Washington State Health Care Authority

Whole Genome Sequencing

Draft key questions: public comment and response

November 15, 2023

Health Technology Assessment Program (HTA)

Washington State Health Care Authority

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The information in this document is intended to help the Washington HCA make well-informed coverage determinations and thereby improve the quality of health care services. This document is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this document in the same way as any medical reference and in conjunction with all other pertinent information (i.e., in the context of available resources and circumstances presented by individual patients).

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Public Comments Submitted

The State of Washington's Health Technology Assessment Program posted for public comment the draft key questions and proposed scope for a health technology assessment (HTA) on the topic of "Whole Genome Sequencing" between October 18 and 31, 2023. **Table 1** lists the comments received and submitting organization.

Table 1. Number of Comments Received on Draft Key Questions on Whole Genome Sequencing

Comment Number	Organization	Location
1	Pickhandle Consulting on behalf of Seattle Children's	Seattle, WA
2	Northwest Rare Disease Coalition	Seattle, WA

Summary of Comments and Response

The comments provided did not suggest any changes to the key questions or scope of the review. The comments are summarized in **Table 2**.

Table 2. Summary of Comments Received on Draft Key Questions on Whole Genome Sequencing

Comment Number	Summary of comment	Response
1	Suggested revising key questions as follows: 1. *Efficacy Question:* What is the efficacy of whole genome sequencing for use in diagnosing <u>and managing possible genetic disorders compared to current covered benefits</u>? 2. *Safety Question:* What are the harms associated with whole genome sequencing for use in diagnosing <u>and managing possible genetic disorders compared to current covered benefits</u>? 3. *Cost Question:* What is the cost-effectiveness of whole genome sequencing for use in diagnosing <u>and managing possible genetic disorders compared to current covered benefits</u>? In addition, consider the potential harms of *not* providing access to whole genome sequencing for us in the diagnosis of possible genetic disorders.	The management of detected genetic disorders is addressed as an outcome of interest. Covered benefits would be in scope for the review if the included studies addressed this. We have not made changes to the text based on this suggestion. The potential harms of NOT providing access to WGS can be inferred from the efficacy KQ and a separate research question is not required.

1	Study Selection Criteria: *Comparator:* Modify inclusion language to include chromosomal microarray, which is missing from the list of existing testing technologies utilized in usual care.	We have added chromosomal microarray to the list of eligible comparator tests.
1	*Outcome:* Modify inclusion language to include "Change in planned procedures or surveillance; withdrawal of care/initiation of palliative care; surveillance of later-onset comorbidities; Reducing diagnostic uncertainty". In addition, modify the inclusion language under Cost to include, "Cost per diagnosis; cost per additional diagnosis." We also recommend including (rather than excluding), "Health outcomes related to secondary findings".	We have changed the text to include other changes in care. The text now reads: 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. Cost per diagnosis and cost per additional diagnosis is out of scope of this review because of the rapidly changing costs of genome sequencing. We have not changed the text based on this comment. Health outcomes related to secondary findings are out of scope for feasibility reasons. We have not changed the text based on this comment.
1	*Setting:* Table listed "inpatient" in both the include and exclude columns. Suggested including inpatient settings, since rapid whole genome sequencing is an included intervention. Also, recommended including countries beyond those that are 'very high' on the UN HDI, as this would exclude all of Africa and China and raise concerns in the context of rare diseases.	We have updated the draft inclusion table to remove "inpatient" from included settings. 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. Countries other than "very high" on the UN HDI are out of scope because of potential differences in health care systems and standards of medical care that reduce the generalizability of findings to a US context.
1	*Study Design:* Include systematic evidence reviews, meta-analyses, and guidelines. Rare diseases are collectively common, but individually rare, making randomized-control trials challenging in this space. Include prospective and retrospective cohort studies and single arm observational cohort studies (these types of studies were included in the 2019 whole exome sequencing technology assessment).	We will review relevant systematic reviews and meta-analyses to identify potentially eligible studies. Single arm observational studies are included for the harms question only.
2	Efficacy Question 1: Shared a 2023 meta-analysis and 2019 literature review documenting efficacy of WGS. 1. Chung et al. Meta-analysis of the diagnostic and clinical utility of exome and genome sequencing in pediatric and adult patients with rare diseases across diverse populations. Genet Med 25, 100896 (2023) https://linkinghub.elsevier.com/retrieve/pii/S1098-3600(23)00909-7. Shickh, S., Mighton, C., Uleryk, E. et al. The clinical utility of exome and genome sequencing across clinical indications: a systematic review. Hum	Thank you for sharing this information. We will review the cited references for eligible studies.

	Genet 140, 1403–1416 (2021). https://doi.org/10.1007/s00439-021-02331-x	
2	Safety Question 2: Provided evidence documenting lower rates of inconclusive results from exome and genome sequencing compared to multigene panels. Also, recommended patients and families have access to genetic counselors to support pre-and post-test counseling, including results support. 1. Rehm et al; Medical Genome Initiative Steering Committee. The landscape of reported VUS in multi-gene panel and genomic testing: Time for a change. Genet Med. 2023 Jul 30;25(12):100947. doi: 10.1016/j.gim.2023.100947. Epub ahead of print. PMID: 37534744. Cost Question 3: Noted costs of whole genome sequencing have been declining steadily and shared evidence documenting costs of rare disease diagnosis. Recommended considering outcomes from Project Baby Bear.	Thank you for sharing this information. We will review the cited references for eligible studies.

From: [redacted]
To: HCA ST Health Tech Assessment Prog
Cc: [redacted]
Subject: Whole Genome Sequencing - NW RARE DISEASE COALITION Comments.
Date: Wednesday, November 1, 2023 11:49:11 AM
Attachments: image001.png
10-31-2023 HCA Tech Assesment WGS - NW Rare Disease Coalition.pdf

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External Email

Happy November.

Please see the attached comments from the NW Rare Disease Coalition on the Health Technology Assessment of Whole Genome Sequencing.

If you have any questions, please let me know. Have a great day!

R

Rose Feliciano
[redacted]

November 1, 2023

Dear Health Care Authority Leadership,

The Northwest Rare Disease Coalition is pleased to see that the topic of whole genome sequencing (WGS) is under review by the Washington Health Technology Assessment program. We write to you today in support of the WGS petition on behalf of Washington's rare disease patients, caregivers and health care specialists and community of advocates.

Northwest Rare Disease Coalition (Coalition) supports the review of WGS by the Health Technology Assessment program because we believe it will meet the criteria of determining the safety, efficacy, and cost-effectiveness of the technology, as set out in RCW 70.14.110 (2) (a). We respectfully submit our responses to the questions you have asked.

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

There is strong and extensive evidence to support the efficacy of WGS testing in diagnosing possible genetic disorders. In a 2023 meta-analysis of 161 studies on the diagnostic utility of WGS in pediatric and adult patients with rare diseases across diverse populations[1] the efficacy ranged as high as 72%. Furthermore, a 2019 literature review of the clinical utility, or the potential for improving a patient's clinical outcome of WGS, was found to be more effective than standard genetic tests[2].

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

WGS is considered a non-invasive test. While specific techniques vary, it is typically performed using a blood draw of 8ml (adults) or 2-4ml (children). While there are risks associated with any procedure, we would argue the risk for WGS is not making it available to patients.

Approximately 1 in 10 Americans, an estimated 30 million individuals, are affected by rare disease. In Washington state alone, over 750,000 people have rare diseases. Further, it is estimated that 80% of rare

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[1] Chung et al. Meta-analysis of the diagnostic and clinical utility of exome and genome sequencing in pediatric and adult patients with rare diseases across diverse populations. *Genet Med* 25, 100896 (2023) https://linkinghub.elsevier.com/retrieve/pii/S1098-3600(23)00909-7.

[2] Shickh, S., Mighton, C., Uleryk, E. *et al.* The clinical utility of exome and genome sequencing across clinical indications: a systematic review. *Hum Genet* **140**, 1403–1416 (2021). https://doi.org/10.1007/s00439-021-02331-x

diseases have identified genetic origins. The diagnostic odyssey for many patients takes years, during which they receive a variety of treatments to address symptoms but not their diagnosed disease.

Potential harm associated with WGS due to uncertain results (variants of uncertain significance) has been postulated. However, Rehm et al recently found[3] lower rate of inconclusive results from exome and genome sequencing compared to multigene panels. Further, we recommend that patients and families have access to genetic counselors to support pre-and post-test counseling, including results support.

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

The cost of WGS has declined steadily over the years, from $10,000 in 2008 to around $400-600 today, with many companies working toward a goal of lowering that cost further to $100 per genome.

While studies differ, it takes an average of 5-7 years and consultation of more than 8 specialists for a rare disease patient to receive an accurate diagnosis, an odyssey that is typically accompanied by $19K in diagnostic testing and significant additional healthcare cost for the patient, their families, and the healthcare system.

Early diagnosis can be a game changer for patients, their family and health care providers. As mentioned above, without a proper diagnosis patients receive a variety of treatments which do not address their true problem. These treatments can include prescriptions or surgeries which do not improve the patient's overall health. WGS reduces the diagnostic odyssey, which results in appropriate treatment.

The diagnostic odyssey spans from the time a patient first experiences rare disease symptoms to the time that a final, accurate diagnosis is made. The average rare disease patient will also experience 2-3 misdiagnoses along the way. The Coalition believes that the use of WGS will result in reduced healthcare costs by allowing patients to address the underlying disease instead of managing symptoms. Knowing what a diagnosis is quickly can make a significant difference in the short- and long-term health of a patient. Having this knowledge can result in not having unnecessary surgery, or receiving the proper medication or better understanding what treatment options are available to a patient. A proper diagnosis also empowers patients and families to learn and understand what their treatment options are.

Also, consider a study by Genetics in Medicine[4] that revealed single-year US spending on rare diseases totaled $880 billion while spending on all other diseases totaled $768 billion. Though rare disease patients represent approximately 10% of the population, the economic burden of rare diseases on our healthcare system is nearly equal to the economic burden of all other common conditions. Patients and families bear the brunt of these expenses out-of-pocket as finding the pathway to correct diagnosis and

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[3] Rehm et al; Medical Genome Initiative Steering Committee. The landscape of reported VUS in multi-gene panel and genomic testing: Time for a change. Genet Med. 2023 Jul 30;25(12):100947. doi: 10.1016/j.gim.2023.100947. Epub ahead of print. PMID: 37534744.

[4] Navarrete-Opazo, A.A., Singh, M., Tisdale, A. *et al.* Can you hear us now? The impact of health-care utilization by rare disease patients in the United States. *Genet Med* **23**, 2194–2201 (2021). https://doi.org/10.1038/s41436-021-01241-7

eventual treatment is lengthy and expensive for all parties. Misdiagnosis, incorrect treatments, and other preventable issues stem from a lack of access to WGS for rare disease patients.

The Coalition recommends you consider the outcomes of Project Baby Bear, a $2 million project launched in California in 2018, provided rapid whole-genome sequencing to critically ill newborns. Rapid analysis has an average turnaround time of less than 14 days, and typically less than 7 days. Final reporting on the project reflected a diagnostic yield of 43%, and ultimately resulted in a change in management for 72% of the patients who were diagnosed using rapid WGS technologies. Rapid WGS results were also delivered in 3 days on average, meaning that adequate care adjustments were made quickly and with accuracy. For those seeking a first-time diagnosis or for an end to a patient's diagnostic odyssey, WGS is a proven solution.

For these reasons, the Coalition recommends the Health Technology Assessment program support Whole Genome Sequencing. We believe it is safe, it has proven efficacy, and it is cost-effective. WGS has been a true game changer for many patients and their families in providing a quick diagnosis.

The Coalition would also recommend, in addition to WGS testing, patients and families should have access to genetic counselors. Genetic counselors are a critical support for patients and families navigating the complicated world of rare diseases and help with appropriate test selection and coordination, results interpretation and guidance for potential treatment options.

We appreciate your consideration and are available to answer any questions you may have.

Sincerely,

Northwest Rare Disease Coalition Founders

Carolina Sommer Joshua Henderson Max Brown

From: [redacted]
To: HCA ST Health Tech Assessment Prog
Cc: [redacted]
Subject: Feedback on draft key questions and study selection criteria for WGS
Date: Tuesday, October 31, 2023 2:14:11 PM
Attachments: image001.png

External Email

To Whom it May Concern:

On behalf of Dr. Michael Astion (Medical Director, Department of Laboratories, Seattle Children's) and Dr. Jane Dickerson (Director, Laboratory Stewardship Program, Seattle Children's), we would like to share the following feedback with the WA HTA program regarding the draft key questions for whole genome sequencing to consider as part of your review.

Research Questions: We suggest a slight modification to the questions to improve specificity and scope of the review. The WA HCA currently provides coverage for exome sequencing and chromosomal microarray, both of which are used in diagnosing possible genetic disorders. Coverage for whole genome sequencing should be considered in the context of existing standards of care, including current covered benefits. In addition, the impact of this technology supports not only diagnosis but also impacts management considerations. We suggest revising the questions as follows:

1. *Efficacy Question*: What is the efficacy of whole genome sequencing for use in diagnosing and managing possible genetic disorders compared to current covered benefits?
2. *Safety Question*: What are the harms associated with whole genome sequencing for use in diagnosing and managing possible genetic disorders compared to current covered benefits?
3. *Cost Question*: What is the cost-effectiveness of whole genome sequencing for use in diagnosing and managing possible genetic disorders compared to current covered benefits?

In addition, for the Safety question, consideration could be given to the potential harms or consequences of *not* providing access to whole genome sequencing for use in the diagnosis of possible genetic disorders.

Study Selection Criteria: In reviewing the study selection criteria (Table 1) that will be used to include studies in the HTA, we have additional feedback as follows:

- **Domain – Comparator**: Modify inclusion language to include chromosomal microarray, which is missing from the list of existing testing technologies utilized in usual care.
  *Usual care (including clinical, laboratory, or imaging evaluation; **chromosomal microarray**; exome sequencing; single gene testing; and/or multigene panel testing)*
- **Domain – Outcome:** Modify inclusion language under Clinical utility to include, "Change in planned procedures or surveillance; withdrawal of care/initiation of palliative care; surveillance of later-onset comorbidities; Reducing diagnostic uncertainty". In addition, modify the inclusion language under Cost to include, "cost per diagnosis; cost per additional diagnosis". We also recommend including (rather than excluding), "Health outcomes related to secondary findings".
- **Domain – Setting**: In the current table, the following details are listed in the Included column, "Any outpatient or inpatient clinical setting…", while "inpatient hospital settings" is listed within the Excluded column. Since rapid whole genome sequencing is included within the

Intervention domain to be reviewed with the assessment, we recommend that "inpatient hospital setting" be included as part of the Setting domain. The exclusion of Countries categorized as other than 'very high' on the UN Human Development Index 2021 raises concerns, particularly in the context of rare disease where numbers are small. Reviewing the map, this excludes all of Africa and would also exclude studies from China (but not "Hong Kong China"). When considering evidence assessments for genomic testing, a broader inclusion of studies from these countries is recommended.

- **Domain – Study Design**: Similar to the HTA process, which includes a systematic literature review, we encourage the analysis to consider review of systematic evidence reviews, meta-analyses, and guidelines. Rare diseases are collectively common, but individually rare, making randomized-control trials challenging in this space. It will be valuable to include both prospective and retrospective cohort studies, as well as single arm observational cohort studies (these types of studies were included in the 2019 whole exome sequencing technology assessment).

We look forward to providing additional review and feedback on this topic going forward. Please let us know if we can provide additional information or clarification.

Sincerely,

Jessie Conta

Jessie H. Conta, MS, CGC (she/her)
Licensed Genetic Counselor
Owner – Pickhandle Consulting LLC
[redacted]
[redacted]