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Genetic screening: birthright or earned with age?

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1. Introduction

Since the inception of genomic medicine, the goal of using the message encrypted in the 6 billion basepairs of the human genome as a blueprint to guide clinical care, lifestyle choices and family planning has been an ambitious vision shared by both clinicians and scientists [1,2]. The growing knowledge of the genome coupled with reduced costs and expanded capabilities of next-generation sequencing technology make implementation of universal genomic medicine possible within the near future. With this in mind, some visionaries assert that it would be beneficial to sequence the genome of every newborn. In this sense, an individualized genetic resource would be bestowed upon each newly born child as if it were a birthright. But is this really in the best interest of the child? Could there be other ways to enable parents to leverage medically actionable information about their child while also respecting the child's future capacity to participate in their own decision-making?

2. Newborn genomic screening – not as simple as one might wish

2.1. Ethical considerations

Newborn genomic sequencing could essentially provide a blueprint to construct beneficial health outcomes derived from early interventions, precision medical treatments and proactive engagement of the parents and the growing child in making informed decisions about their health [3]. Newborn genomic screening is alluring, but a host of ethical, legal and

Declaration of Interest

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social implications (ELSI) arise when considering the use of genomic sequencing in newborn populations, particularly healthy ones[4].

Perhaps the most salient issue is that genomic sequencing can identify an extraordinarily wide range of genetic predispositions for various ailments that might be imminent to the well-being of the child or only distantly relevant to the health of the future adult. In addition, genomic sequencing does not discriminate between the types of genetic conditions that are subject to detection. This means that rare, devastating conditions that have no treatments, or conditions that only have medical interventions in adulthood would all be potentially identifiable in a newborn. If genomic sequencing is viewed as a birthright that all newborns are entitled (or perhaps more problematically, obliged) to receive, society must address if it is ethical to screen for conditions that do not present imminent harm or that have no treatment [4]. All genetic knowledge is not universally beneficial and ultimately could create problems such as impairing parental bonding, creating “patients-in-waiting,” or impinging on the ability of the newborn to make their own healthcare decisions in the future [5–7].

2.2. Technical considerations

Inextricably linked with these ethical dilemmas is the fact that our ability to sequence the human genome has dramatically outpaced our ability to interpret the clinical significance of genetic variation [8]. Thus the genetic variation detected in genes that have not been functionally characterized or within non-coding regions, which accounts for the majority of the genome, may not be clinically useful when screening asymptomatic newborns. Even protein-coding changes can be challenging to interpret, and the performance of sequencing as a screening tool (its clinical sensitivity and clinical specificity) are yet to be determined. Additionally, sequencing the entire genome for the purposes of pre-symptomatic genetic screening in the entire newborn population would require the establishment of an infrastructure to sequence, interpret and securely maintain the enormous volume of genetic data generated for each newborn [9]. Most of the sequencing data would align to regions of the genome that are not well understood and therefore would not contribute to any discernable genetic risk factors. Based on our current understanding of the genome, screening of newborns by way of genome-scale sequencing could be viewed as a wasteful use of resources since most of the data would not be clinically relevant at this time [10].

2.3 Parental decision-making

In contrast to the use of next-generation sequencing technologies to diagnose rare Mendelian disorders [11], to prevent a diagnostic odyssey [12] and to direct precision medicine treatments [13], where parental decision-making is similar to any other diagnostic test that might be suggested by their child’s physician, the directive to act in their child’s best interest mandates that parents more deeply consider the pros and cons of screening via genomic sequencing. Current public health newborn screening programs offer little in the way of information to parents, and do not require parental consent [14]. This approach is typically justified by the highly actionable nature of the information provided, and the overriding public health interests of case finding have typically favored high sensitivity with the trade-off of numerous false positives [14]. In the context of genome-scale sequencing, these priorities may no longer be sustainable. Engagement of prospective parents in true informed

decision-making will require innovative methods [15] and engagement that may simply be unwelcome and untenable in the immediate peripartum period.

Whereas diagnostic sequencing illuminates the current capacity of next-generation sequencing to alter clinical care, application of the same promising technology for precision medicine in healthy newborns introduces significant challenges. Thus, the shortcomings of the "birthright" approach to population-level genetic screening of newborns warrants the investigation into alternative approaches to integrating genetic screening into public health interventions.

3. Age-based genetic screening (ABGS)

3.1. A novel paradigm of genomic knowledge that is "earned with age"

Instead of deciphering the entire genome as a "birthright," we propose a novel approach to genetic screening that represents staged genomic analysis that is "earned with age." In this approach, discrete intelligible excerpts of the genome are targeted and interpreted in an age-based screening program that maps to other routine care that occurs during childhood. This gradual introduction of genetic information throughout the child's development enables genetic conditions to be detected at specific developmental stages in time for pre-emptive care or surveillance to take place. Just as growth and developmental progress is tracked to ensure that the child is meeting milestones, and hearing and vision are screened prior to the accelerating academic demands of elementary school, ABGS would examine conditions that are relevant to the age of the child. As the child progresses from neonate to infant to childhood to adolescence, each developmental stage would include screening for genetic conditions that are expected to manifest or have recommended interventions during the corresponding age range. This experience could also include gradual involvement of the child in providing assent for screening, preparing them to make well-informed decisions about the potential benefits and risks of screening for adult-onset conditions once they achieve the age of majority.

3.2. ABGS mitigates ELSI concerns

We propose that ABGS would address many of the ELSI concerns associated with genome-scale screening in neonates and children. First, ABGS focuses screening on conditions that are relevant to the age of the child, preventing the detection of conditions that have an adult onset. Second, ABGS prioritizes screening for conditions with higher actionability, maximizing the expected acceptability to parents [16] and avoiding parental concerns involving learning about conditions that have no treatments or interventions. Third, ABGS could be restricted to conditions with substantial knowledge-base supporting the gene-disease association and subsequent clinical interventions. The use of targeted gene panels ensures that the gene-disease pairs meet predetermined criteria including the availability of medical treatments. The exact make-up of the gene lists and the precise criteria used to determine this content would be the subject of much research and stakeholder deliberation, but could leverage existing efforts such as the Advisory Committee on Heritable Disorders in Newborns and Children [17] and/or robust, transparent parameters such as those we have described previously.[18]

3.3. ABGS and cost-effectiveness

Approximately four million children are born in the United States annually, most of which undergo the recommended uniform screening for metabolic conditions, congenital heart defects and hearing loss within the first 24 to 48 hours following birth [19]. The costs associated with newborn screening varies by state and ranges from free to the patient to over $100 [20]. For genetic screening to be incorporated into standard screening programs, the costs need to be on par with other public health interventions. Even with dramatic declines in the cost of sequencing [21] the combined outlays for analysis and interpretation are still comparatively exorbitant. Conversely, the availability of affordable targeted-sequencing technology combined with the ability to sequence multiple samples in unison (referred to as multiplexing) could conceivably bring the cost of ABGS to under $100 per person/per panel.

4. Implementation of ABGS

This proposal for ABGS is based on expansion of the United States recommended uniform newborn screening program, however ABGS could have international uptake because of its ability to be incorporated into routine well-child care. ABGS offers a feasible option to integrate next-generation sequencing technology into a staged screening program for newborns and children in an affordable way that alleviates many of the ELSI concerns of using genome-scale sequencing for genetic screening. In one potential implementation, ABGS would involve repeated sampling (either blood or buccal swab/saliva) at various developmental stages. Alternatively, implementation could involve utilization of DNA from stored blood spots for targeted analysis. The staged analysis proposed here could also be accomplished through targeted informatics analysis of existing genome-scale sequencing data. However, no matter which form the biospecimen sampling and DNA analysis takes, parental engagement will still be required for consent. Therefore, to reduce the burden on parents, we propose that the timing of ABGS could occur concomitant to other age-based pediatric interventions (such as growth and developmental milestones, hearing and vision screening, blood pressure measurement, vaccinations, etc.) that are introduced at certain time points in the well-child clinical care paradigm. This approach would facilitate the gradual provision of educational materials to parents, allow parents who initially declined ABGS to opt-in during a subsequent clinic visit and foster opportunities for clinicians involved in the child's care to weigh in on the details. Any ABGS program would also need to have standard management plans in place for the conditions being evaluated, as well as the availability of specialists for follow-up care.

4.1 ABGS allows room for growth

We have presented an outline of a plan through which next-generation sequencing could be utilized to screen for actionable single-gene disorders in newborns and children, which could continue into adulthood to include adult-onset conditions. Advances in the science of medicine will require the expansion of panels to incorporate new conditions and potentially other types of information such as pharmacogenomics and common variants associated with multifactorial disorders, when these types of information are proven to be broadly useful. Efforts will be needed to balance clinical sensitivity and clinical specificity to optimize case finding and minimize false positives and overdiagnosis [8] especially for conditions where

no confirmatory diagnostic test exists. Eventually our knowledge of the human genome may grow to a level of complete understanding of the message within our 6 billion nucleotide diploid genome. Until that time, a staged, age-based genetic screening program could enhance our ability to pre-symptomatically detect and treat Mendelian disorders using current scientific knowledge and evidence-based medicine, providing information that is readily understandable to parents and less troubled with serious ethical concerns.

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