History in Genetics
From Watson & Cricks to NGS
What it meant for the patients and their families

Ségolène Ayme
Brain and Spine Institute, Paris
Segolene.ayme@icm-institute.org

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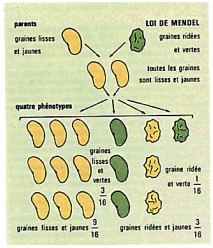
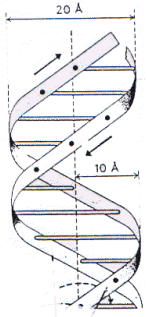
History in Genetics

Slide by courtesy of Prof. Gael Nicolas

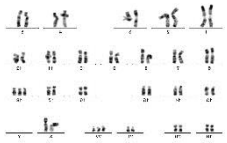
1865
Mendel's laws



1953
Structure Of ADN
Watson Crick

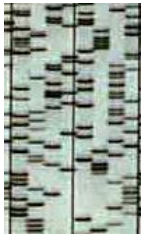


1959
Trisomy 21
Gauthier
Lejeune
Turpin

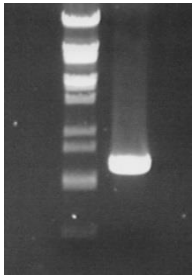


1975
Southern

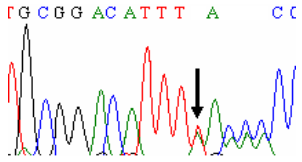
Sanger sequencing



1985
PCR
(Mullis)



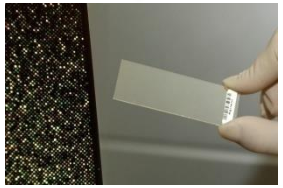
1993
Automated ADN Sequencers

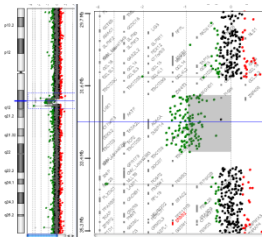


2004
Human Genome sequenced

2007
Pangenomic Analyses

2009
NGS





1865 – 1975
Premolecular Era

1975 – 2004
Molecular Era

2004-
Genomics Era

History of Medical Genetics

- **1960: The pioneering era**
  - A few centers offering clinical diagnostic, genetic counselling + cytogenetics and biochemistry
- **1975: Development of prenatal diagnosis**
- **1980: Zoom on clinical diagnosis**
  - Dysmorphology clinics + computerized systems to retrieve diagnosis
- **1990: Estalishment of the medical specialty**
  - Genetic clinics in most public hospitals
  - Molecular testing
  - Less interest for the clinical aspect
  - Autonomisation of oncogenetics
- **2000: Intégration of genetics in all medical specialties**
  - Genetic diseases became rare diseases
  - Lost interest for the familial dimension of genetic diseases
- **2012: Total confusion between research and services**

History of the Relationship between Genetics and Medicine

- Article by Peter Harper, European Journal of Human Genetics (2017),1–18
- In Europe, after 1945, the field has been strongly influenced by the characters and interests of the relatively small number of founding workers in different European countries, as well as by wider social, medical and scientific factors in the individual countries.
- 100 recorded interviews of Pioneers at https://genmedhist.eshg.org/interviews/recorded-interviews/

- The founders of the field promoted the specialty as a whole, not just their own interests, with a strong tradition of mutual help, especially in medical genetics services
- The field has also shown a strong talent for opportunism where funding is concerned !

50 years of History of Human Genetics in Europe

- 1967: First European meeting of Human Geneticists in Denmark, then annual meetings
- 1988: European School of Human Genetics in Italy in collaboration with Victor McKusick (OMIM) (90 students/year)
- 1990: First election of board members of the European Society of Human Genetics ESHG (Corfou)
- 1998: Establishment of the Public and Professional Policy Committee of the ESHG
- 2001: Establishment of the International Federation of Human Genetics Societies
- 2004: First joint meeting with EMPAG (Psycho-social aspects of genetics)
- 2005: EuroGenTest for Quality issues

Public and Professional Policy at ESHG

- Genetic technology was accompanied by an increasing concern about the use and misuse of genetic information in society

- Feeling that the duty of professionals was
  - to anticipate the potential applications of their discoveries
  - to transfer their knowledge as fast as possible where a benefit could be expected for the community
  - to provide guidelines and recommendations to help the less experienced professionals minimise misuse and misinterpretations

Public and Professional Policy at ESHG 1998- 2007

- It was not possible to issue sound opinions or recommendations in such a complex and controversial field, without enough resources to organise a wide consultation of the community and prepare well-documented reports
- An EC grant was requested for:
- Genetic screening: technical and ethical issues, including commercialisation of genetic tests
- Genetic testing, insurance and employment: technical, social and ethical issues
- Guidelines for the provision of genetic services in Europe
- Data storage and DNA banking: quality issues, confidentiality, informed consent

Public and Professional Policy at ESHG 2007- 2018

- 2008: Patenting and licensing in genetic testing
- 2009: Whole-genome sequencing in health care
- 2013: Whole-genome sequencing in health care
- 2015: Human germline gene editing
- 2015: Towards a European consensus for reporting incidental findings during clinical NGS testing
- 2015 Current issues in medically assisted reproduction and genetics in Europe: research, clinical practice, ethics, legal issues and policy
- 2018: Human germline gene editing

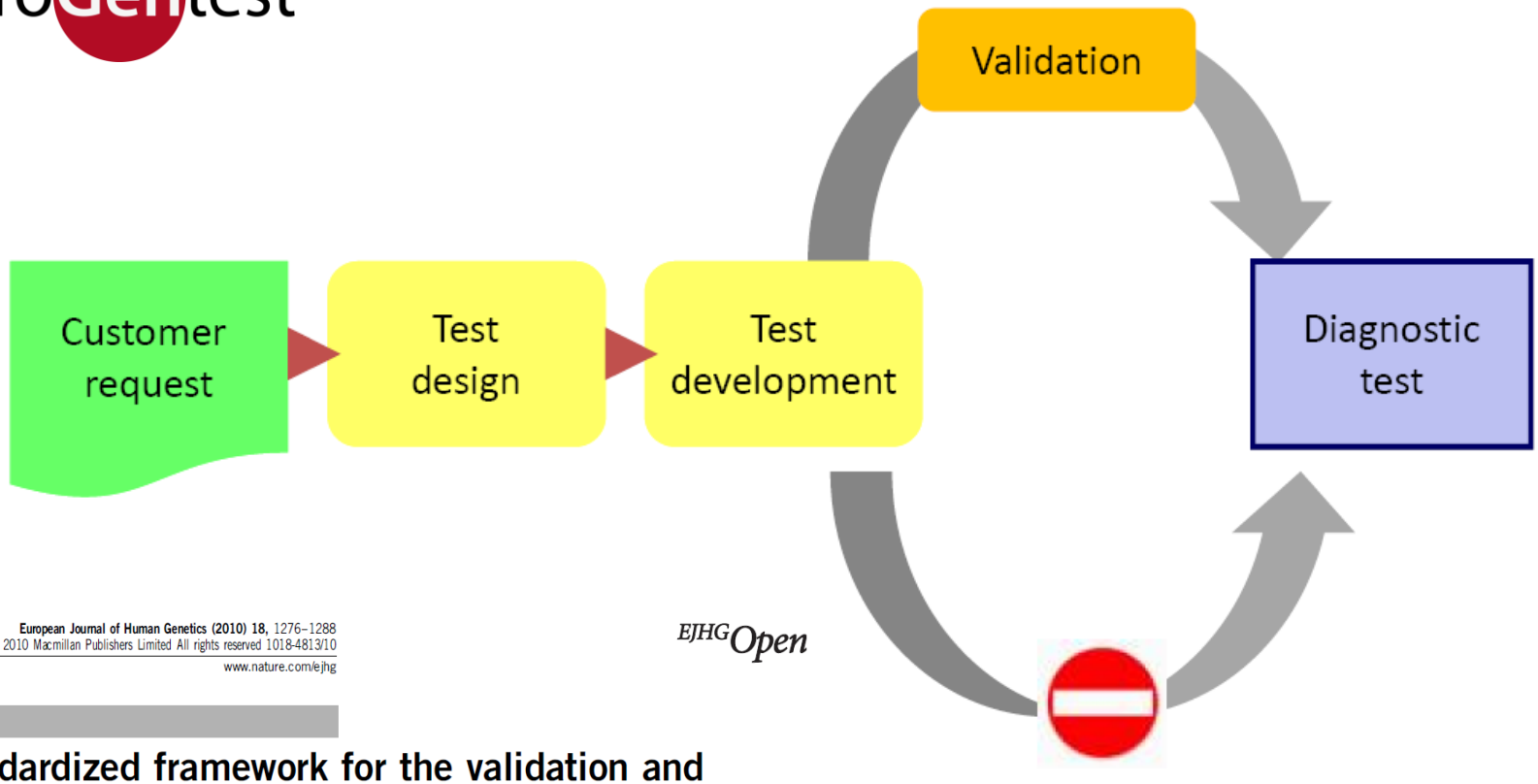
EuroGenTest
2005 - 2011

- Goal: Test development, harmonisation, validation and standardisation of services
- Tools: Resources, guidelines, procedures
- Means: network of lab experts, researchers, SMEs, Ethicists, Public health experts, sociologists, educational authorities and consumers
- Eurogentest.org

EuroGenTest Output 2005 - 2011

- Establishment of External Quality Assessment for molecular, cytogenetic, and biochemical tests
- Training sessions on EQA
- Information with Orphanet on quality of labs
- Criteria for quality of genetic counseling
- Gene cards on clinical utility of tests
- 15 leaflets for patients on aspects of genetics
- Core competencies in genetics for health professionals
- Network of European genetic counsellors

EuroGentest



European Journal of Human Genetics (2010) 18, 1276–1288

www.nature.com/ejhg

EJHG Open

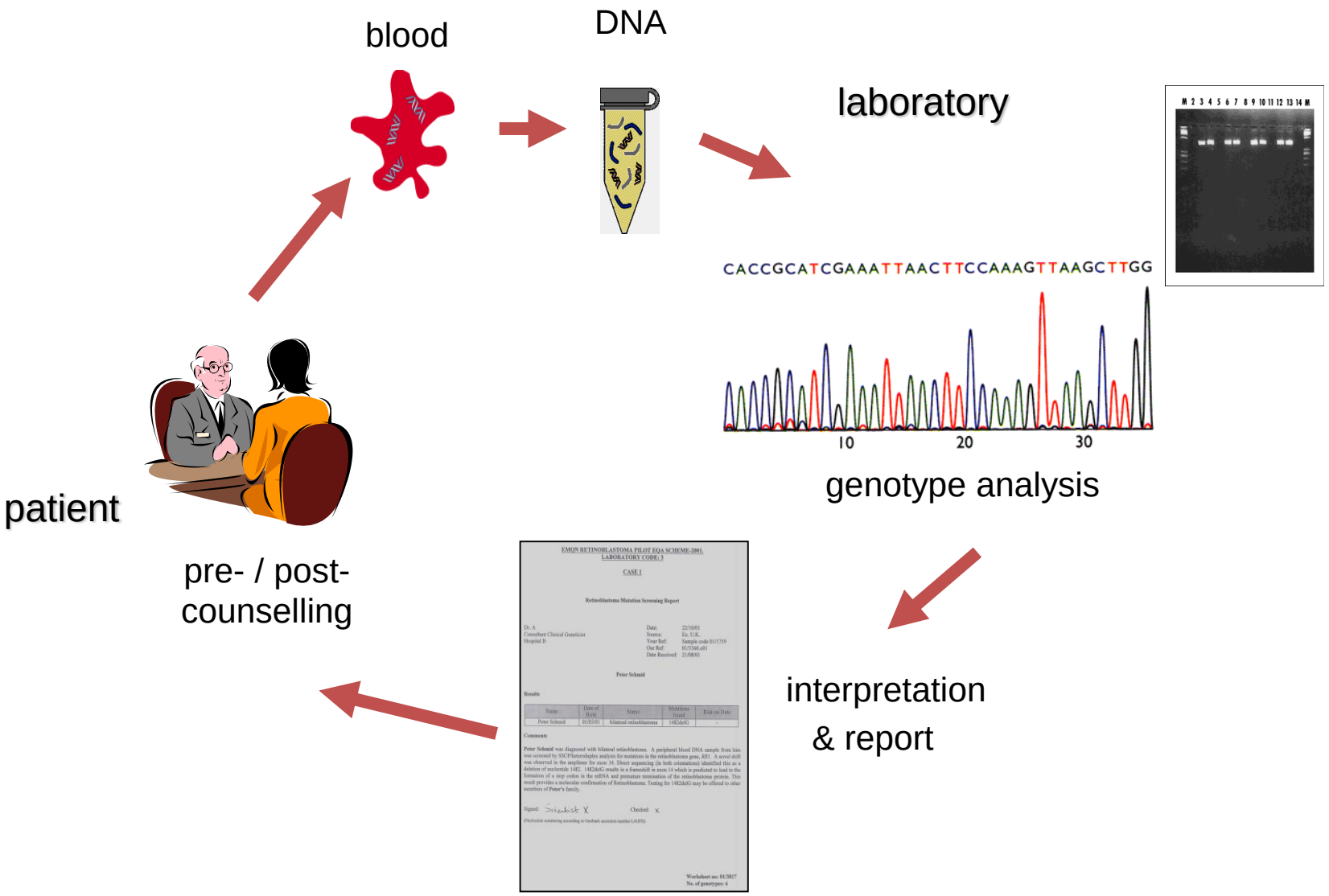
ARTICLE

A standardized framework for the validation and verification of clinical molecular genetic tests

Christopher J Mattocks*[,1,7], Michael A Morris[2,7], Gert Matthijs[3,7], Elfriede Swinnen[3], Anniek Corveleyn[3], Els Dequeker[3], Clemens R Müller[4], Victoria Pratt[5] and Andrew Wallace[6], for the EuroGentest Validation Group[8]

The validation and verification of laboratory methods and procedures before their use in clinical testing is essential for providing a safe and useful service to clinicians and patients. This paper outlines the principles of validation and verification in the context of clinical human molecular genetic testing. We describe implementation processes, types of tests and their key validation components, and suggest some relevant statistical approaches that can be used by individual laboratories to ensure that tests are conducted to defined standards.
European Journal of Human Genetics (2010) **18**, 1276–1288; doi:10.1038/ejhg.2010.101; published online 28 July 2010

Assessing Quality Genetic Testing Service

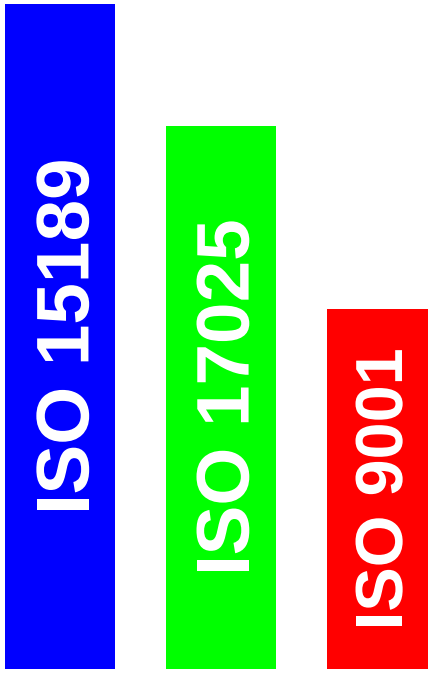


Slide by courtesy of Prof. Els Dequeker
University of Leuven

ISO 9001: 2000
Quality Management Systems
Requirements

ISO/IEC 17025:2005
General requirements for the competence
of testing and calibration of laboratories

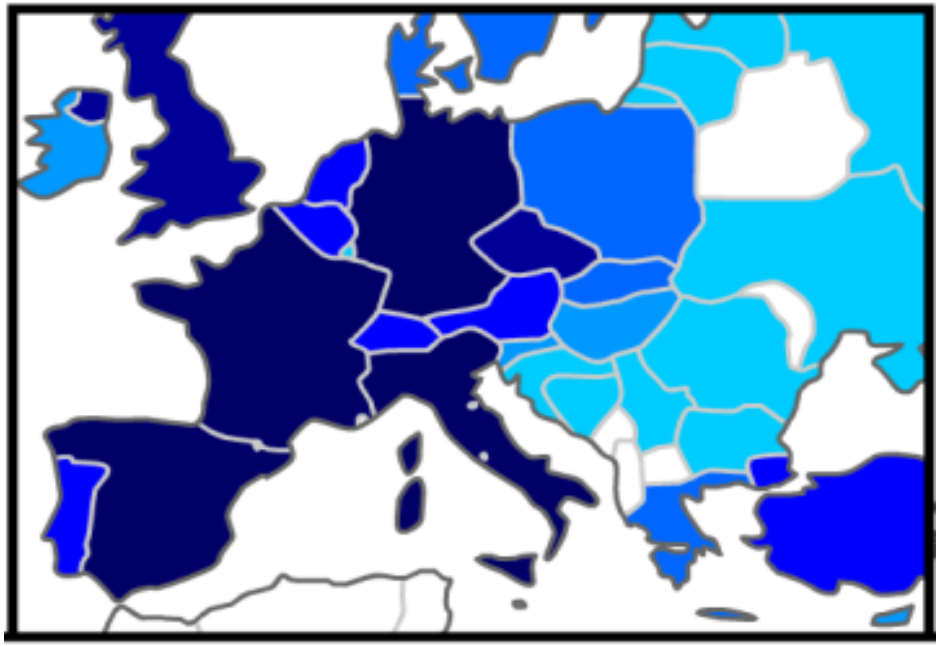
ISO 15189:2007
Medical laboratories, particular requirements
for quality and competence



Slide by courtesy of Prof. Els Dequeker
University of Leuven

External Quality Assessment (EQA)

- Assess the interpretation and the quality of the report
- Offer training sessions
- Define good practice
- ISO



CEQA Cytogenetic European Quality Assessment

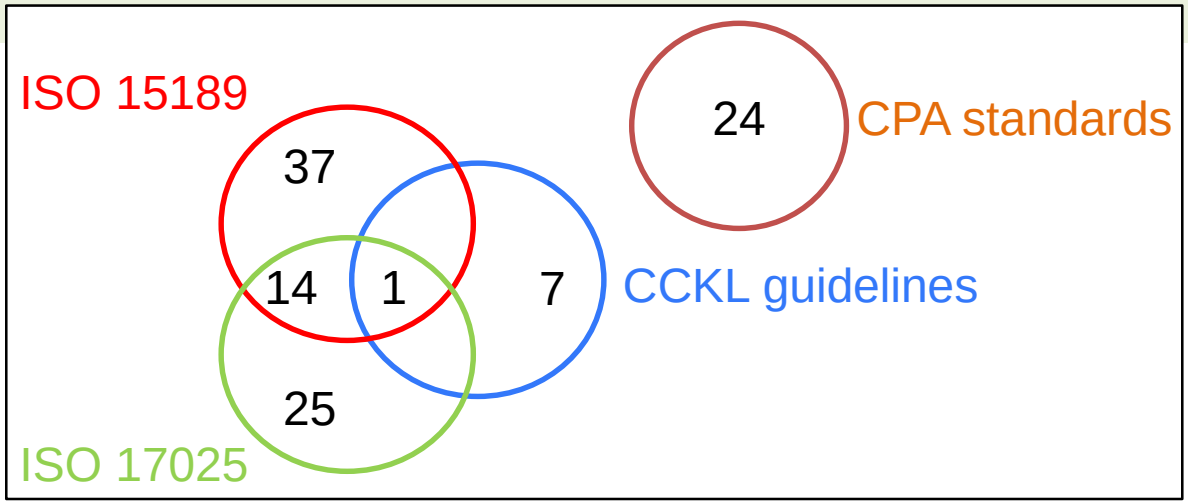
ERNDIM QUALITY ASSURANCE IN LABORATORY TESTING FOR IEM

EMQN The European Molecular Genetics Quality Network

CF network

Quality Assurance of genetic services

- 107 laboratories are accredited for at least some part of their diagnostics activities:



- 432 laboratories participated in at least one External Quality Assessment scheme during the last 5 years through 46 different EQA organizations

: 198 participating laboratories

: 155 participating laboratories

SPECIAL ARTICLE

Human Mutation

OFFICIAL JOURNAL HGVS HUMAN GENOME VARIATION SOCIETY www.hgvs.org

PERSPECTIVES

Next-Generation Sequencing Demands Next-Generation Phenotyping

Raoul C.M. Hennekam[1]* and Leslie G. Biesecker[2]

[1]Department of Pediatrics and Translational Genetics, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands;
[2]Genetic Disease Research Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland

APPLICATIONS OF NEXT-GENERATION SEQUENCING — VIEWPOINT

Next-generation sequencing in the clinic: are we ready?

Leslie G. Biesecker, Wylie Burke, Isaac Kohane, Sharon E. Plon and

Abstract | We are entering an era in which the cost of clinical whol targeted sequencing tests is no longer prohibitive to their applica

Next-Generation DNA Sequencing, Regulation, and the Limits of Paternalism

The Next Challenge

James P. Evans, MD, PhD
Jonathan S. Berg, MD, PhD

Another emerging application of next-generation sequencing in public health is preconception screening in which prospective parents ascertain their carrier status for

Assuring the quality of next-generation sequencing in clinical laboratory practice

To the Editor:

We direct your readers' attention to the principles and guidelines (**Supplementary Guidelines**) developed by the Next-generation Sequencing: Standardization of Clinical Testing (Nex-StoCT) workgroup. These guidelines represent initial steps to ensure that results from tests based on next-

The workgroup recommendations are summarized in **Table 1**. Although the workgroup focused on detection of DNA sequence variations associated with heritable human disorders, many of the principles and recommendations described are also relevant to the application of NGS to other areas of laboratory medicine,

treatment of cancer and infectious-disease testing.

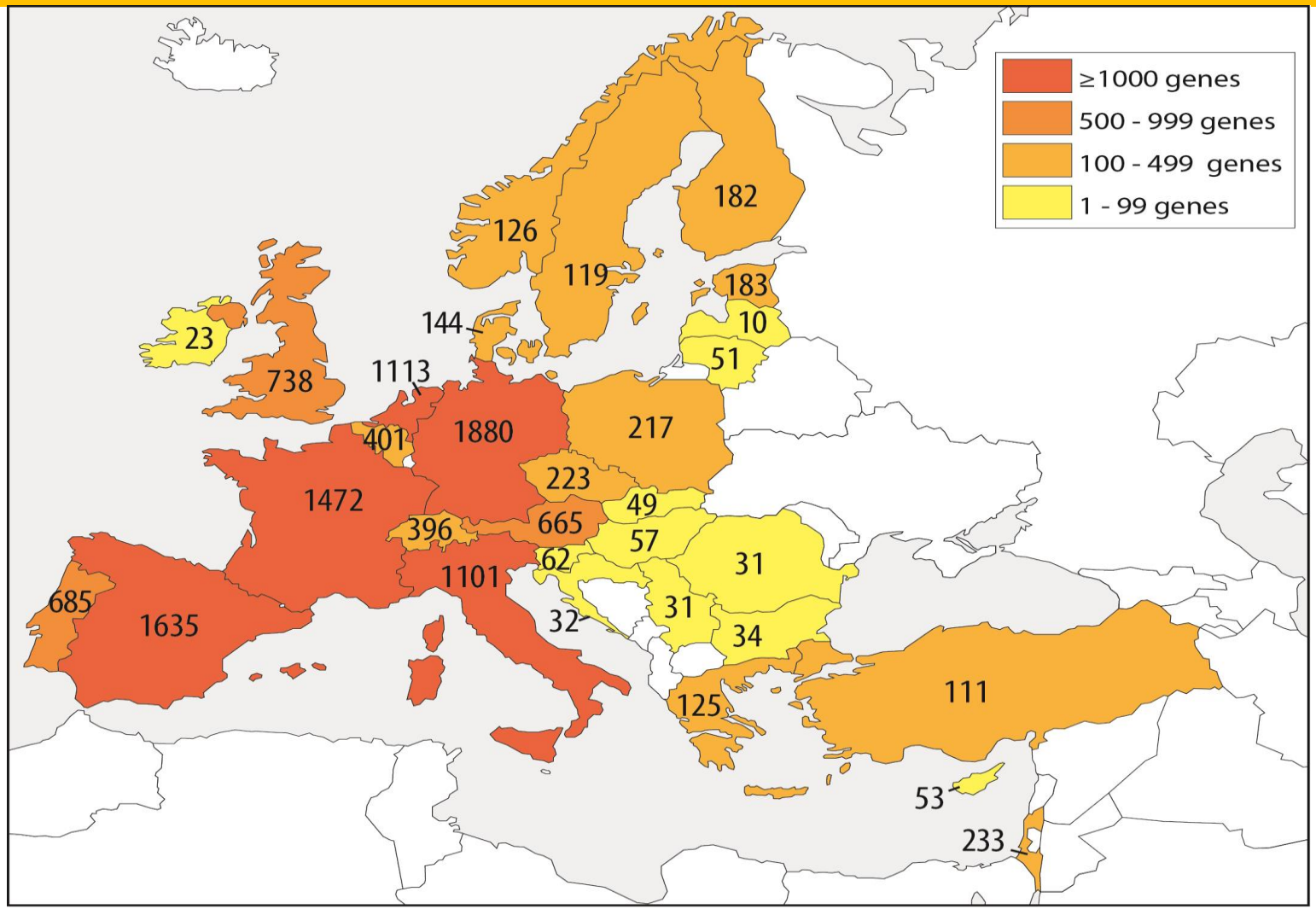
Validation is the process of establishing analytical performance specifications for a clinical test system developed in house to confirm that the system is suitable for its intended use[1]. During the validation process, the laboratory must demonstrate that the

Genetics as a Medical Specialty

Eur J Hum Genet. 2017 Dec; 25(Suppl 2): S53–S59

Country	Year/birth	Training yrs
Austria	2006	6
Belgium	2017	6
Bulgaria	2006	4
Croatia	2017	5
Czech Rep.	2009	4
Denmark	1996	5
Estonia	2009	4
Finland	1981	
France	1995	4
Germany	1992	5
Greece		
Hungary	2012	4
Iceland	2015	5
Ireland	2012	4
Italy	1970	4
Latvia	2000	5
Lithuania	2004	
Malta	2005	5
Netherlands	1987	4
Norway	1973	4
Poland	2003	5
Portugal	2001	5
Romania	2008	4
Slovakia	2006	4
Slovenia	2001	5
Spain	2014	4
Sweden	1992	
UK	1984	4

Number of testable Genes in 2014 (out of 2500)



Organisation of Genetic services at country level

- France:
  - National organisation regulated by Law since 1994 but no territoral organisation
  - Same countraints for public and private labs
  - Very few tests are covered (the unuseful ones) – global budget for public labs
  - Poor quality control
- UK:
  - Genetic services embeded in the NHS
  - Planification of tests to be offered and territorial organisation
  - Fully covered
  - National quality control
- Germany:
  - Liberal system. Many private labs
  - Reimbursement of tests if prescribed

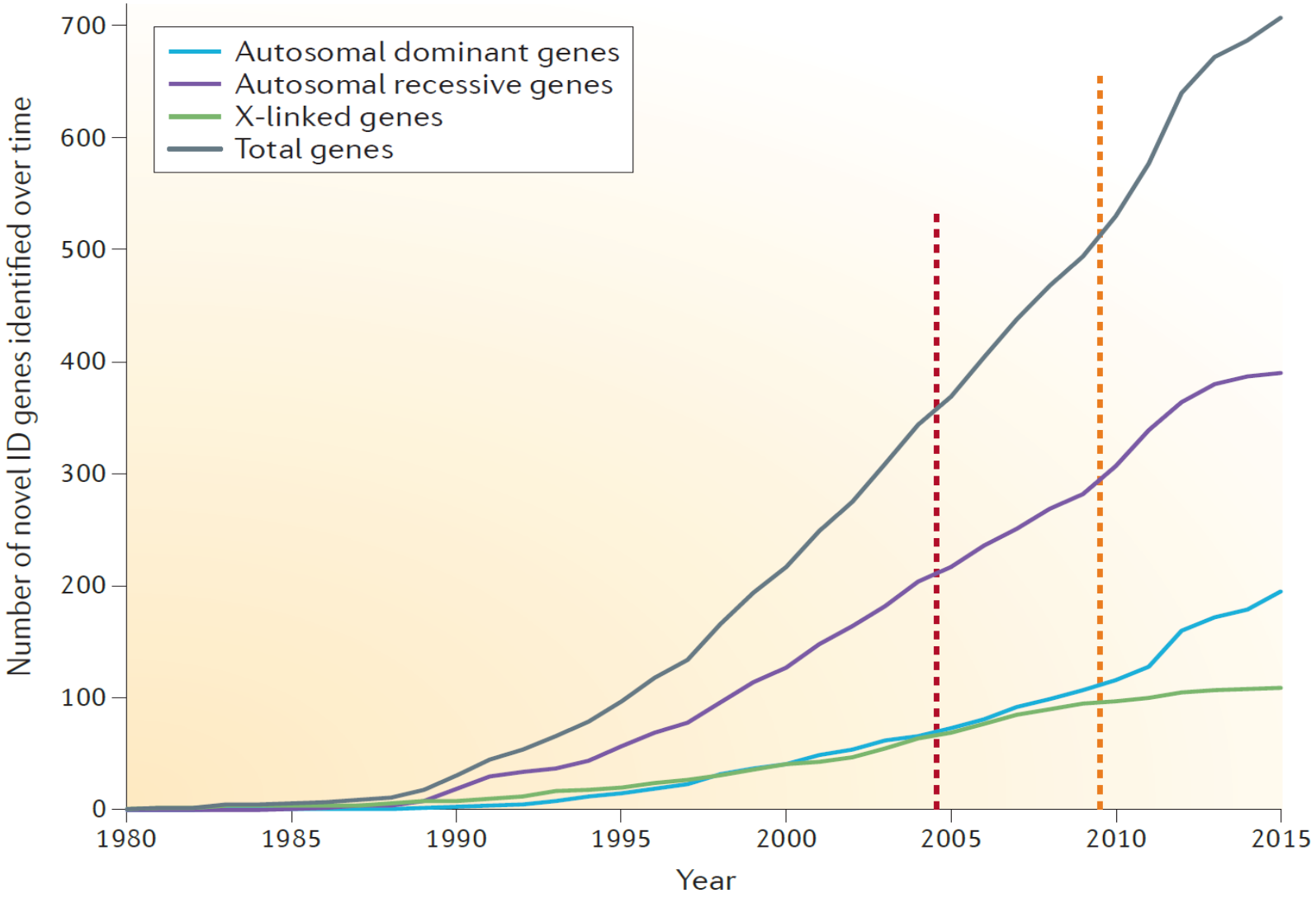
Core objectives of Genetic Services in Medicine

- Establish the diagnosis for appropriate care
  - Refer to appropriate experts for further management
- Explain the origin of the disease
- Explain its mode of inheritance
- Explain reproductive options if relevant
- Assess the associated risk for relatives
- Make possible prenatal/preimplentation diagnosis
- Screen relatives
  - If potential intervention, preventive or curative
  - If relevant for reproductive or life style decisions

Core objectives of Genetics in Medical Research

- Identify new genes
- Study gene expression and gene regulation
- Establish how the defective protein disturb biological processes
- Establish the catalog of variants and their predictive value
- Establish animal models
- Invent new therapies / better diagnostic tools

Identification of New Genes: a Success Story



Vissers, Veltman & Gilissen, Nat Genet Reviews 2016

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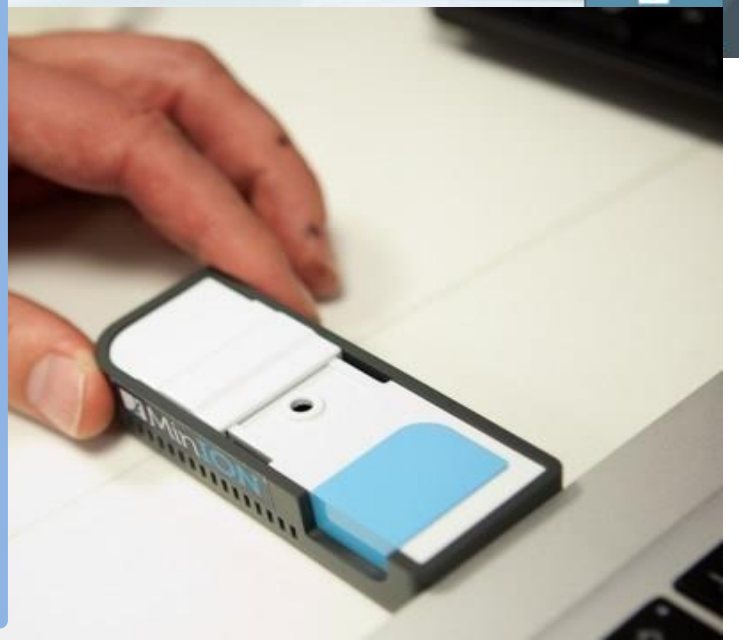
Run Until...



Is the future so bright ?

Or are we facing a disorganisation of genetic services ?

Limitations of the Current Approach

- Exome is not entirely covered
- Limited to exons (and flanking regions)
  - Impossible to detect (deep) intronic mutations
- Not quantitative
  - Impossible to detect deletions or duplications
- Thousands of SNPs and variants of unknown significance
- Time consuming interpretation

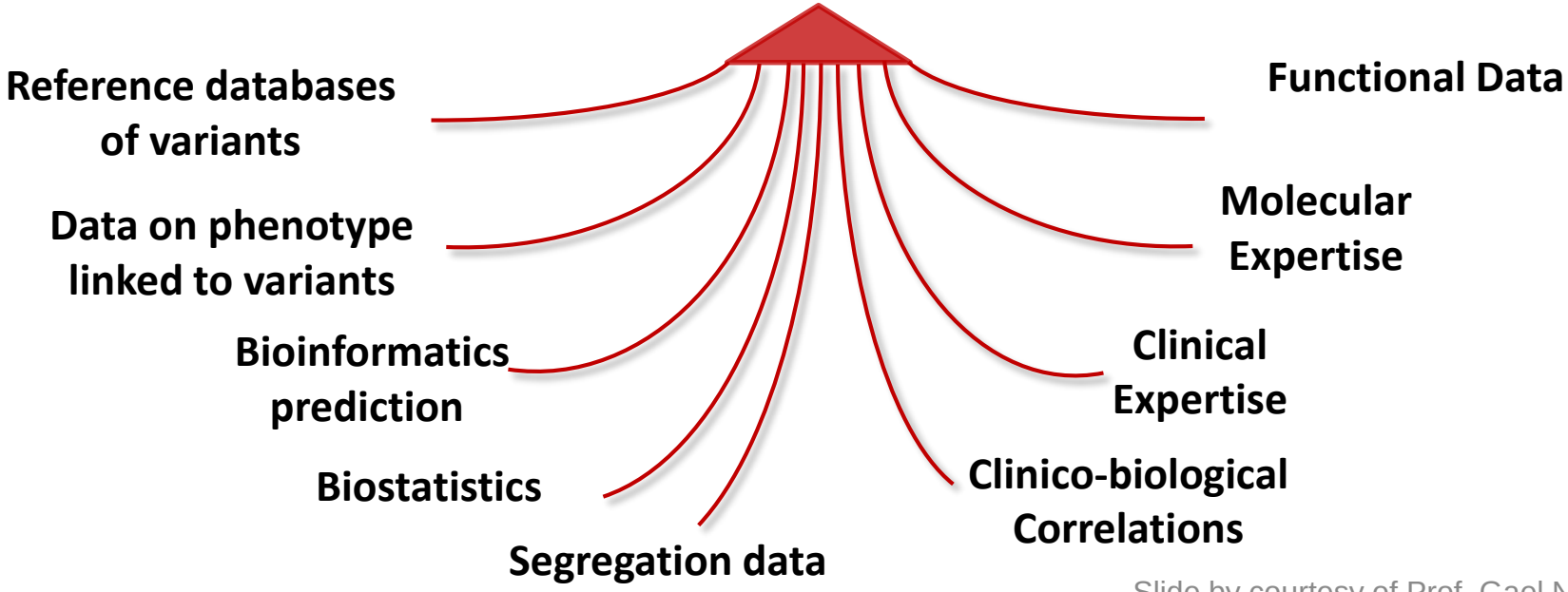
How to define Norms when our knowledge is so limited ?

- Need to link variants with phenomes (likelihood and severity)
- The efficiency of the filter process depends on the reference data:
  - Number of reference genomes and geographic diversity
- Difficulty to establish norms due to heterogeneity
  - Heterogeneity of experimental methodologies
  - Heterogeneity of filtering methodologies
  - Mediocre quality of databases of variants

What is necessary to interpret Genomics Data

American College of Medical Genetics and Genomics (ACMG) – Association of Molecular Pathology (AMP)

Class 5: Pathogenic
Class 4: Likely pathogenic
Class 3: Variant of uncertain significance (VUS)
Class 2: Likely benign
Class 1: Benign



Slide by courtesy of Prof. Gael Nicolas

Themes that matter

1. Quality of genetic services
    1. Validation of Next Generation Sequencing (NGS) platforms and applications
    2. Long term organization of External Quality Assessment (EQA)
    3. Distinction between services and research
2. Organisation of genetic services
    1. Offer comprehensives clinical services to those at needs
    2. Regional distribution of genetic services
    3. Rationalisation of services

Prerequisite for clinical use of NGS

Interpretation of the genomic sequence should:

- Only be done for **validated** genotype-phenotype correlations: panels of genes per indication
- Take all other variables into account that will influence the significance of a given variant:
  - family history
  - personal antecedents
  - clinical features
  - results of other tests, …

NGS Technologies: recommendations to serve the patients

- Collect evidence for clinical utility of tests
- Ensure that undiagnosed patients with rare diseases benefit rapidly from being sequenced
  -> inclusion of NGS laboratories in ERNs
- Promote early translation of genomic discoveries into quality services
- Offer only ‘stable’ technology (guidelines)
- Open source tools
- Open source clinical and mutation data

Transversal organization

- Provide the ERNs with a set of services
  - Quality issues and EQA
  - Validation of technologies
  - Bio-informatics
  - Interpretation of (rare) variants
  - Legal and ethical requirements
  - Guidelines

Difference between clinical services and research activities

- Clinical laboratories
  - Use validated technologies to obtain results, which interpretation is straitforward
  - Quality control is in place and turn-around time is standard
  - Patient consent to a clinical test
- Research laboratories
  - Use technologies that are validated or not, to obtain results of know or unknow significace , that may be useful or not, obtained after a time period which is not previsible
  - No obligation to return a result
  - Patient consent to participate in a research study

Difference between Diagnosis and Screening

- Clinical laboratories
  - Use validated technologies to obtain results, which interpretation is straitforward
  - Quality control is in place and turn-around time is standard
  - Patient consent to a clinical test
- Research laboratories
  - Use technologies that are validated or not, to obtain results of know or unknow significace , that may be useful or not, obtained after a time period which is not previsible
  - No obligation to return a result
  - Patient consent to participate in a research study

Differences diagnostics / screening

- Diagnostic tests
  - Individual request
  - Seek person
    - probably
    - surely
  - Element of a care management
  - Financially supported by the health care budget

- Screening tests
  - No individual request
    - Most often
  - Systematic offer
  - Healthy individuals
    - At low risk
  - Element of a public health policy
  - Financially supported by the Public Health budget

Conclusions

- NGS has to be established in the context of the clinical framework
- Clinical services in Genetics go far beyond the technological approach which is currently promoted
- So called « unsollicited variants » should not be part of clinical services but evaluated as a potential new offer for screening campaigns
- Fight the confusion between services and research
- Fight the confusion between diagnosis and screening