Washington State Health Care Authority

Final Key Questions and Background

Whole Genome Sequencing

November 15, 2023

Background

There are approximately 7,000 rare disorders that affect 6% to 8% of the US population[1], a substantial portion of which have genetic origin. In addition to the clinical burden associated with these illnesses, patients and families often experience delays in diagnosis and encounter diagnostic odysseys that can introduce delays in diagnosis, substantial psychosocial costs and potentially preventable use of health care resources.[2-5]

Whole genome sequencing (WGS; also called genome sequencing or full genome sequencing) is a laboratory procedure for determining an organism's entire DNA sequence in one procedure. In contrast to whole exome sequencing, which identifies only the exome – the 1%-2% of the genome that code for proteins – genome sequencing focuses on nearly all of the genome.

In the context of genetic disease diagnosis, WGS could potentially avoid or shorten diagnostic odysseys, speed the time to appropriate intervention, guide disease management, and alleviate and patient and family burden. Use of whole genome sequencing could aid in diagnosing a wide array of genetic diseases. However, questions remain about the clinical utility of genome sequencing compared to WES or traditional approaches. Evidence about the clinical utility of WGS in providing accurate diagnosis that guides clinical management and improve patient outcomes could guide assessments of appropriate use of WGS in clinical settings.[5] However, any benefits must be weighed against its potential harms and costs.

The purpose of this health technology assessment (HTA) on the efficacy, safety, and cost-effectiveness of the clinical use of whole genome sequencing (WGS) for diagnosis of suspected genetic disorders.

Policy context

The State of Washington Health Care Authority selected WGS for a health technology assessment (HTA) because of high concerns for safety, medium concerns for efficacy, and high concerns for cost.

Scope of this HTA

The analytic framework (***Figure 1***), research questions, and key study selection criteria (***Table 1***) are listed in this section.

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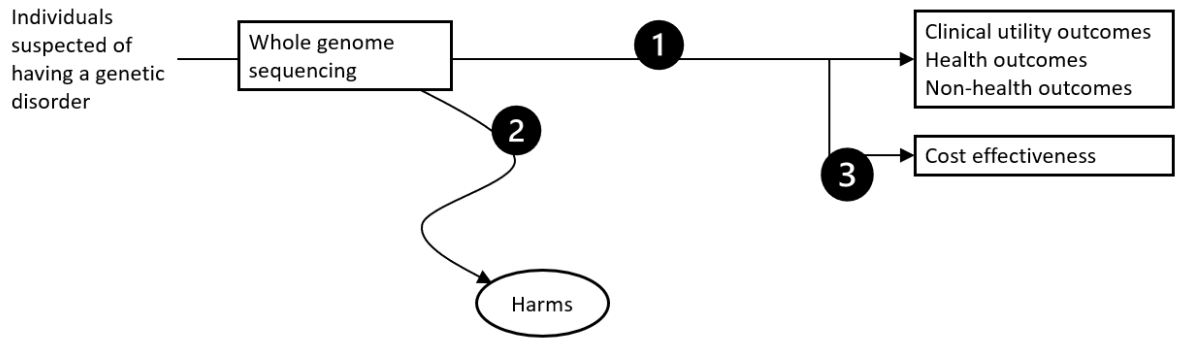
Figure 1. Analytic Framework Depicting Scope of this Health Technology Assessment



Research Questions

Efficacy Question 1. What is the efficacy of whole genome sequencing for use in diagnosing possible genetic disorders?

Safety Question 2. What are the harms associated with whole genome sequencing for use in diagnosing possible genetic disorders?

Cost Question 3. What is the cost-effectiveness of whole genome sequencing for use in diagnosing possible genetic disorders?

Study Selection Criteria

Table 1 provides the study selection criteria we will use to include studies in the HTA and are organized by population, intervention, comparator, outcomes, timing, setting, and study design (PICOTS) criteria.

Table 1. Proposed Population, Intervention, Comparator, Outcome, Timing, and Setting for Health Technology Assessment

Domain	Included	Excluded
Population	Children or adults, with or without a clinical diagnosis, suspected of genetic disorder	• Embryos and fetuses • Persons with nonsyndromic cancer or infections, where WGS is being used to characterize the tumor or microbe • Deceased persons • Healthy persons
Intervention	Diagnostic standard or rapid genome sequencing, alone or as part of a testing pathway including clinical, laboratory and imaging evaluation	• Single gene sequencing • Multi-gene panels • Mitochondrial sequencing • Genome-wide association studies • Exome sequencing • WGS for purposes other than diagnosis (e.g. pharmacogenetic; screening or risk

Domain	Included	Excluded
		assessment; characterization of tumors or infectious agents; research) • Long-read WGS
Comparator	Usual care (e.g. clinical, laboratory, or imaging evaluation; exome sequencing; single gene testing; and/or multigene panel testing; chromosomal microarray) Alternative test results in same participant, including reanalysis (diagnostic yield outcomes only) Single arm studies (harms outcomes only)	Literature-based outcome estimates (e.g. diagnostic yield from previously published papers)
Outcomes	Clinical utility: diagnostic yield for initial and/or subsequent reanalysis, including uncertain or secondary actionable findings; time to diagnosis; clinician referral and treatment selection or other changes in care; at-risk relative identification. Health: (mortality, survival, morbidity) Non-health: (e.g., personal utility; psychosocial outcomes; patient experience related to diagnostic odyssey) measured with a validated scale where possible. Cost: Cost-effectiveness Harms: any clinical utility, health, or non-health outcome or other findings that suggest harm (e.g., psychosocial distress; false negative or false positive results)	• Health outcomes related to secondary findings • Hypothetical patient, family, or provider preferences • Non-U.S. costs
Setting	Any outpatient setting in countries categorized as 'very high'[a] on the UN Human Development Index 2021	Inpatient hospital settings[a] Non-clinical settings Countries categorized as other than 'very high'[b] on the UN Human Development Index 2021
Study Design	Study designs • Randomized controlled trial; controlled clinical trial; comparative cohort studies (non-comparative studies for harm outcomes only) • Cost utility analysis, cost-effectiveness analysis performed from societal or payor perspective	• Editorials, commentaries, narrative reviews, or letters; conference abstracts; case reports or case series; case-control studies; other observational study designs with comparator group specified • Relevant systematic reviews and meta-analyses will be excluded but may be hand searched to identify potentially eligible studies. • Qualitative studies
Language and Time Period	• English • 2013 or later	• Any language other than English

Abbreviations: WGS=whole genome sequencing; UN=United Nations; US = United States
Notes: [a] Studies that take place in inpatient hospital settings, such as intensive care units, are excluded. Though rapid genome sequencing may be used in these settings, this use is not within the scope of this HTA. This is because such testing would be part of the care and services attributed to billing codes covering inpatient care.
[b] Countries identified as very high with the 2021 UN Human Development Index: Andorra, Argentina, Australia, Austria, Bahamas, Bahrain, Belarus, Belgium, Brunei, Canada, Chile, Costa Rica, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Georgia, Germany, Greece, Hong Kong China (SAR), Hungary, Iceland, Ireland, Israel, Italy, Japan, Kazakhstan, Kuwait, Latvia, Liechtenstein, Lithuania, Luxembourg, Malaysia, Malta, Mauritius, Montenegro, Netherlands, New Zealand, Norway, Oman, Panama, Poland, Portugal, Qatar, Romania, Russian Federation, San Marino, Saudi Arabia, Serbia, Singapore, Slovakia, Slovenia, South Korea, Spain, Sweden, Switzerland, Taiwan, Thailand, Trinidad And Tobago, Turkey, United Arab Emirates, United Kingdom, United States, Uruguay.

References

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5. Wu AC, McMahon P, Lu C. Ending the diagnostic odyssey-is whole-genome sequencing the answer? *JAMA Pediatr*. 2020 Sep 1;174(9):821-2. doi: 10.1001/jamapediatrics.2020.1522. PMID: 32597967.