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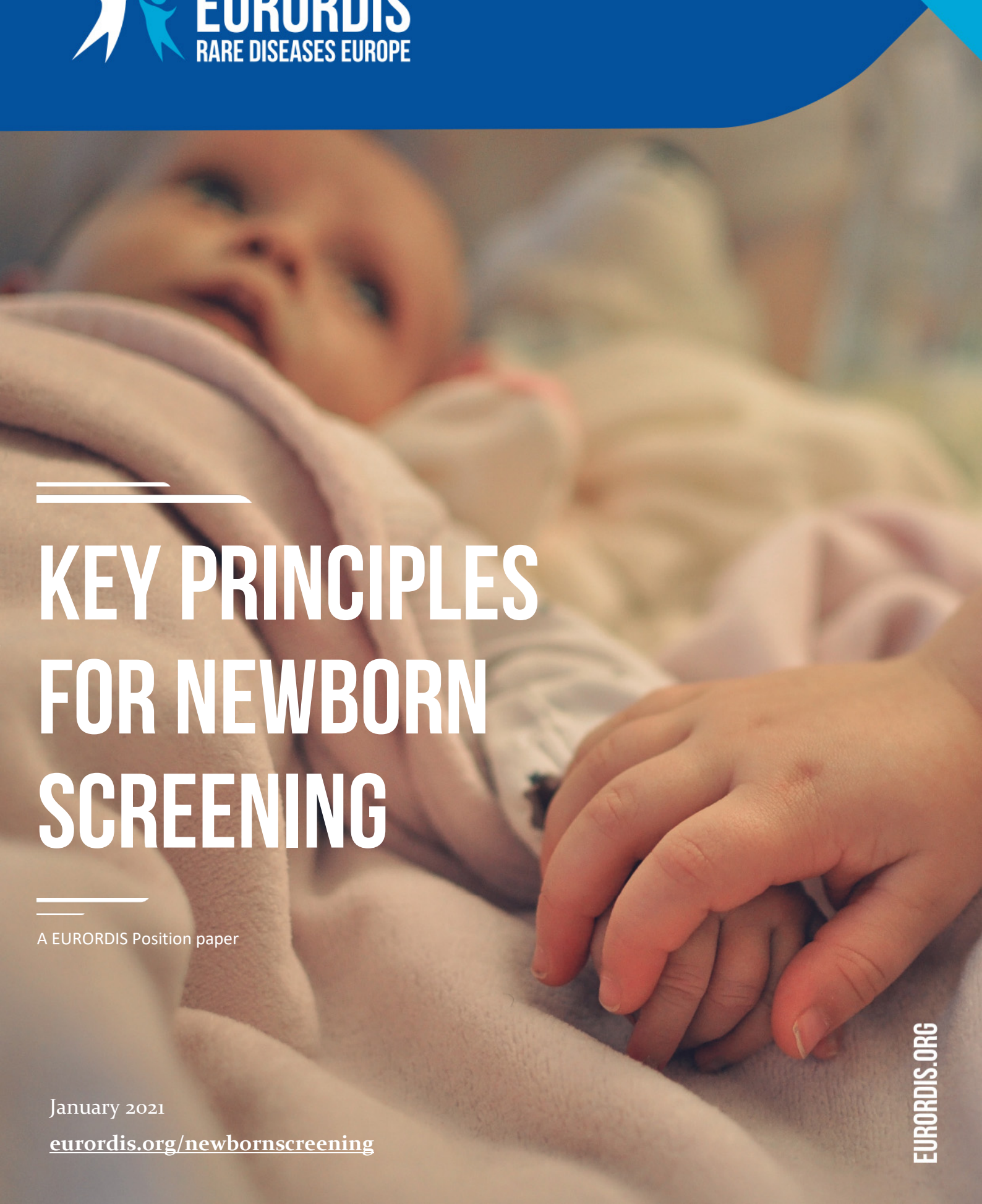

KEY PRINCIPLES FOR NEWBORN SCREENING

A EURORDIS Position paper

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KEY PRINCIPLES FOR NEWBORN SCREENING

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9. European-wide standards addressing the timing, sample collection methods, follow-up, and information shared with parents are needed to guarantee uniformity and quality throughout the process.

10. Blood spot samples should be stored in national biobanks for research purposes while ensuring appropriate safeguards for data protection and data access are in place.

11. ERN affiliated centres should be integrated in the care pathways of the different Healthcare systems and should be considered as preferential partners in providing recommendations on NBS policies.

1 INTRODUCTION

The right of the child to the enjoyment of the highest attainable standard of health is enshrined into the human rights framework that is established and recognised at global level. In the Universal Declaration of Human Rights, the United Nations has proclaimed that "childhood is entitled to special care and assistance". Notably the UN Convention on the Rights of the Child recognises that "every child has the inherent right to life" (Art. 6) and states "shall strive to ensure that no child is deprived of his or her right of access to such health care services" and they "pursue full implementation of this right … to diminish infant and child mortality; …to develop preventive health care" (Art. 24)[1].

In its recently published Standards for Improving the Quality of Care for Small and Sick Newborns in Health Facilities[2], the World Health Organisation recalled the need for newborns' rights to be respected, protected and fulfilled without discrimination, with preservation of dignity at all times and in all settings during care, transport and follow-up.

The Special Rapporteur on the Right to Health (OHCHR), Dainius Puras, recalled that each child has the right to life and survival, to be protected from early childhood adversities and that children with rare diseases should not be discriminated, as they too have the right to quality treatment, care and support (Dainius Puras (2017) The Right to Health and Rare Diseases)[3]

[1] https://www.ohchr.org/en/professionalinterest/pages/crc.aspx
[2] World Health Organization. Standards for Improving the Quality of Care for Small and Sick Newborns in Health Facilities. 2 September 2020 https://www.who.int/publications/i/item/9789240010765
[3] http://download2.eurordis.org.s3.amazonaws.com/rdi/2.Puras%20Presentation-%20Rare%20diseases.pptx

It is estimated that 72% of rare diseases are of genetic origin and almost 70% of rare diseases have an exclusively pediatric onset (up to 88% can have a pediatric onset, with 18% having a variable onset including infancy-childhood)[4] . For many rare diseases which can be chronic and progressive, signs may be observed at birth or in early childhood. Screening newborns for certain disorders can make a real contribution to improve the quality of life of children. Traditional Newborn Screening (NBS) programmes in public health settings aim to identify newborns with treatable conditions where early identification helps to avoid irreversible health damage. Screening enables disease prevention through the diagnosis of severe and rare disorders as early as possible so that they can be appropriately treated, better managed and even cured. It also provides opportunities for patients and families to plan their future.

There is marked variation in how NBS is conducted within and between countries and in the coverage of NBS programmes. Moreover, there is striking variation in the consequences of a positive screen across Europe, including divergent approaches to health care and social, economic, and psychological support to families.

EU action in the field of public health needs to respect the subsidiarity principle, competencies and responsibilities of the Member States for the organisation and delivery of health services and medical care, including NBS. The Council of the EU and the former Committee of Experts on rare diseases recommended coordinated action at the EU level while preserving national competences[5].

Despite this recommendation, the EURORDIS Newborn Screening Working Group (see below) recognises that no collaborative action has been pursued at the EU level since. Nowadays, the advancement of screening techniques and the increased possibility to reach out to a much broader infant population imposes to review the status quo. At present, significant discrepancies exist among NBS policies and programmes across the EU countries, with a remarkable impact on newborns' access to early prevention and opportunities of improving the quality of their lives.

Accordingly, EURORDIS set up the Newborn Screening Working Group to define 11 key principles **which can be adopted at the national level in order to frame policy discussions and developments of NBS screening programmes.** This document describes the principles scoped by the Working Group, further developed following consultations with different groups of stakeholders[6] and provides the position of the consulted rare disease patients on NBS programmes.

[4] Nguengang Wakap S, Lambert DM, Olry A, Rodwell C, Gueydan C, Lanneau V, Murphy D, Le Cam Y, Rath A. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. Eur J Hum Genet 28, 165–173 (2020) doi:10.1038/s41431-019-0508-0

[5] The Council Recommendation of 8 June 2009 on an action in the field of rare diseases, recommends that the Member States "Gather national expertise on rare diseases and support the pooling of that expertise with European counterparts in order to support: the development of European guidelines on diagnostic tests or population screening, while respecting national decisions and competences". Moreover, the EU Committee of Experts on Rare Diseases identified areas where collaboration between MS would have an added value and respect the principle of subsidiarity (Newborn Screening in Europe: Opinion of the EUCERD on Potential Areas of European Collaboration, July 2013).

[6] Several rounds of consultation have been carried out between June 2020 and December 2020 including Council of National Alliances, Council of European Federations, EURORDIS Roundtable of Companies Workshop participants and EURORDIS members. As well as consultation by voting on the principles and the call to action, the participants have been invited to provide written and verbal feedback and the document has been edited accordingly after each consultation, considering the input and views provided by the stakeholders.

The EURORDIS Newborn Screening Working Group believes that it is high time to thoroughly reconsider Wilson and Jungner criteria, come up with harmonised criteria that work in the context of NBS and can be uniformly applied because they have been designed for that purpose.

The principles are accompanied by a Call to Action in support of a wide uptake of the key principles and of the policies developments that are necessary both at the EU and Member States levels to ensure that all newborns across the EU benefit from NBS programmes where possible, thus addressing the vast inequalities existing across Europe.

2 CALL FOR ACTION

The positive impact of NBS and its significant contribution to disease prevention, treatment and care, require that all newborns across the EU benefit from it where possible and that current vast inequalities existing in Europe are addressed. NBS programmes vary significantly across EU Member States and the lack of a common approach contributes to important disparities across countries and diseases.

In line with the EU commitment to achieve Universal Health Coverage in its territory by 2030 and with the UN Political Declaration on UHC adopted in September 2019, the EURORDIS WG on NBS calls for adequate NBS policies to be put in place and for consistent approaches to NBS across geographical Europe as a way to ensure the enforcement of human rights, attain the highest standard of health for newborns born with a rare disease and ensure a positive impact on the lives of newborns.

Therefore, EURORDIS with the WG on NBS, its Council of National Alliances, its Council of European Federations and all its members call for:

1) the creation of a **EU-level expert working group** composed of Member States representatives, relevant experts and stakeholders to enact EU-level collaboration in areas where it would have an added value, while respecting the principle of subsidiarity e.g.:
   - exchanging knowledge and best practices on NBS for rare diseases;
   - horizon scanning for new therapies in development which will enable timely decision making and designing of appropriate pilot studies
   - gathering evidence and natural history data on efficacy from pilot studies or field trials in view of including specific diseases in NBS programmes;
   - entrusting assessment of new proposals for NBS, when new technologies allow for such a consideration, to EU level HTA joint assessment;
   - identifying and agreeing upon criteria and mechanisms for expanding disease panels;
   - defining guidelines on for example education and training of professionals, on communication with families and citizens at large, etc. and
   - other areas for collaboration as already identified in the 2013 Opinion of the EU Committee of Experts on Rare Diseases[2].

   The WG will explore the possibility of entrusting the Joint Research Centre of the European Commission or other EU level bodies or agencies (incl. the ECDC, European Centre for Disease Prevention and Control) with the coordination and the hosting of the committee.

2) Moreover, we call upon relevant EU bodies and Institutions and EU Member States to promote the uptake of the Key Principles enclosed to this Call to Action and in particular:

   - the **Steering Group on Health Promotion and Prevention (SGPP),** as the main committee advising the European Commission on activities in the field of health promotion, prevention and management of non-communicable diseases, to initiate a best practice collaboration with a few Member States willing to pilot NBS programmes using these principles, in view of scaling them up to other Member States. As a result, the SGPP may recommend EU Member States to consider these principles as support for the development and implementation of their NBS programme;
   - the **European Commission,** in light of the recommendations of the SGPP, to support this effort by means of endorsing the Key Principles as best practice supported by extended evidence, and recommending their uptake at the national and European level;
   - **Member States' governments** to consider the uptake of these Principles for the development and implementation of their NBS programmes and policies at the national/regional levels;

3) The WG also calls on the **European Parliament** to:

endorse initiatives aimed at designing harmonious NBS programmes across Europe and filling the existing gaps in NBS practice in Europe; and, to this aim, to continue to put pressure on other EU

Institutions by means, for example, of Parliamentary questions, in line with the call for action promoted by Screen4Rare[7].

PRINCIPLES

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.

Traditional NBS programmes in public health settings aim to identify infants with treatable conditions where early identification helps to avoid irreversible health damage. This focus on benefit to the individual identified creates a narrow scope for accessing the benefits of NBS. A wider set of benefits should be accessible that include patients and parents. Actionable conditions include (1) conditions where early interventions lead to health gain for the newborn, (2) conditions where early diagnosis avoids the lengthy diagnostic odyssey and (3) conditions where parents will have reproductive options during subsequent pregnancies (see also principle 3):

- From the perspective of patients, the benefit of NBS for untreatable but actionable diseases lies in the possibility of appropriately managing the disease, thus improving health and social outcomes for the newborn. Even in the absence of a cure or a treatment, early diagnosis may lead to strategies of care that address multiple components and facilitate access to integrated medical and social care. Health and social benefits include, for example, provision of improved care based on a diagnostic-informed management of the disease, prevention of comorbidities, facilitated access to social care and support, increased quality of life and potentially life span, resulting also ultimately, in better integration into society.
- From the perspective of parents and family members, avoiding a diagnostic odyssey and being informed about an increased risk for subsequent pregnancies to allow for informed reproductive choice and actionable lifestyle decisions for parents (living in the close proximity of healthcare services and education facilities) and other family members can also be relevant benefits of screening for untreatable yet actionable conditions[8]. Finally, from a broader societal perspective, screening for actionable diseases would support access to research, as having a pool of diagnosed individuals fosters research in terms of providing the possibility of having a natural history and a cohort for studies.

[7] Screen4Rare is a multi-stakeholder initiative launched by the International Patient Organisation for Primary Immunodeficiencies (IPOPI), the International Society for Neonatal Screening (ISNS), the European Society for Immunodeficiencies (ESID).

[8] https://www.healthcouncil.nl/documents/advisory-reports/2020/09/30/screening-early-in-life-for-untreatable-conditions

2 NBS should be organised as a system with clearly defined roles, responsibilities, accountability and communication pathways that are embedded into the national health care system and recognised as a mechanism for earlier diagnosis of actionable conditions as part of the broader care pathway.

The system has multiple components that need to be fully defined at all stages of the screening pathway and all elements of the screening platform. A single point of national accountability is needed to ensure the function, quality and integration of the pathway and the platform. Newborn blood screening needs to be incorporated into a comprehensive NBS programme that can include screening for hearing loss, cardiac abnormality, developmental dysplasia of the hip.

The stages of the NBS pathway include informing and educating parents, taking the sample, appropriate referral of screen positive newborns, diagnosis and interventions. Each stage needs to be adequately planned and performance managed (including regular audits).

The screening platforms need to include the following elements:

- **Awareness campaigns for the public, preconception education and information during each pregnancy.**
- **Comprehensive coverage and access to the newborn population, either through access to locations of birth or through visitation or clinics in the immediate postnatal period**. Standards for delivery and quality of transportation of the samples should be identified. All clinical staff that meet pregnant women or newborns should have specific training that is relevant to their role and regularly updated. Appropriate staffing is needed to conduct the tests and follow-up of results, including dealing with insufficient tests and positive screens.
- **New-born screening laboratories** should partner to deliver comprehensive coverage of the target population. They should be identified and accredited at national level to ensure uniformity of the methods used optimized to avoid risks of false positive screens.
- **Accredited laboratories for confirmatory diagnostic tests**.
- **Clinical centres for screened diseases for the follow up** of positive newborns. They should be members of the national network of centres of expertise**. Comprehensive treatment/care and/or support must be available to all newborns diagnosed through NBS**

Each element of the screening platform needs to have sufficient resources, sufficient training, standardised and accredited procedures, and a quality programme that meets international standards. The system needs to be coherent in order to function properly, each element needs to communicate with the other elements and the oversight of the system needs to account for a seamless integration.

A NBS programme will generate significant amounts of valuable data. It is important to the rare disease community that this data is used. Data should be used internally to facilitate regular review

and improvement of the screening programmes. Data should be shared appropriately externally to support research and facilitate planning within the health service. Informed consent for the collection and use of this data should be built into the process (See principle 10).

3 The family of the newborn who has been diagnosed through NBS should be provided with psychological, social and economic support by the competent national healthcare authorities.

Psychological support should be planned for families at the time of the screening test itself and also following both the first screening test and confirmatory testing results. The parents of the newborn who has been diagnosed through NBS must be informed quickly about the results, the disease, possible treatment and care, and centres of expertise for the specific disease. Moreover, they should receive, from the time of confirmed diagnosis, psychological, economic and social support including information on relevant patient organisations.

4 All stakeholders should be included in the different stages of the NBS process.

All stakeholders including patients, patient advocates, the general public, hospitals, healthcare professionals, researchers, ERNs, biobanks, national authorities and EU States should be included in the NBS process and must consider the newborn as the centre of the process. Patients & patient advocates should have a role/an input in the decision making process as they are the most affected group by the outcome of the decision.

The EU Member States should develop plans to coordinate the NBS processes looking for efficiency and effectiveness around the improvement of the health of these patients in the short term. Since NBS is performed for all newborns, neonatologists and primary caregivers and other professional organisations should also be included as stakeholders. A comprehensive programme must consider families of healthy newborns and false positive newborns as stakeholders and should provide them with follow up and support as well.

5 Transparent and robust governance for expanding NBS programmes is needed. Every country/region should have a clearly defined transparent, independent, impartial and evidence-based process for deciding which conditions are covered by the NBS programme that includes all stakeholders.

All health care provision involves trade-offs about the uses of resources. One organisation needs to be accountable for decisions about NBS. This organisation needs to involve all stakeholders so that a balanced decision can be made, this involvement should be in both decision-making and evidence provision. Decisions for including/excluding a condition in the screening programme should be made according to the perspectives of the rare disease community concerned and scientific evidence –all evidence should be available internationally.

Decision making bodies including all stakeholders should discuss the technical, financial and ethical aspects (sensitivity, specificity of the test, HTA, reporting of carrier status) before introducing a new disease into the national NBS programme. The process should include measures to ensure that rejected proposals have a clear explanation of the evidence gaps that need to be filled for a future application to be successful. These requirements should be proportionate to the reality of evidence challenges in the rare disease world and should not be unreasonable or impossible. Rejected proposals should be able to re-enter the evaluation process swiftly once missing evidence has been collected (and should not have to wait for a cycle to complete). From the patient and parent

perspective, it would be preferred to have equal access to the screening process across Europe. The diseases included in the NBS programmes should preferably be the same in each country (a European NBS programme) except for diseases that are known as highly prevalent in one region and almost non-existent in others.

6 Governance of NBS programmes should be explicit, comprehensive, transparent and accountable to national authorities.

The governance of NBS programmes should flow from a national mandate and be embodied in a National Coordination Centre. The establishment of National Coordination Centres at MS level should be provided to monitor the implementation of standards and activities required.

Transparency in the governance structure of the NBS programme in each country should be increased, both for policy decisions such as adding/excluding new diseases to the programme, as well as for executing the programme. Patients and their families together with rare disease experts and other relevant stakeholders at national level, such as representatives of ethical committees and citizens or health insurance companies, should be included in governance structures and discussions on potential expansion of NBS programmes for their conditions.

Each Member State should regulate the process by means of a national law or equivalent binding legislation, depending on the competent level of governance, in order to grant NBS to all newborns as a right to health, maintaining the possibility to opt-out by the parents. Specific state funds should be allocated to NBS so that the test is granted free-of-charge to all newborns. Lastly, the national coordination centres should be connected with the EU-level committee as indicated in the Call For Action.

7 The evaluation process on the inclusion/exclusion of diseases in NBS programmes needs to be based on the best available evidence, reflecting health economic evidence but not determined only by health economics.

NBS policies and practices should be analysed by each MS to develop common guidelines for the evaluation process on the inclusion of NBS methods into national programmes. There should be a minimum representation of patient associations and professional experts specifically for the conditions to be discussed, included on committees responsible for the evaluation of NBS programmes.

Cost-effectiveness should be integrated into a comprehensive health economic analysis, including additional outcomes and case studies of high importance for patients and their families on financial, psychological and societal burden including comparative modelling of the impact of receiving a late diagnosis versus receiving one at birth or shorty after. A mechanism needs to be in place to determine the efficiency of incorporating a disease into NBS programmes that have already been implemented in other Member States and to share evaluations especially for low and middle-income countries where it might not be feasible to conduct a cost-effectiveness study.

8 Information and education of all stakeholders on rare diseases and the whole NBS process is essential for a broad and fair implementation of NBS programmes.

Activities in spreading information on the need for expansion/ improving of/ equal access to NBS and raising awareness on the life changing impact of an early diagnosis among the public should be made through publicly funded awareness campaigns. All healthcare professionals involved in the NBS

process (including gynaecologists, nurses, midwives, genetic counsellors, neonatologists, paediatricians, clinical geneticists, and general practitioners/primary physicians) should be trained. Training should be tailored to reflect the uncertainties, exceptions or omissions and the impact of the evolution of the NBS test and the post diagnosis pathways. Follow up protocols should be designed for education of parents of the newborns that have been diagnosed through NBS.

Legislators should be advised on the importance of NBS regarding figures from best practices to underline the value and the positive outcomes on health and social care budgets. They also should engage with industries to be informed on therapies under development and to ensure that there's a timely decision making for diseases with therapies close to market authorisation. Moreover, European and national competent authorities should support patient organisations to provide information via specific funded projects or calls and create links between all stakeholders spreading awareness on NBS.

9 European-wide standards addressing the timing, sample collection methods, follow-up, and information shared with parents are needed to guarantee quality throughout the process.

Each Member State should provide standards to guarantee a certain level of consistency in the quality and implementation of the different steps and procedures involved in NBS including the timing for execution of the test, informing families, collecting blood samples, shipping them to the screening centre, processing the samples, calling the family of the newborn back in case a second confirmatory test is required, providing emergency hospitalisation when needed, confirming the diagnosis and communicating the result to the family. These standards should be appropriately monitored, reported and enforced through quality assurance, quality control procedures and regular accreditation.

The process of applying / implementing appropriate procedures to the activity of the laboratory and of certification for premises and methods according to international validated standards is particularly important in NBS. Healthcare professionals must attend specialised training courses; furthermore, a registry should be created in order to have systematic follow-up of all newborns detected with a condition through NBS.

10 Blood spot samples should be stored in national biobanks for quality control and research purposes while ensuring appropriate measures for data access as well as robust safeguards for data protection and privacy are in place.

In many countries, dried blood spots are stored after the screening tests have been performed. The objectives of storage are primarily for quality control purposes but stored samples can also be used in the interest of research. Stored samples can be used for future studies to improve NBS and healthcare. Parents must be clearly informed of storage and the possibility for the samples to be used for potential future research studies. Parents must be asked to opt-in or opt-out via an informed consent.

The collection of heelprick cards may be organised in collaboration with European biobank infrastructures. Storage and access to collections of dried blood spots can build on the technology used in biobanks which take appropriate safeguards for secondary use of data. The right of access should be transferred from the parent to the concerned individual or to the legal guardian once the adult age is reached.

Each MS should be responsible for ensuring that appropriate standards and protocols (compliant with GDPR, and other national legislations if relevant) are followed to access data and for establishing its data sharing framework and infrastructure.

11 ERN affiliated centres should be integrated in the care pathways of the different Healthcare systems and should be considered as preferential partners in providing recommendations on NBS policies.

In order to avoid the current disparity of NBS programmes across Europe, the ERN affiliated centres of expertise should be involved in the development of NBS regulation across National Health Systems through expert opinion so that the opportunity of access across the EU countries to NBS is the same for each person independently of where they are born. As ERNs harbour patients and clinicians of different backgrounds in their structure, they are the ideal thinktank for the development of NBS guidelines that would take ethical, legal and geographic constraints into consideration.

The registration and follow up of all positive cases in the ERNs registries, could allow to gather a wealth of knowledge with up-to-date epidemiological data and other types of information including surveillance and follow up on the impact of treatment and interventions.

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"Our vision is harmonised newborn screening programmes across Europe that leave no families of a newborn with a rare disease in uncertainty regarding their diagnosis, care and treatment, regardless of the country where they are born."

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