ERN-ITHACA
Webinar 2024

Webinar #14 - ERN ITHACA

Innovation in Newborn Screening across Europe: Part 2

Pr Laurence FAIVRE

Chair Workgroup Teaching & Education

April 09, 2024

European Commission

EUROPEAN REFERENCE NETWORKS

Helping patients with rare or low-prevalence complex diseases

European Reference Networks ITHACA

Welcome – Technical points

- **We are please to be numerous**
- **Webinar being recorded**

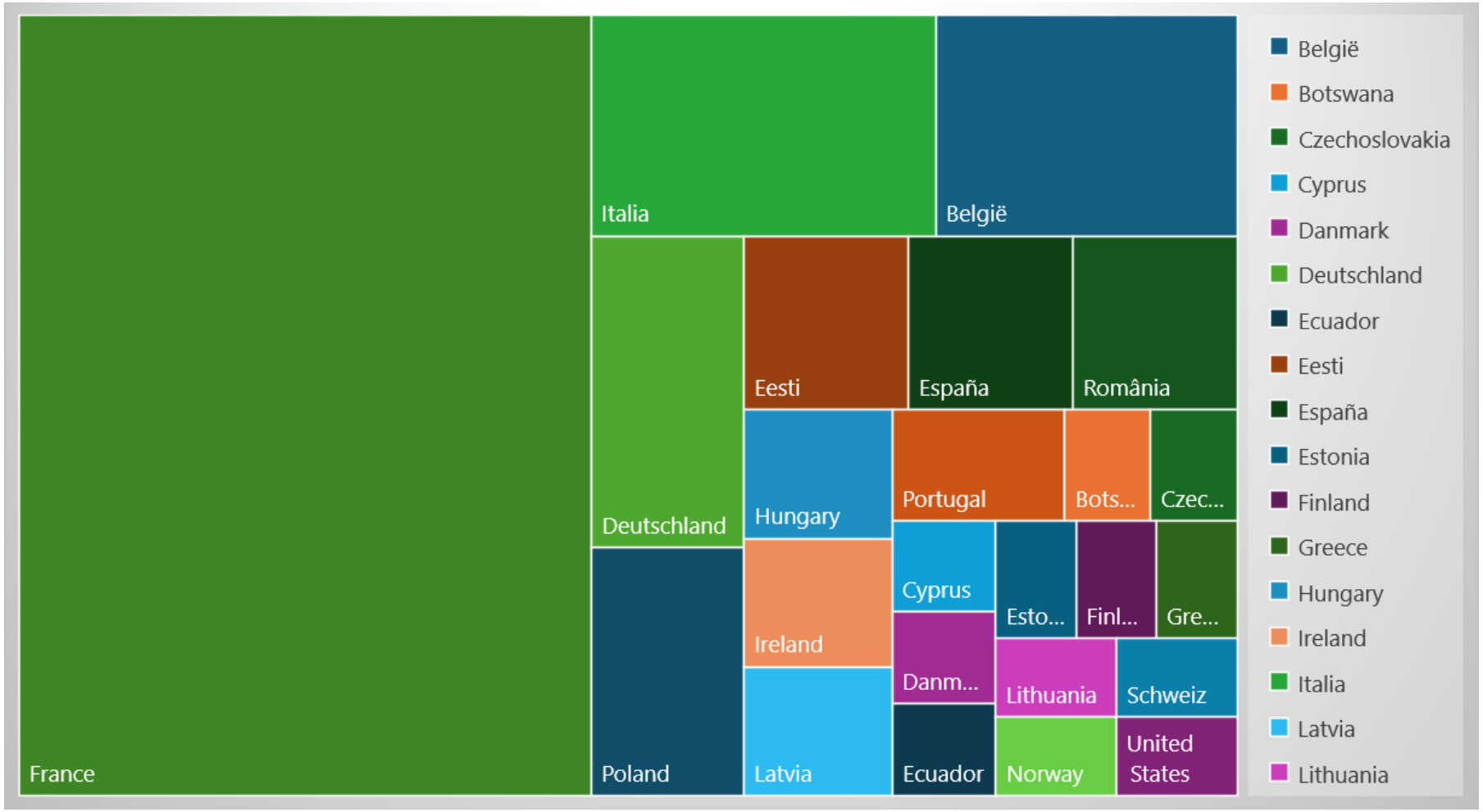
- **Thank you for**
  - Turn off your microphone and disconnect your camera
  - Use the chat for your questions
  - Raise your hand at the time of the questions and discussions
  - We will try to answer most of your questions
  - ➢ A satisfaction survey : https://forms.office.com/e/kF13wdXEvk

- **Webinar will be available on ITHACA's Website**

https://ern-ithaca.eu/documentation/educational-resources/

- Anne Hugon Project Manager ERN ITHACA - anne.hugon@aphp.fr

125 registrations



European Reference Networks ITHACA

Welcome and Introduction

- **Chaired by Pr Laurence FAIVRE, Workgroup Teaching and Education**

  The teaching and Training working group have proposed in March 2023 a webinar entitled "ERN ITHACA Innovation in Newborn Screening across Europe", which was a great success. ERN members requested that we organize another one to have better knowledge on the genomic initiatives NBS across Europe.

  With this webinar, we will present four additional European pilot programs to extend NBS with a genomic approach. We will also present the voice of patients issued from Eurordis rare barometer.

  Finally, we will discuss the technical, clinical, and ethical aspects of such projects.

- **Public: all, mostly professionals**

Agenda

- **Welcome and Introduction**
  - Pr. Laurence Faivre, Centre de Génétique, Dijon (France)

- **Topic 1 - Presentation of 4 European genomic NGS pilot projects in Europe**
  - The NEW LIVES German program, Dr. Nicola Dikow, Institute of Human Genetics, at Heidelberg University. (Germany)
  - The FirstSteps Greek program, and its interaction with Screen4Care and BeginNGS, Pr. Petros Tsipouras (Greece)
  - The Danish approach: Targeted Genetic Analyses: Reducing False Positives and Enhancing Performance in Danish Newborn Screening, Alberte Lundquist, MD, Department of Paediatrics and Adolescent Medicine, Copenhagen University Hospital (Denmark)
  - The GenNatal Spanish program, Pr. Francesc Palau, Genetic Medicine Service of the Hospital Sant Joan de Déu, Barcelona (Spain)

- **Topic 2 - The Rare Barometer survey on the opinion of people living with a rare disease on NBS**
  - Jessie Dubief, Social Research Director, EURORDIS-Rare Diseases Europe

- **Discussion and Conclusion with speakers and moderator**

The NEW LIVES German program

Dr. Nicola Dikow, Institute of Human Genetics, at Heidelberg University. (Germany)

European Reference Networks ITHACA

UNIVERSITÄTS KLINIKUM HEIDELBERG

GEFÖRDERT VOM
Bundesministerium für Bildung und Forschung

NEW LIVES

Balancing Opportunities and Challenges in Genomic Newborn Screening:

Ethical, Legal, Social and Technical Aspects

UK HD

Newborn screening in Germany (2024)

Newborn screening programs are among the most effective programs of public healthcare of the 20th and 21st century

currently 19 diseases in Germany

Table 1: Current target disorders of newborn screening in Germany (as of October 2021) and screening markers used.

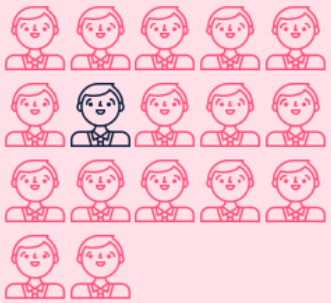
Disorders		Primary screening markers	Second-/third-tier markers
Endocrine disorders	Congenital hypothyroidism	TSH	
	Congenital adrenal hyperplasia	17-OH-progesterone	Steroid profile (used in single German laboratories)
Metabolic disorders	Biotinidase deficiency	Biotinidase activity	
	Galactosemia (classical)	GALT activity	Total galactose
	Phenylketonuria/hyperphenylalaninemia (including cofactor deficiencies)	Phenylalanine	
	Tyrosinemia type I	Succinylacetone	
	Maple syrup urine disease	Xle (leucine + isoleucine + alloisoleucine + OH-proline)	Alloisoleucine – in principle available as second-tier test but not routinely used in German laboratories [6]
	Glutaric aciduria type I	Glutarylcarnitine	
	Isovaleric aciduria	Isovalerylcarnitine (C5)	
	Medium-chain acyl-CoA dehydrogenase deficiency	Octanoylcarnitine (C8)	–
	Long-chain 3-OH-acyl-CoA dehydrogenase deficiency	C16OH, C18:1OH	
	Very long-chain acyl-CoA dehydrogenase deficiency	C14:1	
	Carnitine palmitoyltransferase I deficiency	C0, decreased long-chain acylcarnitines	
	Carnitine palmitoyltransferase II deficiency	Long-chain acylcarnitines (C16–C18:2)	
	Carnitine acylcarnitine translocase deficiency	Long-chain acylcarnitines (C16–C18:2)	
Cystic fibrosis		IRT	PAP (second tier) 31 *CFTR* mutations (Germany) or *CFTR* sequencing (second or third tier [7])
Severe combined immunodeficiencies (SCID)		TREC (qPCR)	
Sickle cell disease (SCD)		HbS	
Spinal muscular atrophy (SMA)		SMN1, homozygous exon 7 deletions (qPCR)	

Abbreviations: C_x = respective chain length of acylcarnitines; CFTR = cystic fibrosis transmembrane conductance regulator; GALT = galactose-1-phosphate uridyltransferase; TREC = T-cell receptor excision circles; IRT = immunoreactive trypsine; TSH = thyroid-stimulating hormone; HbS = hemoglobin S; PAP = pancreatitis-associated protein; SMN = survival motor neuron; qPCR = quantitative polymerase chain reaction.

Gramer et al., Medizinische Genetik, 2022

There are over 7000 Rare diseases

1/17
people develop
a rare disease



400m
people with
rare diseases

>7000
different types

25%
adults

75%
children

28%
neonatal intensive
care deaths

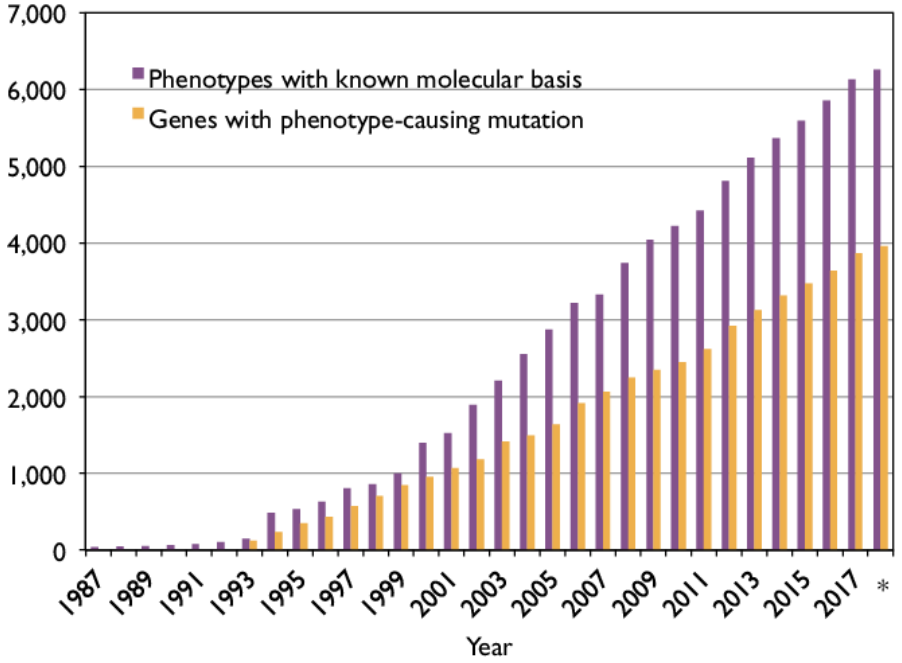
80%
are genetic
in origin

30%
of affected children
never reach their
5th birthday

5years
on average
to diagnose

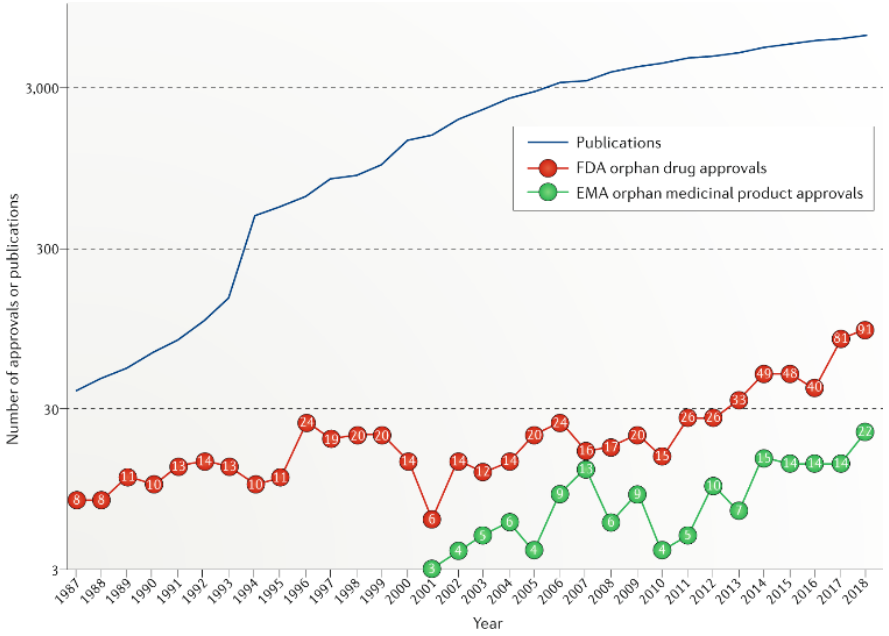
https://blog.congenica.com/why-a-diagnosis-is-so-important-for-rare-disease-patients

Better understanding of the genetic causes of disease



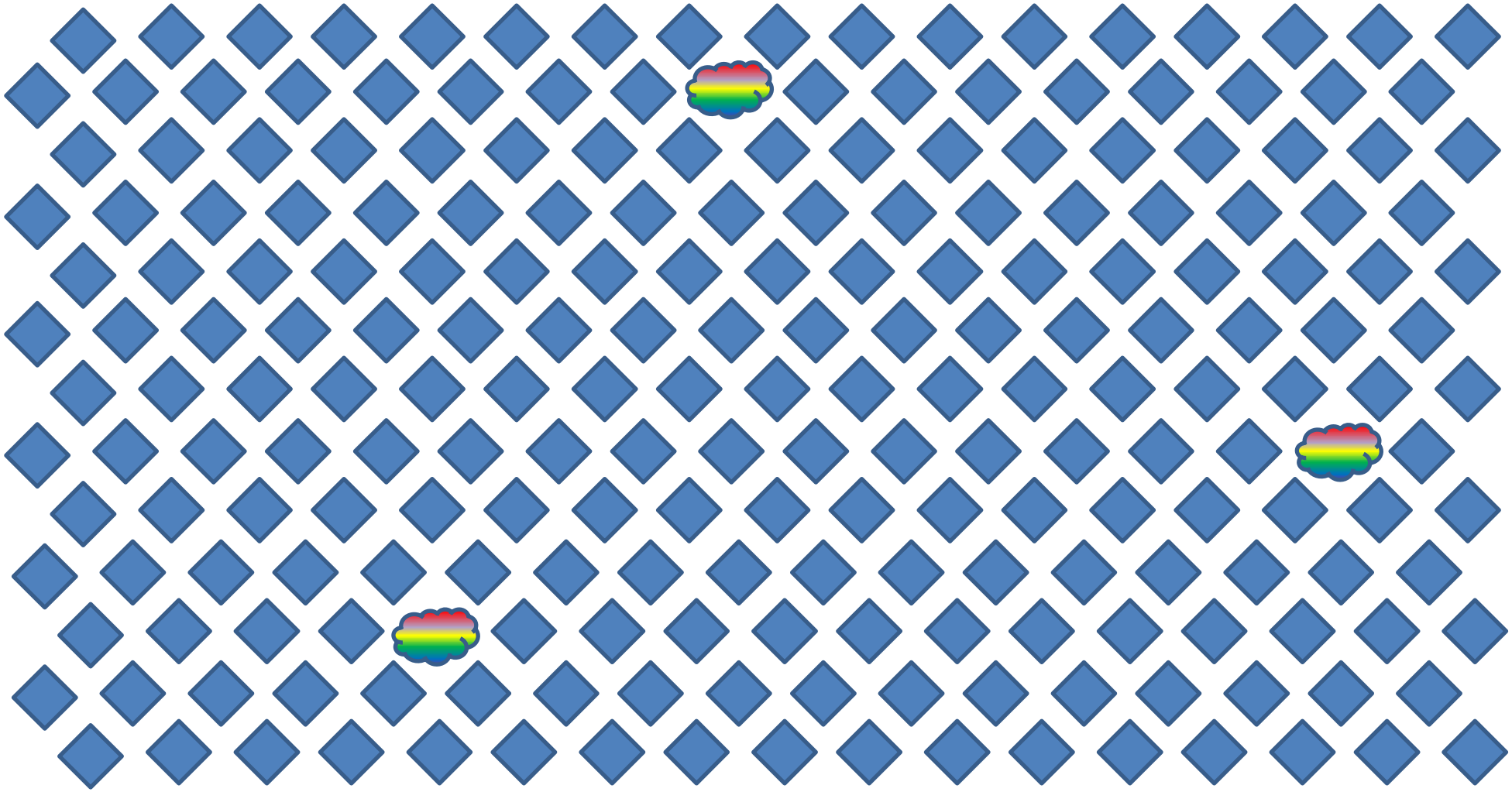
omim.org

More therapeutic opportunities for rare disorders

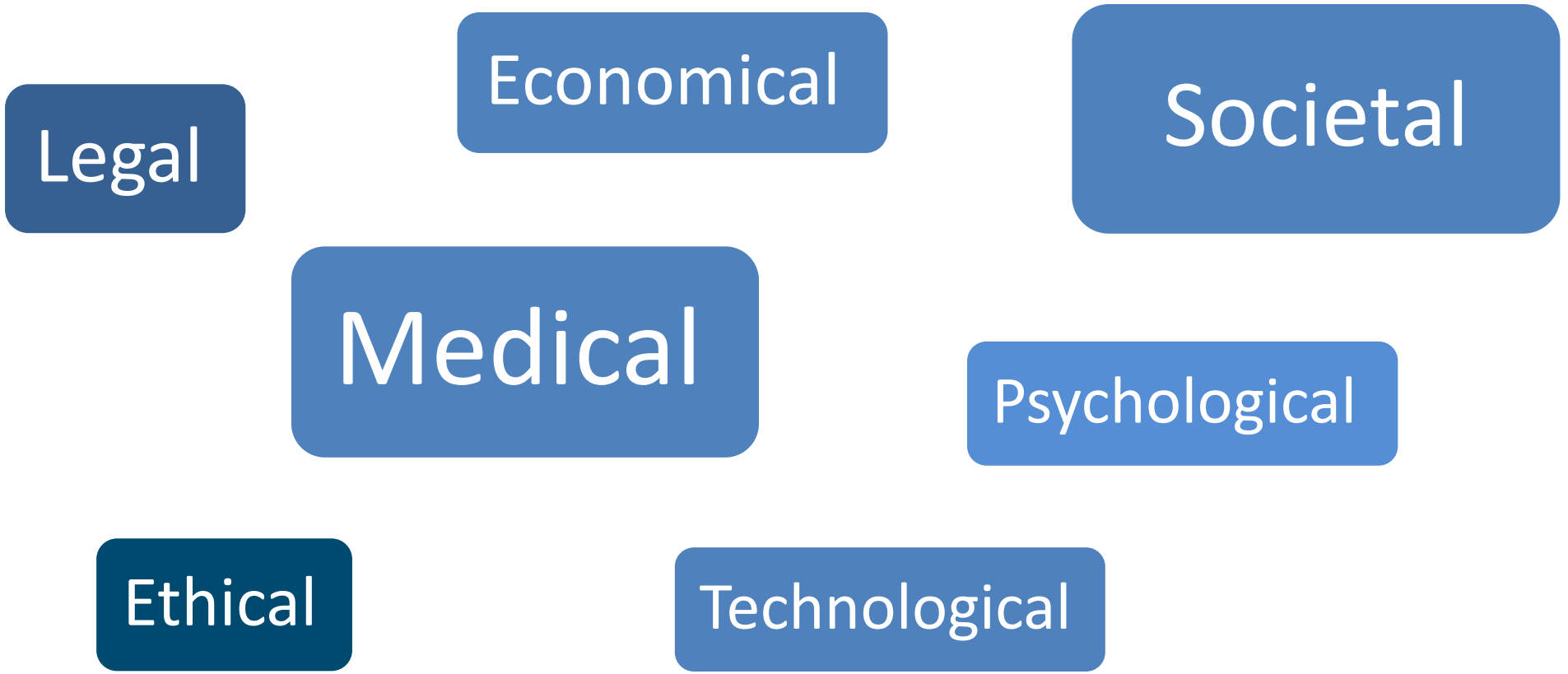


Tambuyzer et al., 2019

But which findings should we report?



And which arguments should we consider?



NEW_LIVES:

Genomic NEWborn Screening Programs
Legal Implications, Values, Ethics and Society

TP1: Ethics – Section of Translational Medical Ethics, National Center for Tumor Diseases (NCT) Heidelberg

TP2: Law – Department of Law, University of Mannheim

TP3: Medical Psychology – Institute of Medical Psychology, Heidelberg University

TP4: Human Genetics – Institute of Human Genetics, Heidelberg University

TP5: Pediatrics –Section for Neuropediatrics and Metabolic Medicine, Heidelberg University Hospital

Research Question:

1. Which criteria should be considered when choosing diseases for future gNBS-programs in Germany?

NEW LIVES

Benefits

Harm

→ reduce uncertainty
→ Criteria for choosing gene-disease pairs

Test, Investigation, Treatment, Financial, Psychological distress

UK HD

(I) Clinical Criteria	1)	**Gene-Disease-Association**
	2)	**Penetrance**
	3)	Severity of Disease
	4)	**Disease Onset**
(II) Analytic-Diagnostic Criteria	5)	Advantage over alternative methods
	6)	Quality parameters of test
	7)	**What to Report**
	8)	Confirmatory diagnostics
(III) Therapeutic Criteria	9)	**Availability of Intervention**
	10)	Benefits and Burdens of Intervention
	11)	Early Intervention Better
(IV) Program Design Criteria	12)	Equal Access and Acceptability
	13)	Informed Consent: When and Who
	14)	Informed Consent: What and How
	15)	Sample Collection and Analysis
	16)	Communication of Positive Test Result, Further Procedure
	17)	Data and Sample Storage
	18)	Central Coordination of Program

NEW LIVES

UK HD

Gene-Disease-Association

ClinGen Gene curation Expert Panels on Gene-Disease Validity: „The role of the gene in this particular disease“

Semiquantitative measurement for the strength of evidence of a gene-disease relationship that correlates to a qualitative classification:

Definitive,
Strong,
Moderate,
Limited,
No Reported Evidence, or
Conflicting Evidence

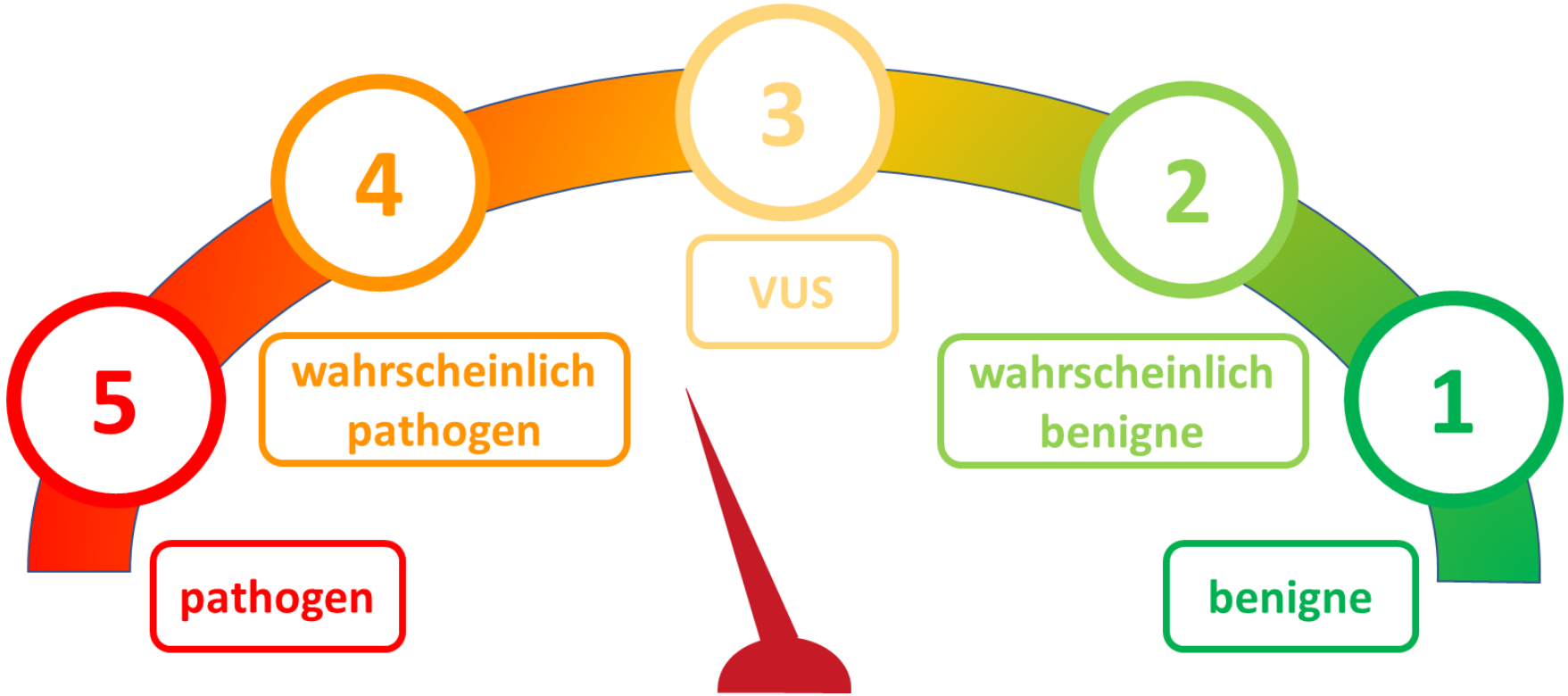
https://clinicalgenome.org/curation-activities/gene-disease-validity/ Strande et al., 2017, PMID: 28552198

What to Report

Only variants of class 4 (likely pathogenic) and 5 (pathogenic) according to the ACMG classification are reported. Carriers and variants of unclear significance (VUS) are not reported.

What to Report

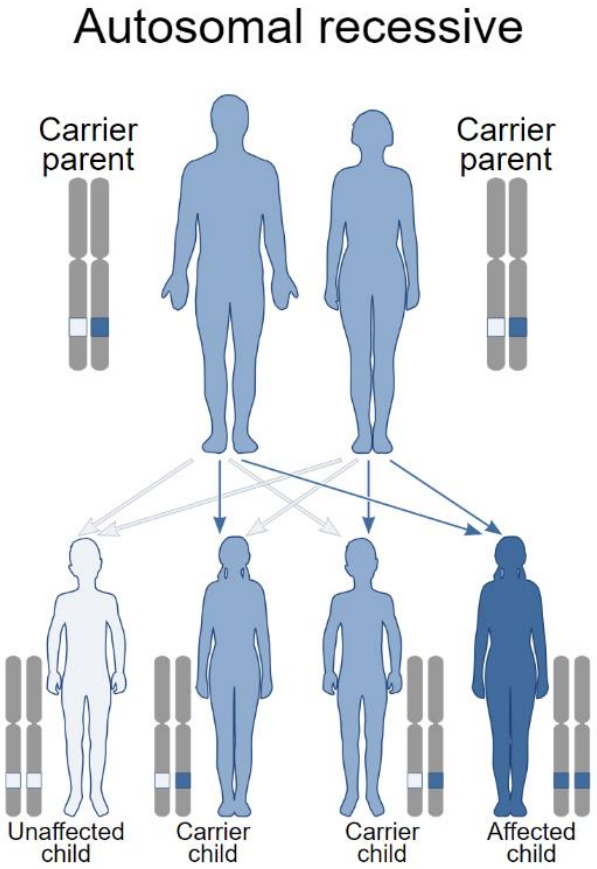
VUS not reported!

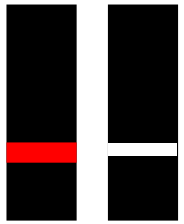


nach: Plon et al., Hum Mutat. 2008 Nov;29(11):1282-91

What to report

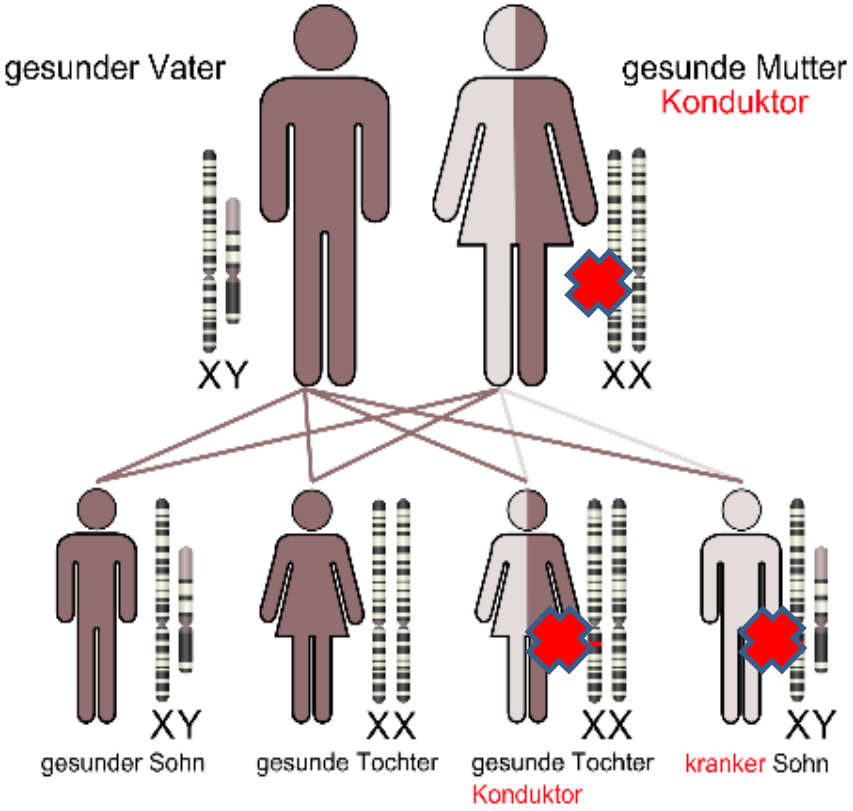
Carriership not reported!

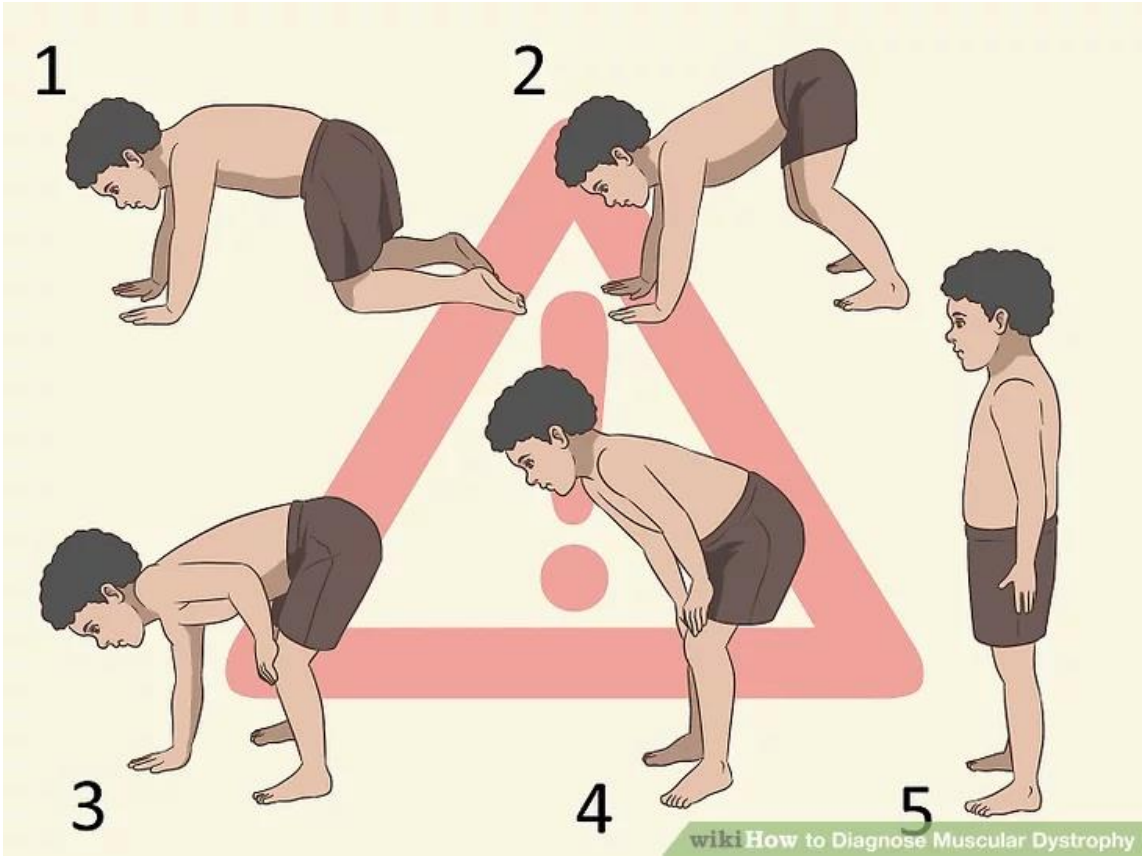




What to report

Carrier status not reported!





http://www.wikimedia.org

How to Diagnose Muscular Dystrophy: (wikihow.health)

Penetrance Will it even occur?

Likelihood of onset (at any time) of a specified health condition

The *penetrance* of disease-associated genes that require **therapeutic intervention** is **at least 80%.**

- Genomics England: „A high proportion of individuals (...) to have symptoms"
- BabySeq PMID: 28079900: High (High: > 80%, Low: < 20%) + evidence level
  (A: substancial evidence to D: poor or conflicting evidence and N: non-systematically identified or expert contributed evidence)
- Kingsmore et al., 2022, PMID: 36007526: high likelihood of rapid progression without treatment
- Berg et al., 2016, PMID: 26270767:

Likelihood of disease: "What is the chance that a serious threat will materialize?" (somewhat akin to penetrance)	>50%	3	Most individuals develop the severe outcome
	6–49%	2	Some individuals develop the severe outcome
	1–5%	1	Few individuals develop the severe outcome
	<1%	0	Outcome is very rare or cannot be reasonably estimated

Penetrance

Will it even occur?

The *penetrance* of disease-associated genes that require **therapeutic intervention** is **at least 80%**.

The penetrance of disease-associated genes requiring only recurrent monitoring is at least 50%.

Penetrance

Cancer predisposition syndromes (CPS)

APC – FAP ClinGen Definitive Actionability 10CA

1/70000 - 1/30000

20%-30% *de novo*

Cancer Lifetime risk almost 100% (med. AO CRC 39 years)

by 15 yrs, 50% of pat. have adenomas

Colonoscopy beginning at age 10 yrs

Penetrance

RB1 – Retinoblastoma ClinGen Strong Actionability 10CB

1/15000-1/18000 live births

Childhood-onset (most < 5 yrs)

With few exceptions, *RB1* null alleles show complete penetrance

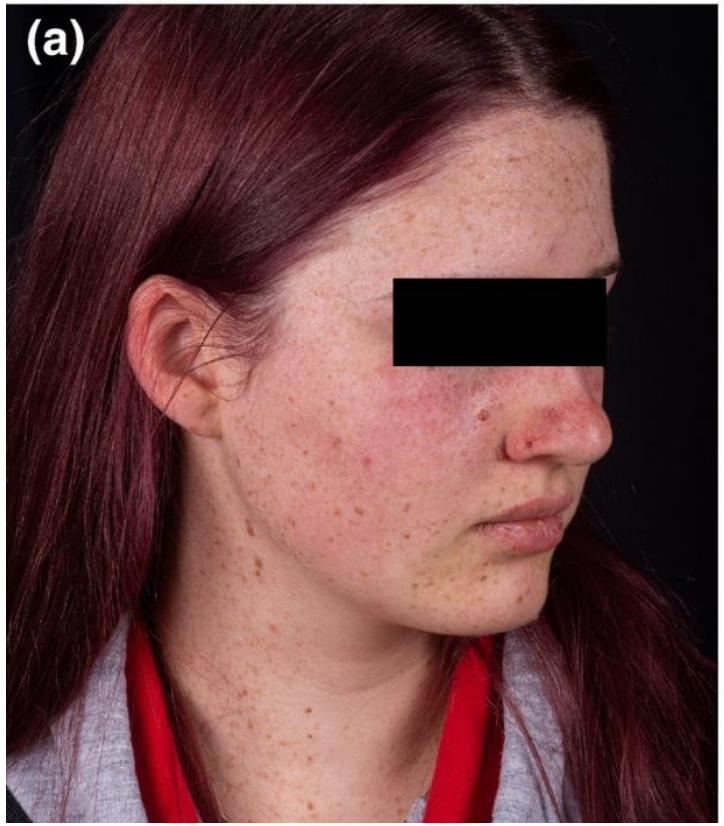
Surveillance: from birth

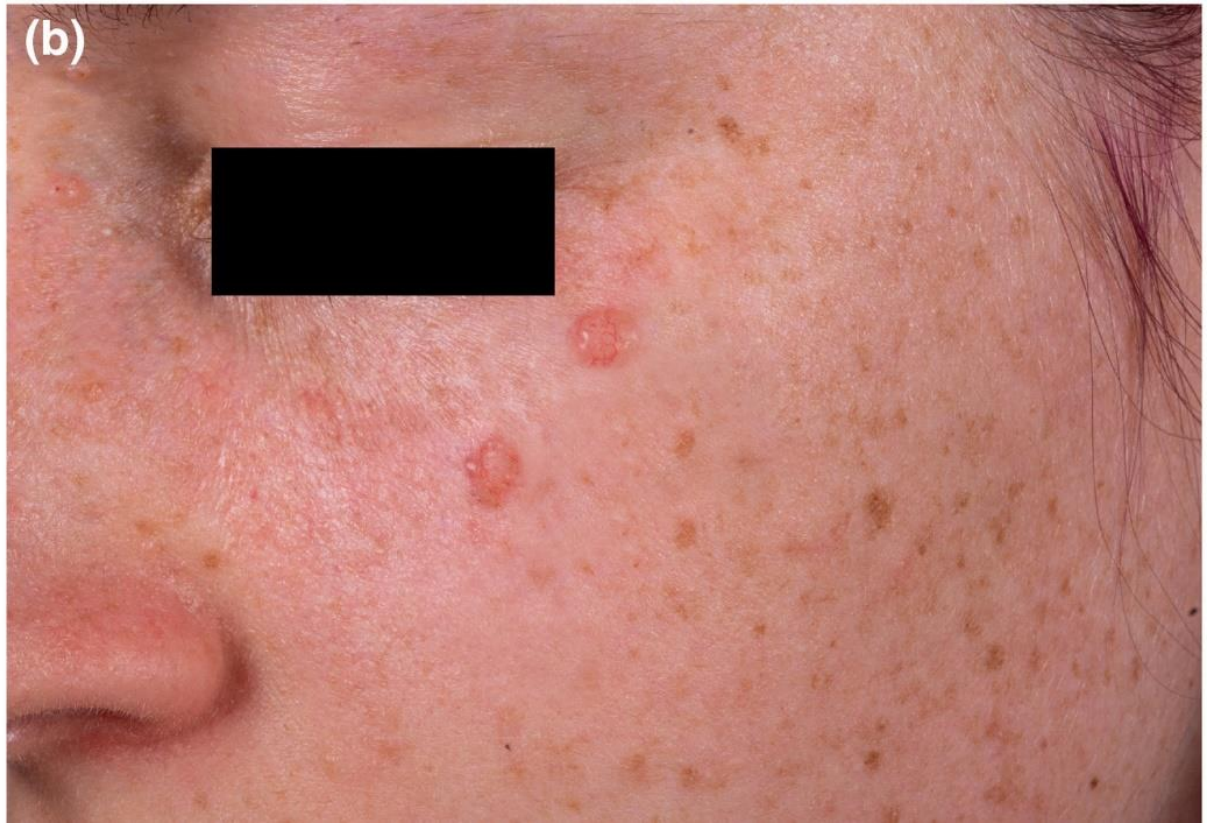
Good prognosis when diagnosed and treated early, lethality <5%, but when left untreated lethality > 99%

Metastasized retinoblastomas have a bad prognosis

Penetrance

Adolescent with multiple basal cell carcinoma

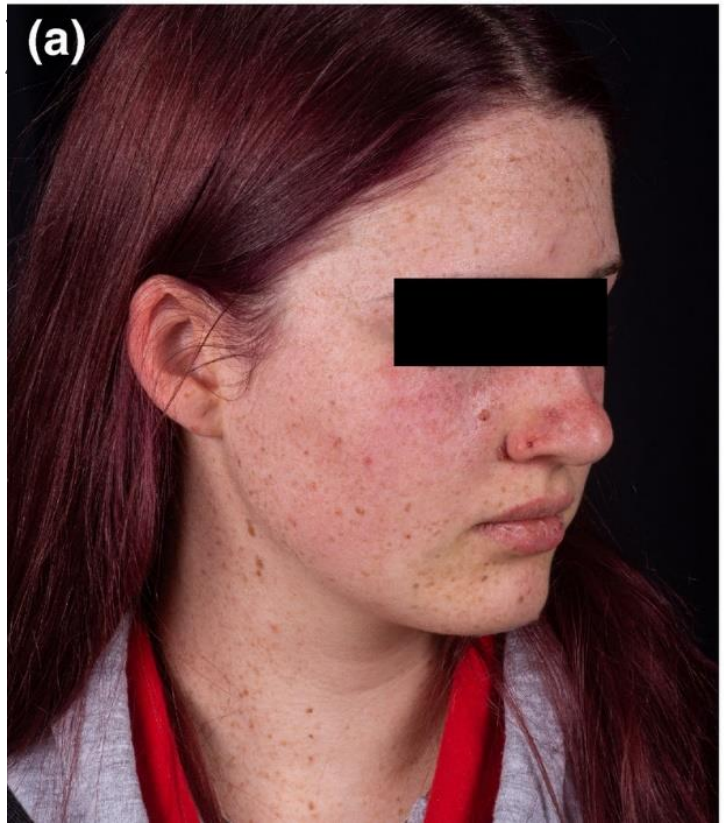




PMID: 34570363

Penetrance

Adolescent with multiple basal cell carcinoma and squamous cell carcinoma



POLH (NM_006502.2):
c.(660+1_661-1)_(764+1_765-1)del, p.?
c.1189_1196del;p.(His397Ilefs*8)
→ Xeroderma Pigmentosum

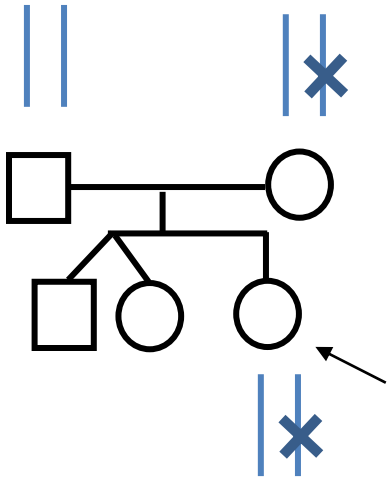
XP: Nucleotide excision repair (NER)
POLH: DNA polymerase eta

PMID: 34570363

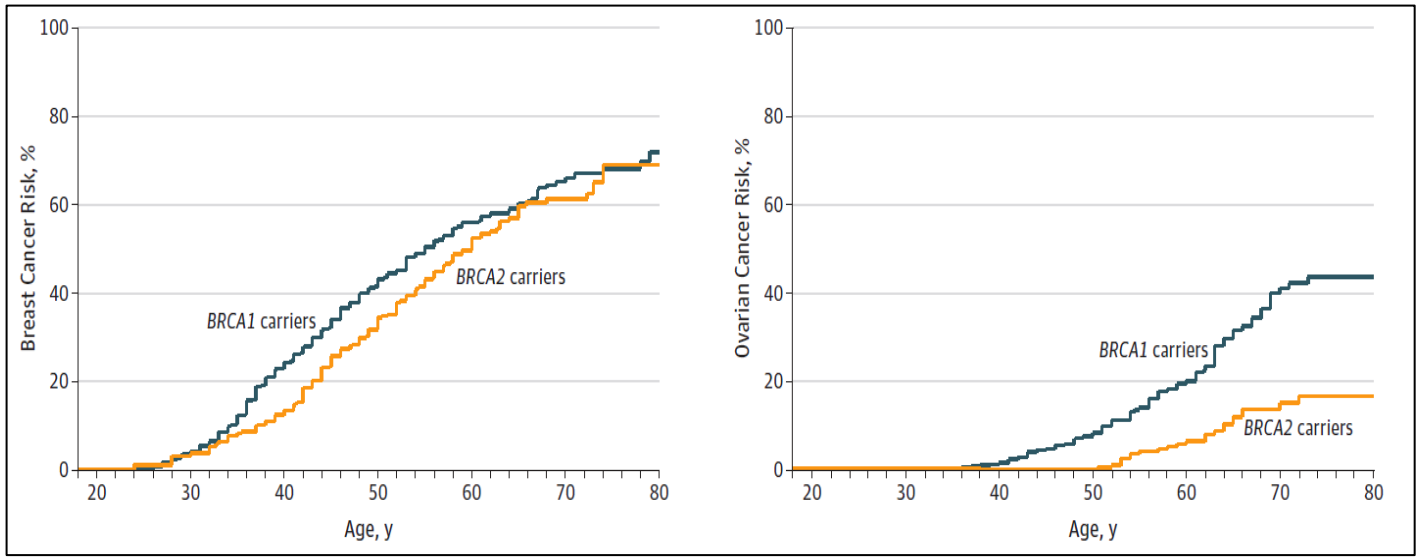
Disease Onset

The average age of onset of the disease is before school age (up to 7 years).

adult-onset



BRCA1 : PV



BRCA1
BK (80 J.): 72%
OK (80 J.): 44%

Kuchenbaecker et al., JAMA. 2017; 317:2402-2416

- BabySeq: in 3,5% adult onset diseases (PMID: 30609409)

Flaticon.com

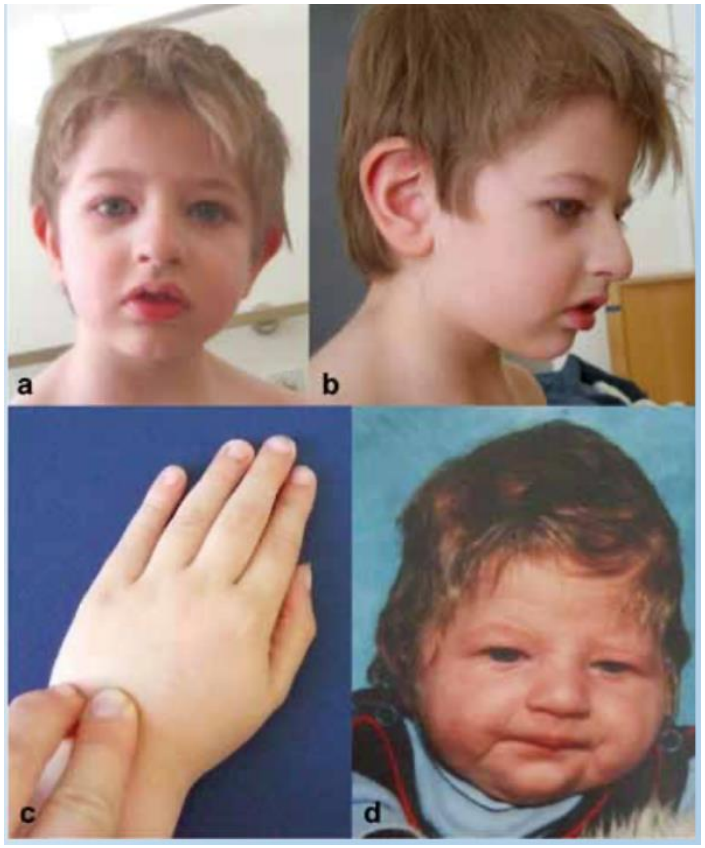
Availability of Intervention

A therapeutic intervention is established and available that has a beneficial effect on the natural course of the target disease, i.e. alleviates disease symptoms or prevents or delays their occurrence.

- W&J: There should be an accepted treatment
- BeginiNGS PMID: 36007526 „Effective treatment“
- Babydetect Belgien „Treatable“

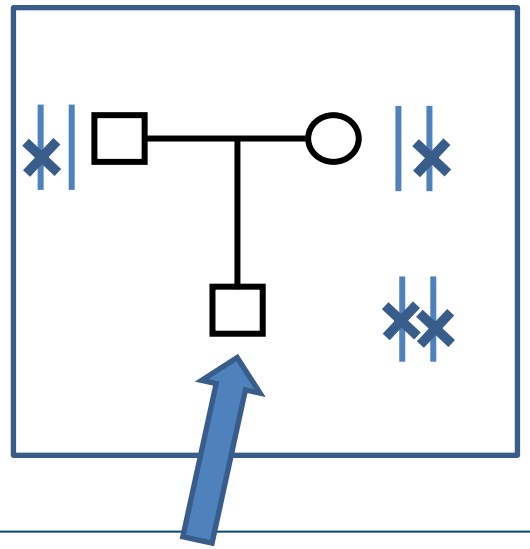
What to Communicate

Non - “actionable”



Dikow et al., 2011

- „Actionability is a continuum, not a binary state.“ (Berg et al., 2016)
- „Disease association and penetrance could be considered a priority above actionability“ (Downie et al., 2021)



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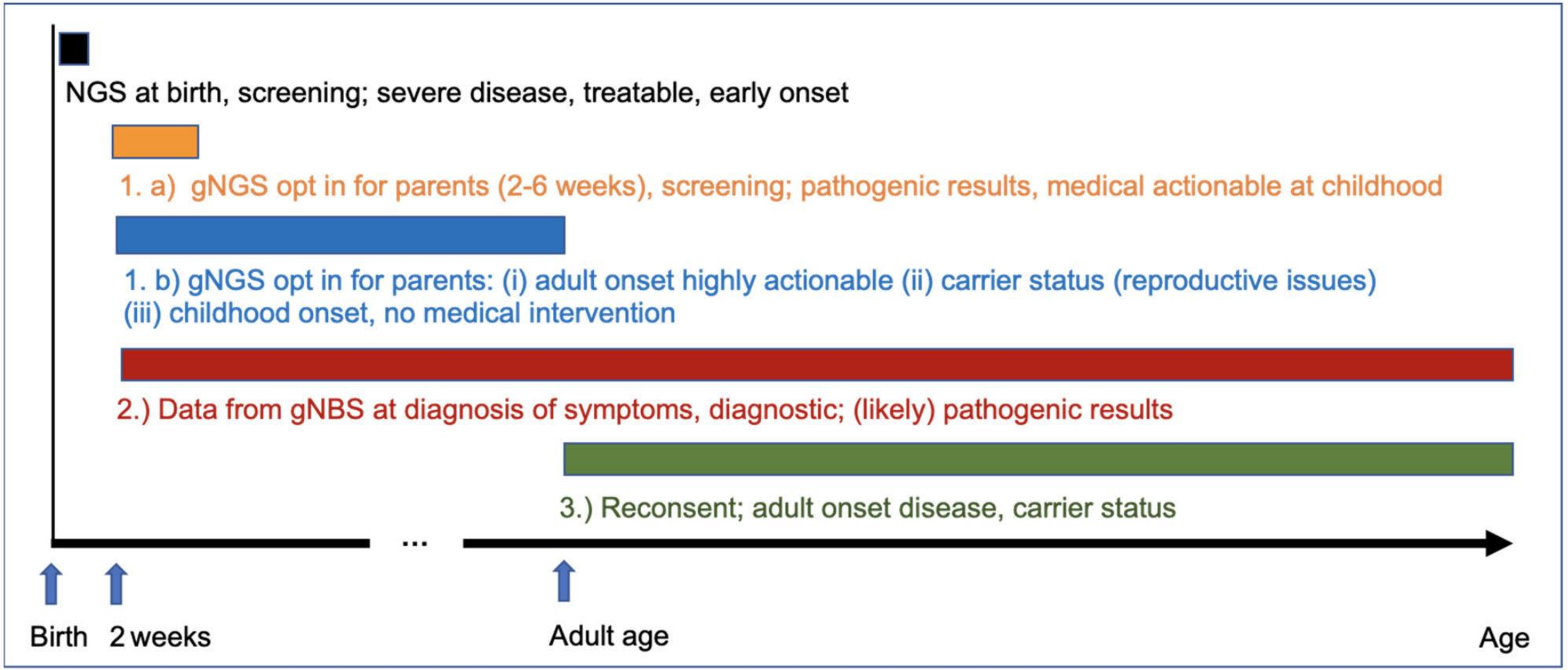
When to communicate (and what)?



Dikow et al. 2022, https://doi.org/10.1515/medgen-2022-2113

Thank you very much! Vielen Dank!

***NEW_LIVES**:*
*Genomic **NEW**born Screening Programs*
***L**egal **I**mplications, **V**alue, **E**thics and **S**ociety*

***TP1: Ethics* – Translationale Medizinethik, Nationales Centrum für Tumorerkrankungen Heidelberg**
Prof. Dr. Dr. Eva Winkler, Karla Alex, Sascha Settegast M.A.

***TP2: Law* – Abteilung Rechtswissenschaft, Universität Mannheim**
Prof. Dr. Ralf Müller-Terpitz, Hannah Straub

***TP3: Medical Psychology* – Institut für Medizinische Psychologie, Universitätsklinikum Heidelberg**:
Prof. Dr. Beate Ditzen, Dr. Julia Mahal, Elena Sophia Doll M.Sc., Seraina Lerch M.Sc., Carlotta Mayer M.SC.

***TP4: Human Genetics* – Institut für Humangenetik, Universitätsklinikum Heidelberg**
Prof. Dr. Christian Schaaf, Dr. Nicola Dikow, Dr. Heiko Brennenstuhl

***TP5: Pediatry* – Sektion Neuropädiatrie und Stoffwechselmedizin, Zentrum für Kinder-und Jugendmedizin, Universitätsklinikum Heidelberg**
Prof. Dr. Stefan Kölker, PD Dr. Ulrike Mütze, Elena Schnabel

The FirstSteps Greek program, and its interaction with Screen4Care and BeginNGS

Pr. Petros Tsipouras (Greece)

Newborn Genome Screening: Opportunities and Challenges Setting up a National Program in Greece

Petros Tsipouras, MD

ERN Ithaca Webinar # 2

April 9, 2024

NATIONAL NETWORK

MANAGER

FirstSteps
NEWBORN GENOME SCREENING

SPONSOR

ΕΘΝΙΚΟΣ ΟΡΓΑΝΙΣΜΟΣ ΔΗΜΟΣΙΑΣ ΥΓΕΙΑΣ

EODY National Public Health Organization

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Real World Evidence

SITES

AUTH-Papageorgiou Hospital, Thessaloniki
1st Academic Department of Obstetrics-Gynecology
Prof. G. Grimbizis
Department of Neonatology
Prof. C. Tsakalidis

University of Thessaly-University Hospital, Larissa
Department of Obstetrics-Gynecology
Prof. A. Daponte
Department of Neonatology
Prof. I. Grivea

EKPA Alexandra Hospital, Athens
1st Academic Department of Obstetrics-Gynecology
Prof. G. Daskalakis
Department of Neonatology
Prof. I. Loukatou

Newborn Genome Screening| International Projects

Several initiatives on newborn genomic screening have been launched globally. The guiding principle for all programs is early detection & intervention which lead to better health outcomes, signaling a clear shift to preventive medicine.

ICONS

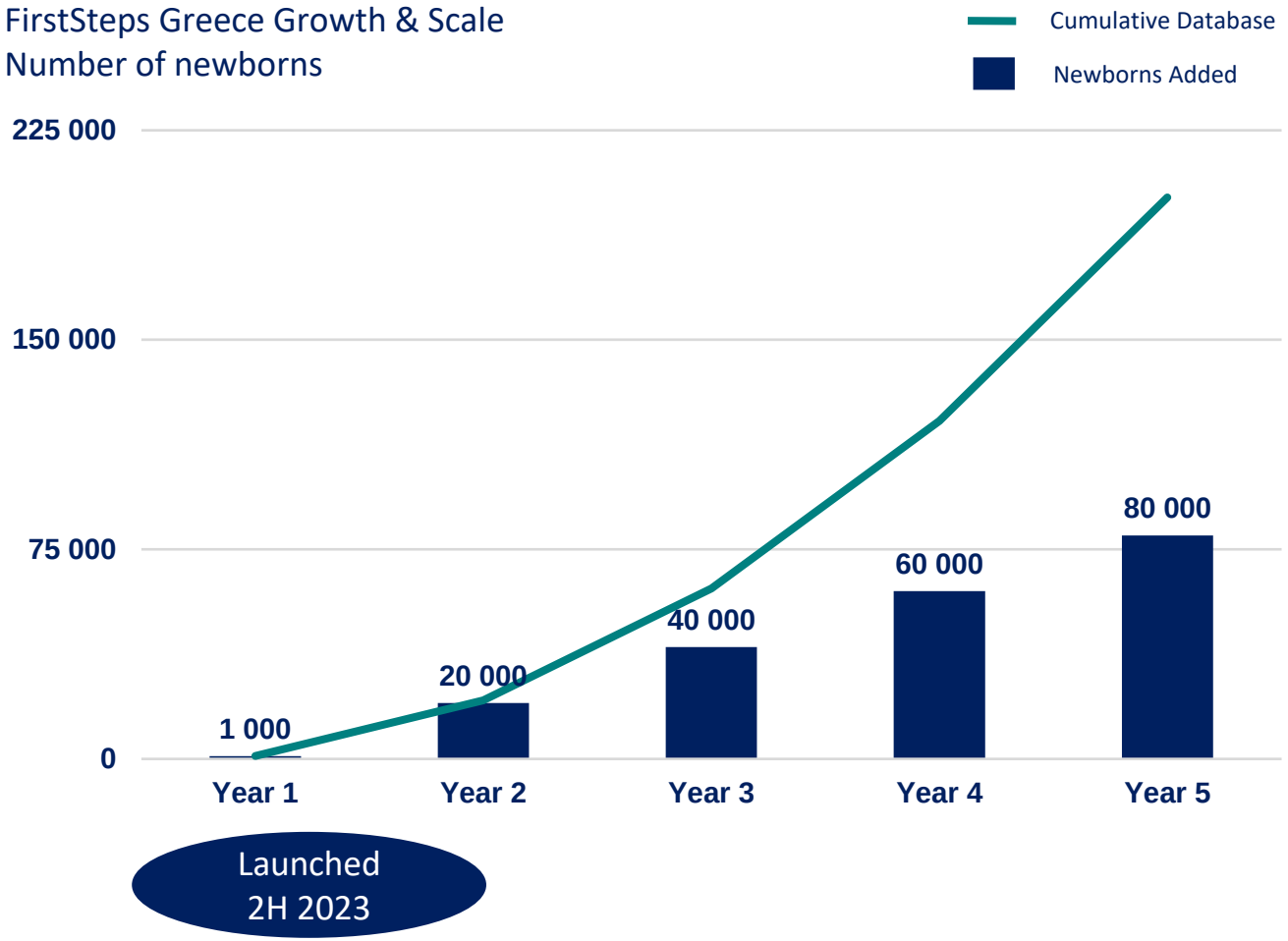
An international consortium under which global projects share the vision of responsibly implementing newborn sequencing to accomplish early diagnosis and accurate treatment.

ENROLL Actively enrolling families

- Source: Deloitte Research

FirstSteps IS UNDERWAY

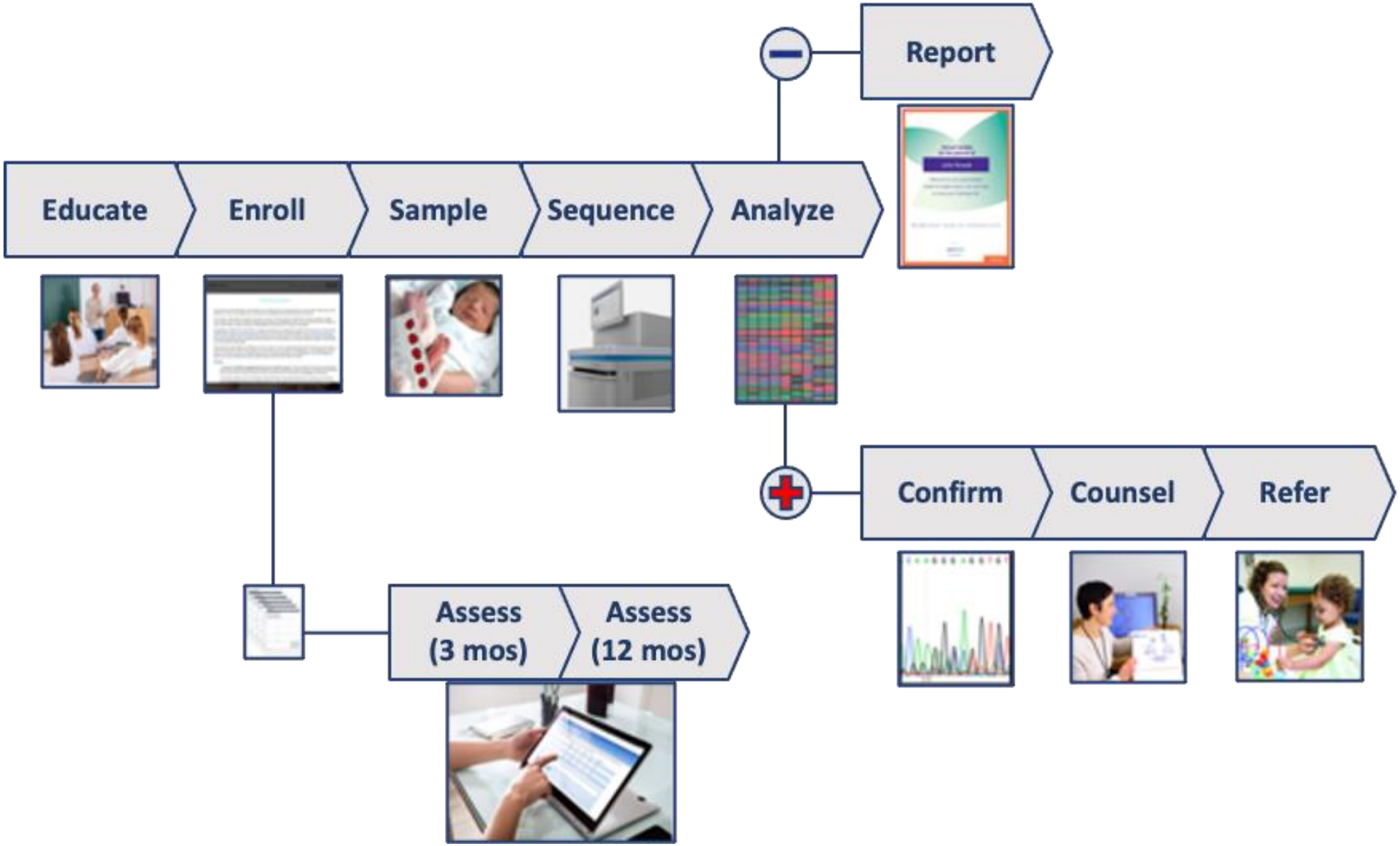
FirstSteps Greece Growth & Scale
Number of newborns



FirstSteps Greece Site Launches
Date Recruiting Started

Phase 1 Sites	Recruiting Start
EKPA-Alexandra Hospital, Athens	July 2023
AUTH-Papageorgiou Hospital, Thessaloniki	August 2023
University of Thessaly-University Hospital, Larissa	September 2023

OPERATIONAL WORKFLOW



PROGRAM DASHBOARD

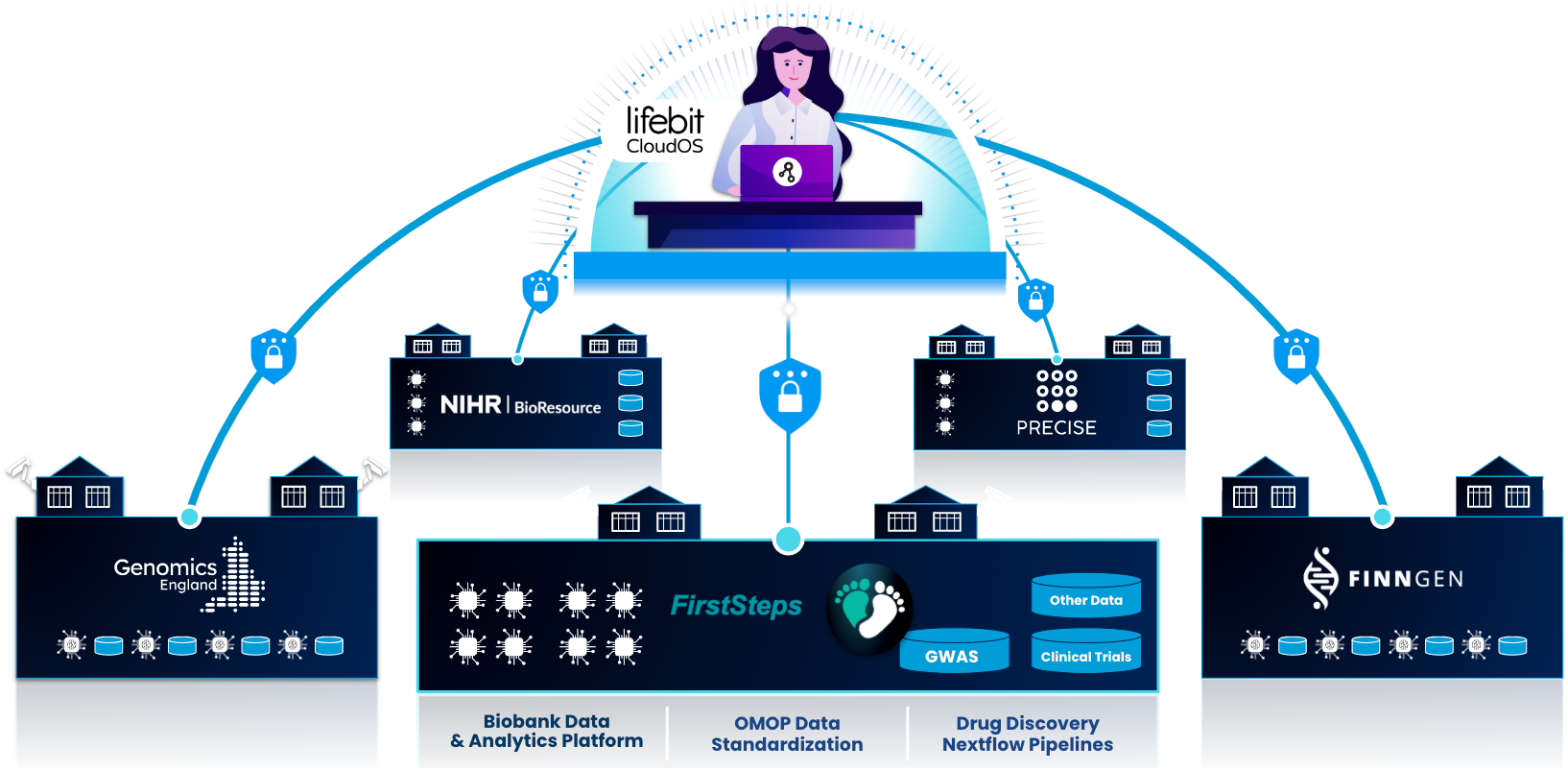
Enrol/Consent	Positive Cases
178	3
Processed/Reported	**Participant Feedback**
73	17

SCREEN POSITIVES

Gene	Variant	Disease	Diagnosis & Intervention
• F8	c.4825dup p.Thr1609fs NM_000132.4	Hemophilia A	• Factor VIII: 0.64% (rv: 50-150%) • Referred to ped. hematologist for managmt. • Genetic counselling to parents & aunt • Family trio testing (parents + mat. aunt)
• TCF3	c.219+1G>C NM_00320.5	A-gamma-globulinemia	• Orthogonal testing • Referred to ped.immunologist for managmt. • Genetic counseling
• CBS	c.341C>T p.Ala114Val NM_000071.3	Homocysteinouria	• Metabolic testing • Genetic counseling • Referral for managmt.

FEDERATED DATABASES FOR DATA INTEGRITY AND PROTECTION

- Better, Faster Diagnosis
- Accelerated Drug Discovery
- More Impactful & Translational Research, Faster



FirstSteps| Ecosystem

A dynamic and growing group of international and Greek partners to deliver the FirstSteps program.

SEQUENCING & INTERPRETATION

- FABRIC GENOMICS — Variant Interpretation
- PacBio — Sequencing Technology
- Oxford NANOPORE Technologies — Sequencing Technology
- dante labs — Lab Solution

DATA & RESEARCH

- Pre-Competitive Pharma Consortium: ultragenyx
- Federated Database: lifebit
- Research Member: SCREEN 4CARE
- Cloud: aws
- Program Member: ICONS

HEALTHCARE PROVIDERS

- Clinical Trial Sponsor: ΕΘΝΙΚΟΣ ΟΡΓΑΝΙΣΜΟΣ ΔΗΜΟΣΙΑΣ ΥΓΕΙΑΣ
- MedEd Sponsor: illumina
- Clinical Trial Sites: Γ.Ν.Α. ΑΛΕΞΑΝΔΡΑ; ΓΕΝΙΚΟ ΝΟΣΟΚΟΜΕΙΟ ΘΕΣΣΑΛΟΝΙΚΗΣ ΠΑΠΑΓΕΩΡΓΙΟΥ

- Source: Management Information


FirstSteps®
NEWBORN GENOME SCREENING

The Danish approach: Targeted Genetic Analyses: Reducing False Positives and Enhancing Performance in Danish Newborn Screening

Alberte Lundquist, MD. Department of Paediatrics and Adolescent Medicine, Copenhagen University Hospital (Denmark)

European Reference Networks ITHACA

Danish Approach on Newborn Screening

ERN ITHACA - Innovation in Newborn Screening across Europe: Part 2
April 9, 2024

Alberte A. Lundquist, MD, PhD student
Department of Paediatrics and Adolescent Medicine, Rigshospitalet, Denmark
Danish Center for Neonatal Screening, Statens Serum Institut, Denmark

Rigshospitalet
The Juliane Marie Centre

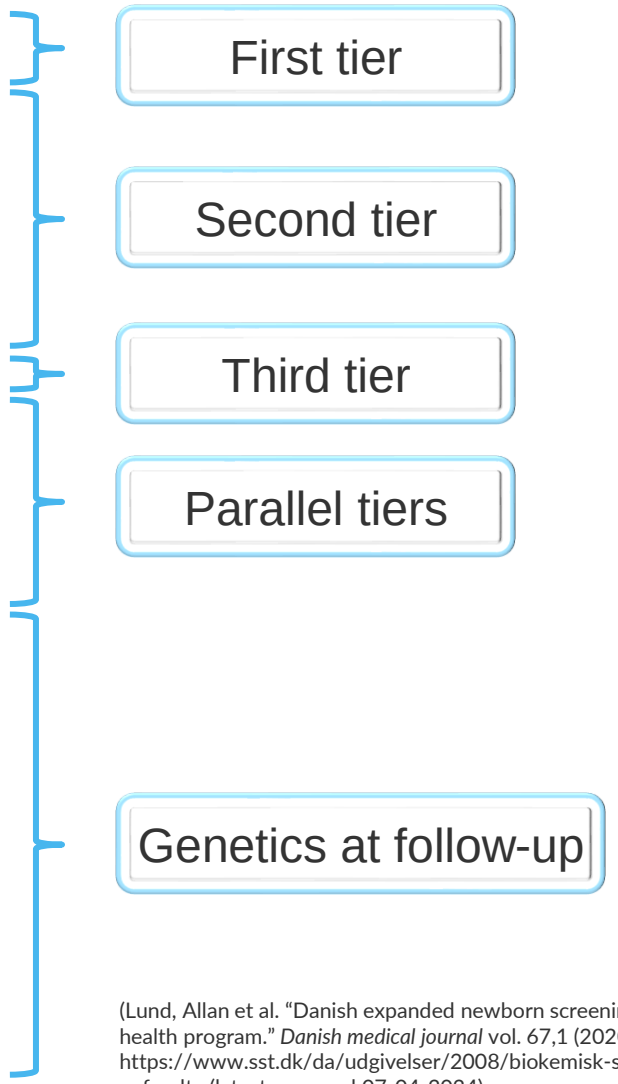
Newborn screening in Denmark

- The Kingdom of Denmark, the Faroe Islands, and Greenland
- 60.000 newborns/year (99% uptake)
- 25 disorders
- Screening
  - 2-3 days after birth
  - Guthrie cards
  - Since 1975
  - Stored since 1982
- Screened at Statens Serum Institut

(Fødsler - Danmarks Statistik (dst.dk)) (latest accessed 07-04-2024)
(Notat-om-organiseringen-af-neonatal-biokemisk-screening-af-nyfoedte-2021.ashx (sst.dk)) (latest accessed 07-04-2024)
(Lund, Allan et al. "Danish expanded newborn screening is a successful preventive public health programme." *Danish medical journal* vol. 67,1 (2020): A06190341)
(Screening for medfødte sygdomme (ssi.dk)) (latest accessed 07-04-2024)
(Opbevaring og brug af blodprøven efter screeningen (ssi.dk)) (latest accessed 07-04-2024)

Genetic testing in the Danish NBS

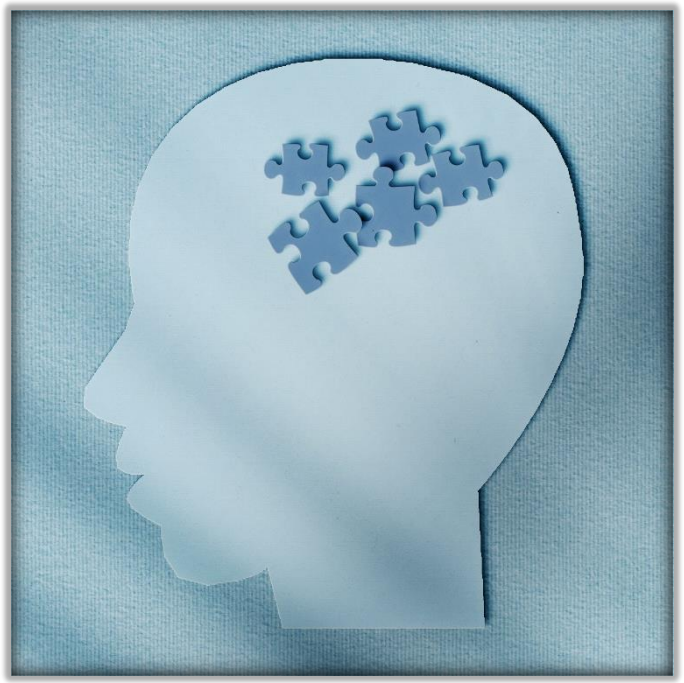
SCID	Severe Combined Immunodeficiency
SMA	Spinal muscle atrophy
BTD	Biotinidase deficiency
CF	Cystic fibrosis
CPT1	Carnitine palmitoyltransferase I deficiency
MCD	Holocarboxylase synthetase deficiency/multiple carboxylase deficiency
MPS1-H	Mucopolysaccharidosis type I
CTD	Carnitine Transporter Deficiency/Systemic Primary Carnitine Deficiency
HCU	Homocystinuria (classic)
GALT	Galactosemia
IVA	Isovaleric acidemia
LCHAD	Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency
MCAD	Medium-chain acyl-CoA dehydrogenase deficiency
VLCAD	Very long-chain acyl-CoA dehydrogenase deficiency
ALSD	Argininosuccinate Lyase Deficiency
CAH	Adrenogenital syndrome/Congenital adrenal hyperplasia
CH	Congenital hypothyroidism
GA1	Glutaric acidemia type 1/Glutaric aciduria type 1
MMA	Methylmalonic acidemia
MSUD	Maple syrup urine disease
PA	Propionic acidemia
PKU	Phenylketonuria
TT1	Tyrosinemia Type 1
CPT2/CACT	Carnitine-acylcarnitine translocase deficiency
MADD	Multiple Acyl-CoA Dehydrogenase Deficiency



(Lund, Allan et al. "Danish expanded newborn screening is a successful preventive public health program." *Danish medical journal* vol. 67,1 (2020): A06190341)
https://www.sst.dk/da/udgivelser/2008/biokemisk-screening-for-medfoedt-sygdom-hos-nyfoedte (latest accessed 07-04-2024)
(Screening for medfødte sygdomme (ssi.dk)) (latest accessed 07-04-2024)
Internal reports

Challenges

Legal matters



Scaling up

Ethics

Technical

Targeted Genetic Analyses: Reducing False Positives and Enhancing Performance in Danish Newborn Screening

Alberte A. Lundquist[1,2], Jonas Bybjerg-Grauholm[2], Marie Bækvad-Hansen[2], Rikke K. J. Olsen[3],Morten Dunø[4], Lone G. Stensballe[1], and Allan M. Lund[1]

[1]Department of Paediatrics and Adolescent Medicine, Rigshospitalet, Denmark.

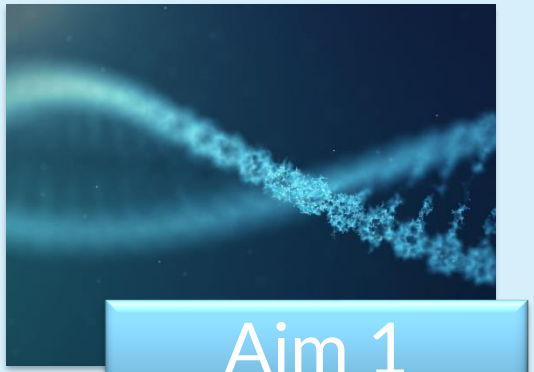
[2]Danish Center for Neonatal Screening, Department of Congenital Disorders, Statens Serum Institut.

[3]Research Unit for Molecular Medicine, Department of Clinical Medicine, Aarhus University, Denmark.

[4]Molecular Genetic Laboratory, Department of Clinical Genetics, Rigshospitalet, Denmark.

*Subject to ethical approval

Aims & Background



Aim 1

Investigation of Molecular Genetic Analyses

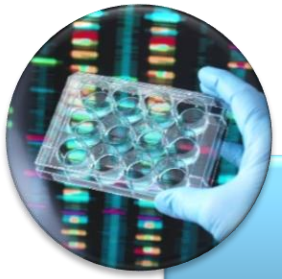
Aim 2

Reduction of False Positives

Aim 3

Understanding Marker Pathogenicity

Health data



Screening data

Genetic data

Design & Methods

- Retrospective (2002-2023)
- 3000 Guthrie cards
- Targeted molecular genetic analyses
  - WES
  - 84 genes

Expected Outcomes

Aim 1

- An evaluation of suitability of targeted genetic analyses
  - 1. tier approach
  - 2. tier approach

Aim 2

- Screening algorithms for reduction of false positives

Aim 3

- Increased understanding of pathogenicity of markers

Acknowledgements

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- David M. Hougaard
- Christine Bugay Valdez
- Mia Egeberg Engwald
- Tage Claes Jørgensen
- Jacob Sønderby Pedersen

UNIVERSITY OF COPENHAGEN

AARHUS UNIVERSITY

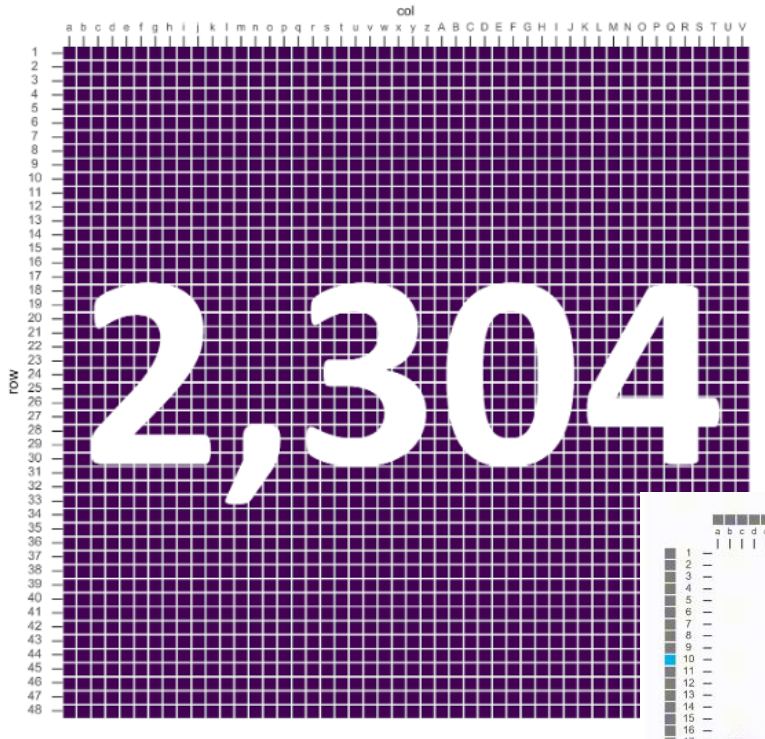
STATENS SERUM INSTITUT

Rigshospitalet

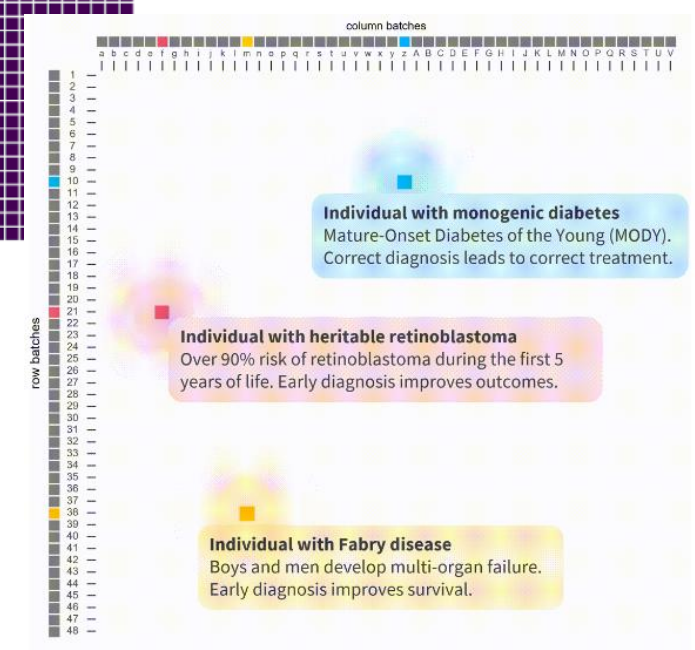
PREDISPOSED

Population-based **R**etro- & prospective **E**valuation of **D**iagnostic **S**equencing for **P**ediatric & **O**ncogenetic **S**yndromes' **E**arly **D**etection

- Double-Batch Sequencing (DoBSeq)
- Exploring:
  - Cost-effective
  - Genotype-first
  - Population-wide genomic sequencing
- 2,304 patient samples
- Use of only 96 tests
- >20-fold reduction
- Proved method at medium scale[1]
- Plan to scale fully



Homepage:
[2]https://sites.google.com/view/predisposed/the-predisposed-project



"Rare disease detection so low cost, we can't afford not to do it"[2]

[1]Stoltze, U.K., Hagen, C.M., van Overeem Hansen, T. *et al.* Combinatorial batching of DNA for ultralow-cost detection of pathogenic variants. *Genome Med* **15**, 17 (2023). https://doi.org/10.1186/s13073-023-01167-6

Rigshospitalet
The Juliane Marie Centre

PREDiSPOSED

Population-based Retro- & prospective Evaluation
of Diagnostic Sequencing for Pediatric & Oncogenetic Syndromes' Early Detection

https://sites.google.com/view/predisposed/the-team

- **Copenhagen University Hospital**
  - Kjeld Schmiegelow (Professor, Pediatric Oncology)
  - Ulrik Stoltze (PhD-student, Clinical genetics, Pediatric oncology, Bioinformatics)
  - Thomas v. O. Hansen (Professor, Molecular biology, Functional genetics)
  - Karin Wadt (Assoc. Professor, Clinical oncogenetics)
  - Allan Lund (Professor, Rare diseases, Metabolic disorders)
- **University of Copenhagen (KU)**
  - Ayo Wahlberg (Professor, Anthropology)
  - Simon Rasmussen (Assoc. Professor, Bioinformatics)
- **Danish Cancer Society (KB), Copenhagen**
  - Henrik Hjalgrim (Professor, Epidemiology)
  - Signe Holst Søegaard (Post Doc, Epidemiology)

Statens Serum Institut, Copenhagen

- Jonas Bybjerg-Grauholm (Section Head, Neonatal Screening)
- Marie Bækvad-Hansen
- David M. Hougaard (MD, Congenital disorders)
- Christian Munch Hagen (Data Expert, Bioinformatics)

PREDiSPOSED Steering Committee

- Merete Lange (Head of the board, Center Director at RH)
- Henrik Ullum (Head of SSI)
- Bettina Lundgren (Head of NGC)
- Mads Melbye (Head of KB)
- Charlotte K. Lautrup (Clin. Assoc. Prof. at AUH)
- Jan Johnsen (parent to pediatric cancer patient)
- Monica M. Ehlers (Innovation fund Denmark rep)

Region Hovedstaden
STATENS SERUM INSTITUT
Kræftens Bekæmpelse
UNIVERSITY OF COPENHAGEN

Funders: 10.000.000 DKK or more:
Innovation Fund Denmark
børne|cancer|fonden

Funder: 1,000,000 DKK to 10,000,000 DKK:
novo nordisk foundation

The GenNatal Spanish program

Pr. Francesc Palau, Genetic Medicine Service of the Hospital Sant Joan de Déu, Barcelona (Spain)

European Reference Networks ITHACA

The GenNatal Spanish program

Pr. Francesc Palau, Genetic Medicine Dept. of the Hospital Sant Joan de Déu, Barcelona (Spain)

SJD Sant Joan de Déu Barcelona · Hospital

CEDEM Centro de Diagnóstico de Enfermedades Moleculares

ciberer Centro de Investigación Biomédica en Red Enfermedades Raras

isc Instituto de Salud Carlos III

frA FUNDACIÓN RAMÓN ARECES

April 9, 2024 webinar #14 ERN ITHACA

European Reference Networks ITHACA

OBJECTIVES

***GenNatal* is a pilot project on genomic sequencing in neonatal medicine and newborn screening**

- Explore how genomic information can help to better know and understand diseases identified in the neonatal and childhood period
- Analyze the medical-care, family and social, and economic impact of genomic sequencing in the health care of newborns and infants.
- Study the possible benefits of genetic screening compared to the current biochemical NBS

SCOPE

- Reasons for accepting/rejecting participation in the study
- Perception and knowledge about neonatal screening (biochemical vs genetic)
- Opinions on genetic screening
- Feelings and perception of possible results and their family implications
- What type of results would you like to know depending on whether they are actionable, by age of onset, carrier status...Impact of different results
- Family impact
- Evaluation of teaching material

1. Pre-recruitment session: motivation
2. Pre-test session: before delivery. Informed Consent
3. Post-test session: delivery of results

INCLUSION/EXCLUSION CRITERIA

INCLUSION CRITERIA

- Healthy couples
- Third trimester
- Controlled pregnancy
- Absence of ultrasound findings, maternal pathology, or family history of genetic disease
- Both members of the couple

EXCLUSION CRITERIA

- No parental samples
- Fetal pathology detected prenatally
- Pregnancy per gametes from donors or single-parent
- Lack of Informed Consent

WORKFLOW DESIGN

INFORMATIVE SESSION

- Obstetrics
- 28-36 pregnancy weeks
- Brochure delivery
- Form

PRE-TEST SESSION

- Genetic counselling
- Pregnancy weeks
- Educational/informational material
- Data analysis forms
- Informed consent

NEWBORN RECRUITMENT

- Neonatal screening consultation
- Sample collection (dried drop of blood from the heel, also shows oral mucosa of the parents)

EXOME ANALYSIS

- Sequencing and interpretation
- Results meeting
- Report making

POST-TEST SESSION

- Genetic counseling
- Post-test form

INFORMATIONAL MATERIAL FOR COUPLES

- RECRUITMENT BROCHURE

EN LOS ÚLTIMOS AÑOS SE HA PRODUCIDO UNA GRAN REVOLUCIÓN DE LA TECNOLOGÍA EN EL CAMPO DE LA GENÉTICA. ¿CÓMO PODEMOS APLICARESOTS AVANCES EN EL DIAGNÓSTICO PRECOZ DE ENFERMEDADES GENÉTICAS.

PROYECTO GenNatal

¿Qué queremos saber?

Queremos evaluar los beneficios y el impacto que puede tener implementar estudios genéticos avanzados en el cribage neonatal.

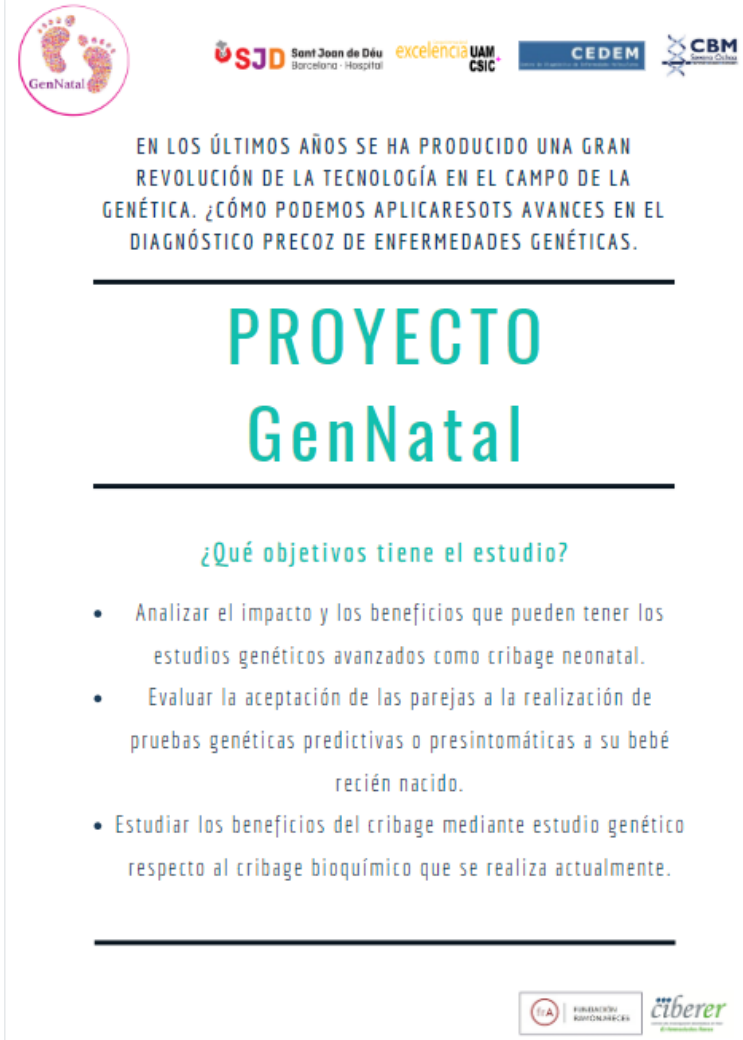
¿Quién puede participar?

Parejas con un embarazo en curso entre las 30 y 36 semanas, con una evolución normal del feto.

¿Qué implicará vuestra participación?

-Toma adicional de muestra de sangre de talón del bebé
-2 sesiones presenciales antes y después del test
-Cumplimentar formularios online

SI QUIERES PARTICIPAR:
PUEDES PEDIR INFORMACIÓN A TU GINECÓLOGO/A O COMADRON/A, O ESCRIBIRNOS UN CORREO ELECTRÓNICO EN
gennatal@sjdhospitalbarcelona.org



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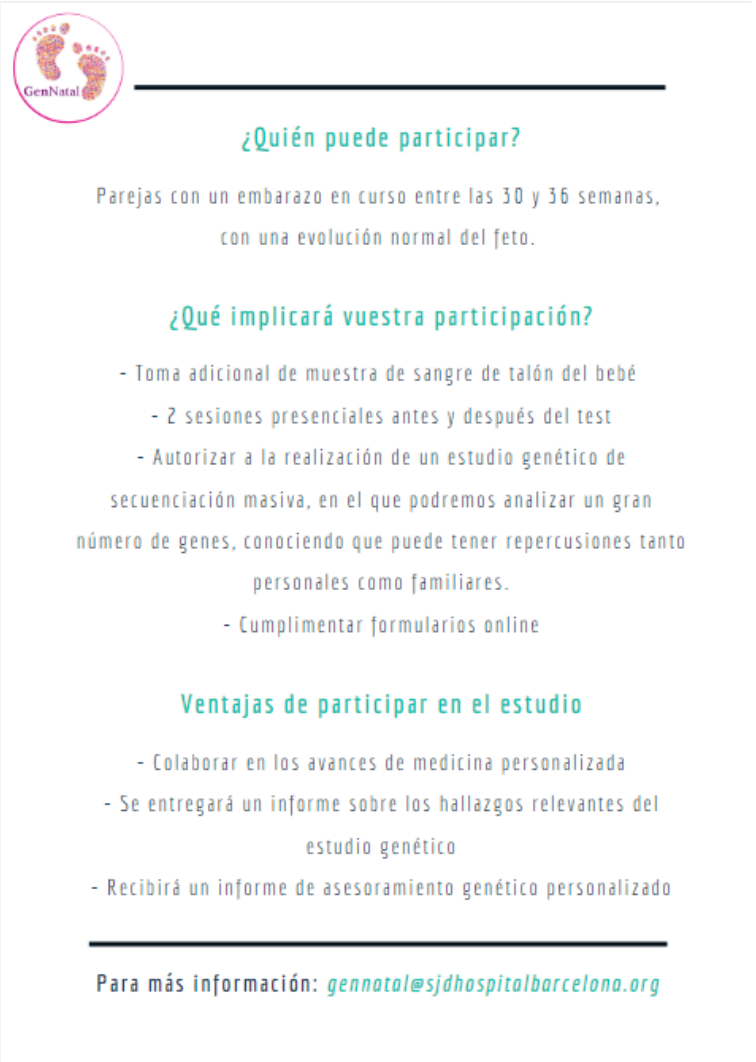
PROYECTO GenNatal

¿Qué objetivos tiene el estudio?

- Analizar el impacto y los beneficios que pueden tener los estudios genéticos avanzados como cribage neonatal.
- Evaluar la aceptación de las parejas a la realización de pruebas genéticas predictivas o presintomáticas a su bebé recién nacido.
- Estudiar los beneficios del cribage mediante estudio genético respecto al cribage bioquímico que se realiza actualmente.



¿Quién puede participar?

Parejas con un embarazo en curso entre las 30 y 36 semanas, con una evolución normal del feto.

¿Qué implicará vuestra participación?

- Toma adicional de muestra de sangre de talón del bebé
- 2 sesiones presenciales antes y después del test
- Autorizar a la realización de un estudio genético de secuenciación masiva, en el que podremos analizar un gran número de genes, conociendo que puede tener repercusiones tanto personales como familiares.
- Cumplimentar formularios online

Ventajas de participar en el estudio

- Colaborar en los avances de medicina personalizada
- Se entregará un informe sobre los hallazgos relevantes del estudio genético
- Recibirá un informe de asesoramiento genético personalizado

Para más información: *gennatal@sjdhospitalbarcelona.org*

INFORMATIONAL MATERIAL FOR COUPLES

- PRE-TEST VISIT BROCHURE

Proyecto Gennatal

Estudio de exoma neonatal

GenNatal

El secuenciador es una maquinaria que va leyendo y comparando cada una de las letras del ADN con la secuencia que se emplea como referencia. Aquellas letras que son diferentes de la referencia (variantes) quedan anotadas y serán después analizadas mediante programas bioinformáticos e interpretadas para clasificarlas y determinar si alguna puede ser causante de alguna enfermedad.

La técnica de exoma puede detectar cambios puntuales, de una letra por otra o pocas letras, pero no detecta con precisión si falta o sobra algún fragmento más grande de material genético.

En el estudio de exoma podemos encontrar los siguientes resultados:

- **RESULTADO POSITIVO O PATOGÉNICO:** se identifica un cambio en la secuencia por el cual encontramos suficiente evidencia de su asociación con una enfermedad
- **RESULTADO NEGATIVO:** no se identifica ningún cambio que se considere asociado a una enfermedad.
- **RESULTADO INCIERTO:** se identifica un cambio del cual se desconoce su posible implicación con una enfermedad, pero no se puede establecer tampoco que sea benigno con evidencia.

Si se encuentra alguna alteración en los genes estudiados se contrastarán los resultados analizando la muestra de los padres, para saber si es un cambio nuevo o heredado.

¿QUÉ RESULTADOS SE COMUNICAN A LAS FAMILIAS?

Quedarán reflejados en el informe de resultados solo aquellos cambios/mutaciones que se consideren patogénicas, por lo tanto, que haya bastante evidencia de su asociación a una enfermedad, en genes con elevada penetrancia[1].

SE INFORMARÁ DE ENFERMEDADES CON:

- Inicio en edad pediátrica y con un tratamiento médico o dietético disponible
- Riesgo elevado que la enfermedad aparezca en un futuro hijo de la pareja, u otros miembros de la familia, aunque no afecte el neonato.

LOS PADRES PARTICIPANTES PUEDEN ELEGIR SI SER O NO INFORMADOS DE:

- Enfermedades de debut en edad pediátrica sin tratamiento, pero con seguimiento preventivo o atención temprana.
- Enfermedades de inicio en edad adulta con posibilidad de aplicar medidas preventivas o de detección temprana.

NO SE INFORMARÁ aquellas enfermedades de debut en edad adulta que hoy en día no haya ningún tipo de acción que permita prevenir, retrasar o mejorar el pronóstico de la enfermedad.

GRACIAS POR VUESTRA PARTICIPACIÓN

INFORMATIONAL MATERIAL FOR COUPLES

- PRE-TEST VISIT BROCHURE

INTRODUCCIÓN

Actualmente, cuando nace un bebé se realizar un **cribado neonatal o prueba del talón**, que en el programa de Cataluña, permite detectar mediante estudio bioquímico 24 enfermedades de manera precoz. El objetivo de este programa es poder iniciar actuaciones sanitarias para prevenir complicaciones graves de estas enfermedades.

El proyecto GenNatal pretende evaluar cuál es el impacto y las posibles mejoras de un estudio genético neonatal en comparación al programa de cribado bioquímico que se realiza actualmente.

El estudio genético incluido en el proyecto permite evaluar un número mucho más grande de enfermedades que no son detectables por valores bioquímicos. Los potenciales beneficios del estudio son la detección temprana de enfermedades no incluidas en el programa actual, y el asesoramiento genético de la familia.

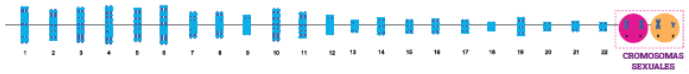
FASES DEL ESTUDIO

GENÉTICA

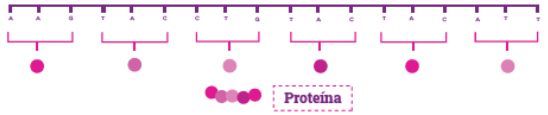
Los individuos estamos formados por muchas células y cada una de ellas contiene toda nuestra información genética, que está constituida por una cadena muy larga de ADN, formada por un código de 4 letras en diferente orden.

Lo podríamos visualizar como una biblioteca con todos los libros de instrucciones que explican cómo tiene que funcionar nuestro cuerpo, a la que denominamos Genoma.

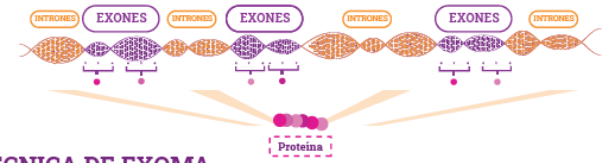
Cada uno de los libros corresponde a un **CROMOSOMA**, tenemos 23 pares, donde de cada par recibimos uno del padre y uno de la madre. Los cromosomas sexuales X e Y son los que diferencian biológicamente hombres y mujeres.



En las instrucciones genéticas hay regiones codificantes, que serían los **GENES**, y que se traducen a las proteínas que son las que realizan una función específica en el cuerpo.



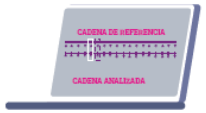
El resto son regiones no codificantes, y que contienen información importante, como por ejemplo, como la célula lee e interpreta cada gen. Cada gen tiene trozos que se traducen y formarán parte de la proteína, los **EXONES**, y otros que ayudan en el proceso de preparación de la proteína pero no forman parte, que serían los **INTRONES.**



TÉCNICA DE EXOMA

La técnica de exoma consiste en el análisis del conjunto de **todos los exones de todos los genes.** El exoma corresponde solo a un **1%** de todo el genoma, pero se estima que **se pueden encontrar hasta un 80% de las alteraciones que dan lugar a enfermedades genéticas.**

En el estudio Gennatal se han seleccionado 3200 genes y clasificado en categorías según la penetrància[1], la edad de inicio y la accionabilidad[2].



1. PROBABILIDAD QUE ANTE UNA ALTERACIÓN GENÉTICA PATOGÉNICA SE EXPRESEN SIGNOS DE LA ENFERMEDAD
2. POSIBILIDAD DE APLICAR ACCIONES QUE CONTRIBUYAN A MEJORAR EL IMPACTO DE LA ENFERMEDAD EN EL INDIVIDUO O SU FAMILIA

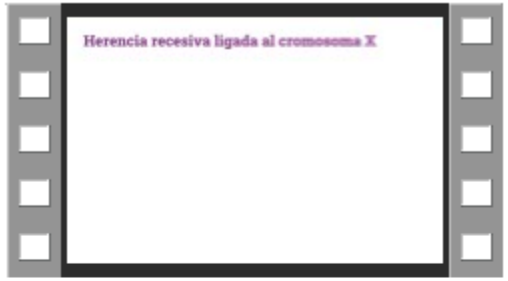
INFORMATIONAL MATERIAL FOR COUPLES

- VIDEO CONSULTATION GENETIC COUNSELLING

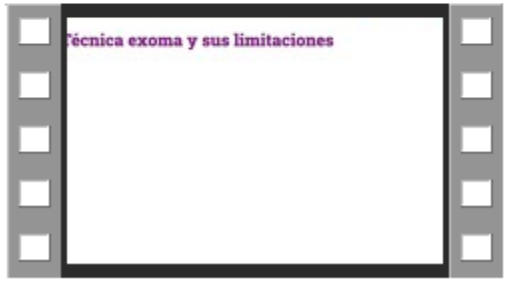
INFORMATIONAL MATERIAL FOR COUPLES

01 GENNATAL PRESENTATION

02 GENNATAL GENETICS - INTRODUCTION



03 GENNATAL INHERITANCE PATTERNS



04 GENNATAL EXOME NGS TEST

05 GENNATAL MICROARRAY TEST

06 GENNATAL POSSIBLE RESULTS

07 GENNATAL ANALYSIS OF RESULTS

GENNATAL

METHODOLOGY

- PREPARATION OF LIST OF GENES (initial)

We planned to define entry criteria for the genes to be analyzed in the project

Genomics England PanelApp

A crowdsourcing tool to allow gene panels to be shared, downloaded, viewed and evaluated by the Scientific Community

- Classification of genes according to their evidence of association with pathology for different panels

  GREEN
  AMBER
  RED

- Each reviewed by three reviewers
- Redundant (same gene in different categories, depending on the panel)
- Genes with high evidence not analyzed because they are associated with pathologies not included in any of the PanelApp panels

OMIM®

Online Mendelian Inheritance in Man®

- OMIM'

  Phenotype "?" *
  Susceptibility "{}"
  No associated phneotype

* We verified that all genes with phenotype "?" were not in PanelApp or they were in the amber or red categories

CONTRAST OF **GREEN** GENES WITH OMIM' + INCLUSION OF PANELAPP SYNONYMS

CONTRAST, REVIEW AND REINCLUSION OF BabySeq, HSJD-DB WITH **AMBER** AND **RED** GENES

METHODOLOGY

- PREPARATION OF LIST OF GENES (initial)

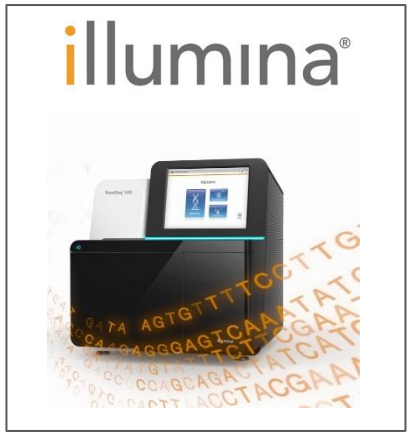
Analysis of a total 3245 genes

High evidence genes associated with pathology according to the OMIM and PanelApp databases, enriched with genes associated with metabolic disorders

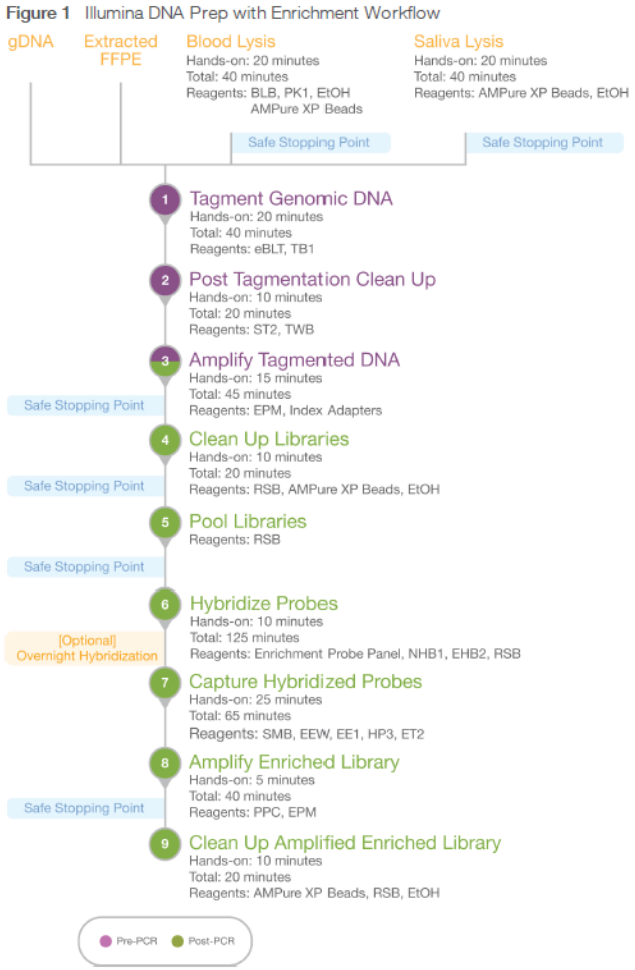
METHODOLOGY

- *Whole Exome Sequencing* (*WES*)

ILLUMINA TECHNOLOGY



NetSeq 500



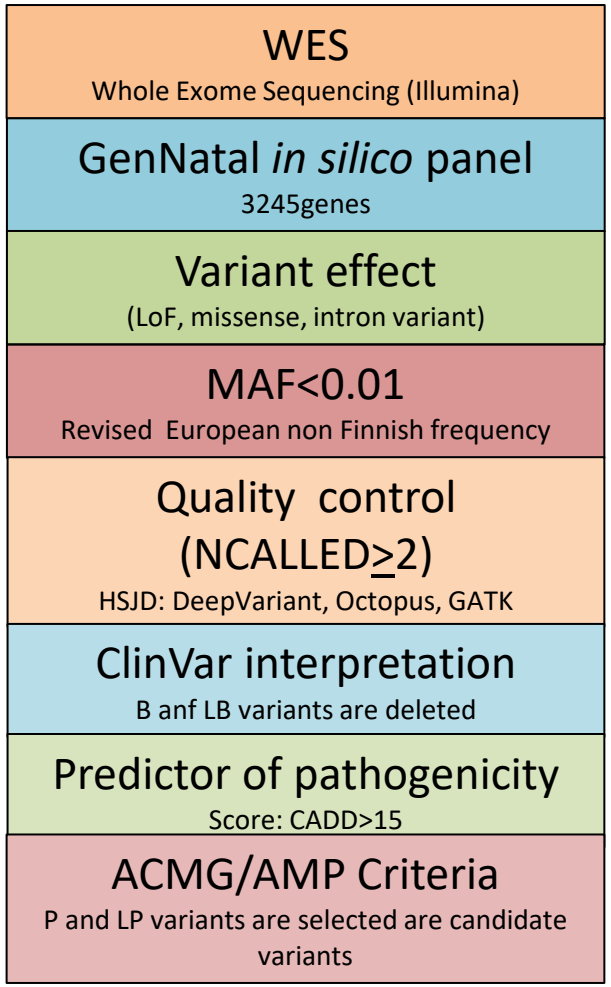
6 MAIN STEPS ARE PERFORMED

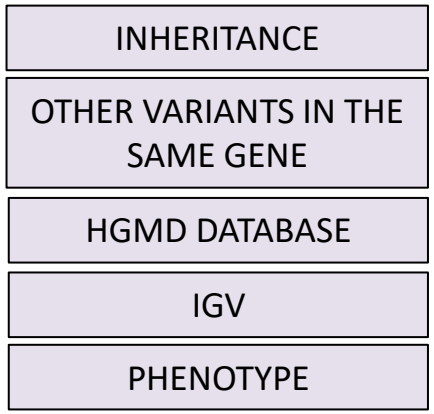
1. QUALITY CONTROL
2. ALIGNMENT
3. VARIANT CALLING
4. VARIANT ANNOTATION
5. FILTERING
6. ANALYSIS AND INTERPRETATION

METHODOLOGY

- ANALYSIS AND INTERPRETATION OF VARIANTS

Flowchart. Variant filtering





REPORTABILITY OF RESULTS

Disease list		
Evidence	Fixed or determined variable	High
Penetrance		High/Moderate
Age of onset	Combination for each category	Pediatric/Adult
Actionability*		Yes/No

*** Type of Actionability:**
1. Medical/nutritional treatmetn only
2. Preventive follow-up OR Early care (i.e., CDIAP healthcare provider)
3. Reproductive measures or actions

Reporting

CATEGORY A
Pediatric age
Actionable 1

CATEGORY B
X-linked carrier status
Actionable 3

To be decided

CATEGORY C
Pediatric age
Actionable 2

CATEGORÍA D
Adult age
Actionable 2

No reporting

CATEGORY E
E1. Adult age
E2. Status Carrier AR
No actionable

CATEGORY F
Low penetrance
Low evidence

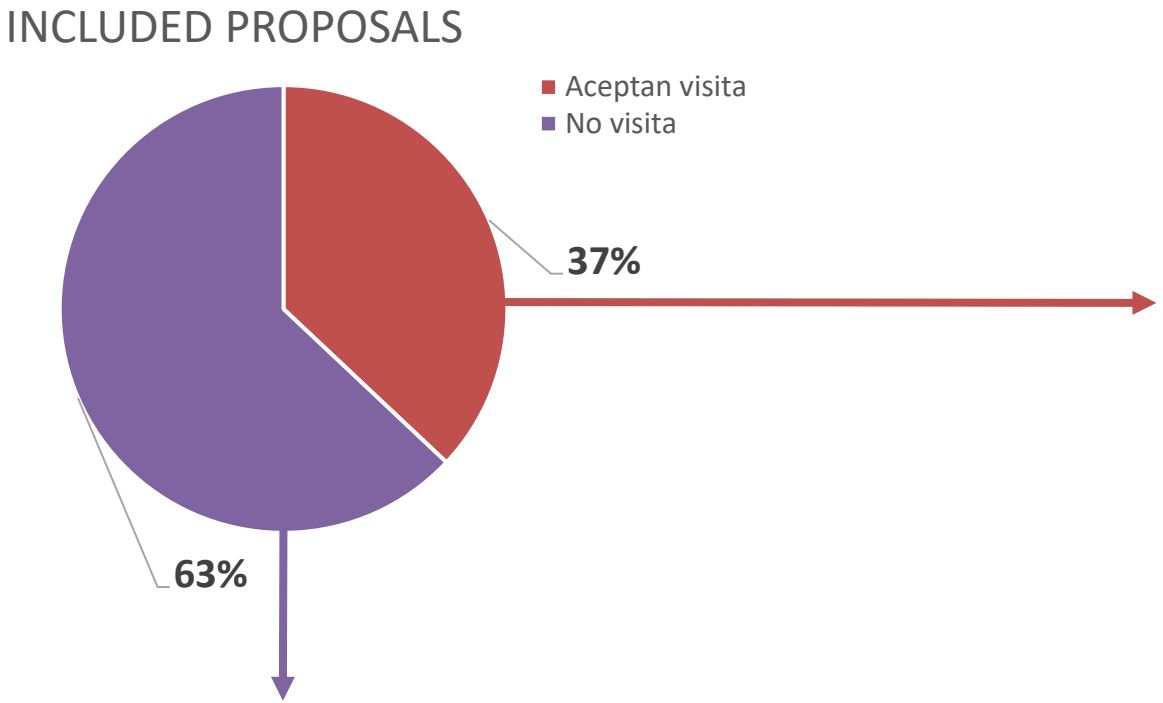
RECRUITMENT OF PARTICIPANT COUPLES

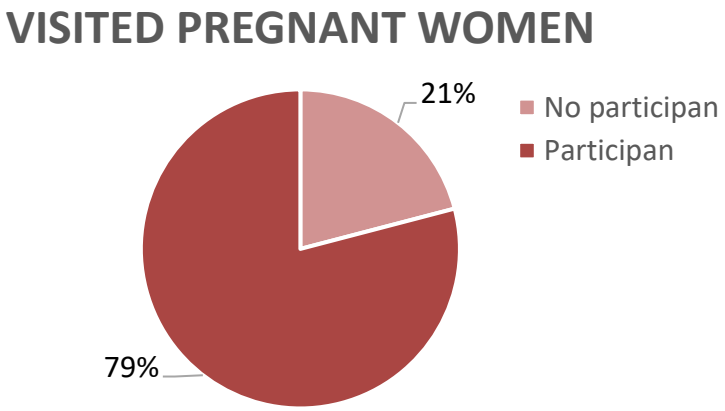
More than 250 couples expressed interest in the project

Couple contacts	181
Visit accepted	67
Visited	63
Participants	**53**
Canceled after pre-test session	10

Post-test genetic counselling	**No.**
Already informed	17
Cited	6
Pending results/citation	30

RECRUITMENT OF PARTICIPANT COUPLES



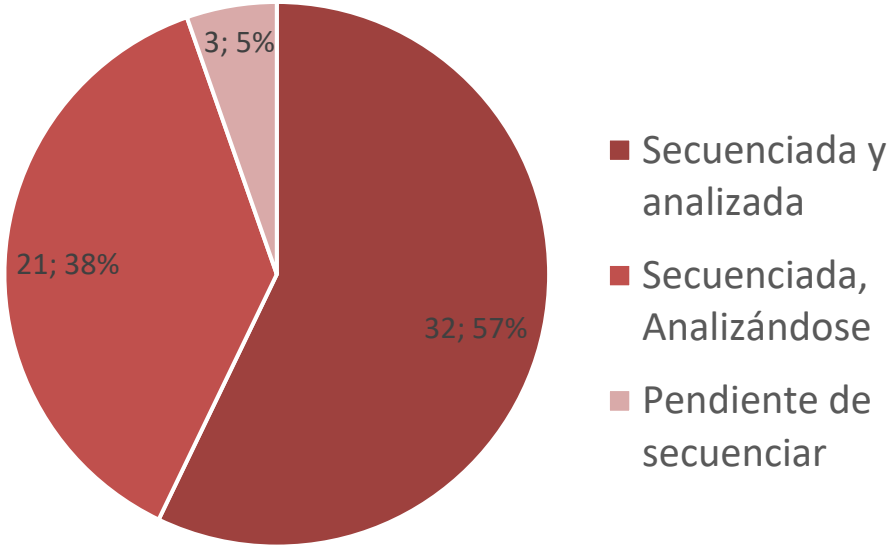


CAUSES OF CANCELATION
Premature delivery
They don’t come to the clinic/logistic problems
We cannot contact them
Delievery before the planned visit
COVID-19

SAMPLE STATUS

Current situation	No.
Sequenced and analyzed	32
Sequenced and analysis **in progress**	21
Pendinf of sequencing	3
Total	53

Muestras analizadas	N
Pending of validation + parental segregation (Sanger)	9*
Normal result	23



- No pathogenic/likely pathogenic variants have been detected in the genes analyzed.
- VUS and carrier status have been detected.

LABORATORY (WES) REPORT

Servei de Medicina Genètica i Molecular – IPER
Laboratori de Neurogenètica i Medicina Molecular – IPER
Hospital Sant Joan de Déu
Pg Sant Joan de Déu, 2
08950 – Esplugues de Llobregat
Tlf: +34932532100

INFORME DE LABORATORIO. SECUENCIACIÓN MASIVA

Paciente		**Análisis**	SECUENCIACIÓN EXOMA COMPLETO
Sexo		**NHC**	
Fecha de nacimiento		**Tipo de muestra**	SANGRE SECA EN PAPEL
Madre			
Padre			

Motivo de estudio

Participación en el proyecto GenNatal: un proyecto piloto sobre secuenciación genómica en medicina neonatal y salud pública.

Nombre del solicitante

Equipo de asesoramiento genético (GenNatal)

Hallazgos genéticos

Variante genética	Posición cromosómica	Patrón de herencia del gen[1]	Genotipo	Clasificación de patogenicidad[2]

[1] *Patrón de herencia (Fuente: OMIM). AD, Autosómico Dominante. AR, Autosómico Recesivo.*
[2] *Clasificación de patogenicidad siguiendo las normas de la ACMG (American College of Medical Genetics) (Fuente: Franklin genomic tool).*

Valoración de los hallazgos

Interpretación

Validación

Firmado por equipo GenNatal.

Metodología

EXAMPLES

CASE 7

♂

Hallazgos genéticos

Variante genética	Posición cromosómica	Patrón de herencia del gen[1]	Genotipo	Clasificación de patogenicidad[2]
GNRHR (NM_000406.2) p.Gln106Arg/c.317A>G	4-68619737-T-C	AR	Heterozigosis	Patogénica
LAMA2 (NM_000426.3) p.Ala1496Val/c.4487C>T	6-129670493-C-T	AR	Heterozigosis	Variante de Significado Incierto
KLKB1 (NM_000892.4) p.Ser151fs/c.451dupT	4-187158050-G-GT	AR	Heterozigosis	Variante de Significado Incierto
PDE11A (NM_016953.3) p.Arg307*/c.919C>T	2-178879181-G-A	AD	Heterozigosis	Variante de Significado Incierto

[1]Patrón de herencia (Fuente: OMIM). AD, Autosómico Dominante. AR, Autosómico Recesivo.
[2]Clasificación de patogenicidad siguiendo las normas de la ACMG (American College of Medical Genetics) (Fuente: Franklin genomic tool).

Valoración de los hallazgos

- La variante p.Gln106Arg/c.317A>G en el gen *GNRHR* reúne los criterios para ser considerada patogénica, pero al tratarse de un gen con patrón de herencia autosómico recesivo, la variante por sí sola no es suficiente, por lo que no se reporta a la familia.
- La variante p.Ala1496Val/c.4487C>T en el gen *LAMA2* y la variante p.Ser151fs/c.451dupT en el gen *KLKB1* no reúnen los criterios suficientes para ser consideradas patogénicas. Además, se trata de genes con patrón de herencia autosómico recesivo, las variantes por sí sola no son suficientes, por lo que no se reporta a la familia.
- La variante p.Arg307*/c.919C>T en el gen *PDE11A* no reúne los criterios suficientes para ser considerada patogénica. No se reporta.

Interpretación

Los hallazgos se han discutido en el equipo. No se ha encontrado ninguna variante genética que pueda implicar a día de hoy con la información disponible un cambio de manejo clínico en el participante del estudio.

EXAMPLES

CASE 15

♂

Hallazgos genéticos

Variante genética	Posición cromosómica	Patrón de herencia del gen[1]	Genotipo	Clasificación de patogenicidad[2]
ATP7B (NM_000053.3) p.Ile1230Val/c.3688A>G	13-52513198-T-C	AR	Heterozigosis	Patogénica
FRAS1 (NM_025074.6) p.Arg124*/c.370C>T	4-79173606-C-T	AR	Heterozigosis	Patogénica
LEPR (NM_002303.6) p.Arg612His/c.1835G>A	1-66075712-G-A	AR	Heterozigosis	Probablemente Patogénica
VPS53 (NM_001128159.2) p.Arg584*/c.1750C>T	17-456657-G-A	AR	Heterozigosis	Probablemente Patogénica
ACE (NM_000789.3) p.Arg228Cys/c.682C>T	17-61557724-C-T	AR	Heterozigosis	Variante de Significado Incierto
LMAN1 (NM_005570.3) p.Asn171Ser/c.512A>G	18-57021778-T-C	AR	Heterozigosis	Variante de Significado Incierto
DOK7 (NM_001301071.1) p.Glu188Asp/c.564G>C	4-3487297-G-C	AR	Heterozigosis	Variante de Significado Incierto
AMPD1 (NM_000036.2) p.Leu631Phe/c.1893A>T	1-115217379-T-A	AR	Heterozigosis	Variante de Significado Incierto
CCDC151 (NM_145045.4) p.Arg176Gly/c.526A>G	19-11537779-T-C	AR	Heterozigosis	Variante de Significado Incierto
IFT80 (NM_020800.2) p.Arg628Gln/c.1883G>A	3-159995412-C-T	AR	Heterozigosis	Variante de Significado Incierto
WDR62 (NM_001083961.1) p.Leu757Val/c.2269C>G	19-36583649-C-G	AR	Heterozigosis	Variante de Significado Incierto
FAM20C (NM_020223.3) p.Ser214Tyr/c.641C>A	7-195589-C-A	AR	Heterozigosis	Variante de Significado Incierto
ABCD1 (NM_000033.3) p.Ser606Pro/c.1816T>C	X-153008476-T-C	RLX	Hemizigosis	Variante de Significado Incierto
LRIT3 (NM_198506.4) p.Leu585del/c.1752_1754delTCT	4-110791654-CCTT-C	AR	Heterozigosis	Variante de Significado Incierto
SLC22A5 (NM_001308122.1) p.Arg512His/c.1535G>A	5-131729380-G-A	AR	Heterozigosis	Variante de Significado Incierto
RYR1 (NM_000540.2) p.Glu4502Gly/c.13505A>G	19-39057618-A-G	AD, AR	Heterozigosis	Variante de Significado Incierto

[1]Patrón de herencia (Fuente: OMIM). AD, Autosómico Dominante. AR, Autosómico Recesivo. RLX, Recesivo Ligado a X.

[2]Clasificación de patogenicidad siguiendo las normas de la ACMG (American College of Medical Genetics) (Fuente: Franklin genomic tool).

EXAMPLES

PACIENTE 15

♂

Valoración de los hallazgos

- La variante p.Ile1230Val/c.3688A>G en el gen *ATP7B* reúne los criterios para ser considerada patogénica, pero al tratarse de un gen con un patrón de herencia autosómico recesivo, la variante por sí sola no es suficiente. Se decide hacer segregación para consejo genético.

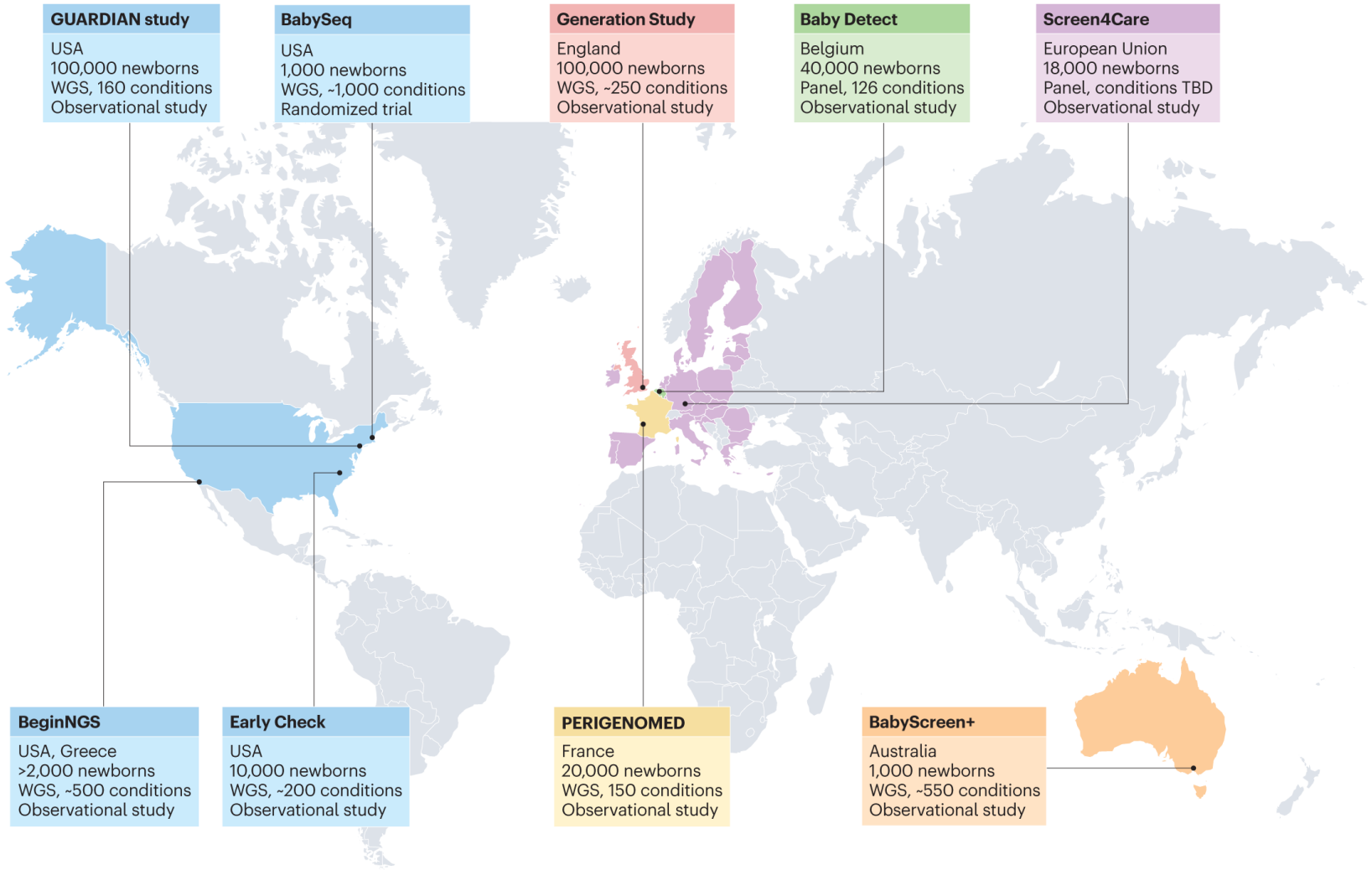
- Las variantes p.Arg124*/c.370C>T en el gen *FRAS1*, p.Arg612His/c.1835G>A en el gen *LEPR* y p.Arg584*/c.1750C>T en el gen VPS53 reúnen los criterios para ser consideradas patogénicas, pero al tratarse de genes con un patrón de herencia autosómico recesivo, las variantes por sí solas no son suficiente. No se reporta.

- El resto de variantes de la tabla superior no reúnen los criterios suficientes para ser consideradas patogénicas.

Interpretación

Los hallazgos se han discutido en el equipo. No se ha encontrado ninguna variante genética que pueda implicar a día de hoy con la información disponible un cambio de manejo clínico en el participante del estudio.

GENNATAL TEAM MEETINGS 2023/2024



Review Article | Published: 29 June 2023

Genomic newborn screening for rare diseases

Zornitza Stark & Richard H. Scott

Nature Reviews Genetics **24**, 755–766 (2023) | Cite this article

Genes to be analysed – exome capture

History	Years	No. of genes	Source of information
1º Approach	2019-2023	3,245	OMIM + Green PanelApp
2º Approach	2024	** <1,000	Analysis of other newborn genomic screening projects (**7**) [Stark& Scott, Nat Rev Genet 2023] Curated by HSJD multidisciplinary expert team

Objective: decrease the number of analysed genes

2º Approach – New selection criteria

1. Genes/diseases included in the current newborn screening
   - Biomarkers: metabolic, endocrine, hematologic, immunologic
   - Hipoacusia and others non-metabolic

2. Actionability
   - Biomarkers: metabolic, endocrine, hematologic, immunologic
   - Hipoacusia and others non-metabolic

3. Technologically can be analyzed (WES)

SMN and DMD genes discarded

CHALLENGES

- Importance of genetic counseling
- Which genes?
- Which variants?
- Relevance of the definition of actionability

The Rare Barometer survey on the opinion of people living with a rare disease on NBS

Jessie Dubief, Social Research Director, EURORDIS-Rare Diseases Europe

European Reference Networks ITHACA

Discussion Time and Conclusion

- AOB

Thank you for your attention !

- **Register to the Web site to get NewsLetter and calls for collab !**
  - https://ern-ithaca.eu

https://forms.office.com/e/kF13wdXEvk

FIRST RESULTS:
THE OPINION OF PEOPLE LIVING WITH RARE DISEASES ON NEWBORN SCREENING

A Rare Barometer survey
with the Screen4Care project

ITHACA webinar
9th April 2024

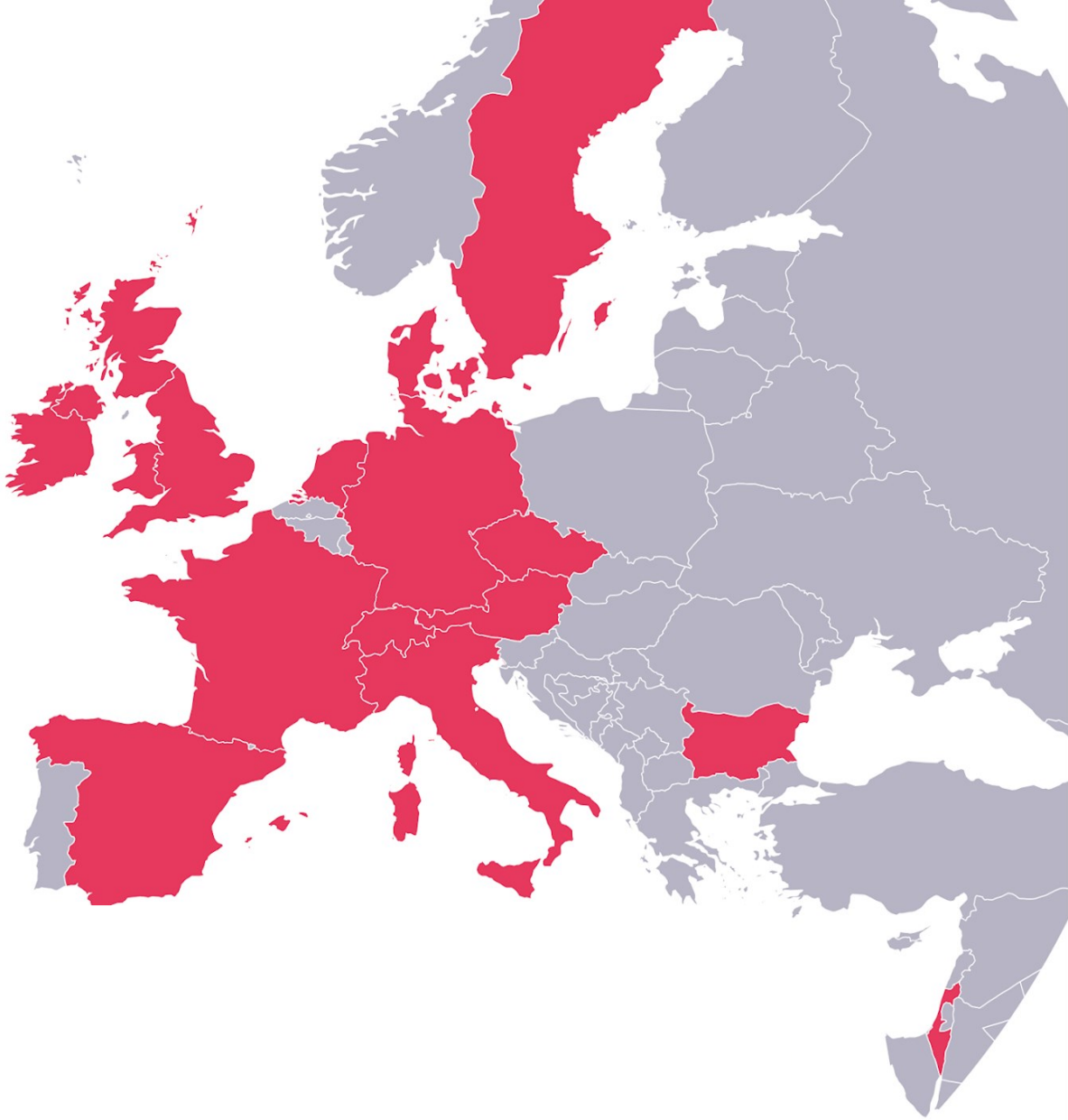
AGENDA

- Some context
- Relying on the lived experience of people living with a rare disease

1 SOME CONTEXT

SCREEN 4CARE

Accelerating Diagnosis for Rare Disease Patients Through Genetic Newborn Screening and Artificial Intelligence



START DATE
1 OCTOBER 2021

DURATION
5 YEARS

BUDGET
25 MIO €

14 COUNTRIES
35 PARTNERS

screen4care.eu

EURORDIS RARE DISEASES EUROPE

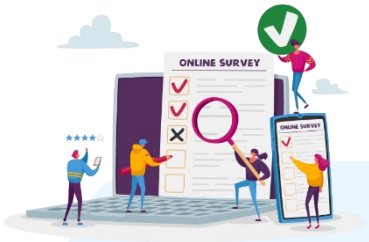
SCREEN 4CARE

Rare Barometer
A EURORDIS INITIATIVE

THE RARE BAROMETER PROGRAMME

eurordis.org/rare-barometer

EURORDIS' survey initiative to support evidence-based advocacy



Surveys

Patients, families and patient representatives

1-3 surveys per year

23 languages

Worldwide

Up to 13,000 respondents to our surveys

Panel

20,000+ people living with a rare disease registered

2,300+ rare diseases

120+ countries

People DO NOT have to register to participate in surveys

Make your voice heard!

Collective results shared with participants, patient organisations, decision makers and the wider public

Information only accessible to the Rare Barometer team, saved on a secured server in Europe

SHAPING THE ONLINE QUESTIONNAIRE

Literature review

Identify main issues and criteria to define treatable and actionable conditions for newborn screening

Expert consultations

11 experts consulted to **provide inputs** into priorities and criteria for newborn screening

Topic Expert Committee

Contribute to clarifying topics and criteria to include in the questionnaire

EURORDIS' Council of National Alliances Members

Input on topics and criteria to be included in the questionnaire

Feedback on the questionnaire

Pilot test with patients and family members

15 participants

Translations checked **in 15 languages** by native speakers

OBJECTIVES OF THE QUANTITATIVE SURVEY

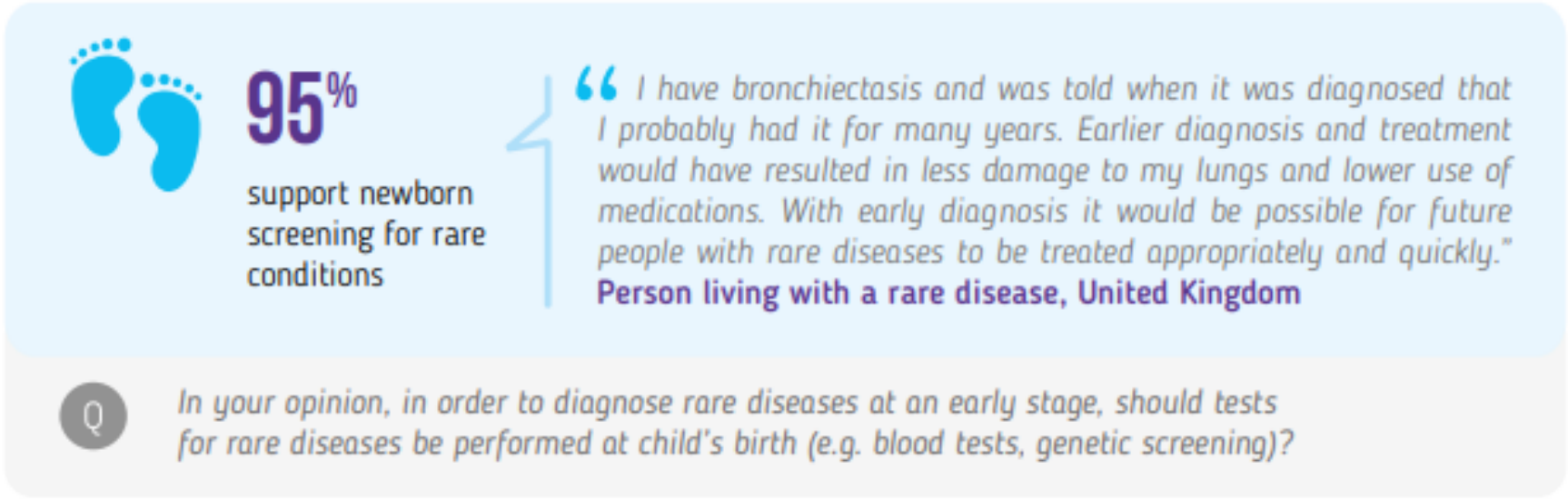
CREATING A SOUND BASIS TO

- **Advocate** for harmonised principles and adequate policies for newborn screening.
- **Define** a list of conditions to be tested in the Screen4Care project.

UNDERSTANDING

- **The attitudes and perceptions** of people living with a rare disease towards newborn screening.
- How the opinion of people living with rare diseases on newborn screening relates to **their characteristics** (age, gender, country, family situation…) and those of **their rare disease**.

REMINDER:
PLWRD STRONGLY SUPPORT TESTING RARE DISEASES AT BIRTH



Rare Barometer and Rare 2030 survey on the future of rare diseases (n=3,981)

→ tiny.cc/futureRD-results

ONLINE QUESTIONNAIRE

24 MAY ⇢ 23 JULY 2023

6,179 respondents worldwide and **5,569** in Europe

24 languages

TARGET POPULATION

All patients living with a rare disease and their family members

50 countries

1,300+ diseases represented

2 RELYING ON THE LIVED EXPERIENCE OF PLWRD

RELYING ON THE LIVED EXPERIENCE OF PLWRD

PATIENTS

2,567 respondents (46%)

If it is or were possible, I would have liked to be diagnosed at birth

CARERS

3,002 respondents (54%)
Mostly parents of people living with rare diseases (49% of the sample)

If it is or were possible, I would have liked the person I care for to be diagnosed at birth

Strongly agree
Agree
Neither agree nor disagree
Disagree
Strongly disagree

CARERS STRONGLY SUPPORT NEWBORN SCREENING

8/10 **Carers** would have liked the person they care for to be diagnosed at birth

Rare on Air podcast with Iuliana Dimitriu:
Her 7-years-long odyssey for her son to have a confirmed diagnosis of Coffin-Lowry syndrome, and how she thinks that early diagnosis could have improved his health and everyday life.

eurordis.org/rare-on-air

Q: If it is or were possible, I would have liked the person I care for to be diagnosed at birth (agree + strongly agree). N=3,002

PATIENTS SUPPORT NEWBORN SCREENING

6/10 **Patients** would have liked to be diagnosed at birth

↳ **7/10** among patients who:

- Have a rare disease with an **age of onset** before or during infancy (Orphanet)
- Have a rare **genetic** disease
- Waited for a diagnosis for **more than 5 years**
- have **improving symptoms**

- **Live with a developmental anomaly during embryogenesis (Orphanet)**

Q: If it is or were possible, I would have liked to be diagnosed at birth (agree + strongly agree). N=2,567

PATIENTS SUPPORT NEWBORN SCREENING

6/10 **Patients** would have liked to be diagnosed at birth.

No significant difference depending on:

- If they have access to a **treatment** and its effectiveness (declarative)
- If they have access to **supportive care** and its effectiveness (declarative)
- Their health status and satisfaction with health
- The level of pain they experienced
- Their gender
- Their knowledge in genetics
- The **prevalence** of their rare disease (Orphanet)

Q: If it is or were possible, I would have liked to be diagnosed at birth (agree + strongly agree). N=2,567

OPINION ON NEWBORN SCREENING FOR ANY RARE DISEASE

90% PLWRD think that any rare disease should be screened at birth if no treatment exists and:

- It allows a quicker diagnosis, to the benefit of the individual person and their carers.
- The disease can be followed-up on and harm can be avoided through prevention practices
- It would allow the person to have their disabilities better recognised, and to obtain a more adequate social support and independent living

Q: In your opinion, should ANY rare disease be screened at birth IF NO TREATMENT EXISTS AND…
(agree + strongly agree)

FINAL RESULTS PRESENTED APRIL 30TH 2PM (CET)

Register to our webinar

to learn more about key European results and how to use them for action

→ tiny.cc/RB_NBS_webinar

OVERALL EUROPEAN RESULTS

REPORT

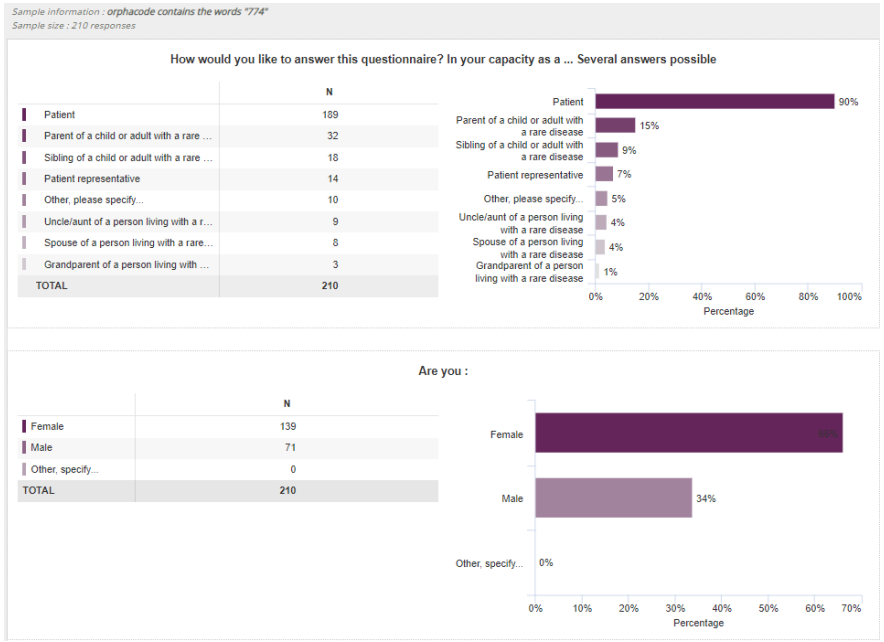
English

FACTSHEET

4 pager - 13 languages
+ on-demand

DASHBOARD

Each question of the questionnaire
Frequency and percentages
24 languages



eurordis.org/rare-barometer/english/#surveyResults

COMMUNICATION OF RESULTS FROM ANY RARE BAROMETER SURVEY

Results shared only if we can ensure anonymity

		European results	European results for one disease or group of diseases	Results for one country on all rare diseases	Specific results (one group of diseases in one country…)
	Everyone	X			
EURORDIS members	European Federations	X	X		
	National Alliances	X		X	
	Other EURORDIS members	X			X

Rare Barometer only analyses European results, and only communicate on European results. Our reports do not include distributions per country, diseases or groups of diseases corresponding to ERNs.

EURORDIS members can have access to their own results, use them and communicate on them as they want (for advocacy, writing papers, taking actions, defining their strategy…), we only ask them to refer to Rare Barometer when communicating their results.

THANK YOU!

to all Rare Barometer participants,
partners and corporate donors in 2023!

Funded by the European Union. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union or HaDEA. Neither the European Union nor the granting authority can be held responsible for them.


THANK YOU!
to the IMI2 programme and the Screen4Care partners
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CRG Centro for Genomic Regulation
SBA Research
Bambino Gesù Ospedale Pediatrico
FERARIAE UNIVERSITAS 13 91 EX LABORE FRUCTUS UNIFE
Pfizer
SANOFI
illumina
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Bulgarian Association for Promotion of Education and Science BAPES
ukb universitäts klinikumbonn
research institute
UCD DUBLIN University College Dublin
novo nordisk
CBS COPENHAGEN BUSINESS SCHOOL HANDELSHØJSKOLEN
EURORDIS RARE DISEASES EUROPE
Universitätsklinikum Erlangen
BULGARIAN ASSOCIATION FOR PERSONALIZED MEDICINE Each patient matters
Università di Siena 1240
NOVARTIS
siteminsel
Takeda
CHARITE UNIVERSITÄTSMEDIZIN BERLIN
SDU UNIVERSITY OF SOUTHERN DENMARK
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lysogene
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LUDWIG BOLTZMANN GESELLSCHAFT
FindZebra
SECOND FACULTY OF MEDICINE CHARLES UNIVERSITY
UNIVERSITÄTSMEDIZIN GÖTTINGEN UMG
UPPSALA UNIVERSITET
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ProQR
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SCREEN 4CARE
Rare Barometer A EURORDIS INITIATIVE