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

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Newborn or neonatal screening (NBS) is a population-based program aimed at the pre-symptomatic detection, shortly after birth, of serious treatable conditions. NBS thus permits the early delivery of appropriate therapy, preventing long-term disability or premature death.

First introduced by Robert Guthrie in the 1960s to screen for phenylketonuria, NBS is now performed in many countries in the world, all US states and almost all European countries. Where newborn screening is available, the number of disorders included in NBS panels (many inherited metabolic diseases, but also cystic fibrosis, severe combined immunodeficiency, and others) varies (from one to over 40).[1,2] This variation is influenced by many factors (e.g., the disease prevalence in the population, the availability of treatment). Consideration of these factors, usually following criteria established in 1968 by Wilson and Jungner,[3] determines national decision-making, and variation in screening panels is caused by the level of evidence required, e.g. the weight placed upon the relative specificity and sensitivity of the available tests, or the need for rigorous assessment of cost effectiveness.

While NBS is universally acknowledged as a major public health achievement, screening also causes harm, e.g. by medicalising families who receive a false positive result or by over-treatment of children with an ambiguous or mild phenotype.[4,5]

To prevent these negative effects from outweighing the benefits, information, care, support, monitoring, and management need to be carefully organised to improve the outcome for patients and their families.

In other words, NBS should always be regarded as an integrated system, not as an isolated laboratory test.

This is an important guiding principle when seeking to gain equity and promote good practice NBS programmes in Europe. A newly formed collaboration between the European Reference Networks (ERNs) (including MetabERN for IMDs and RITA for immunodeficiencies, autoinflammatory and autoimmune conditions), the International Society for Neonatal Screening (ISNS), the International Patient Organisation for Primary Immunodeficiencies (IPOPI), and the European Society for Immunodeficiencies (ESID-ISNS, IPOPI and ESID operate within the Screen4Rare initiative) has considered ten elements for effective operation of NBS programmes in Europe:

1. Selection of (new) conditions in NBS panels should be based on published criteria, the procedures 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 performance (e.g., ISO15189).
5. Laboratories and programmes should be able to produce data on key performance indicators relating 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

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support, and, when appropriate, genetic counselling should be provided.

7. Confirmatory testing should be established and consistently applied with a short and defined turnaround 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 performance managed on a national basis to encourage continuous improvement.

The continued expansion of metabolite-based screening and the potential offered by the rapid advance of genomic-based technologies emphasise the need to consider all aspects of the screening pathway alongside the possible ethical, social, and legal impacts for our societies.[2,6-9]

In the coming years, the ERNs and Screen4Rare aim to promote and disseminate examples of good practice to support the organisation and conduct of NBS in Europe. Notably, Screen4Rare has issued a Call to Action to recruit support from Health Policy makers and European members of parliament (MEPs) to:

- Develop agreed case definitions and confirmatory testing for European screening.
- Support the development of interoperable disease registries for screened conditions within Europe.
- Develop a blueprint for best practice to guide neonatal screening in Europe.

The call to action is signed by 30 MEPs and the aims are crafted into workstreams to be jointly executed by the ERNs and Screen4Rare.

Declaration of interests

All authors have no relationship, activities, or interests to disclose in relation to the present manuscript.

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