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Ending the Diagnostic Odyssey: Is whole genome sequencing the answer?

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When medical diagnoses are diffficult to achieve based on clinical information alone, a patient experiences a diagnostic odyssey and undergoes multiple clinical evaluations, imaging studies, and laboratory tests. The challenges brought on by the odyssey result in delayed or inaccurate clinical management. Shortening or ending the odyssey could have significant clinical, psychosocial and economic benefits.[1] Symptoms that may lead to diagnostic odysseys include seizures, respiratory failure, cardiac failure, hypotonia, hypoglycemia, and jaundice. Individuals with rare diseases are most often under age 5 years and undergo lengthy diagnostic odysseys; 80% of rare diseases are genetic related.

In August 2019, the bill, H.R. 4144, the "Ending the Diagnostic Odyssey Act was introduced."[2] The bill's aims include providing a more timely diagnosis for children who may have an underlying genetic disease, decreasing costs related to later diagnoses which result in avoidable testing and treatment, and providing psychological benefits from peace of mind.[2] Specifically, the bill would allow states to provide certain children under the Medicaid program with access to whole genome sequencing (WGS) clinical services, including analysis and interpretation. Eligible individuals would be those (1) under age 21 years who receive medical assistance under the State plan, and (2) who have been referred to or admitted to an intensive care unit, or have been seen by at least one medical specialist for a suspected genetic or undiagnosed disease, or is suspected by at least one medical specialist to have a neonatal or pediatric-onset genetic disease.[2] The proposal of this bill brings to light a few questions.

First, how would WGS reduce diagnostic odysseys?

Achieving medical diagnosis

Approximately 25–30 million people in the U.S. have one of the 7,000 rare diseases, which are responsible for 25% of pediatric hospitalizations and significant impact on the health care system. Traditional medical genetics diagnostic evaluations — in which medical geneticists choose laboratory testing based on phenotypic features — only reach a medical diagnosis in less than half of patients. The remaining 50% of the undiagnosed patients could

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potentially receive a diagnosis through WGS, and conducting WGS early could be beneficial.

Time until diagnosis

Time until diagnosis of rare diseases could be as long as 5 to 30 years through current standards of care.[1] Genomic tests early in life could shorten the time to medical diagnosis, curtailing the odyssey. WGS traditionally takes weeks to return results, which can delay needed treatment. However, a recent study by Kingsmore, et al. showed the possibility of returning WGS results in less than five days (ultra-rapid WGS),[3] making this method even more attractive for clinical practice.

Secondly, what is the appropriate test?

A few genetics-related tests are in question: WGS, whole exome sequencing (WES), and chromosomal microarray, which is also known as molecular karyotyping, and others. WES allows examination of the part of the human genome that encodes proteins, approximately 1%−1.5%, while WGS captures the entire genome. A meta-analysis[6] of 37 studies showed that the diagnostic utility (rate of causative, pathogenic, or likely pathogenic genotypes in known disease genes) and clinical utility (proportion in whom medical or surgical management was changed by diagnosis) of WGS and WES were greater than chromosomal microarray in children with suspected genetic diseases. Interestingly, the bill does not consider WES, which is less expensive than WGS by ~$500–1,000 per person in 2015;[4] additionally, some evidence suggests WES has a similar ability as WGS to achieve medical diagnosis,[3] while other studies suggest the likelihood of medical diagnosis of WGS is twice that of WES. Further research is needed to understand whether WGS or WES is more adequate to help with reducing diagnostic odysseys. Current studies under the NIH-funded Newborn Sequencing in Genomic Medicine and Public Health (NSIGHT) consortium are investigating the clinical benefits of WGS in healthy newborns, and additional studies are needed to understand the benefits of testing symptomatic newborns and children.

Third, what would offering WGS as outlined in the bill entail?

While the cost of the first human genome sequence was around $2.7 billion, the cost of WGS decreased to $1,500-$2000 per person with interpretation (not including the costs of clinic visits, non-genetic laboratory tests, or procedures).[5]

Of the 3.8 million U.S. births in 2018, 350,000 (9.2%) newborns were admitted to the neonatal intensive care unit (NICU). Given 15% of NICU babies have an underlying genetic disorder,[3] ~22,000 newborns insured by Medicaid could be eligible for WGS. For these newborns, WGS would total around $33–44 million in the U.S per year for Medicaid. An additional 70 million children under age 18 years insured by Medicaid and individuals under age 21 years would be eligible for WGS as described in this bill. Thus, the total costs would be well more than $44 million. Studying the health and economic consequences of this bill would improve our understanding of the cost-effectiveness of WGS and could be extrapolated to evaluating other tests such as WES.

Fourth, what are the unintended consequences of WGS as outlined in this bill?

Diagnoses of children could lead to diagnoses of family members and thus bring additional benefits. Systematic reviews of psychological outcomes of single and multi-gene testing suggest test result disclosure does not cause depression or anxiety.[6] Further, a recent meta-analysis[6] of seven Clinical Sequencing Evidence-Generating Research (CSER) consortium studies across multiple clinical settings suggest no clinically significant psychological harms from the return of WES/WGS results when only clinically actionable results are disclosed.

The economic benefits of WGS are currently unclear. A systematic review[7] indicates limited evidence of economic benefits to support widespread use of WES/WGS in clinical practice. The cost of WGS may be less than it once was and WGS could lead to earlier medical diagnosis and treatment; WGS could also lead to increased health care expenditures without substantial clinical benefits. For example, inconclusive WGS results can lead to additional testing and follow up and its own costly diagnostic odyssey. Importantly, discovering variants of unknown significance could increase psychological harm or identify a diagnosis for which no treatment is available (yet). Nevertheless, determining which findings are clinically actionable is difficult and is the focus of the Precision Medicine Policy and Treatment (PreEMPT) Model (HD090019) which will simulate long-term clinical and economic outcomes of genomic sequencing in sick and healthy newborns. The CSER consortium is studying the use of genomic sequencing in medically underserved populations to improve our understanding of diagnostic odysseys in diverse populations.

The title of this bill is ambitious, as ending the diagnostic odyssey for all is unlikely. Even with WGS, around a quarter of patients with rare diseases still would not obtain a medical diagnosis. Currently, the economic benefits of WGS in adult or pediatric populations are unclear, although cost-effectiveness studies are ongoing and will help answer whether WGS in select populations makes sense from a societal perspective. The gold standard study, a randomized clinical trial, could address the question of whether this bill should be passed, but the large study population and timeframe needed are likely impractical for the pace of politics. Simulation studies and quasi-experimental evaluations of the impacts of such a bill, if passed, could provide valuable information. Regardless of whether the bill passes, its introduction shows that genomic medicine is significantly changing clinical practice and patient care.

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