation stemming from the charter does not grant subjective rights to European citizens to access healthcare. Rather, it gives Member States agency to ensure that the overall social welfare structures are accommodating and striving towards equal and effective coverage.

The interplay between risk-sharing and human rights is an important factor when considering how the Finnish government should proceed with the future of conditional reimbursement. The call for equality in reimbursed treatments can clash with the notion of cost-effectiveness that is required for a reimbursement decision. Conditional reimbursement scheme tries, in principle, to tackle the unequal access to expensive products.⁵⁰ However, limits are still set in terms of cost-effectiveness as seen from Chapter 6, section 6a of the Health Insurance Act, and it seems no alternative criteria are being presented. The question is then whether the scheme can increase access enough to better the overall welfare state?

49 Charter of Fundamental Rights of the European Union *OJ C 326*, 26.10.2012, pp. 391–407, Article 25.

50 Boon – Martins – Koopmanschap 2015 pp. 180–185.

8.3 Results of the 2017–2019 Experiment: Overall Positive Remarks Despite Inefficient Experiences and the Lack of Transparency of the Agreements

With the current interest given by the Finnish legislator in the continuation of the experiment, CRAs seem to have had the desired impact and that both the government as well as the interest groups were eager to share their opinions. All in all, there were 33 replies sent to the Ministry during the public consultation between 8 August 2019 and 6 September 2019.⁵¹ Mostly giving the green light to the Ministry's proposal for Government Bill 40/2019. There were also 11 expert statements delivered during the proceedings.⁵²

A primary success of the experiment was the achieved savings on governmental expenditures on pharmaceuticals; the amount of reimbursements refund reached the projected EUR 14 million marker that was projected at the introduction of the experiment.⁵³ This, combined with the knowledge that the reduction of the total number of declined general reimbursement applications could potentially lead to a better functioning reimbursement scheme, as with added efficiency, future savings on expenditure could be possible. This also demonstrated that an earlier involvement and possible reimbursement could have a positive impact on the overall efficiency of the reimbursement scheme. However, it was highlighted by the Ministry of Finance that purely relying on refunds will not give the full overview of the economic impact of CRAs as the agreement has the potential of affecting the wholesale price of the drug. Hence, comparisons between the prices of products between the EU Member States were recommended.⁵⁴

The government as well as a few interest groups highlighted the increase in patients' access to treatment, and increased the amount of products on the market, in cases where there has been substantial uncertainty concerning the product.⁵⁵ According to a review by the Social Insurance Institution of Finland (Kela) it would

51 See n17 for the list of replies.

52 The statements were given by: THL, Association of Finnish Municipalities, Fimea, KELA, Association of Finnish Pharmacies, Rinnakkaislääketeollisuus ry, Pharma Industry Finland, Suppliers of Parallel Imported Medicines in Finland, SOSTE, The Finnish Medical Association, Ministry of Social Affairs and Health.

53 Government Bill 40/2019, Government Bill 184/2016.

54 Valtiovarainministeriö (Ministry of Finance), Lausuntopyyntö VM/1397/00.00.05/2019, 30.8.2019, p. 2.

55 Government Bill 40/2019, Sairaanhoitajaliitto, Sairaanhoitajaliiton lausunto hallituksen esitykseen eduskunnalle laiksi sairausvakuutuslain muuttamisesta ja väliaikaisesta muuttamisesta. 08/2019; Soste, suomen sosiaali ja terveys RY, Lausunto. 08/2019 (STM060:00/2019); Syöpäjärjestöt (Cancer Society of Finland), Lausunto Sosiaali- ja terveysministeriölle. 09/2019 (STM060:00/2019).

appear that the introduction of conditional reimbursements has reduced the time between market authorisation and reimbursement decision of oncological drugs.⁵⁶ However, it should be noted that no specific study was presented to measure the impact of the past experiment in whether the increasing number of reimbursed products did positively impact access in reality. The government and parts of the industry operate with the assumption that the introduction of 33 new products into the sphere of reimbursement is enough to increase access.⁵⁷ More research is required to fully grasp the whole extent of the impact CRAs have on the access to treatment to better weight and further justify the usage of a legislative experiment.

The matter of the fact was that there were no performance-based agreements conducted within the three years of the experiment, a vacuum that was noted by both the government as well as the interest groups.⁵⁸ This was due to both the short duration of the first experiment and a lack of a clear structure for their introduction. Financial-based agreements are considered less complex to manage,⁵⁹ and the data in question does not necessarily require a clear exchange of information between clinicians, patients, the pharmaceutical company, and the government. Despite not proposing any clear solutions to facilitate the increase of performance-based agreements, apart from acknowledging for the need for additional resources, the increase of performance-based agreements is highlighted within the bill as a target for the future.⁶⁰

Overall results from the experiment are limited. As the number of decisions made keeps increasing, some information on the evaluation of reimbursements and the decision-making process has been generated. Experience was also gained concerning the enforcement and evaluation of the agreements, the enforcement of the rebate and renewal of agreements. What has not been evaluated is the administration and securing of medicines when the conditional reimbursement decision has expired and transition to the regular reimbursement scheme should take place.⁶¹ According to the Finnish Institute for Health and Welfare (THL), further emphasis is needed in relation to the enforcement, evaluation, rebate

56 KELA, Lausuntopyyntö 10/2019 (STM060:00/2019).

57 Government Bill 40/2019, p. 5; Lääketeollisuus (Pharma Industry Finland), Ehdollisen korvattavuuden jatkaminen mahdollistaa uusien lääkkeiden saamisen ripeästi ja tasapuolisesti niitä tarvitsevien potilaiden käyttöön. 09/2019 (STM060:00/2019).

58 Government Bill 40/2019, p. 10; Cancer Society of Finland 2019; THL. Lausunto/1811/4.00.02/2019. (STM060:00/2019).

59 Faulkner and others 2016 p. 731.

60 Government Bill 40/2019, p. 10.

61 Government Bill 40/2019, p. 6.

and the expiry of the agreements.⁶² Yet, all this is in relation to financial-based agreements.

The experiment of 2017–2019 was still a partial success; the budgetary goals were met, there was an increase of pharmaceutical products on the market, and both the government as well as the private interest groups appear to be interested in further bettering the system within the following six years. Despite the success, the results were limited, as medicines have a long lifetime and three years is not long enough to fully grasp the impact of RSAs. Whether the lack of gained results was due to the limited time available or lack of effective measurements in place is unknown. Statistical information will arrive in due course; however, to ensure the attainment of robust data, wider application of CRAs and different types of RSA should be utilised.

8.3.1 Issues with the Current Risk-sharing Model in Finland:

Transparency, Performance-based Agreements and Sustaining the Level of Healthcare

Perhaps the clearest drawback of the CRA is the decrease of transparency within the Finnish reimbursement scheme as this was voiced by nearly all the interest groups taking part in the public consultation. In practice, having confidential agreements between FPPB and pharmaceutical companies might be required to incentivise the companies to partake in risk-sharing; however, the overall situation appears unclear. There was some increased clarity with the added Chapter 6, section 7(4) of the Health Insurance Act⁶³ that now only bars products with a CRA from being used in the determination of the wholesale price of a similar product. Based on the idea that due to the product's probability of returning part of its sales profit to the health insurance fund, the agreed wholesale price would not then be the true final price⁶⁴ making it unreasonable to appraise another product with an incomplete price of the reimbursed product. However, the section only bars appraisal in relation to the wholesale price, and as also noted in the government bill, a CRA product should otherwise be used as a comparator, thus lowering the artificial veil created by a reimbursed product. It remains to be seen how pharmaceutical companies will utilise this clarification, whether the competition for CRAs will become increased now that these products may be

62 THL 2019.

63 Health Insurance Act Chapter 6, section 7, subsection 4.

64 Government Bill 40/2019 p. 13.

used as comparators, however without knowing the wholesale price the picture might be too incomplete to be fully seen.

Despite the lack of a law defining the usage of experimental legislation, it is taken for granted in Finland that the Constitution does not ban the creation of temporary legislation, despite it departing from the traditionally perceived ideals of good legislation, permanence and abstractness. The object of experimental legislation is the attainment of information should permanent legislation be altered based on the experiment.⁶⁵ This obligation is not clearly defined under Finnish law; however, to echo the results of the Swedish RSAs,⁶⁶ there has been more focus on cost-sharing than risk-sharing, and this should apply in Finland as well. In principle, it should be observed that as the legislator itself views this experiment to be part of risk-sharing, it should follow that when conducting a legislative experiment on risk-sharing, risk-sharing measures should also be prioritised⁶⁷ instead of cost-sharing. The challenge for the ongoing trial will be to shift this paradigm to ensure enough experiences are gained from both financial and performance-based agreements.

In addition, the issue with a temporary act affecting social welfare is that if the legislation is not made permanent, there is a possibility that achieved social welfare is then weakened after the expiry of the legislation. The principle of the prohibition to weaken fundamental rights (*heikennyskielto*) is the reverse of the agency effect in social rights law. If the legislation requires the development of the social security system to a certain level, it also means that the system cannot be weakened below that required level. However, if there is no clear description of the appropriate stage, but rather an expectation of continuous development, it would then follow that potentially any decline in social security could be prohibited.⁶⁸ The obligations to ensure access to treatment under section 19, Subsection 3, of the Constitution does not pose a clear level required to be achieved. There is no mention of the type or extent for universal access, but rather ensuring that everyone has access to an acceptable level of health care. However, if CRAs indeed increase the access to treatment it could be argued that the overall betterment of the system could trigger the protection of the prohibition to weaken. According to the Constitutional Law Committee, it is reasonable to consider the national economy when determining the extent of the benefits granted by the state, which

65 Pauli Rautiainen. *Kokeilulainsäädäntö ja sen perusteelliset reunaehdot*, Lakimies 2/2019 pp. 192, 200–201.

66 Andersson – Svensson – Persson – Lindgren 2020 p. 409.

67 Government Bill 40/2019 pp. 5–6.

68 Tuori – Kotkas, 2016 pp. 207–208.

could potentially then call for the reduction of certain social benefits in case of a depression or other financial instability. Although fundamental rights should be considered as the priorities given by the legislator, and even if there would be financial grounds to reduce the benefits granted, the source from which the reduction should be targeted should be prioritised to come from those services and schemes that do not originate from fundamental and human rights obligations.⁶⁹ Hopefully after the current experiment, there will be more substantial evidence to consider about the increase of access to treatment and the general level of healthcare provided by CRAs.

Lastly, reimbursement is not granted to every type of product. The two primary defining requirements were novelty and products that are applied to 'treat an illness'. Novelty is simply referring to the fact that the product needs to be new, barring older inventions that might struggle with a smaller patient base. On the other hand, to 'treat an illness' is used to single-handedly exclude treatments designed to prevent an illness from the possibility of reimbursement.⁷⁰ Especially concerning the current Covid-19 pandemic, and the general importance of preventative action in health care, the exclusion of vaccination⁷¹ and other preventative measures could, in principle, be reconsidered. Having an emphasis on new entries to the market does limit the potential coverage and access to preventative care as for instance products such as Pre-exposure prophylaxis (PrEP) given to people with a risk to contract HIV are not part of the reimbursement scheme.

8.4 The Future of Conditional Reimbursement in Finland

Hopefully, within the following six years, a plethora of CRAs can be conducted to facilitate the development of evidence to both reach a conclusion about the future of risk-sharing in pharmaceutical reimbursement in Finland, as well as fulfil the requirements of using a legislative experiment in gathering enough data on risk-sharing. Yet to reach that goal, there is a need to increase the number

69 Pauli Rautiainen. *Perusoikeuden heikennyskielto*. Oikeus 2013(42) pp. 261–283, 270–271, Tuori – Kotkas, pp. 207–208.

70 Klaus Nyblin. *Mihin suuntaan lääkekorvausjärjestelmä kehittyy*. Defensor Legis N:o 6/2009 p. 942.

71 Vaccines are covered in Finland if they are part of the national vaccination strategy.

of performance-based agreements, and whilst both providers and payers seem motivated in doing so, concrete measures need to be made. The conflict exists with the call for transparency and protection of confidential information, and the question is, will this also expand to cover the results of the trials? However, there are also already identifiable questions to consider about the principles of the reimbursement scheme and what product types should be covered.

8.4.1 Mitigating the Loss of Transparency through Focusing on the Transparency the Process and Accepting a Level of Confidentiality

From the new phrasing of section 7 Subsection 4,⁷² and the government's clarification on how to use CRA products as comparators it appears that some added transparency would be brought into the agreements. Despite the wholesale price still being treated as confidential, the new stage in the discussion should revolve around the transparency of potential endpoints considered in performance-based agreements. For these types of agreements, the gathering of information is required, and new infrastructure needs to be introduced to ensure that the evidence created will be applicable in the future. With learnings gained from the experiences of other EU Member States where performance-based agreements have been tested, availability of information was said to be the key for purposeful and effective information gathering.⁷³ As identified by the OECD, confidentiality of the research outcomes of performance-based agreements has limited third-party access to assess the agreements' effectiveness.⁷⁴ However, the balance between commercially sensitive data and transparency can be difficult to ascertain. While full third-party access might be difficult to accept, focus should also be placed on the cooperation with other EU pricing boards. Partially also provide an answer to the potential imbalance identified by the Finnish Competition Authority, where different pricing boards were said to be in a weaker position to negotiate with a company that has access to multiple European markets, as the company has access to its own negotiations and reimbursement decisions while Member State pricing boards cannot exchange the same information⁷⁵

Multiple interest groups called for the re-evaluation of the level of confidentiality given to these arrangements. Either stating that the government does not give

⁷² Health Insurance Act Chapter 6, section 7, subsection 4.

⁷³ Garrison et al., 2013 pp. 711–713.

⁷⁴ Wenzel – Chapman 2020 p. 47.

⁷⁵ European cooperation was also promoted by THL2019.

enough reasoning as to the necessity of such wide application, or that increased lack of transparency goes against the current practices and trends in governance.⁷⁶ There is no clear mentioning of the appropriate level of confidentiality in the government bills, and as performance-based agreements are yet to be tested in Finland, the practice is also lacking. However, if European trends are followed, pharmaceutical companies are sure to opt to keep the evidence developed as confidential as has been the current practice.⁷⁷ The reason for confidentiality, especially for the wholesale price, as earlier pointed out, stems from the application of external price referencing, which has the adverse effect on the overall structure of financing pharmaceuticals promoting optimisation in the varying stages.⁷⁸ Finland, as a smaller market, might also struggle to receive more competitive prices without confidentiality as not to drag the price of the product down for larger markets.⁷⁹ Nonetheless, the confidentiality of the wholesale price can be currently justified with commercial sensitivity of the data, yet it should be re-evaluated at the end of the current experiment.

For the promotion of performance-based agreements and the requirement of the attainment of evidence enshrined in the usage of a legislative experiment, there is a need for wider access to the possible data generated. As the 2017–2019 experiment clearly did not fulfil this general objective with the reported lack of evidence, wider cooperation between the actors should be enforced. There should be greater transparency used with the future reporting performance outcomes of CRAs to favour the proper functioning of the experiment, which can then be reassessed after its expiry. Greater transparency would ensure that other countries might also benefit from the knowledge sharing, with less likely duplication of studies conducted.⁸⁰

76 Lääkäriliitto (The Finnish Medical Association), lausunto Sosiaali- ja terveysministeriölle 09/2019. Cancer Society of Finland 2019.

77 Wenzel – Chapman 2020 p. 55; Garrison and others 2013 p. 714.

78 Kilpailu ja kuluttajavirasto (Finnish Competition and Consumer Authority), Lausunto. 09/2019 (STM060:00/2019); THL 2019.

79 Ministry of Finance 2019.

80 Wenzel – Chapman 2020 p. 4.

8.4.2 The Potential Changes to CRA Legislation After the 2020-2025 Experiment

Depending on the learning outcomes of the current experiment, the health insurance act can undergo many potential changes. The way the agreements are governed, which type to favour, the recommended forms of risk-sharing should be utilised, however, as the aforementioned benefit from having more health economic data, based on the previous experiment there are already few identifiable subjects that can be considered for the next length of reimbursement policy.

Currently, CRAs are only available for pharmacy drugs, and a natural step would be to expand this possibility also to cover hospital drugs. However, as there are already many institutions in Finland evaluating the cost-effectiveness of pharmaceutical products, this might prove an opportunity to reconsider the fractured layout of the current reimbursement actors, with FPPB managing outpatient care and FIMEA hospital drugs. There is a recommendation to unify all the actors under a single organisation referred to as ‘the Finnish medicines agency’. To better use the evaluation of drug treatment to support decision making, acquisition, and pricing of medicines as under the current legal framework, there are parallel proceedings with different methods and processes.⁸¹ It should be recognised that all the actors carry specialised tasks; however, there are potential benefits both from governance as well as the industry’s perspective that could be reached, at least in principle, if all performance evaluations were conducted by the same actor. This could potentially also fall in line with the European Commission’s recent directive proposal in unifying and giving further guidelines on Health Technology Assessments (HTA), and how they should be made more compatible within Europe.⁸²

The discussion still exists of whether reimbursements should be expanded to cover new categories of products, either preventative treatments or older less-novel treatments that might have struggled with their initial reimbursement application. This would inevitably impact the overall principles of the Finnish reimbursement scheme and require a larger change in its foundations. However, currently, there is a lack of data to further promote this claim, and as such, it is left as more of a concluding theoretical observation.

81 Ruskoaho 2018 pp. 48–49.

82 See: European Commission, Proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on health technology assessment and amending Directive 2011/24/EU. 01/2011.

8.4.3 How to Enable Risk-Sharing Instead of Cost-Sharing: Clear Definition of a Strategy and Reconfiguration of the Agreements Made

There is a risk that the Finnish experiments will repeat Sweden's experience and focus on affordability rather than managing the risks due to the uncertainty of the products. Practising cost-sharing, rather than risk-sharing. With only performing financial-based agreements, it is difficult to say what the lack of performance-based counterparts has had on the reimbursements overall, as the thresholds for a product to be accepted into the different agreement types can vary. Performance-based agreements can have a much higher threshold for cost-effectiveness as its evaluation would be based on the accumulated data rather than the projection based on a list price.⁸³ However, to facilitate performance-based agreements, the issue of sensible data collection needs to be solved. The data collection also needs to also fulfil the requirements set in the General Data Protection Regulation (GDPR) of the European Union.⁸⁴

In principle, data collection should be divided into two distinct parts: the process and the content. Through a clearly defined process, both parties might gain clarity of the obligations related to the practicalities of the agreement and communicating this to the data subjects during data collection would fulfil the notification obligations under GDPR. Currently, in Finland, there is no public design of evidence gathering for CRAs, and there is no clear strategy which platforms are used or what critical infrastructure should be designed. It might not be efficient to rely on the case by case cooperation between the FPPB and pharmaceutical companies, and to utilise existing patient data reporting systems, there should be a clearly defined practice. With more public participation in data gathering, the industry might require fewer incentives to partake in the agreements, and the transparency of the process would have stronger legal protection. However, if privately managed data collection is utilised instead, the potential to incentive evidence generation should be explored. By restructuring the incentivisation and focusing less on upfront payments, and more on rewarding performance (or the opposite of penalising underperformance), companies might consider it more beneficial to invest in thorough evidence gathering, as there would be a clear incentive in doing so.⁸⁵ The content of the data collection should be determined

83 Andersson – Svensson – Persson – Lindgren 2020 p. 409.

84 European Commission, Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation).

85 Wenzel – Chapman 2020 p. 47; Bouvy – Sapede – Garner 2018, p. 7.

based on a case-by-case analysis of the product in question as having a rigid system of fixed endpoints brings limited flexibility and cannot adapt to the changes in the market.⁸⁶

Another possibility to impact the overall numbers of performance-based agreements would be to reconsider the contracts used in CRAs. Using a more specialised contract model intended to protect both the commercial interest as well as set clear and transparent goals for data collection could be recommended. Following a model inspired by the NHS England Cancer Drugs Fund, each CRA could consist of two contracts, a ‘data collection agreement’ and the commercial agreement.⁸⁷ The data collection agreement would explain the planned data collection and what uncertainty it is aimed at tackling. The commercial agreement would then contain the agreed endpoints as well as other commercial information related to the price of the product.

There is a potential to further incorporate HTA into reimbursement decisions. When evaluating the cost-efficiency of a product, the decision should also make a statement concerning whether the product is recommended for an RSA, either financial or performance-based. With early involvement of RSAs into the evaluation of a product, both manufacturers as well as reimbursement boards might be more ready to act upon based on the recommendation, also streamlining the interpretations of the requirements for products to enter the risk-sharing arrangements. HTAs also already include the relevant information of the uncertainties of the product in relation to comparative effectiveness to other products, cost-effectiveness and budgetary implications.⁸⁸

8.4.4 Risk-Sharing and Personalized Medicine

Personalized medicine will impact the setting of clinical trials, as the typical stage III trial of thousands of patients does credibly display the effectiveness and safety of a product used to treat widely spread diseases; however, it performs poorly when measuring the benefits and disadvantages of a drug used to treat a rare hereditary disease. It is already common that novel products are intended for smaller patient bases or orphan diseases, and that its use is limited, which is then

⁸⁶ Pauwels and others 2017, p. 5.

⁸⁷ NHS England Cancer Drugs Fund Team, Appraisal and Funding of Cancer Drugs from July 2016 (including the new Cancer Drugs Fund) A new deal for patients, taxpayers and industry. 07/2016.

⁸⁸ Wenzel – Chapman 2020 p. 45.

expanded further with increased evidence development.⁸⁹ As the market seems to be moving from a traditional ‘bulk’ entry into specialised, consistent evidence gathering, CRAs can be a good tool for governments to facilitate a more joint evidence development.

From the study commissioned by the Ministry of Social Affairs and Health, the overall conclusion was that the general Finnish reimbursement scheme does not adequately take into account the requirements of the changes in health care by personalized medicine.⁹⁰ While the criticism was directed at the system in general, citing inequality in cancer treatment. Wherein certain cases, if there is a treatment based on a limited grounds due to mutation, the best practice for treatment in the hospital is not reimbursable; however, the new drugs available in outpatient care are, creating inequality between the intravenous treatments and ingestible products.⁹¹ This, however, akin to the earlier discussion of the leaving preventative treatments outside of the scope of the reimbursement decision, is a wider discussion on the overall future of the Finnish reimbursement scheme. CRAs remain a natural partner with personalized treatments as they enable the reimbursement of products with a clear focus on continuous evidence gathering, as well as products that might struggle with the ‘traditional’ accumulation of clinical data.

8.5 Conclusions

It appears that the new experiment brings more potential trial performance-based agreements and conditional reimbursement has the potential to increase access to new treatments. Yet, conditional reimbursements are still finding their way into the practices of payers and producers in Finland, and more data on the economic and health benefits of the new system are required, data of which is hopefully generated by all possible agreement types. When the current experiment comes to an end in 2025, the legislator will be determining the overall worth of the past three plus six years of conditional reimbursement and is faced with a similar decision whether to discontinue, continue or make the experiment a permanent part of the reimbursement scheme. A lot can happen in six years; however, already based

89 Ruskoaho 2018, p. 57; see also James P. Bishop – Sonal B. Halburnt – Patrick A. Akkari – Scott Sundseth – Iris Grossman, Roadmap to Drug Development Enabled by Pharmacogenetics in Godfrey Grech – Iris Grossman (Eds) *Preventive and Predictive Genetics: Towards Personalized Medicine*. Springer 2015 pp. 43–69.

90 Ruskoaho 2018, pp. 71–72.

91 Ruskoaho 2018, pp. 56–57.

on the first experiment there are strong grounds to consider the permanence of conditional reimbursement and section 6a.⁹² With the new experiment, there is an increased possibility of piloting different types of agreements and considering raising the number of performance-based agreements, if society can meet the requirements posed by increased need for data collection. An increase in a wider variety of agreements can also help shift the overall focus of the current scheme to prioritise impact and effectiveness of treatment instead of amounts of units sold. With personalized medicines looming in the near future, more specialised treatments will become available to purchase that might struggle to gain enough of a patient base to warrant a standard reimbursement initially, with having a conditional reimbursement scheme, and lowering the threshold for risk-sharing to take place, access to treatment will be increased, bettering the overall social welfare system.

⁹² Health Insurance Act, Chapter 6, section 6 a.

9

Transatlantic Comparative Perspectives on Patenting Genome-editing Technologies – A Case Study of Patents on CRISPR/Cas9 Technology

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Abstract

This chapter investigates the patentability of CRISPR/Cas9 technology in Europe and the United States. Special attention is paid to the recent legal dispute over a patent concerning the use of the CRISPR/Cas9 system in eukaryotic cells. The parties involved in the dispute are two academic institutions, the University of California (the ‘UC’) and the Broad Institute of MIT and Harvard (the ‘Broad Institute’), which have been investigating the system and its potential use as a genome-editing tool. Interestingly, the United States Patent and Trademark Office (the ‘USPTO’) and the European Patent Office (the ‘EPO’) have granted the patent to both of the parties of the legal dispute. In particular, the two patent offices have adopted a very different approach to the concepts of innovative step and obviousness in inventions. This dispute influences the scientific community and those who wish to use this technology commercially. This chapter will look in more detail into the implications of this legal dispute as well as some lessons learned.

9.1 Introduction

The CRISPR/Cas9 system, i.e. ‘Clustered Regularly Interspaced Short Palindromic Repeats’ and ‘CRISPR-associated protein 9’, is a pivotal genome-editing technology that has gained substantial attention since 2012. It is a rather simple but powerful tool for editing genomes, which enables scientists to change DNA sequences and modify gene function. This technology has myriad possible applications in several

fields of science and engineering ranging from agriculture to biomedical research. It has the great potential to transform medicine and diagnose, treat and prevent many diseases, and more recently it has been used in developing diagnostic tools, which may be used to detect infectious diseases such as COVID-19. A great variety of possible applications results in a wide array of commercial possibilities. Therefore, understanding the scope and limitations of the patent protection of this technology is of paramount importance for those who wish to use the technology in their research and for those would like to commercialize their innovations in Europe and beyond.

Globally speaking, there are thousands of patent applications on CRISPR/Cas9 technology and new ones are constantly emerging. In recent years, the most burning topic has been the title and rights to the so-called ‘founding patent’ of the CRISPR/Cas9 system’s use on editing on cells, in particular eukaryotic cells (a group of organisms including plants and animals). Interestingly, the European and United States Courts have adopted very different approaches to resolving this exceptional patent dispute between the UC and the Broad Institute. In the United States, the UC has a right to the genetic engineering in prokaryotic cells and the Broad Institute has been granted a patent on engineering eukaryotic cells. The USPTO has viewed that the innovative step from using CRISPR/Cas9 on prokaryotic cells to using it on eukaryotic cells is significant enough to grant a patent. In Europe, the EPO has taken an opposite view and granted the UC a patent that covers all cell types. As there are substantial financial interests and some significant commercialization potential in the genetic engineering of eukaryotic cells, both parties to the dispute have pursued a patent covering them. Consequently, the UC contested the United States patent decision, while the Broad Institute tried the same in Europe. After many years of legal battle and some decisive rulings, which were expected to end the dispute, the proceedings are still ongoing.

At this stage, there is a need to explore further the actual differences in what was perceived as innovative in the United States as compared to Europe in the context of patenting genetic editing technologies in light of these recent rulings. There is also a need to analyze the implications of the rulings from the viewpoint of the commercialization prospects of CRISPR/Cas9-based technologies in Europe and beyond. As this patent case has very exceptional features, there is a need to consider whether there is anything that we could learn from this case thus far.

9.2 What Is CRISPR/Cas9 and Why Is It So Pivotal?

The CRISPR/Cas9 system is opening up a new era in molecular biology. In the field of genome editing, researchers have been striving for years to find efficient, reliable, and safe ways to alter the genome of living cells. In terms of precision, the CRISPR/Cas9 system represents a significant step forward, in comparison to the older generation gene-editing technologies, including zinc finger nucleases and transcription activator-like effector nucleases (TALENs). The previous genome engineering technologies, like agrobacterium mediated gene transfer or mutagenesis, are generally known to be very hard to control, imprecise, and often not yielding the desired outcomes. Now, the CRISPR/Cas9 system provides scientists with the tools to edit the human DNA present in living human cells, letter by letter. However, it should be noted that although the CRISPR/Cas9 system has been described as revolutionary, in light of the current scientific understanding, the procedure of modifying genes has not been proven safe yet. Among other things, it should be investigated what kind of damage the CRISPR-Cas9 causes to human DNA, as it is known that gene editing may in some cases disrupt healthy genes even though its purpose is to only fix defective ones.¹

Similarly to other gene-editing technologies, the CRISPR/Cas9 system comprises two separate parts. In the case of CRISPR/Cas9, there is the part that can be engineered to recognize the different parts of the genome sequence (CRISPR-sequence) and the enzyme part that cuts the targeted sequence (Cas9 enzyme). Then, what makes CRISPR/Cas9 so special? Compared to other genome-editing techniques, CRISPR/Cas9 has been found to be much easier, more precise, and affordable to use.² Consequently, the CRISPR/Cas9 technology was rapidly adopted as a useful gene-editing tool in all fields of biology and science dealing with molecular biology. None of the older generation techniques ever reached the same utilisation rate among researchers despite the fact that they have been available for use much longer. CRISPR/Cas9 is not only paving its way as a ground-breaking laboratory tool, but the practical uses of this technology offer even more significant opportunities. Firstly, CRISPR/Cas9 provides new opportunities in agricultural genomic engineering and breeding that have not been previously within our reach. Secondly, a very significant commercial application of this technology is to be found within the (bio)medical field. In theory, the possible uses are nearly endless; any

1 See Michael Kosicki – Kärt Tomberg – Allan Bradley, Repair of Double-Strand Breaks Induced by CRISPR–Cas9 Leads to Large Deletions and Complex Rearrangements. *Nature Biotechnology* 36 2018, pp. 765–771.

2 Heidi Ledford, Titanic Clash over CRISPR Patents Turns Ugly. *Nature* 537(7621) 2016a, p. 460.

illness that has genetic roots could possibly be cured by means of the CRISPR/Cas9 technology. In addition to inherited genetic diseases, this technology has been thought to be a possible cure for a wide array of diseases, ranging from HIV to malaria as well as all the different types of cancers.³

Currently, the possible applications of CRISPR/Cas9-assisted genome therapy appear almost endless. The high financial value of the CRISPR/Cas9 system has resulted in a wide array of university spin-off and start-up companies in the field operating on both sides of the Atlantic. In addition, numerous patent applications relating to some forms of CRISPR/Cas9 technology have been filed in the US, Europe, and beyond. As vast amounts of capital have been invested in CRISPR/Cas9-assisted genome editing technologies, expectations for success are high and the competition is getting intense. Hence, understanding the scope and possible limitations of the patent protection of the CRISPR/Cas9 system becomes increasingly important when navigating in this highly competitive environment.

9.3 Patentability of Gene-Editing Technology

9.3.1 Patent System as an Incentive for Promotion of Technological Innovation

International intellectual property conventions set forth the global regulatory framework for patent protection, and national patent laws supplement this framework. Patent legislation provides the patent holder an exclusive right to prevent others from using the patented invention for commercial purposes during a limited term of patent protection, usually 20 years from the filing date of the application. An objective of this legal monopoly, as set out in art. 7 of the Agreement on Trade Related Aspects of Intellectual Property Rights ('TRIPS Agreement'), is to contribute to the promotion of technological innovation and to the transfer and dissemination of technology, to the mutual advantage of producers and users of technological knowledge and in a manner conducive to social and economic welfare. Thus, the patent legislation aims at providing to universities, technological companies, and other researchers a favorable operational environment in which innovation, research, and development are encouraged by legislative incentives.

3 Mohammad-Reza Mahmoudian-sani – Gholamreza Farnoosh – Ali Mahdavinezhad – Massoud Saidijam, CRISPR Genome Editing and Its Medical Applications. *Medical Biotechnology* 32(2) 2018, p. 289.

Strong patent protection is often required to fund the very significant R&D associated with the development of new technologies. This is particularly true in the case of pharmaceutical and biotechnology patents.⁴ Patents are frequently used for raising capital, and they have become increasingly important for developers of new technologies. Patents may signal quality as well as technical progress to capital markets or to venture capitalists, and sometimes they also serve as collateral for bank loans.⁵ Furthermore, universities need patents to attract investors for university spin-offs.⁶

For the above-mentioned reasons, to name a few examples, applying for a patent may be a potentially financially lucrative possibility for researches. In exchange for the exclusive right to monetize the invention during the term of patent protection, the patent holder's exclusive right ceases to exist upon the expiration of the term, and thereafter the invention falls in the public domain and may be used by others without paying any royalty fees. In addition, when a patent application is published during the patent proceedings, the invention must be fully disclosed to the public in a sufficiently clear manner in order to be carried out by a person skilled in the art. Once fully disclosed, the invention can be used as a basis for further innovations after the expiration date. Therefore, the patent system sets a framework for progress of science, as researchers might otherwise prefer to keep their inventions in secret.

Consequently, a patent can be seen as a contract between the inventor and the rest of the society that provides benefits for both parties. Instead of being kept in secret, an invention benefits the society while the patent protection incentivizes inventors to invent.⁷ However, by virtue of their exclusivity, patents may also be deemed as blocks for science, which is entirely against the purpose of the existence of the patent system. This has been a subject of public discussion especially in the field of biotechnology, and this also seems to be the case in the CRISPR/Cas9 dispute at hand.

4 See for example Juli Mansnéus, *Commercialisation of Advanced Therapies: A Study of the EU Regulation on Advanced Therapy Medical Products*. LL.D. Dissertation. University of Helsinki, Faculty of Law 2016, p. 109.

5 Åsa Hellstadius, *A Quest for Clarity: Reconstructing Standards for the Patent Law Morality Exclusion*. LL.D Dissertation. Stockholm University 2015, pp. 84–86.

6 Mansnéus 2016, p. 109.

7 See Hannah M. Mosby, *Biotechnology's great divide: strengthening the relationship between patent law and bioethics in the age of CRISPR-Cas9*. *Minnesota Journal of Law Science & Technology* 19(2) 2018, pp. 565–604.

9.3.2 Gene-Editing Technologies' Eligibility for Patent Protection

In order to be eligible for patent protection, an invention must meet all mandatory patentability requirements. The eligibility for patent protection of a biotechnological invention, including gene-editing technology, is mainly dependent on the same requirements as inventions in other fields of technology. As a starting point, an invention must be of *patentable subject matter*. Not all subjects are considered inventions; for instance, mere discoveries of substances in nature are not patentable. Some subject matter has also specifically been excluded from patentability by way of exceptions stipulated by patent laws. In the context of biotechnology, the America Invents Act of 2011 § 33(a) rejects patent protection for inventions directed at or encompassing human organisms. Similarly in Europe, art. 53(a) of the European Patent Convention (the 'EPC') and art. 6 of Directive 98/44/EC (the 'Biotech Directive') excludes inventions the commercial exploitation of which would be contrary to '*ordre public*' or morality from patentability. This could be relevant when applying for a patent for a gene-editing technology related invention.

Additionally, an invention must be *novel*. In practice, this means that an invention must be considered new in comparison with the applicable prior art in the field, if it does not form part of the state of the art. The degree of novelty is not only an indispensable prerequisite for a patent grant, but from the perspective of commercialization of the invention, it also plays a key role as a determinant of patent value. Carpenter et al. have provided a concept of 'scientific linkage' in seeking to describe the technical novelty of a patented innovation. Their findings empirically support the idea of theoretical assumptions of novelty being a determinant of patent value. Their key finding is that references, i.e. 'citations' to the scientific literature, correlate with the value of a patented innovation.⁸

Furthermore, in the United States, an invention must be *non-obvious*, whereas in Europe it must involve an *inventive step* (for comparative perspectives see Table 1 below). Additionally, in the United States, an invention must be *useful*, and in Europe it must be *susceptible of industrial application*. Despite the deviating wordings in patent legislation on both sides of the Atlantic, the requirements are similar, but the USPTO and the EPO sometimes take rather different stands with regard to interpretation, which appears to be the case in the CRISPR/Cas9 dispute at hand.

There are certain challenges specifically related to the patentability of biotechnological inventions. The complexity and unpredictability of biological

8 See Mark P. Carpenter – Martin Coope – Francis Narin, Linkage Between Basic Research Literature and Patents. Research-Technology Management 23(2) 1980, pp. 30–35.

systems may cause difficulties for the patent applicant in demonstrating that the patentability requirements have in fact been met. Firstly, differing from so-called classic inventions for instance in the field of mechanics, presenting a biotechnological invention only by means of a written description of its component parts is challenging. In some situations, a deposit of biotechnological material would be significantly more informative, but patent legislation requires a written description of the invention.

Secondly, drawing a line between a mere discovery and a patentable invention may be difficult. Many biotechnological inventions have existed in nature for a long time, but they have not been isolated and specified until recently, and therefore they may not be unambiguously distinguished as mere discoveries or as inventions within the meaning of patent legislation. As stated above, a mere discovery of a substance in nature cannot be an invention, however, the process for obtaining a substance to be isolated from its surroundings may be a patentable invention. The substance itself may also be patentable if it can be characterized by its structure and its existence has not been recognized before.⁹

Thirdly, complex ethical questions are often addressed as regards biotechnological patents.¹⁰ These ethical considerations have also been raised in the context of the use of the CRISPR/Cas9 system, but such aspects are left outside the scope of this chapter. Yet, it should be mentioned that especially the question regarding inheritable editing of human genome has been subject to vivid ethical debate ever since the inception of the CRISPR/Cas9 system. The system could be used to avoid harmful mutations in future generations' genome in order to prevent serious illnesses. Yet, some concerns have been voiced that this technology is still not safe to be applied in humans and it could be conducive to increased social inequality in our society. The Convention of Human Rights and Biomedicine of the Council of Europe (1997) allows genetic engineering only for preventive, diagnostic, or therapeutic reasons and only where it does not aim to change the genetic make-up of a person's descendants. However, an alternative approach has been recently proposed. In fact, the Nuffield Council on Bioethics has argued that heritable genome editing is not morally unacceptable *per se*. In its new report, the Council approves the use of genome editing to engineer the traits

9 See Sasa Bavec – Peter Raspor, Patenting Biotechnological Inventions in Europe, Food Technology and Biotechnology 40(4) 2002, pp. 353–359.

10 See Mosby 2018.

of future progeny under certain specific circumstances.¹¹ It finds that changing the DNA of a human embryo could be morally permissible if it is in the child's best interests and if it does not add to the kinds of inequalities that already divide our society. This approach has already triggered some significant criticism in the public sphere. Among other things, concerns have been voiced that heritable editing of human genome would lead to social inequality. As discussed above, beyond moral considerations, the procedure of modifying genes in human embryos has not been proven safe as of yet. Among other things, it should examine what kind of undesired alterations the CRISPR-Cas9 system may cause to human DNA.¹² In any case, although the wider ethical considerations are outside the primary scope of this chapter, heritable editing of human DNA is a matter of highly ethically sensitive nature, and thus there is clearly a need to ensure that a great variety of voices is heard in public discussions at a global scale as to what should and should not be allowed if we are to allow any heritable modification of human genome in the foreseeable future.¹³

Despite the wide array of challenges in patent application proceedings, biotechnological patents constitute an increasingly large proportion of patented inventions, some of which are also high-profile and attractive patents, such as the CRISPR/Cas9 patents. Biotechnologies such as the CRISPR-Cas9 system can be highly lucrative because of their immense potential for public health, which raises the stakes of the patent bargain.¹⁴

11 Nuffield Council on Bioethics, *Genome Editing and Human Reproduction: Social and Ethical Issues*. 2018. Available at: <http://nuffieldbioethics.org/project/genome-editing-human-reproduction>, accessed 9 September 2020. For further details, see Blick, in chapter 6 of this anthology.

12 See Kosicki et al. 2018.

13 Juli Mansnérus – Céline Dujardin – Raimo Lahti, *Forms and Levels of Legal Protection of the Human Embryo in Biomedical Research in Finland and France*, pp. 199–224 in Ewa M Guzik-Makaruk – Emil W Plywaczewski (eds.), *Current Problems of the Penal Law and Criminology: Aktuelle Probleme des Strafrechts und der Kriminologie*. Wydawnictwo C.H. Beck 2019.

14 See Mosby 2018.

9.4 CRISPR/Cas9 Patent Dispute in Europe and the United States

9.4.1 The Emergence of CRISPR/Cas9 Technology

The CRISPR/Cas9 system has been perceived as one of the most significant innovations influencing the dynamics of the field of biotechnology.¹⁵ This great scientific potential has been accompanied by some significant endeavours to capitalize the invention. Therefore, the patentability of CRISPR/Cas9 technology has been in the limelight ever since its potential to engineer genetic material was disclosed for the first time. In 2012, Jennifer Doudna from the University of California and Emmanuelle Charpentier from Umeå University ('Team California') were heading the first group to report that they had been able to reprogram CRISPR/Cas9 to target specific DNA.¹⁶ Their experiment was conducted *in vitro*. The publication of Team California's research report fuelled the emergence of further research regarding CRISPR/Cas9 technology. Shortly, another team of researchers headed by Feng Zhang from the Broad Institute ('Team Broad Institute') published another significant research article, in which successful use of CRISPR/Cas9-assisted gene targeting was reported in eukaryotic cells, including human cells.¹⁷ After the publication of these articles, both teams established spin-off companies to administer licensing rights to their CRISPR/Cas9-related patents.

9.4.2 The United States: Team Broad Institute Prevails over Team California

In May 2012, Team California filed the very first provisional patent application (No. 61/652,086) regarding the use of the CRISPR/Cas9 technology with the USPTO. The application asserted patent rights covering the use of CRISPR/Cas9 technology without any specific indication on cell types, however, disclosing data obtained from prokaryotic cell types and *in vitro*. Nearly seven months later, in December 2012, Team Broad Institute submitted their provisional patent application (No.

15 Ledford 2016a, p. 460.

16 Martin Jinek – Krzysztof Chylinski – Ines Fonfara – Michael Hauer – Jennifer Doudna – Emmanuelle Charpentier, A Programmable Dual-RNA-Guided DNA Endonuclease in Adaptive Bacterial Immunity. *Science* 337(6096) 2012, pp. 816–821.

17 See Le Cong – Fei Ann Ran – David Daniel Cox – Shuailiang Lin – Robert Barretto – Naomi Habi – Patrick D Hsu – Xuebing Wu – Wenyan Jiang – Luciano A Marrafini – Feng Zhang – Multiplex Genome Engineering Using CRISPR/Cas Systems, *Science* 339(6121) 2013, pp. 819–823.

61/736,527) to the USPTO, covering the use of a similar technology in eukaryotic cell types. Due to an expedited review by the USPTO, Team Broad Institute was granted the US patent no. 8,697,359 on the CRISPR/Cas9 technology already in April 2014, prior to Team California.

Some authors¹⁸ have suggested that Team Broad Institute's receipt of the patent '359 prompted Team California to amend the claims of its patent application (No. 13/842,859), removing any reference suggesting that they are limited to a particular cell type. Allegedly, such amendments enabled Team California's grounds for a suggestion for an interference proceeding before the US Patent and Trademark Office's Patent Trial and Appeal Board (the 'PTAB') against Team Broad Institute, which it requested in April 2015.¹⁹ In the proceedings, Team California demanded a nullification of Team Broad Institute's CRISPR/Cas9 patents, claiming that the patents overlapped with Team California's patent application.

The USPTO announced the interference proceedings in January 2016.²⁰ In Team California's view, the scope of their first patent application - which only clearly explained the use of CRISPR/Cas9 on prokaryotic cells - also encompassed the use of CRISPR/Cas9 in eukaryotic cells. Team California claimed that a person having ordinary skill in the art - a post-doctoral researcher with relevant skills - could have understood that CRISPR/Cas9 applied on prokaryotic cells could be applied on eukaryotic ones as well, which should render Team Broad Institute's invention 'obvious' for a person skilled in the art and, hence, unpatentable due to obviousness.²¹ The Broad Institute presented a counterargument that they had to tweak and modify the system to be able to use CRISPR/Cas9 on eukaryotic cells. In their view, the modifications were so significant and non-obvious that the invention did not interfere with Team California's invention and a separate patent on the use of CRISPR/Cas9 on eukaryotic cells should thus be granted.

In February 2017, the PTAB decided the interference proceedings in Team Broad Institute's favor. The decision focused mainly on whether there would have been a *reasonable likelihood to success* for Team California's CRISPR/Cas9

18 See for example James W Sanner, The Struggle for CRISPR: A Billion Dollar Question in Intellectual Property. *Journal of Law, Technology and Policy* 431 2016, pp. 431-453.

19 Under 37 C.F.R § 41.202, any patent applicant who believes that another application claims the same invention may suggest an interference. If the inventions are identical, the PTAB determines the priority of the inventions and only the preceding invention will be patentable. However, if the inventions are distinct, e.g. due to a non-obvious improvement compared to the preceding technology, there is no interference. Jacob S Sherkow, Inventive Steps: The CRISPR Patent Dispute and Scientific Progress. *EMBO Reports* 18(7) 2017, pp. 1049.

20 Patent Interference No. 106,048.

21 See Ledford 2016a.

technology *in vitro* and in prokaryotic cell types in eukaryotic cells as well.²² Relying on various expert opinions, Team California's article on the invention²³ and their key inventor Jennifer Doudna's public statements, where she expressed her doubts on getting the technology to work in an eukaryotic cell environment,²⁴ the PTAB was convinced that Team Broad Institute did accomplish a non-obvious and additional inventive step in relation to the state of art by making the technology usable in eukaryotes. As a result, the patents of Team Broad Institute were not considered to overlap with Team California's patent application; the inventions were considered distinct.²⁵

Subsequent to the decision of the USPTO, some significant confusion has remained as to what is the mutual relationship between the contested patents.²⁶ Some commentators (including Team California's own attorneys) were still convinced that Team California's patent should be considered the actual 'founding patent' of CRISPR/Cas9 genome editing technology, and the Broad Institute's patent should subordinate to this first 'parent patent'. Team California appealed the PTAB's decision in July 2018, claiming that incorrect standards were applied in determining the obviousness. In September 2018, the US Court of Appeals for the Federal Circuit ('US Court of Appeals') rejected Team California's appeal. Team California did not appeal the decision and it seemed that the dispute had finally come to an end.

It was, however, already in 2019, when the dispute came to light again. By this time, the initial patent application filings had been followed by many more and both parties had obtained several patents for various CRISPR/Cas9 applications. Team California had also filed for several patent applications claiming CRISPR/Cas9 based methods specifically in eukaryotic cell types, which made the USPTO's PTAB declare a second interference proceeding between Team California and Team Broad Institute.²⁷ Subject to the proceedings is 10 patent applications filed by Team California including claims relating to the use of CRISPR/Cas9 based methods in eukaryotic cell types, and 13 CRISPR/Cas9 patents and one patent

22 Sherkow, 2017 p. 1049.

23 Martin Jinek – Alexandra East – Aaron Cheng – Steven Li –Enbo Ma – Jennifer Doudna, RNA-Programmed Genome Editing in Human Cells. *eLife* 2 2013.

24 Melissa Pandika – Jennifer Doudna, CRISPR Code Killer. *Ozy* 2014, available at: <https://www.ozy.com/rising-stars/jennifer-doudna-crispr-code-killer/4690>, accessed 9 August 2020. Michael Barnes. The CRISPR Revolution. *Catalyst Magazine* 9.1 2014, pp. 18–20.

25 Patent Interference No. 106,048.

26 See Arti K Rai – Robert Cook-Deegan, Racing for Academic Glory and Patents: Lessons from CRISPR. *Science* 358(6365) 2017, pp. 874–876.

27 Patent Interference No. 106,115.

application of Team Broad Institute. In these second proceedings, the parties expect to receive a final decision on which party was the first to invent the use of the CRISPR/Cas9 in eukaryotic cell types.²⁸ On 18 May 2020, the oral argument on motions in the interference was heard by the USPTO's PTAB.

As for the very latest developments in the US, it appears that the latest round in battle has an apparent winner, but the fight goes on.²⁹ The PTAB ruled on 10 September 2020 that a group led by the Team Broad Institute has 'priority' in its already granted patents for uses of the original CRISPR system in eukaryotic cells covering potentially lucrative applications in lab-cultured human cells or in humans directly. Yet, the ruling can be also seen to give Team California an advantage on the invention of one critical component of the CRISPR tool kit.³⁰

Interestingly, the Team Broad Institute issued a statement that seems to call for a 'peace treaty' According to the statement:

'Although we are prepared to engage in the process before the PTAB and are confident these patents have been properly issued to Broad, we continue to believe it is time for all institutions to move beyond litigation and instead work together to ensure wide, open access to this transformative technology. The best thing, for the entire field, is for the parties to reach a resolution and for the field to focus on using CRISPR technology to solve today's real-world problems.'³¹

The timeline of the US proceedings is presented in the Appendix 1 of this chapter. To date, the proceedings have not been decided.

28 Julian Cockbain – Sigrid Sterckx, Patenting Foundational Technologies: Recent Developments in the CRISPR Patent Struggle. *The American Journal of Bioethics* 20(4) 2020, pp. 11–12, 11.

29 Jon Cohen, The latest round in the CRISPR patent battle has an apparent victor, but the fight continues. *Scientific Community Technology*. Available at: <https://www.sciencemag.org/news/2020/09/latest-round-crispr-patent-battle-has-apparent-victor-fight-continues>. doi:10.1126/science.abe7573. Accessed 27 November 2020.

30 Ibid. The court refers to as CVC because it includes the University of Vienna and scientist Emmanuelle Charpentier.

31 Broad Institute, For Journalists: Statements and Background on the : CRISPRpatent process. September 27, 2020. Available at: <https://www.broadinstitute.org/crispr/journalists-statement-and-background-crispr-patent-process>. Accessed 27 November 2020.

9.4.3 Europe: Team California Prevails over Team Broad Institute

It appears that the status of the European CRISPR/Cas9 patents is even more complicated than of those in the United States. The same parties, i.e. the UC and the Broad Institute, have been involved in a legal race for a patent in Europe as well. Similarly as in the United States, Team California was the first to file its European patent application in March 2013, claiming priority of their earlier United States patent application of May 2012. Team Broad Institute filed their European patent application eight months later, in December 2013, similarly claiming priority of their United States patent application of December 2012.

Both Team Broad Institute and Team California succeeded in their applications and obtained respective European patents covering an extensive and fundamental range of uses of the CRISPR/Cas9 technology. Interestingly, however, the EPO arrived at an opposite approach than the USPTO with regard to the patent application filed by Team California and, in April 2017, it granted Team California a broad patent (No. EP2800811) on the CRISPR/Cas9 system in all cell types including eukaryotic cells.³² The awarding of the patent constituted a significant victory for Team California in the ongoing patent dispute.

Simultaneously, Team Broad Institute was facing difficulties with regard to their patent applications. Similarly as in the United States, the team was granted their first European CRISPR/Cas9 patent (No. EP2771468) prior to Team California, already in February 2015, but the patent was soon subject to an opposition proceeding. During the nine-month opposition phase, nine notices of opposition were submitted against the patent. It was brought to the attention of the EPO that Team Broad Institute could not claim priority stemming from their United States patent application, as the inventors had been named differently on the respective applications. Under European patent law, a priority claim can only be made by the same applicants who have been assigned in the earlier application or by applicants to whom the right to claim priority has been transferred before the application is filed.³³

The EPO agreed with the opposition notices, finding that one of the inventors named in the Broad Institute's United States patent application was indeed omitted from the European application: inventor and co-applicant Luciano Marraffini, a researcher at Rockefeller University. Neither had Marraffini transferred his

³² Rai et al. 2017.

³³ Ulrich Stroz, CRISPR Cas9 – Licensing What Can't Be Licensed. *Les Nouvelles - Journal of the Licensing Executives Society* LIII(2) 2018, pp. 123–131, 91.

priority rights to the Broad Institute.³⁴ Consequently, priority could not be claimed, which resulted in a calculation of the patent's priority date from the date when the EPO had received the patent application in December 2013. Crucially with regard to Team Broad Institute's patent application, many research articles about eukaryotic genome editing with CRISPR/Cas9 were published during the period between December 2012 and December 2013.³⁵ These publications caused a lack of novelty of the invention, as by December 2013, the CRISPR/Cas9 system's use in editing eukaryotic genome could no longer be perceived as novel in relation to the prior art. Thus, Team Broad Institute's invention was not patentable in Europe. The EPO revoked Team Broad Institute's CRISPR patent (No. EP2771468) in March 2018, denying its reliance on its United States priority and citing a lack of novelty over prior art. Team Broad Institute immediately appealed the decision of the opposition division, but the appeal was dismissed in January 2020. The revocation of the patent was confirmed.³⁶ In November 2020 the EPO finally published its reasoning for its Decision confirming that it did have right to decide on priority entitlement. It was found that EPO case law on the issue of priority was well established and that there is no reason to deviate from it. It also stated that all applicants must be listed on both an initial application and subsequent application to be entitled to priority.³⁷

Something that seems to have been a mere technical formality turned into a crucial failure in Team Broad Institute's patent case, potentially resulting in the revocation of not only the CRISPR patent (No. EP2771468), but also of Team Broad Institute's any related patents and patent applications with similar listings of inventors. Not all patents and patent applications of Team Broad Institute suffer from the same problem, however, even if Team Broad Institute would obtain protection for a narrower application of the CRISPR/Cas9 technology, Team

34 Storz 2018, p. 91, see also Catherine Coombes, Opinion: How to Avoid Legal Problems in Collaborative Research', *The Scientist* 2016. Available at: <https://www.the-scientist.com/online-first/opinion-how-to-avoid-legal-problems-in-collaborative-research-32953>, accessed 9 August 2020.

35 Prashant Mali – Luhan Yang – Kevin M Esvelt – John Aach – Marc Guell – James E DiCarlo – Julie E Norville – George M Church, RNA-Guided Human Genome Engineering via Cas9. *Science* 339(6121) 2013, pp. 823–826. Woong Y Hwang – Yanfang Fu – Deepak Reyon – Morgan L Maeder – Tsai Shengdar – Jeffry D. Sander – Randall T Peterson – Jing-Ruey Joanna Yeh – Keith Joung, J, Efficient Genome Editing in Zebrafish Using a CRISPR-Cas System. *Nature Biotechnology* 31(3) 2013, pp. 227–229.

36 Case T 844/18.

37 EPO, Datasheet for the decision, of 16 January 2020, case number T 0844/18 - 3.3.08. Available at: [http://documents.epo.org/projects/babylon/eponet.nsf/o/22848DBA6784C883C1258617004D48BB/\\$File/0844.18.3308\(decision\).pdf](http://documents.epo.org/projects/babylon/eponet.nsf/o/22848DBA6784C883C1258617004D48BB/$File/0844.18.3308(decision).pdf). Accessed 17 December 2020.

California appears to have a substantially stronger patent position in Europe.³⁸ The timeline of the European proceedings is presented in the Appendix 2 of this chapter.

9.5 Comparative Perspectives on the Approaches of the USPTO and the EPO to the Assessment of the Patentability Criteria of the CRISPR/Cas9 System

Table 1. The Inventiveness Analysis

Europe	The United States
European Patent Convention Article 52 An invention must be new and involve an inventive step	35 US Code Sections 102 and 103 An invention must be novel and it must not be obvious
Problem-solution approach 1. What is the closest prior art? 2. What is the objective technical problem that the invented solution solves? 2. Would the invented solution, considering the closest prior art and the objective technical problem, have been obvious to the skilled person?	Non-obviousness approach 1. What is the scope and content of prior art? 2. What are the differences between the prior art and the claimed innovation? 3. What is the ordinary skill level in the field? 4. Would the prior art have suggested to a person having ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success?
Would the solution by which Team Broad Institute transferred the CRISPR/Cas9 system to eukaryotic cells have been perceived obvious by a bioscientist?	Would the step from bacterial cells to eukaryotic cells have been obvious to Team California with a reasonable likelihood of success?

As discussed above, in addition to the requirement of *usefulness* of an invention in the United States and the European equivalent of *industrial application*, *novelty* and *non-obviousness*, and the corresponding *novelty* and *inventive step*, are two additional patentability requirements applied by the USPTO and the EPO. In order for an invention to be novel, it must not have been known to the public prior to the filing of the patent application. The novelty of an invention is assessed by comparing the invention to applicable prior art in the field. In order for an invention to be non-obvious, it shall not be obvious for *a person having ordinary skill in the art*. Respectively, the perspective of *a person who is skilled in the art* is applied in the assessment of inventive step in Europe.

³⁸ Cockbain – Sterckx 2020.

Although the requirements of non-obviousness in the United States and inventive step in Europe are very similar, different outcomes may arise from the application of different approaches to these criteria. The USPTO approaches non-obviousness typically by first determining the state of art, thereafter the difference between the prior art and the claimed innovation and finally the ordinary skill level in the field. In contrast in Europe, the EPO applies a so-called ‘problem-solution’ approach to the inventive step assessment, in which it first identifies ‘an objective technical problem’ and thereafter it assesses whether the invention would have been obvious to a person with ordinary skill in the field.³⁹ See Table 1 above for further details.

After analysing the merits of the CRISPR/Cas9 patents in relation to their prior art, the patent offices have ultimately reached opposite outcomes. In its analysis, the USPTO assumed that the CRISPR/Cas9 system in a generic environment constituted the ‘prior art’. This claim was compared with the claim concerning the technology in a eukaryotic cell environment. The USPTO confirmed that the step from using the technology in a generic cell environment to using it in the eukaryotic cell environment constitutes a *non-obvious* innovative step that qualifies for patent protection. In contrast, the EPO found the same step to be *obvious*.⁴⁰

The US Patent Board of Appeals further analyzed whether it was possible and how likely it would have been for Team California to get the CRISPR/Cas9 system to function in eukaryotic cells.⁴¹ This resulted in investigations on the differences between cell types and how differences in cellular environments could affect the function of the CRISPR/Cas9 system. The Board of Appeals of the USPTO concluded that all of these environmental conditions create uncertainty as to how Team California’s CRISPR/Cas9 system works within eukaryotic cells. The Board of Appeals referred to one of Team California’s key researchers who had expressed difficulties in getting CRISPR/Cas9 to function in other types of cells. All in all, the impact of the differences in the cellular environments, together with the scientist’s comments, resulted in the Board of Appeals concluding that an ordinary researcher in biosciences could not have a reasonable expectation of getting Team California’s CRISPR/Cas9 system to function in eukaryotic cells. Hence, the Broad Institute’s patent was not found to be in breach of Team California’s patent.

It could possibly be argued that the decision seems justified given that the opposite result could have led to the patent holder being able to prevent anyone else

39 Zachary Quinlan, Hindsight Bias in Patent Law: Comparing the USPTO and the EPO. *Fordham International Law Journal* 37(6) 2014, pp. 1797–1804.

40 Sherkow 2017, p. 1049.

41 *Ibid.*

from developing an improvement that they might never accomplish themselves. In the decision on the interference proceeding, the USPTO stated that if they were to accept that success is reasonably expected for every experiment, the subject matter would always be obvious under 35 U.S.C. § 103 12 when there is a design need or market pressure to solve a problem, a finite number of solutions, and those of ordinary skill have the technical capability. Instead of creating a presumption of obviousness when researchers attempt experiments to advance a field, the US Court of Appeals has recognized that the methodology of science and the advance of technology are founded on the investigator's educated application of what is known, to intelligent exploration of what is not known. Each case must be decided in its particular context, including the characteristics of the science or technology, its state of advance, the nature of the known choices, and the specificity or generality of the prior.

The decision by the US Patent Office's Board of Appeals has, however, been subject to criticism. Some commentators have argued that it fails to take into consideration the actual realities of biological research that relies on experimenting and testing out different hypotheses by trial and error. It has been argued that the notion of a 'reasonable expectation of success' could possibly be challenged in the context of biological systems.⁴² It could be argued that there are some techniques to get the bacterial system to work in eukaryotic cells that are well known to anyone with a basic knowledge of molecular biology. Despite the fact that Team California did not have a specific plan that included a '*reasonable expectation of success*', they possibly still had some kinds of plans on how to get the CRISPR/Cas9 system to function in eukaryotic cells. In favor of Team California, it could be argued that molecular biology as a field has a rather high level of 'ordinary' skills and the techniques used by Team Broad Institute to adapt the CRISPR/Cas9 to function in eukaryotic cells are generally well known to all bio-scientists operating in laboratories.

Hence, some significant differences can be seen in the approaches of the USPTO and the EPO in their assessment of innovativeness. The USPTO poses a question as to whether the innovation would be an obvious step to a person with an ordinary skill level in the art with reasonable expectations of success. In the case of CRISPR/Cas9, this approach boiled down to a question of whether the step from bacterial cells to eukaryotic cells would have been obvious to Team California with a reasonable expectation of success. In contrast, the EPO analyzes whether a person with an ordinary level of skills in the field would find this solution to be an obvious answer to an objective question – in this case, whether a bio-scientist

42 See Sherkow 2017.

would have perceived the way the Broad Institute transferred the CRISPR/Cas9 system as an obvious solution or not. The differences in the approaches applied by the patent offices have resulted in the situation at hand, where the step from bacterial to eukaryotic cells is perceived as innovative in the USA, but not in Europe.

On a more general note, patenting biological inventions is particularly challenging due to a number of reasons. One of them is unpredictability. Biological systems are often complex and may result in unpredictable outcomes even in the case of routine research. Results can also be quite difficult to reproduce. All this significantly complicates the innovativeness assessment of a 'person with ordinary skills in the art' in the context of biology. Furthermore, the non-obviousness assessment applied in the United States has been subject to criticism. It has been found to be quite problematic and ill-suited for rapidly evolving fields such as biotechnology, as it does not always properly address the above-mentioned lower possibility of success in the field of biotechnology due to the unpredictability and the rather high skill level of a person with 'ordinary skills in the art'.⁴³

9.6 Some Practical Implications of the Case

In light of the current developments in the patent proceedings, the state of the contested CRISPR/Cas9 patents appears somewhat unclear. Team California seems to hold a stronger position in Europe, while the situation appears quite opposite in the United States. However, the situation may also change as the next moves of the parties and possible further decisions of any instances remain to be seen. Therefore, on a transatlantic scale, this pending dispute on CRISPR/Cas9 patents creates some difficulties for commercialization of the technology and uncertainties affecting potential licensing of this technology.⁴⁴

These challenges notwithstanding, both parties are licensing their patents. Licenses granted by the parties relate to 1) basic research 2) the development and sale of tools for CRISPR/Cas9 use, and 3) the developing and selling of CRISPR/Cas9-aided technology.⁴⁵ Within the first category of CRISPR/Cas9 licenses, i.e. licenses for basic research, tools for non-profit research are granted

43 See for example Timo Minssen, *Meanwhile on the Other Side of the Pond: Why Biopharmaceutical Innovations that Were 'Obvious to Try' Still Might Be Non-Obvious*. *Chicago-Kent Journal of Intellectual Property* 9(1) 2010, pp. 60–131.

44 Ledford 2016a, p. 460.

45 Jorge L Contreras – Jacob S Sherkow, *CRISPR, Surrogate Licensing, and Scientific Discovery*. *Science* 355(6326) 2017a, p. 699.

free of charge for researchers and academic institutions. However, for the other categories of commercial licenses, the situation appears more complicated. Both patent holders have granted exclusive licenses to commercial uses of CRISPR/Cas9 through their spin-off companies.⁴⁶ Subsequent to the decision of the US Court of Appeals stating that Team Broad Institute's patent did not breach the patent of Team California, patent licensees and possible licensees are now wondering to whom they should be paying the license fees, as it is still under dispute which party will obtain the CRISPR/Cas9 patent on the eukaryotic cells. This situation appears rather confusing for potential licensees.⁴⁷ Until the dispute is resolved, anything developed under the wrong license could later be jeopardized, contested, or in need of an additional license, if the final victor were to decide to enforce its patents against the inventor.⁴⁸ Which one of the parties should be entitled to collect license fees? Which party will have the patent rights in the future? What kind of licenses are needed for transatlantic research co-operations or if a product crosses from Europe to the USA or *vice versa*?

This situation becomes even more complicated when considering Team California's position in accordance with which their patent should be perceived as the 'founding patent' and the Broad Institute's patent as its sub-type. As the PTAB found that Team Broad Institute's invention did not overlap with Team California's invention and was separately patentable, room was left for such interpretation.⁴⁹ In practical terms, this would mean that Team California would be able to block any subsequent inventions building on their founding invention and, on the other hand, that Team Broad Institute would be able to block any use of their improvement.⁵⁰ In this setting, a party willing to use CRISPR/Cas9 for commercial applications would possibly have to enter into license agreements with both patent holders.⁵¹

As far as academic researchers do not attempt to commercialize their research, they are given a CRISPR/Cas9 license free of charge for non-profit purposes by both parties. Yet, the current licensing model is unclear with respect to any

46 Knut J Egelie – Gregory D Graff – Sabina P Strand – Berit Johansen, The Emerging Patent Landscape of CRISPR–Cas Gene Editing Technology. *Nature Biotechnology* 34 2016, p. 1030.

47 Jon Cohen. CRISPR Patent Ruling Leaves License Holders Scrambling. *Science* 355(6327) 2017, p. 786.

48 Nicola Dagg – Marc Döring – Joachim Feldges – Derek Lim, Editing the Future: A Brief Introduction to CRISPR. *The Licensing Journal* 37(4) 2017, pp. 1–4. Jacob S Sherkow, Patents in the Time of CRISPR. *Biochemist* 38 2016, pp. 26–29.

49 Dagg et al. 2017.

50 Stroz 2018 p. 124.

51 Rai et al. 2017, p. 875.

innovations arising in the context of basic non-profit research using CRISPR/Cas9 or, furthermore, in the event that an innovation using CRISPR/Cas9 is made.⁵² It is not fully clear whether a researcher that makes this kind of an invention needs to get a commercial license for such use from either one or both of the patentees. In this context, it has been seen as problematic that both license holders are only granting exclusive commercial licenses, which complicates the commercialization of innovations.⁵³ From the perspective of academic researchers who are willing to commercialize their innovations, the situation is very far from an optimal one. Licenses on CRISPR/Cas9 are hard to get for commercial use and, even then, there is a high risk of uncertainty, as it might still be unclear from which one of the patent holders a license is needed.

Given the actual circumstances, criticism regarding the exclusivity of the licensing may appear quite understandable from the potential licensees' perspective, as exclusivity will block out some start-up companies from the market and prevent them from commercializing their CRISPR/Cas9-based inventions. As a classical argument against exclusivity, this may in turn result in the slowing down of the technical innovation relating to this technology and the hampering of the competition in the field. There is also a risk that some uses of CRISPR/Cas9, such as therapies meant for rare diseases or for less privileged groups of patients, which have not appeared commercially attractive enough, risk becoming neglected.⁵⁴

Furthermore, the uncertainty regarding the scope and the actual holder of the patent rights for the use of the original CRISPR/Cas9 patent(s) in eukaryotic cells has created a situation where third parties have pursued to circumvent the patent(s) by trying to create new versions of the CRISPR-system that do not fall within the scope of protection of the existing patents.⁵⁵ It appears that new applications of the CRISPR system are constantly emerging and experimented with – some of them seem to be even more prominent gene-editing tools than the original ones(s) and some patents are pending for such new applications.⁵⁶ Beyond these considerations, the scope of the CRISPR/Cas9 patent(s) still remains uncertain. It should be noted that the contested CRISPR/Cas9 patents represent just one subcategory found in one bacterial species out of numerous other CRISPR

⁵² Egelie et al. 2016, p. 1030.

⁵³ *Op. cit.*, p. 1031.

⁵⁴ Contreras and Sherkow 2017a, p. 700.

⁵⁵ Rai et al. 2017.

⁵⁶ Jacob S Sherkow, The CRISPR Patent Landscape: Past, Present, and Future. *The CRISPR Journal* 1(1) 2018, p. 6.

and Cas-enzymes or Cas-like enzymes present in nature. It appears that new versions, some of which are potentially even more prominent than the original CRISPR/Cas9 system, are continuously discovered in nature and being tested for use as genome editing tools. It is not sure whether these types of CRISPR editing tools fall within the scope of protection of the contested patents.⁵⁷

Some American patent experts have speculated that the legal battle between the Broad Institute and the UC could finally end in a cross-licensing agreement where they share the licensing revenue from the patents.⁵⁸ Others have suggested that the establishment of a patent pool would provide the necessary efficient, non-exclusive, and non-discriminatory solution, which would increase competition and accelerate the commercialization of CRISPR/Cas9 products and therapies.⁵⁹ While this view has also been subject to criticism, as patent pools are rarely seen within the biopharmaceutical sector where development processes are usually exceptionally costly and lengthy,⁶⁰ the creation of a patent pool has been announced by a Californian company named MPEG LA, LLC. By far, only Team Broad Institute has publicly expressed interest in taking part in the pool,⁶¹ and as the patent litigations continue, both parties' participation remains uncertain.

Thinking beyond the discussion on the commercial aspects of the case at hand - or perhaps going to the very heart of it - there are some curious public policy issues present in the case as well. The institutions racing for the patent protection, which by now have spent millions of dollars on litigation, are universities, i.e. non-profit, public-funded research institutions, aimed at developing science for public good.⁶² The CRISPR/Cas9 technology unquestionably has great potential for the benefit of the public, but the idea of university research institutions as promoters of the public on the one hand and as parties in a protracted legal dispute aimed at profit maximization on the other hand seems somewhat contradictory.

University researchers are no exception from inventors who are allowed to seek patent protection for their inventions. As with the possibility for patent

57 Rai et al. 2017, p. 878.

58 Cohen 2017, p. 786.

59 Lawrence Horn, Patent Pools for CRISPR Technology. *Science* 355(6331) 2017, p. 1274.

60 Jorge L Contreras – Jacob S Sherkow, Patent Pools for CRISPR Technology – Response. *Science* 355(6331) 2017b, pp. 1274–1275.

61 Amy Dockser Marcus – Joe Palazzolo – Jonathan D Rockoff, Crispr Patent-Holders Move Toward Easing Access to Gene-Editing Technology. *Wall Street Journal* 2017. Available at: <https://www.wsj.com/articles/crispr-patent-holders-move-toward-easing-access-to-gene-editing-technology-1499527983>, accessed 9 August 2020.

62 John Conley, Clash of Titans: The Fight Over the CRIPR Gene-Editing Patent Rights. *The Privacy Report* 2018. Available at: <https://theprivacyreport.com/2018/10/08/clash-of-titans-the-fight-over-the-crispr-gene-editing-patent-rights/>, accessed 9 August 2020.

protection in general, this opportunity serves the purpose of providing an incentive to innovate for these institutions. Profits are often further ensured through the establishment of spin-off companies, to which exclusive rights to commercial uses of the innovation are given.⁶³ The present case is no exception in this perspective. Yet, in big financial interests may also lie challenges and risks, where these interests have the potential to steer the focus away from public interests towards private ones. Innovators involved in extensive and intensive patent litigations may halt the progress of scientific research while focusing on the infringement proceedings rather than on sharing knowledge and improving technology. Patent litigations may also create significant legal uncertainty for those wishing to exploit and further develop an invention.⁶⁴ Broad patents on a technology in a very early phase and fierce and protracted patent litigations can therefore not be considered very beneficial for the scientific community. At the end of the day, such may have quite the opposite effect than patent protection is intended to have, leading to a situation where the patented invention is more likely to impede research and development than promote it.

This all brings us down to the question of what the role of universities as research institutions should be. At the end of the day, is their purpose to develop science for own profit or for public good?

9.7 Conclusions

CRISPR/Cas9 is a pivotal technology with a high commercialization potential. Now, regrettably this potentially profitable technology is risking to lose its financial edge and competitive advantage in the absence of clarity as to who has the right and title to the ‘founding’ patents. Some potential third party licensees wishing for a license to the technology are facing uncertainty and/or being rejected due to the exclusivity of the license. The parties to the dispute are not only losing money in the litigation, but also potential license holders because of this uncertainty. While both teams are spending substantial amounts of time and financial resources on the patent litigation, some others in the scientific community are moving ahead and striving to improve said technology. Some researchers are already investigating new innovative applications that could potentially circumvent or even replace the CRISPR/Cas9 system.

⁶³ See e.g. Conley, 2018.

⁶⁴ Franc Mali, *Is the Patent System the Way Forward with the CRISPR-Cas 9 Technology?* Science & Technology Studies 2020, pp. 2–3, 15.

The CRISPR/Cas9 litigation appears exceptional in many senses. It seems that the underlying motives behind the dispute are not only about the patent, but also, and perhaps more, about academic pride and prestige.⁶⁵ In fact, it is common for two academic institutions to end up in massive and prolonged litigations on both sides of the Atlantic. It is even more common that academic parties try to reach a satisfactory solution, such as a cross-licensing agreement, that would be mutually beneficial for both parties. In this very exceptional situation where the rights to CRISPR/Cas9 are divided between the parties, settling the case by entering into a cross-license agreement would possibly benefit both parties and also create certainty for those third parties who wish to get a license to use the CRISPR/Cas9 system on eukaryotic cells. Both parties have entered into cross-licensing agreements on CRISPR/Cas9 technology with third parties, but not with each other.⁶⁶ Given the exceptionally fierce litigation strategies of the parties, the current likelihood of reaching a settlement seems unlikely. Both parties have an immense interest in not only getting the legal rights, but also for being recognised as the innovators of the ground-breaking CRISPR/Cas9 technology.

Generally speaking, this exceptional case also illustrates the major differences between the patent granting approaches in Europe and the United States, especially in the case of patents on biotechnological innovations. The EPO assesses innovativeness as a matter of whether a person with ordinary skill in the art would, in light of the scientific understanding of the moment, reach the technological step as a solution to an objective question or problem. In contrast, in its non-obviousness assessment, the USPTO seeks to evaluate whether a person with ordinary skills in the art has a reasonable chance of success in reaching the same outcome as the potential inventor. This approach has been criticized because in the field of biotechnology, there are multiple factors that affect the chances of success in a scientific experiment. Some of the variables in an experiment can also be interdependent and/or otherwise very hard to control. In addition, it is very hard to define the concept of a 'reasonable chance of success', as in some cases reaching a desired outcome can be very hard for even the most skillful and senior researchers. It should be noted that, in practice, in the field of biotechnology, a doctoral degree seems to appear as a minimum educational standard for 'a person with ordinary skills in the art'. Yet, this standard is not applied equally in other fields of technology, so the USPTO should perhaps somehow clarify its standards concerning qualification as 'a person with ordinary skills in the art' for each field of science.

65 Rai et al. 2017, p. 877.

66 Sherkow 2018, p. 6.

In conclusion, the battle on the ‘founding’ patent rights to CRISPR/Cas9 technology on eukaryotic cells does not seem to benefit either one of the parties. It also creates some significant uncertainties over the commercial use of the technology for existing third-party licensees or potential licensees. A cross-licensing agreement between the parties to the dispute could be a viable solution. However, as of today, reaching such an agreement to settle the case seems quite unlikely. The unclear patent situation creates some significant uncertainties that risk hampering the commercialization prospects of the CRISPR/Cas9 technology on eukaryotic cells and slowing down the development and market access of any future applications of said technology.

What can we then learn from this exceptional dispute? Some of the lessons learned could be summarized as follows:

- (1) This present case constitutes an excellent example of what can be accomplished through collaboration between researchers from different institutions. Simultaneously however, it should be considered as a warning on the disastrous that can follow where explicit ownership of intellectual property rights is not assigned in advance.⁶⁷ It was not until the first patent applications were filed in the United States that an inventorship analysis was conducted, which resulted in the exclusion of Marraffini from the list of inventors. The consequences of Marraffini disputing this decision were decisive in the patent dispute in Europe. Accordingly, it is important always to draw up collaboration agreements. Questions on intellectual property rights should be addressed and agreed upon as early as possible, and in any case before filing any patent applications.⁶⁸ The patenting failure of the Broad Institute in Europe has also shown the importance of having in place appropriate university invention policies and robust processes regarding administration of patents to ensure that the know-how and patentable inventions are adequately protected and patent filings are complete (i.e. all inventors are duly mentioned in order to meet the requirement of novelty).

67 Catherine Coombes, Opinion: How to Avoid Legal Problems in Collaborative Research’, *The Scientist* 2016. Available at: <https://www.the-scientist.com/online-first/opinion-how-to-avoid-legal-problems-in-collaborative-research-32953>, accessed 9 August 2020.

68 *Ibid.*

- (2) In the United States, on the other hand, the public statements by the key inventor Jennifer Doudna with respect to Team California's CRISPR/Cas9 technology, together with an article on the same matter, turned into one of the decisive factors for the outcome of the patent dispute. In addition to presenting the invention, the article⁶⁹ also explained some unresolved challenges of the technology, which were repeatedly confirmed by Doudna in interviews given in 2014. While this is typical in research and academia, it is good to keep in mind that these kinds of statements are exactly what the counterpart in a patent dispute will look for, and hence, they might later be crucial for a patent dispute.⁷⁰
- (3) The intention of both Team California and Team Broad Institute in their respective patent applications appear to have been to cover possible CRISPR/Cas9 applications as broadly and comprehensively as possible in various cell environments, including prokaryotic cell types and eukaryotic cell types. However, at the time of filing the first patent applications, it was only Team Broad Institute that succeeded in making this technology work in eukaryotes. The consequences of this can be witnessed in the United States, and these remind every inventor to carefully consider and evaluate their early patent filing strategies.⁷¹
- (4) Further, it is likely that the present case complicates the manner in which obviousness for CRISPR technologies will be assessed in the future. As explained above, Cas9 is not the only possible nucleus to be used in relation to CRISPR, and there may potentially be even more efficient and useful nucleases.⁷² The decision in the CRISPR dispute has raised discussion as it fails to address the question of how future applications of CRISPR will be evaluated. Will the common knowledge on the CRISPR/Cas9 mechanism render all future applications of the technology obvious?⁷³ Furthermore, considering the differing approaches in the obviousness assessment in the United States and

69 See Jinek et al. 2013.

70 Stroz 2018, p. 131.

71 Dagg et al. 2017.

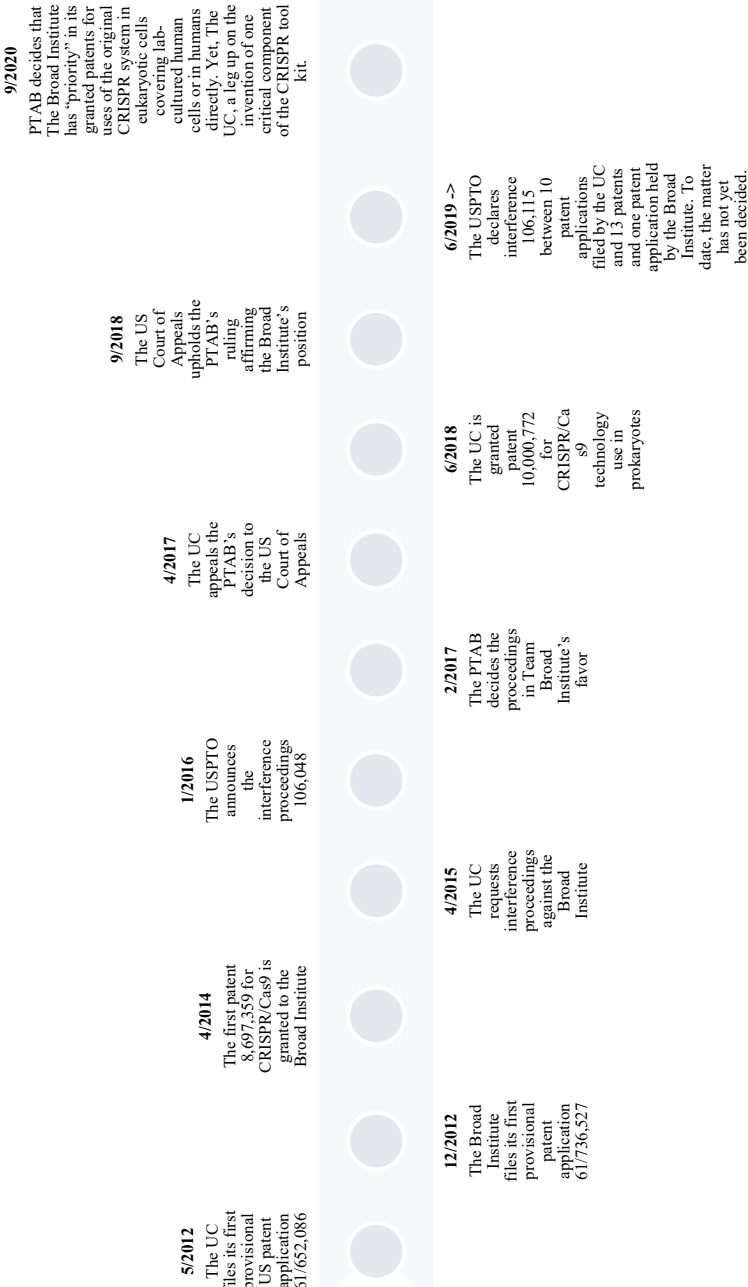
72 Deborah Ku, The Patentability of the CRISPR-Cas9 Genome Editing Tool. *Chicago-Kent Journal of Intellectual Property* 16(2) 2017, pp. 408–439, 15.

73 See Jacob S Sherkow. Law, History and Lessons in the CRISPR Patent Conflict. *Nature Biotechnology* 33(3) 2015, pp. 256–257.

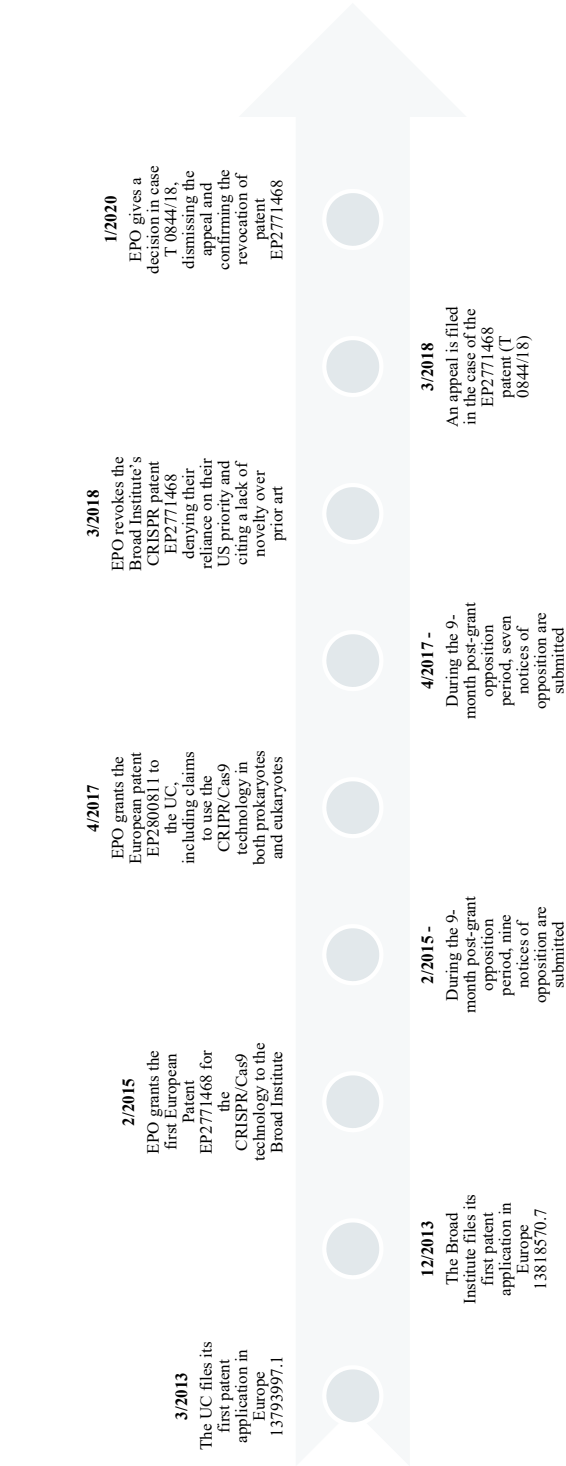
Europe, will these prospective future CRISPR applications be subject to contradictory decisions on different sides of the Atlantic Ocean. The Broad Institute is one of many actors with patents and pending patent applications in this particular field of technology. Furthermore, there are also patents, and patent applications covering later, more specific inventions and platforms. This means that disputes on patents relying on this technology are likely to continue in the foreseeable future. Most recently, when it comes to the mere battle for academic glory, the Nobel Prize 2020 in Chemistry was awarded to Emmanuelle Charpentier and Jennifer A. Doudna on 7 October 2020.

Appendices

Appendix 1. Timeline of the Patent Proceedings in the USA. Situation as at 27 November 2020.



Appendix 2. Timeline of the Patent Proceedings in Europe. Situation as at 27 November 2020.



10

Interpretation of the Patient's Need for Help Can Be Supported with Machine Learning

by Dr. Sc. (Tech.) Lauri Lahti¹

Abstract

Machine learning is a methodology that aims at learning to recognize statistical patterns in data. Developing machine learning methods enables identifying dependencies in the knowledge processes of healthcare and thus to support providing personalized care that addresses the patient's needs. However, the computations and results of machine learning are often difficult to interpret in an intuitive human-understandable way. Furthermore, besides modelling the patterns of biomedical data, it has remained challenging to develop machine learning methods on a linguistic and semantic level that can support the patient's appropriate involvement in all the phases of decision making to support his/her best care. To address this, based on online questionnaire answers (n=673) our current research analyzes how different people rate the 'need for help' for a set of health-related expression statements and how this rating depends on the background information about the person (such as his/her evaluation of the health and wellbeing). The respondents were recruited from various Finnish patient and disabled people's organizations, other health and wellness organizations, and educational institutions as well as organizations of healthcare professionals, and they represented a great diversity of current personal health conditions, abilities, and attitudes. We have carried out machine learning experiments to find out what kind of results can be gained when training a convolutional neural network model based on the 'need for help' ratings to classify persons into groups relying on the background information. We report our preliminary results showing that it is possible to categorize and distinguish respondent groups based on the patterns of their answer distributions.

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10.1 Introduction

Due to rapid technological advances, personal health-related information can be gathered and analyzed with an increased detail and efficiency. At the same time, it is evident that handling the sensitive personal data requires addressing ethical principles and privacy measures that are enforced with legislation and global-level regulation². To enable active deployment of health analytics that protects data privacy and ensures transparency of methods³, there is a need for research that develops methods that specifically support the patient's appropriate and sufficient involvement in decision making concerning his/her care and also evaluates how much and what kind of information is sufficient to identify certain characteristics of a person and to make reliable reasoning and predictions based on them.

In this current research article, we report some preliminary results gained in DIHEML research project at Aalto University ('Development of method for interpretation of health expressions based on machine learning to support various care events and persons, DIHEML', 2018-2021) that is actively developed and initiated by its main researcher Lauri Lahti^{4 5}. DIHEML research project aims at finding new innovative solutions to the traditional challenge that machine learning can generate impressive results but still it is often hard to interpret them with human reasoning and to illustrate and explain in an intuitive human-understandable way the steps leading to the results⁶. DIHEML research project develops measuring of the health condition and quality of life to assist in developing machine learning methods to support public sector healthcare and wellbeing by addressing the personalized needs of the patient. This new research approach gets motivation from the previous research^{7 8 9}. With machine learning, we aim to contribute to the broader developmental context of artificial intelligence supporting personalized care.

DIHEML research project relies on conducting broad interactive adaptive questionnaire surveys with various population groups to gather large sets of human answers that can depict how different persons conceptualize and interpret diverse

2 Cohen et al., 2018.

3 Kaplan, 2020.

4 Lahti, 2017.

5 Lahti, 2018.

6 Gehrmann et al., 2018.

7 Bradley & Lang, 1999.

8 Warriner et al., 2013.

9 Mauss & Robinson, 2009.

imagined health conditions and care situations, and what kind of impressions and reactions these situations induce in the minds of these persons. The health conditions and care situations are shown to the person as textual expressions, images, and videos. DIHEML research project aims at identifying from human thinking and communication such patterns that are important to be carefully addressed in respect to 1) evaluating the person's need for getting care, 2) the person's learning about health-related information, and 3) supporting the person's advantageous health behavior.

DIHEML research project has already established a broad collaboration network with a large set of Finnish patient and disabled people's organizations and has so far gathered a large collection of answers that represent persons having different backgrounds. These gathered answers reflect a great diversity of current personal health conditions, abilities and attitudes towards health problems and ways to deal with them, besides information about the gained care, satisfaction about the gained care and wishes for developing the care. DIHEML research project collects answers about various imagined scenarios concerning symptoms, health conditions, getting care from health-care professionals, implementing self-care and various alternative forms of interaction between the patient and the doctor concerning decision making about the patient's care, as well as activities of everyday life surrounding health-related themes and managing with health problems. Besides patient and disabled people's organizations, human answers are currently collected also from various other health and wellness organizations and educational institutions as well as organizations of healthcare professionals.

Also all the readers of this research article who are at least 16 years old are freely welcome to participate voluntarily in the data acquisition of DIHEML research project by answering the online questionnaire at the following web address: <https://ilmaisu.cs.aalto.fi/tutkimus/osallistu/avain-XE4WKP-67RW3PEMHX>

DIHEML research project develops new methods to support healthcare with machine learning. Machine learning is a methodology that aims at learning to recognize statistical patterns in data with tailored algorithms that usually benefit from large samples of input data to increase accuracy. Machine learning can be considered to have two major types of approaches: supervised learning and unsupervised learning.

Supervised learning is carried out often with an aim to predict an outcome, and this may consist of classification tasks in which a trained human can succeed well and thus the algorithms typically aim at approximating an appropriate human performance¹⁰. Supervised learning usually tries to perform classification by

¹⁰ Deo, 2015.

choosing among subgroups such a subgroup that can best describe a new instance of data and also to produce a prediction that consists of estimating an unknown parameter¹¹. Supervised learning is also actively used to estimate risk and this can be considered to extend further than just approximating human performance and to aim at identifying hidden characteristics of data¹².

In contrast with supervised learning, unsupervised learning is typically carried out without an exact aim of predicting a direct outcome and instead unsupervised learning aims at identifying naturally occurring patterns or groupings that are present in the input data¹³. With this more relaxed initial learning goal, it is often challenging for humans to directly judge the actual appropriateness and meaningfulness of the generated groupings and thus usually they are evaluated based on the performance they achieve in a subsequent supervised learning task¹⁴.

In our current research, we aim to develop both supervised and unsupervised machine learning methodologies to support the patient's appropriate involvement in decision making concerning his/her care. This machine learning relies on measurements that we gather from patients concerning their care. We aim at gathering the patient's interpretations about expressions and experiences increasingly also in acute real-life care situations but since that kind of data acquisition is ethically challenging and laborious to be performed we thus currently emphasize measuring the patient's interpretations with imagined situations.

10.2 Previous Research

Mental imagery has been considered to offer a measurable phenomenon that opens important possibilities to increase understanding about the human cognitive processes, and mental imagery has been linked to functional properties of the maintenance and treatment of clinical disorders^{15 16}, and kinaesthetic and somatic imagery have been promisingly applied in neurological rehabilitation¹⁷.

¹¹ Deo, 2015.

¹² Deo, 2015.

¹³ Deo, 2015.

¹⁴ Deo, 2015.

¹⁵ Hackmann et al., 2011.

¹⁶ Holmes & Mathews, 2010.

¹⁷ Braun et al., 2006.

It has been shown that the patterns of neural activation during imagery and actual perception have a strong overlap^{18,19}. Neuroimaging experiments have given preliminary indication that self-reported ratings of the vividness of mental imagery can correlate with activation of the same sensory-specific cortices as activated in perception^{20 21 22}.

Comparative experiments have verified that the spontaneous use of mental imagery in daily life varies between different persons²³. Clark et al.²⁴ showed experimentally that introducing a positive mood change increased the probability of experiencing a positive involuntary autobiographical memory about it during the following week.

It has been shown that imagining a future event increases the person's perception concerning the probability that the imagined event will occur^{25 26}. Furthermore, people perceived the likelihood of contracting a disease higher when the description of the disease is easier to imagine rather than harder to imagine²⁷, and people prioritized selecting a simpler separate cause for imagined symptoms rather than a more complex combination of causes even if the likelihood value for the combination of all the causes was displayed to be higher than for simple separate causes²⁸.

Think-aloud studies have identified that the background of people, such as sex and age, affects how the person describes and perceives health-related knowledge and its meaning to them^{29,30}. Age-induced changes in cognitive and communicative functioning are also reflected in self-reported health questionnaire answers³¹.

It has been suggested that the human experiences and biological response systems are fundamentally rooted in certain affective dimensions, such as

18 Ganis et al., 2004.

19 McNorgan, 2012.

20 Cui et al., 2007.

21 Herholz et al., 2012.

22 Belardinelli et al., 2009.

23 Davies et al., 2012.

24 Clark et al., 2013.

25 Carroll, 1978.

26 Sherman et al., 1985.

27 Sherman et al., 1985.

28 Lombrozo, 2007.

29 Joffer et al., 2016.

30 Borraccino et al., 2019.

31 Knäuper et al., 2016.

pleasure, arousal, dominance, and approach-avoidance^{32 33}. Already gathered affective dimensional measurements about a broad set of health-related semantic expressions have identified variations and dependencies based on the person's background³⁴. Berna et al.³⁵ experimentally gathered a list of self-identified most significant mental imagery describing the patient's pain combined with associated triggers, affects, meanings, and avoidance patterns.

In the supervised form of machine learning, to enable predicting an outcome from a classification task typically requires first identifying some possible predictors, i.e. features, and this forms the feature selection phase. After that, there is a need to identify a function that relates values of the features to a prediction outcome and this phase can be referred to as the class assignment phase³⁶. Various alternative types of functions can now be chosen to address different requirements and offering more flexible modeling than offered by for example logistic regression models of traditional statistics. Possible function classes include for example decision trees, artificial neural networks, support vector machines, and prototype methods, such as k-nearest neighbors.

The choice of a function class is associated with the challenge of fitting free parameters that are weights applied to individual features, somewhat resembling the regression coefficients used in logistic regression. Corresponding to the selected models and functions, dedicated algorithms are then used to test different value combinations to find optimal values for free parameters to achieve a good model³⁷. This is typically carried out with a training data set of examples and involves also estimating the training error, i.e. assessing how similar the predicted outputs are to the known outputs, with an aim to minimize this error according to a loss function (illustrated by the training loss). After that the algorithm is applied with a validation data set, containing examples not present in the training data set, to evaluate the model's performance by measuring the validation loss.

Using informative features and expressive functions can help to achieve a low training error but it has been found out that highly complex models (also involving a large number of features) have a tendency to generalize poorly due to overfitting data, although this can be counteracted by increasing the number of

32 Bradley & Lang, 1999.

33 Mauss & Robinson, 2009.

34 Warriner et al., 2013.

35 Berna et al., 2011.

36 Deo, 2015.

37 Deo, 2015.

training samples³⁸. On the other hand, using fewer features and a less expressive model can unnecessarily lower the quality of models and thus a common practice is to apply flexible models but penalize excessive complexity, for example too many free parameters or a too broad range of parameter values, with a process of regularization³⁹.

In our current research, we have conducted our initial machine learning experiments especially with a convolutional neural network model since it has been shown to succeed well in the classification of medical literature, patient records, clinical narratives, and patient phenotypes^{40 41 42 43 44 45 46}.

10.3 Experiment

We have developed an online questionnaire system enabling to gather from varied persons the personal interpretation ratings about the ‘need for help’ concerning health-related expression statements. To enable this, we have first gathered a large collection of health-related texts covering among others authorized healthcare guidelines (such as Terveyskirjasto⁴⁷, International Classification of Diseases⁴⁸ and International Classification of Functioning, Disability and Health⁴⁹), support materials of the organizations of patients and impaired, and other health and wellness organizations, and texts of online discussion forums. From that large text collection, we have identified and extracted some essential health-related expression statements with a method we developed and reported in our previous research⁵⁰.

In this research article, we report some preliminary results gained in DIHEML research project concerning a current data subset ‘Need for help related to

38 Deo, 2015.

39 Deo, 2015.

40 Hughes et al., 2017.

41 Zhao et al., 2017.

42 Gehrman et al., 2018.

43 Rojas-Barahona et al., 2018.

44 Yao et al., 2019.

45 Qing et al., 2019.

46 Shickel et al., 2019.

47 Terveyskirjasto, 2020.

48 International Classification of Diseases, 2011.

49 International Classification of Functioning, Disability and Health, 2013.

50 Lahti et al., 2018.

coping independently' that is a part of a broader data acquisition entity that we have gathered in respect to interpretations about health-related expression statements (ES) about the coronavirus COVID-19 epidemic and everyday life. For that purpose, we have first extracted a set of expression statements from official national guidelines of National Institute for Health and Welfare in Finland⁵¹ and international guidelines of World Health Organization⁵² concerning the coronavirus epidemic. These expression statements included among others descriptions of possible symptoms of the coronavirus, how to deal with mild cases of the coronavirus with just self-care, when one should seek admission for professional care, and what kind of practicalities are suggested as prevention. A broader description and motivation about the data acquisition and analysis will be reported by us in more detail in another future publication.

We now report preliminary results concerning specifically six expression statements ES12-ES15 and ES19-20 belonging to the data subset 'Need for help related to coping independently'. Between 30 May and 3 August 2020 with an online questionnaire we have gathered from 673 voluntary human evaluators the 'need for help' ratings for these six health-related expression statements (ES12-ES15 and ES19-20) on an 11-point Likert scale. The respondents were recruited from various Finnish patient and disabled people's organizations, other health and wellness organizations, and educational institutions as well as organizations of healthcare professionals.

Besides the 'need for help' ratings, we have gathered answers to seven background questions (BQ). The person was asked to give answers concerning his/her evaluation about own health (BQ1) and quality of life (BQ5) on a 9-point Likert scale as well as answers about the sex (BQ8, answer alternatives 'man' or 'woman' to maintain comparability with the previous Finnish health surveys), and age (BQ9), adapted from de Bruin et al.⁵³, Koskinen et al.⁵⁴, Nosikov & Gudex⁵⁵ and Aalto et al.⁵⁶. Furthermore, we have gathered binary no/yes answers to two health-related questions, adapted from Koskinen et al.⁵⁷: 'Do you have a permanent or long-lasting disease or such a deficit, ailment or disability that reduces your ability to work or to perform your daily living activities?' (BQ2, Onko sinulla jokin

51 National Institute for Health and Welfare in Finland, 2020.

52 World Health Organization, 2020.

53 de Bruin et al., 1996.

54 Koskinen et al., 2012.

55 Nosikov & Gudex, 2003.

56 Aalto et al., 2013.

57 Koskinen et al., 2012.

pysyvä tai pitkäaikainen sairaus tai jokin sellainen vika, vaiva tai vamma, joka vähentää työ- tai toimintakykyäsi?) and ‘Do you need continuously or repeatedly care given by a doctor for a long-lasting disease, deficit or disability that you have just mentioned?’ (BQ4, Tarvitsetko jatkuvasti tai toistuvasti lääkärinhoitoa jonkin äsken mainitsemasi pitkäaikaisen sairauden, vian tai vamman takia?). In addition, with a question (BQ3) the respondent was asked to indicate if a doctor had identified one or more diseases in him/her and to describe them (in a form adapted from Koskinen et al.⁵⁸).

The expression statements ES12–ES15 and ES19–20 are shown in Table 1 and the details of background questions BQ1 and BQ5 in Table 2. We have gathered questionnaire answers in Finnish language but we now report our results in English. Since the semantic meanings in the translated English texts typically cannot fully match with the original Finnish meanings due to linguistic and cultural differences we provide in this article text also the original Finnish texts used in the questionnaire.

Table 1. Expression statements ES12–ES15 and ES19–20 that were rated by the person in respect to the impression about the ‘need for help’.

Compact notation	Expression statement	Range of values for the person’s answer (indicating the ‘need for help’ rating)
ES12	‘I must be inside a house without getting out.’ (Joudun olemaan talon sisällä ilman ulospääsyä.)	0–10
ES13	‘I must be without a human companion.’ (Joudun olemaan ilman ihmisseuraa.)	0–10
ES14	‘I do not cope in everyday life independently without getting help from other persons.’ (En pärjää arkielämässä itsenäisesti ilman avun saamista muilta henkilöiltä.)	0–10
ES15	‘I do not cope at home independently without getting help from persons who originate outside of my home.’ (En pärjää kotona itsenäisesti ilman avun saamista kotini ulkopuolisilta henkilöiltä.)	0–10
ES19	‘I have a bad health condition.’ (Minulla on huono olo.)	0–10
ES20	‘I have an ordinary health condition.’ (Minulla on tavallinen olo.)	0–10

Table 2. Details about background questions BQ1 and BQ5.

Compact notation	Question about the person's background information	Range of values for the person's answer
BQ1: an estimated health condition	'What kind of health condition you have currently according to your opinion?' (de Bruin et al., 1996; Koskinen et al., 2012) (Minkäläinen terveydentilasi on mielestäsi nykyisin?)	A 9-point Likert scale supplied with the following partial labeling: '9 Good', '8 -', '7 Rather good', '6 -', '5 Medium', '4 -', '3 Rather bad', '2 -', '1 Bad'. (9 Hyvä, 8 -, 7 Melko hyvä, 6 -, 5 Keskitasoinen, 4 -, 3 Melko huono, 2 -, 1 Huono.)
BQ5: the quality of life	'How would you rate your quality of life? Give your estimate based on the latest two weeks.' (Nosikov & Gudex, 2003; Aalto et al., 2013) (Minkäläiseksi arvioit elämänlaatusi? Anna arviosi viimeisimpien kahden viikon ajalta.)	A 9-point Likert scale supplied with the following partial labeling: '9 Very good', '8 -', '7 Good', '6 -', '5 Neither good nor bad', '4 -', '3 Bad', '2 -', '1 Very bad'. (9 Erittäin hyväksi, 8 -, 7 Hyväksi, 6 -, 5 Ei hyväksi eikä huonoksi, 4 -, 3 Huonoksi, 2 -, 1 Erittäin huonoksi.)

When accessing the online questionnaire, the person was informed that only persons who are at least 16 years old are allowed to participate. Furthermore, to address the General Data Protection Regulation of the European Union a privacy notice about the research was shown to the person and he/she was asked to give approval for handling his/her data.

Before our online questionnaire started to gather actual interpretations from the human evaluator a guidance and training section was provided to him/her. In brief, the person was advised to interpret how much each expression tells about the need for help, and to give his/her interpretation about the expression on a numeric scale 0-10 so that 0 indicates the smallest possible need for help and 10 indicates the greatest possible need for help.

Then a small training phase allowed the person to get accustomed to giving the 'need for help' ratings by rating three expression statements: 'I have a good health condition.' (Minulla on hyvä olo.), 'I have a bad health condition.' (Minulla on huono olo.), and 'I have an ordinary health condition.' (Minulla on tavallinen olo.). The answers of this training phase were excluded from the following analysis. After that, as a clarification, the person was asked to not interpret how much the expression tells about just his/her own situation but instead to interpret what kind of impression this expression induces in him/her, thus giving his/her interpretation about the expression's meaning in respect to the mentioned property.

Then the actual interpretation tasks finally began and the expression statements ES12-ES15 and ES19-20 (see Table 1) were shown, one at a time, in a speech bubble above a simple briefly animating face figure that remained the same for all the expression statements (see Figure 1). The person gave his/her rating about the

‘need for help’ for each shown expression statement by pressing one of the eleven alternative number buttons depicted by the values 0-10. After the interpretation tasks, the person was asked to answer to the background questions BQ1-BQ5 and BQ8-BQ9.

In the analysis, we use traditional statistical tests. First, we compute Kendall rank-correlation measures and cosine similarity measures for each comparable pair of parameter values of the ‘need for help’ ratings of expression statements and the answers to the background questions. Then we compute Wilcoxon rank-sum test (i.e., Mann–Whitney U test) and tests of one-way analysis of variance (ANOVA) between two groups to identify statistically significant rating differences for each expression statement in respect to groupings based on the answer values of each background question.

After that, we carry out machine learning experiments with a basic implementation of a convolutional neural network algorithm that we run in a TensorFlow programming environment (adapted from TensorFlow image classification tutorial⁵⁹). By contrasting the overall findings, we make conclusions about the applicability of the machine learning approach in this knowledge context.

[Guidance: Give your interpretation by pressing one of the number buttons 0-10.]

I have an ordinary health condition.



the need for help

0	1	2	3	4	5	6	7	8	9	10
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the smallest
the greatest

Figure 1. In the online questionnaire, the person is asked to interpret the shown expression statement in respect to the impression about the ‘need for help’. The original Finnish texts were: Ohje: Anna tulkintasi painamalla jotakin numeropainikkeista 0–10. / Minulla on tavallinen olo. / avun tarve / pienin / suurin.

59 TensorFlow image classification tutorial, 2020.

10.4 Results

We received questionnaire responses from 673 persons of which 123 (18%) were men and 550 women (BQ8). They represented ages from 16 to 89 years (BQ9; $M=46,93$, $Mdn=51$, $SD=19,57$). There were 454 (67%) persons who answered having a permanent or long-lasting health problem that reduces ability (BQ2) and 219 persons who did not. There were 309 (46%) persons who answered having a continuous or repeated need for a doctor's care due to a long-lasting health problem (BQ4) and 364 persons who did not.

The respondents ($n=673$) reported in the following way to represent seven disease categories (BQ3, the number of unique persons who selected a category): lung diseases: 126; heart and circulatory diseases: 177; joint and back diseases: 301; injuries:103; mental health problems: 188; vision and hearing deficits: 191; other diseases: 345. When considering all the respondents, the mean value was approximately the same for the answers about the estimated health condition (BQ1; $M=6,53$, $Mdn=7$, $SD=1,97$) and the quality of life (BQ5; $M=6,53$, $Mdn=7$, $SD=1,77$).

Table 3 shows Kendall rank-correlation measures and cosine similarity measures for each comparable pair of parameter values of the 'need for help' ratings of expression statements ES12-ES15 and ES19-ES20 and the answers of the background questions BQ1 and BQ5 ($n=673$). Motivated by a recommendation of Akoglu⁶⁰ we considered a Kendall rank-correlation measure greater than or equal to 0,70 to indicate a significant correlation and the statistical significance levels were defined as $p<0,05$, $p<0,01$ and $p<0,001$. Thus it appears that a significant correlation was found between only the expression statements ES14 and ES15 (0.86) and this same pair of expression statements gained also the highest cosine similarity value (0,95).

60 Akoglu, 2018.

Table 3. Kendall rank-correlation measures (on the upper-right region of the table) and cosine similarity measures (on the lower-left region of the table) for each comparable pair of parameter values of the ‘need for help’ ratings of expression statements ES12-ES15 and ES19-ES20 and the answers of the background questions BQ1 and BQ5 (n=673). Before computing cosine similarity measures the answer values of each parameter were normalized by the formula $(x - \min(x))/(\max(x) - \min(x))$ and then these new values were shifted so that the mean value was positioned to the zero by the formula $(x - \text{mean}(x))$. The statistical significance levels were defined as $p < 0,05$, $p < 0,01$ and $p < 0,001$, denoted by symbols *, ** and ***, respectively.

	ES12	ES13	ES14	ES15	ES19	ES20	BQ1	BQ5
<i>ES12</i>		0,65***	0,57***	0,54***	0,43***	-0,09**	0,01	0,01
<i>ES13</i>	0,77		0,51***	0,49***	0,47***	-0,02	0,00	0,01
<i>ES14</i>	0,69	0,62		0,86***	0,42***	-0,16***	0,02	0,04
<i>ES15</i>	0,67	0,60	0,95		0,40***	-0,18***	0,04	0,05
<i>ES19</i>	0,55	0,58	0,55	0,52		0,03	-0,06	-0,05
<i>ES20</i>	-0,24	-0,17	-0,36	-0,37	-0,15		-0,01	-0,05
<i>BQ1</i>	0,01	0,01	0,00	0,04	-0,08	0,03		0,63***
<i>BQ5</i>	0,02	0,02	0,03	0,05	-0,05	-0,01	0,75	

Table 4 shows the ‘need for help’ ratings of each expression statement ES12-ES15 and ES19-ES20 that are evaluated in respect to groupings based on the answer values of the background questions BQ1 and BQ5, for two groups, the number of persons denoted by n_1 and n_2 (n=673). We created groupings of two groups so that ‘group 1’ contained those respondents who gave an answer value that was lower than the mean value of all the answers to the background question, and ‘group 2’ contained all the other respondents.

We computed for each group the mean of the ratings given by the respondents belonging to this group (denoted by M_1 and M_2). We computed Wilcoxon rank-sum test (i.e., Mann–Whitney U test) between two groups to identify statistically significant rating differences but in this observation we did not find any statistically significant differences at significance levels $p < 0,05$, $p < 0,01$, and $p < 0,001$. Supplementing tests of one-way analysis of variance (ANOVA) supported these findings.

Table 4. The 'need for help' ratings of each expression statement ES12–ES15 and ES19–ES20 are evaluated in respect to groupings based on the answer values of the background questions BQ1 and BQ5, for two groups, the number of persons denoted by n_1 and n_2 ($n=673$). We computed for each group the mean of the ratings given by the respondents belonging to this group (denoted by M_1 and M_2). We computed Wilcoxon rank-sum test (i.e., Mann–Whitney U test) between two groups to identify statistically significant rating differences but in this observation we did not find any statistically significant differences at significance levels $p<0,05$, $p<0,01$ and $p<0,001$. M=mean, Mdn=median, SD=standard deviation.

Grouping based on the answer value (x) of the background question (BQ)	ES12	ES13	ES14	ES15	ES19	ES20
BQ1, two groups:	$M_1=0,465$	$M_1=0,440$	$M_1=0,605$	$M_1=0,584$	$M_1=0,396$	$M_1=0,257$
$x<7$ ($n_1=263$),	$Mdn_1=0,5$	$Mdn_1=0,5$	$Mdn_1=0,8$	$Mdn_1=0,8$	$Mdn_1=0,4$	$Mdn_1=0,2$
$x\geq 7$ ($n_2=410$)	$SD_1=0,123$	$SD_1=0,105$	$SD_1=0,138$	$SD_1=0,154$	$SD_1=0,075$	$SD_1=0,072$
	$M_2=0,495$	$M_2=0,454$	$M_2=0,625$	$M_2=0,629$	$M_2=0,370$	$M_2=0,261$
	$Mdn_2=0,6$	$Mdn_2=0,5$	$Mdn_2=0,8$	$Mdn_2=0,8$	$Mdn_2=0,4$	$Mdn_2=0,1$
	$SD_2=0,114$	$SD_2=0,103$	$SD_2=0,148$	$SD_2=0,157$	$SD_2=0,071$	$SD_2=0,088$
BQ5, two groups:	$M_1=0,477$	$M_1=0,441$	$M_1=0,598$	$M_1=0,584$	$M_1=0,404$	$M_1=0,255$
$x<7$ ($n_1=274$),	$Mdn_1=0,5$	$Mdn_1=0,45$	$Mdn_1=0,8$	$Mdn_1=0,75$	$Mdn_1=0,4$	$Mdn_1=0,2$
$x\geq 7$ ($n_2=399$)	$SD_1=0,124$	$SD_1=0,106$	$SD_1=0,140$	$SD_1=0,152$	$SD_1=0,073$	$SD_1=0,069$
	$M_2=0,487$	$M_2=0,454$	$M_2=0,630$	$M_2=0,630$	$M_2=0,364$	$M_2=0,262$
	$Mdn_2=0,5$	$Mdn_2=0,5$	$Mdn_2=0,8$	$Mdn_2=0,8$	$Mdn_2=0,3$	$Mdn_2=0,1$
	$SD_2=0,113$	$SD_2=0,101$	$SD_2=0,147$	$SD_2=0,159$	$SD_2=0,073$	$SD_2=0,091$

We carried out machine learning experiments with a basic implementation of a convolutional neural network algorithm that we run in a TensorFlow programming environment (adapted from TensorFlow image classification tutorial⁶¹).

Our approach consisted of creating an image classifier using a *keras.Sequential* model with *layers.Conv2D* layers and then providing input data to the model in the form of images. We used a model consisting of three convolution blocks with a max pool layer in each of them and having on the top a fully connected layer that is activated by a *relu* activation function. We compiled our model with the *optimizers.Adam* optimizer and the *losses.SparseCategoricalCrossentropy* loss function. Table 5 describes layers of the convolutional neural network model used in the machine learning experiments.

Since the convolutional neural network model required labeled input data in the form of images, we transformed with an R language script our originally character-encoded questionnaire data into a set of grayscale raster images before feeding it to the model.

61 TensorFlow image classification tutorial, 2020.

First, the original rating answer values in the range 0-10 were transformed linearly into the range 0,0-1,0. Each entity of six transformed rating answers (in the range 0,0-1,0) of expression statements ES12-ES15 and ES19-ES20 given by a certain person were transformed into an individual raster image so that each single rating answer value was represented by a region of 25 pixels (width 5 pixels and height 5 pixels) having a brightness value in the range 0-255 directly proportional to the greatness of the transformed answer value in the range 0,0-1,0. All the six separate 25-pixel-sized regions were then joined as a 3×2 matrix to form a combined grayscale raster image (width 15 pixels and height 10 pixels).

Table 5. Layers of the convolutional neural network model used in the machine learning experiments.

Model: 'sequential'		
Parameters: total 32162; trainable: 32162; non-trainable: 0		
Layer (type)	Output shape	Number of parameters
rescaling_1 (Rescaling)	(None, 10, 15, 3)	0
conv2d (Conv2D)	(None, 10, 15, 16)	448
max_pooling2d (MaxPooling2D)	(None, 5, 7, 16)	0
conv2d_1 (Conv2D)	(None, 5, 7, 32)	4640
max_pooling2d_1 (MaxPooling2D)	(None, 2, 3, 32)	0
conv2d_2 (Conv2D)	(None, 2, 3, 64)	18496
max_pooling2d_2 (MaxPooling2D)	(None, 1, 1, 64)	0
flatten (Flatten)	(None, 64)	0
dense (Dense)	(None, 128)	8320
dense_1 (Dense)	(None, 2)	258

We performed machine learning experiments with labeled images so that their labeling matched the groupings that we have just previously analyzed with Wilcoxon rank-sum test (i.e., Mann–Whitney U test) and tests of one-way analysis of variance (ANOVA) between two groups to identify statistically significant rating differences (see Table 4). We allocated for the training and validation 80 percent and 20 percent of the data, respectively.

Table 6 shows our results about training and validation of the convolutional neural network model based on the labeling in respect to groupings based on the answer values of the background questions BQ1 and BQ5, for two groups (n=673). For each grouping we report training and validation metrics gained when reaching the lowest value for the validation loss (ensured by further 50

evaluation steps with a patience procedure), averaged from 100 separate training and validation sequences.

Table 6. Results about training and validation of the convolutional neural network model based on the labeling in respect to groupings based on the answer values of the background questions BQ1 and BQ5, for two groups (n=673). M=mean, Mdn=median, SD=standard deviation.

<i>Training and validation metrics gained when reaching the lowest value for the validation loss</i>					
<i>Grouping based on the answer value (x) of the background question (BQ)</i>	<i>Epoch step</i>	<i>Training loss</i>	<i>Training accuracy</i>	<i>Validation loss</i>	<i>Validation accuracy</i>
BQ1, two groups: x<7 (n ₁ =263), x>=7 (n ₂ =410)	M=14,07 Mdn=14 SD=3,2	M=0,63 Mdn=0,63 SD=0,01	M=0,66 Mdn=0,66 SD=0,01	M=0,66 Mdn=0,66 SD=0,01	M=0,64 Mdn=0,63 SD=0,02
BQ5, two groups: x<7 (n ₁ =274), x>=7 (n ₂ =399)	M=3,56 Mdn=3 SD=1,51	M=0,66 Mdn=0,66 SD=0,01	M=0,62 Mdn=0,61 SD=0,02	M=0,67 Mdn=0,67 SD=0	M=0,60 Mdn=0,60 SD=0,01

Figure 2 illustrates the loss and accuracy for training and validation of the convolutional neural network model for one sequence based on the labeling in respect to the grouping of two groups based on the answer values of the background question BQ1 (n=673), as indicated in Table 6. In this illustrated single sequence the lowest value for the validation loss was reached at the epoch step 14 and at that step the following metrics were gained: training loss 0,63, training accuracy 0,67, validation loss 0,66 and validation accuracy 0,65.

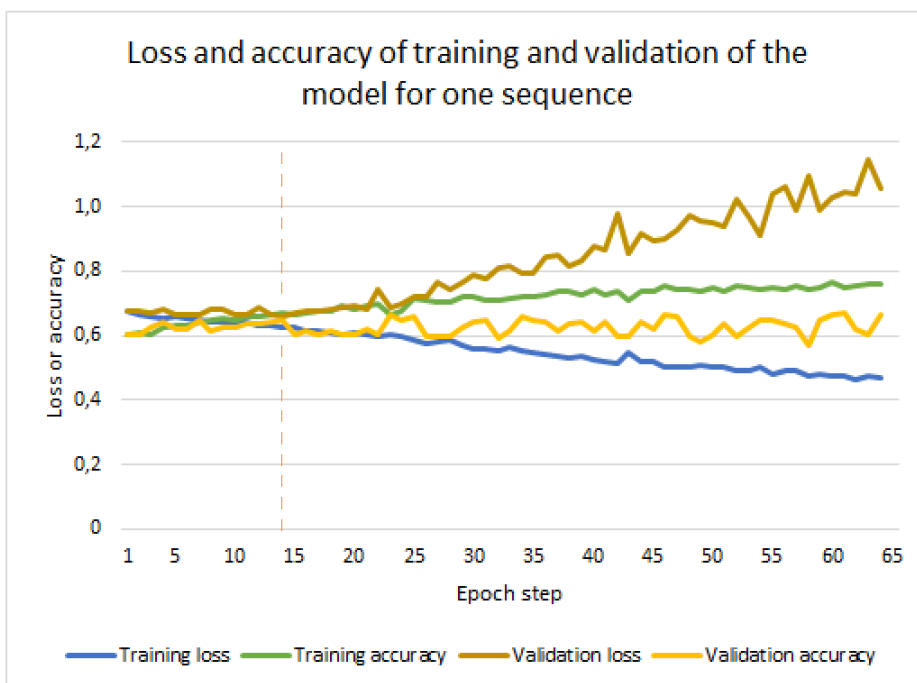


Figure 2. Loss and accuracy for training and validation of the convolutional neural network model for one sequence based on the labeling in respect to the grouping of two groups based on the answer values of the background question BQ1 (n=673).

10.5 Discussion and Future Work

Our current research has aimed to explore and analyze how different people rate the ‘need for help’ for a set of health-related expression statements and how this rating depends on the background information about the person (such as his/her evaluation of the health and wellbeing). Furthermore, we have carried out machine learning experiments to find out what kind of results can be gained when training a convolutional neural network model based on the ‘need for help’ ratings to classify persons into groups relying on the background information.

With Kendall rank-correlation measures we found a significant correlation between only the expression statements ES14 and ES15 (0,86) which gained also the highest cosine similarity value (0,95). With Wilcoxon rank-sum test (i.e., Mann–Whitney U test) and tests of one-way analysis of variance (ANOVA) we did not find statistically significant rating differences between two groups in respect to the answer values of the background questions BQ1 and BQ5, for two groups.

Anyway, we still noted an emerging polarization of the ratings. Among the six expression statements only ES19 gained higher mean ratings from the respondents who indicated a lower estimated health condition (BQ1) or a lower quality of life (BQ5) than from the respondents who indicated a higher estimated health condition or a higher quality of life, respectively. The other expression statements ES12-ES15 and ES20 gained lower mean ratings from the respondents who indicated a lower estimated health condition (BQ1) or a lower quality of life (BQ5) than from the respondents who indicated a higher estimated health condition or a higher quality of life, respectively.

Based on our gathered rating values we can conclude that in accordance with the previous research^{62 63 64 65 66} we have identified complex variations in personal interpretations about health-related expression statements depending on the background information about the person. However, this complex variation is not random but instead with suitable statistical and machine learning methods we show that it is possible to categorize and distinguish respondent groups based on the patterns of their answer distributions. Although the values of validation accuracy remain relatively low in our initial machine learning experiments they are still above the values of pure chance and offer a way to complement other analysis methods concerning the modeling of knowledge processes of healthcare.

Anyway, creating highly accurate machine learning models and results requires typically having large data sets for the training and validation of the models. Since our current data set contains a relatively moderate number of questionnaire answers (n=673), our current experiments focus on evaluating the general applicability of machine learning approach in this knowledge context. When our data set progressively grows, we expect to shift emphasis more to developing fine-tuned machine learning models with an increased validation accuracy. In our current observation, a relatively narrow distribution of answer values caused groupings of unequal size that can introduce a bias to training and validation results. In any case, at the same time the current data set enabled to identify some computational borderlines for the applicability of machine learning in this context.

It is worth noting that although Kendall rank-correlation measures and cosine similarity measures were relatively low and the groupings based on the answer values of the background questions BQ1 and BQ5 did not show statistically

62 Bradley & Lang, 1999.

63 Mauss & Robinson, 2009.

64 Joffer et al., 2016.

65 Borraccino et al., 2019.

66 Knäuper et al., 2016.

significant rating differences with Wilcoxon rank-sum test (i.e., Mann–Whitney U test) and tests of one-way analysis of variance (ANOVA), the machine learning experiments still managed to categorize and distinguish respondent groups based on the patterns of their answer distributions. Relying on the interpretation measurement data gathered in our DIHEML research project we aim to cover a broader set of expression statements, answers to background questions, and extended analysis results in future publications. In addition, while taking appropriate and sufficient anonymization actions in respect to addressing the General Data Protection Regulation of the European Union in handling the research data, DIHEML research project also aims to produce and publish results, models, algorithms, and data openly as much as possible to be used by anyone for non-commercial purposes.

There remains a lot of alternative approaches to be explored in future research concerning the structure and details of affective dimensions concerning health-related knowledge and their relationship to decision making. We decided to gather now ratings in respect to the ‘need for help’ since this semantic dimension emerged strongly in the context of health-related online discussions in our previous analysis⁶⁷. However, the selection of the ‘need for help’ dimension can be motivated also by its intuitive relatedness to the dominance dimension⁶⁸ that reflects the degree of ability to cope and to be in control of one’s own life situations, and also to the approach-avoidance dimension⁶⁹ that reflects the desire to reach some relieving assistance or to be reached by this assistance. In addition, Berna et al.⁷⁰ have found links between self-identified most significant mental imagery describing the patient’s pain and associated triggers, affects, meanings, and avoidance patterns.

When developing methods to support care based on the person’s interpretations about expressions and their relationship to experiences in various situations it is also important to address and counteract various sources of measurement biases. For example, the findings of the previous research^{71,72,73} indicate that interpretations and explanations gained about more complex health-related expressions concerning causes and likelihoods of diseases can have inherently different distributional properties, reliability, and validity than those gained about less complex health-

67 Lahti et al., 2018.

68 Bradley & Lang, 1999.

69 Mauss & Robinson, 2009.

70 Berna et al., 2011.

71 Carroll, 1978.

72 Sherman et al., 1985.

73 Lombrozo, 2007.

related expressions. Furthermore, the comparability of interpretations gathered from persons representing different ages can be influenced by various age-induced changes in cognitive and communicative functioning⁷⁴, possibly related to the challenges of understanding and remembering correctly. On the other hand, to realistically capture dependencies between interpretations and background information about the person, it is important to explore and analyze interpretations gained from multiple sufficiently diverse populations and life conditions. Our current research has addressed this by gathering answers from respondents representing a great diversity of current personal health conditions, abilities, and attitudes, belonging to various Finnish patient and disabled people's organizations, other health and wellness organizations, and educational institutions as well as organizations of healthcare professionals.

Our results can be used for developing adaptive computational methods that can identify the patient's needs from any kind of free text passages, such as from healthcare chatbots, patient diaries, online guidance and screening for care, or their derivatives, for example, emergency phone calls that are immediately annotated with a speech recognition (resembling the proposals of Zhao et al.⁷⁵, Gehrmann et al.⁷⁶, Rojas-Barahona et al.⁷⁷, and Shickel et al.⁷⁸). Our current methodology relying on interpretations of imagined situations can be extended to be applied also in real-life situations thus enabling for example to automatically screen and monitor the person's ordinary knowledge processes (such as speech and writing) so that assistance can be alerted to him/her in the case that certain risk-related patterns are detected.

According to two reviews, there is still a lack of systematic development for reliable evaluation metrics for healthcare chatbots⁷⁹ and their algorithms have challenges in semantic understanding⁸⁰. Therefore future work should emphasize the creation of comprehensive open-access resources of data, models, and algorithms about knowledge processes of healthcare that can be used in standardized ways and are well-understandable for everyone. Our current research aims to advance the development of human-understandable machine learning methodologies by a scalable modular approach that relies on identifying and

74 Knäuper et al., 2016.

75 Zhao et al., 2017.

76 Gehrmann et al., 2018.

77 Rojas-Barahona et al., 2018.

78 Shickel et al., 2019.

79 Abd-Alrazaq et al., 2020.

80 Laranjo et al., 2018.

addressing the personal needs of the patient and highlights the importance to ensure his/her appropriate involvement in all the phases of decision making to support his/her best care.

Besides contributing to the development of the methods that support the patient's care, our research approach and results offer insight that can be used also to enhance understanding of how to ensure the protection of data privacy, in accordance with the previous research^{81 82}. Our results show that with relatively basic statistical and machine learning methods it is possible to identify sensitive characteristics of a person indirectly from even a relatively small data set and a low number of personal answers that may initially seem to be non-sensitive. Furthermore, it is possible to make reasoning and predictions based on these identified characteristics thus making a person's privacy even more vulnerable. Therefore in the development of health analytics, it is important to address such technical solutions that can keep the person appropriately informed about the amount and depth of details that the available analysis can possibly directly or indirectly identify, reason, and predict about him/her. The person should be provided with the possibility to make a well-informed decision about the amount and depth of the analysis that he/she is participating in. While quickly evolving methodologies of machine learning can offer desired and valuable enhancement for health analytics, it is important to implement them so that the person and his/her needs and rights become appropriately and ethically respected.

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81 Cohen et al., 2018.

82 Kaplan, 2020.

Ethical statement: Aalto University Research Ethics Committee has carried out an ethical evaluation concerning the personal data acquisition of the current research project 'Development of method for interpretation of health expressions based on machine learning to support various care events and persons' (DIHEML, see Lahti 2017; Lahti 2018) and has given a supporting ethical statement for it on 18 June 2019. DIHEML research project addresses the General Data Protection Regulation of the European Union in handling the research data.

Open data availability: While taking appropriate and sufficient anonymization actions in respect to addressing the General Data Protection Regulation of the European Union in handling the research data, DIHEML research project will publish an anonymized version of the current research data (a data subset 'Need for help related to coping independently') as a part of a greater data entity along with another future publication that reports the results of DIHEML research project, to be used by anyone for non-commercial purposes.

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