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Comment

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Implementing genomic newborn screening as an effective public health intervention: sidestepping the hype and criticism

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Genome-wide sequencing of the DNA that can be obtained from a newborn screening blood spot could provide predictions of thousands of genetic diseases that are not currently included in universal newborn screening. Most of the serious ethical, legal, privacy, and social concerns raised by genome sequencing of all infants can be avoided by implementing genomic newborn screening in accordance with widely-accepted public health criteria.

The development and implementation of population-based newborn screening was one of the most successful public health interventions of the twentieth century. Newborn screening is now routinely provided to almost all infants in many jurisdictions and usually includes a number of Mendelian diseases as well as some other treatable conditions of infancy. Genome-wide sequencing of the DNA that can be obtained from a small drop of an infant's blood would permit the identification of genomic variants that are predictive of thousands of additional genetic diseases and provide the opportunity to treat many more healthy-appearing babies with childhood-onset disorders. Newborn genomic sequencing could also give parents information about genetic variants associated with conditions for which there is currently no treatment, that do not have onset until much later in life, or that only raise concern in relatives of the infant. However, our knowledge of the penetrance, natural history, and variability of most rare genetic diseases is limited, the clinical validity and utility of genomic diagnosis for many of these conditions have not yet been established, and the value of presymptomatic treatment is often unclear. As a consequence, much of the information obtained through newborn genomic screening may be of no benefit to, or could even harm, a baby. Genomic sequencing data might be stored indefinitely in an infant's electronic health record, a prospect that raises serious ethical, legal, privacy, and social concerns. Implementing universal genomic newborn screening in accordance with widely-accepted public health disease screening criteria would sidestep most the concerns that have been raised.

Potential benefits and harms of genomic newborn screening

Universal newborn screening programs are usually designed to detect serious conditions in asymptomatic infants in order to provide treatment that can greatly ameliorate a disease or even prevent it from occurring. The medical, financial, and social costs and benefits of such programs can be evaluated using standard public health criteria[1,2], and recent commentaries[3,4] present a strong case for why we need to collect large-scale trial data that will enable us to do such evaluations.

Discussions of genomic newborn screening often focus on sequencing all of the protein-coding genes, but the function of most human genes is unknown, and sequencing these genes would be of no immediate value. Almost all concrete proposals and pilot projects for genomic newborn screening actually involve bioinformatics analysis of only a panel of genes, usually, just a few hundred, that are known to be associated with serious mendelian diseases that occur in young children and are clinically "actionable". However, genome sequencing also provides information on single nucleotide polymorphisms (SNPs), the genetic markers that are used in most studies of common adult-onset diseases as well as of traits like IQ, height, and ancestry. The fact that population-based genome sequencing would provide information on thousands of genes that are not the targets of newborn screening and on millions of SNPs in every infant has led to suggestions that genomic newborn screening might be valuable for many purposes beyond detecting potentially treatable childhood-onset genetic diseases in healthy-appearing babies. These "additional benefits" might include shortening the diagnostic odyssey in children who subsequently develop symptoms of a genetic disease or informing a family of the likelihood that an infant will develop a genetic disease for which no effective treatment currently exists. Genomic data could also be used to provide risk stratification for common diseases of later life, pre-emptive pharmacogenomic testing, or heterozygous carrier status for thousands of recessive diseases. In addition, genomic screening of newborn infants could provide information for parents and other family members regarding their own risks for developing a serious genetic disease or for having a child with such a disease.

The costs and benefits of using genomic data for purposes other than screening for serious diseases that can be effectively prevented or treated in infancy cannot be evaluated using the public health criteria that justify conventional newborn screening[3,4]. Routine genome sequencing for any purpose has the potential to harm some of the infants who are screened[5,6], and there is usually no laboratory test or imaging study that can reliably establish the clinical diagnosis of a genetic disease in an asymptomatic child. Thus, it may be necessary to follow children clinically for many years to recognize false positive and false negative newborn screening results for many genetic diseases.

One of the most important reasons that many conventional newborn screening programs have been successful is that they are universal – almost every baby born within the jurisdiction receives newborn screening[7,8]. An important factor in achieving such inclusive coverage is thought to be the use of implied consent – all parents are assumed to want this screening because of the severity of the diseases included and the urgency and effectiveness of available treatments for the baby[7,8]. The assumption of potential benefit for all infants may also apply to newborn screening for other genetic diseases that meet standard public health disease screening criteria[1,2], and

implied consent may also suffice for these conditions. However, genomic newborn screening to achieve additional potential benefits like those listed above is very likely to require explicit parental consent for screening[7–9]. Moreover, many of these additional benefits cannot be achieved without long-term storage of the baby's genomic data, which would require explicit parental consent in most jurisdictions[10].

Long-term storage of genomic data raises a number of legal, ethical, and privacy concerns[9,11,12]. The benefit of maintaining an electronic record of an individual's genome sequence is predicated on the assumption that genome sequencing is difficult to obtain and very expensive. This is no longer true, and if genome sequencing were cheap enough for universal genomic newborn screening to be practical, repeat sequencing would probably be less expensive and more informative than storing a person's genomic data securely for many years. Resequencing a stored newborn screening blood spot or sequencing a sample from concerned individuals or family members when they need or desire the information could provide most, if not all, of the additional benefits suggested for genomic newborn screening without the need for long-term storage of the baby's sequence data.

Use of standard public health disease screening criteria would sidestep most concerns about genomic newborn screening

Most of the concerns that have been raised can be avoided by implementing genomic newborn screening in a manner that meets standard public health guidelines for disease screening[1,2]. This can be done by (1) limiting the program to a panel of genes for high-penetrance genetic diseases that have been shown to be effectively preventable or treatable in early life, (2) not storing any genomic data beyond the standard newborn screening report in the infant's electronic health record, and (3) assuring the universality of screening, follow-up disease confirmation, and treatment (if indicated) for all "screen positive" infants[1,2].

Even if this were done, implementing genome sequencing in every newborn infant would still raise some important health policy issues. One is that a screening test, no matter what it is, is only a small part of a newborn screening program. Once "screen positive" infants are found, the family (or in some programs, the responsible healthcare professional) must be notified and the child recalled for further evaluation, which may require additional testing and specialist assessments that differ for each disease. The infant must then be treated if necessary and followed clinically to determine disease onset or progression, observe for complications and beneficial or adverse effects of treatment, and provide other necessary services such as genetic counseling for the family[8,13]. It is important to note that the testing, follow-up, and treatment needed for genomic newborn screening would largely be in addition to services that are currently in place for other forms of newborn screening, so universal genome sequencing would constitute a substantial increase in the overall cost of a jurisdiction's newborn screening program, even if the genomic testing itself were inexpensive[6,9,14,15].

Cost-effectiveness, which is an important consideration for all public health interventions, has not yet been demonstrated for genomic newborn screening for any disease. Implementation of genomic newborn screening before it has been shown to be cost-effective and to meet other standard public health criteria risks damaging the current widespread public and political support for conventional newborn screening, thus harming the babies who benefit from existing universal screening programs[6,15]. Several large-scale pilot studies of genomic newborn screening are currently underway, and it is important that the results of these studies be obtained and analyzed in a manner that permits accurate assessment of the sensitivity and specificity of genomic newborn screening for serious genetic diseases, the clinical utility of pre-symptomatic diagnosis and intervention, cost-effectiveness, and the overall net benefit to children[3,4].

Conclusion

Most of the serious ethical, legal, privacy, and social concerns raised by genome sequencing of all infants can be avoided by implementing genomic newborn screening in accordance with widely-accepted public health criteria.

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Competing interests

The author declares no competing interests.

Additional information

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