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Rapid whole genome sequencing and precision neonatology

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ARTICLE INFO

Keywords:
Genomics
Neonatology
Genetic testing
Precision Medicine
Genetic diagnosis

ABSTRACT

Traditionally, genetic testing has been too slow or perceived to be impractical to initial management of the critically ill neonate. Technological advances have led to the ability to sequence and interpret the entire genome of a neonate in as little as 26 h. As the cost and speed of testing decreases, the utility of whole genome sequencing (WGS) of neonates for acute and latent genetic illness increases. Analyzing the entire genome allows for concomitant evaluation of the currently identified 5588 single gene diseases. When applied to a select population of ill infants in a level IV neonatal intensive care unit, WGS yielded a diagnosis of a causative genetic disease in 57% of patients. These diagnoses may lead to clinical management changes ranging from transition to palliative care for uniformly lethal conditions for alteration or initiation of medical or surgical therapy to improve outcomes in others. Thus, institution of 2-day WGS at time of acute presentation opens the possibility of early implementation of precision medicine. This implementation may create opportunities for early interventional, frequently novel or off-label therapies that may alter disease trajectory in infants with what would otherwise be fatal disease. Widespread deployment of rapid WGS and precision medicine will raise ethical issues pertaining to interpretation of variants of unknown significance, discovery of incidental findings related to adult onset conditions and carrier status, and implementation of medical therapies for which little is known in terms of risks and benefits. Despite these challenges, precision neonatology has significant potential both to decrease infant mortality related to genetic diseases with onset in newborns and to facilitate parental decision making regarding transition to palliative care.

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http://dx.doi.org/10.1053/j.semperi.2015.09.009
0146-0005/

Introduction

The completion of the first composite human genome sequence in April, 2003 marked the dawn of the promise of precision medicine—a new approach to medicine wherein diagnosis, treatment, and risk factor modification would be informed by an individual's unique genetic make-up. While mature models of precision medicine remain to be defined, changes in the speed and cost of whole genome sequencing (WGS) are bringing the details of initial applications into focus. NIH Director, Francis Collins, foresees a society in which every baby will have access to their sequenced genome in order to modify their strategies for disease prevention, detection and treatment.[1] In the 2015 State of the Union Address, President Barack Obama announced the creation of a precision medicine initiative, ultimately to provide each individual with personalized information to drive expedient diagnoses and individualized, more effective treatments. The transformation of healthcare through the use of personal WGS information has already begun in Neonatal Intensive Care Units (NICUs). Since 2011, neonatologists at our institution have, through research protocols, used research-based rapid WGS in acutely ill infants and their parents to diagnose the underlying genetic cause of the neonates' conditions.[2–4] Furthermore, in a research setting, it is now possible to sequence human genomes at a cost of less than $1000 per individual. At this early stage in its evolution, we review the premise, practicality, and potential of rapid WGS for neonatal precision medicine.

Monogenic diseases: neonatal impact and incidence

Monogenic diseases are conditions causally related to genomic change(s), or variant(s), in a single gene. This collection of diseases is currently most amenable to diagnosis through WGS because the causative variants frequently involve one or a few contiguous DNA nucleotides in one or a handful of genes. These variants interfere with the efficient functioning of a gene product through disruption of transcription, translation, protein modification, complex assembly, or function. They may be inherited from a parent or occur *de novo* as a mutation in the germ cell of one of the parents. It is estimated that each individual's germline genome harbors about 74 *de novo* single nucleotide variants.[5–7] When these *de novo* variants are associated with dominantly expressed phenotypes, they tend to present in the newborn period because they are often more deleterious than inherited variants due to the absence of evolutionary selection.[8,9]

As a proportion of overall disease burden, monogenic diseases decrease in importance with age, and their impact is highest in fetal, perinatal, and neonatal care, respectively. The incidence of each individual monogenic disease is rare, but *in toto*, they are common. It is estimated that 60 million people in the United States and Europe have rare genetic diseases, of which 75% are children. Of these 45 million children, an estimated 30% will die before the age of 5 years.[10] Genetic diseases and birth defects are the leading cause of infant death in the United States with many of these being monogenic.[11] While the proportion of newborns admitted to the NICU with genetic disorders is unknown, 76% of NICU patients are admitted for reasons other than prematurity.[12,13] A 1991 study from Scotland determined, in a cohort of 821 consecutive admissions to the NICU, that 5.7% of the admissions were for chromosomal or monogenic disorders.[14] This is likely a considerable underestimate given lack of NGS at that time. Infants with recognizable genetic disorders have disproportionately longer hospitalizations and more frequent neonatal death.[15–20]

At present, newborns and infants with congenital malformations, syndromes, and inherited disorders typically undergo an extensive diagnostic process, with relatively low rates of etiologic diagnosis.[4] It is suspected that 3% of babies born in the US and Europe will have a major birth defect, with only 10–20% of these having an identifiable syndrome.[21] Acute management decisions are therefore typically made in the absence of a definitive diagnosis, which leads to delays in initiation of effectual treatments or to the use of empiric treatments that are ineffective, have adverse effects, or exacerbate symptoms. Thus, the timely return of definitive diagnoses of monogenic diseases during a NICU stay can potentially result in substantive changes in practice for neonatologists and consulting subspecialists.[4] In addition to having the potential to modify medical treatment in amenable cases, rapid genetic diagnosis allows for rational refocusing of care to diminish neonatal suffering and to support familial grieving in futile situations. These end-of-life decisions are common in neonatal genetic diseases, with most deaths resulting from withholding or withdrawing care.[22] Given the limitations to parental bonding and contact with the baby in the NICU setting, earlier holistic, end-of-life care decisions shifts focus from invasive medical management to the alleviation of suffering, allowing the family to bond, say "goodbye," baptize or give last rites, and facilitate the grieving process. Thus, early definitive diagnosis may actually increase neonatal (28 day) mortality in patients with genetic diseases, while having the potential to decrease infant (1 year) mortality.

Genetic diseases also have significant societal costs associated with profound emotional, financial, social, and physical stress within families.[23,24] The impact of newborn genetic diseases and birth defects on family structure is profound with studies identifying increased maternal depression and anxiety. The presence of maternal anxiety and depression are associated with childhood behavioral, developmental, and persistent health complications.[25] In a 1997 report, parental divorce occurred in 50% of families with a child with a genetic disease.[26] Rapid, precise diagnosis coupled with robust treatment and support teams may offset not just direct medical expense but larger familial and societal costs of genetic disease in infancy.

Rapid whole genome sequencing methods

While the specifics of rapid WGS will differ from institution to institution, we have reported on our 3 year experience of sequencing selected neonates and infants for diagnosis of