Whole-genome sequencing in critically ill infants and emerging ethical challenges

Several of the authors of Laurel Willig and colleagues’ report1 in The Lancet Respiratory Medicine have previously described their concerns that the use of whole-genome sequencing and other next-generation sequencing in clinical care could give rise to various novel ethical challenges, but that “the ethical issues that arise from new uses of new technologies...cannot be understood until the technologies are deployed in the real world.” Other authors, myself included, have put forward perspectives on the potential ethical challenges that could arise with implementation of whole-genome sequencing.3 With the findings described by Willig and colleagues, several of these potential ethical challenges of applying whole-genome
sequencing in clinical care, particularly the care of critically ill infants, are beginning to emerge.

In their compelling report, Willig and colleagues describe that a rapid whole-genome sequencing technique and service (STATseq) can be effectively used to alter the care of selected critically ill neonates and infants. Whole-genome sequencing has previously been piloted in critically ill infants because more than 20% of deaths in infants are caused by chromosomal abnormalities, congenital malformations, deformations, and genetic diseases; many of the 3528 monogenic diseases of known cause are present during the first 28 days of life; and neonatal intensive care units (NICUs) are thought to be suitable for early adoption of genomic medicine because extraordinary interventional efforts are customary and innovation is encouraged. Whole-genome sequencing has been used to search for diagnoses in critically ill infants with suspected neurodevelopmental disorders, dystonia, and congenital cardiac disease. Proof-of-concept of the usefulness of whole-genome sequencing to diagnose suspected genetic disease has already been shown in the acute care setting of the NICU and, together with the findings from Willig and colleagues’ study, suggest that whole-genome sequencing is no longer a theoretical care choice. Infants in acute care and the NICU environment are in need of the diagnostic methods provided by the introduction of genomic medicine because “rapid diagnosis is critical for timely delivery of interventions” and also because diagnosis can avoid futile intensive care. Thus, genomics is potentially highly relevant for critically ill neonates and infants.

However, the whole-genome sequencing technology is novel. Whole-genome sequencing is intended to be predictive of the short-term and long-term functioning of an entire genome, as opposed to older genetic and genomic testing that examined single genes or gene clusters, and ethical considerations affect all steps in the implementation of a whole-genome sequencing programme including test design, patient selection, consent, sequencing analysis of patient DNA and delivery of results to the patient and family. How to best select patients and provide appropriate whole-genome sequencing services to them still needs to be defined. Willig and colleagues chose to assess parent–child trios for children suspected by their clinicians to have monogenic disorders of an unknown genetic cause; children with signs and symptoms suggesting an elusive underlying genetic cause and whose clinicians were beginning to pursue a diagnostic odyssey. The patients were nominated by their treating clinicians and the nomination for study was reviewed before the research team decided to apply whole-genome sequencing in the patient (that a selection bias might account for some of the benefits with whole-genome sequencing in this study is noted by the investigators in their discussion). Interestingly, only half the nominated families enrolled in the study and Willig and colleagues cited parental refusal as a major reason. Parental perceptions of whole-genome sequencing and genomics in general, since analysis of parent–child trios involves the parents or families as study subjects, might need to be more carefully investigated as whole-genome sequencing is used in clinical care.

Additionally, use of whole-genome sequencing increases the focus on previously identified ethical and social issues surrounding the return of results, particularly the return of so-called incidental findings. Willig and colleagues reported no incidental findings but by identifying all variants in a genome, it is no longer a question of whether incidental findings or clinically useful results will be found, but rather how many such results will be identified. What to do with these findings is a challenge that still needs to be addressed.
Efficacy endpoints for idiopathic pulmonary fibrosis trials

Despite groundbreaking advances in the development of treatments for idiopathic pulmonary fibrosis, many questions remain unanswered—eg, what causes this deadly disease and what represents a clinically meaningful benefit for patients? Since idiopathic pulmonary fibrosis is a progressive and ultimately fatal disorder, with survival worse than many types of cancer,\(^1\) translating meaningful benefit into prolonged survival seems obvious. However, international debate on the benefits and drawbacks of using mortality as the primary efficacy endpoint in clinical trials in idiopathic pulmonary fibrosis has been active and sometimes heated.\(^2\)–\(^4\)

The feasibility of mortality trials in patients with idiopathic pulmonary fibrosis (or, at least, in early or intermediate stages of the disease) has been challenged by analyses of large clinical trials.\(^5\) Yet, this discussion seemed anachronistic on Oct 15, 2014, when two drugs—nintedanib and pirfenidone—were approved simultaneously by the US Food and Drug Administration (FDA) for treatment of idiopathic pulmonary fibrosis.

The FDA’s decision was based on the effect of these drugs on lung function, measured as a decline in forced vital capacity (FVC), making reduction in mortality seem redundant as an endpoint, at least with respect to drug approval. However, the FDA looked at the mortality data very carefully.\(^4\) In all the trials that assessed the two approved drugs, mortality was a secondary endpoint: although none of the individual studies was powered to show a significant reduction in mortality, for both drugs, a non-significant improvement in survival was seen. These results lend support to the intuitive idea that, in a disease such as idiopathic pulmonary fibrosis that is restricted to the lungs, preserving lung function would ultimately translate into a survival benefit. However, the threshold for a clinically meaningful decline in FVC

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