7th ERN EURO-NMD

ANNUAL MEETING

The NBS workpackage of Screen4Care and ERN involvement

21st – 23rd February 2024

Jan Kirchner

University of Freiburg

European Reference Network
for rare or low prevalence complex diseases

Network Neuromuscular Diseases (ERN EURO-NMD)

Funded by the European Union

The ERN EURO-NMD is funded by the European Commission under the EU4Health programme (EURO-NMD 23-27 — 101156434 — EU4H-2023-ERN2-IBA)

WP3 Overview – Genetic Newborn Screening

Number	Description	Lead partner
T3.1	Stakeholder preference assessment for a sustainable and ethical NBS	9-UU
T3.2a	Development of a genetic NBS for treatable RDs (TREAT-panel)	3-OPBG
T3.2b	Development of a genetic NBS for actionable RDs (ACT-panel)	25-EURORDIS
T3.3	Running and validating the NBS protocol	1-UNIFE
T3.4a T3.4b T3.4c	Post-diagnosis planning and recommendation Whole genome sequencing for early symptomatic cases Assessment to what extent newborn screening and its follow up will empower exposed families	16-UKLFR 16-UKLFR 9-UU
T3.5	Evidence on cost-effectiveness of NBS for RDs	5-UBERN

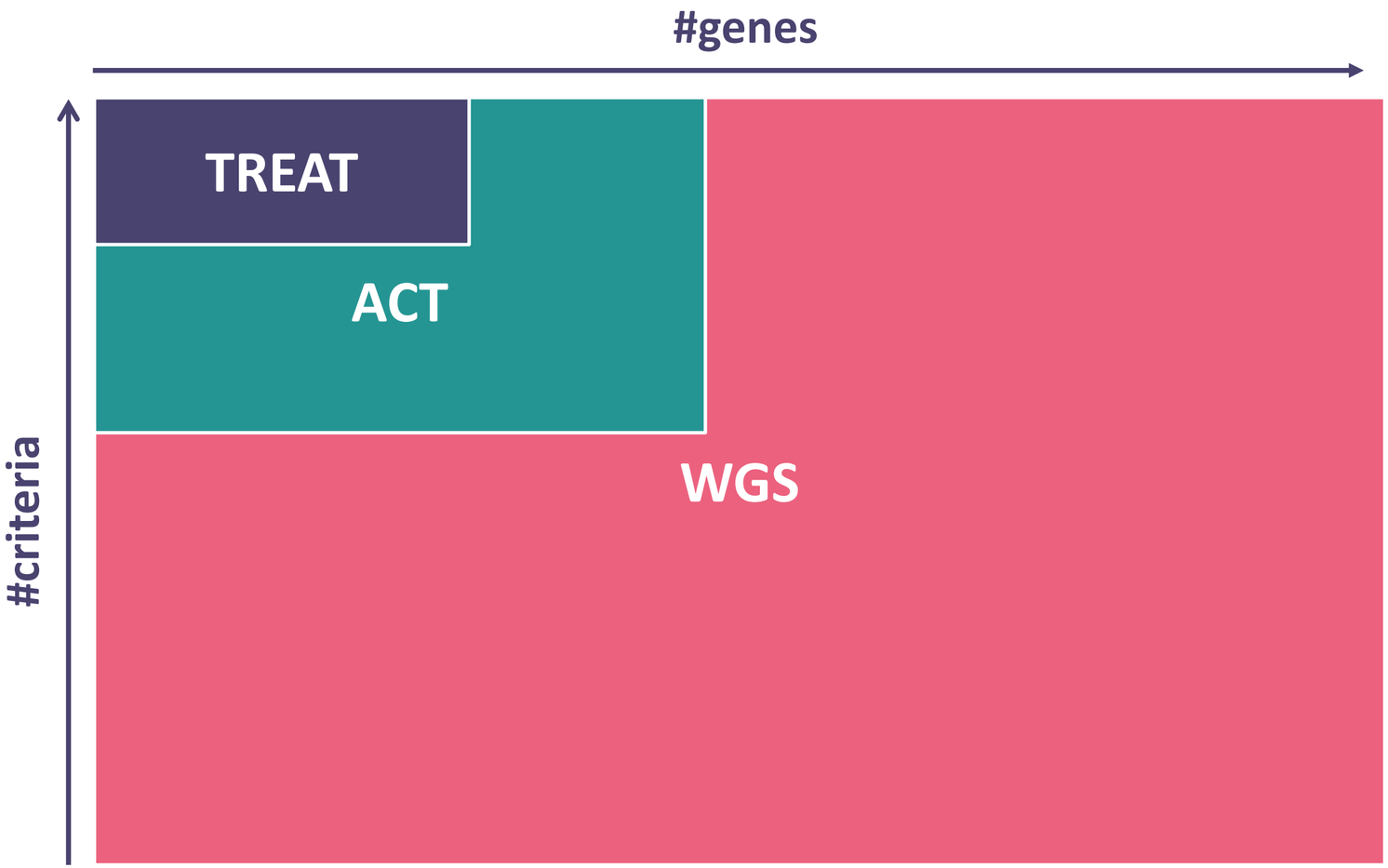
Introduction

NBS opting in to:

OPTION 1:
NGS gene panel for treatable (TREAT) Rare Diseases

OPTION 2:
Add NGS gene panel for actionable (ACT) Rare Diseases

OPTION 3:
Complement Whole Genome Sequencing (WGS) should the infant develop symptoms suggestive of a rare disease of genetic origin



TREAT-panel – Criteria

TREATability	
YES	Approved drug treatment (EMA) incl. gene therapy and/or other treatment/intervention (drug, diet, bone marrow transplantation, supplements, vitamins, etc) that is recommended by guidelines (at least for a subgroup of the disease) and Treatment available in Germany and Italy
NO	All genes/diseases not fulfilling the criteria above

disease onset*	
2	Predominantly paediatric onset of disease
1	Spectrum of onset across age groups, difficult to predict onset/limited knowledge about natural
0=No	Mainly adult onset (> 18 years)

disease severity	
2	Most likely to cause significant health problem
1	Spectrum of severity, difficult to predict
0=No	Not causing significant health problem

penetrance	
2	Penetrance > 80%
1	Intermediate penetrance (20-80%)
0=No	Low penetrance (< 20%)

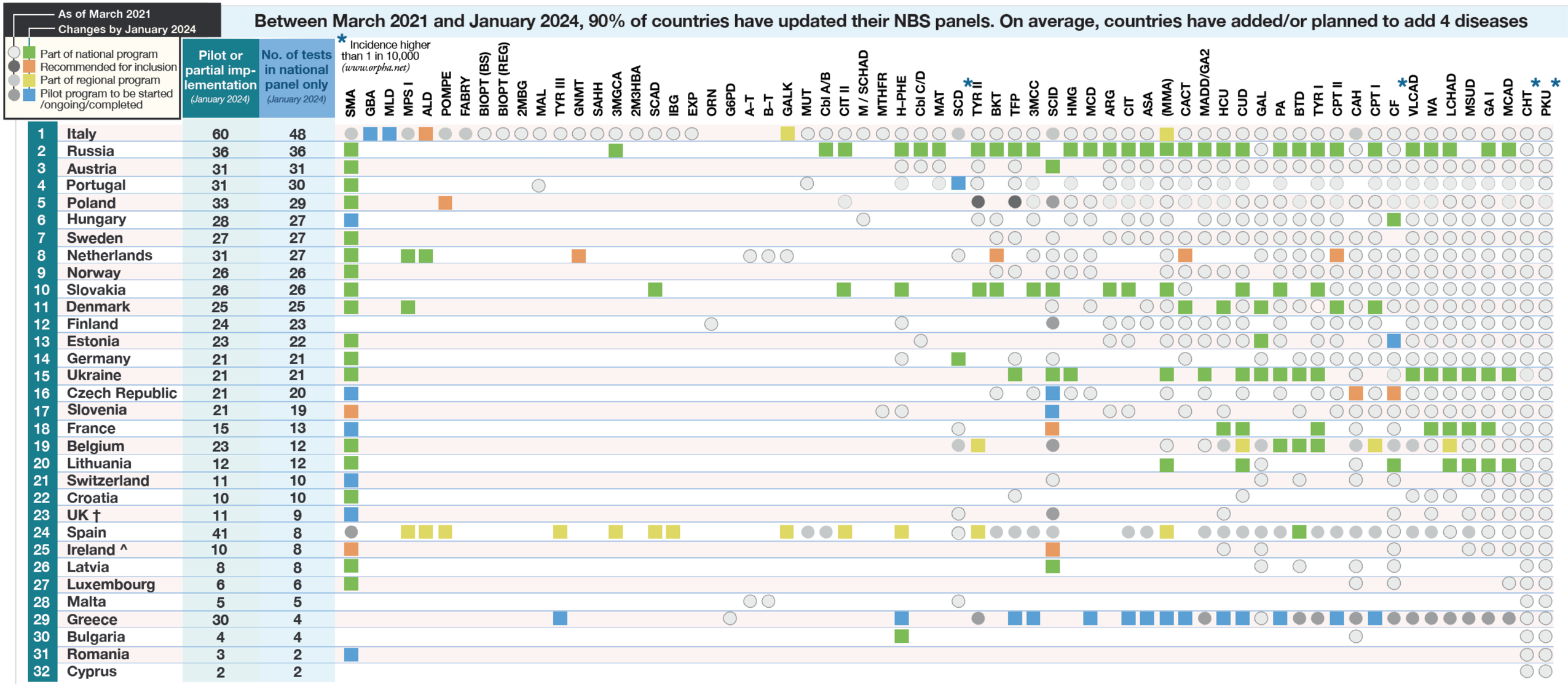
clinical validity	
2	known pathogenic variants with clear phenotype-genotype correlation
1	genes with known pathogenic variants and partial genotypephenotype correlation (as in ultrarare
0=No	genes with only benign variants or variants of unknown significance, no established genotype-

genetic feasibility	
YES	significant number of pathogenic variants annotated in database, detectable by our
NO	Non-mendelian inheritance, not identifiable by chosen NGS approach

* Addition of further “sub-criterion” for age of onset: **treatment needed within the first 2 years of life (yes/no)**

→ manual inclusion of this criterion

Disease Selection – Current NBS programs across Europe



^ *ADA-SCID is part of the national screening program, however other SCID disease sub-types have not yet been included* - † *The SMA pilot program in the UK is local, with only a small number of babies being screened for SMA each year*

Disease selection: Starting list

- RxGenes - Bick et al (2021)
  - https://www.rx-genes.com/
  - Required, "Evidence for treatment" = Guideline
  - n=211 unique genes
- GTRx - Kingsmore et al (2022)
  - Group A adjudicated gene-disease dyad , n=248 unique genes. Group A contains conditions for which there were not major gaps in the evidence, high likelihood of benefit, and low risk of harm.
- NBS programs
  - RUSP (Core conditions and secondary conditions)
  - Italy and Germany
- EMA approved orphan drugs

Received: 12 November 2020 | Revised: 20 November 2020 | Accepted: 24 November 2020
DOI: 10.1002/ajmg.c.31874

RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART C Seminars in Medical Genetics

An online compendium of treatable genetic disorders

David Bick[1] | Sarah L. Bick[2] | David P. Dimmock[3] | Tom A. Fowler[4,5] | Mark J. Caulfield[4,5] | Richard H. Scott[4,6]

ARTICLE

A genome sequencing system for universal newborn screening, diagnosis, and precision medicine for severe genetic diseases

Stephen F. Kingsmore,[1,2,3,*] Laurie D. Smith,[1] Chris M. Kunard,[4] Matthew Bainbridge,[1,2] Sergey Batalov,[1,2] Wendy Benson,[1,2] Eric Blincow,[1,2] Sara Caylor,[1,2] Christina Chambers,[6] Guillermo Del Angel,[5] David P. Dimmock,[1,2] Yan Ding,[1,2] Katarzyna Ellsworth,[1,2] Annette Feigenbaum,[1,2,6] Erwin Frise,[7] Robert C. Green,[8] Lucia Guidugli,[1,2] Kevin P. Hall,[4] Christian Hansen,[1,2] Charlotte A. Hobbs,[1,2] Scott D. Kahn,[11] Mark Kiel,[9] Lucita Van Der Kraan,[1,2] Chad Krilow,[10] Yong H. Kwon,[1,2] Lakshminarasimha Madhavrao,[1,2] Jennie Le,[1,2] Sebastien Lefebvre,[5] Rebecca Mardach,[1,2,6] William R. Mowrey,[5] Danny Oh,[1,2] Mallory J. Owen,[1,2] George Powley,[10] Gunter Scharer,[1] Seth Shelnutt,[10] Mari Tokita,[1,2] Shyamal S. Mehtalia,[4] Albert Oriol,[1,2] Stavros Papadopoulos,[10] James Perry,[2,6] Edwin Rosales,[1,2] Erica Sanford,[1] Steve Schwartz,[9] Duke Tran,[4] Martin G. Reese,[7] Meredith Wright,[1,2] Narayanan Veeraraghavan,[1,2] Kristen Wigby,[1,2,6] Mary J. Willis,[1] Aaron R. Wolen,[10] and Thomas Defay.[5]

Disease selection: complexity – further sources

- Age-based Semi-Quantitative Metric (ASQM, 2019)- Milko et al (2019)
  - Category 1, n = 429 genes, childhood onset, high actionability

ORIGINAL ARTICLES
www.jpeds.com • THE JOURNAL OF PEDIATRICS

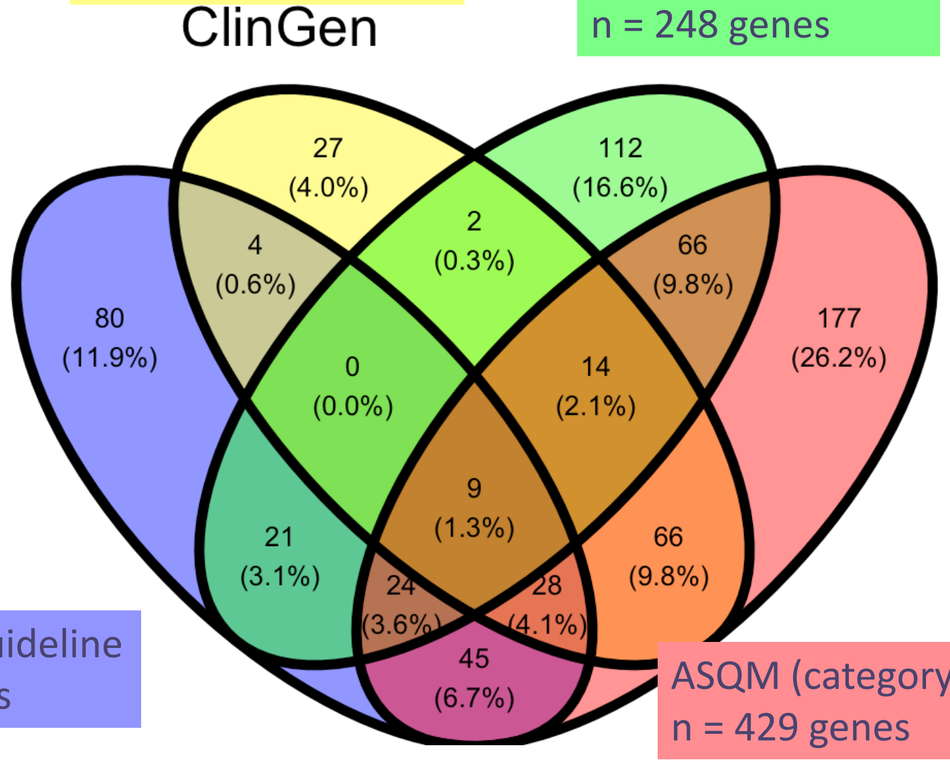
An Age-Based Framework for Evaluating Genome-Scale Sequencing Results in Newborn Screening

Laura V. Milko, PhD[1], Julianne M. O'Daniel, MS[1], Daniela M. DeCristo, BS[1], Stephanie B. Crowley, PhD[1], Ann Katherine M. Foreman, MS[1], Kathleen E. Wallace, BS[1], Lonna F. Mollison, PhD[1], Natasha T. Strande, PhD[1,2], Zahra S. Girnary, MS[1,*], Lacey J. Boshe, BS[1,†], Arthur S. Aylsworth, MD[3], Muge Gucsavas-Calikoglu, MD[3], Dianne M. Frazier, MD[3], Neeta L. Vora, MD[4], Myra I. Roche, MS[1,3], Bradford C. Powell, MD, PhD[1], Cynthia M. Powell, MD[1,3], and Jonathan S. Berg, MD, PhD[1]

- ClinGen Pediatric Actionability (2023)
  - https://actionability.clinicalgenome.org/ac/Pediatric/ui/summ/assertion
  - Required (ClinGen), gene in resource with at least one assertion, n = 150 unique genes

ClinGen actionability (pediatric), n = 150 genes

GTRx (group A), n = 248 genes



RxGenes, guideline n=211 genes

ASQM (category 1), n = 429 genes

Disease selection: TREAT panel-size

- Status after scoring and ranking

Score	#genes	#genes-sum	Kb	Kb - sum	Comment
8	108		420 Kb		
7	92	200	360 Kb	780 Kb	
6	26	226	100 Kb	880 Kb	
5	60	286	220 Kb	1.1 Mb	Low or absent penetrance data and intermediate severity
4	2	288			
3	1	289			Validity ‘0’

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→ minimal scoring of 7 needed for inclusion into the panel
→ 200 genes included into the panel

Manual curation period: WP3

- Input from members of WP3 involved in developing the panel
- Several discussions on inclusion or exclusion of genes
- Inclusion of further information from experts for different genes

→ exclusion of 32 genes

→ further inclusion of 51 genes

→ 219 genes included in the panel

Manual curation period: S4C-consortium, PAB, SAB

Form to propose an additional gene for the TREAT-panel:

GA no. 101034427 SCREEN4CARE TREAT-panel selection

Proposal of genes for TREAT-panel

Contact details from person submitting the proposal

Name: Organization:

Email address:

Details on the gene suggested for inclusion on the TREAT-panel

Gene name: Associated diseases:

HGNC symbol for gene: Orphanet-ID of diseases:

Treatment (mandatory)

Please describe available treatment with supporting references (PMID):

Please propose scoring according the TREATpanel selection criteria

Disease onset

X	Score	Definition
○	2	Predominantly paediatric onset of disease
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◉	0	Mainly adult onset (>18 years)

Disease severity

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○	2	Most likely to cause significant health problem
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Penetrance

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Clinical validity

X	Score	Definition
○	2	Known pathogenic variants with clear genotype-phenotype correlation
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◉	0	Genes with only benign or variants of unknown significance, no established geno/phenotype correlation

Additional comments:

Manual curation period: S4C-consortium, PAB, SAB

- 42 genes proposed for **inclusion** by 10 persons

→ **29 genes included**

- 3 genes proposed for **exclusion** by 2 persons

→ **3 genes excluded**

TREAT PANEL: PHENOMICS

Category	Total number of genes (out of 245) and 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
Neurolologic/neurodegenerative and neuromuscular disorders	25 - ERN-RND, EURO-NMD, ITHACA
Syndromic	6 - ITHACA
Others	7 - ERN-BOND, ERN-LUNG, ERN-EYE

Final panel

TREAT-panel validation ongoing

- Total number of genes: **245**
- Total size of the TREAT-panel: below **900 Kb**

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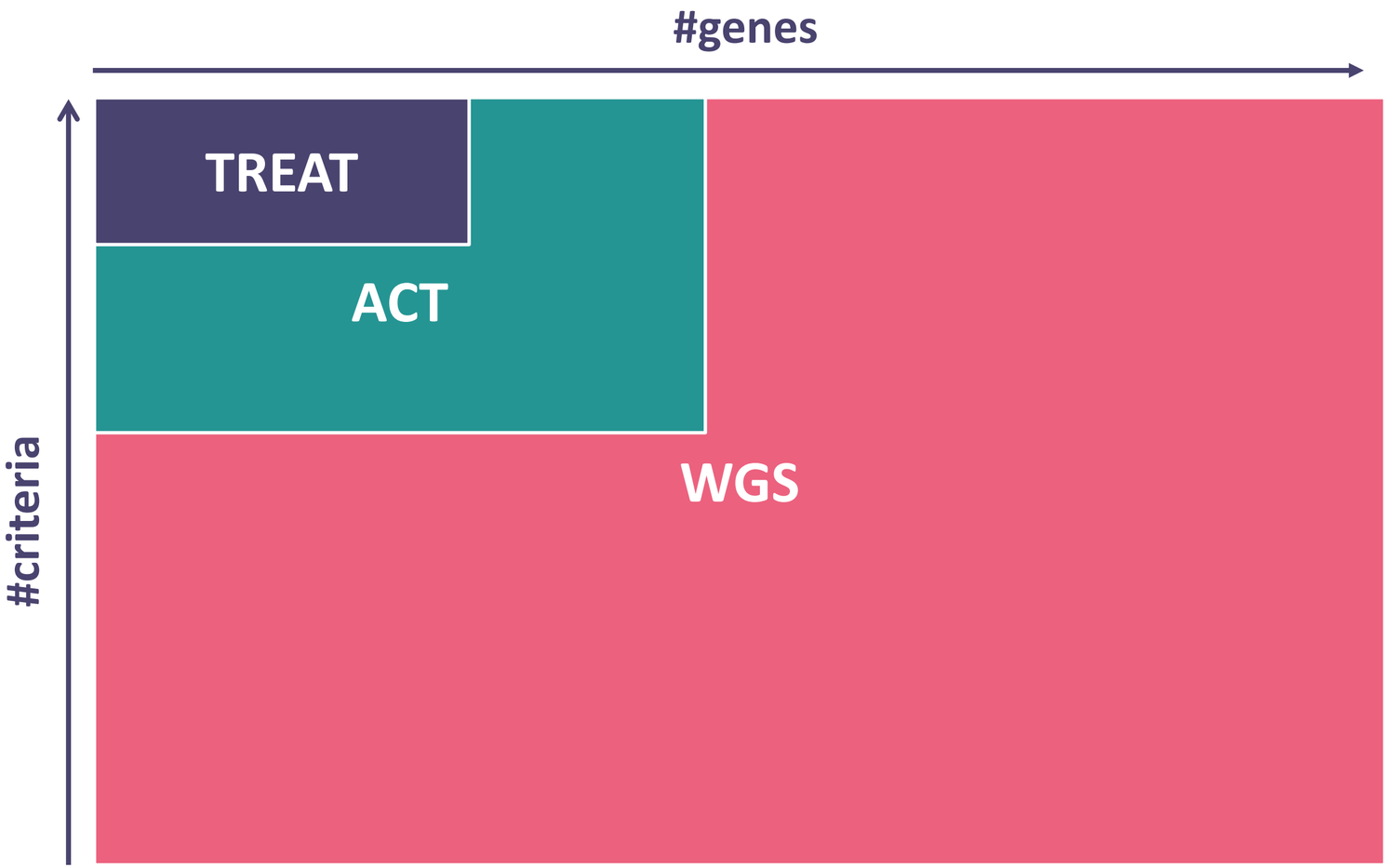

ACT- Panel Update

EURORDIS Newborn Screening Working Group: 11 Key Principles

Framing Paper on Actionability: Definition of Actionability

Stakeholder preference study

Rare Barometer Survey on Diagnosis: Patient preferences

Screen4Care NBS Forum: Defining the criteria

Consultations with Screen4Care NBS Forum members:

Preparing the Information Package and revision by NBS Forum members:

Preparing the ACT Nomination Document:

Collecting Nominations

Initial analysis, data sorting and scoring

Consultations with clinicians and manual curation

Consultations with S4C Forum members (Illumina, CHU Dijon)

Analysis of ClinVar P/LP variants (Illumina)

Feedback from the S4C Scientific Advisory Board

Availability of research and support for patients

Final consultation with clinicians, analysis, Exclusion of genes

FINAL LIST FOR THE ACT PANEL

SCREEN 4CARE

A Recruitment

Information to the parents through videos, flyers, meetings through checkpoints (CKPTs)

- **«Early» CKPT:** short video in the 1st half
- AND/OR
- **«Major» CKPT:** long video at pre-delivery meetings
- AND/OR
- **«Rescue» CKPT:** at DBS collection
- Maternity unit/midwives

↑ Informed consent

B Dried blood spot sampling

- DBS Sample with S4C logo
- Birth centers

↑ Sample from newborn's heel

Pseudo-anonymized DBS sample

C

Sample delivery to HUB

- Pseudo-anonymized DBS Sample with S4C logo

If report confirms the presence of a P/LP genotype

- S4C centers' interaction with ERNs

S4C Recruiting center

D Laboratory

- cnag
- Genoox
- BaseSpace (raw data)
- NBS data management system
- HUB Sequencing OPBG Rome — Bambino Gesù Ospedale Pediatrico

Confirmation Report

E

- Variants' technical validation
- S4C Hub (OPBG and UNIFE)

Scientific Report (CNAG/Geenox)

- IF VUS → VUS protocol at the ERN diagnostic centre
- IF NEGATIVE → Written information to the family → WGS in case of symptoms suggestive of a genetic disease within 12-24 months of life
- IF POSITIVE

F

- Referral of the family to the closer specific ERN
- New sample from the newborn and parents
- DIAGNOSTIC REPORT
- DIAGNOSIS COMMUNICATION, ACCESS TO THERAPY AND FOLLOW-UP, EXPLAINATON OF CLINICAL AND REPRODUCTIVE IMPLICATIONS

↑ Sample from newborn and parents

PARENTS/PATIENT

PREGNANCY | BIRTH | NEWBORNS

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Collaboration with ERNs

Regular meetings of Screen4Care with ERNs

Consultation with ERNs for selection of ACTionable diseases

MetabERN with extensive experience on metabolic NBS

ERNs will be involved with clinical follow-up of positive cases from NBS

Inter-ERN working group on NBS?

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Thank you!

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