Molecular genetics in clinical laboratory

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Online Mendelian inheritance in man

OMIM Morbid Map Scorecard  (Updated 19 March 2013) :

- Number of phenotypes* for which the molecular basis is known  4,866
- Number of genes with phenotype-causing mutation  2,973

* Phenotypes include single-gene Mendelian disorders, traits, some susceptibilities to complex disease (e.g., CFH and macular degeneration, [134370.0008](https://www.omim.org/entry/134370.0008)), and some somatic cell genetic disease (e.g., FGFR3 and bladder cancer, [134934.0013](https://www.omim.org/entry/134934.0013))
Common forms of inherited disease testing

**Diagnostic testing** of a patient w/ symptoms

**Predictive testing**
- testing before symptoms begin

**Carrier testing**
- testing of an unaffected carrier of a known mutation
  - family planning
Common forms of molecular pathology

Diagnostic testing of a patient w/ symptoms

Companion testing
-testing for mutations in malignant tissue before selection of treatment

Minimal residual disease
-testing for disease relapse
DNA diagnostics @ HUSLAB

Chromosome abnormalities
Laboratory of Cytogenetics

Inherited diseases & genetic errors
Labotary of Molecular genetics

Somatic genetic errors
Laboratory of Molecular pathology
DNA diagnostics @ HUSLAB

- Chromosomal abnormalities

- Retardation
  - Inherited?
    - Balanced translocation?
    - De novo?
  - Is next child in danger?
DNA diagnostics @ HUSLAB

- **Hematological cancers**
  - Clonal B- or T-cells
  - MRD

- **Chromosomal abnormalities in cancer tissue**

- **Efficiency of treatment**
  - **Companion testing**
    - Drug allowed / banned based on genotype
      - BCR-ABL fusion
        - Glivec
      - Her2 / breast cancer
        - Herceptin

- **rapidly growing field**
DNA diagnostics @ HUSLAB

- Inherited diseases
- Inherited coagulation errors
- Inherited cancers
- Farmacogenetics
  - Companion testing
    - CYP profiles
  - Drug selection
    - statins
  - Drug dosing
    - warfarin

Laboratory of Molecular genetics
DNA diagnostics @ HUSLAB

Laboratory of Cytogenetics

Laboratory of Molecular pathology

Laboratory of Genetics
DNA diagnostics @ HUSLAB

- Virology
- Bacteriology
Diagnostic genetic test or not

- What can you say to the ordering physician about the result?
  - Can you make or rule out Diagnosis?
  - Calculate predicting value?
  - Is it an inherited form of the disease?
    - Are relatives at risk

- Relative risks at population level are not used in diagnostic genetic testing
Classical mutation

Not affected

Affected

-
Predisposing polymorphism

Great majority of polymorphism carriers are not affected!
Clinical impact

- Positive result is usually clear
  - If not, it is not a diagnostic test

- The key factor of test utility is the explaining power of the NEGATIVE result
  - Sufficient explaining power of the mutation (panel) in your local population (aim at >80% positives covered)
Reliable technology

- Often very hard clinical decisions are made based solely on the gene test result
  - Pregnancy termination
    - Lethal (metabolic) syndromes
    - Severe mtDNA errors
  
- Cost is not a major factor in severe inherited diseases
Choosing Diagnostic genetic test kit

KIT:
- Do you trust the kit technology?
- Do you trust the kit provider?
  - Single assay kit provider: usually NO !!
Inexpensive technology

- Assay cost strongly affects the use of “less critical” polymorphism tests
  - Lactose intolerance
  - Warfarin dosing
  - Simvastatin side effects
  - Hemochromatosis
  - Coagulation risk

- Process harmonization and automation
  - Assays performed in strictly controlled way
  - Combining multiple test in one run
  - Lab automation decreases unit costs
Current trends

- More inherited diseases with known genes & mutations are studied
  - Technology allows more and more mutations to be analyzed.
  - Mutation packages
    - when explaining power of a single mutation is poor

- Pharmacogenetics grows
  - Personalized medicine
  - Drug dosage / selection based on metabolic pathways
  - Companion testing

- Search for family specific mutations grows with development of sequencing technologies
Current trends

- Somatic mutations and rearrangements in cancer tissue
  - Companion diagnostics
  - New drugs against specific (mutant) proteins
  - Blocking of over-expressed proteins
Molecular genetics: Basic methods
DNA synthesis: 3’OH
DNA structure

CCCAAGTGTGACTCCGTGTTTGAC

OH\textbf{→}GGGTTCACACTGAGGCACAAACTG

OH\textbf{←}
DNA errors

Deletion

TGACCCTGGTGCACTTAACAGCGTTAGT
ACTGGGACCACTGAATTTGTCGCAATCA
DNA errors

Deletion
TGACCCTGGTGGCGTTAGT
ACTGGGACCACCGCAATCA

Insertion
TGACCCTGGTCACTTTAACAGCGTTAGT
ACTGGGACCACGTGAATTGTGCAATCA
DNA errors

**Deletion**
- TGACCCTGGTG GCGTTAGT
- ACTGGGACCACCGCAATCA

**Insertion**
- TGACCCTGGTG ACTTAACAGCGTTAGT
- ACTGGGACCACCTGAATTGTCGCAATCA

**Repeat expansion**
- TGACCC CAGCA GCCGCGTGTTAGT
- ACTGGG GTGGCCGGTGGCGCAATCA
DNA errors

Deletion
TGACCCTGGGTGCGTTAGT
ACTGGGACCACCGCAATCA

Insertion
TGACCCCTGTGCTTTAACAGCGTTAGT
ACTGGGACCACCTGAAATGTCGCAATCA

Repeat expansion
TGACCCCAAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGT
ACTGGGCTCGTGTGCTCGTGTGCTCGTGTGCTCGTCTGTCGCAATCA

Point mutation / SNP
TGACCCCTGTGCTTTAACAGCGTTAGT
ACTGGGACCACCTGAAATGACGCAATCA
Role of reading frame

DNA

mRNA

protein

ATG CAG TCC GGT GCT CCT ATC TGG TGA ...
Met Gln Ser Gly Ser Pro Ile Trp *S*

ATG CAG TGA GGT GCT CCT ATC TGG TGC ...
Met Gln *S*
Point mutation / SNP

- Same mutation affects differently in different reading frames

```plaintext
TGACCCTGGTG
GACCTTTACAGCGTTAGT
ACTGGGACCAC
TGAATGACGCAATCA
```

- TGG (Trp) → TGA (*S*) nonsense
- GAC (Asp) → AAC (Asn) missence
Chromosomal deletion

- Gene dose decreases
  - Lower enzyme activity

Gene 1  Gene 2  Gene 3  Gene 4  Gene 5  Gene 6
Gene 1  Gene 2  Gene 3  Gene 4  Gene 5  Gene 6
Chromosomal amplification

- Gene dose increases
  - Higher enzyme activity
Chromosomal translocation

- Balanced translocation
  - Gene dose unchanged
  - Affects mainly next generation
Chromosomal translocation

- Unbalanced translocation in next generation
  - Gene dose changes

Gene 1  Gene 2  Gene 3  Gene 4  Gene 5  Gene 6
Gene 1  Gene 2  Gene 3  Gene 4  Gene 5  Gene 6
Gene 11 Gene 12 Gene 13 Gene 5  Gene 6
Gene 11 Gene 12 Gene 13 Gene 14 Gene 15 Gene 16
Probe hybridization
Specific hybridization of a probe

- Only fully complementary strands hybridize

5′-GTCACTTAT-OH

3′-TGACCCCTGGTGCACTTAACAGCGTTAGT-5′
Structural changes

* Fluorescent *in situ* hybridization
  - FISH
  - Chromosomal level
    - Translocations
    - Deletions
Fluorescent *in situ* hybridization (FISH)

- Deletion
Fluorescent *in situ* hybridization (FISH)

- Chromosomal painting
Competitive genomic hybridization (CGH)

Cromosomal

Array
Structural changes

- Southern blotting
  - Too large for gene amplifications
  - Borders / Location unknown
  - Multiple changes
Southern blot:
Restriction endonucleases

- Restriction enzymes block entry of foreign DNA into bacteria
- Cut double stranded DNA at highly sequence restricted palindromic sites

Eco RI

GAATTC
CTTAAG
G    AATTC
CTTAA    G
Southern blot: Agarose gel electrophoresis

- DNA fragments separated at electric field by size
- Smallest fragment is fastest
Southern blot

Normal

GAATTCT...........GAATTC..................TCGGAATCCGT

Mutation

GAATTCT..................................................TCGGAATTTCGT
Southern blot

Normal

\[ \text{GAATTCT} \ldots \quad \text{CAGCAG} \ldots \quad \text{TCGGAATTCGT} \]

Repeat expansion

\[ \text{GAATTCT} \ldots \quad \text{CAGCAG\,(CAG)_100\,CAGCAG} \ldots \quad \text{TCGGAATCCGT} \]
Southern blot

- Restriction enzyme fragments separated in agarose gel electrophoresis

- Label hybridization probe:
  - binds to fragments containing gene of interest
Southern blot

- Transfer to Nylon filter
- Probe hybridisation
- Washes + Detection using X-ray film

- Probe binds only to complementary DNA strands
Smaller structural changes

- PCR amplification
  - Short repeat expansions
    - unexpanded repeats
    - short tandem repeats (STR)
      - forensic and paternity testing (ID)
  - Short deletions or insertions (Indel)
    - known location
    - short enough for amplification
  - Point mutations / single nucleotide polymorphisms (SNP)
in vitro DNA synthesis

- DNA synthesis initiates from free 3’OH group of a hybridized primer
- DNA polymerase reads template strand and synthetises complementary strand

5’ – GTGAATTGCTTTAATCAGTT
3’ – TGAATAGGCACCTTAACAAGGCTTAGTCAA – 5’
PCR amplification

- Polymerase chain reaction (PCR)
  - Formation of a specific product
  - Product length
  - Amplification of the area of interest for structural analysis by other methods
Identification using short tandem repeats (STR)

- Genome full of STRs
- Inherited from parents

Allele 1

Allele 2
Identification using short tandem repeats (STR)
Point mutation / SNP / Indel - methods

- Hybridisation based
  - Specific hybridisation
    - labelled probe
    - labelled PCR product
Allele specific oligo (ASO) hybridization

5′-GTGAATTGT-3′
3′-TGACCCTGGTGCACTTAAACAAGCGTTAGT-5′
Hybridisaatio assay

---

Genotyyppi

AA
Hybridisäatio assay

Genotyyppi GG

C-oligo

T-oligo
Hybridisaatio assay

C-oligo

T-oligo

Genotyyppi AG
Hybridisation based assays cannot detect very similar / close mutations.
Companion testing

Bardelli A, Siena S JCO 2010;28:1254-1261
KRAS

- 7 mutations:
  - Gly12Arg (GGT > CGT)
  - Gly12Cys (GGT > TGT)
  - Gly12Ser (GGT > AGT)
  - Gly12Val (GGT > GTT)
  - Gly12Ala (GGT > GCT)
  - Gly12Asp (GGT > GAT)
  - Gly13Asp (GGC > GAC)

```plaintext
atg act gaa tat aaa ctt gtg gta gtt gga gct ggt ggc gta ggc aag agt gcc ttg acg ata cag cta att cag aat cat ttt gtg gac gat tat gat cca aca cta ga
```
Point mutation / SNP / Indel - methods

- Hybridisation based
  - Specific hybridisation
    - labelled probe

- Enzyme assisted
  - Enzymes recognizing DNA sequence
    - DNA polymerase
    - Restriction enzymes
Allele specific PCR

- 3’ end of the primer is used for genotyping
3’ end mismatch blocks extension

5’-GTGAATTGG AATCAGTT
3’-CACTTAACC CGGCTTAGTCAA-5’

5’-GTGAATTGGA
3’-CACTTAACCGGCTTAGTCAA-5’

5’-GTGAATTGGA
3’-CACTTAACCGGCTTAGTCAA-5’

5’-GTGAATTGG AATCAGTT
3’-CACTTAACC CGGCTTAGTCAA-5’

C-Allele

T-Allele
Agarose gel electrophoresis
Minisequencing

- Uses template reading specificity of the DNA polymerase for nucleotide
Nucleotide specificity of the DNA polymerase

dTTP reaction

C
T
A
A
G
T
A
A
C
G
T
T
A
A
G
- Bio

Pol

dTTP

dTTP

dTTP

dTTP

dTTP

dTTP

dTTP

dTTP

Pol

dTTP reaction

C
T
A
A
G
T
T
A
A
G
- Bio

dTTP

dTTP

dTTP

dTTP

dTTP

dTTP

dTTP

dTTP

Pol

dCTP

dCTP

dCTP

dCTP

dCTP

dCTP

dCTP

dCTP

dCTP

dCTP

dCTP

dCTP

dCTP

dCTP

dCTP

dCTP

Pol
Minisequencing

WT template sequence = T, nucleotide = dATP

Normal: dATP, dATP, dATP, dATP, dATP, dATP

Heterozygous: dATP, dATP, dATP, dATP, dATP, dATP

Homozygous: dATP, dATP, dATP, dATP, dATP, dATP
Minisequencing

Mutant template sequence = C, nucleotide = dGTP

normal: dGTP dGTP dGTP

heterozygous: dGTP dGTP C

homozygous: dGTP dGTP C
Calculate mutant / WT ratio (R-value)

- R=0.01
- R=1
- R=100

normal  heterozygous  homozygous
Laboratory automation and multiplexing needed

- Multiple rare diagnostic tests run simultaneously
  - Sample number / test very low
- Mutation packages
  - Limited clinical value of individual genes / mutations
  - Together have diagnostic impact
- Pharmacogenetics
  - Gene variants affecting drug metabolism
- Predisposing polymorphisms
Multiplexing
Cyclic primer extension

DNA pol
Cyclic primer extension
cMS
184 samples w/ replicates
Luminex internally color-codes microspheres with precise concentrations of various fluorescent dyes yielding up to 500 distinctly colored bead sets.

The microspheres can be coupled with reagents specific to a particular bioassay such as antigens, antibodies, oligonucleotides, enzyme substrates, or receptors.
The microspheres pass through a red laser or LED, which excites the internal dyes to distinguish the microsphere set and then a green laser or LED, which excites the fluorescent dye on the reporter molecule to determine result of the assay.
Illumina Veracode
Homogeneous methods

- Unbound labels are not removed
- Signal only from bound molecules
- Molecular interaction, depends on the distance between molecules
  - Fluorescence resonance energy transfer (FRET)
  - Fluorescence polarisation (FP)
Real Time PCR

- Fluorescent dye binds to dsDNA
- Measure fluorescence during PCR
TagMan

- Quenching fluorescence energy
- 5’-exonuclease activity of DNA polymerase removes quencher
LightCycler® FRET
Melting point analysis

Figure 2: Principle of melting curve analysis.
In this example, Hybridization Probes were used in a LightCycler Instrument.

A: Schematic of labeled probes binding to a wild-type sequence (bottom) or a mutant sequence (e.g., SNP) (top).
B: A melting curve depicts changes in fluorescence as temperature is slowly raised.
C: The negative first derivative of the melting curve depicts the melting temperature ($T_{m}$) of the products present in each sample, revealing genotypes that can be easily called.
Future trends

- Point mutation analysis

vs.

- Sequencing
Sanger DNA sequencing

- Read DNA base order
- DNA polymerase + ddNTP ("terminaattori")
dideoxy “terminator”

dGTP  ddGTP
DNA sequencing

- Both dNTPs and ddNTP:s in reaction mix
- ddNTP lottery
- DNA synthesis continues until ended by ddNTP

ddATP

ACCGTATACTCGAACC...
DNA sequencing

- Fragment separation by electrophoresis
  - PAGE
  - Capillary EF
- Shortest fragment is fastest

ddATP

ACC GTATCGAACC
DNA:n sekvenointi
Future trends

- FISH

vs.

- array CGH
Future trends

- Mutation analysis on micro chips

vs.

- NGS
Next generation sequencing
Conventional DNA sequencer

- ABI 3130xl
- Target PCR
- fluoro-ddNTP terminators
- 16 reactions / run
Next Generation Sequencing

- Sample prep
  - No PCR, random fractionation
  - Clonal Bridge PCR
- Upto 3 billion reactions / run
- Target enrichment required
Illumina

**b** Illumina/Solexa

Solid-phase amplification
One DNA molecule per cluster

- Sample preparation DNA (5 μg)
- Template dNTPs and polymerase

**c** Helicos BioSciences: one-pass sequencing
Single molecule: primer immobilized

- Cluster growth
- Billions of primed, single-molecule templates

100-200 million molecular clusters

Bridge amplification
Illumina chip
### Sequencer specs

![Sequencer specs](image)

**Fig 3 Sequencing instrument comparison (select platforms, list prices, US$)**

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Instrument Cost (incl ancillary equipment costs)</th>
<th>Run Time</th>
<th>Reads/run (millions)</th>
<th>Bases/read</th>
<th>Mb/run</th>
<th>Reagent cost/ run (US$)</th>
<th>Reagent cost/ Mb (US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIFE - 3730xl (capillary)</td>
<td>$300K</td>
<td>2 hours</td>
<td>0.000096</td>
<td>750</td>
<td>0.08</td>
<td>$90</td>
<td>$1,000</td>
</tr>
<tr>
<td>Roche 454 Junior</td>
<td>$100K</td>
<td>10 hours</td>
<td>0.1</td>
<td>400</td>
<td>50</td>
<td>$1,100</td>
<td>$33</td>
</tr>
<tr>
<td>ILMN - HiSeq2000</td>
<td>$690K</td>
<td>12 days</td>
<td>~3000</td>
<td>100+100</td>
<td>600,000</td>
<td>$25,000</td>
<td>$0.04</td>
</tr>
<tr>
<td>LIFE - Ion Torrent (318 chip)</td>
<td>$75K</td>
<td>2 hours</td>
<td>1</td>
<td>200</td>
<td>1000</td>
<td>$750</td>
<td>$0.75</td>
</tr>
<tr>
<td>ILMN - MiSeq</td>
<td>$125K</td>
<td>1 day</td>
<td>3.4</td>
<td>150+150</td>
<td>1500</td>
<td>$750</td>
<td>$0.50</td>
</tr>
</tbody>
</table>

Source: Sanger Institute, Company data, Macquarie Capital (USA), August 2012
APECED
FIN Major: C889->T (R257X)
Seq = Illumina GA II
Electrosequencing
Ion Torrent
Electrosequencing
Next Generation Sequencing

- Efficient target enrichment required
  - Target capture
  - Pull down
  - Multiplex PCR

- When data reliable enough?
- What do we understand?
- What can we report?
Single molecule sequencing

- Helicos BioSciences: two-pass sequencing
  Single molecule: template immobilized

- Pacific Biosciences, Life/Visigen, LI-COR Biosciences
  Single molecule: polymerase immobilized

NATURE Reviews | Genetics 2010
Companion testing

- Choosing a cancer drug based on somatic changes in tumor cell DNA
  - Companion testing
BCR-ABL-fuusio KML:ssä ja ALL:ssä

95% KML-potilailla
20% aikuis-ALL-potilailla
2-5% lapsi-ALL-potilailla

Fuusioproteiini, tyrosiinikinaasi
BCR-ABL-fusion testaaminen

t(9;22)(q34;q11)

kromosomitutkimus, FISH-tutkimus
Kvantitatiivinen BCR/ABL-fuusiotranskriptin määritys, -BCR-QR
Companion testing
Companion testing

Bardelli A, Siena S JCO 2010;28:1254-1261
Chromosomal translocations & cancer
Examples:
Lung cancer classification
&
Personalized medicine
Lung cancer classification

- Small cell lung carcinoma: 15%
- Non-small cell lung carcinoma: 85%
## 2004 WHO Classification of Lung Tumors

<table>
<thead>
<tr>
<th>NSCLC (87%)</th>
<th>SCC (33%)</th>
<th>LCC (9%)</th>
<th>SCLC (13%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adenocarcinoma (45%)</strong></td>
<td><strong>Mixed Subtype</strong></td>
<td><strong>Acinar</strong></td>
<td><strong>Papillary</strong></td>
</tr>
<tr>
<td><strong>BAC</strong></td>
<td><strong>Nonmucinous</strong></td>
<td><strong>Mucinous</strong></td>
<td><strong>Mixed</strong></td>
</tr>
<tr>
<td><strong>Solid</strong></td>
<td><strong>BAC</strong></td>
<td><strong>Small cell</strong></td>
<td><strong>Basaloid</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Lymphoepithelioma-like</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>SCLC</strong></td>
</tr>
</tbody>
</table>

BAC=bronchioloalveolar carcinoma; LCC=large cell carcinoma; LCNEC=large cell neuroendocrine carcinoma; SCC=squamous cell carcinoma; SCLC=small cell lung cancer.
Mutations in Non–Small Cell Lung Cancer

Lung Cancer

- Unknown
- KRAS
- EGFR
- ALK
- PIK3CA
- NRAS
- MEK1
- HER2
- BRAF
- AKT1
Lung cancer classification

- Small cell lung carcinoma (15%)
  - Treatment 1

- Non-small cell lung carcinoma (85%)
  - Treatment 2
Lung cancer classification

Non-small cell lung carcinoma 85%

Genotype 1
Genotype 2
Genotype 3
Genotype 4
Genotype 5
Genotype 6

Treatment 1
Treatment 2
Treatment 2
Treatment 2
Treatment 3
Treatment 3
Treatment 4
Approved somatic marker-dependent drugs

- Companion testing
  - Tumor tissue genotype must be known before using the drug

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug target</th>
<th>Cancer type (or types)</th>
<th>Somatic markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab</td>
<td>EGFR</td>
<td>Colorectal, head and neck</td>
<td>EGFR and KRAS</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>EGFR</td>
<td>Lung, pancreatic</td>
<td>EGFR</td>
</tr>
<tr>
<td>Exemestane</td>
<td>Aromatase</td>
<td>Breast</td>
<td>ESR1, ESR2 and PGR</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>EGFR</td>
<td>Lung</td>
<td>EGFR</td>
</tr>
<tr>
<td>Imatinib</td>
<td>BCR–ABL, KIT and PDGFRα tyrosine kinases</td>
<td>Chronic myeloid leukaemia, gastrointestinal</td>
<td>Philadelphia chromosome, KIT and PDGFRA</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>ERBB2 receptor</td>
<td>Breast</td>
<td>ERBB2</td>
</tr>
<tr>
<td>Letrozole</td>
<td>Aromatase</td>
<td>Breast</td>
<td>ESR1, ESR2 and PGR</td>
</tr>
<tr>
<td>Panitumumab</td>
<td>EGFR</td>
<td>Colorectal</td>
<td>EGFR and KRAS</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>Oestrogen receptor</td>
<td></td>
<td>ESR1, ESR2 and PGR</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>ERBB2 receptor</td>
<td>Breast, stomach</td>
<td>ERBB2</td>
</tr>
</tbody>
</table>

Heather E. Wheeler, Michael L. Maitland, M. Eileen Dolan, Nancy J. Cox & Mark J. Ratain
Nature Reviews Genetics 14, 23-34 (January 2013)
Vemurafenib: the first drug approved for BRAF-mutant cancer
Vemurafenib: the first drug approved for BRAF-mutant cancer
Personalized medicine

- Choosing a drug based on patients DNA metabolic profile
  - Pharmacogenetics

- Choosing a cancer drug based on somatic changes in tumor cell DNA
  - Companion testing
Access to relevant patient information

Access to clinical knowledge
(e.g., diagnostic tools, knowledge of causes of diseases, empirical evidence or comparative effectiveness)

Poor

Good

Access to relevant patient information

Personalized
(based on me or people like me)

Evidence-based
(Based on patient populations)

Clinician consensus-based

Trial and error
(Based on clinician expertise and experience)

Intuitive medicine
(Based on complete access to available patient information and clinical knowledge)

More art than science

More science than art

Sources: IBM Global Business Services; IBM Institute for Business Value.
“Personalized Medicine”

The tailoring of medical treatment to the individual characteristics of each patient. It does not literally mean the creation of drugs or medical devices that are unique to a patient, but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not.

Priorities for Personalized Medicine.
President’s Council of Advisors on Science and Technology. September 2008.
Complicated data interpretation
Gene expression profile

- Tumor classification
- mRNA expression levels compared
Copy number variants

- Copy number variant (CNV)
  - Thousands
  - Biological role under investigation

- New tools needed
  - DNA Micro chips
  - Next generation sequencing