LE MALATTIE RARE

IRDiRC
INTERNATIONAL RARE DISEASES RESEARCH CONSORTIUM

MALATTIE RARE

- Malattia che colpisce **non più di 5 persone ogni 10.000 abitanti.**
- Le Malattie Rare conosciute e diagnosticate sono circa **8000:**
- **80% origine genetica**
- **75% insorgenza in età pediatrica**

- Nei 25 paesi dell'Unione Europea
- **30 milioni di persone soffrono di una malattia rara**
- Italia: 61 milioni di persone (dati ISTAT al 1 gennaio 2013)
- Il 6-8% della popolazione italiana è affetto da malattie rare
- **5 milioni**
- Lombardia: 10 milioni di residenti
- **800.000**
- Provincia di Brescia : 1.2 milioni di residenti
- **96.000**

legislazione

- **DECRETO MINISTERIALE N° 279 DEL 18 MAGGIO 2001 Istituzione della Rete nazionale per la prevenzione, sorveglianza, diagnosi e terapia delle Malattie Rare Individuazione di un gruppo di malattie rare che godono dell'esenzione dalla partecipazione al costo delle prestazioni sanitarie correlate in fase diagnostica e terapeutica**
- Creazione del **Registro Nazionale delle Malattie Rare**
- Creazione di presidi : medici esperti in singole malattie rare, formulano diagnosi, forniscono esenzione e piano terapeutico

Certificazione: la rete

- Certificazione di malattia rara
- 2006: zero
- 2007: 22
- 2008: 143

- 2009: 150
- 2010: 465
- 2011: 783
- 2012: 826
- TOTALE: 2389
- S. Di Ehlers-Danlos: 94
- M. Arnold-Chiari: 30

DIAGNOSTIC GENETIC TESTS

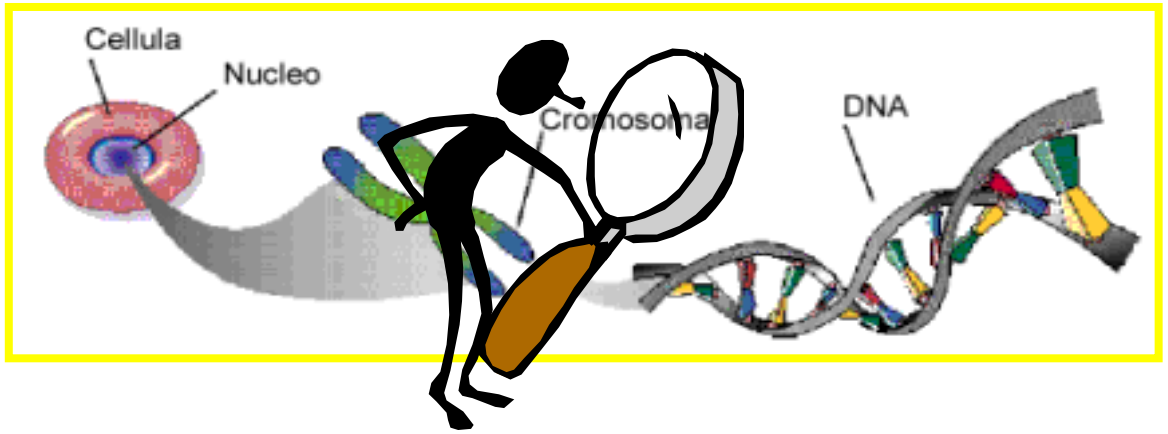
- **Definition**

  The analysis of human DNA, RNA, chromosomes in order to detect heritable disease-related genotypes/ mutations for clinical purposes

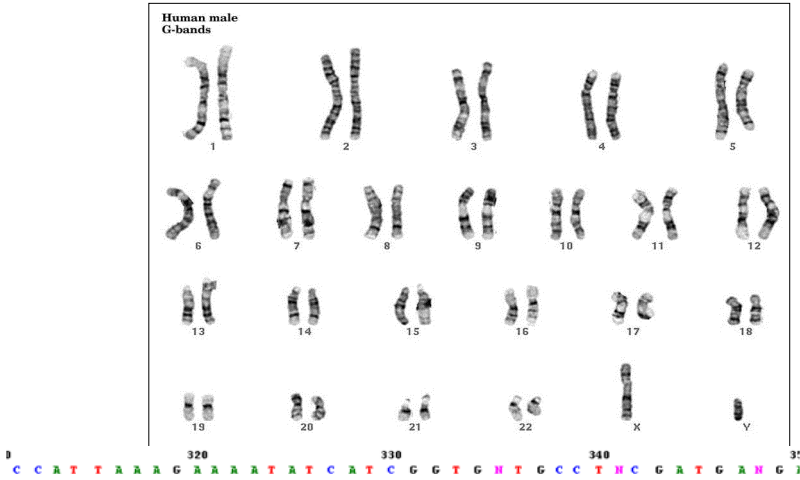
  (US Task force on genetic testing 1999)

- **-MANDATORY FOR ADDRESSING ALL DISEASE CARE LANDSCAPES**

- Confirmation of the clinical diagnosis
- Information about preventive measures
- Feasibility of prenatal testing
- Enrollment in novel trials
- Having appropriate, suitable therapies
- Facing and following ethical issues

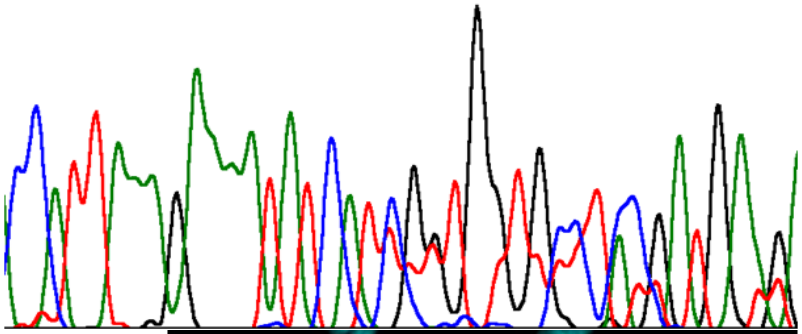


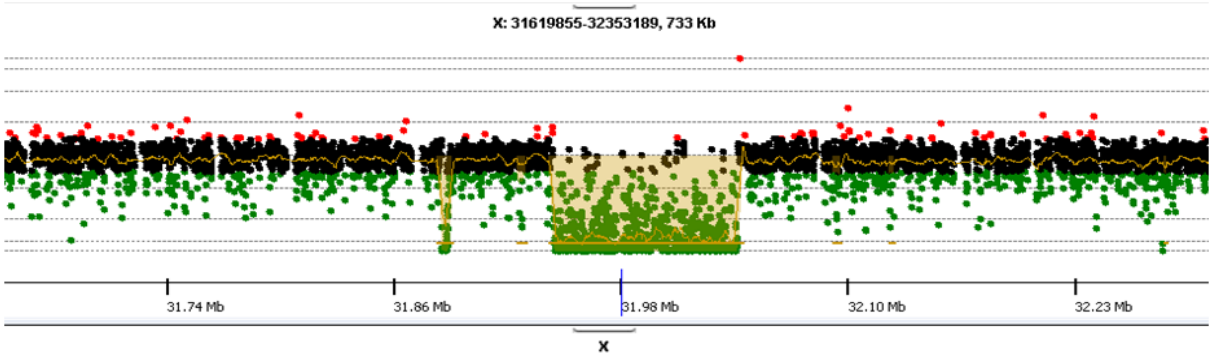
GENETIC TESTS: types

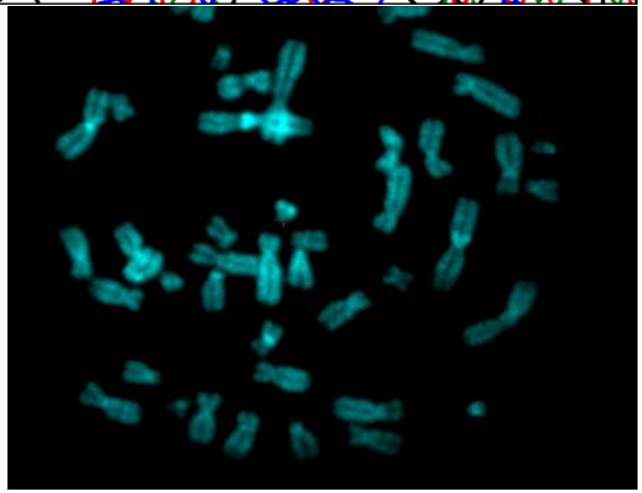


- Chromosomal testing
- (karyotype)

- Molecular testing
- (including a variety of tests to identify mutations at the DNA/RNA level)





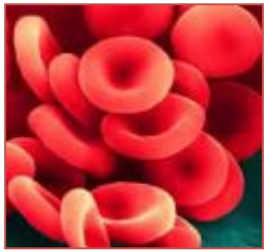


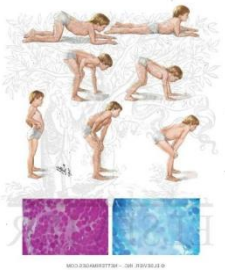
GENETIC TESTING

- **PrenataL**
  - Intellectual disability (FRAXA)

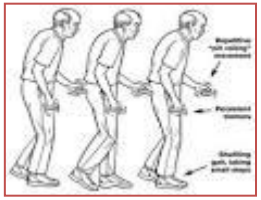
- **Perinatal (screening)**
  - PKU, Hypothyroidism

- **Postnatal**
  - •Diagnostic
  - •Cystic Fibrosis, Duchenne muscular dystrophy, Thalassemia





  - Presymptomatic
    - •Huntington, Spinocerebellar Ataxias



  - Predictive (susceptibiity genes)
    - •Diabetes, Alzheimer, Breast Cancer

- **Preconceptional (couple)**

GENETIC TESTS

ANALYTICAL VALIDITY

- **SENSITIVITY**
- ACCURACY
- **REPEATABILITY**

- FOR DIAGNOSTICS

THE ABOVE

PARAMETERS

SHOULD BE >95%

GENETIC TESTS

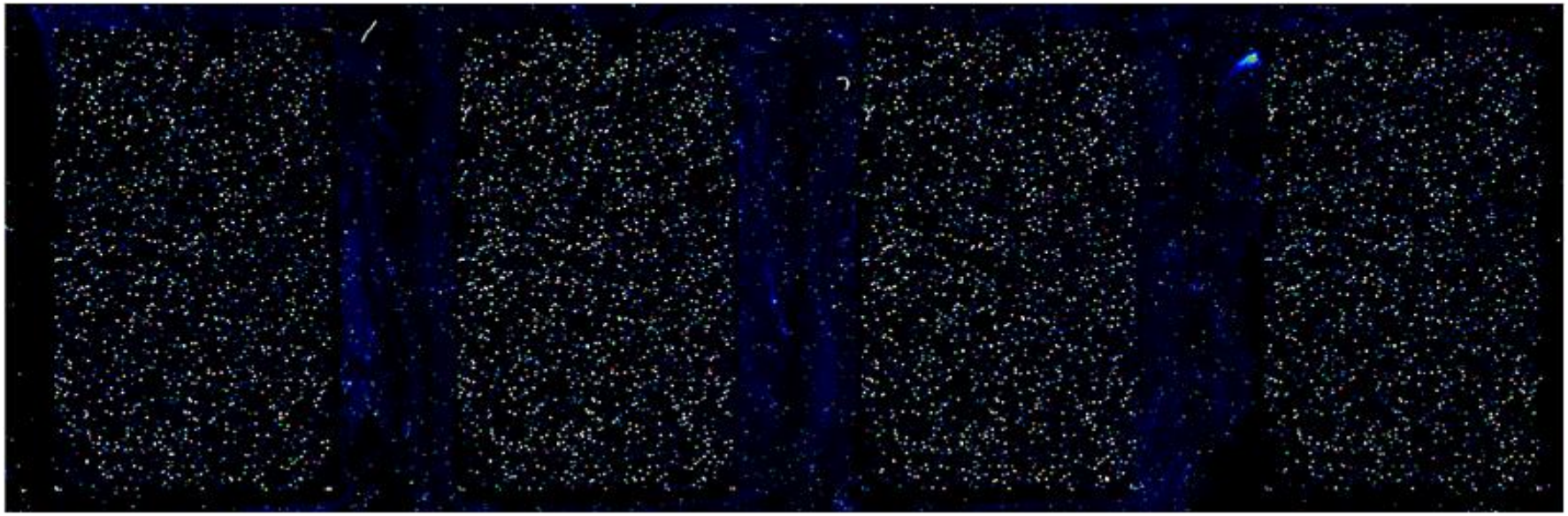
CLINICAL VALIDITY

SPECIFICITY OF THE TEST IN THE RARE DISEASE

Genetic tests interpretation
the bioinformatics
The clinical competence

MEDICAL GENETICISTS

Array



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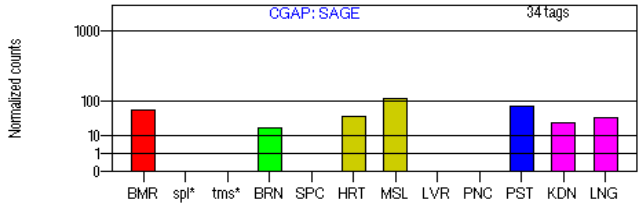
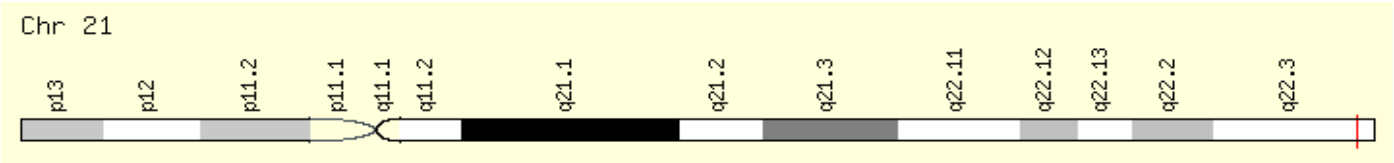
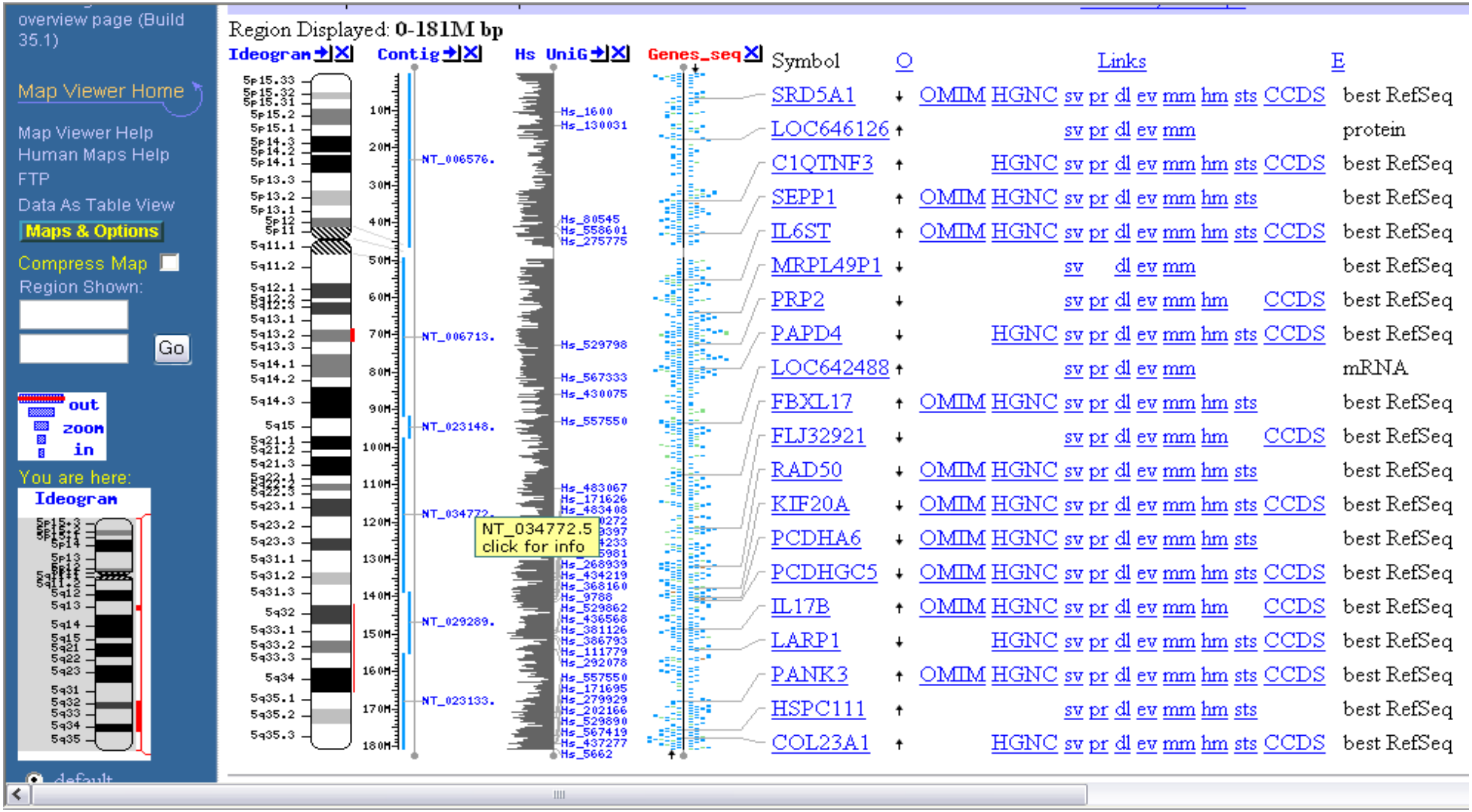


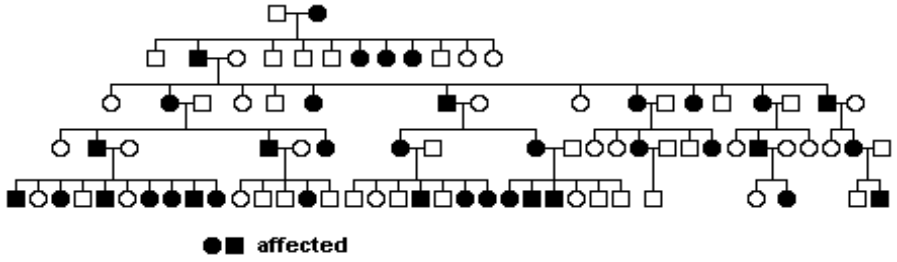


Gene card for

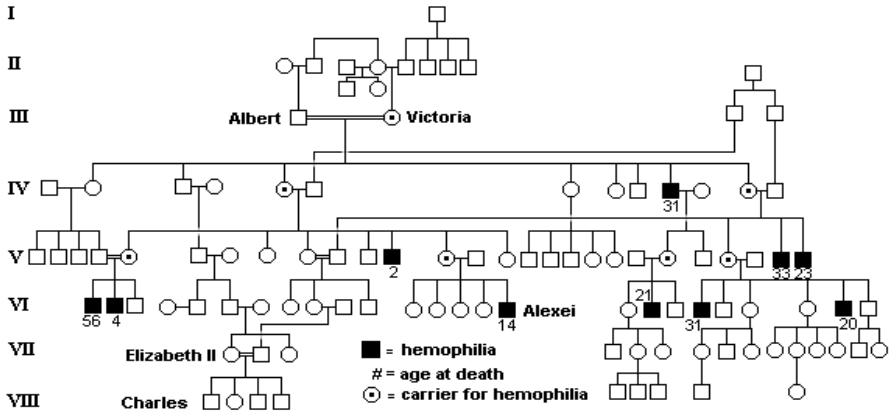
(congenital muscular dystrophy Ullrich type)

The genes library, how to read the DNA book

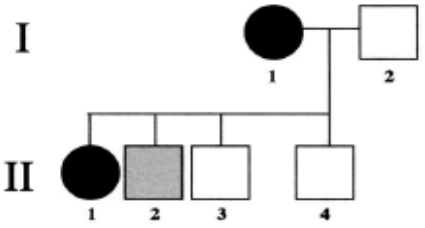




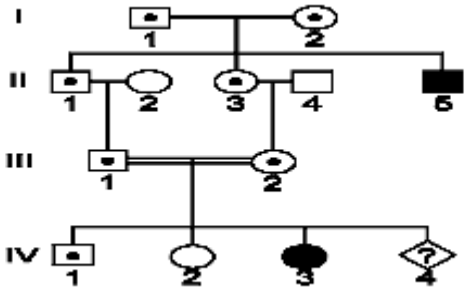
AUTOSOMAL DOMINANT



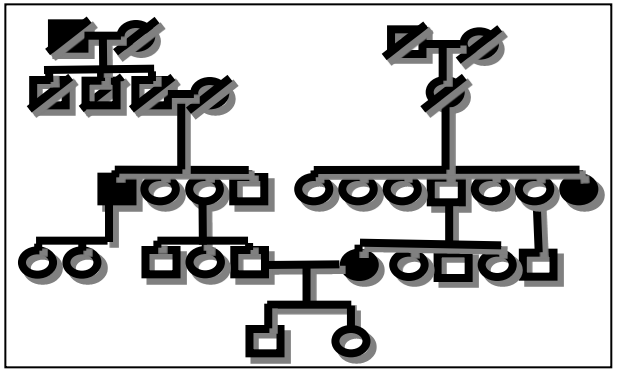
X-LINKED



MATRILINEAL



AUTOSOMAL RECESSIVE



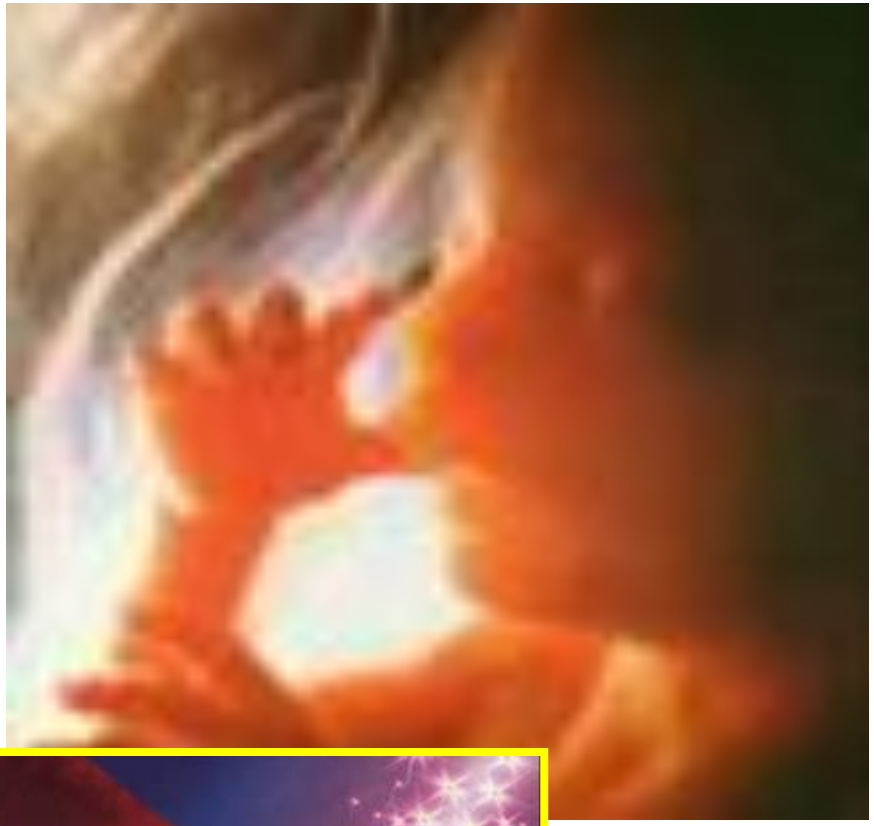
POLYGENIC

OBJECTIVES OF GENETIC COUNSELLING

- To discriminate between environmental and genetic factors in the presenting phenotype
- To address a better phenotype definition
- To identify the possible mode of inheritance of the condition
- To identify the causative genotype
- To identify the at risk individuals
- To provide information regarding the quality and quantity of risk
- To provide support in the autonomous decision process in prevention and therapeutic strategies, taking into account the ethical issues

- The prenatal diagnosis

- INVASIVE
- NON INVASIVE



Donne in Gravidanza e Tutela della Maternità

Decreto Legge 10.9.98 - G.U. n° 245 del 20.10.98

Allegato C

Risk for Mendelian diseases RARE DISEASES

(maternal age independent)

Family recurrence of a specific mendelian disease

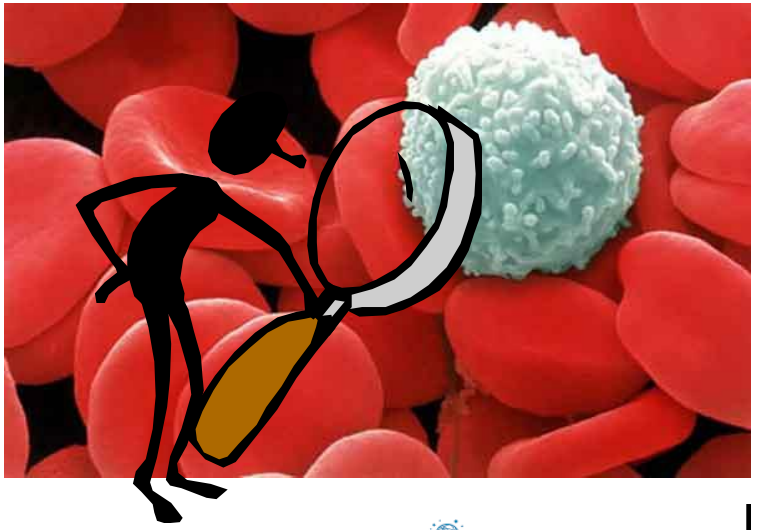
(Thalassemia, cystic fibrosis, Duchenne muscular dystrophy etc.)

Prenatal diagnosis APPROPRIATE

(under Italian LEA and covered by SSN)

Non Invasive Prenatal genetic Testing (NIPT) on maternal blood

- Non-invasive
- Molecular testing
- Highly accurate
- Highly informative
- Pilot screenings in progress



OPEN ACCESS Freely available online

PLoS one

Prenatal Detection of Aneuploidy and Imbalanced Chromosomal Arrangements by Massively Parallel Sequencing

Journal of Maternal-F

ISSN 1476-7058 print/ISSN 1476-4954 online
DOI: 10.3109/14767058.2011.635730

informa
healthcare

Noninvasive prenatal diagnosis of common fetal chromosomal aneuploidies by maternal plasma DNA sequencing

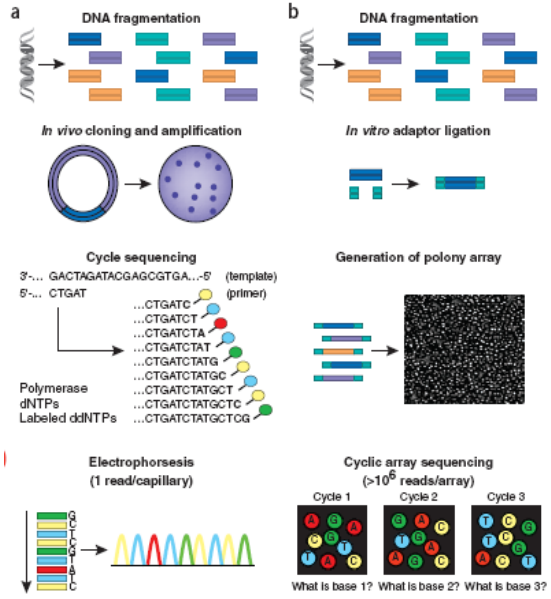
NEXT GENERATION SEQUENCING

-SEQUENZIAMENTO AD ELEVATO PARALLELISMO
-DEEP SEQUENCING

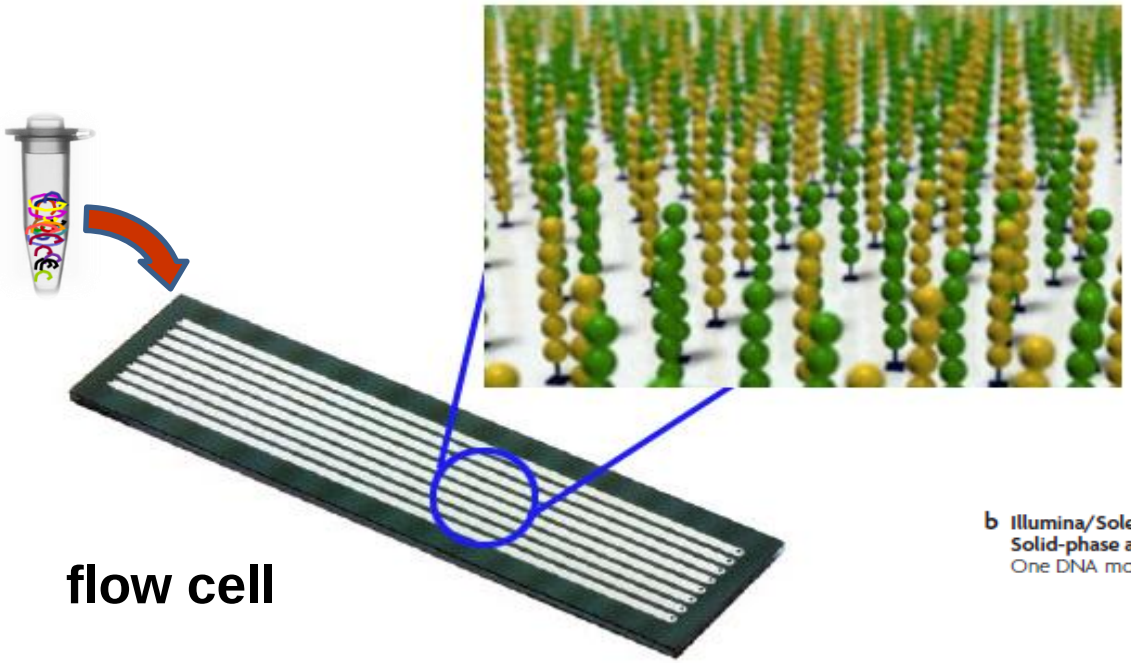
INNOVATIVITA'

-ALTA CAPACITA' DIAGNOSTICA
-TECNICHE DI SEQENZIAMENTO BASATE SU LIBRERIE GENOMICHE
-ALTA PROCESSIVITA'
-TEMPI DI RISPOSTA RIDOTTI
-COSTI RIDOTTI

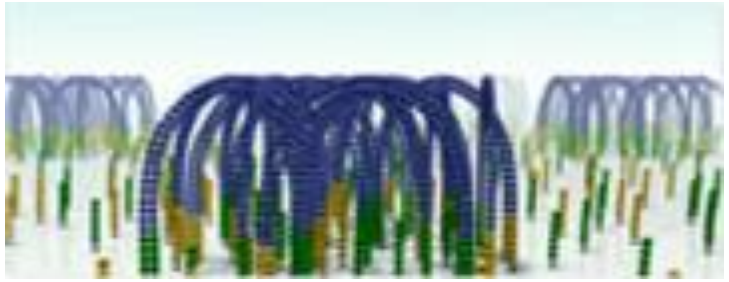
<u>MA:</u>
<u>ANCORA IN FASE DI VALIDAZIONE</u>



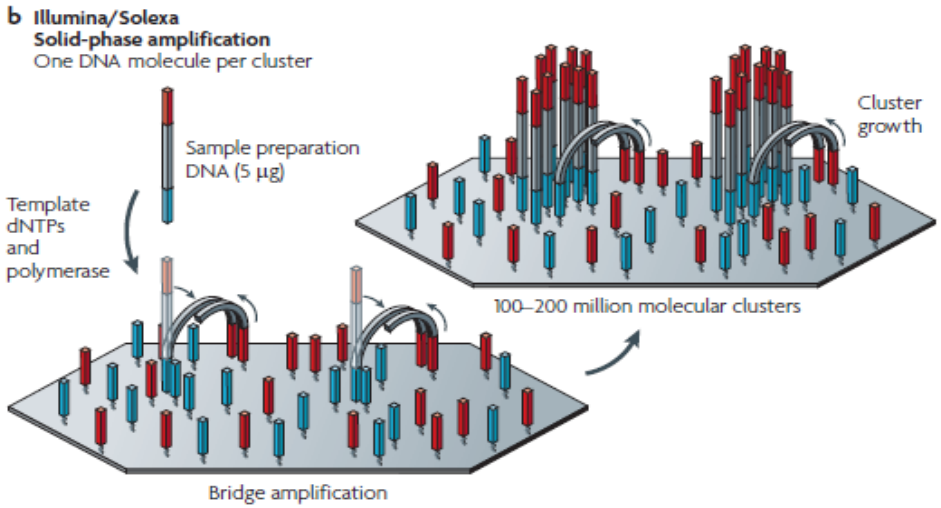
solid-phase amplification can generated up to 2,000 millions of individual reactions per flow cell



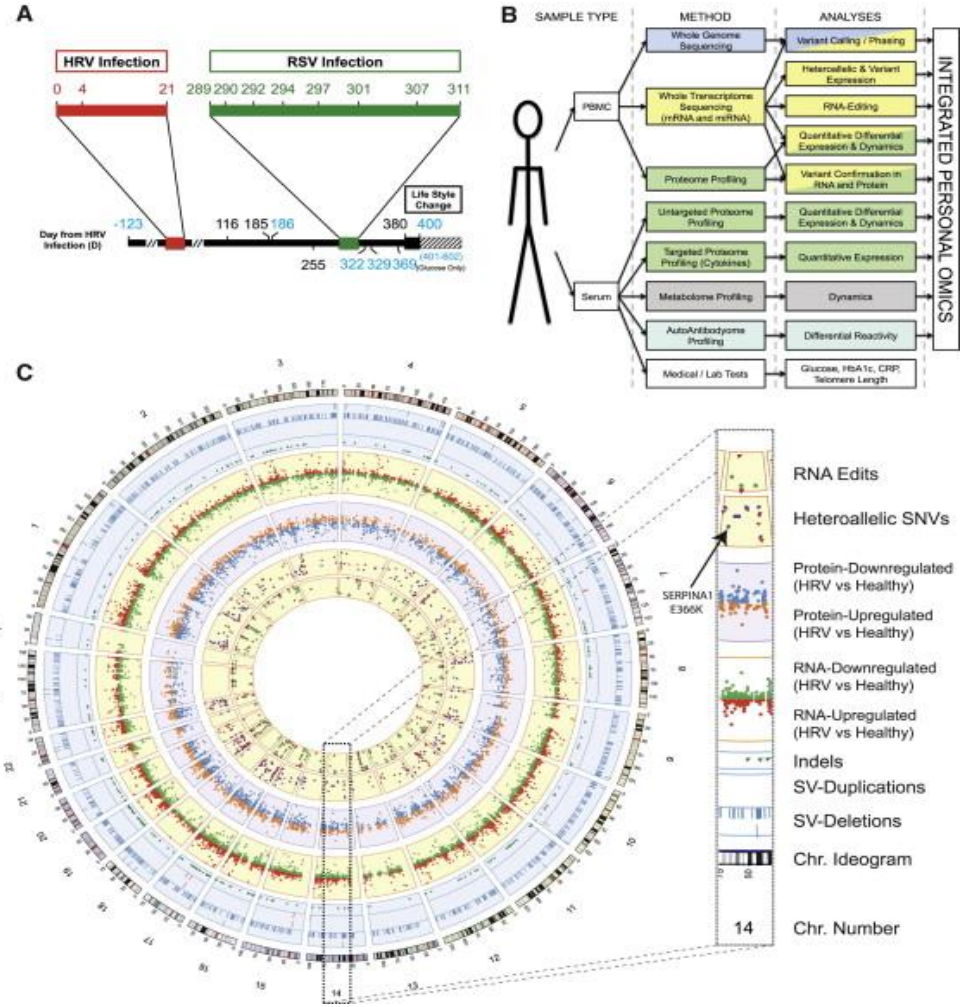
flow cell



illumina®



Proteomic and transcriptomic biomarkers: affected by POP (Personal Omics Profiling)



Personal Omics Profiling Reveals Dynamic Molecular and Medical Phenotypes

Cell

Cell 148, 1293–1307, March 16, 2012 ©2012 Elsevier Inc.

-extensive dynamic changes in molecular components and biological pathways depending on ages, conditions, environment, diseases, etc

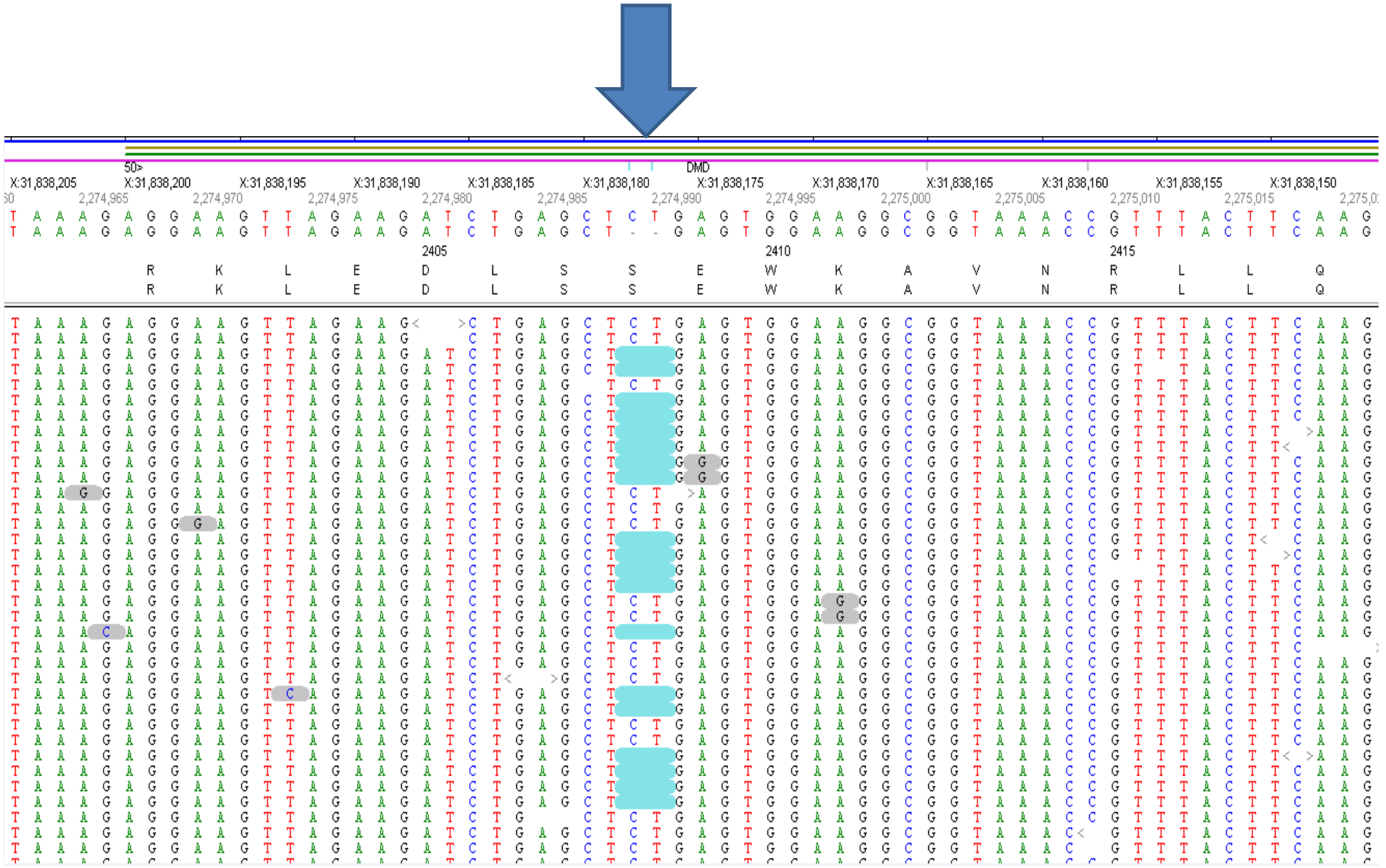
-need of a longitudinal Integrated POP (iPOP) using all omics analyses to interpret healthy and diseases states

-Key: connecting genomic information with dynamic omics activities

What NGS does analyses

- **Whole genome** @40 x (~ **140** Gb of sequences/sample) √
- **Whole exome** @60 x (~ **5** Gb/sample) √ √
- A set of **100 aver. candidate genes** (exons) @100 x (~ **0.1** Gb/sample) √ √ √
- A single **medium-size gene** (exons and introns) @100x (~ **0.005** Gb/sample) √

DYSTROPHIN GENE HETEROZYGOUS 2619/11 DMD c.7223_7224delCT



NGS GENETIC DIAGNOSIS

- **Whole genome sequencing (300 Gb) in 72 hours at 1500 Euros**

- GENETIC DIAGNOSIS FOR RDs
- Bottlenecks
- Bioinformatics
- Outflow stratification and analysis
- Variants interpretation (databases and registreis)
- Guidelines determined at the National and EU level for the health service costs sustainability

Rare Diseases
The diagnostic network

- The diagnostic genetic tests
- The prevention and genetic counselling
- The prenatal testing
- Ethical issues
- A view on the future: next generation sequencing
- The clinical care

- NGS Molecular genetics diagnostics in a few competence lab centers with high expertise
- Genetic counselling centers with Ethical Committees
- NGS Technology in a few competence lab centers with high expertise
- Genetic counselling centers with Ethical Committees
- NGS Technology in a few competence lab centers with high expertise
- Clinical excellence Centers with trial facilities and research for clinical outocme measures

ALL THESE ISSUES ARE NEEDED FOR RD MANAGING AND SHOULD BE ENSURED BY THE NATIONAL HEALTH SYSTEMS IN A SUSTAINABLE INTEGRATED AND EXCELLENCE NETWORK

TELEGENETICS: concepts

- Telemedical technology in genetics (telegenetics) can fill the gap between the specialist and the patients
- Multimedia telegenetics provides interactive genetic consultations at a distance , accordingly to the European Reference Networks (ERNs) policy
- Best-practice-based communication of genetic testing results

GOAL

Facilitating communication among geneticists, obstetricians, pregnant women and all stakeholders involved in prenatal care and diagnosis

TELEGENETICS: concepts

- Medical genetics and genetic counselling represent **vital tools** for **communicating with patients** about genetic risk, reproductive options, prenatal testing and novel therapies.
- There is a general consensus, promoted by the Eurogentest Network of Excellence (www.eurogentest.eu) that **genetic counselling should be a mandatory accompaniment** to all medical genetics interventions.
- Telemedical technology in genetics (telegenetics) can fill the gap between the specialist and the patients
- Multimedia telegenetics provides interactive genetic consultations at a distance , accordingly to the European Reference Networks (ERNs) policy
- Best-practice-based communication of genetic testing results

GOAL

Facilitating communication among geneticists, obstetricians, pregnant women and all stakeholders involved in prenatal care and diagnosis

- https://www.youtube.com/watch?v=BoqY4w6QyDI&feature=youtu.be

LETTER TO THE EDITOR | Genetics inMedicine

GENETICS in MEDICINE | Volume 16 | Number 10 | October 2014

Open

Genetic counseling for women referred for advanced maternal age: a telegenetic approach

Francesca Gualandi, MD, PhD[1,2], Stefania Bigoni, MD[1,2], Loredana Melchiorri, PhD[1,2], Barbara Buldrini, PhD[1,2], Alessandra Balboni, PhD[1,2], Marcella Neri, MD[1,2], Annarita Armaroli, MD[1,2], Giulia Parmeggiani, MD[1,2], Eleonora Italyankina, MD[1,2], Antonio Mauro, MD[1,2], Anna Ravani, PhD[1,2], Sergio Fini, MD[1,2], Stefano Caracciolo, MD[3] and Alessandra Ferlini, MD, PhD[1,2]

ACKNOWLEDGMENT

The SIGN project (Slovenian-Italian Genetic Network, http://www.signgenetics.eu) is acknowledged.

European Reference Networks

Criteria for Networks and Providers
Implementation Framework

Directive of patients' rights in cross-border healthcare

Enrique Terol;
DG SANCO – Directorate D
European Commission

Key issues addressed by the Directive

European Commission

Directive 2011/24/EU of patients' rights in cross-border healthcare

- Right to **choose and be reimbursed** for **healthcare provided** by public or private providers located in the EU
- More **transparency about their rights**, treatment options or , the quality and safety levels of healthcare providers
- Strong focus on **cooperation among Member States**

Entry into force at National level 25 October 2013

Health and Consumers

European Reference Networks

Scope and Context

European Commission

Cooperation between MS: Article 12 European Reference Networks

Networks of healthcare providers aiming at

Improving quality and safety and access to highly specialised healthcare

- ✓Patients affected by **rare or low prevalence and complex diseases**
- ✓Added **value** at EU level
- ✓Need of **cooperation**:
  - Scarcity knowledge / need education
  - Complexity / high cost
- ✓**multidisciplinary approach** (different specialities/areas of knowledge)

Health and Consumers

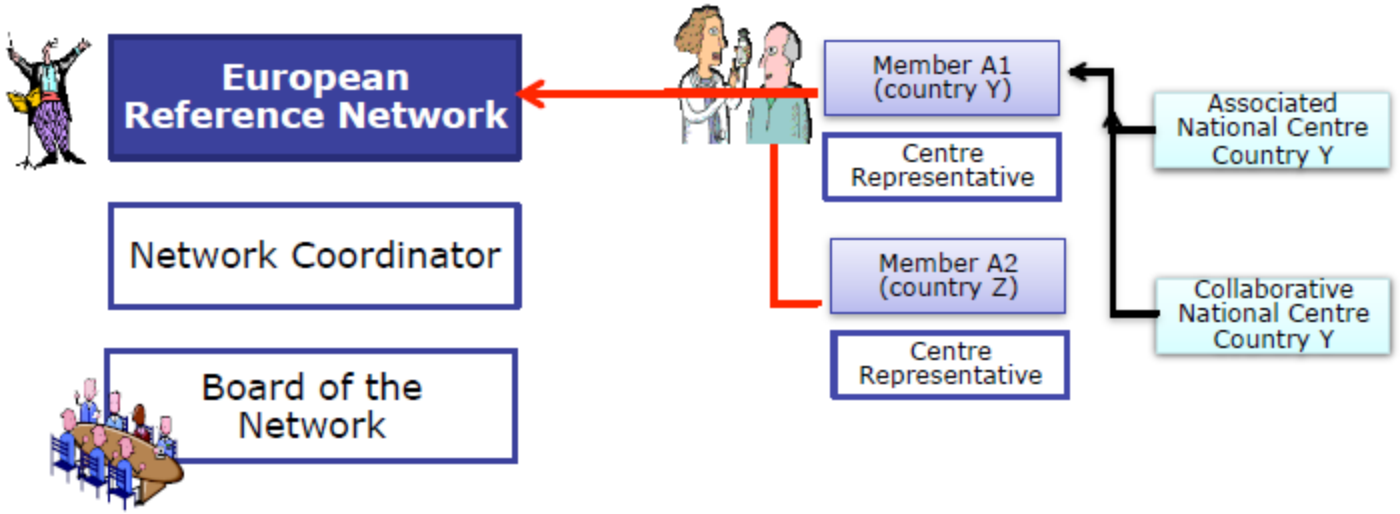
European Reference Networks

European Reference Networks: networking dimension

- *Key issues:*
  - **Exchange of expertise** and clinical data through the network and across the EU
  - Swift and smooth **contact between providers and between patients and providers at a distance**
  - **Collaborative/cooperative actions and systems**
- ***Networking activities*** *and availability of specific network tools -It solutions- are the basis for this project.*

Governance / coordination Networks

- ✓ ***Transparent and effective*** *coordination & governance (adequate structures and elements)*
- ✓ ***Networks can be flexible*** *& have different architectures and internal relations* ***but there are key organizational features.***



Governance / coordination Networks

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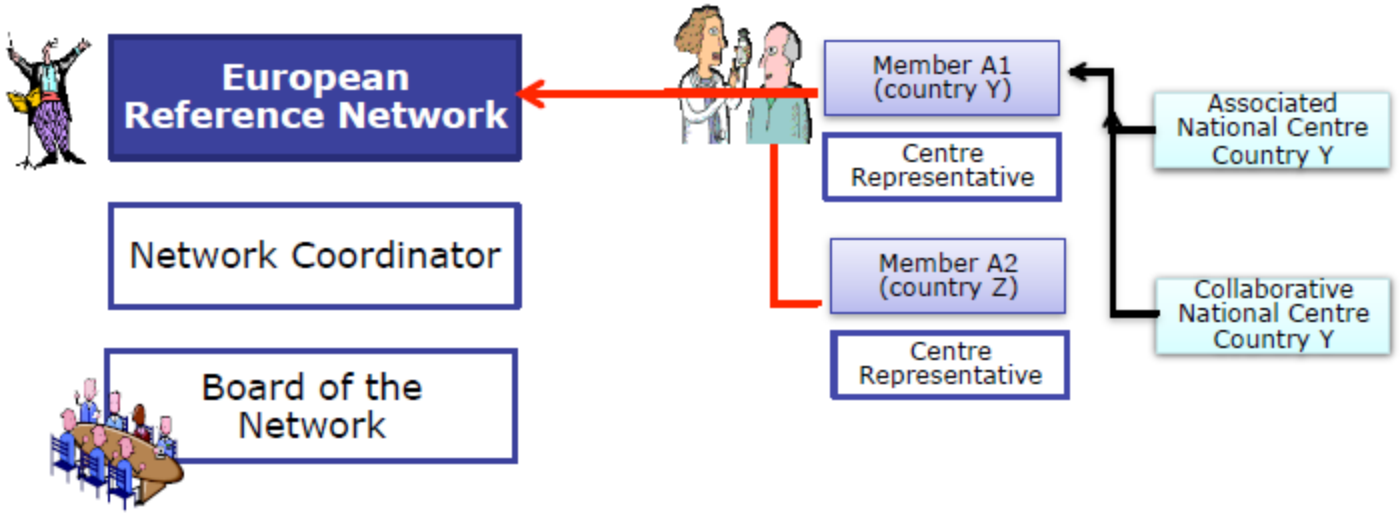
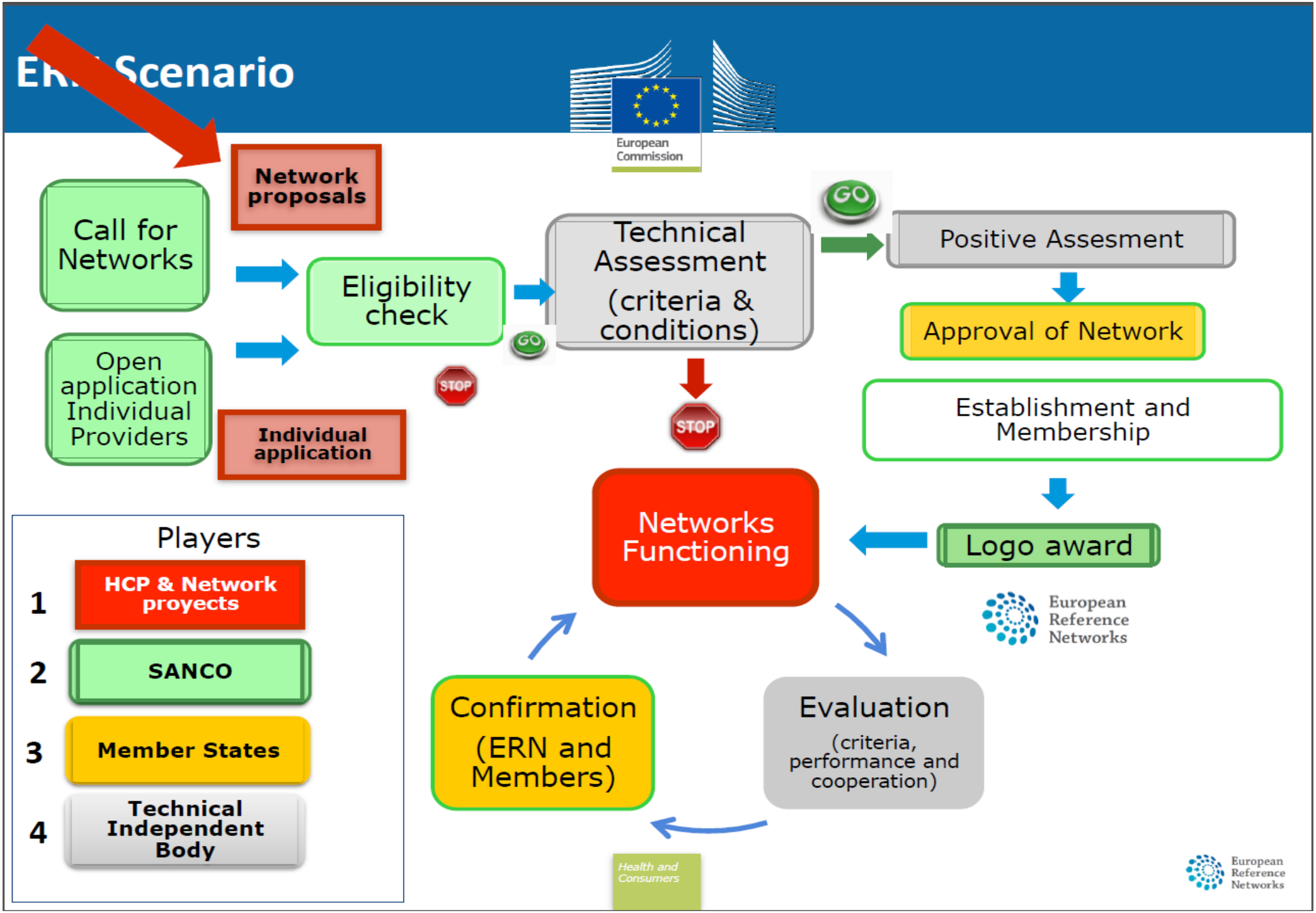


ER… Scenario


European Commission
Network proposals
Call for Networks
Eligibility check
Open application Individual Providers
Individual application
GO
STOP
Technical Assessment (criteria & conditions)
GO
STOP
Positive Assesment
Approval of Network
Establishment and Membership
Logo award
Networks Functioning
European Reference Networks
Evaluation (criteria, performance and cooperation)
Confirmation (ERN and Members)
Players
1 HCP & Network proyects
2 SANCO
3 Member States
4 Technical Independent Body
Health and Consumers
European Reference Networks

Networks criteria and capacities (From the Delegating and Implementing acts):

- Knowledge and expertise to diagnose, follow up and manage patients

- Evidence of good outcomes
- Multi-disciplinary approach
- Capacity to produce and implement: good practice guidelines, outcome measures and quality control
- Research, teaching and training
- Collaborate with other centres of expertise and networks

How to prove this?

Rare NMD ERN

Identify:

- The expertise (Paediatrics and Adults + multidisciplinary approach)
- The coordination of the network (who will deal with the planning of the network)

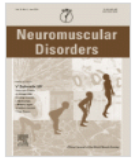
10 Members in at Least 8 Countries

Most healthcare providers are involved in the care of all groups of NMD, adding to that a super-specialized ar of expertise / research

EUROPEAN NEURO MUSCULAR CENTRE

Neuromuscular Disorders

Volume 24, Issue 6, June 2014, Pages 537–545



Workshop report

200th ENMC International Workshop "European Reference Networks: Recommendations and Criteria in the Neuromuscular field", 18–20 October 2013, Naarden, the Netherlands

Teresinha Evangelista[a], Baziel van Engelen[b], Kate Bushby[a]

Aims of the workshop:

1. exchange of knowledge and expertise in processes for the delivery of NMD care
2. assessment of existing resources both at national and international level
3. identification of gaps which need to be addressed
4. decide on a guideline document for the implementation of a ERN in the NMD field

EUROPEAN NEURO MUSCULAR CENTRE

PARTICIPANTS:

A.Ambrosini (IT)
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M.de Visser (NL)
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V.Karcagi (HU)
J.Kirschner (DE)
F.Macchia (FR)
M.Moggio (IT) C.Paradas (ES)
S.Parker (FR)
M.Pohlschmidt (UK)
J.Pouget (FR)
T.Sejersen (SE)
V.Straub (UK)
P.Van den Bergh (BE)
B.Van Engelen (NL)
J.Verschuuren (NL)
JL.Vives Corrons(ES)

Current status of specialized neuromuscular centres in Europe

- **Experience in the neuromuscular field on networking activities and Biobanks**:
  - European Neuromuscular Centre (ENMC)
  - TREAT-NMD Alliance
  - Telethon Network of Genetic Biobanks (TNGB) and/or the EuroBioBank (EBB)
  - RD-Connect
- **The role of the learned societies in an ERN:**
  - Current resources, such as e-learning, teaching courses and guidelines should be integrated into a future ERN.
  - Contribute to the establishment of a European NM curriculum and to the structure of the European Board Examination.
- **e-health:**
  - E-learning programmes are in place through the scientific societies, can be adjusted to different needs.
  - Other resources are being assembled through projects like the cross border EU project SIGN (telegenetics system to perform genetic counselling and clinical genetics consultations)

www.treat-nmd.eu

2007-2011
EU funded Network

2012 onwards
Alliance funded through multiple streams with global partners & membership

Governance
Chair – Annemieke Aartsma-Rus
Vice Chair – Eric Hoffman

Executive Committee
Supported by academic advisory board ("task force") of NMD leaders

Total of 360 members

100 organizations – 40 countries

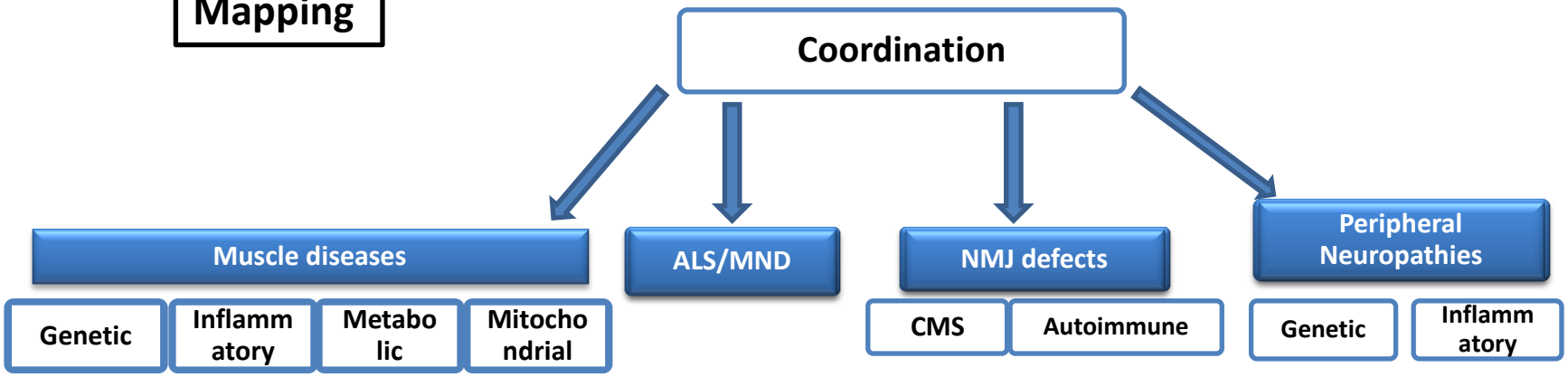
260 individuals – 42 countries

Members in every continent apart from Africa ☹

Rare Neuromuscular Diseases ERN

Areas of interest – How to map different participants?

Mapping



COUNTRIES ENGAGED
UK
Italy
Netherlands
Germany
Cyprus
Spain
France
Belgium
Hungary
Sweden

Action Points

Contact 1 or more experts in the different areas, cascade the information through those experts

Establish the connection between the different centres
Involve patient organizations
Establish the aims, structure, governance, services to be offered, integration of existing networks (most of them research based networks)

Mapping

Coordination

Muscle diseases

- **Genetic**
  - K Bushby
  - H. Lochmuller
  - V. Straub
  - UCL
  - Treat-nmd
- **Inflammatory**
  - Marianne de Visser
- **Metabolic**
  - Ans van der Ploeg
- **Mitochondrial**
  - Stefano Di Donato
  - Thomas Klopstock

ALS/MND

- Ludolph, Albert C.
- Silani, Vincenzo
- OTHER :
  - Leonard H van den Berg
  - Pamela Shaw
  - ...

NMJ defects

- **CMS**
  - Jackie Palace /David Beeson
  - Hanns Lochmuller
- **Autoimmune**
  - Isabella Illa
  - Amelia Evoli
  - Angela Vincent

Peripheral Neuropathies

- **Genetic**
  - Mary M. Reilly
  - Eduardo Nobile-Orazio
- **Inflammatory**
  - Sommer, Claudia
  - Peter Van den Bergh

COUNTRIES

- UK
- Italy
- Netherlands
- Germany
- Cyprus
- Spain
- France
- Belgium
- Hungary
- Sweden

Common purpose

- Improve quality and equity of healthcare for patients with NMDs

  Equity in diagnostic

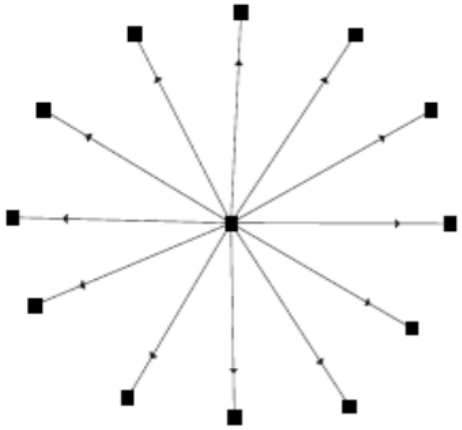
  Uniform care standards

- Enable exchange of knowledge (teaching and training)

- Help with translational research: the development of new drugs and the recruitment into clinical trials – **link to research**

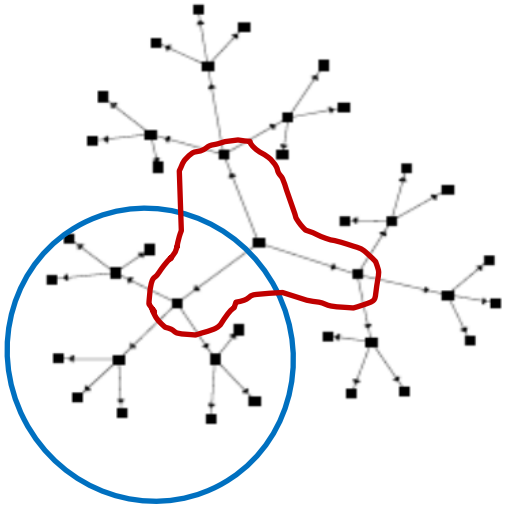
Structure

Hub-and-Spoke Structure



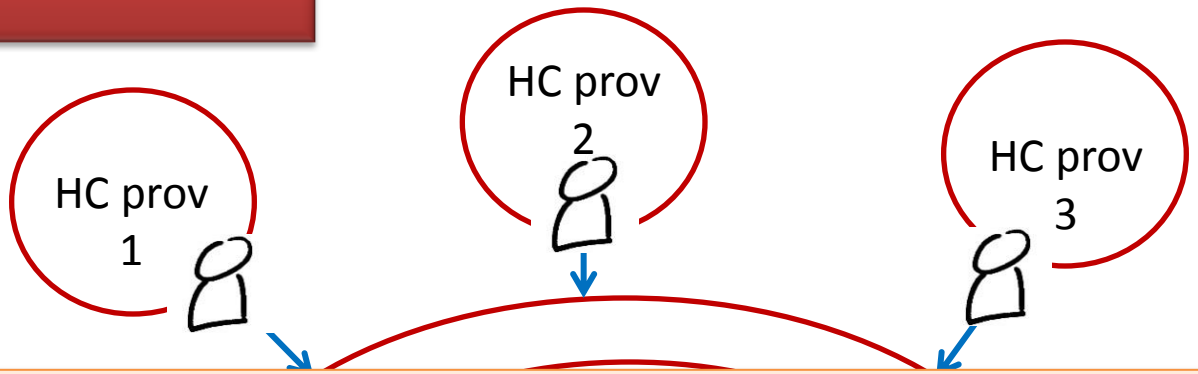
This is the model proposed by the EU.

Multi-Tiered Hub Structure



Country level

Governance



ISSUES:

- ✓ Where are **patients representatives** going to be represented? At a country level? At an European Level?
- ✓ How many HC providers are there going to be in the ERN? Depending on this number; the Board of the ERN could become non governable.
- ✓ How is the Coordinator going to be nominated?

Main functions of the ERN

- Promote and sustain good practice
- Organise and manage all relevant information/data
- Help to diffuse valid information to patients, other healthcare providers and the public
- Teleconsultation/Tele expertise
- Training and teaching

Rare Neuromuscular Diseases ERN
Services To Be Offered

Still under discussion at the EC level, it is likely that the themes will include:

- healthcare in a network environment,
- clinical guidelines development,
- training
- provision of a better environment for clinical research including clinical trials

What Services should we offer?

- **Clinical**

  Direct: teleconsultation, ?traditional clinical appt?

  Support to healthcare providers: e-Health
  (Exchange, gather and disseminate knowledge)

- **Non Clinical**

  Clinical guidelines / patient pathways
  (Implement outcome and performance indicators)

  Epidemiological surveillance, registries

  Training and continuous education programmes

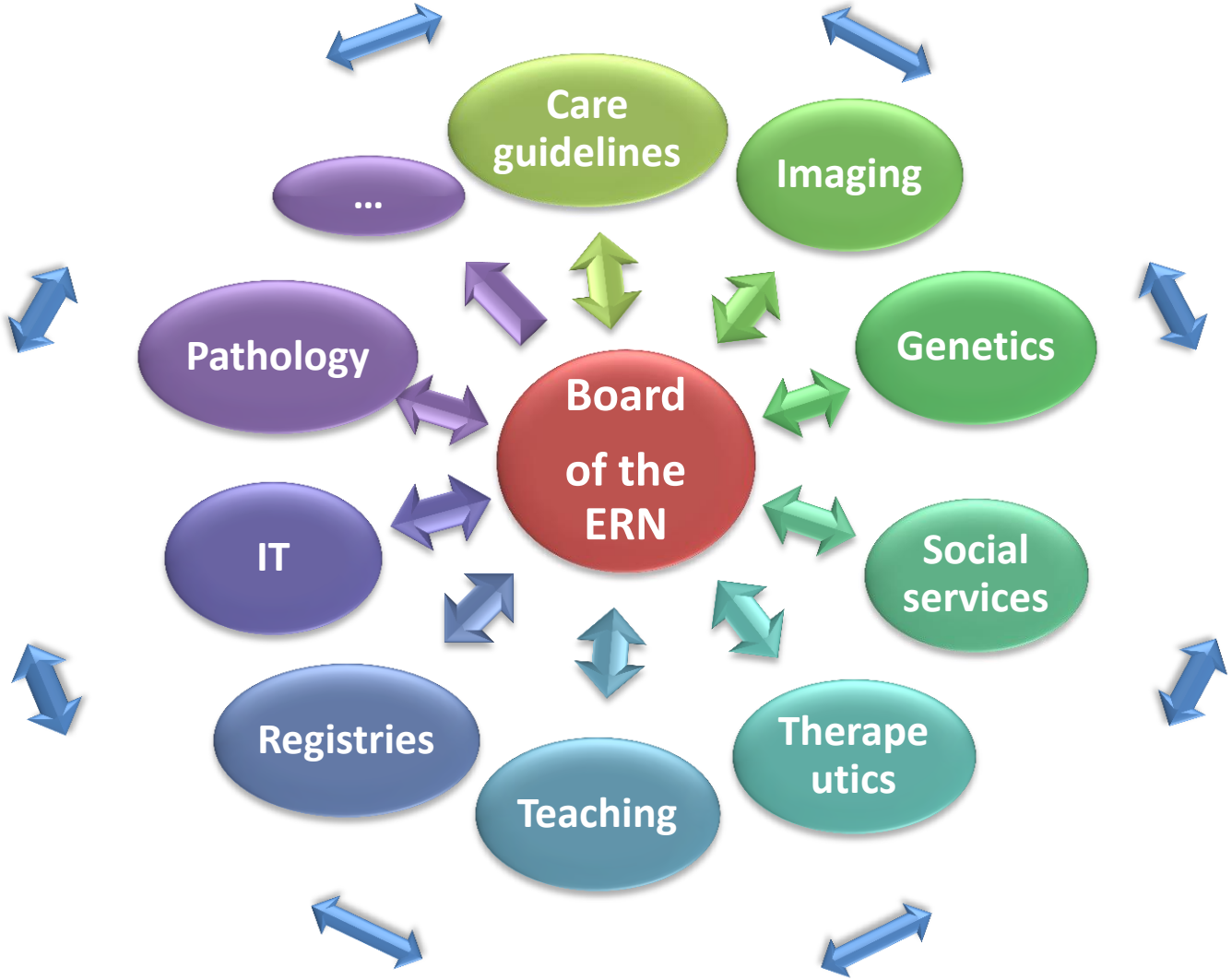
  Dissemination of information

- **Trials**

  Selection of patients (registries)

  Training of professionals in assessment protocols

Possible working Groups that could feed into the Board of the ERN



Board of the ERN should be supported by:

Among others
Grant Search for sustainability
Contacts with Industry

Input about the teaching priorities
Evaluation of the initiatives

Input on common research priorities
Screening of research projects
Grant applications for research

Care

Outcome measures

Training

Training and education

Research

Clinical Trial Coordination Centre

Trials/ Research

Registries

Global patient registries

Communication infrastructure

Regulatory information

TREAT-NMD

Neuromuscular Network

Trials/ Research

TACT

Advisory committee for therapeutics

Care and trials

CTSR

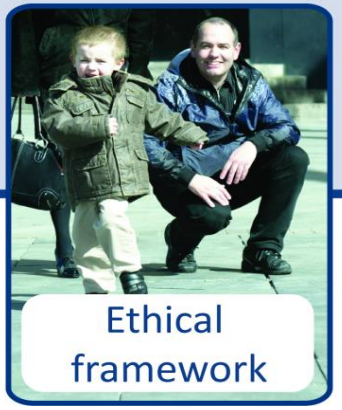
Care and trial site registry

Research

Standards for animal assessment

Care

Care standards



Ethical framework

Research

EuroBioBank

Care and Trial Site Registry – CTSR

A Powerful Tool for Clinical Research and Networking in Rare Diseases

Jan Kirschner

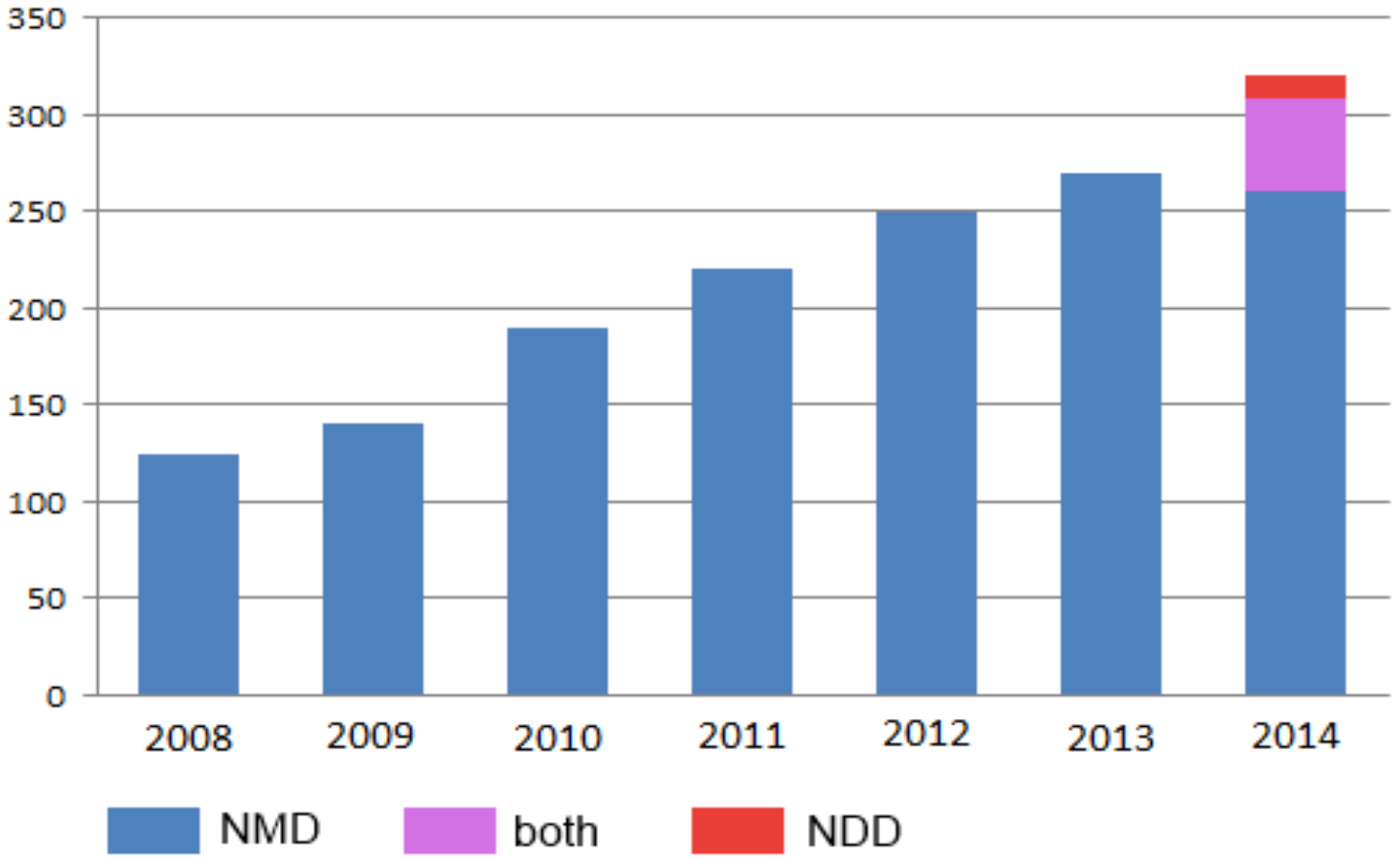
Dept. of Neuropaediatrics and Muscle Disorders

Universitätsklinikum Freiburg, Germany

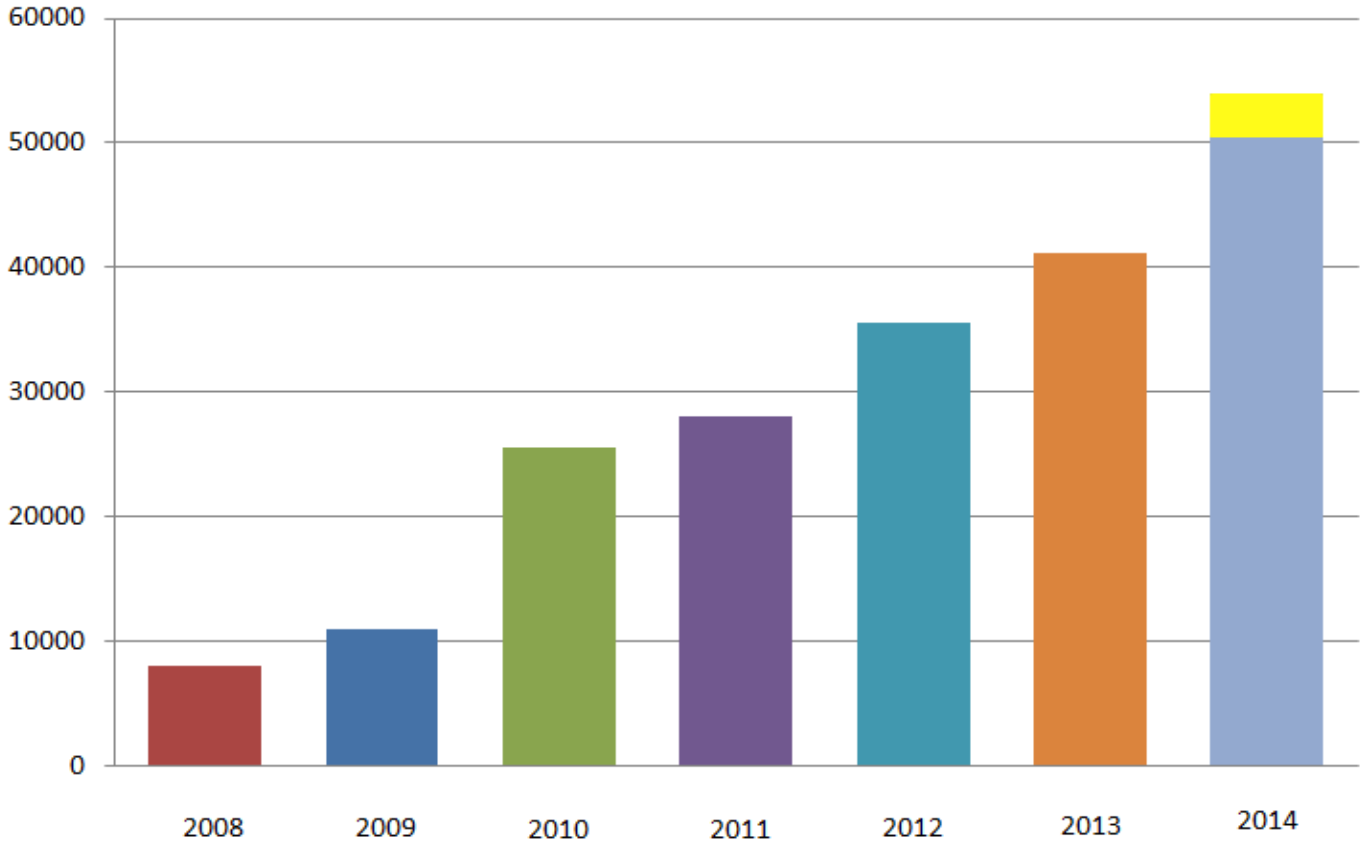
Background

- Established in 2007 in the scope of the TREAT-NMD project.
- In September 2013 the CTSR expanded to cover the field of rare neurodegenerative diseases as a branch of NeurOmics (FP7, 2012-2017) and now encompasses 32 rare diseases subdivided into two groups.

Number of sites since 2008



Patient numbers since 2008



Potential role for ERN

- Motivate all centres interested to participate in ERN to register or to update information in the CTSR
- Use the content of the database for the application, e.g. infrastructure of existing centres and networks, identify gaps for patient care in different European countries

INCOME AND NON-MONETARY RESOURCES

- The ERN needs to take into consideration:
  - Cross-country payments
  - IT platform maintenance
  - Technical support
  - Administrative work
  - Network meetings
  - Dissemination costs
  - Care coordination

ERN IMPLEMENTATION: the way forward

Cross-sectorial cooperation and funding sources

- ✓ Public health program 2014-2020: studies & project grants to approved ERN
- ✓ RTD horizon 2020 : 2016 research on networks organizational models
- ✓ Connecting European Facilities (CEF): the eHealth dimension
- ✓ Structural funds (cross border cooperation)
- ✓ Social funds (training and better skills)

Preparatory and strategic activities
From Enrique Terol presentation

- Strengthening the network value and capacities:
  and Identify Multidisciplinarity
  Avoid fragmentation: Grouping of diseases
  Identify mature and clear EU added value type of diseases
  Discuss y other players, partners and members

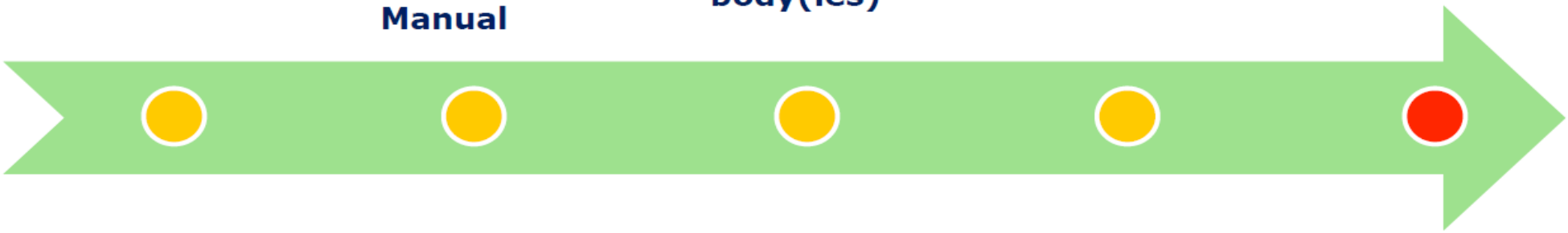
- Liaison with MS authorities

- **Define the services of the Network**
- **Agree on the specific criteria for each area of expertise**
- **Self-assessment exercise (Network and members): decision of participation as members or as Associated National Centres**
- **Define Pathways models, referral criteria, clinical decision tools**
- **Information system/indicators**

ERN tentative timeline & milestones

European Commission

May 2014	July 2014	II quarter 2015	IV quarter 2015	II quarter 2016
				
Entry into force legal acts	**Call for Assessment Manual**	**Call for selection independent body(ies)**	**Call for Networks**	**Establishment of Networks**



Health and Consumers

European Reference Networks

- **Harmonizing genetic testing across Europe**
- **Harmonizing guidelines for genetic testing across Europe**
- **Implementing RD research at the international level**

RD Connect

EUROPEAN NEURO MUSCULAR CENTRE

NeuroOmics

IRDiRC
INTERNATIONAL RARE DISEASES RESEARCH CONSORTIUM

EMQN
The European Molecular Genetics Quality Network

EuroGentest

ESHG