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Transnational access to large prospective cohorts in Europe: Current trends and unmet needs

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ABSTRACT

Biobank samples and data from studies of large prospective cohorts (LPC) represent an invaluable resource for health research. Efficient sharing and pooling of samples and data is a central pre-requisite for new advances in biomedical science. This requirement, however, is not compatible with the present scattered and traditional access governance structures, where legal and ethical frameworks often form an obstacle for effective sharing. Moreover, the EU General Data Protection Regulation (GDPR) is demanding increasingly rigorous administration from all those organisations processing personal data. The BBMRI-LPC project (Biobanking and Biomolecular Research Infrastructure — Large Prospective Cohorts) assembled 21 LPCs from 10 countries and two EU-wide multinational cohort networks with a key objective to promote collaborative innovative transnational research proposed by external researchers on the broad field of common chronic diseases, and analyze the gaps and needs involved. BBMRI-LPC organized three scientific calls to offer European investigators an opportunity to gain free of charge transnational access to research material available in the participating cohorts. A total of 11 high-quality research proposals involving multiple prospective cohorts were granted, and the access process in the individual projects carefully monitored. Divergent access governance structures, complex legal and ethical frameworks and heterogeneous procedures were identified as currently constituting substantial obstacles for sample and data transfer in Europe. To optimize the scientific value and use of these research resources, practical solutions for more streamlined access governance in collaborative projects are urgently needed. A number of infrastructure developments could be made to improve time-efficiency in access provision.

Abbreviations: BBMRI, biobanking and biomolecular research infrastructure; DTA, data transfer agreement; EEA, European economic area; ELSI, ethical, legal and social implications; ERIC, European research infrastructure; GDPR, general data protection regulation; LPC, large prospective cohort; MTA, material transfer agreement; PPP, public-private partnership

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1. Introduction

Prospective large population-based cohort studies (i.e. longitudinal studies on a collection of biological, clinical and other data from large numbers of individuals with shared characteristics) have a fundamental role in identifying etiological risk factors for common chronic diseases [1–4]. In contrast to other study designs (e.g. case-control studies), prospective studies are not affected by recall or other biases, as the risk factors are measured prior to the onset of the targeted disease outcomes [5]. A high number of large prospective cohort (LPC) studies have been carried out across Europe over the last decades. These cohorts constitute a mixture of ‘mature cohorts’ with an extensive follow-up of several decades, and ‘contemporary cohorts’ with more recent and often enriched exposure information. Some of these cohorts have recruited hundreds of thousands of study participants (e.g. UK Biobank and the EPIC cohort), representing major investments of public funding, as well as time and effort from study participants and researchers. With their clinical samples and extensive exposure information stored in biobanks (biorepositories accepting, processing, storing and distributing biospecimens and associated data for use in research and clinical care), the LPC studies represent an invaluable resource for health research [4,6].

To enable analysis of diseases in a reliable manner, prospective cohorts need to be large enough to accrue sufficiently high numbers of incident disease cases during the follow-up. Consequently, studying rare or moderately common endpoints in a single prospective cohort is often challenging. In many cases, pooling resources across multiple cohorts from different countries is required to assemble sufficient sample size for answering important research questions. Consortium-based cohort studies are instrumental to study less common disease endpoints, highlighting the importance of collaborative cohort research in Europe. These multinational research projects, however, are often challenged by sample and data sharing difficulties due to limited resources and heterogeneous, country- and cohort-specific access procedures.

A major logistical hurdle for effective transnational sharing is the absence of centralized and uniform access governance [7]. Multiple time-consuming processes specified in the national legislations and local rules have to be complied with, which may markedly increase the time needed before the actual research can commence. Heterogeneity in access procedures is not only observed across regions (e.g. the EU), but even between different cohorts/biobanks within a single country [8]. Regrettably, the burden of current fragmentation falls on the scientist and the laboriousness of transnational access procedures tend to impede the actual science [9,10].

While streamlining access governance systems is not a straightforward task, there are already a number of initiatives ongoing to rationalize and harmonize access policies and procedures across Europe. There is a growing international consensus on the need for improved access to optimize the long-term value of available sample and data collections and to exploit their full potential for health discovery and validation [7]. The pan-European BBMRI-ERIC (Biobanking and Biomolecular Resources Research Infrastructure - European Research Infrastructure Consortium) may prove a promising platform for increased access harmonization, centralization and e-governance [11]. Another way to promote more harmonized and streamlined access solutions is an international Charter that outlines guiding principles for international sample and data sharing, accompanied by a general model for a Material and Data Transfer Agreement (MTA/DTA) [7].

In this paper, we report and discuss the specific bottlenecks identified in the transnational access process identified during the four-year (2013–2017) EU infrastructure project BBMRI-LPC. Furthermore, we provide a set of recommendations to improve the efficacy of access provision to the cohort research resources in Europe. This information is envisaged to benefit the entire biobanking and medical research community, as well as to promote more harmonized and accessible biobanks.

2. BBMRI-LPC project

From 2013–2017, the BBMRI-LPC project (EU FP7 GA no. 313010)

Table 1

<table>
<thead>
<tr>
<th>Cohort name</th>
<th>Study design</th>
<th>Country</th>
<th>Target number of participants</th>
<th>Website</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort of Norway (CONOR)</td>
<td>Cohort study</td>
<td>NO</td>
<td>200,000</td>
<td><a href="https://www.fhi.no/studier/cohort-of-norway/">https://www.fhi.no/studier/cohort-of-norway/</a></td>
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<td>Constances</td>
<td>Cohort study</td>
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</tr>
<tr>
<td>Danish National Birth Cohort (DNBC)</td>
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<td>DK</td>
<td>100,000</td>
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</tr>
<tr>
<td>Estonian Genome Project (EGP)</td>
<td>Cohort study, Other</td>
<td>EE</td>
<td>51,535</td>
<td><a href="https://www.greenivaramu.ee/en">https://www.greenivaramu.ee/en</a></td>
</tr>
<tr>
<td>European Prospective Investigation into Cancer and Nutrition (EPIC network)</td>
<td>Cohort study</td>
<td>EU-wide</td>
<td>521,468</td>
<td><a href="http://epic.iarc.fr/">http://epic.iarc.fr/</a></td>
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<tr>
<td>Epidemiology of Health (EPiHealth)</td>
<td>Cohort study</td>
<td>SE</td>
<td>300,000</td>
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<tr>
<td>National FINRISK Study</td>
<td>Cohort study</td>
<td>FI</td>
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<tr>
<td>Gazel</td>
<td>Cohort study</td>
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<td>20,625</td>
<td><a href="http://www.gazel.inserm.fr">http://www.gazel.inserm.fr</a></td>
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<tr>
<td>Genomes for Life. Cohort Study of the Genomes of Catalonia (GCAT)</td>
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<tr>
<td>Cooperative health research in the region of Augsburg (KORA)</td>
<td>Cohort study</td>
<td>DE</td>
<td>18,000</td>
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<tr>
<td>LifeGene</td>
<td>Cohort study</td>
<td>SE</td>
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<td>Lifelines Cohort Study</td>
<td>Cohort study</td>
<td>NL</td>
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<td>Norwegian Mother and Child Cohort Study (MoBa)</td>
<td>Case-control study, Other</td>
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<td>284,000</td>
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</tr>
<tr>
<td>MONICA Risk, Genetics, Archiving and Monograph (MORGAM network)</td>
<td>Cohort study</td>
<td>EU-wide</td>
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<td><a href="https://thl.fi/morgam/">https://thl.fi/morgam/</a></td>
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<tr>
<td>Netherlands Cohort Study (NLCS)</td>
<td>Cohort study</td>
<td>NL</td>
<td>120,852</td>
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</tr>
<tr>
<td>Rotterdam study</td>
<td>Cohort study</td>
<td>NL</td>
<td>15,000</td>
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</tr>
<tr>
<td>TwinGene</td>
<td>Cohort study</td>
<td>SE</td>
<td>12,600</td>
<td><a href="https://ki.se/en/research/the-swedish-twin-registry">https://ki.se/en/research/the-swedish-twin-registry</a></td>
</tr>
<tr>
<td>United Kingdom Biobank (UK Biobank)</td>
<td>Cohort study</td>
<td>UK</td>
<td>500,000</td>
<td><a href="https://www.ukbiobank.ac.uk/">https://www.ukbiobank.ac.uk/</a></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>3,378,310</td>
<td></td>
</tr>
</tbody>
</table>
3. Trends and needs in the current access procedures

Any researcher accessing samples or data in a cohort or biobank typically needs to complete three general steps of the access process: (1) requesting the access, (2) obtaining the necessary study approvals, and (3) executing the access. Below, we describe the current bottlenecks for each of these steps as revealed by close follow-up of transnational research projects in the BBMRI-LPC project.

3.1. Requesting the access

3.1.1. Cataloguing of samples and data

Evaluating which individual cohorts are suitable to answer a specific research question is rarely straightforward, as most cohorts do not provide detailed information on their research resources in a harmonized fashion. To facilitate this process for the BBMRI-LPC-supported access research projects, a specific access web portal (http://bbmri-lpc.iarc.fr/mica/) was launched where the most relevant information on research resources was made easily available in a searchable form. In addition, data in the BBMRI-LPC cohort catalogue, a sub-catalogue of the BBMRI-ERIC catalogue of European biobanks [12], was updated by inviting 21 participating cohorts to take part in a harmonized exposure and clinical endpoint data inventory (http://www.bbmri-lpc-biobanks.eu/). Information on epidemiological exposure data (i.e. any factor, which may be associated with an outcome of interest) was received for 13 cohorts, whereas eight cohorts were unable to provide all relevant information mostly due to insufficient financial resources to support this activity. Information on clinical endpoints (i.e. primary outcomes, such as diseases or other measurable events, measured in a clinical trial) were received for 9 cohorts. For another 12 cohorts, the endpoint data were not available at the time of request.

3.1.2. Centralized support

For researchers formerly unfamiliar with European cohorts, information provided in the cohort catalogue itself was in many occasions not sufficient to allow preparation of competitive research proposals. Supplementary support by the BBMRI-LPC access team was often required to guide investigators in defining the requirements of samples and data for their research project, the specific structure and set-up of individual cohorts, as well as how to approach the cohorts.

3.1.3. Identification of a correct contact person for the access correspondence

In some cases, identification of the correct contact person for access correspondence at the cohort took a surprisingly long time. This caused unnecessary delay in initiating the actual access procedures. It is worth noting that while the principal investigator of the original cohort study is basically the ideal contact person for all scientific matters regarding the cohort, they are generally not the most suitable point of contact for assisting with the various administrative and technical practicalities related to access.

3.2. Obtaining the necessary study approvals

3.2.1. Heterogeneous access governance

Some contemporary European cohorts have adopted a service-oriented access governance structure with minor scientific involvement required in the downstream research. Such cohorts tend to have strong research support to handle the relevant study administrative tasks. Other cohorts, most of which can be considered more mature, often require the research to be conducted in close collaboration with a local scientist, who would also be in charge of handling many of the local study administrative duties. Whilst the role of a local scientist is beneficial in ensuring that the idiosyncrasies of individual cohorts are
samples proved to be a complicated administrative effort, typically
establishing the necessary MTAs that govern use of the cohort data and
3.3.1. Material Transfer Agreement (MTA) negotiations
3.3. Executing the access

appropriately accommodated in the study setup and conduct, this
approach is often rate-limiting as the local scientist may have limited time
to handle such tasks. Regardless of governance structure, individual
cohorts each have their own procedures and rules for organizing access
to their samples and data, requiring individual users who seek access to
multiple cohorts to comply with multiple, and often strongly divergent,
access procedures. The scope and validity of informed consent from the
research participants is often subject to evaluation and may limit the
secondary uses and data sharing, even if the actual access procedures
were smooth. The new EU General Data Protection Regulation (GDPR)
became effective on May 25, 2018, and imposes reassessment of the
validity of existing informed consents, if they are used as a lawful basis
for research.

3.2.2. Time-consuming local approval procedures

One of the most time-consuming tasks in the access process is ob-
taining the necessary local scientific and ethical approvals. Most co-
horts have a local scientific access committee or an equivalent decision
body for evaluating new access requests. In many cases information
about these cohort-specific committees and their requirements only
became known following the initial access request. As meetings of the
local committees are typically organized at monthly or bi-monthly in-
tervals, gaining approvals from each of the multiple cohorts caused
inevitable and varying delays. On some occasions, applicants were also
asked to modify their proposal or to provide complementary informa-
tion, which led to additional round(s) of committee review(s) before the
final decision was made.

Whilst some selected cohorts have provided overarching ethical
approval for future use of their data and samples, most require local or
national ethics committees (or similar body) to approve any proposed
research wherein the cohort’s data and/or samples would be accessed.
Some national laws also require a review from the data protection au-
thorities. The local ethics committees meet at regular intervals, but
rarely in conjunction with the local access committees, which tends to
genenerate an additional delay in the approval process. In the cohorts
with a very streamlined process, the time taken by the local access and
ethics committees to grant approval was approximately three to four
months, while in the worst case the approval process took more than a
year.

3.3. Executing the access

3.3.1. Material Transfer Agreement (MTA) negotiations

Following approvals from the local access and ethics committees,
establishing the necessary MTAs that govern use of the cohort data and
samples proved to be a complicated administrative effort, typically
taking many months up to one year to complete. Initially, BBMRI-LPC
developed a uniform MTA template that was offered as an option to be
used by the supported research projects. Despite this effort, the MTA
negotiations remained restrictively cumbersome. As there are few im-
portant differences in laws or regulations at national level which should
complicate the transfer of samples or data within the EU, the problem
seemed rather to lie at the institutional level, as most cohorts expressed
a strong preference for using their own specific MTAs. Transfers of
personal data to non-EU or non-European Economic Area (EEA) coun-
tries complicate agreements even further due to the EU data protection
regime that requires adequate safeguards to be fulfilled by the re-
cipient.

3.3.2. Delays in organizing and shipping of study samples

Whilst the cohorts generally have well-organized routines for re-
trieving, preparing and shipping samples, in some instances 3–12
months’ delay occurred in retrieving the relevant samples and pre-
paring them for transfer. The extended sample retrieval times were
interpreted to be largely dependent on the availability of personnel as
well as on the extent of automatic sample manipulation implemented in
each of the respective cohorts.

3.3.3. Data harmonization

In contrast with sample access, organizing and transferring cohort
data was relatively straightforward and further facilitated by the cohort
catalogues. Here, however, a more important bottleneck turned out to
be the downstream data harmonization. While this activity was not
supported under the present BBMRI-LPC project, it needs to be com-
mented on here as an important hurdle in multinational cohort science.

4. Smoother access solutions for the cohort-based research

projects

Below, we provide a set of recommendations for addressing the
bottlenecks identified in collaborative cohort-based transnational re-
search. The identified challenges and subsequent recommendations are
summarized in Table 3.

4.1. Importance of cataloguing the cohort resources

The importance of a searchable database with detailed, standar-
dized information on the available cohort samples and data is evident.
Further, to maintain such a catalogue up-to-date as well as to allow
enriching the catalogue through generation of new data, sufficient
personnel resources along with appropriate IT systems for (semi-) au-
tomated updates of the individual cohort information are necessary. In
By agreeing the timeframe beforehand, it is possible to avoid juxtaposition between the actors and ensure a timely local dialogue between the scientists and the administrators, improving transparency and accountability from both sides.

Many consortium projects have put a lot of effort into developing standardized MTA templates [7]. However, without including the legal departments in the development phase to have the majority of institutes agreeing on such a template, practical implementation thereof is not realistic. Establishing a truly uniform MTA template (or at least a collection of standardized building blocks) has the potential to revolutionize the rate by which transfer of data and samples can occur in Europe, hence substantially accelerating biomedical discoveries. This is, however, a challenging task that requires close collaboration and mutual agreement of each cohort-associated institution. Failing this, applicants in consortium-based research projects will continually be obliged to establish a number of different MTAs. In any given research project requiring transfer of data and/or samples, we strongly recommend initiating the MTA processes as early as possible, ideally before or as soon as all necessary study approvals are in place.

4.5. Investments into sample management and harmonization

Sufficient and project-independent core funding is necessary to efficiently fulfill access claims and swiftly process the sample requests in the individual cohorts. Whilst for some cohorts a certain gain in efficiency might be achievable through organizational changes, substantial reduction of sample preparation time would typically require increasing the personnel resources involved in sample retrieval and manipulation and/or introducing automation, which would again require additional investments in machinery and robotic sample handling.

In terms of data harmonization, it can often take several months for a skilled computer technician to harmonize a complex study database. To avoid having each consortium re-harmonizing the same cohorts’ data for each new project, we recommend individual cohorts to assign resources allowing one-off harmonization of common study variables required in any consortium-based research project [13, 14]. As an example of such an effort, in 2013 the US National Cancer Institute supported a comprehensive harmonization effort of a large number of commonly used study variables for cohorts participating in the Diabetes and Cancer Initiative (n = 28). The code book for this harmonization will be made available for other investigators seeking to harmonize data from these cohorts. Also, the previously initiated large collaborative FinnGen project (https://www.finngen.fi/en) employs clinical expert groups to harmonize endpoint data acquired from the national health registries. Adopting this kind of principle would provide one of the most cost-efficient improvements in cohort-based research. As the data evolves over time, smart and appropriate IT-solutions are necessary for keeping the information up-to-date and documenting the data provenance. Also, innovative ways of sharing data are needed. When samples become data via laboratory analyses, it may be feasible to “bring analysis to the data instead of bringing the data to the analysis” [15], rather than go through all the steps described above. It should be noted, however, that by GDPR, having access to data is equal to data transfer, albeit the data download would have been made technically impossible.

5. Conclusions

Sharing samples and data from different study sources is crucial in attaining new biomedical breakthroughs. Divergent access governance structures, complex legal and ethical frameworks and heterogeneous cohort access procedures currently constitute substantial obstacles for sample and data transfer in Europe. In addition, lack of resources in the publicly funded cohorts is an issue. Public-private partnership (PPP) in large projects, such as FinnGen (https://www.finngen.fi/en), a collaborative research project of nine Finnish biobanks and seven pharma
companies, is an example of how to overcome the funding issues that are often related to the large projects, particularly in small countries. On the other hand, PPP naturally creates other layers of complexity which need to be dealt with. While the GDPR (EU 2016/679) will harmonize EU practices on personal data protection at the meta-level, a lot of decision power, particularly on scientific projects, has been left for the member countries. GDPR also sets out rigorous provisions for data processing, administration and privacy impact assessments. The validity of old consent may be at stake, if used as a lawful basis for data processing. This will probably not ease the challenges described above, but rather re-boot the field in many ways that make it necessary for the scientists and ELSI (ethical, legal and social implications) experts to map the situation all over again. Streamlining of access provision processes has the potential to greatly enhance use of the unique and invaluable cohort research resources and to maximize their impact on high-quality health science. This is a mandatory route, as it is the only way to provide health care benefits and lifestyle improvements to the public at large, justifying the efforts of the biobank participants. All in all, if the data and samples are used for the original purpose for which they were collected, as well as in accord with the informed consent for their use, we see that all unnecessary restrictions and artificial boundaries should be curtailed in the interest of public good.

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**Declarations of interest**

None.

**References**