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PERSPECTIVE

Challenges of using next generation sequencing in newborn screening

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Summary

Whole-genome and whole-exome sequencing for clinical applications is now an integral part of medical genetics practice. The term newborn screening refers to public health programs designed to screen newborns for various treatable metabolic conditions, by measuring levels of circulating blood metabolites. The availability and significant decrease in sequencing costs has raised the question of whether metabolic newborn screening should be replaced by whole-genome or whole-exome sequencing. While newborn genome sequencing can potentially increase the number of disorders identified by newborn screening, the generalization of its practice raises a number of important ethical issues. This short article argues that there are medical, psychological, ethical and economic reasons why widespread dissemination of newborn screening is still premature.

Whole-exome sequencing (WES) for clinical applications is now an integral part of medical genetics practice. Though most studies are performed in order to establish diagnoses in individuals with rare and clinically unrecognizable disorders, due to the constantly decreasing costs and commercial (academic and industrial) availability, in some centres there is inclination to use this tool for other purposes in at risk and even in healthy adult populations (Manolio *et al.*, 2013; Biesecker & Green, 2014; Feero, 2014). For example, exome sequencing in patients with clinically recognized disorders when more than one gene is responsible for the phenotype is sometimes more cost-effective compared to a limited gene panel (i.e. for patients with Noonan-like phenotype or familial thoracic aortic aneurysm). WES can also be used in cancer patients in which the major contributing genes have been excluded (i.e. BRCA-negative familial breast cancer), and even to screen healthy individuals for future planning and predictive outcomes. Though WES is not generally applied to newborns, in critically ill infants it has shown a high rate of diagnosis of genetic disorders that have a direct effect on management and outcome (Saunders *et al.*, 2012; Willig *et al.*, 2015).

Genetic testing carried out at the population level is referred to as genetic screening. The term newborn screening refers to public health programs designed to screen newborns for various metabolic conditions that are treatable, but not clinically evident during the newborn period. These screening tests are based on blood levels of certain metabolites and the results are returned in a timely manner, so that medical or dietary treatment can be initiated promptly, before disease symptoms appear. Screening programs have been carried out for several decades in many countries with the goal of screening all infants born in a certain district or municipality (Goldberg & Sharp, 2012; Solomon *et al.*, 2012; Goldenberg *et al.*, 2014). While such screening could be expanded to include genetic tests for many more diseases, without effective treatment measures, this is of limited use.

The availability and significant decrease in sequencing costs has raised the question of whether metabolic newborn screening should be replaced by whole-genome sequencing (WGS) or WES. While the potential benefits of newborn genome sequencing are obvious, especially the potential to increase the

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number of identified disorders, the generalization of its practice raises a number of important ethical issues. These issues have raised public debate and have been discussed thoroughly in previous communications (see for example Berg *et al.*, 2011; Biesecker, 2012; Dondorp & de Wert, 2013; Botkin *et al.*, 2014; Burke & Dimmock, 2014; Feero, 2014; Beckmann, 2015). In this short article I argue that there are medical, psychological, ethical and economic reasons why widespread dissemination of this practice in newborn screening is still premature.

Medical and technical considerations – is there such a thing as too much information?

Next generation sequencing (NGS) encompasses several technologies of rapid, high yield, parallel DNA sequencing. It is currently used to sequence large gene panels for specific groups of disorders (such as epilepsy, cancer, cardiomyopathies, etc.), the whole exome or the entire genome (WGS). WES examines only a small part of the genome with high coverage of the coding regions but is superior to WGS in finding DNA changes of known and important clinical significance. Because WES requires capture and enrichment of the exome, it may fail to capture certain exons and thus has the potential for false negative results in coding regions (i.e. an individual, who is found not to carry a mutation for a particular disorder may develop the disease in the future and transmit it to his children). WGS has an important advantage over WES. While it also covers the exome, it identifies not only variations in the coding regions but also sequence changes in non-coding regions that may modify gene expression, thus increasing the likelihood of establishing a genetic diagnosis. In both sequencing approaches, however, differentiating disease-related mutations from variations of unknown clinical significance is a major problem, even in the known coding regions of genes. In WGS this represents an even greater challenge in the non-coding parts of the genome where function is not yet clearly defined for many sequences. Thus, the clinical significance of thousands of genomic and exomic variants detected by NGS cannot presently be interpreted with complete certainty, preventing evidence-based decisions being made to guide treatment and clinical surveillance (Green *et al.*, 2013; Koboldt *et al.*, 2013; Dewey *et al.*, 2014; Johansen Taber *et al.*, 2014; Landau *et al.*, 2014; Yang *et al.*, 2014). If we also consider complex disorders that are caused by a combination of multiple genetic variations, each increasing disease risk only slightly, then the picture is even more complex. Hence, when parents can get infant screening results that suggest, for example, a 10% increase in the chance of being diagnosed with a certain disease, such as autism or Alzheimer's disease, then the question is what will be the psychological, economic and overarching ethical consequences of this non-actionable information. Thus, the question remains in the clinical genetic testing arena, how much information is too much information? For the parents? For the children? For the genetic professional?

Psychological outcomes

Difficult questions may confront families and genetic professionals involved in newborn genetic screening. For each newborn baby, NGS could detect genetic variations in genes encoding high-penetrant, adult-onset disorders. These include cancer (e.g. breast, ovarian and colon), neurological disorders (e.g. CADASIL syndrome), connective tissue (e.g. Marfan syndrome), arrhythmias and many others. The potential ethical and practical problems of dealing with this knowledge will need to be very seriously considered. Since the parents have the ethical and legal authority to make medical decisions on behalf of their newborn, they are expected to make decisions that are in the best interests of their children. Testing newborns for late-onset genetic diseases denies newborns the option of deciding about testing later in life, thus denying them future adult autonomy and confidentiality. Other potential harms caused by newborn genetic testing include damage to the child's self-esteem, and potential difficulties in their future ability to form relationships. There may also be associated mental health issues for parents who receive the information of their newborn being a carrier of a serious, untreatable disease. Increased knowledge is not an absolute good: denial may be a coping mechanism; parents may feel guilty for passing on harmful mutations to their children or stigmatized as having the potential to do so. Moreover, as future treatment may be available, perhaps lack of knowledge is a better option than fear and depression for individuals and their families in the present. Finally, as the child or their parents may be required to disclose this information in various circumstances, it may cause discrimination against the child in several circles of life including education, employment and medical insurance (Tarini & Goldenberg, 2012; Wade *et al.*, 2013; Frebourg, 2014).

Ethical outcomes

An ethical consideration is what life is best worth living. Do we support genetic determinism in which all information is present at the beginning with a clear path and destiny and no ultimate freedom of choice? Supporters of this doctrine claim that we could use this knowledge to study and find new cures for the anticipated diseases and rather be "architects" that restructure the genetic make-up instead of victims with no autonomous choice. However, if parents adhere

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to the idea of genetic determinism and believe that their child's life is simply the mechanical and unchangeable combination of forces beyond their control, then how does this affect their relationship to the world and other people? Does adherence to determinism not lead them into a sense of meaninglessness and helplessness regarding their child's fate and actions? Thus, in choosing NGS newborn screening and administering this test early on, we will be breaking the commitment to free choice (Chadwick, 2011; Rosoff, 2012; Botkin *et al.*, 2014; Gannet, 2014).

Economic considerations

Compared to the typical short turnaround time of metabolic screening (a few days), the time for receiving results of WES and WGS can be weeks. In order to establish a timely diagnosis and to initiate treatment, the turnaround time of WES and WGS would have to be substantially reduced. A major challenge would be the bioinformatics required for analyzing the huge amount of data generated, especially when dealing with rare or novel genetic changes. Even if we focus only on known disease-related genes, the expected number of variants with incomplete knowledge regarding their clinical significance that would be detected carries a major interpretive challenge.

Presently, the cost of genomic sequencing is much too high for application to newborn screening but is rapidly decreasing and, in the near future, may approach the price at which it could be used for newborn screening. It should be noted, however, that the added costs of clinical interpretation and validation of sequencing results are probably higher than the generation of the sequencing data. These costs should also be lowered, allowing genomic screening to become more affordable. Additional family testing and follow-up that would likely be required, at least in some cases, could add substantial additional costs to the already high cost of NGS (Sboner *et al.*, 2011; Beckmann 2015).

The cost of delivery of this sensitive information to the newborn's parents, pre- and post-testing, is also a major factor in the decision to implement NGS screening to newborns. A pre-testing consultation will have to be completed during pregnancy. Sessions should discuss the expectations of parents from their newborn's genomic analyses, what information they would like to be disclosed, explanation of the meaning and significance of the screening results and at the same time ensuring that they understand it. When returning sequencing results, the genetic counsellors must give individualized attention to each clinical situation and to each family. They have to be familiar with the pre-test expectations of the parents and accordingly to counsel them based on the screening results. Not all variants present on a newborn genome are clinically relevant, and decisions have to be made as to what information to communicate, and to what extent, and how much time will be required to communicate this information to the parents. In addition, there will need to be a mechanism to provide social, emotional and clinical support for families receiving difficult news. With this in mind, proper counselling of the parents will be a lengthy, difficult and expensive process as many more genetic personnel will have to be recruited for this purpose alone (Ormond *et al.*, 2010; Feero, 2013).

To summarize, while availability and costs have made NGS a potential attractive mode of screening, its implementation as a general medical practice for newborn screening is still premature. We are not ready for instituting population-based newborn screening because adequate detection rates are compromised by the heterogeneity of DNA changes found and the clinical course of the disease remains difficult to predict in many cases. We have to make sure, beyond all doubt, that knowledge of the screening results will benefit the newborns and is free of potential harmful consequences later in life or of detrimental impacts on child–parent–society relationships.

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Declaration of Interest

None.

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