European Reference Network
for rare or low prevalence complex diseases

Network Neuromuscular Diseases (ERN EURO-NMD)

7th ERN EURO-NMD
ANNUAL MEETING

21st – 23rd February 2024

EU-IMI PROJECT SCREEN4CARE

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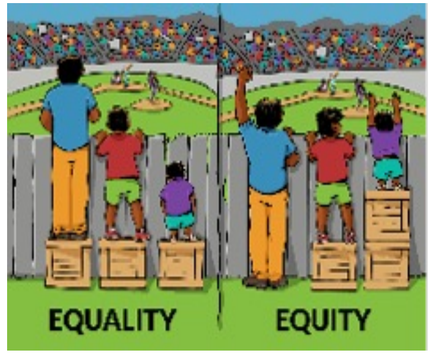
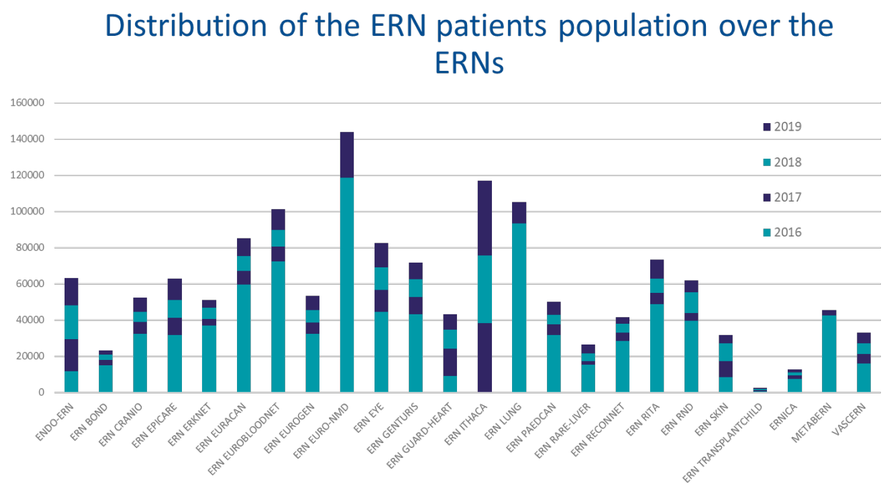
Funded by the European Union

RARE DISEASES IN EU: SOME NUMBERS AND THIER IMPACT ON NEWBORNS SCREENING

24 European Reference Networks (ERNs) were funded by EU in 2016, and represent a network of excellence centers in charge of about 8,000 different RDs, which have been categorized by phenotypic-driven approach in 24 groups (https://ec.europa.eu/health/ern_en).





NBS dimension in EU (2020 EU data source)
EU Inhabitants 447.000.000
Newborn/Year: **4.000.000**

RDs 6-8% of EU population
27-36 million persons
72 % are genetics (**23million persons!**)

- equality (every child is provided with the same health offer and opportunity)
- equity (<u>every child can benefit of the full potential of health and well-being tools</u>)

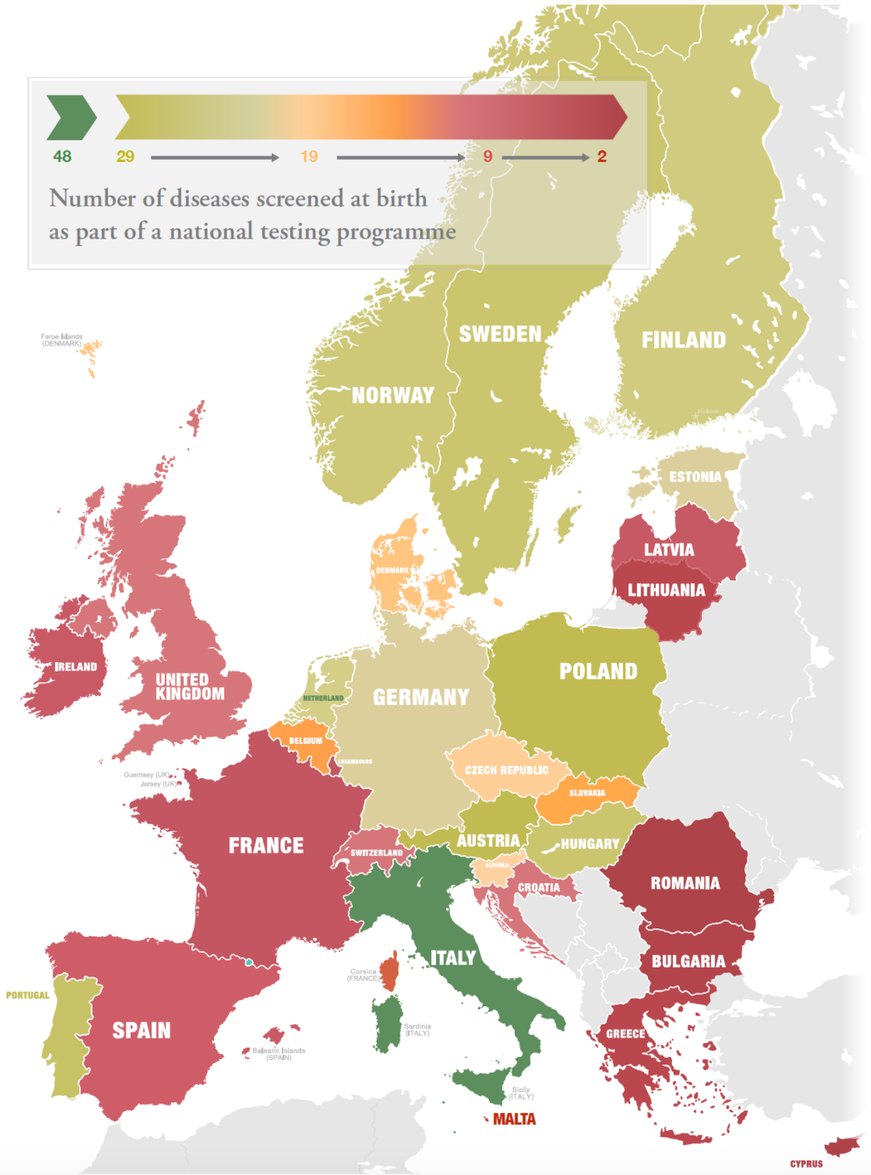
S4C will screen up to **25.000** infants/1 year (Italy, Germany, France, Greece)

WHERE ARE WE TODAY IN EU?

DK-UNB-21-0002 | March 2022

Newborn Screening: 1 heel prick test has the potential to diagnose 50 diseases

SIGNIFICANT VARIATIONS EXIST ACROSS COUNTRIES



1 test — **More than 50 diseases**

Disease Abbreviations (used overleaf...)

ALD Adrenoleukodystrophy
ASA Argininosuccinic aciduria
ARG Arginase deficiency
A-T Alpha Thalassemia
BIOPT (BS) Biopterin cofactor biosynthesis deficiency
BIOPT (REG) Biopterin cofactor regeneration deficiency
BKT Beta-ketothiolase deficiency
B-T Beta thalassemia
BTD Biotinidase deficiency
CACT Carnitine-acylcarnitine translocase deficiency
CAH Congenital Adrenal Hyperplasia
Cbl A Methylmalonic acidemia (CblA)
Cbl B Methylmalonic acidemia (CblB)
Cbl C Methylmalonic Acidemia with Homocystinuria (CblC)
Cbl D Methylmalonic Acidemia with Homocystinuria (CblD)
CF Cystic Fibrosis
CHT Congenital Hypothyroidism
CIT Citrullinemia type I
CIT II Citrullinemia type II (Citrin deficiency)
CPT I Carnitine palmitoyl-transferase (L) deficiency
CPT II Carnitine palmitoyl-trans-ferase II deficiency
CUD Carnitine uptake defect
FABRY Fabry Disease
GA I Glutaric acidemia type I
GA2 Glutaric acidemia type II
GALK Galactokinase deficiency
GBA Gaucher disease
GNMT Glycine N-methyltransferase deficiency
G6PD Glucose-6-phosphate dehydrogenase deficiency
HCU Homocystinuria (CBS deficiency)
HMG 3-Hydroxy 3-methylglutaric aciduria
H-PHE Benign hyperphenylalaninemia
IBG Isobutyryl-CoA dehydrogenase deficiency
IVA Isovaleric acidemia
LCHAD Long-chain hydroxyacyl-CoA dehydrogenase deficiency
MADD Multiplex acyl-CoA dehydrogenase deficiency
MAL Malonic aciduria
MAT Methionine adenosyltransferase deficiency
MCAD Medium-chain acyl-CoA dehydrogenase deficiency
MCD Multiple carboxylase deficiency
MLD Metachromatic Leukodystrophy
MMA Vitamin B12 deficiency
MPS I Mucopolysaccharidosis Type I
M / SCHAD Short / medium chain 3-OH acyl-CoA dehydrogenase deficiency
MSUD Maple syrup urine disease
MTHFR Homocystinuria due to MTHFR deficiency
MUT Methylmalonic acidemia (Mut)
ORN Hyperornithinemia with Gyrate Atrophy of Choroid and Retina
PA Propionic Acidemia
PKU Phenylketonuria
POMPE Pompe Disease
SAHH S-Adenosylhomocysteine hydrolase deficiency
SCD Sickle cell disease
SCID Severe combined immunodeficiency
SMA Spinal Muscular Atrophy
TFP Trifunctional protein deficiency
TYR I Type I tyrosinemia
TYR II Tyrosinemia type II
TYR III Tyrosinemia type III
VLCAD Very long-chain acyl-CoA dehydrogenase deficiency
2MBG 2-Methyl butyryl-CoA dehydrogenase deficiency
2M3HBA 2-Methyl-3-hydroxybutyric aciduria
3MGCA 3-Methylglutaconic aciduria
3MCC 3-Methylcrotonyl-CoA carboxylase deficiency (also known as 3-MCC deficiency)

Country Rankings

	Country	Screening for...
1	Italy	48 Diseases
2	Poland	29 Diseases
3	Austria	29 Diseases
4	Portugal	29 Diseases
5	Hungary	27 Diseases
6	Sweden	26 Diseases
7	Norway	26 Diseases
8	Netherlands	25 Diseases
9	Finland	23 Diseases
10	Germany	21 Diseases
11	Estonia	20 Diseases
12	Slovenia	19 Diseases
13	Czech Republic	19 Diseases
14	Denmark	18 Diseases
15	Slovakia	13 Diseases
16	Belgium	11 Diseases
17	Switzerland	10 Diseases
18	UK	9 Diseases
19	Croatia	9 Diseases
20	Spain	8 Diseases
21	Ireland	8 Diseases
22	France	6 Diseases
23	Latvia	6 Diseases
24	Luxembourg	5 Diseases
25	Malta	5 Diseases
26	Greece	4 Diseases
27	Lithuania	4 Diseases
28	Bulgaria	4 Diseases
29	Cyprus	2 Diseases
30	Romania	2 Diseases

RESEARCH PUBLISHED MARCH 2022

CRA Charles River Associates

Research supported by Novartis AG

Screenshot

Genetic newborn screening as a gate for genomic medicine

What is a genetic screening test?

- A screening test search for potential health disorders or diseases in **a population of individuals** **who do not** **have any symptoms** of disease and whom higher percentage is healthy.

It defines a risk

What is diagnostic test?

- A diagnostic test is applied to a **patient** with a **pathological** phenotype and belongs to a (often complex) diagnostic **cohort** of ascertainments to diagnose a disease.

It defines a disease etiology

SCREENING AND DIAGNOSTIC TESTS HAVE DIFFERENT SCOPES, QUALITY ASSESSMENT, PIPELINES, AND…NUMBERS!

GENETIC NEWBORN SCREENING

- **WHY…….**
- Novel therapies for RDs
- High throughput genetic strategies for genetic screening
- Beyond metabolic diseases
- Applicable to hundreds RDs

- **HOWEVER ISSUES EXIST….**
- Non mendelian inheritance
- Variant of uncertain significance (VUS)
- Variants' incomplete penetrance
- Reporting of heterozygotes for recessive variants
- Turnaround reporting time
- Costs (centralized platforms)

- **…….TO BE ADDRESSED**
- false positives (anxiety)
- false negatives (accuracy)
- Ethical issues (genetic testing)
- Late onset diseases: to report?
- Data ownership (infants? Parents? Who?)
- Data storage
- Ethical and legal issues

New application of genetic tests:
From diagnosis to screening: ethical, legal, privacy issues and (not lastly) costs are oustanding since gNBS should be «universal» and will impact on 95% of normal babies

SCREEN 4CARE

Shortening the path to rare disease diagnosis by using newborn genetic screening and digital technologies

AN EU-IHI FUNDED RESEARCH PROJECT 2021-2026

Alessandra Ferlini

Università degli Studi di Ferrara

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 €

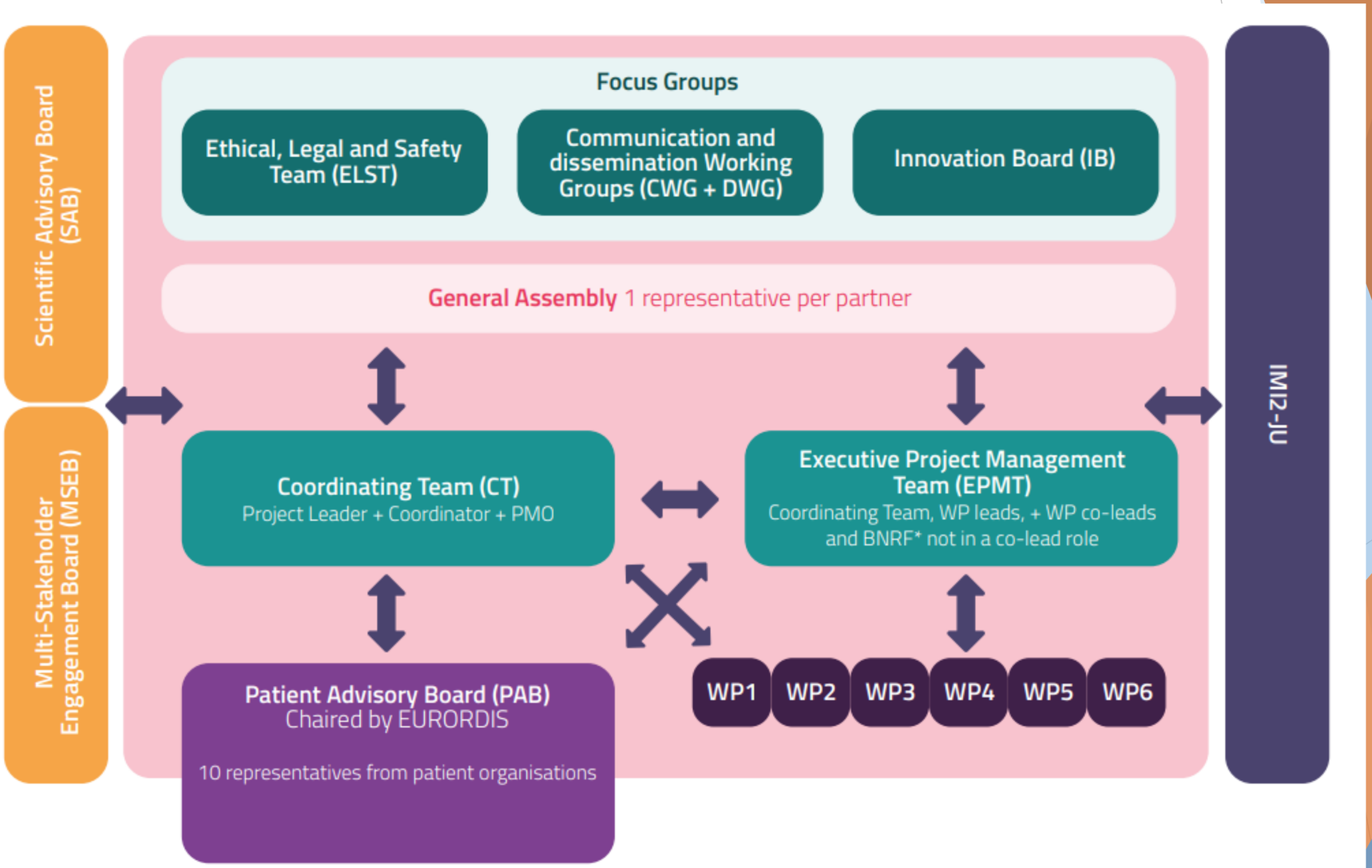
14 COUNTRIES
35 PARTNERS

Aldona Zygmunt

Pfizer

This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking (JU) under grant agreement No 101034427.
The JU receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA.

S4C Governance



SCREEN4CARE pillar aims

1. **Federate the complex RD diagnosis / NBS EU ecosystem**

2. **Champion a sustainable genetic NBS framework for RD early diagnosis**

3. **Improve accuracy & speed of patient diagnosis using innovative digital tools**

6 interconnected work packages (WPs)

Multistakeholders, multidisciplinary boards, including Patient Organization, academia, SMEs, Public Health Decision Makers, Regulators, health technology assessment experts

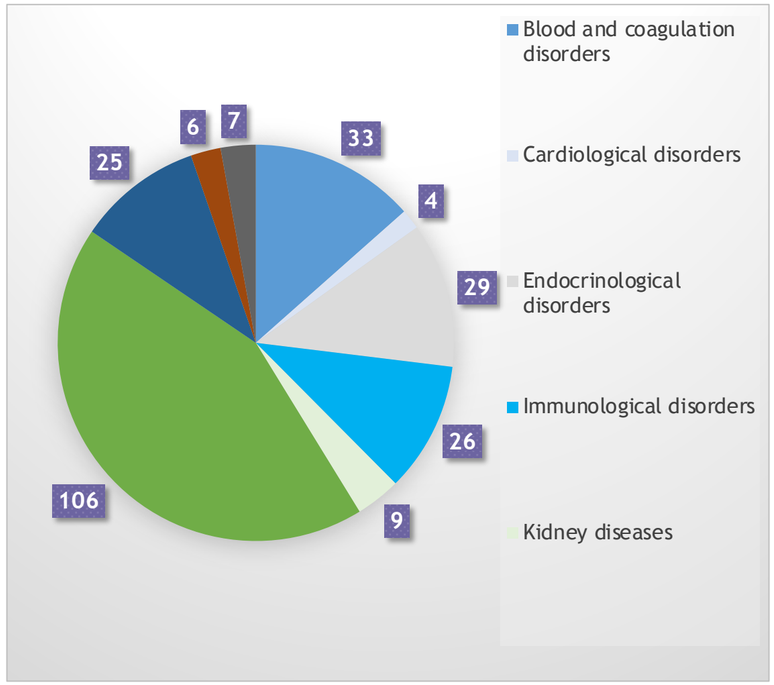
Genetic Newborn Screening tasks in WP3
(Jan Kirschner and Stefaan Sansen WP leaders)

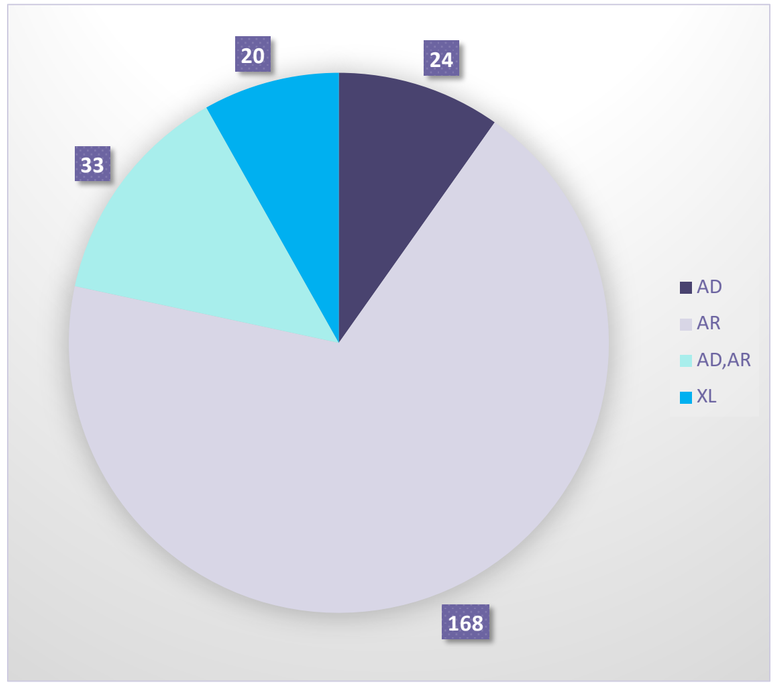
- ✓ **Treatable diseases selection for TREAT-panel design**
- ✓ **Actionable diseases selection ACT-panel design**
- ✓ **TREAT-panel finalized: 245 genes related to treatbale diseases**
- ✓ **Whole Genome Sequencing offered to all enrolled babies with early symptoms and negative at the genetic TREAT and/or ACT panel NBS**
- ✓ **Ethical applications for real life gNBS using TREAT panel and WGS**
- ✓ **Countries: France (Dijon), Greece (Athen and Tessalonika), Italy (Rome, Ferrara, Siena), Germany (Freiburg, Gottingern, Erlangen)**
- ✓ **Number of screened infants: up to 25.000 infants (pending, cost-dependent)**

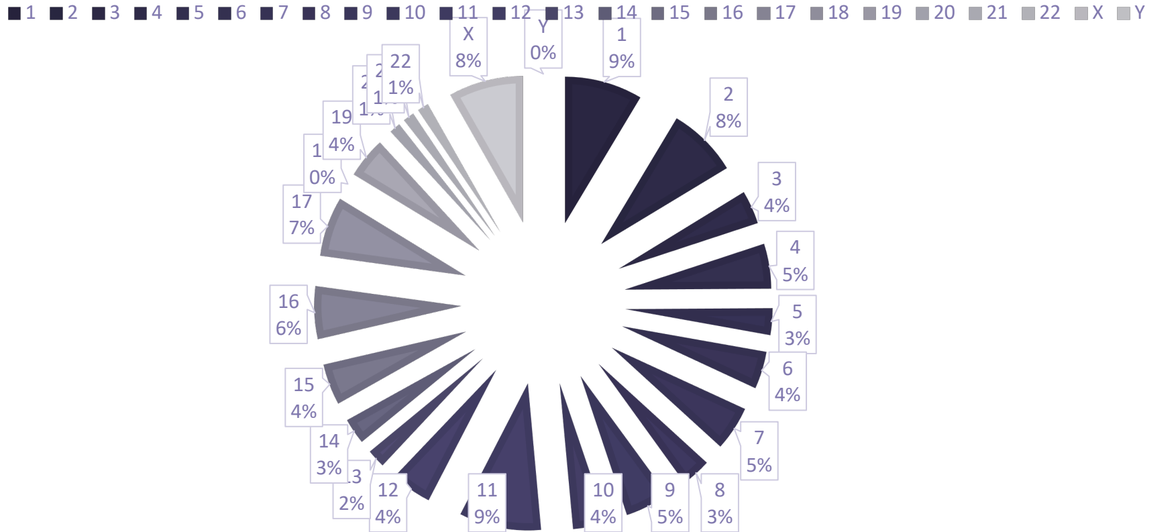
TREAT PANEL: PHENOMICS

Category	Total number of genes (out of 24 associated ERN
Blood and coagulation disorders	33 - EuroBloodNet
Cardiological disorders	4 - GUARD-HEART
Endocrinological disorders	29 - Endo-ERN
Immunological disorders	26 - ERN RITA
Kidney diseases	9 - ERKNet
Metabolic (including mithocondrial disorders, oxidation disorders, lysosomial disorders, etc…)	106 - MetabERN
Neuromuscular disorders	15 Euro-NMD
Neurolologic/neurodegenerative	10 - ERN-RND
Syndromic	6 - ITHACA
Others	7 - ERN-BOND, ERN-LUNG, ERN-EYE

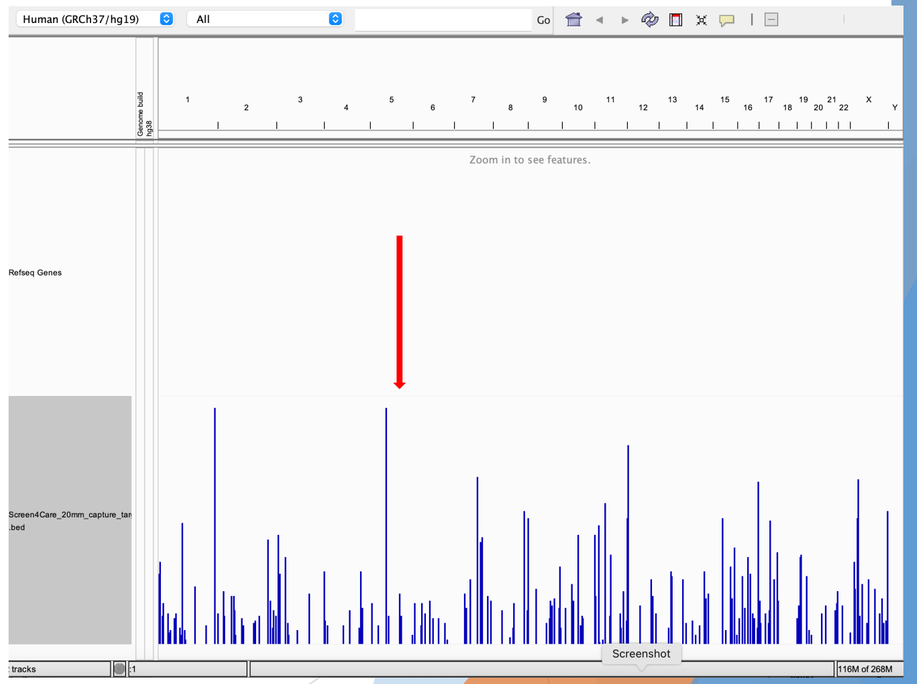
TREAT PANEL : FEATURES







ROCHE DESIGN :TREAT PANEL CAPTURE TARGET



TREAT PANEL ITALIAN ETHICAL APPLICATION: SUBMITTED ON NOVEMBER 2023

CRUCIAL STEPS

List of genes: 245 disease genes

➢ **Inclusion criteria:**
- Newborns in a specific temporal window of 12 months (from the day 1 when the first couple is enrolled) from **participating hospitals**
- **Informed consent** signed by **both parents/legal guardian**

➢ **Exclusion criteria:** **Lack** of the above criteria

➢ **Recruitment:**
- **Competitive**
- Information through **videos**, **flyers**, and **meetings** during three **pregnancy checkpoints** (**CKPTs**):

✓ **early** (first half of pregnancy)
✓ **major** (end of pregnancy)
✓ **rescue** (after birth)

- **"Communication module"** for **parents** certifying successful communication of **projects contents**

➢ **Type of variants which will be reported:**
- **Pathogenic** or **likely pathogenic variants**

→ clinical evaluation and genetic counselling trough the ERNs

- **Carrier status** for **recessive pathogenic variants** (**it might be country-dependent and** only if **agreed** on the **informed consent**)

➢ **Type of variants which will NOT be reported:**
- **VUS**
- **Benign polymorphisms**

→ «ad hoc» in silico and/or functional studies at both S4C and ERN centres

THE 1ST YEAR OF SCREEN4CARE

OCTOBER 2021– OCTOBER 2022

2021

- **1, Project Start** with 35 Beneficiaries — **OCTOBER**
- **25,** Launch of the **LinkedIn and Twitter Accounts**
- **26–27,** Virtual **Kick-Off Meeting**

2022

- **JANUARY** — **25,** Project Presentation at the **EURO-NMD Meeting**
- **FEBRUARY** — **10,** Project Presentation at the **InnoForum at sitem-insel**
- **17–19,** Project Presentation at the **International Conference on Duchenne and Becker Muscular Dystrophy**
- **28,** Launch of the **Website**
- **28,** Social Media Campaign for **#RareDiseaseDay**
- **MARCH** — **1-2,** Project Presentation at the 2nd International Conference on Rare Diseases
- **APRIL** — **1,** Launch of the **YouTube Channel**
- **1, UKLFR** Joins the Consortium
- **MAY** — **31, 10th Video** Uploaded to YouTube
- **JUNE** — **23, PTC** Joins the Consortium
- **JULY** — **13,** Project Presentation at the **World Orphan Drug Congress**
- **15,** Publication in the **International Journal of Neonatal Screening**
- **23,** Project Presentation at the **"Early Diagnosis of Patients with Rare Disorders in the EU: Crucial Role of The Newborn Screening"** Technical Meeting
- **AUGUST** — **30,** Presentation at the **SSIEM Annual Symposium**
- **SEPTEMBER** — Social Media Campaign for **Newborn Screening Awareness Month**
- Publication in the IJNS Featured on the **Journal Cover**
- **OCTOBER** — **160+ Reactions** to a LinkedIn Post
- **5–6,** Project Presentation at the **ICoNS Conference**
- **17–18,** Poster Presentation at the **NORD Summit**
- A Total of **16 Deliverables** Submitted in the First Year

Consortium · Social Media · Conferences · Publications

WWW.SCREEN4CARE.EU

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THE 2ND YEAR OF SCREEN4CARE

NOVEMBER 2022–OCTOBER 2023

2022

- **7,** 1st Screen4Care Annual Meeting (virtual) — **NOVEMBER**
- **18,** Project Presentation at EDGE Europe 2022
- **10,** Project Presentation at the Annual Board of ERN-Ithaca — **DECEMBER**

2023

- **JANUARY** — **26,** 1st Screen4Care and ERN Joint Meeting
- **FEBRUARY** — **11,** Campaign for the International Day of Women and Girls in Science
- **16–18,** Project Presentation at the **International Conference on Duchenne and BeckerMuscular Dystrophy**
- **28,** Campaign for **#RareDiseaseDay**
- **28,** Project Presentation at the **3rd International Conference on Rare Diseases: Greek Chapter**
- **MARCH** — **6–7,** 1st **Face-to-face Consortium Meeting** (Hybrid)
- **17,** Project Presentation at the **European Molecular Imaging Meeting**
- **21,** Project Presentation at the **ITHACA Webinar: Innovation in Newborn Screening across Europe**
- **22–24,** Project Presentation at the **German Neurological Society Congress**
- **24,** Project Presentation at the **26th Congress of the Medical-Scientific Advisory Board of the German Society for Muscle Patients**
- **APRIL** — **7,** Campaign for **World Health Day**
- **19–20,** Project Presentation at the **Frontiers in Pediatric Genomic Medicine 2023**
- **28,** Campaign for **Undiagnosed Day**
- **MAY** — **16–18,** Project Presentation at the **Rare Disease Innovation & Partnership Summit**
- **20,** Project Presentation at the **16th International Congress of Pediatric Laboratory Medicine-Satellite Meeting**
- **24,** Participation in the **Signalise Podcast**
- **JUNE** — **7,** Project Presentation at the **Duchenne Care Conference 2023**
- **12,** Project Presentation at the **European Society of Human Genetics**
- **28,** Campaign for **International Neonatal Screening Day**
- **SEPTEMBER** — Campaign for the **Newborn Screening Awareness Month**
- **15,** Publication in the **„Frontiers in Public Health" Journal**
- **24,** Finalisation of the **TREAT Panel**
- **27, 2nd Screen4Care** and **ERN Meeting**
- **27–28,** Project Presentation at the **3rd World Congress on Rare Diseases & Orphan Drugs**
- **30,** Project Presentation at the **Bulgarian National Conference for Rare Diseases and Orphan Drugs**
- **9 Deliverables Submitted in 2023**
- **OCTOBER** — **1000 Followers on LinkedIn**
- **4,** Publication in the **„Orphanet Journal of Rare Diseases"**
- **5–6,** Project Presentation at the **Annual ICoNS Conference**
- **9,** 1st **Newborn Screening Forum Meeting**
- **12–13,** Project Presentation at the **Precision Medicine Networking Forum Meeting**

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Consortium · Social Media · Conferences · Publications

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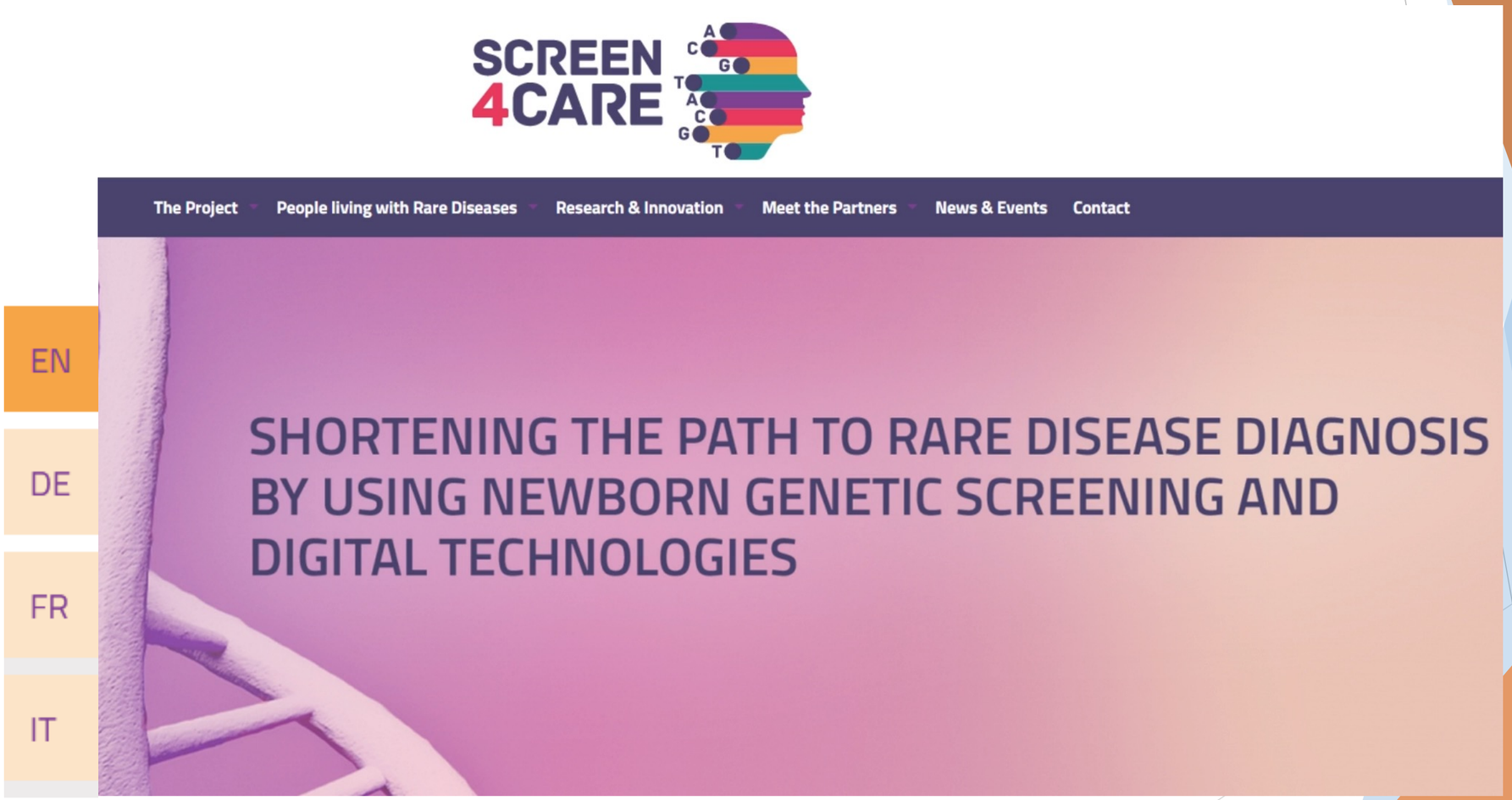
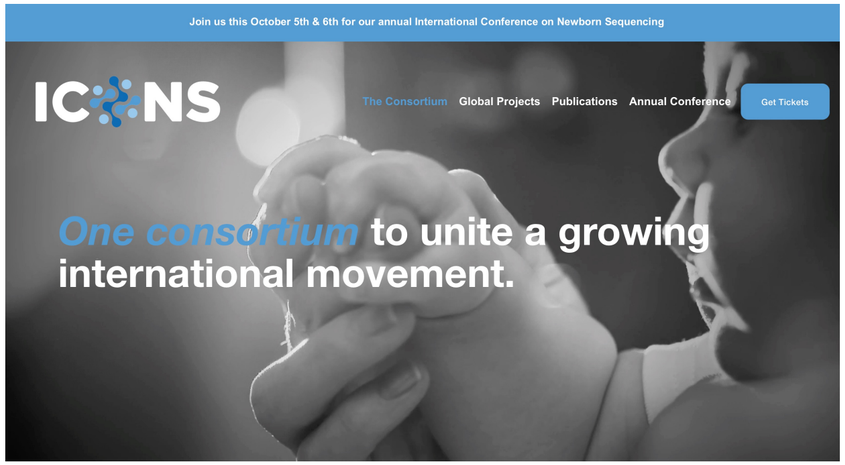
Website:
screen4care.eu
(EN,DE,IT,FR,...)



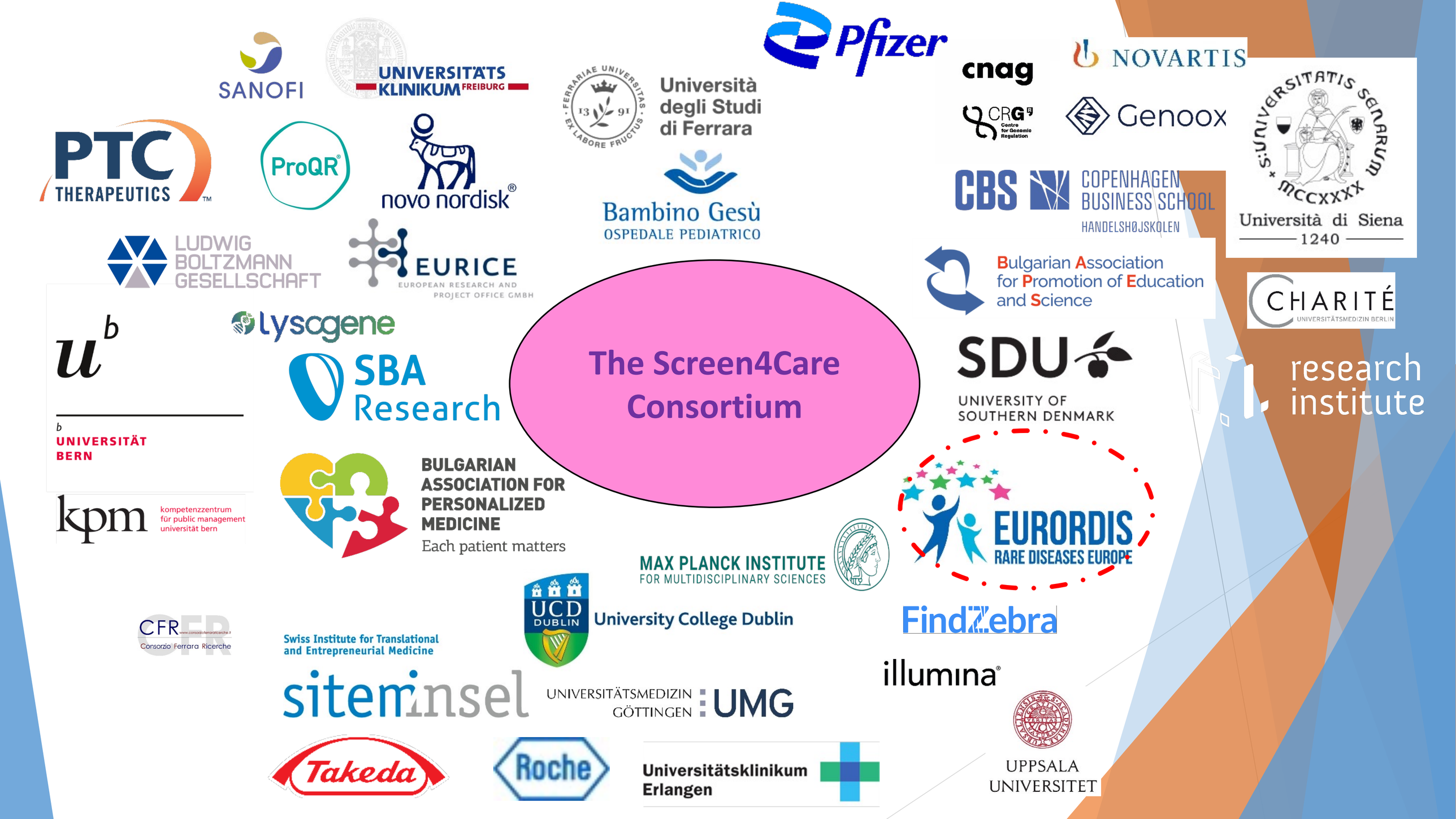
Genetic and Genomic newborn screening
INITIATIVES AND INTERNATIONAL COOPERATIONS ON gNBS



International Consortium Of Newborn Sequencing
ICoNS

PLANNED ACTIVITES:
-protocol sharing
-datasets co-design (annotation, nomencalture, etc)
-gene list sharing
WW gNBS core gene list (!)

The Screen4Care Consortium



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