European Reference Network
for rare or low prevalence complex diseases
Network Hereditary Metabolic Disorders (MetabERN)

IMPORTANCE OF NEONATAL SCREENING FOR THE EARLY DIAGNOSIS OF RARE DISEASES

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in collaboration with the International Society for Newborn Screening
And Screen4Rare

EU2022.CZ
Czech Presidency of the Council of the European Union

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ISNS
International Society for Neonatal Screening

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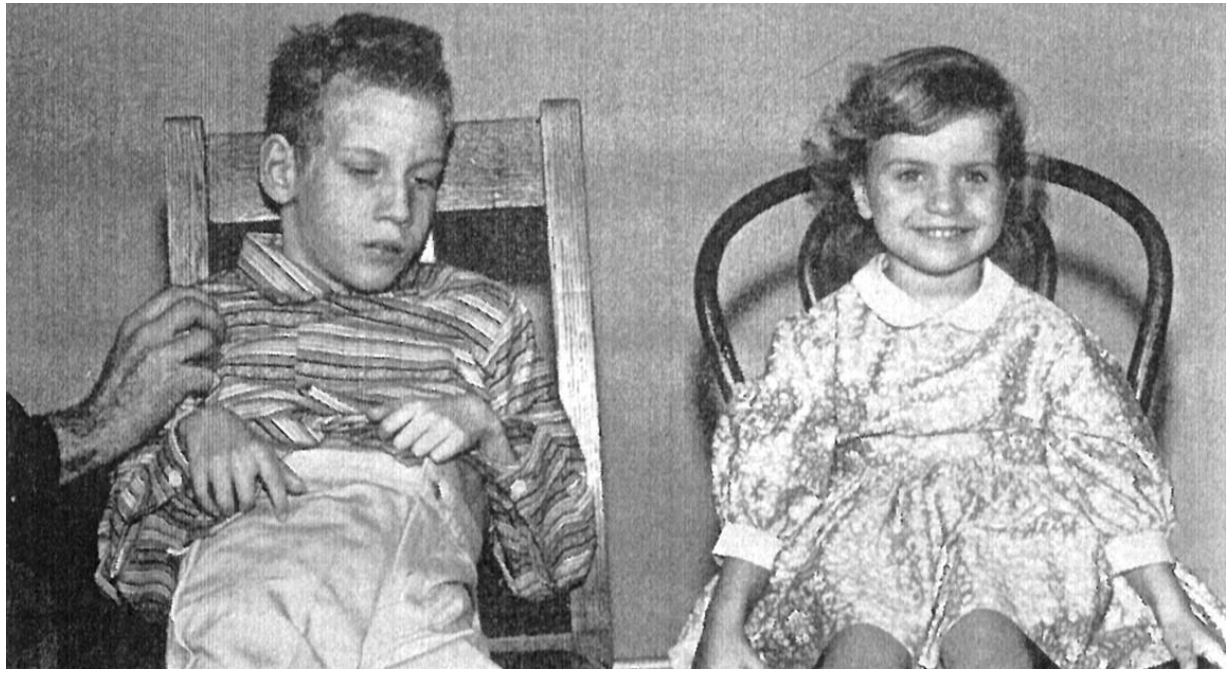
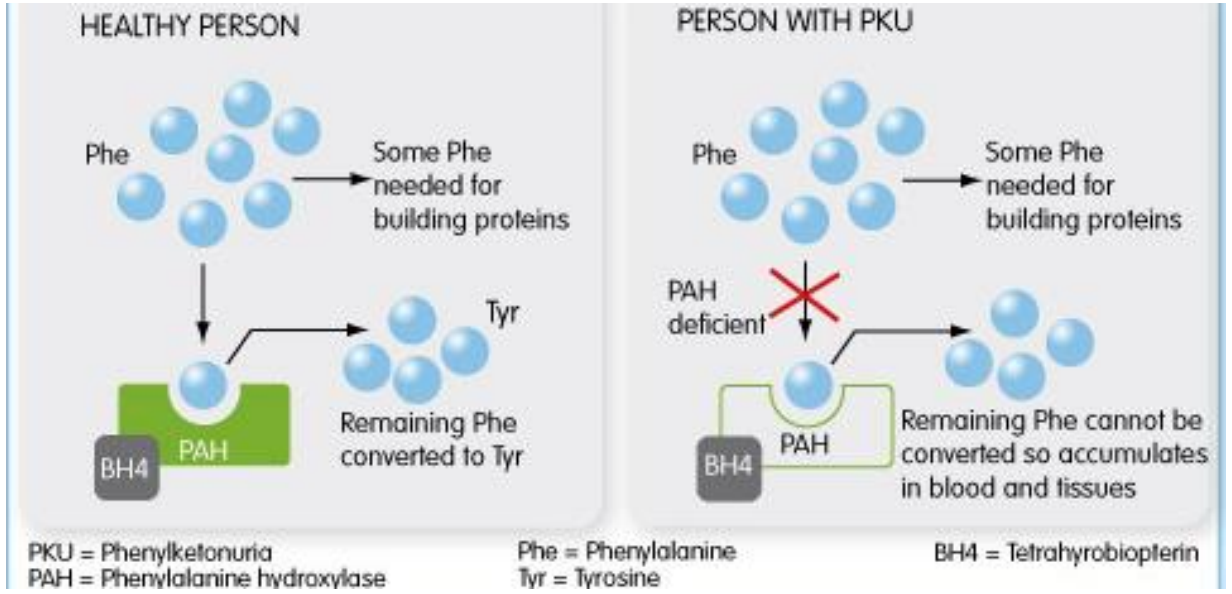
Disclosures

- I have received unrestricted grants and travel honoraria from Actelion, Alexion, Azafaros, BioMarin, Chiesi, DENALI, Sanofi Genzyme, Takeda, Ultragenyx, Paradigm, Orchard, PTC Therapeutics, .
- I have no economic or stock market interest in any Rare Disease product.
- This presentation reflects the clinical experiences and opinions of the speaker.

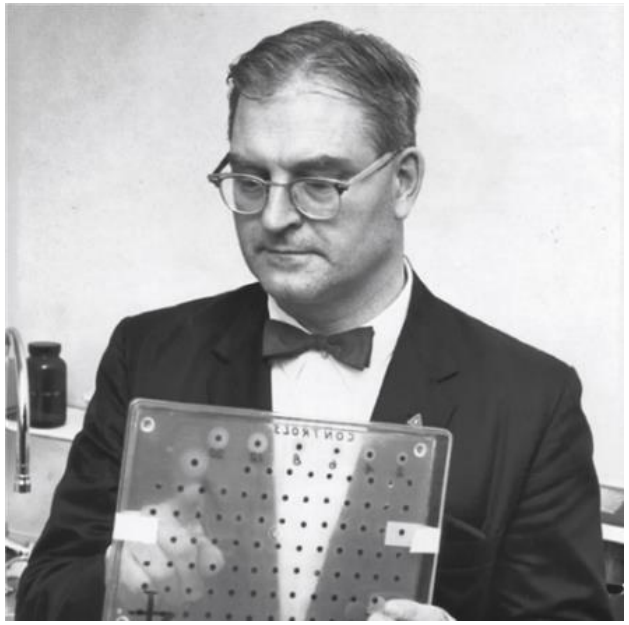



Vegetables
Beans
Corn
Pork Chops
BEST
PHENYL-FREE
FOODS
Juices
Fruits
Chicken
Peas
Bread
Eggs
Nuts
Low Protein Breads and Pastas
Potatoes
French Fries
Cheese
They are BEST for YO


HEALTHY PERSON
Phe
Some Phe needed for building proteins
Tyr
BH4
PAH
Remaining Phe converted to Tyr
PERSON WITH PKU
Phe
Some Phe needed for building proteins
PAH deficient
BH4
PAH
Remaining Phe cannot be converted so accumulates in blood and tissues
PKU = Phenylketonuria
PAH = Phenylalanine hydroxylase
Phe = Phenylalanine
Tyr = Tyrosine
BH4 = Tetrahyrobiopterin

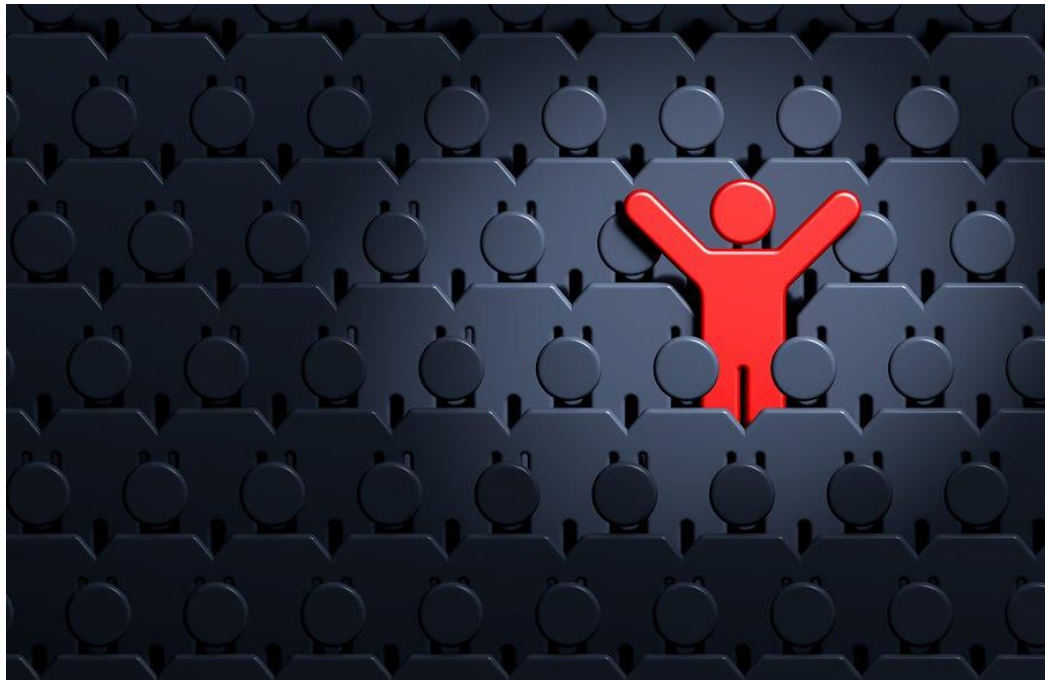
We have much to celebrate!

- It is now more than 50 years since Dr Robert Guthrie described a test to detect phenylketonuria (PKU) shortly after birth
- Perhaps even more importantly he also described a simple and effective means of blood collection using a ‘dried blood spot card’ to allow this to be carried easily to a testing laboratory
- Since then it is estimated that worldwide approximately 750 million babies have been screened we have detected more than 60,000 children with PKU who have benefited from this life changing intervention
- Of course this did not stop there, and in the intervening years disorders were added progressively to the growing list of conditions that could be detected by newborn screening. Starting with congenital hypothyroidism (CHT) but progressing to other disorders where this would significantly benefit the child.
- This led many around the world to describe newborn screening as: **‘One of the major Public Health Advances of the 20th Century’**



Despite this success we need to be careful

- The patients/families believe themselves to be well and this gives us a particular burden of responsibility
- "All screening programmes do harm; some do good as well, and, of these, some do more good than harm…." *Gray, BMJ (2008) 336:480*
- More screening does not mean better screening
- Screening which is well designed properly organised and delivered as a carefully monitored programme linked to structured treatment where outcomes are assessed is most effective



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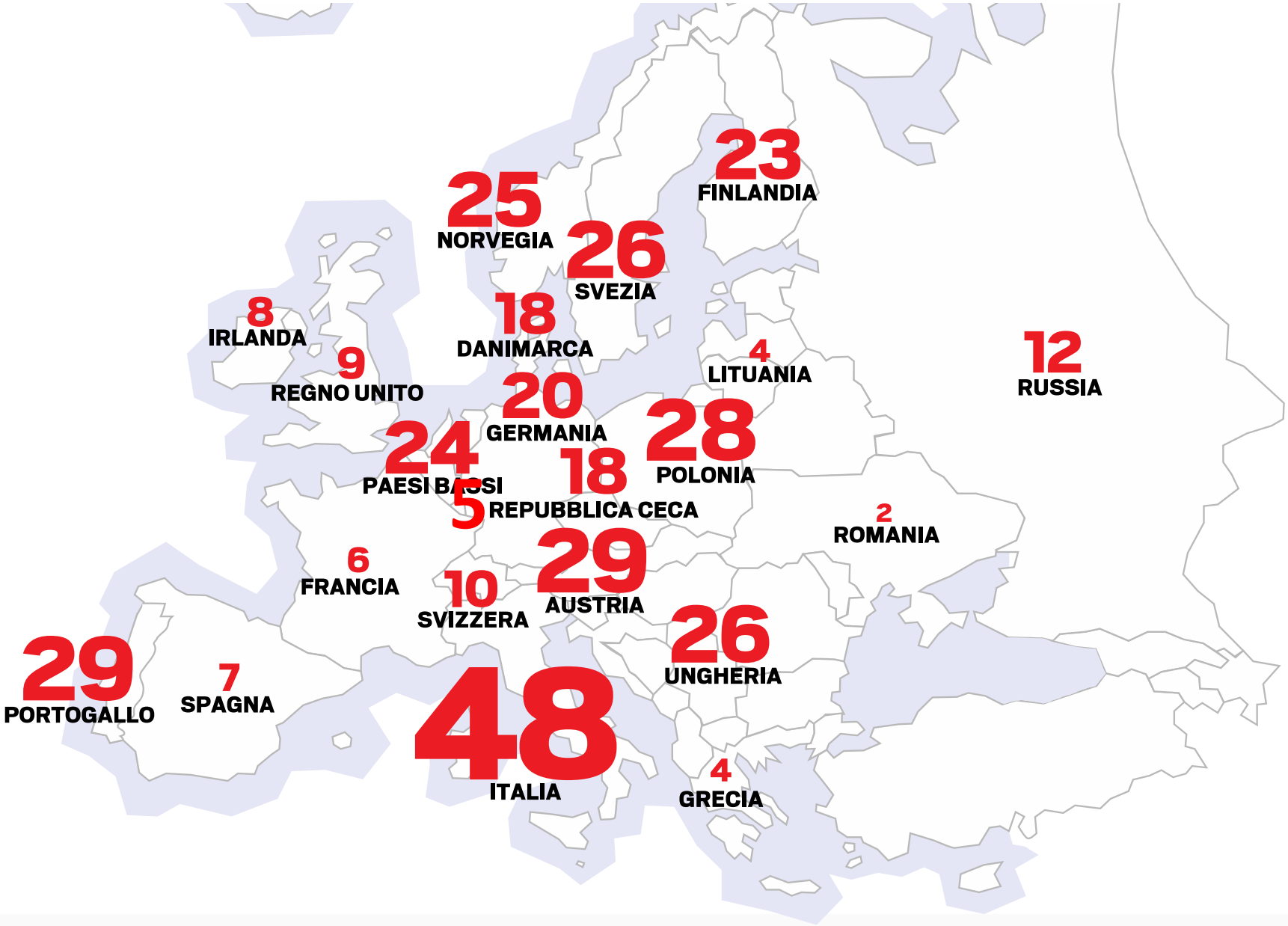

The NBS of IMDs in Europe

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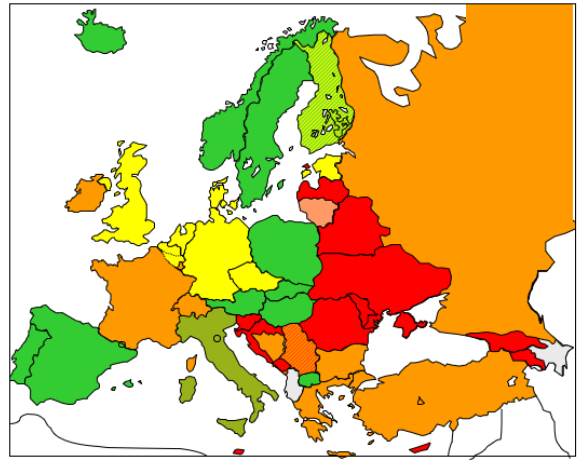
ISNS International Society for Neonatal Screening

Where are we in Europe?

- The conditions that we have chosen to screen
  - *Neonatal Screening in Europe Revisited: An ISNS Perspective on the Current State and Developments Since 2010 J. Gerard Loeber et al (*Int. J. Neonatal Screen. 2021, 7, 15. https://doi.org/10.3390/ijns7010015
  - Still shows considerable variation in practice both in the way that newborn screening is conducted and the number of conditions screened.
  - *Number of conditions* 0 - 48 conditions screened in different countries in Europe

Number of conditions per country (2018)



- The way in which we conduct screening

Day of sampling	24h – 120h
Sampling to analysis	1-2d, to 30d
Screening is optional or compulsory	30 optional, 17 compulsory
Informed of the outcome of screening	30 No, 10 Yes
Consent to storage	34 – No, 10 - Yes

Difference
Difference
Difference

The causes of variation and why the hesitancy?

- The early detection offered by screening can be life saving (MSUD, MCADD etc) or changing (PKU, HCU etc) and in some cases can be curative eg SCID
- We can also cause severe and lasting stress to families (false positive results) and medicalise asymptomatic children without a clear role for treatment (CFSPID)
- So how do we choose?
- While all countries recognise Wilson & Jungner criteria in some form, we see differences in policy, largely because they are applied very differently in relation to:
  - The level of evidence required
  - The role of cost effectiveness studies and the acceptable cost/qualy or similar
  - The make-up of the decision making bodies – whether they are drawn from a public health background or a specialist medical background and the level of input from patient groups

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Why is this important now?

- Genomics is rapidly providing new opportunities to detect and treat rare disorders and more than 80% of rare disorders are genetic in origin
- Nevertheless, this takes us even further away from the clinical phenotype and there are serious ethical and practical issues to consider when thinking of this as a first line test, particularly if whole genome sequencing (WGS) in newborns is being considered
- It offers the potential to detect >500 treatable disorders at birth and we do not want the variation in the conditions screened in Europe as an example to move from the current 0 – 48 to 0 - >500. To achieve this we a firm basis to select conditions to include based on a proper understanding of the outcome from treatment.
- There are two studies planned in Europe:
  - The Innovative Medicines Initiative – Screen4Care aiming to include children in Italy, Germany and the Czech Republic – 18,000 births
  - The Genomics England study – aiming to include 100,000 children in the first instance
  - Similar studies are planned or underway in the US, Australia and China

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How can we ensure that progress is soundly based?

- Recognise that screening can bring life changing benefits but can also cause harm if badly organised or inappropriate
- Be clear about the definitions of the disease(s) that we wish to screen
- Look carefully at long term outcomes to assess impact
- Assess the 'process' of screening so that we can learn from one another and determine the best way to do this well
- Respect national autonomy and work with health policy makers to provide 'evidence based' and unbiased information free from commercial influence
- Involve key stakeholders: the public, patients, physicians, scientists, health economists and ethicists
- Foster discussion and develop trusted sources of advice such as a recognised 'expert group' that will support rather than dictate policy development
- Ensure that we put the public and those families who are touched by rare disease at the centre of our thinking

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SSIEM ANNUAL SYMPOSIUM 2019
3-6 SEPTEMBER | ROTTERDAM, THE NETHERLANDS

ISNS International Society for Neonatal Screening

NBS collaborative meeting MetabERN & ISNS

Agenda:

11-12: Introduction

11:00-11.10: Maurizio Scarpa/Trine Tangeraas MetabERN:
Welcome and introduction (& points of discussion)

11.15-11.30: Gerard Loeber ISNS:

Screening practices in Europe 2018 –what has changed since 2009 and the 2010-2011 EHAC project

11.30-11.40: Jim Bonham ISNS

The points of agreement and potential barriers to achieving a European Screening Panel

11.45-12.00: Stefan Koelker MetabERN

U-IMD and its future role in NBS outcome studies

12:00-13:00: Discussion

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What have we achieved so far?

- Brought this together with the formation of Screen4Rare (comprising ESID, IPOPI, ISNS and the European Reference Networks) in 2020 with a dedicated website
- The formation of an EU Health Policy Platform
- The formation of an MEP Alliance including Roberta Metsola – the new President of the European Parliament – January 2022
- A series of high level meetings
  - The ERN Screening Group – 14th September 2021
  - This accompanying event of the Slovenian Presidency – 11th October 2021
  - 'Moving toward NBS as a System' – A special event at the ISNS European Symposium – 11th November 2021
  - Meetings in London, Turku and at the EU Parliament to celebrate 'International Neonatal Screening Day' – 28th June 2022
  - Appropriately as we consider Mendel's legacy, this event important supported by the Czech Presidency
- An impressive series of publications – such as the recent paper: Newborn Screening by Genomic sequencing: Opportunities and Challenges, Bick et al, Int J Neonatal Screen, 8, 40 part of a Special Issue in IJNS focusing on Newborn Screening in Europe.
- The aim is to form an Expert Screening Group in the EU with EC support

NOVEMBER 28-29 2022
MetabENR NBS MEETING
FRANKFURT

MetabERN: Hereditary Metabolic Diseases

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PROGRAMME JULY 23, 2022

Time	Programme	Speaker
13:15 – 13:30	WELCOME	
	Prof. Vlastimil Válek, MD, PhD., MBA, EBIR (TBC) Minister of Health of the Czech Republic **Jakub Dvořáček MSc., LLM** Deputy Minister of Health of the Czech Republic **Lumír Kantor, M.D** (video presentation) Senate of the Parliament of the Czech Republic **Prof. Milan Macek Jr., MD., DSc.** National Coordination Center for Rare Disease **Prof. Viktor Kožich, M.D, CSc.** Coordination Center for Neonatal Screening **Ondřej Májek, RNDr. PhD** National Screening Centre, Institute of Health Information and Statistics of the Czech Republic	
13:30 – 15:30	**SESSION I. – NEWBORN SCREENING (NBS): A GATEWAY TO EARLY DIAGNOSIS** (CHAIRS: Dr. Gulcin Gulmus and Prof. Viktor Kožich)	
13:30-13:50	Overview of European NBS activities-synergies and overlaps	**Prof. Jim Bonham,** United Kingdom
13:50-14:05	Role of European Reference Networks for rare diseases in NBS	**Prof. Maurizio Scarpa,** Italy
14:05-14:20	Developing a blueprint of NBS in Europe: overview of workstreams	**Dr. Peter Schiele** The Netherlands
14:20-14:35	Key indicators for planning, monitoring and evaluation of newborn screening: international context and future perspectives for cooperation	**Dr. Ondřej Májek** Czech Republic
14:35-14:50	The tower of Babel: why do we need case definitions?	**Dr. Rolf Zetterstroem,** Sweden
14:50-15:05	The key role of registries in assessing clinical outcome	**Prof. Stefan Koelker,** Germany
15:05-15:20	Experience with expanding NBS in Czechia	**Ms. Anna Arellanesová,** Czech Association for Rare Diseases, Czech Republic
15:20 – 15:45	**Coffee break**	
15:45 – 16:30	**SESSION II. – CURRENT EXPERIENCE AND FUTURE DEVELOPMENTS IN NBS** (CHAIRS: Ms. Anna Arellanesová and Prof. Maurizio Scarpa)	
15:45-16:05	Newborn screening: the perspective of people with RD and future potential	**Dr. Antoni Montserrat,** EURORDIS
16:05-16:20	The use of a patient management system to improve long-term outcome	**Dr. Rolf Zetterstroem,** Sweden
16:20-16:35	Screen4care EU IMI project	**Prof. Alessandra Ferlini,** Italy
16:35-17:10	Panel discussion (CHAIRS: Dr. Antoni Montserrat and Dr. Peter Schielen)	
	Ms. Martine Pergent IPOPI President/Screen4rare, France **Mr. Stelios Kympouropoulos** MEP (TBC) **Dr. Jose Valverde** European Commission, DG SANTE Unit B3 (TBC)	

Technical meeting under the auspices of the Presidency of the Czech Republic in the Council of the EU. Brno, Czech Republic July 23, 2022

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International Journal of *Neonatal Screening*

MDPI

Review

Towards Achieving Equity and Innovation in Newborn Screening across Europe

Jaka Sikonja [1,2,†], Urh Groselj [1,2,*,†], Maurizio Scarpa [3], Giancarlo la Marca [4,5], David Cheillan [6], Stefan Kölker [7], Rolf H. Zetterström [8,9], Viktor Kožich [10,11], Yann Le Cam [12], Gulcin Gumus [12], Valentina Bottarelli [12], Mirjam van der Burg [13], Eugenie Dekkers [14], Tadej Battelino [1,2], Johan Prevot [15], Peter C. J. I. Schielen [16] and James R. Bonham [16,17,*]

Comment

The Lancet Regional Health - Europe 2022;13:

Newborn screening as a fully integrated system to stimulate equity in neonatal screening in Europe

Maurizio Scarpa,[a,] James R. Bonham,[b] Carlo Dionisi-Vici,[c] Johan Prevot,[d] Martine Pergent,[d] Isabelle Meyts,[e] Nizar Mahlaoui,[f] and Peter C.J.I. Schielen[g]*

1. Selection of (new) conditions in NBS panels should be based on published criteria, the proce- dures should be standardised, open to public scrutiny and the result of deliberations should be published.
2. Information (preferably communicated during pregnancy) describing the diseases to be tested and the implications of a positive result should be available to parents to permit an informed choice concerning participation.
3. Clear case definitions of the screened disorders should be determined when screening is being planned.
4. Screening should be undertaken in laboratories whose accreditation demonstrates compliance with international standards for laboratory perfor- mance (e.g., ISO15189).
5. Laboratories and programmes should be able to produce data on key performance indicators relat- ing to the entire NBS process, including blood sampling, transport conditions, blood spot quality, time to generate a laboratory result and refer screen positive cases.
6. Information should be available to parents at the time of clinical referral, the first contact should be with an experienced physician able to offer support, and, when appropriate, genetic counselling should be provided.
7. Confirmatory testing should be established and consistently applied with a short and defined turn- around time to allay parental anxiety and stress.
8. Plans to assess long term outcome data should be in place and reported.
9. Screen negative results should be reported to all parents and form part of the child health record.
10. Policies to store and access residual blood-spot samples should be defined and practice monitored. NBS programs should be coordinated, and perfor- mance managed on a national basis to encourage continuous improvement.

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Moving towards NBS as a system: the next steps

MONITORING, EVALUATION UPDATING OF NBS SYSTEM

- Defining guidelines & framework for the monitoring, evaluation and updating the NBS system
- observatory of new treatments and drugs that require NBS to ensure real access to newly authorized treatments/drugs

SETTING UP NBS EXPERT ADVISORY COMMITTEE (NBS-EAC)

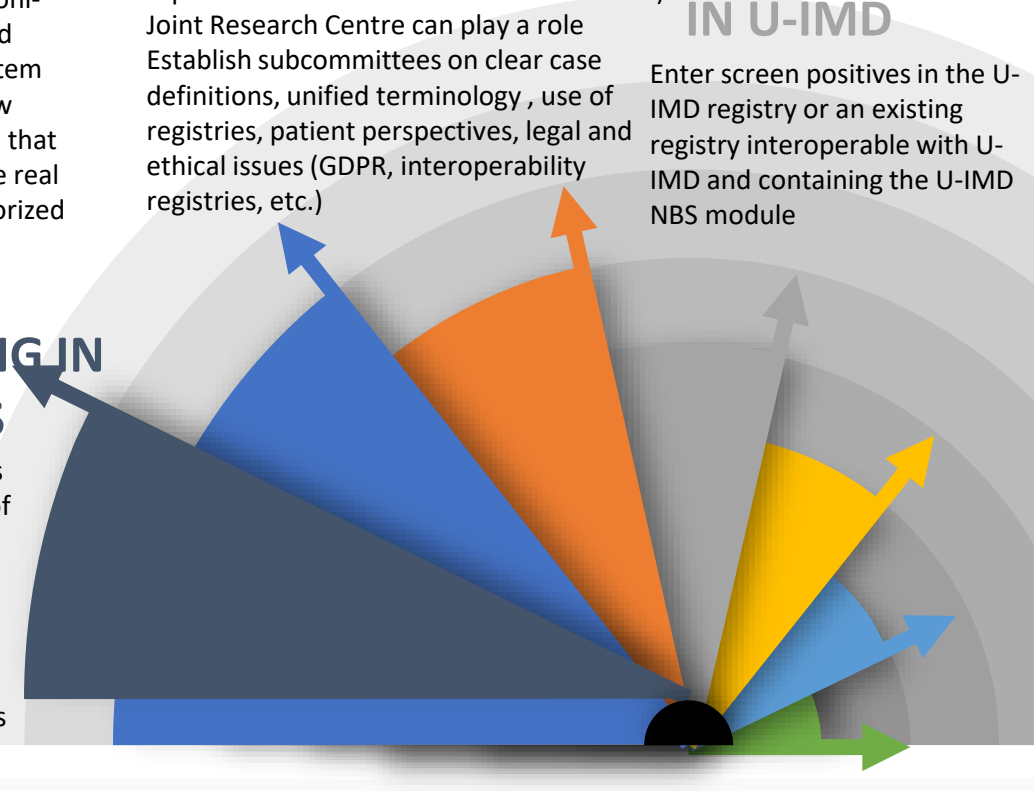
Decide on participants (policymakers, representatives of national health institute) Joint Research Centre can play a role
Establish subcommittees on clear case definitions, unified terminology , use of registries, patient perspectives, legal and ethical issues (GDPR, interoperability registries, etc.)

DEVELOPING A NBS MODULE IN U-IMD

Enter screen positives in the U-IMD registry or an existing registry interoperable with U-IMD and containing the U-IMD NBS module

DEFINING CLEAR CASE DEFINITIONS & UNIFIED TERMINOLOGY

- Develop a European model for confirmatory testing
- Encourage editors to scrutinize terminology in publications is one option.
- Accreditation of NBS labs through ISNS (all labs reporting the same data)
- Identifying relevant HPO terms and choose from predefined list of the clinical presentations for follow-up and case definition.



PUBLISHING IN JOURNALS

- Publish the results of the outcomes of the projects in medical journals
- Creating unified terminology by approaching journals about this topic

INVOLVING PATIENT ORGANIZATION AND NATIONAL POLICY MAKERS

Mapping of and involving policymakers on the right level (national/federal, regional, medical associations) and their main barriers/questions on NBS

CREATING AN INVENTORY OF GOOD PRACTICE

- Sharing of best practices in repository Screen4Rare
- Using existing models as examples of good practice for MS to learn from
- Confirmatory testing

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Conclusions

- Newborn Screening is one of the major achievement in the history of medicine and public health.
- The diagnosis of a rare disease in an asymptomatic child allows the choice of the best care and therapies, possibly able to drastically and/or positively modify the natural history of the disease.
- Newborn screening, however, is not a only a diagnsotic test, it must be considered a health integrated system involving a multidisciplinary team of professional to inform properly the family during pregnancy and fully assist the family in the case of a positive birth.
- The availabilty of newborn screening is an indicator of equity and equality among countries.
- The possibility of screening a disease at the newborn age is a trigger factor for the development of therapies.
- Newborn screening is often thought as a public COST, however, it represents and public INVESTEMENT economically rewarding in terms of health cost savings.
- Our Consortium (ERNs, ISNS and Screen4Rare) is willing to support Member States in the choice of expanding Newborn Screening by providing expert technical and scientific evidencies and advices.