A NOVEL ALGORITHM TO FACILITATE THE INCLUSION OF IMDs ON NBS PROGRAMMES

Dr. Alberto Burlina, Dr. David Cheillan, Dr. Heather Church, Prof. Simon Heales, Teresa Hoi Yee Wu, Georgina Morton, Patricia Roberts, Erica Sluys, Dr. Anupam Chakrapani
Newborn screening (NBS) programmes are essential for the diagnosis of inherited metabolic diseases (IMDs) and timely access to disease modifying treatment.

Most European countries follow the World Health Organisation criteria to determine which disorders are appropriate for screening at birth; however, these criteria are interpreted and implemented differently by individual countries thus creating disparities. Advances in research and diagnostics, together with the promise of new treatments, offer new possibilities to accelerate the expansion of evidence-based screening programmes.

Our objective was to develop a novel algorithm, based on the Wilson & Jungner classic screening principles, that generates a weight-based score for inherited disorders. The algorithm was designed to be a first step in the complex process of identifying disorders for inclusion on NBS programmes by allowing national authorities to objectively evaluate and prioritise inherited metabolic diseases (IMDs) for inclusion on NBS programmes. If a high score is calculated for a given disorder, it would then need to be evaluated at the local level to assess the economic, societal and political aspects of a potential screening programme. The proposed algorithm could: limit the room for interpretation on which IMDs could be added to NBS programmes, reduce the disparity across European countries, and allow for horizon scanning of disorders for future consideration.

**Methods**

The Wilson & Jungner classic screening principles (Wilson JM, Junger YG 1968) were used as a foundation to develop individual and measurable criteria, that could be applied to objectively evaluate inherited disorders and provide a weight-based score to prioritise disorders for inclusion on expanded NBS programmes.

The Wilson & Jungner classic screening principles (Wilson JM, Junger YG 1968) were organised into four categories: “Condition”, “Diagnosis”, “Treatment” and “Other”. With the objective of identifying measurable and clinical criteria, three of these categories became the pillars of the novel NBS algorithm, as presented in Table 1.

Table 1. Three pillars of the NBS evaluation algorithm

<table>
<thead>
<tr>
<th>Pillar</th>
<th>Wilson and Jungner classic screening principles</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Condition</strong></td>
<td>Principle 1: The condition sought should be an important health problem</td>
</tr>
<tr>
<td></td>
<td>Principle 4: There should be a recognisable latent or early symptomatic stage</td>
</tr>
<tr>
<td></td>
<td>Principle 7: The natural history of the condition, including development from latent to declared disease, should be adequately understood</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td>Principle 5: There should be a suitable test or examination</td>
</tr>
<tr>
<td></td>
<td>Principle 6: The test should be acceptable to the population</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Principle 2: There should be an accepted treatment for patients with recognised disease</td>
</tr>
</tbody>
</table>

Principles 3, and 8–10 (Wilson JM, Junger YG 1968) fell into the category “Other” and are related to economic, societal and political aspects of screening programmes such as infrastructure (principle 3), cost-effectiveness (principle 9), and patient-finding and treatment policies (principles 8 & 10).

- **Principle 3**: Facilities for diagnosis and treatment should be available
- **Principle 8**: There should be an agreed policy on whom to treat as patients
- **Principle 9**: The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole
- **Principle 10**: Case-finding should be a continuing process and not a “once and for all” project

If a disorder is highly-ranked by the NBS evaluation algorithm, and therefore strongly fulfils the Wilson & Jungner criteria, a country or regional assessment would be required to consider these important aspects as a second step.

IMD, inherited metabolic disorder; NBS, newborn screening
The NBS evaluation algorithm

With the intention of developing a point-based system, we explored the nuances of the six identified screening principles included in the NBS evaluation algorithm, aiming to parse out individual criterion so that each factor could be assessed, and therefore, measured separately. Within each pillar, categories and then criteria, were defined in order to capture individual aspects of the screening principles.

The NBS evaluation algorithm is a point-based system structured upon three pillars: natural history of the disorder, called Condition, Diagnosis and Treatment. A disorder can score a maximum of 13 points; six for Condition, three for Diagnosis and four for Treatment. Within each pillar there are categories, in some category's points are cumulative as indications by “AND” and in other categories, points are selective, as indicated by “OR”.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Score range (0-6)</th>
<th>Severity</th>
<th>AND</th>
<th>0.5 The disorder only has severe forms</th>
<th>0.5 There is a rapidly progressing form</th>
<th>1 The disorder can be fatal by adolescence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Onset</td>
<td>AND</td>
<td>1 All forms of the disorder are asymptomatic for the first few weeks of life</td>
<td>1 More than 50% of cases are an early-onset phenotype</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Frequency</td>
<td>OR</td>
<td>2 Greater than or equal to 1 in 50,000</td>
<td>1.5 Greater than or equal to 1 in 100,000 and less than 1 in 50,000</td>
<td>1 Greater than or equal to 1 in 150,000 and less than 1 in 100,000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Score range (0-3)</th>
<th>Availability</th>
<th>OR</th>
<th>2 DBS test is available and in use</th>
<th>1 DBS test is not yet available, but is in development with published evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Performance</td>
<td>OR</td>
<td>1 DBS test has a low false-positive rate or a high positive predictive value (PPV)</td>
<td>0.5 DBS test has a high false-positive rate and/or a low PPV and/or requires additional confirmatory strategies that are available to improve screening performance</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Score range (0-4)</th>
<th>Availability</th>
<th>OR</th>
<th>1.5 An EMA-approved treatment is available</th>
<th>1 A treatment intervention is available (diet, HSCT, BMT)</th>
<th>1 A treatment is in late development (phase 3)</th>
<th>0.5 A treatment is in early development (preclinical, phase 1, or phase 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Outcomes</td>
<td>OR</td>
<td>1.5 The treatment strategy changes the prognosis for all forms of the disorder</td>
<td>1 The treatment strategy changes the prognosis for some forms of the disorder</td>
<td>0.5 The treatment strategy does not change prognosis or improves only some symptoms of the disorder</td>
<td>1 Pre-symptomatic initiation results in better outcomes</td>
</tr>
</tbody>
</table>

BMT, bone marrow transplant; DBS, dry blood spot; HSCT, hematopoietic stem cell transplantation; IMD, inherited metabolic disorder; NBS, newborn screening; PPV, positive predictive value.
Weighted scoring of the NBS evaluation algorithm

As in the Wilson and Jungner classic screening principles, the pillar Condition carries the most weight and therefore contributes to nearly half, 46%, of the total score in this proposed algorithm (see Figure 1A). The pillar Treatment contributes 31% of the total score, while the more straightforward pillar Diagnosis contributes to 23% of the total score. The proposed algorithm prioritises severity of the disorder (23%) and treatment outcomes (20%), with other criteria contributing as follows to the total score: frequency of disorder (16%), availability of diagnostic test (15%), treatment availability (11%), performance of diagnostic test (8%) and onset of disorder (7%) (see Figure 1).

Validation of the algorithm

The NBS evaluation algorithm was validated by applying the current IMDs that are approved by the National Screening Committee in the United Kingdom, assuming that these would be highly ranked by our algorithm. These disorders: glutaric aciduria type 1 (GA1), homocystinuria (HCU), isovaleric acidaemia (IVA), maple syrup urine disease (MSUD), medium-chain acyl-CoA dehydrogenase deficiency (MCADD) and phenylketonuria (PKU), and all scored above 8.5 points. Therefore, we propose that a disorder scoring above 8.5 points on the NBS evaluation algorithm would be consistent with other disorders currently screened for and therefore could be highly recommended for inclusion on NBS programmes.

PKU
11.5 out of 13 points

HCU
11.5 out of 13 points

MCADD
11 out of 13 points

MSUD
9 out of 13 points

IVA
8.5 out of 13 points

GA1
11.5 out of 13 points

GA1, glutaric aciduria type 1; HCU, homocystinuria; IVA, isovaleric acidaemia; MCADD, medium-chain acyl-CoA dehydrogenase deficiency; MSUD, maple syrup urine disease; NBS, newborn screening; PKU, phenylketonuria.
Conclusions

The NBS evaluation algorithm generates a weight-based score that could be used as the first step in the complex process of evaluating disorders for inclusion on NBS programmes. By prioritising disorders as a first step, individual countries are then able to assess the economic, societal and political aspects of implementation in their individual screening programmes for those disorders that most strongly fulfil the Wilson & Jungner criteria.

Despite the rich discourse on how to come together across the European Union and harmonise NBS programmes (Loeber JG et al. 2021, Cornel M et al. 2011, Castineras DE et al. 2019), there has been little forward motion. This algorithm attempts to provide a concrete tool for the progress that is so desired. As a tool, the NBS evaluation algorithm, could, in principle, also be applied to other types of conditions such as neuromuscular diseases spinal muscular atrophy and Duchenne muscular dystrophy. Expanded NBS programmes benefit patients, society, and the healthcare system. NBS programmes add to the current body of knowledge on the natural history of disorders, because screening increases patient finding and with more information on genotype/ phenotype correlations, disease progression and treatment outcomes further advances can be made. Our goal is for this algorithm to pave the way forward for evidence-based expansion of NBS programmes, by allowing countries to objectively evaluate disorders while maintaining the ability to separately evaluate specific economic, societal and political aspects of their own screening programmes.

Acknowledgements

The authors thank ArchAngel for the inception of this work, Charlotte Chanson & Annamarie Dillon of Orchard Therapeutics for their support in coordinating and supporting the expert group during the whole project, and Helvet Health for medical analysis and writing.

References


