SCREEN 4CARE

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

ACT Panel – updates

CNA meeting

08/02/2024

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.

Introduction

Screen4Care Project

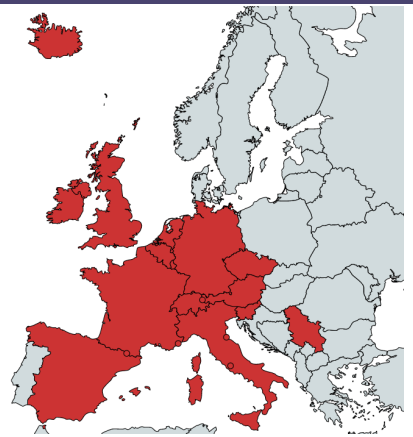
Shortening the path to rare disease diagnosis by using newborn genetic screening and digital technologies

- 5-year project funded by IMI (public private partnership)

EURORDIS' involvement in the S4C Project

- To facilitate networking through its stakeholder Newborn Screening Working Group.
- Stakeholder workshops on NBS (NBS Forum)
- Patient Advisory Board
- Rare Barometer Survey on NBS
- Focus groups
- …..

Newborn Screening Working Group



- 30+ Members
- 15 countries
- A multistakeholder working group

Position Paper available in 13 languages

Czech English German Georgian Greek Italian Macedonian Portuguese Serbian Slovenian Spanish Turkish

1. *Screening should identify opportunities to help the newborn and the family as broadly as possible. That is,* ***screening should identify actionable diseases including treatable diseases.***
   - ***Avoid the diagnostic odyssey***
   - ***Plan for the newborn's care and therapy***
   - ***Make informed decisions on future pregnancies***
   - ***Support research***

The process

Newborn Screening Working Group

Multistakeholder working group

Actionability Framing Paper

Definition of actionability

Systematic Literature Review

Opportunities, barriers and attitudes

Rare Barometer Survey Results on Newborn Screening

PLWRD and their families

NBS Forum

PAB, NBS-WG members and Screen4Care partners

Criteria for actionability & chosing conditions

RB Survey on Newborn Screening

SHAPING THE ONLINE QUESTIONNAIRE

Literature review
Identify main issues and criteria to define treatable and actionable

Expert consultations
11 experts consulted to provide inputs into priorities and

Topic Expert Committee
Contribute to clarifying topics and criteria to include in the

EURORDIS' Council of National Alliances Members
Input on topics and criteria to be included in the questionnaire

Pilot test with patients and family members
15 participants
Translations checked in 15 languages

ONLINE QUESTIONNAIRE

24 MAY ·····→ **23 JULY 2023**

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

24 languages

50 countries

1,300+ diseases represented

TARGET POPULATION
All patients living with a rare disease and their family members

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

NBS Forum

- 1.8 NBS Forum

- Lead : EURORDIS & Pfizer

- 3 online meetings
- 3 F2F meetings
- NBS Forum Agreements

Share the updates from the S4C project
The landscape of gNBS
Define the criteria on actionability

- 40 participants
- 20 NBS Forum members
- 20 Screen4Care members
- NBS Follow up

ACTion plan

1. Define 4 to 5 areas of actionability

2. Compose a ‘Screen4Care Actionability Information Package’ combining Eurordis barometer findings, task 3.1 preference study results from the systematic literature search, and NBS forum discussion outcome, including the definition of areas of actionability and possible sources of information

3.Get agreement from NBS forum and S4C task 3.2b members ()

4.Send out call for nominations to (first half of December)

- NBS forum members
- EURORDIS partners - NBS WG
- S4C members, S4C Scientific Advisory Board (SAB), S4C Ethical-Legal-Societal task force (ELST)
- ERNs

5.Combine all information and input to generate ‘ACT starting list’ (second half of December)

6.Apply disease-specific criteria on the ‘ACT starting list’ (onset, severity, knowledge, penetrance, NGS applicability) (second half of December)

7.Finalize with representative list of actionable diseases

Areas of Actionability
From the break-out groups during the NBS Forum meeting on October 9th

Groups of actionable diseases – disease characteristics

- **Availability of intervention beyond psychosocial support such as physiotherapy, symptom control (seizure control), hearing aids, prevention of complications,… with a positive impact on quality of life in general.**
- **For diseases associated with long diagnostic odyssey, often with multi-organ involvement**

Importance for reproductive choices

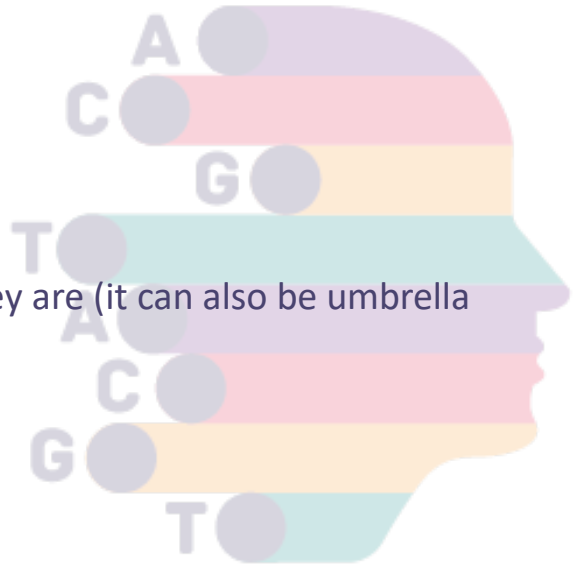
- Guided by lists of diseases screened in pre-implantation genetic testing?
- Or broader and guided by lists of diseases screened in carrier testing?

Availability of support

- Availability of Centers of expertise, ERNs, Patient organizations or communities, how resourced they are (it can also be umbrella organization)

Research and development

- Pending or active clinical development on the particular disease

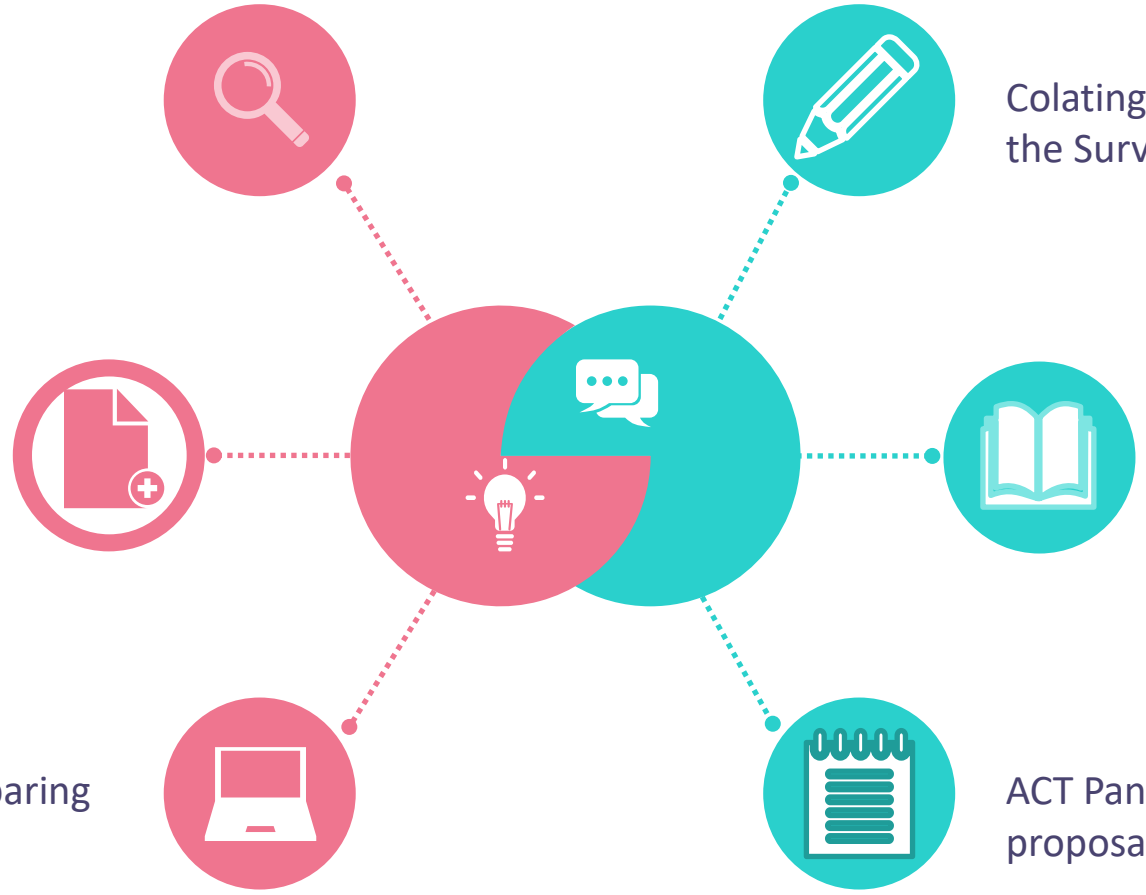


ACT Process

Follow up calls &
Refining categories

Colating information from
the Survey and SLR

Adding resources



Preparing the information
package

Action plan for preparing
the ACT Panel

ACT Panel Form for
proposals

Early results from the RB Survey on Newborn Screening

CONFIDENTIAL

ACTIONABILITY FOR NEWBORN SCREENING: PROPOSED LISTS OF CRITERIA AND DISEASES

A Rare Barometer contribution
Screen4Care - WP3.2b

November 2023

SUPPLEMENTARY MATERIAL 2

RECOMMENDED LIST OF CRITERIA FOR ACTIONABLE DISEASES

Based on the results of the Rare Barometer surveys on the opinion of PLWRD on newborn screening and on the diagnosis journey of PLWRD, it is recommended that the RDs included in the ACT-list are in priority:

- RDs with a paediatric onset, including childhood (2-10 y.o.) and adolescent (10-17 y.o.) onset.
- Severe RDs and those for which diagnostic tests have a high penetrance.
- RDs that are more prevalent in women.
- Complex RDs affecting several body parts and systems.
- RDs with outbreaks (clinical signs or symptoms that come and go).
- Metabolic, developmental, skin and neurological RDs.
- RDs for which medical and social support are available in the country of screening: centres of expertise; social, financial and psychological support.

It is also recommended that the Screen4Care NBS pilot takes into account the specificities of country differences in the opinion of PLWRD on newborn screening, and especially:

- The low acceptance of the principle of NBS from German respondents.
- The relatively high suspicion over the positive effects of NBS in France.

INDICATIVE LIST OF ACTIONABLE RARE DISEASES

METHODS AND LIMITATIONS

The list of actionable RDs presented below is indicative and non-exhaustive. It only considers RDs with at least 20 respondents either in the Rare Barometer survey on the diagnosis journey of PLWRD or in the Rare Barometer survey on the opinion of PLWRD of NBS for RDs, and should be completed based on the criteria defined in section 2, and on resources listed below.

Table 4 presents:
(1) Orphacode of the RD.
(2) Name of the RD.
(3) RDs with more than 20 respondents in the NBS survey. The colour corresponds to the prioritisation of the RD depending on: transmission type, age of onset (Orphanet), classification, point prevalence; opinion on NBS for oneself / the person they care for; opinion on NBS for actionable diseases; opinion on actionability criteria; opinion on possible consequences of NBS.
(4) RDs with more than 20 respondents in the diagnosis survey. The colour corresponds to the prioritisation of the RD depending on: point prevalence, percentage of patients living with the RD who experienced diagnostic delays (more than 1 year between first medical contact and confirmed diagnosis), age of the patient at symptom onset (declarative: mean and median).
(5) RDs that are part of the S4C TREAT-panel.
(6) Additional notes (to be completed)

Priority of RDs with regards to a list of actionable diseases is presented through the following colour code:

- in pink, priority 1 based on criteria from the NBS and diagnosis surveys;
- in green, priorities 2 and 3;
- in orange diseases that are already included in NBS programmes in Europe – they can meet criteria for the actionability list, but should not be prioritised in the Screen4Care pilot.
- in blue, RDs that do not match the criteria from the NBS survey;
- in white RDs with less than 20 respondents in the NBS survey and that do not meet the criteria of the diagnosis survey;

PROPOSED LIST OF ACTIONABLE RARE DISEASES

Table 4. Prioritisation of diseases that could be included in a list of actionable rare diseases.

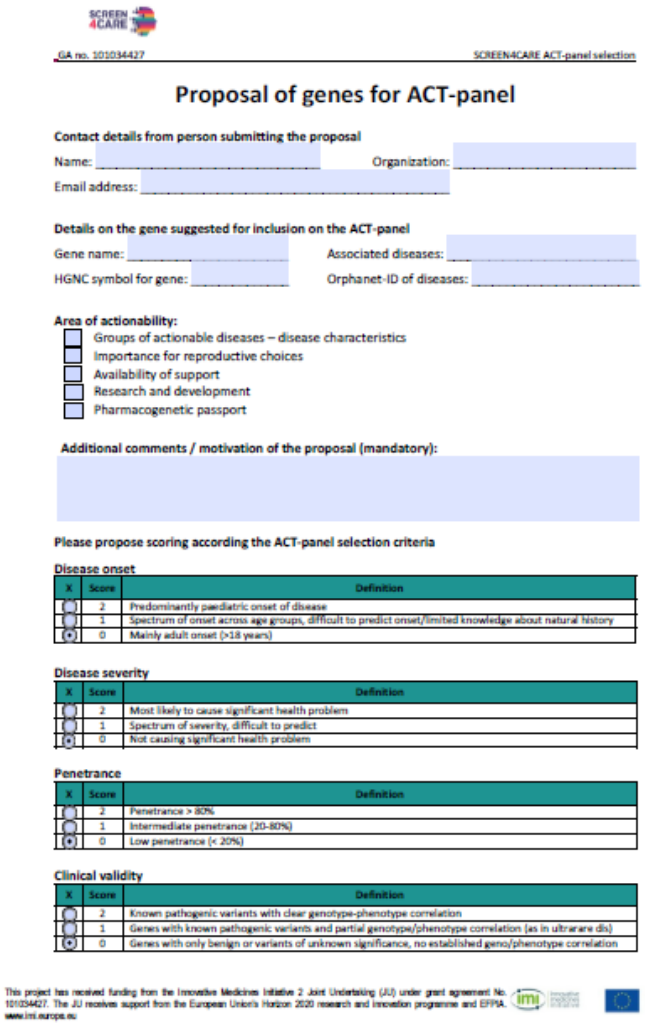
(1) orphacode	(2) Nomenclature	(3) NBS survey	(4) Diagnosis survey	(5) TREAT panel	(6) Notes
192	Coffin-Lowry syndrome	NBS			
230839	Classical-like Ehlers-Danlos syndrome type 1		Diag	TREAT	
2332	KBG syndrome		Diag		
244	Primary ciliary dyskinesia		Diag		
263	Limb-girdle muscular dystrophy		Diag		
281	Monosomy 5p		Diag		
285	Hypermobile Ehlers-Danlos syndrome	NBS	Diag	?	
286	Vascular Ehlers-Danlos syndrome		Diag	?	
287	Classical Ehlers-Danlos syndrome	NBS	Diag	TREAT	
315306	Classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency, salt wasting form	NBS			
324	Fabry disease	NBS	Diag		
33069	Dravet syndrome	NBS	Diag		
355	Gaucher disease	NBS	Diag	TREAT	
365	Glycogen storage disease due to acid maltase deficiency		Diag	?	
513	Acute lymphoblastic leukemia		Diag		
558	Marfan syndrome	NBS	Diag		
567	22q11.2 deletion syndrome	NBS	Diag		
636	Neurofibromatosis type 1	NBS	Diag		
637	Neurofibromatosis type 2		Diag		
646	Niemann-Pick disease type C		Diag	TREAT	
648	Noonan syndrome	NBS	Diag		
666	Osteogenesis imperfecta	NBS	Diag	TREAT	
71277	Classic glucose transporter type 1 deficiency syndrome	NBS	Diag		
72	Angelman syndrome	NBS	Diag		
739	Prader-Willi syndrome	NBS	Diag		
774	Hereditary hemorrhagic telangiectasia	NBS	Diag		
778	Rett syndrome	NBS	Diag		
791	Retinitis pigmentosa		Diag		
79276	Acute intermittent porphyria		Diag		
805	Tuberous sclerosis complex	NBS	Diag		
819	Smith-Magenis syndrome		Diag		
89936	X-linked hypophosphatemia		Diag		
90695	Non-acquired panhypopituitarism		Diag		
908	Fragile X syndrome	NBS	Diag		
95	Friedreich ataxia	NBS	Diag		
98249	Ehlers-Danlos syndrome		Diag	TREAT	
98896	Duchenne muscular dystrophy	NBS	Diag	TREAT	

S4C ACT INFORMATION PACKAGE

- Screen4Care background
- Input from the systematic literature review
- Five areas of Screen4Care actionability and resources
- Executive summary of the NBS Forum meeting in Barcelona, Oct. 9th
- Early results from the Rare Barometer survey on NBS including a proposed list of actionable rare diseases according to the results of the EURORDIS Rare Barometer survey on Newborn Screening

Distribution list:

- Screen4Care NBS Forum members
- Screen4Care members
- ERN coordination teams
- EURORDIS partners (including EURORDIS NBS-WG)
- Screen4Care Scientific Advisory Board (SAB) and Ethical-Legal- Societal impact (ELSI) members



GA no. 101034427 SCREEN4CARE ACT-panel selection

Proposal of genes for ACT-panel

Contact details from person submitting the proposal

Name: Organization:

Email address:

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

Gene name: Associated diseases:

HGNC symbol for gene: Orphanet-ID of diseases:

Area of actionability:

- ☐ Groups of actionable diseases – disease characteristics
- ☐ Importance for reproductive choices
- ☐ Availability of support
- ☐ Research and development
- ☐ Pharmacogenetic passport

Additional comments / motivation of the proposal (mandatory):

Please propose scoring according the ACT-panel selection criteria

Disease onset

X	Score	Definition
☐	2	Predominantly paediatric onset of disease
☐	1	Spectrum of onset across age groups, difficult to predict onset/limited knowledge about natural history
☐	0	Mainly adult onset (>18 years)

Disease severity

X	Score	Definition
☐	2	Most likely to cause significant health problem
☐	1	Spectrum of severity, difficult to predict
☐	0	Not causing significant health problem

Penetrance

X	Score	Definition
☐	2	Penetrance > 80%
☐	1	Intermediate penetrance (20-80%)
☐	0	Low penetrance (< 20%)

Clinical validity

X	Score	Definition
☐	2	Known pathogenic variants with clear genotype-phenotype correlation
☐	1	Genes with known pathogenic variants and partial genotype/phenotype correlation (as in ultrarare dis)
☐	0	Genes with only benign or variants of unknown significance, no established geno/phenotype correlation

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TIMELINE

30 November-6 December

Collect feedback from NBS Forum members

Collect nominations from the contacts on the distribution list.

6 - 20 December

20 - 31 December

Apply disease-specific criteria

The list of actionable diseases to be finalized

31 December

January February 2024

Final consultation with all Screen4Care clinicians for final deliberation and validation of the ACT Panel.

ACT-Panel Update

NEXT STEPS

- New deadline: 31 March 2024
- Finalizing the deliverable report
- Review by WP3 leaders
- Review by 3.2b task partners
- Submission of the ACT-panel