Generade
Applied Genomics for Life

Genetic profiles in relation to sports: a databased approach

NWO & FAPESP Sports & Healthy Living,

Sao Paulo, March 23 2016

Peter Taschner, Professor Genome-based Health

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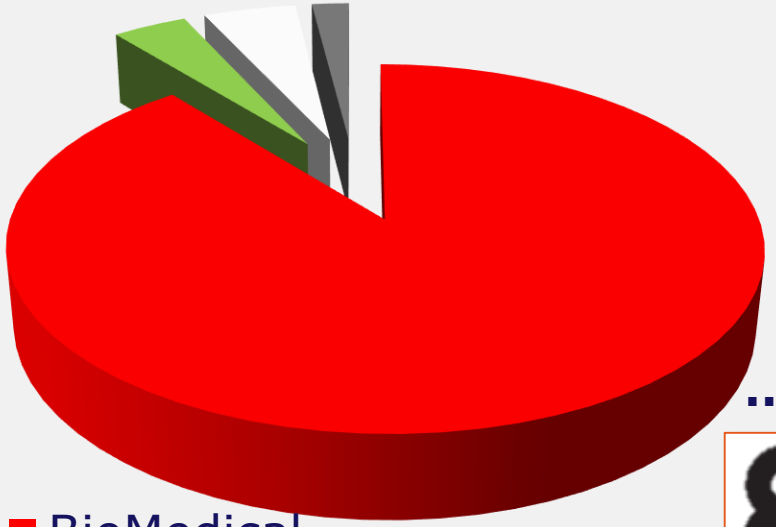
Generade CoE Genomics in perspective

Leiden BioScience Park



[91] BioMedical
[4] Agro/Food/Plant
[5] BioMarine
[2] Industrieel

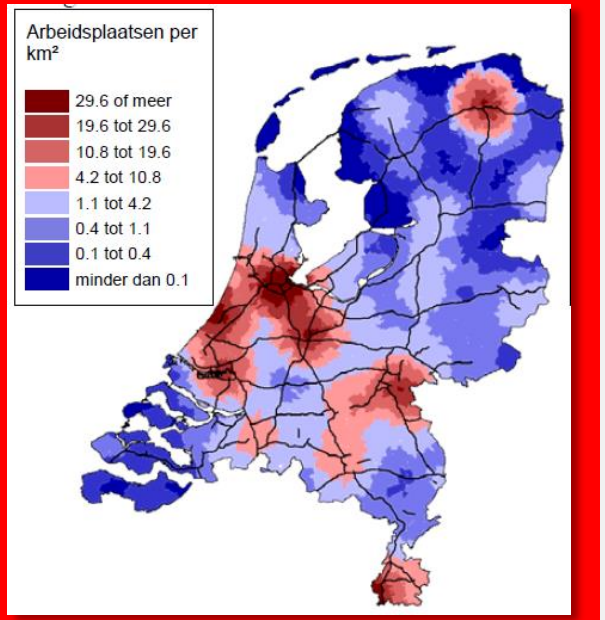
…and the surrounding region

Leiden – Rotterdam – Delft

Medical Delta

- 10 billion € revenue
- Over 300 life sciences companies
- 3 universities
- 4 universities of applied sciences
- 2 science parks
- Targeted molecular diagnostics, image & image guided therapies, interventions and care, vitality

Red life sciences /
Life Science and Health



Dutch Sports Research Agenda

- Themes
- Value of Sports
- **Performance**
- **More people, more active, more often**

Dutch National Research Agenda

- **Sports and healthy living – research questions**

- 072: How do we improve health and prevent disease through healthy lifestyle and behavior?

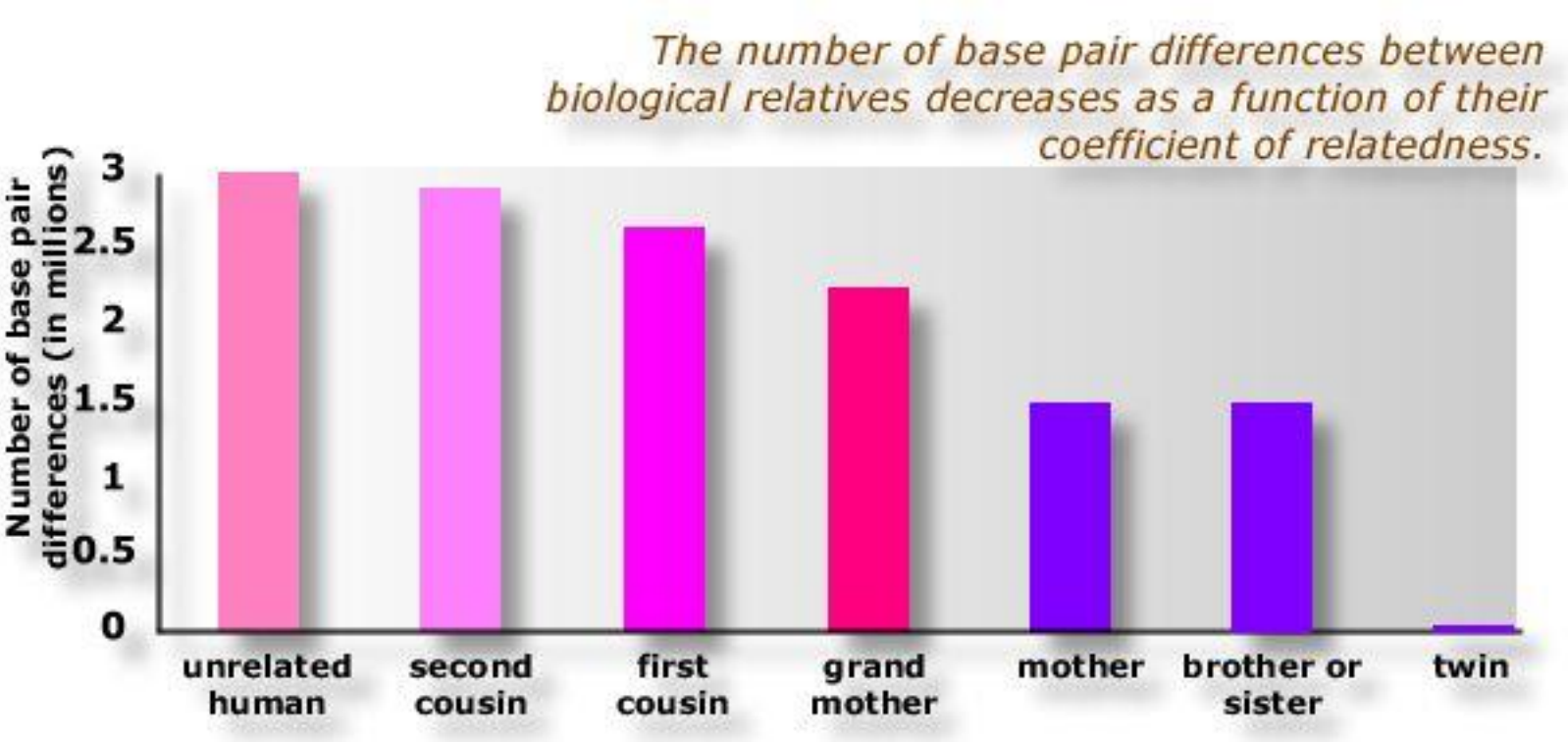
- 075: How can we improve health through sports, exercise and nutrition and which effects will result from this?

- 102: How can we develop new drugs and treatments to remain as vital and healthy as possible?

Current research questions and projects

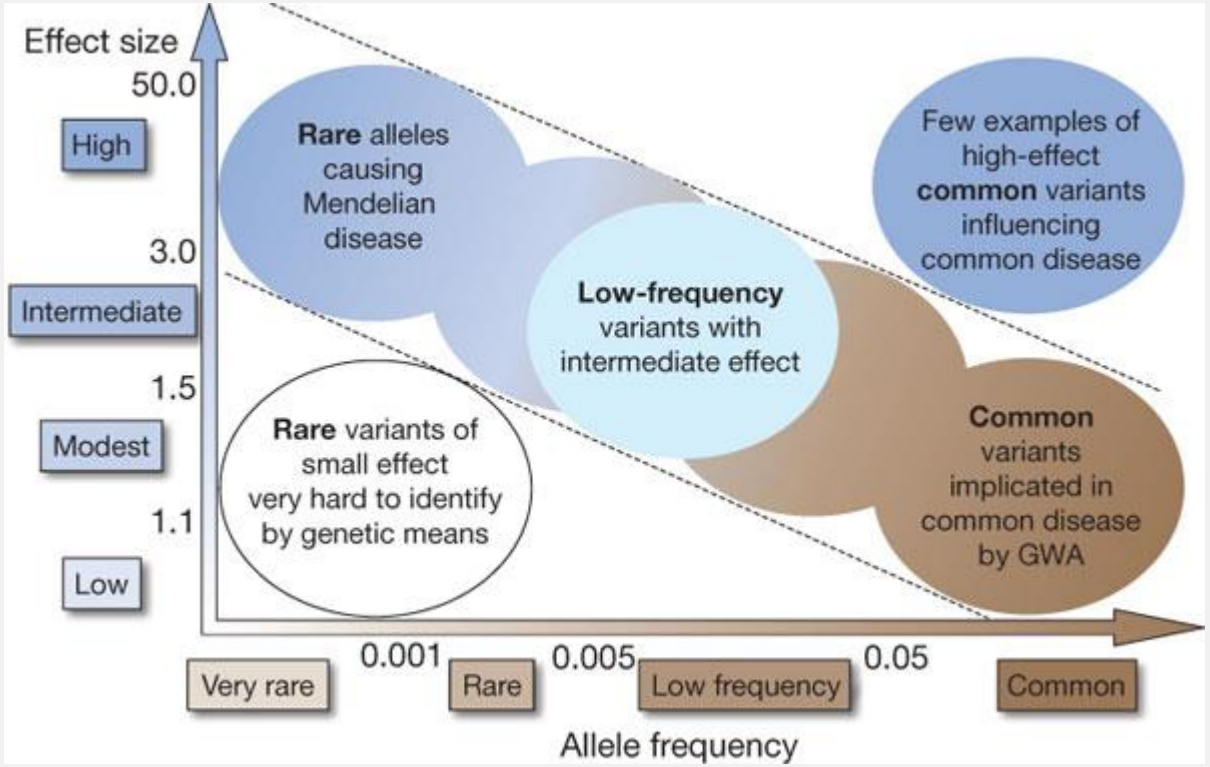
- How can we identify talent at an early age?
  - Genetic (DNA) profiles?
- How can we select the optimal personal training intensity?
- How to monitor recovery of top athletes, normal and revalidating individuals?
  - From better understanding to improving the processes of training and recovery
  - Gene expression (RNA) profiles?
  - Other profiles?

Much natural variation between individuals



Most variants shared between family members

Effect size/frequency also applies to sports



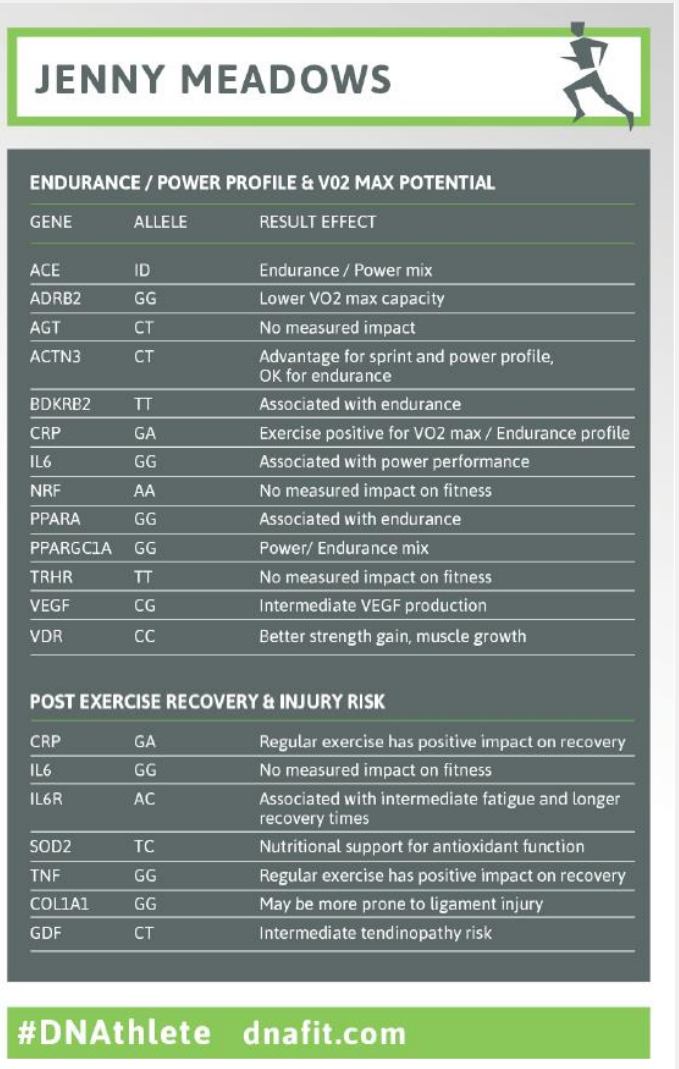
TA Manolio *et al. Nature* **461**, 747-753 (2009) doi:10.1038/nature08494

Most variants: small effects

Rare variants:
specific for family or individual

Variants causing
sub-clinical musculoskeletal disease?

DNA profile – Sports genes



bron: www.dnafit.com

Myostatin-related muscle hypertrophy
MSTN: LRG_200t1:c.373+5G>A

Genome-wide association studies (GWAS)
vs
Monogenic studies

OMIM Online Mendelian Inheritance in Man

GWAS CENTRAL

DNA profile – The new heel prick?

1000 US$

LABORATORY FOR MOLECULAR MEDICINE
65 Landsdowne St, Cambridge, MA 02139
Phone: (617) 768-8500 / Fax: (617) 768-8513
http://pcpgm.partners.org/lmm

PARTNERS HEALTHCARE | CENTER FOR PERSONALIZED GENETIC MEDICINE

A teaching affiliate of: HARVARD MEDICAL SCHOOL

*****EXAMPLE REPORT*****

Name: DOE, JOHN
DOB: 01/23/1900
Sex: Female
Race: Caucasian
Indication for testing: MedSeq, Primary Care
MRN: 0123456789
Specimen: Blood, Peripheral
Received: 05/03/2013
Accession ID: PMXX-12345
Family #: F1234657
Referring physician: Dr. Med Seq
Referring facility: Brigham and Women's
Test: WGS-pnlA, SeqConV2, WGS-GGR

GENOME REPORT

RESULT SUMMARY

Sequencing of this individual's genome was performed and covered 95.3% of all positions at 8X coverage or higher, resulting in over 5.2 million variants compared to a reference genome. These data were analyzed to identify previously reported variants of potential clinical relevance as well as novel variants that could reasonably be assumed to cause disease (see methodology below). All results are summarized on page 1 with further details on subsequent pages.

A. MONOGENIC DISEASE RISK: 0 VARIANTS IDENTIFIED

This test did NOT identify genetic variants that may be responsible for existing disease or the development of disease in this individual's lifetime.

B. CARRIER STATUS: 3 VARIANTS IDENTIFIED

This test identified carrier status for 3 autosomal recessive disorders.

Disease Inheritance	Gene Transcript	Zygosity Variant	Classification	Carrier Phenotype*
B1. Congenital myasthenic syndrome Autosomal recessive	RAPSN NM_005055.4	Heterozygous c.264C>A p.Asn88Lys	Pathogenic	None reported
B2. Cutis laxa, type IC Autosomal recessive	LTBP4 NM_003573.2	Heterozygous c.254delT p.Leu85ArgfsX15	Pathogenic	None reported
B3. Usher syndrome type II Autosomal recessive	USH2A NM_206933	Heterozygous c.609_610insC p.Gly204ArgfsX12	Pathogenic	None reported

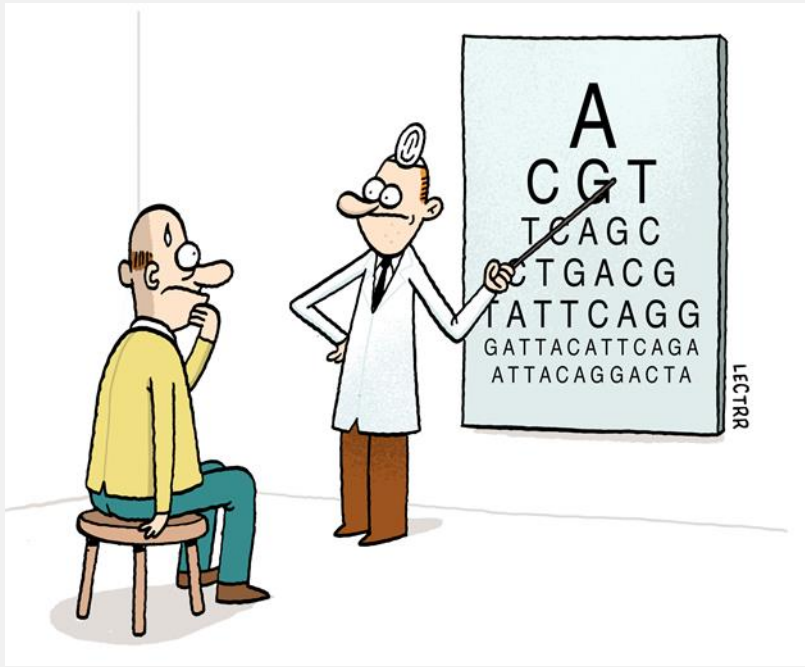
As a carrier for recessive genetic variants, this individual is at higher risk for having a child with one or more of these highly penetrant disorders. To determine the risk for this individual's future children to be affected, the partner of this individual would also need to be tested for variants in these genes. Other biologically related family members may also be carriers of these variants. *Carriers for some recessive disorders may be at risk for certain phenotypes. Please see variant descriptions for more information.

EDITORIAL

nature biotechnology

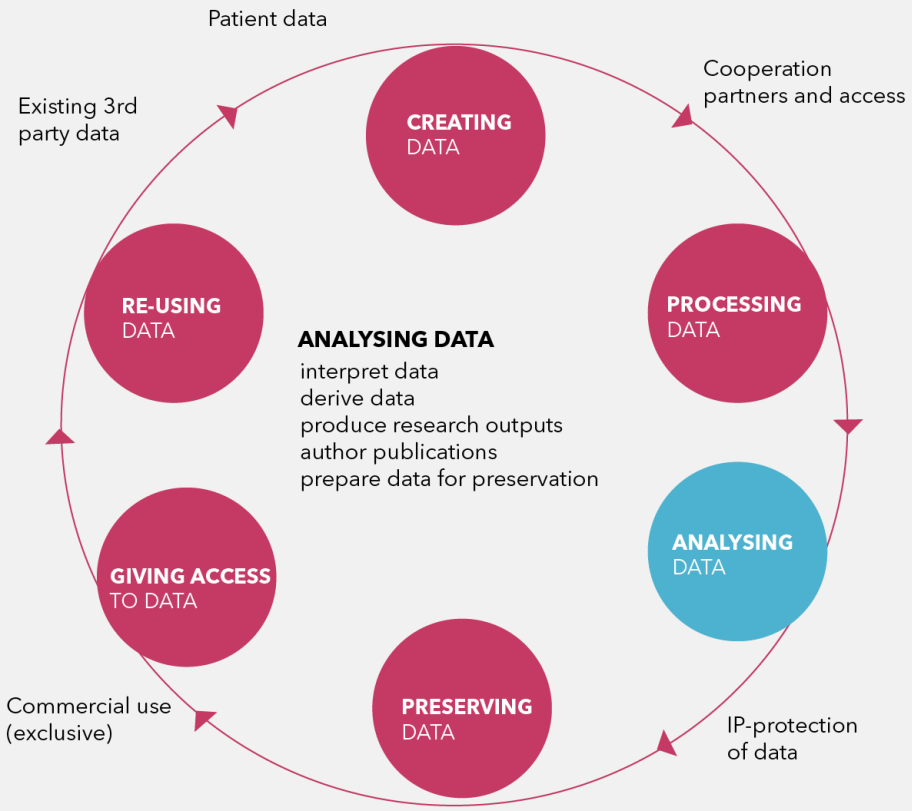
Knocking on the clinic door

High-throughput sequencing for clinical purposes faces technical and quality challenges, but it's worth it.



bron: DOI: 10.1159/000370102

Research data life cycle



http://data4lifesciences.nl/hands/handbook-for-adequate-natural-data-stewardship/

NETHERLANDS FEDERATION OF UMCs
DATA4LIFESCIENCES

FAIR data:

Findable: data uniquely and persistently identifiable.
Others should be able to find your data.

Accessible: conditions for use clear to machines and humans.

Interoperable: machine-readable data,
terminologies, vocabularies, or ontologies commonly used in the field;

Reusable: compliant with the above,
sufficiently well described with metadata and provenance information
supporting linking or integration with other data sources, enabling proper citation.

Where to find genetic variant information?

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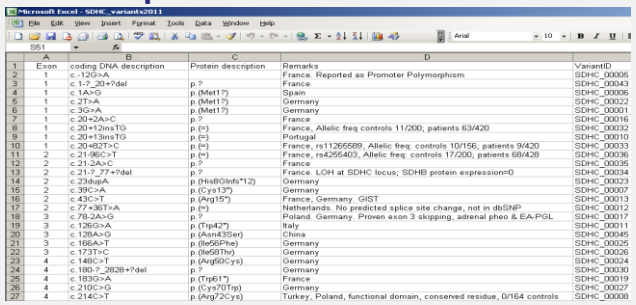
Efficient information retrieval

Private — Local — National — International

Gene and Disease Databases

PC
Spreadsheet



Intranet

Internet

LOVD
Leiden Open Variation Database

FAIR Data

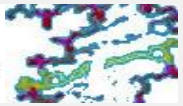
- National Databases

- Ethnic Databases

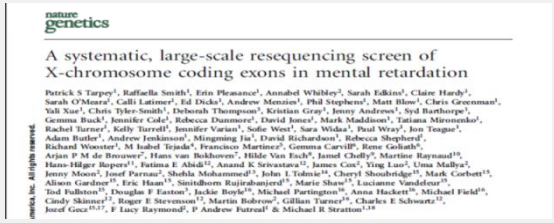
- General Databases

NCBI
ClinVar

dbSNP
Short Genetic Variations



Journals

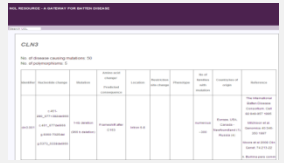


OMIM
Online Mendelian Inheritance in Man

COSMIC
Catalogue of somatic mutations in cancer

HGMD

Static Web Pages



Drawer

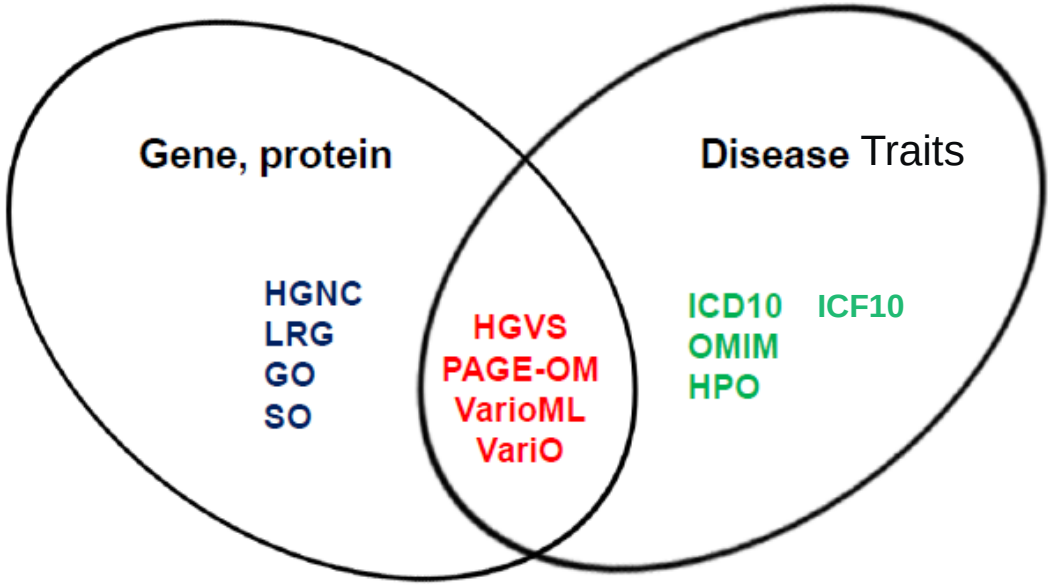
Accessibility

Genetic variant information sources

- Highly heterogeneous
- Vast amounts of data
- Limited data integration or standardization
- Limited search possibilities across databases
- Difficult to maintain or submit new data

NOT FAIR: Standardization necessary

Standardization



HUGO Gene Nomenclature Committee
Locus Reference Genomic
Gene Ontology
Sequence Ontology

International Classification of Diseases
Online Mendelian Inheritance in Man
Human Phenotype Ontology

Human Genome Variation Society Nomenclature
Phenotype and Genotype Experiment Object Model
VarioML
Variation Ontology

Human Variome Project
Recommended systems

http://www.hgvs.org/mutnomen

https://mutalyzer.nl/

http://www.lovd.nl/

Variant assessment and classification

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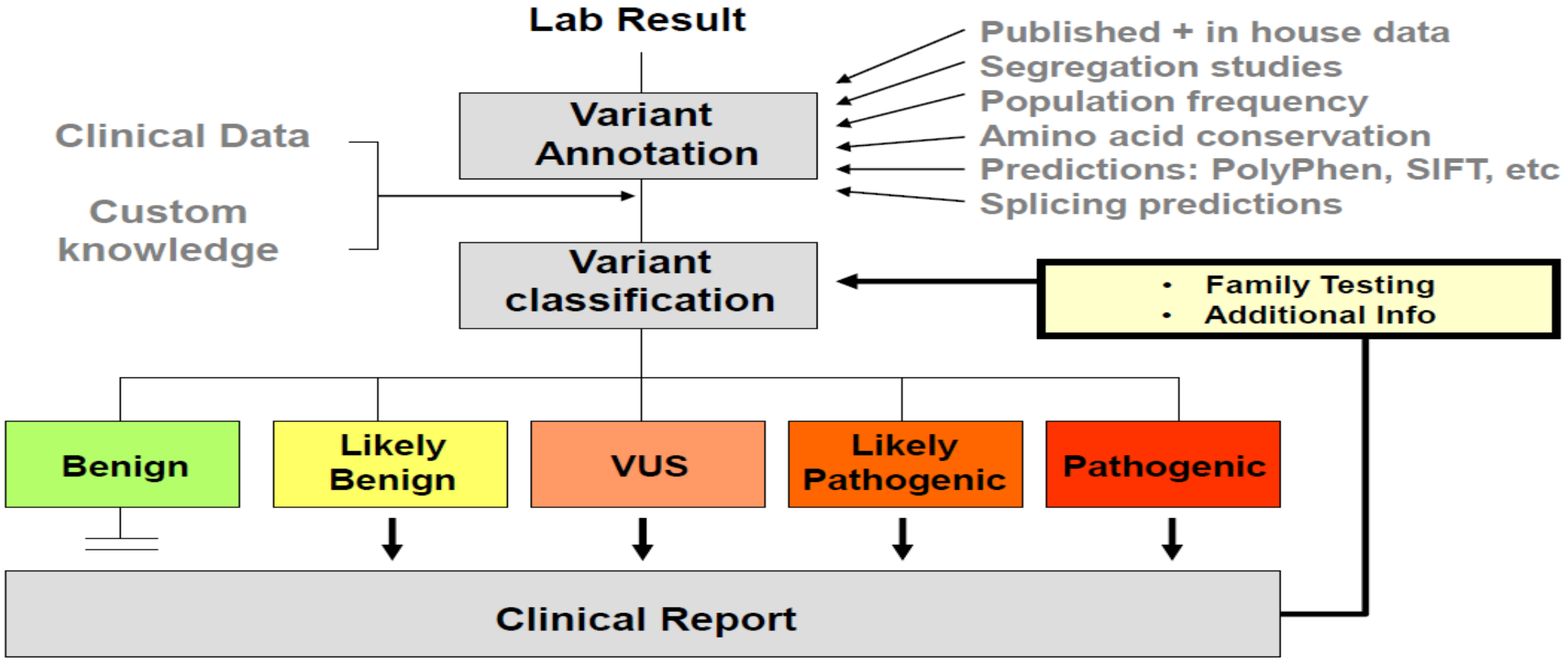

Courtesy of Birgit Funke

Mark variants by level of curation

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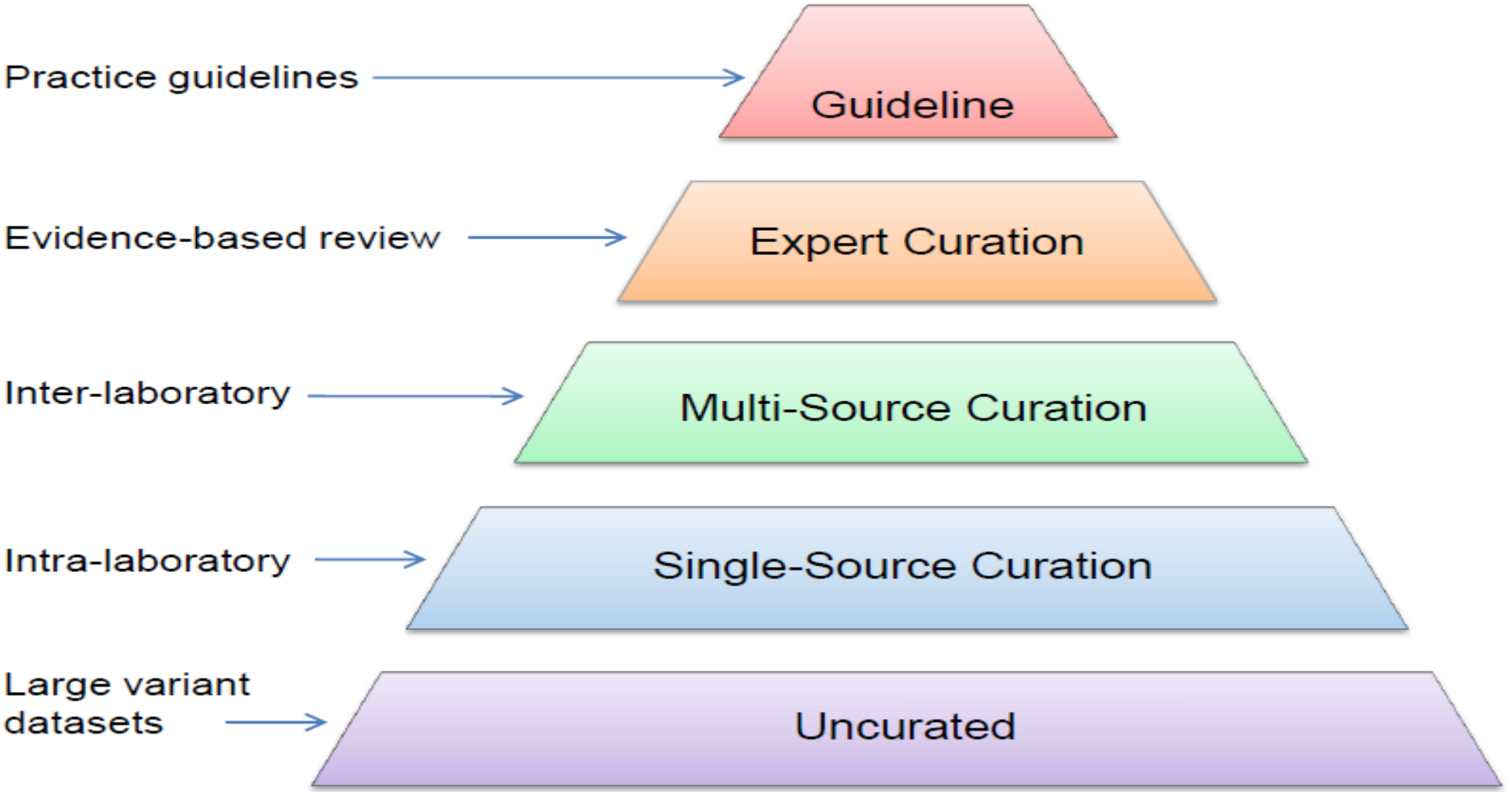


Matchmaker Exchange

Data sharing:

Genome/exome/variants:
Who has seen this variant
or phenotype?

Causative variant identification
Variant effect determination

Global Alliance
for Genomics & Health

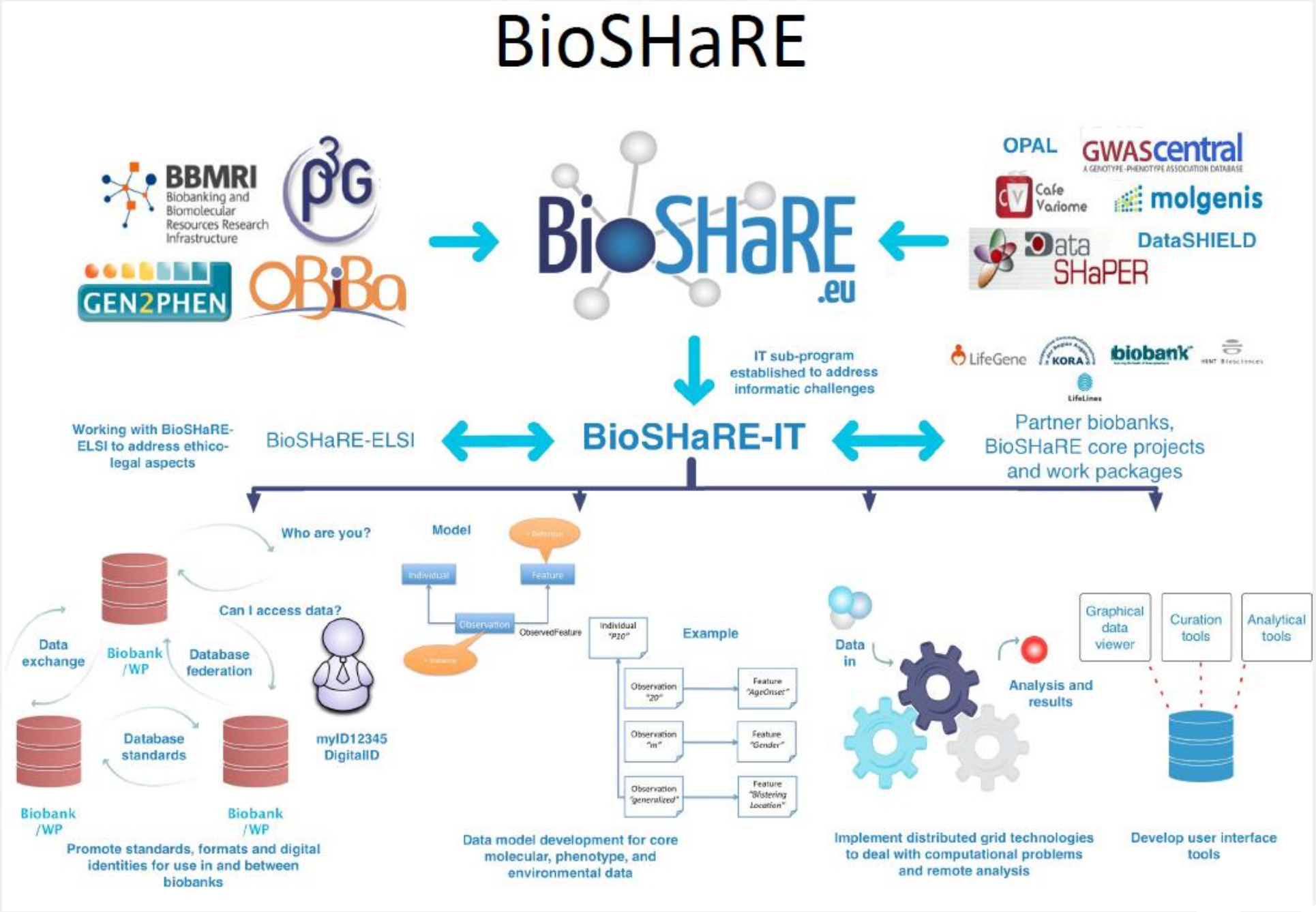
www.ga4gh.org

Beacons:

Advertise variant information

IRDiRC
INTERNATIONAL
RARE DISEASES RESEARCH
CONSORTIUM

BioSHaRE


BBMRI
Biobanking and Biomolecular Resources Research Infrastructure
GEN2PHEN
OBiBa
BioSHaRE .eu
OPAL
GWAScentral
Cafe Variome
molgenis
Data SHaPER
DataSHIELD
IT sub-program established to address informatic challenges
LifeGene
KORA
biobank
LifeLines
Working with BioSHaRE-ELSI to address ethico-legal aspects
BioSHaRE-ELSI
BioSHaRE-IT
Partner biobanks, BioSHaRE core projects and work packages
Who are you?
Can I access data?
Data exchange
Biobank /WP
Database federation
Database standards
myID12345 DigitalID
Biobank /WP
Biobank /WP
Promote standards, formats and digital identities for use in and between biobanks
Model
Individual
Feature
Observation
ObservedFeature
Example
Individual "P10"
Observation "20"
Feature "AgeOnset"
Observation "m"
Feature "Gender"
Observation "generalized"
Feature "Blistering Location"
Data model development for core molecular, phenotype, and environmental data
Data in
Analysis and results
Implement distributed grid technologies to deal with computational problems and remote analysis
Graphical data viewer
Curation tools
Analytical tools
Develop user interface tools

The promise of genomics for sports, health

- Better prediction of personal risk factors
- You in charge: optimise your lifestyle, nutrition, training to increase your performance and health

Gattaca, 1977

Star Trek Into Darkness, 2009

Your own genome in your hand

Genome sequence in an Illumina iPad app

Foto: Adam Jeffery CNBC

Apps and databases:

Efficient links to other databases?

Annotation by patients without privacy issues?

Suitable for DNA bank account?
Transfer/provide access to (anonymized) personal data

Different levels: health care and research

Genotype known: deep phenotyping needed

Generade - Personal Genomes Database

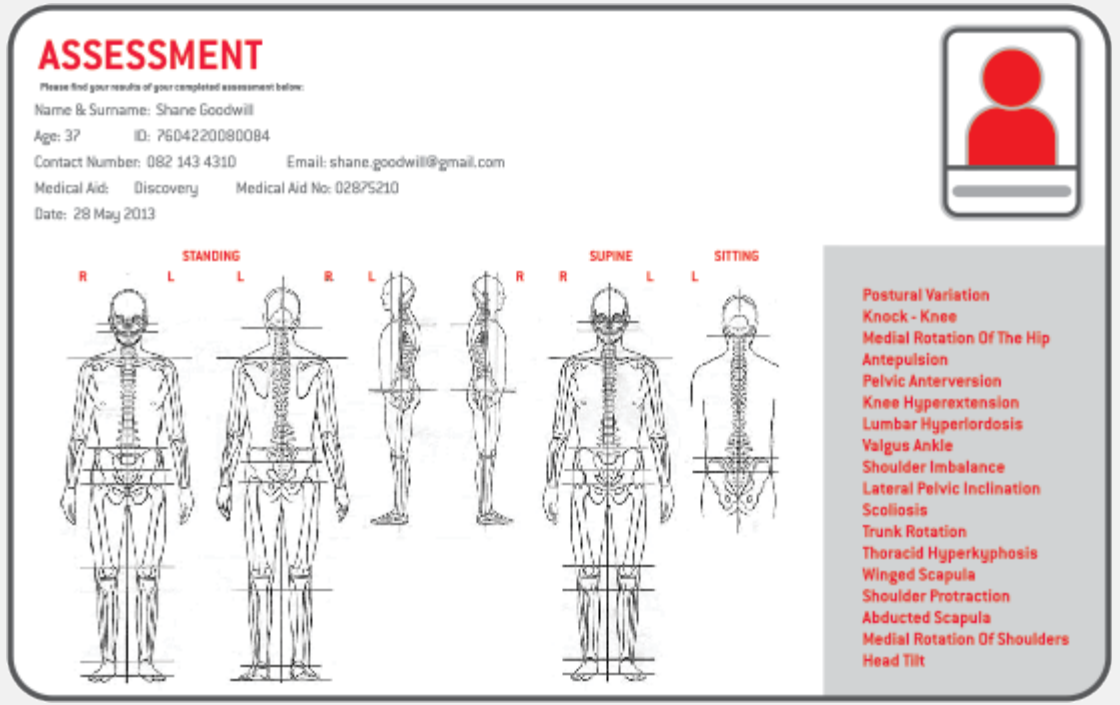
Genes | Transcripts | Variants | Individuals | Diseases | Screenings | Submit | Documentation

View all genes

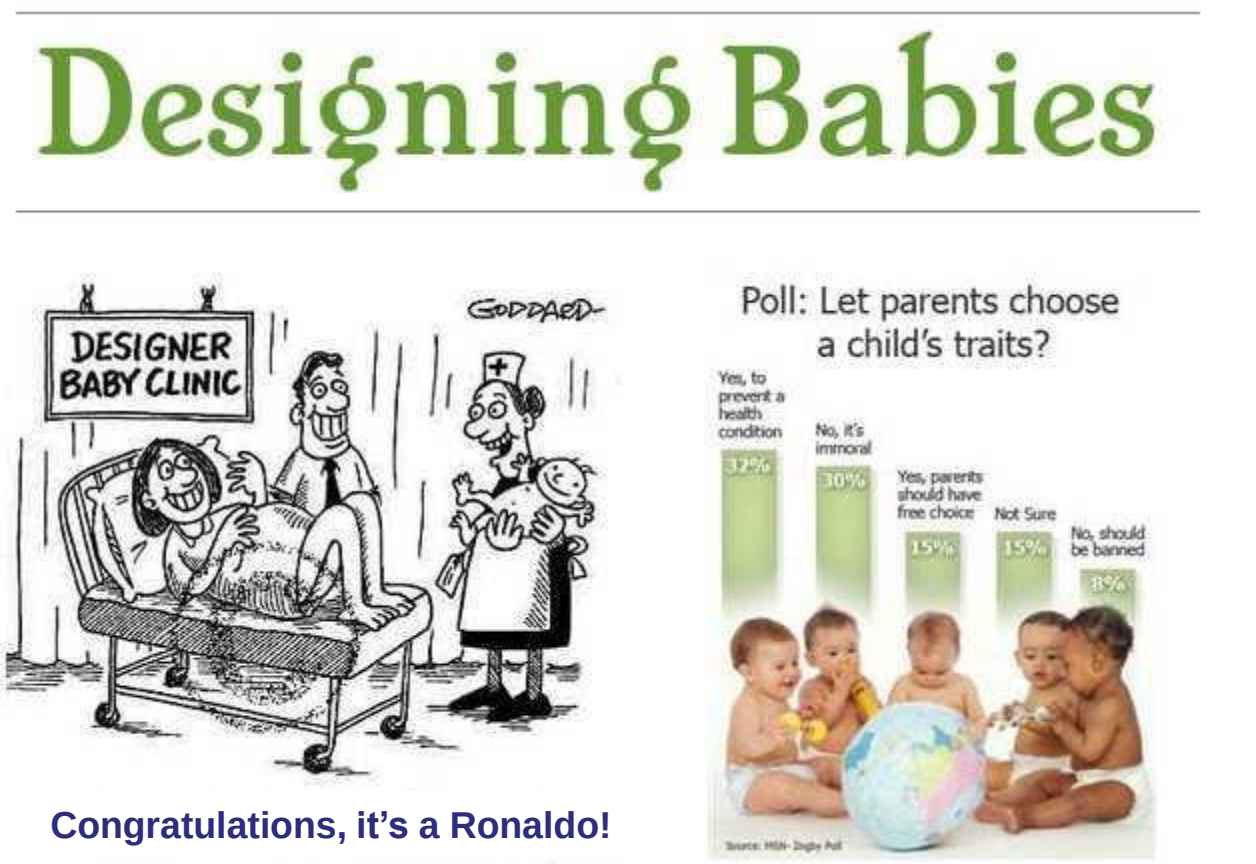
19810 entries on 199 pages. Showing entries 1 - 100.

100 per page | « First | ‹ Prev | 1 2 3 4 5 6 7 8 9 10 11 ... | Next › | Last »

Symbol	Gene	Chr	Band	Transcripts	Variants	Unique variants
A1BG	alpha-1-B glycoprotein	19	q13.43	1	13	13
A1CF	APOBEC1 complementation factor	10	q21.1	6	49	49
A2M	alpha-2-macroglobulin	12	p13.31	1	13	13
A2ML1	alpha-2-macroglobulin-like 1	12	p13	2	31	31
A3GALT2	alpha 1,3-galactosyltransferase 2	1	p35.1	1	9	9
A4GALT	alpha 1,4-galactosyltransferase	22	q13.2	6	96	96
A4GNT	alpha-1,4-N-acetylglucosaminyltransferase	3	p14.3	1	13	13
AAAS	achalasia, adrenocortical insufficiency, alacrimia	12	q13	2	15	15
AACS	acetoacetyl-CoA synthetase	12	q24.31	4	12	12
AADAC	arylacetamide deacetylase	3	q25.1	3	31	31
AADACL2	arylacetamide deacetylase-like 2	3	q25.1	1	17	17
AADACL3	arylacetamide deacetylase-like 3	1	p36.21	2	39	39
AADACL4	arylacetamide deacetylase-like 4	1	p36.21	1	1	1
AADAT	aminoadipate aminotransferase	4	q33	2	13	13
AAED1	AhpC/TSA antioxidant enzyme domain containing 1	9	q22.32	3	1	1
AAGAB	alpha- and gamma-adaptin binding protein	15	q22.33-q23	4	39	39
AAK1	AP2 associated kinase 1	2	p13.3	9	44	44
AAMDC	adipogenesis associated, Mth938 domain containing	11	q14.1	2	15	15
AAMP	angio-associated, migratory cell protein	2	q	1	14	14
AANAT	aralkylamine N-acetyltransferase	17	q25.1	2	27	27
AAR2	AAR2 splicing factor homolog (S. cerevisiae)	20	q11.23	3	13	13
AARD	alanine and arginine rich domain containing protein	8	q24.11	1	16	16
AARS	alanyl-tRNA synthetase	16	q22.1	1	5	5
AARS2	alanyl-tRNA synthetase 2, mitochondrial	6	p21.1	2	47	47
AARSD1	alanyl-tRNA synthetase domain containing 1	17	q21.31	1	19	19
AASDH	aminoadipate-semialdehyde dehydrogenase	4	q12	5	40	40
AASDHPPT	aminoadipate-semialdehyde dehydrogenase-phosphopantetheinyl transferase	11	q22	1	12	12
AASS	aminoadipate-semialdehyde synthase	7	q31.3	1	9	9
AATF	apoptosis antagonizing transcription factor	17	q12	1	9	9
AATK	apoptosis-associated tyrosine kinase	17	q25.3	13	31	31
ABAT	4-aminobutyrate aminotransferase	16	p13.2	4	199	199
ABCA1	ATP-binding cassette, sub-family A (ABC1), member 1	9	q31	1	92	92
ABCA10	ATP-binding cassette, sub-family A (ABC1), member 10	17	q24	2	44	44
ABCA12	ATP-binding cassette, sub-family A (ABC1), member 12	2	q34	2	27	27
ABCA13	ATP-binding cassette, sub-family A (ABC1), member 13	7	p12.3	1	37	37
ABCA2	ATP-binding cassette, sub-family A (ABC1), member 2	9	q34	2	26	26
ABCA3	ATP-binding cassette, sub-family A (ABC1), member 3	16	p13.3	1	21	21
ABCA4	ATP-binding cassette, sub-family A (ABC1), member 4	1	p22	1	16	16



How to increase performance?



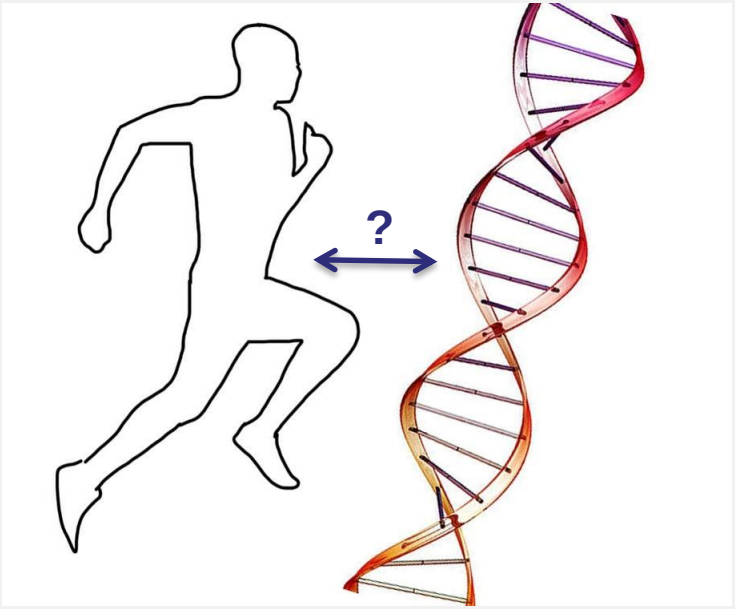
Congratulations, it's a Ronaldo!

Guido de Wert, medical ethicist Maastricht UMC:
'Research shows that people are not at all obsessed getting perfect children.
Medical science enables us to prevent severe suffering.'

Challenges

- Data management
- Implementation of innovation by the sports community
- Multidisciplinary research

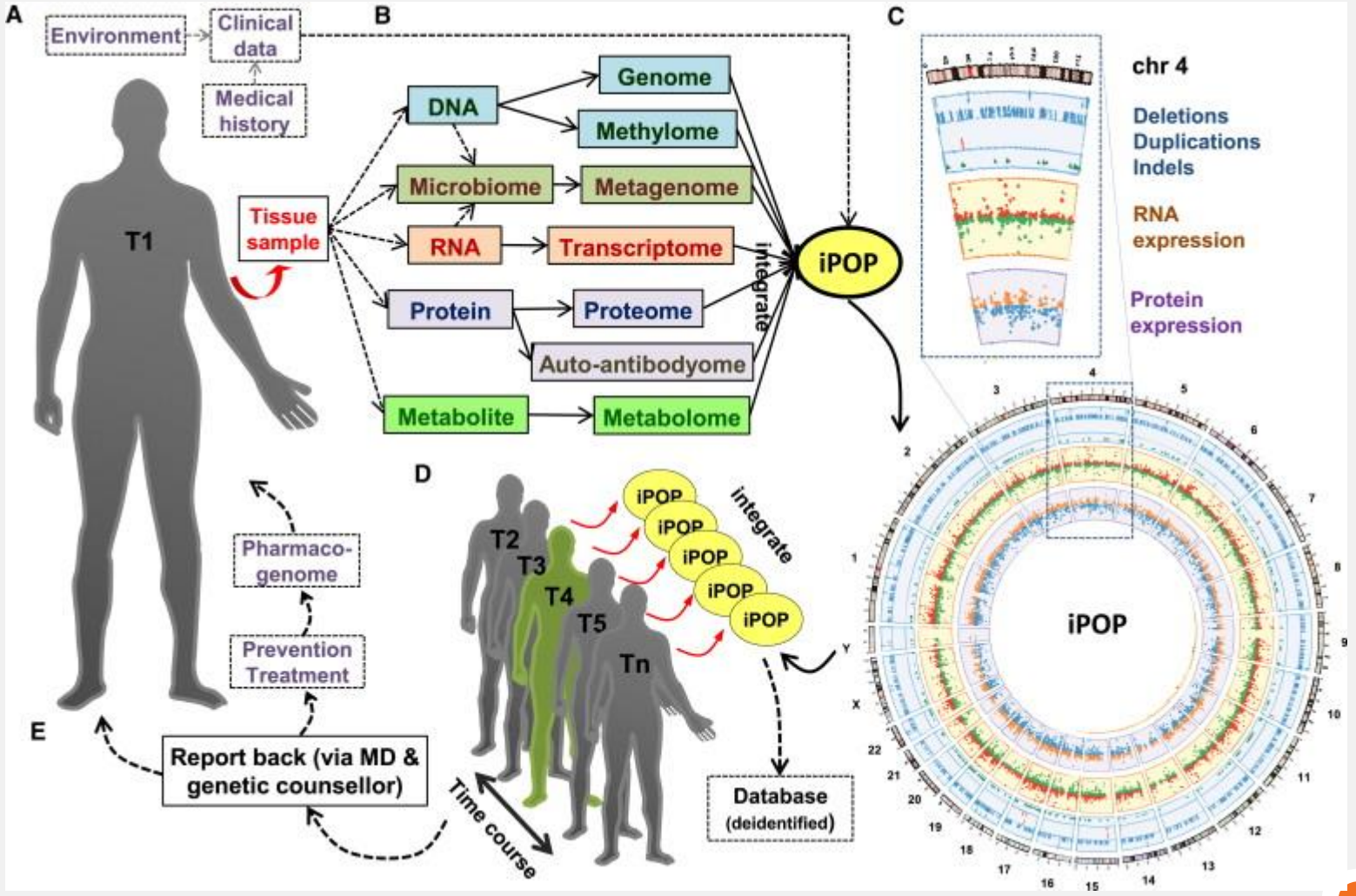
- More knowledge required:
- Genetic basis of sports talent (nature):
  - Variants with small effect size
  - Structural variation
  - Variants in regulatory sequences



Phenotype vs DNA-profile (genotype)

- Influence of and adaptation to environmental factors: lifestyle, training, etc (nurture)

The future: Integrated Personal Omics Profiling



Monitoring:
- at different levels
- longitudinal studies

- preferably on location

RNA-profiling device?

In combination with traditional sports performance data, apps, wearables

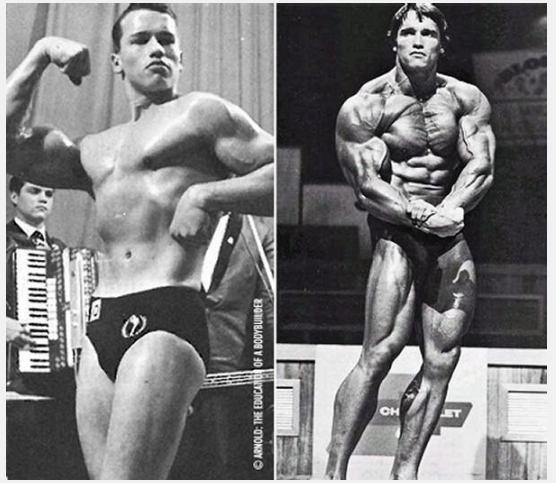
J Chem Biol 20:660-666 (2013)

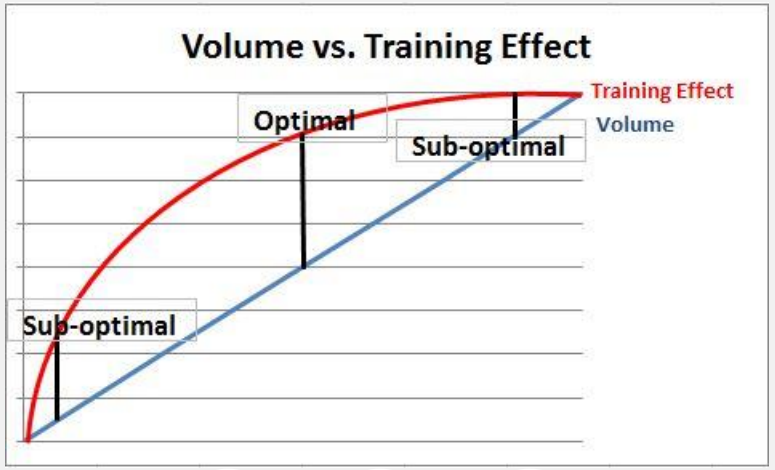
Monitoring of training effects using RNA-profiles

- How to determine the optimal training intensity?

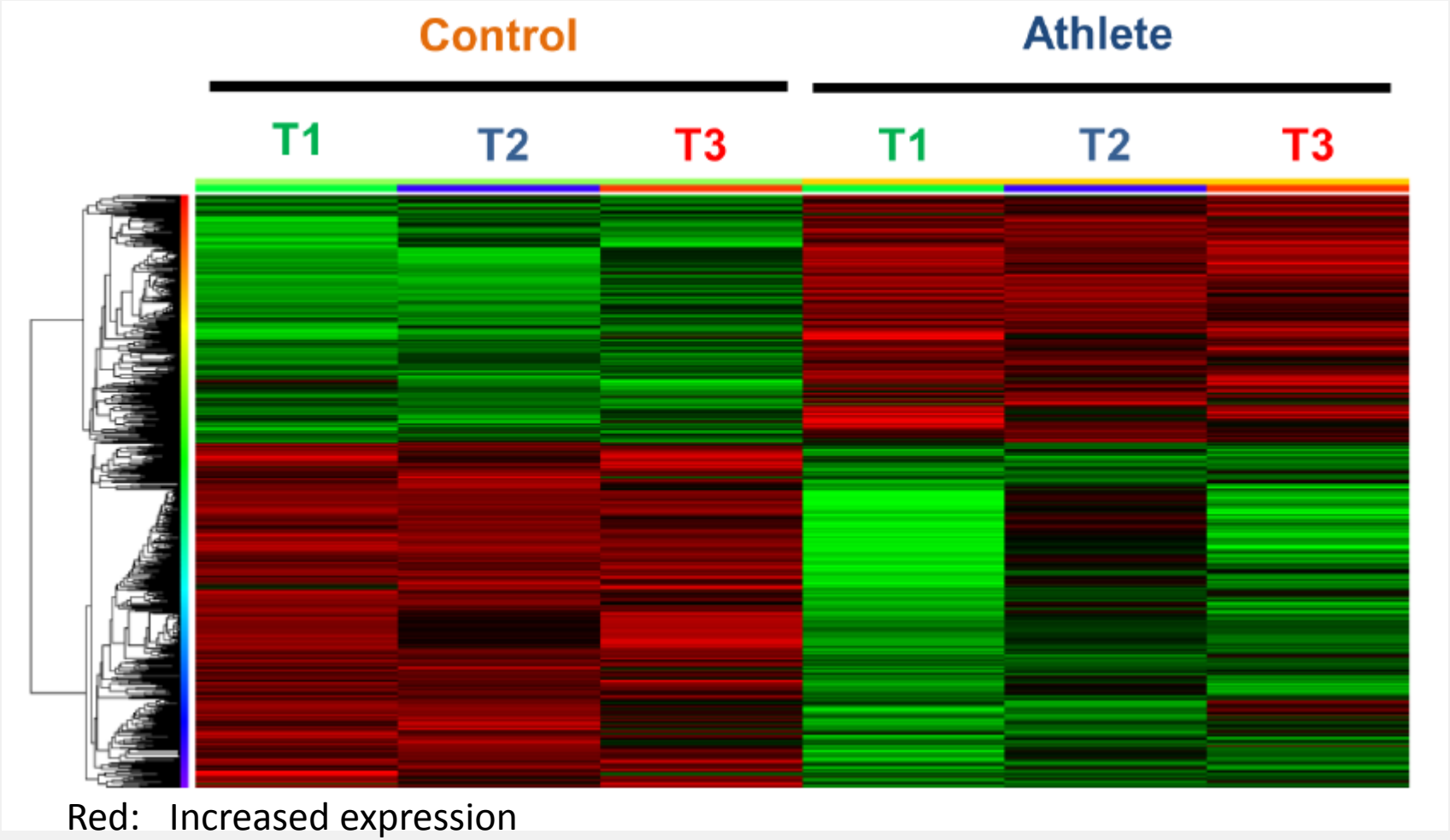
- Concept:
  - Individuals respond differently to training
  - Training induces stress, changes gene expression
  - Personal RNA-profiles in time (RNA-seq)
  - RNA-profile changes as indicators

- Execution: Blood samples taken at different time points
  - In rest (No intense activity in last 48 hours)
  - Directly after exercise
  - After 48-72 hour recovery





Significant gene expression differences



T1: Before exercise
T2: After exercise
T3: After recovery

Repeat measurement after 3-monthly training periods

Red: Increased expression
Green: Decreased expression

PLoS ONE 9: e92031. doi:10.1371/journal.pone.0092031

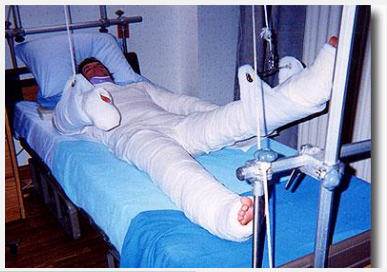
Collaboration with interesting partners?

Human sarcopenia studies
UAS HAN & University Maastricht, NL

Mouse models for sarcopenia +
Accelerator mass spectrometry
TNO Metabolic Health Research, Leiden, NL

Risk factors:

- malnutrition
- aging
- immobilization
- COPD
- chemotherapy
- others



Human intervention + ergometer studies
UAS Utrecht & Wageningen University, NL

food supplements

medical nutrition pharma

International data sharing projects

- BRCA challenge (www.variome.org/brca-challenge.html)
- Globin 2020 (www.variome.org/gg2020/index.html)
- Aims:
  - Collecting all variants involved in breast cancer and hemoglobinopathies
  - Co-developing infrastructure and capacity in participating countries

Thanks!

Questions?

taschner@generade.nl