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LETTER TO THE EDITOR

Genomic newborn screening: Proposal of a two-stage approach

To the Editor

Newborn screening (NBS) programs have become the most effective and efficient measure of secondary prevention in medicine.[1] They shorten the path to early diagnosis and treatment and are a prerequisite for improved outcomes of severe early-onset diseases.[2] Following the decoding of the human genome, medicine has been undergoing a revolution in its diagnostic approach to prenatally and postnatally manifesting disorders, driven by next-generation sequencing, in particular exome and genome sequencing. Rapidly decreasing turnaround time for next-generation sequencing technologies would now allow NBS by genomic sequencing and the inclusion of additional disorders, which remained undetectable for currently applied NBS technologies. In parallel, the first successful gene therapies for monogenic disorders have been introduced and again their impact on health outcomes critically depends on early diagnosis of affected individuals during the early, ideally presymptomatic state of the disease. However, genomic NBS programs come with challenges, technological, and intellectual as well as societal and ethical.[3]

Studies have demonstrated that genomic NBS is technically feasible and can effectively detect risk and carrier status for a wide range of disorders.[4] However, NBS by whole exome sequencing is still both insufficiently sensitive and specific to be considered as the primary screen, at least for most inherited metabolic diseases.[5] In addition, the ethical and societal discussion of whether genomic NBS is desirable and how best to implement it, is lagging behind technological developments. The level of interest in genomic testing of their newborn child varies greatly among parents, and in a substantial fraction of couples, the degree of interest is discordant between partners.[6]

The perinatal period is a time of tremendous emotional impact, and consequently it can be overwhelming for parents to be challenged to make a decision about genomic NBS on behalf of their newborn child. This decision will not only affect medical care and prevention programs, but also issues of privacy, may have legal implications, and potentially even alters the respective individual's perspective on life. There are additional, nonmedical barriers to effective decision-making in the newborn period. These include, but are not limited to, comparative social and cultural influences, perceived legal implications, the influence of family and peers, and information available on the internet, mixed messages, and inconsistent communication by the respective providers.[7]

Effective counseling on genomic NBS necessitates sufficient time for contemplation and discussion prior to consenting. We therefore propose a two-stage approach: (a) population-based NBS programs for severe early-onset disorders requiring timely intervention directly after birth and (b) opt-in genomic NBS programs at 2 to 6 weeks of age (Figure 1). This approach would allow to separate the emotional stress of the immediate peripartum period from the major decision of what to know and what not to know with regard to the child's health by a few weeks. On the other hand, this additional step that necessitates extra time and resources for counseling and consenting represents a challenge and burden on the side of the respective medical providers. The decision-making process can be supported by additional tools, such as web-based decision aids and multimedia interfaces. Such decision aids can also be applied to develop tailored approaches about the timing of return of results for the various types of genomic variants.[8]

When considering a two-stage approach, one would need to decide whether DNA available from the initial screening could be used in case the family consents to genomic NBS in the second stage. Technical feasibility studies have been conducted to determine the quality of DNA isolated from dried blood spots on a filter card for genome sequencing applications.[9,10]

Other approaches to genomic newborn testing have been discussed, including exome sequencing as a second-tier test after a positive MS/MS result,[11] or an approach of offering genomic sequencing only to symptomatic children,[12] though this does not represent a screening test in the strict sense, but rather diagnostic testing subsequent to a clinical or biochemical phenotype. Unlike population mass screening, which assumes an equally low a priori risk of screened individuals for a specific disease, any emerging clinical

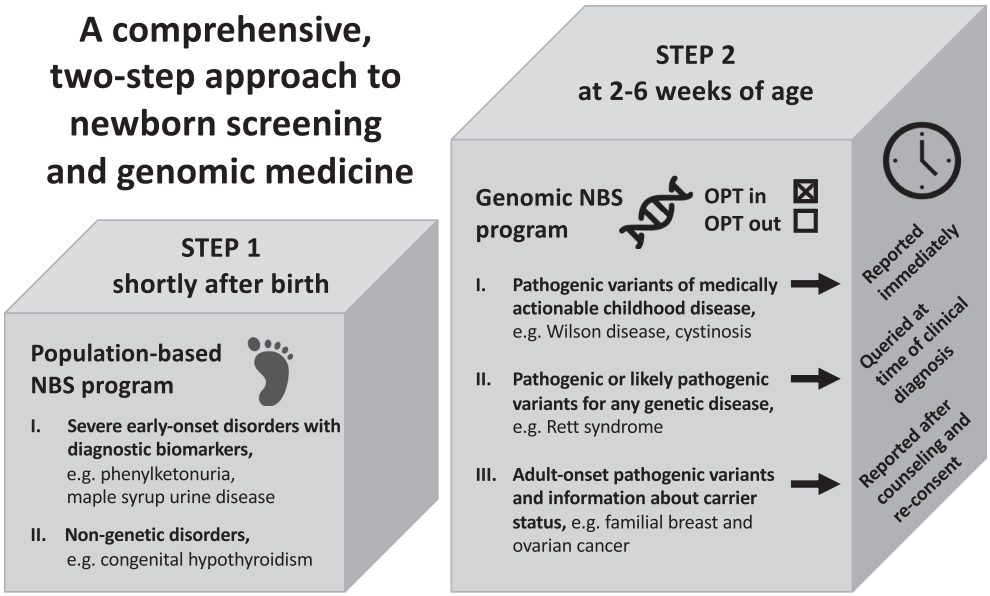

FIGURE 1 A comprehensive, two-step approach to newborn screening and genomic medicine

phenotype clearly increases the a priori risk of the affected individual. At the same time, the presence of an individual's phenotype also allows improved interpretation of gene and variant data.

Others have raised the possibility of offering genomic NBS as a direct-to-consumer service.[13] This, however, draws away from the idea of offering NBS as a public health measure and would make counseling and consenting even more challenging. The challenges of direct-to-consumer genetic testing, resulting in additional requirement of clarification, interpretation, and counseling are already experienced by the respective consumers in clinical practice, even though not yet related to genomic NBS.[14]

How would the results of genomic NBS programs be provided and communicated with families? One could envision providing them in tiers: (a) pathogenic variants of medically actionable childhood disease would be revealed at time of diagnosis. (b) Pathogenic or likely pathogenic variants for any disease could be queried at time of clinical diagnosis, thereby eliminating the need for diagnostic exome or genome sequencing at that time. (c) Finally, adult-onset pathogenic variants and information about carrier status for Mendelian disorders could be revealed after genetic counseling and reconsent when the affected individual has entered adulthood. This is where genomic NBS would extend well beyond the concept of NBS and become a model of genomic medicine more generally. While genomic information would be analyzed during the newborn period, information would be made available to the affected individual at various timepoints. Subsequently, implications of this approach would reach across the entire lifespan.

Genomic medicine challenges existing paradigms. It requires a nonpaternalistic approach, making the family part of the decision-making. As the *Public and Professional Committee of the European Society of Human Genetics*, the *Human Genome Organization Committee on Ethics, Law and Society*, the *PHG Foundation*, and the *P3G International Paediatric Platform* rightly state "the responsible use of genome sequencing within a public health program such as newborn screening should not be technology driven, but rather be adopted on the basis of its public health potential. The primary justification (...) should be the health interests of the child."[15] Planning and implementation of a genomic NBS program require broad, international discussion across disciplines, including patient representatives and policy decision-makers.

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AUTHOR CONTRIBUTIONS

Christian P. Schaaf, Stefan Kölker, and Georg F. Hoffmann conceived the manuscript and the figure. Christian P. Schaaf wrote the manuscript. Stefan Kölker and Georg F. Hoffmann edited the manuscript.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

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