The Second Revolution of Newborn Screening

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Newborn sequencing programs have a lot to learn about traditional Newborn Screening.

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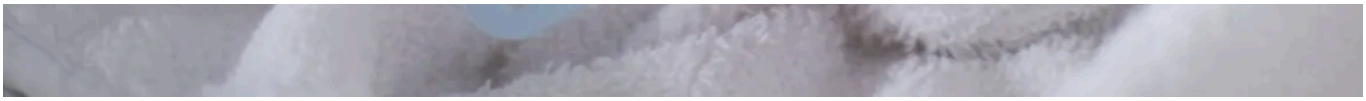

Since its introduction in the early 1960s, newborn screening has saved thousands of lives. Probably millions.

Newborn screening (NBS) began with a bacterial inhibition assay, but has been continuously evolving, constantly adapting to the emerging technologies, and developing specific methodologies to improve its performance and extend its scope. The first revolution came with the development of tandem mass spectrometry, which allowed NBS programs to expand from a few diseases to around 50 additional disorders in a single test.

NBS programs have not only grown and changed technologically; the ethical considerations and patients' perspective have changed over the years. Wilson and Jungner criteria provided a stable guideline that professionals of NSB can rely on when considering expanding NBS programs. Patients' access to a broader health knowledge, along with a more defined ethical framework regarding consent and confidentiality, have made NBS programs more democratic in terms of decision-making. However, policymakers have not evolved in the same way. On the contrary, bureaucracy has slowed down attempts to expand NBS programs in many countries, making it difficult to achieve an equitable access; meanwhile, in countries with a low human development index, NBS often isn't present at all.

The second revolution of NBS programs is about to come. In the last 20 years, genetic sequencing technology, genetics and genomics have rapidly evolved. Next-generation sequencing has substantially reduced sequencing costs while increasing quality and quantity of results. Our knowledge of gene-disease association keeps expanding, along with related sciences such

as bioinformatics, all making whole genome sequencing more and more useful in clinical settings.

These developments have affected NBS programs, which have gradually incorporated whole exome and/or genome sequencing in their algorithms to reach the final diagnosis of affected children. Pilot programs in the U.S., Europe and Australia have started exploring the inclusion of genome or exome sequencing in NBS programs not only for diagnosing affected children, but for the whole newborn population. Now the first results of these pilot programs are becoming public, allowing us to better understand the challenges and possibilities of genomic NBS programs. One such challenge is the lack of consensus on how and when to obtain consent for genomic testing — and, critically, on which genes should be included in this testing. Concerns about confidentiality, data storage and re-use are also important issues that need to be addressed in the near future.

Genomic newborn screening is here to stay, and traditional NBS is not going anywhere. The question is: How do we integrate both? Or should they be integrated at all? Are both approaches complementary, independent, or exclusive? My own opinion, after a few years of experience in traditional NBS and after a first approach to newborn sequencing through the BabySeq project in Boston, is that they should be complementary.

I also think that newborn sequencing has a lot to learn about traditional NBS. Traditional NBS programs have well-established circuits of dried blood spots extraction, transport of those samples to the laboratory, sample reception, and temporary and permanent storage. They also have Laboratory Information Systems collecting all the clinical and demographic data of the newborns. They have built robust relationships with neonatology departments and midwife networks over the years. Professionals of

traditional NBS are used to working with both families and providers; they know how to handle the complexity of NBS from every angle. Newborn sequencing programs should take advantage of all of this, join forces with traditional NBS programs and work together.

The ideal scenario would be a NBS program with only one preanalytical and administrative area; one Laboratory Information System with modules for both traditional NBS and genomic sequencing results; and two laboratories, one for traditional methodologies and one for the genomic analysis. Professionals in these two areas should work closely together, sharing relevant information for every case. Traditional NBS results will be available sooner, but in my experience some doubtful cases can be resolved only through genomic analysis. On the other hand, doubtful genomic results, such as variants of unknown significance, might be resolved with biochemical tests, especially in the metabolic diseases area, as metabolomic approaches seem to be the next revolution for traditional NBS. The combination of both approaches will help improve genomic knowledge and will help to detect cases where there is a genomic alteration, but the biochemistry is not altered yet. With the inclusion of newborn sequencing the NBS programs will expand the range of conditions to be screened, and the improvement in knowledge will allow the inclusion of new conditions easily and at a low cost.

Once newborn sequencing has overcome the unresolved questions mentioned above, policymakers, health professionals, laboratory specialists and patients should advocate for a merger between traditional NBS and genomic sequencing in newborns in one single NBS program. This must be done while maintaining the equity values that have guided NBS for more than 50 years; newborn sequencing should be universally available. If we do

all of this, we will reduce costs, expand the scope of NBS, and improve newborns' care and future.

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