Washington State Health Care Authority

# Whole Genome Sequencing

## Peer review and public comment on draft evidence report

May 16, 2024

Health Technology Assessment Program (HTA)

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This document was created in response to peer review and public comments on a Draft Health Technology Assessment (HTA) report prepared by the RTI-UNC Evidence-based Practice Center through a contract to RTI International from the State of Washington Health Care Authority (HCA). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of the State of Washington HCA and no statement in this document should be construed as an official position of the State of Washington HCA.

The information in the document is intended to help the State of Washington's independent Health Technology Clinical Committee make well-informed coverage determinations. This document and its associated Evidence Report are 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 and the associated Evidence Report 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).



## Acknowledgments

The following individuals contributed to the report associated with this document:

*Lead Investigator:* Leila Kahwati, MD, MPH
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The authors acknowledge the contributions of Nora Henrikson, PhD (Kaiser Permanente) to the scoping of this HTA and drafting of text in the introduction and assistance with early data collection and risk of bias assessment.

# Contents



**List of Tables**

# Peer Review Comments and Responses

Two independent, external peer reviewers were invited to provide comments on the Draft Evidence Report and were provided with an honorarium for their review. The peer reviewer's name, affiliations, and conflicts of interest are reported in ***Table 1***.

**Table 1. External Peer Reviewer of the Draft Evidence Report**

| Name | Title/Affiliation | Summary of Conflicts of Interest Reported |
|---|---|---|
| Carrie Blout Zawatsky, MS, CGC | Director of Research Development, Senior Genetic Counselor Genomes2People, Brigham and Women's Hospital and Harvard Medical School<br>Associate Director of Project Management, Precision Population Health, Ariadne Labs<br>Adjunct Associate Professor, MGH Institute of Health Professions | Published on studies including MedSeq, BabySeq and MilSeq; involved in research related to proactive genomic sequencing and testing |
| Beth A. Tarini, MD, MS, MBA | Associate Director, Center for Translational Research, Children's National Research Institute, Children's National Hospital<br>Associate Professor of Pediatrics (with Tenure), The George Washington University | Published multiple papers genetics and pediatric primary care |

The peer reviewers did not identify any missing studies and did not identify any studies that should have been excluded from the report. We addressed most of the comments submitted by the reviewers in the Final Evidence Report; though some comments or suggestions were outside the scope of the HTA and did not result in revisions to the report. The only substantive revision was that we added additional details of the analysis of diagnostic yield by phenotype, which were previously not included. This was added to substantiate our conclusions about variability in yield by phenotype. We considered other revisions made based on peer review comments as minor revisions. Specific peer review comments and responses are provided in ***Table 2***.

**Table 2. Peer Reviewer Comments on Draft Evidence Report and Response**

| Item | Comment | Response |
|---|---|---|
| **Introduction** | | |
| *Are there any additional issues you think we should cover in the introduction?* | **Reviewer 1:** This introduction has a very clear explanation of the current field.<br>It might be worth noting that even over the course of the paper review, since 2013, WGS technology has improved and can now in many cases detect variation such as copy number variants and short tandem repeats that could not technically be detected a few years ago. Therefore, these improvements may not be captured fully in the data included in the included papers and could impact the diagnostic yield.<br><br>It might also be worth noting in the background potential improvements to sequencing technology expected over time including Long read technology (reference 41), and the use of AI to increase efficiency, which will likely bring down cost. https://pubmed.ncbi.nlm.nih.gov/36939041/<br><br>In addition I would recommend the background address just how many "rare" disorders are expected to be genetic, ~4,000, and that many are treatable ~ 600-700 https://onlinelibrary.wiley.com/doi/10.1002/ajmg.c.31874<br><br>**Reviewer 2:** It is my understanding that most clinicians will turn to exome sequencing before they turn to WGS. The introduction could do more to flesh out the current steps in how these technologies are currently applied. There is a sense that WGS provides information on most of the genetic matter (vs WGE). However, it is my understanding that currently we are not able to leverage that additional data – and so many choose the WGE first. But again, that is my understanding; regardless – how WGS and WGE are differentially used in practice (if true) would be helpful. | We agree, and have added text related to this in the Discussion section.<br><br>We have added some text to the discussion about this.<br><br>This citation has been added to the introduction.<br><br>We have modified text to try to clarify the decisional dilemma regarding utility of WGS relative to WES. |
| *Do you see anything inaccurate, superfluous, or unclear?* | **Reviewer 1:** Everything looks accurate.<br><br>**Reviewer 2:** See # 1 | No response required. |
| *Any additional comments?* | **Reviewer 1:** No additional comments.<br><br>**Reviewer 2:** Is there any interest in explicitly identifying in what populations (children vs. adults, or both) that we expect WGS to be utilized? I have no opinion. I assumed that it was children; but that is an assumption. And so perhaps it would be good to explicitly clarify for the reader. | No response required.<br><br>This is clarified in the methods section; we did not limit the scope of the HTA by age. However, the HTCC could decide to include limits by age in their coverage decision. |
| **Methods** | | |

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| *Do you see any problems with our methods?* | **Reviewer 1:** There are a few considerations I have regarding methodology: 1) Only including papers with a comparator group 2) Not including more information on how phenotypes and methodology impact expected conclusions and 3) Excluding inpatients 4) Excluding cost effectiveness data to only the US<br><br>Though I understand the value of having a comparator group to determine incremental diagnostic yield, and I appreciate that having a comparator group, especially a RCT, is the gold standard, I worry that the pool of studies fully explored in this report is fairly small n= 35. The small n number of studies included is both due to the requirement of a comparator group and to the fact that inpatient studies were not considered in the main data. Though, I appreciate that the authors included ES 3.6 to attempt to address these issues. It might be worth expanding this section a bit more. This 2024 review for example, https://www.nature.com/articles/s41525-024-00396-x , which presents a literature review for a similar purpose, highlights 71 studies.<br><br>Comparator Group/ Testing Methodology/ Indication for Testing Feedback<br>I understand that one of the main conclusions by the authors is that there is not enough data; however, there may be additional data that could be captured if papers not including a comparator group were more thoroughly reviewed. In addition, just because there is a comparator group, this does not necessarily highlight a consistent conclusion, given the methodology that was compared varies widely (WES reanalysis, chromosomal microarray, multigene panel testing, single gene testing, karyotype, and Fragile X syndrome testing), as does the indication for testing (development delay, intellectual disability, autism spectrum disorder, epilepsy, or other neurological disorders). Unless this paper is about universal screening using genomic sequencing, which it is not, the indication for testing and the methodology of the test ordered as a result of the indication (the comparator test) is very relevant to the tests diagnostic yield and the resulting care and cost related to that result. This is briefly mentioned in section 3.3.1 and showcased when the authors review professional guidelines (section 4.3 and Table 6), which often recommend genomic sequencing for specific indications like: seizures, congenital anomalies, and developmental delays/intellectual disability. As a reader, I want to know more about the yield differences by phenotype other than, "we found that incremental diagnostic yield varied as much within a given phenotype as it did across phenotypes". I would expect genomic sequencing to yield a better diagnostic yield for some phenotypes than others, and I would expect certain testing methodologies to be better for specific indications than others. I think grouping all of this together could be confusing for a reader that is not versed in this nuance. | The decision dilemma at hand is whether WGS is more effective than current standard of care for genetic testng; thus, limiting the review to studies evaluating a comparator provides the most robust evidence for making this decision. Because this requirement does limit the pool of included studies, we also included a contextual question regarding diagnostic yield to report on other systematic reviews that did not limit to studies that required a comparator group.<br><br>Because the State of WA HCA already covers WGS testing for inpatients, such studies were excluded from the scope of this review to allow the HTCC to consider the evidence most relevant to a decision about coverage in other settings. The Wigby et al review mentioned by the commenter is aleady included in the Contextual question addressed in section 3.6 (See Table 4 and Figure 10).<br><br>We reported the data on diagnostic yield stratified by comparator type to allow for comparability. We did evaluate for variation by phenotype and did not identify any consistent patterns; this information was not included in the draft but we have added it in for more transparency. However, the ways in which studies defined included phenotypes varied significantly; thus, we have added some language to temper our conclusions about variation by phenotype. |

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| | Setting<br>Often genomic sequencing is ordered on inpatients, not because of the immediate clinical utility for the care of patients in the hospital, which is the ideal ordering reason, but due to lack of insurance coverage for outpatient testing. Therefore, by excluding this group you are missing some who would likely have this testing ordered in an outpatient setting if the cost of the test were covered by insurance. | As noted above, WGS is already covered for patients in inpatient settings so was not the focus of the review. Most of the studies that were excluded for being conducted in inpatient settings concerned populations of critically ill infants and children in NICU and PICU settings. These are unlikely to be patients who were admitted and or remained hospitalized for the purpose of obtaining WGS testing. The decisional dilemma for the HTCC is whether to cover such testing in outpatient settings. |
| | Timeframe<br>In addition, for section ES 3.6, I wondered why the authors selected the past 4 years for this data when the other aspects of the paper represent papers since 2013? | Because this contextual question relied on systematic reviews and we identified 6 reviews within the previous 4 years; it was not necessary to include older reviews as they would not provide any additional information not already covered by the newer reviews |
| | Cost Effectiveness<br>Though in an ideal setting cost effectiveness data would all take place in the US, it's important to acknowledge 1) there is limited cost-effectiveness data available for Whole Genome Sequencing and 2) the US payor system is so complicated there is significant variability even within the US. In order to expand this section beyond 2 papers, I might suggest considering papers even if they were conducted outside of the US, just summarizing the clear limitation. I might also consider including papers that only report cost if other study information can be found in additional publications about the study. For example, I would have expected this study to be reported in the cost section https://pubmed.ncbi.nlm.nih.gov/29565423/ , and it is one the authors reviewed. | Although we agree that there is variability in costs in US settings; there is even more variability between US and non-U.S. costs. Because this review is to inform coverage decisions in a U.S. setting, the decision to limit to U.S. studies is warranted.<br><br>The study mentioned by the commenter is included in the HTA for diagnostic yield outcomes but is not included for cost outcomes because the cost outcomes reported are comparing WGS in a cohort of patients with cardiomyopathy to costs in a cohort of 100, presumably healthy, primary care patients. This is not an eligible comparison. |
| | **Reviewer 2:**<br>1. It would be helpful to understand if the PRISMA guidelines were followed. If they were, it should be stated. This would strengthen the validity of the report. https://www.equator-network.org/reporting-guidelines/prisma/<br><br>2. "One team member extracted relevant study data into a structured abstraction form and a senior investigator checked those data for accuracy." - was this done for all forms? A | Thank you for identifying this; we have added language to indicate our review was conducted and reported in accordance with PRISMA 2020 guideline.<br><br>All abstractions were checked for accuracy; we have added language to clarify this.<br><br>This is not data that we routinely track nor is it required for reporting per PRISMA guidelines. |

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| | random subset? A non-random subset? It would be helpful to clarify.<br><br>3. "Two team members conducted independent risk-of-bias assessments on included studies; discrepancies were resolved by discussion or a third reviewer: how often were there discrepancies that required resolution?<br><br>4. For Appendix E it might be more helpful to list the references alphabetically WITHIN the exclusion categories. So list exclusion categories and list the references alphabetically within those groups (possibly in tabular format). | Over many years of conducting reviews, we have tried multiple ways of conveying this information and have determined this comes down to a subjective preference. Some readers prefer an alphabetical list so they can quickly discern whether a study they think should have been included was missed or excluded. When studies are organized by reason for exclusion, then readers have to check the list for each reason to see whether it was excluded versus checking one list. Figure 3 provides a tally of reasons for exclusion; though we remind readers that many studies often have more than 1 reason for exclusion and we only record 1. |
| *Any additional comments about the Methods section?* | **Reviewer 1:** No additional comments<br><br>**Reviewer 2:** none | No response required. |
| **Results** | | |
| *Are there any studies you believe we may have missed*? | **Reviewer 1:** You might look at these review papers:<br>1. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6929710/<br>2. https://www.nature.com/articles/s41525-024-00396-x<br><br>Cost effectiveness papers to consider reviewing:<br>1. https://pubmed.ncbi.nlm.nih.gov/37106068/<br>2. https://pubmed.ncbi.nlm.nih.gov/38277144/<br>3. https://pubmed.ncbi.nlm.nih.gov/35396982/<br>4. https://www.nature.com/articles/s41436-018-0308-x<br><br>**Reviewer 2:** No, but I am not the expert in this literature | Review Papers:<br>1. This publication was excluded because it is not a systematic review.<br>2. This paper is already included in the first row in table 4 and Figure 10.<br><br>Cost effectiveness papers:<br>1. This paper was excluded because costs were from Sweden.<br>2. This study was published in January of 2024 (after our search), and did not include US based costs.<br>3. This study was included.<br>4. This study was excluded for ineligible intervention as it does not distinguish between WES and WGS<br><br>No response required |
| *Are there studies that you believe we should have excluded?* | **Reviewer 1:** No<br><br>**Reviewer 2:** See #1 | No response required |

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| *Do you believe we have inaccurately described any studies?* | **Reviewer 1:** Not to my knowledge<br><br>**Reviewer 2:** See #1 | No response required |
| *Any additional comments about the Results?* | **Reviewer 1:** As noted above in the comments to the paper Methods, I believe it would be ideal to in some way show the clinical testing indication in the result graphs. Though the authors briefly address that they do not see a difference specifically related to clinical indication, it is known that different clinical indications are expected to have different diagnostic yield by WGS and I find myself wondering how results differ. Based on systematic review, professional organizations referenced in this review, have recommended genomic sequencing for specific indications including: ACMG- Congenial anomalies, developmental delay and intellectual disability https://www.nature.com/articles/s41436-021-01242-6, and for Seizure disorders: NSGC- https://onlinelibrary.wiley.com/doi/10.1002/jgc4.1646. By grouping all conditions together, including those that are more and less likely to have a genetic cause, it has the potential to impact the resulting diagnostic yield. Perhaps the indication for testing could be incorporated into the current results graphs by using different colors for different indications?<br><br>**Reviewer 2:** Could not find the methods for payor scan /coverage analyses; expect them to appear in methods section. Also, not clear why these results and Table ES-2 are placed in the discussion section. They appear to be results. Same concerns stand related to clinical practice guideline review. | We have added this information to the Appendix (See Appendix G ).<br><br>The description of payor coverage policies and clinical practice guidelines are descriptive and are for providing context to the HTCC. They are not conducted using the same systematic review methods as the KQ; rather, they are part of the information requested by the State and the Committee to assist with their decisionmaking. This information could be placed in the introduction. Or a separate section of the results; but historicaly we have placed it in the Discussion. |
| **Discussion** | | |
| *Do you think we missed any important points?* | **Reviewer 1:** I have noted some comments to the methods and results that would impact the overall discussion.<br><br>**Reviewer 2:** I think it is important to emphasize that the 0-12.5% range stems from a limited and potentially biased literature base. While you state this within the report, I think that statement needs to follow any statement of this range (see conclusion section for example). | Thank you, we have incorporated text in the discussion where relevant.<br><br>We have revised the text to convey our very low certainty around this estimate. |

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| *Do you disagree with any of the discussion items?* | **Reviewer 1:** The authors have taken a nice attempt patching together a variety of very diverse studies, which is clearly no easy task. I worry a bit that Table 5 looks extremely negative, not because the results show Whole Genome Sequencing is not beneficial, but because there is a lack of data, especially using the very strict criteria for inclusion into this report. Rather than using terminology like "very low" COE, I suggest something a little more neutral like "lack of evidence". | We appreciate the commenter's sentiments, but the terminology used to convey Certainty of Evidence is standardized.<br>In the discussion we have tried to convey that genetic testing is a challenging intervention to evaluate within the context of current evidence synthesis methods and frameworks. We have added some additional text to this point. |
| | It feels a little odd to me that a review of the peer reviewed published literature included in this review would yield "serious concerns" in almost all areas of consistency, precision, and directness, and that almost all study measures mention "high risk" of bias. It makes me wonder if some papers should be excluded due to concerns or bias, rather than whole categories labeled to have "serious concerns" or "high risk" of bias? It also makes me wonder if some of the measures to determine bias were not reported in the direct paper reviewed, but might have been reported in other papers published on the study. For example, I wondered if the "population described in adequate detail" might not have been reported in a given published manuscript because it was previously reported in another paper about the study? I ask this because of just how many studies were scored a No or Probably No in this category. | Wherever possible, we looked for companion articles describing population or methods details not available in the index publication. Most of the articles we identified were retrospective analyses of data collected through routine clinical care; not data collected prospectively in a standardized way as would be done in a research study. Most studies were not designed as comparative studies. We do not typically exclude studies based on risk of bias. Rather, we note the concerns and reflect on the methodological issues within the body of evidence that preclude robust conclusions, and identify areas to consider in future research. Had we excluded studies with a high risk of bias, we would have been left with a small evidence base that would not be as useful for decision-making. |
| | **Reviewer 2:** no comments provided | No response required |
| *Any additional comments about the Discussion?* | **Reviewer 1:** In the study limitations section I might also note that it often takes years to obtain appropriate health outcome and cost data, and most federal NIH grants, and others, are funded for 4-5 year maximum. This often does not allow for the long-term collection of these important outcomes. Along these lines, in the conclusion section I would call for the need for improved data, that seems like one of the major conclusions from the article text based on table 5 overall COE. | We have added some text to this effect in the "future research' section.<br><br>Conclusion sections are typically brief and summarize the major findings. The need for more robust research is implicit in the very low certainty grade and the mention of evidence as being limited. |
| | **Reviewer 2:** Label on Table ES-2 is a bit confusing – second column says "No. studies" and the formatting between study and labels (cohort, RCT) is inconsistent. Some are in (), some are combined "1 cohort." Also, multiple () when the label indicates () will be used for No. participants. Recommend consistent formatting. | We have revised the formatting in this table and in the corresponding Table 5. |
| **Other Sections** | | |

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| *Any comments on the structured abstract, conclusion, figures, tables and appendices?* | **Reviewer 1:** If possible, I suggest including clinical indication somehow in the diagnostic yield graphs.<br>Table 4: Suggest I would suggest to use Bold vs italicized to make results column easier to read.<br><br>**Reviewer 2:** no comments provided | We have addressed this with a new figure in Appendix G and corresponding text in the main report.<br><br>No response required |
| **General Comments** | | |
| *Is the report clearly written, adequately detailed and of an appropriate length?* | **Reviewer 1:** The report is clearly written. I would defer to comments I have included above regarding suggested additions to the report.<br><br>**Reviewer 2:** Yes, very well written. Length is good because of the digestible balance between text and tables in the appendices. | Thank you for your comments.<br><br>No response required |
| *Please make any additional comments you feel would help us improve the report.* | **Reviewer 1:** I appreciate the rigor the authors used to evaluate papers included in this report. Though I wonder if by being so strict, some important research was left unreviewed. Other reviews and professional guidelines regarding this topic include additional papers and often report on the benefits of whole genome sequencing for specific indications or in specific circumstances. Examples of this include: https://www.nature.com/articles/s41525-024-00396-x, https://www.nature.com/articles/s41436-021-01242-6, https://onlinelibrary.wiley.com/doi/10.1002/jgc4.1646. It is not clear to me if this broad approach was a requirement of the report, or if the authors could include more focused information and data on specific types of conditions or in specific circumstances rather than concluding the certainty is very low and evidence is very limited for all uses of outpatient WGS.<br><br>**Reviewer 2:** no comments provided | The Wigby review was included as part of the Contextual Question.<br>The Manickam et al Guideline is referenced in Section 4.3 and is in Table 6.<br>The Smith et al Guideline is referenced in Table 6.<br><br>No response required |

# Public Comments and Responses

The Draft Evidence Report was posted for public comment from April 4, 2024, to May 6, 2024. Three public comment was submitted. The names and affiliations of those submitting comments are summarized in ***Table 3.***

**Table 3. Individuals or Organizations Submitting Public Comments on the Draft Evidence Report**

| Name | Title/Affiliation |
|---|---|
| Carolina Sommer<br>Joshua Henderson<br>Max Brown | NW Rare Disease Coalition |
| John Fox, MD, MHA<br>Kalliopi Trachana, PhD | Illumina |

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| Theresa Andrews<br>Sucheta Bhatt, MD, FACMG<br>Mauro Longoni, MD, FACMG | |
| Dr. Jane Dickerson<br>Dr. Michael Astion<br>Monica Wellner<br>Jessie Conta<br>Sarah Clowes Candadai | Seattle Children's Hospital PLUGS (Patient-centered Laboratory Utilization Guidance Services) |

Excerpts of relevant public comments and our responses to comments are detailed in ***Table 4***. Complete copies of the comments submitted by individuals follow the table.

**Table 4. Public Comments on Draft Evidence Report and Specific Responses**

| Public Comment | Response |
|---|---|
| **NW Rare Disease Coalition** | |
| We have reviewed the Draft Evidence Report in its entirety and consider it to be comprehensive in response to the key questions and seek to lend our voice as a complement to the report. We want to share the perspective of patients with rare disease and their families and hope the Committee will strongly consider this perspective when determining coverage and criteria development.<br>As we shared in our previous feedback during the stages of the assessment process, rare diseases are individually rare but collectively common. 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 diseases have identified genetic origins. 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. The average rare disease patient will also experience 2-3 misdiagnoses along the way.<br>Early diagnosis is a game changer for patients, their family and health care providers. 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 shortens the diagnostic odyssey - the time a patient first experiences rare disease symptoms to the time that a final, accurate diagnosis is made – which results in appropriate support and treatment for the individual and their family. The Draft Evidence Report supports the favorable diagnostic yield of WGS. | No changes to the report required; we note that the purpose of this comment is not specific to the report but to share a perspective on coverage. |
| Importantly: evidence thresholds used in assessment for common conditions typically fail when considering rare disease patients. The report highlights the challenges with capturing the best available evidence and the authors comment on the variation in rigor and completeness of outcome ascertainment, as well as lack of standard outcome definitions to quantitatively assess clinical utility. They astutely point out that by the time long-term comparative studies assessing health benefits and harms are completed, the technology and approaches used will have evolved. The | We note this a validation of our interpretation of the challenges in this evidence base. We have added some additional text to further describe these limitations in the Discussion and Conclusion. |

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| evidence presented supports WGS as the best available tool to shorten the diagnostic odyssey – it combines many existing tests into one, increasing the diagnostic yield, and reduces the number of steps in the diagnostic process. | |
| The Coalition believes that access to 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 avoiding unnecessary surgery, receiving proper medication earlier, or better understanding what treatment options are available to a patient. A correct diagnosis also empowers patients and families to learn and understand what their treatment options are. | No changes to the report required; we note that the purpose of this comment is not specific to the report but to share a perspective on coverage. |
| The assignment of relative value of an intervention through the criteria: "LOW" vs. "MEDIUM" vs. "HIGH", etc. is difficult to assess without a clearer description of what outcomes constitute an assignment into one category over another. That said, we believe WGS should be assigned a higher efficacy value than "MEDIUM". WGS picks up an estimated 15-20% of diagnoses that would be missed by exome testing when the etiology of the disease is unknown, and the phenotype doesn't fit a well described genetic disease. | No changes to the report required.<br>Our assignment of *Very low, Low, Medium, or High* refers to our certainty of the evidence for each outcome graded. It does not refer to the value or magnitude of the test or intervention evaluated. We applied methods from the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) workgroup to rate our certainty of the evidence, which is a commonly used method in systematic reviews. As per GRADE methods, certainty of the findings is based on concerns related to study limitations (i.e., risk of bias), consistency, precision, directness, and reporting bias. We note that GRADE methods were developed initially for assessing the certainty of evidence related to therapeutic interventions, so have some limitations when applied to the evaluation of diagnostic tests. These limitations are compounded further in the context of genetic tests and diagnostic evaluations for rare diseases. |
| Single arm and DxO cohorts should be emphasized in the evidentiary assessment because of the heterogeneity of rare genetic disease. It's difficult to do separate cohort studies and patient selection may factor into diagnostic yield. When looking at the DxO and single arm studies alone, incremental diagnostic yield metrics look significant. The families who are diagnosed in that 5-20% incremental diagnostic yield experience a huge improvement over the status quo as they avoid the typical 5-7 years of consultation of more than 8 specialist visits before receiving an accurate diagnosis, and/or prevent the average 2 – 3 misdiagnoses that might occur along the way – in turn saving patients, and our state's healthcare system, a tremendous amount of time and expense. | No changes to the report required. We believe we have adequately pointed out the challenges with the separate cohort designs. We are unable to fully explain the variation in incremental yield for the Diagnostic Odyssey vs. single cohort designs. |
| Regarding the HIGH cost assessment based on CMS Clinical Lab Fee Schedule: the cost of WGS trio is $10,451.10 vs. WES trio $28,780.00. We'd ask you consider Lavelle's 2022 CEA (table 1) that shows the incremental cost of GS over ES is ~$2,000 per test.<br>Further, the National Institute of Health's Human Genome Research Institute has studied the declining cost of whole genome sequencing over the past decade. By mid-2015, the cost to generate a high-quality 'draft' whole human genome sequence was just above $4,000, and by late 2015 it had fallen below $1,500. Experts expect the cost of the WGS to continue to decline. | We are unclear what "high" cost assessment this comment refers to. Perhaps this refers to the State's indication for commissioning this HTA, which was based on 'high' concerns for cost.<br>The scope of the Cost Question in our HTA was cost-effectiveness, not cost. We have not confirmed the comment's accuracy with respect to current CMS Clinical lab fee schedules.<br>The Lavelle 2022 study which was included in our HTA used cost imputs of $8,112 and $10,450 for |

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| Factors driving this trend include innovation in sequencing technologies, increased competition, and economies of scale. By 2030, whole genome sequencing is projected to become routinely affordable and accessible for research, diagnostics, and healthcare. | trio WES and trio WGS respectively, which does equate to ~2,000 incremental cost per the comment. In sensitivity analyses, authors reported proband-only WGS cost $3,076 per additional diagnosis compared to proband-only WES. A comparison for trio evaluations was not reported, but based on the data provided we calculated that a strategy of trio WGS costs $-935 per additional diagnosis. This calculated data has been added to Appendix Table D-8. |
| Finally, and most importantly: please consider the EveryLife Foundation's Cost of Delayed Diagnosis – which details the many ways that missing diagnoses is extremely cost inefficient for the health care system and for families. The human cost of choosing not using the best tools available to provide early and accurate diagnosis for patients is difficult to quantify in an evidentiary assessment like this, but you must understand that rare families in Washington state are desperate for earlier and better interventions that can lead to correct diagnoses, potential treatment pathways, or better anticipatory planning.<br>Half of all rare disease patients are children, so time is of the essence for families impacted by rare disease – critical developmental milestones are often missed during the diagnostic odyssey, and helpful interventions don't need to be therapeutic in nature. Often, having the opportunity to find the right clinical care team, understand the trajectory of a diagnosis, or marshal other quality of life supports can have a profound impact on families – and reduce emergent interactions with the healthcare system over time. | No changes to the report required; we note that the purpose of this comment is not specific to the report but to share a perspective on coverage. |
| In summary: we encourage adoption of coverage of WGS, with inclusion criteria, because we deem WGS to be the best tool to end the diagnostic odyssey in specific clinical circumstances based on available evidence. | No changes to the report required; we note that the purpose of this comment is not specific to the report but to share a perspective on coverage. |
| **Illumina** | |
| Our comments, guided by experts deeply familiar with the rapidly advancing body of evidence for WGS in rare disease diagnosis, raise concerns about the interpretation of the evidence presented in the report. We aim to pinpoint specific aspects of WGS performance, which, though supported by the current evidence included in the report, may have been underemphasized or underrepresented in the analysis, which in turn could negatively affect the forthcoming coverage decision. In our view, the authors should highlight the following messages: | The comment appears to agree with our interpretation of WGS performance, but are requesting that we put emphasis on certain aspects to support a coverage decision by the HTCC. Please see our response to specific items identified below. |
| **1. WGS is the most comprehensive genetic test available**<br>Compared to WES and other molecular diagnostic tests (e.g. sequencing panels, microarrays), WGS is more comprehensive for two reasons7,9,10: (i) it allows detection of a broad range of variant types in a single assay, including single nucleotide variants (SNV), small insertions and deletions, mitochondrial variants (MT), repeat expansions (RE), copy number variants (CNV) and other structural variants (SV); and (ii) it is untargeted, resulting in more uniform coverage of exonic regions and added coverage of intronic, intergenic and regulatory regions. In place of the stepwise testing pathway, **WGS consolidates diagnostic findings obtained from other genome-wide tests (WES and CMA) into one comprehensive approach with a simpler workflow, faster turnaround time, and the ability to capture additional variant types leading to higher diagnostic yield**.11 These WGS advantages can improve care experience and efficiency. Therefore, the clinical utility, measured as diagnostic yield, of | The background of the report discusses the workflow, rationale for use of WGS and contrasts the types of findings identified by WGS compared to WES (e.g., CNVs, REs, structural variants). Further, our conclusions regarding diagnostic yield are consistent with the comment; we concluded that based on the included evidence, WGS may increase diagnostic yield relative to other testing strategies. This is based on the entirety of the evidence base, and not based on a selected number of studies.<br><br>The studies listed by the comment were all included in our HTA report. We do not rely on authors' reported conclusions, we extract the data |

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| WGS is better than other genetic tests (individually or in combination). Below, we highlight three recent studies included in the current HTA draft.<br><br>Lowther C, et al. Systematic evaluation of genome sequencing for the diagnostic assessment of autism spectrum disorder and fetal structural anomalies. Am J Hum Genet. 2023 Sep 7;110(9):1454-1469. Doi: 10.1016/j.ajhg.2023.07.010.<br>"*This large-scale evaluation demonstrated that **GS significantly outperforms each individual standard-of-care test while also outperforming the combination of all three tests,** thus warranting consideration as the first-tier diagnostic approach for the assessment of autism spectrum disorder (ASD)*. "<br><br>van der Sanden BPGH, et al. The performance of genome sequencing as a first-tier test for neurodevelopmental disorders. Eur J Hum Genet. 2023 Sep 16. Doi: 10.1038/s41431-022- 01185-9.<br>*"Our data demonstrate the technical and clinical validity of GS to serve as routine first-tier genetic test for patients with NDD. Although the additional diagnostic yield from GS is limited, **GS comprehensively identified all variants in a single experiment, suggesting that GS constitutes a more e=icient genetic diagnostic workflow.**"*<br><br>Lindstrand A, et al. Genome sequencing is a sensitive first-line test to diagnose individuals with intellectual disability. Genet Med. 2022 Sep 5:S1098-3600(22)00874-7.doi: 10.1016/j.gim.2022.07.022.<br>*"Our findings strongly suggest that **genome analysis outperforms other testing strategies and should replace traditional CMA and FMR1 analysis as a first-line genetic test in individuals with ID/NDD**."* | reported and evaluate the data objectively across the entirety of the body of evidence.<br><br>*Lowther et al:*<br>Performed quartet WGS in deeply phenotyped individuals (which may not be applicable to how most WGS is conducted)<br>WGS yield 7.8% (95% CI, 6.5 to 9.1)<br>CMA yield: 4.4% (95% CI, NR); OR 1.8, 95% CI, 1.3 to 2.5)<br>WES yield: 7.4% (95% CI, NR)<br>WES yield from earlier version: 3.0%, (95% CI NR); OR 2.7, 95% CI, 1.9 to 3.9<br>We would characterize these findings as a very modest increase in yield compared to CMA, and no meaningful difference compared with contemporary WES.<br><br>*Van der Sanden et al.*<br>WGS Yield: 30%<br>WES + SOC yield: 29%<br>We interpreted this data the same way as the primary study authors did (similar yield between tests); while certainly important to the return of more timely results and cost efficiencies, our review was not scoped to systematically assess efficiency in diagnostic workflows; therefore we do not report results related to this potential benefit. However, we have added 'more efficient workflows' in the background section of the report under the 'rationale for use of WGS".<br><br>*Lindstrand et al.*<br>First line WGS yield: 30%<br>Second line WGS yield: 26%<br>CMA/FMR 1 testing: 11%<br>We agree with the conclusions that in this study, WGS (1st or 2nd line) resulted in a higher diagnosis. |
| **2. Early access to WGS can prevent or reduce a diagnostic odyssey**. The provision of an early, accurate diagnosis can initiate a cascade of health outcome-altering events including changes in pharmacotherapy, referral to specialists, avoidance of unnecessary procedures or treatments, stoppage of ine\ective treatments, and initiation of palliative or hospice care.12 Withcertain genetic disorders, early interventions can substantially limit the e\ects of the disease and so have a profound e\ect on long-term outcomes.2-4,6 There may be limited time periods —"windows of opportunity"—during which the course of the rare disease can be modified. Outside of those time periods, chances for meaningful intervention may be more limited.<br><br>Lindstrand A, Ek M, Kvarnung M, et al. **Genome sequencing is a sensitive first-line test to diagnose individuals with intellectual disability.** Genet Med. 2022 Sep 5:S1098- 3600(22)00874-7. Doi: 10.1016/j.gim.2022.07.022. | No changes to the report are required. See specific responses for each study below.<br><br>The Lindstrand et al study was included in the HTA; however, we do not see any patient-level data on time to diagnosis that was collected and analyzed by authors and presented as part of the |

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| "*a GS-first approach shortens the diagnostic odyssey for individuals with ID in our region. If ID individuals are first investigated using CMA, diagnosis is delayed approximately 6 to 12 months, including the TAT for genetic analysis as well as time to obtain a new referral for GS. However, for most individuals (90%), no more genetic tests were requested after the negative CMA, and therefore, many individuals who could have received a genetic diagnosis remain undiagnosed*." | results. The excerpt of text provided in the comment appears in the discussion of the paper and appears to be the author's interpretation of the impact that their findings will have on time to diagnosis. |
| Runheim H, et al. The cost-effectiveness of whole genome sequencing in neurodevelopmental disorders. Sci Rep 13, 6904 (2023). https://doi.org/10.1038/s41598-023-33787-8 (Follow-up study for Lindstrand et al; investigates cost-effectiveness)<br>"*the costs when using **WGS as a first-line diagnostic test were $2339 lower compared to the standard of care strategy during the first 2 years from referral**. The diagnostic yield was 23% higher for cohort WGS during the same time period compared to the CMA group. Thus, from a cost-eTectiveness perspective, the WGS test is dominant.*" | No changes to the report required. This Runheim et al study was identified by our search but we excluded it because the cost inputs were from Sweden. We required US-based costs estimates to enhance applicability to US-based care settings and payers. |
| Vanderver A, Bernard G, Helman G, et al. **Randomized Clinical Trial of First-Line Genome Sequencing in Pediatric White Matter Disorders**. Ann Neurol. 2020 Aug;88(2):264-273. Doi:10.1002/ana.25757. PMID: 32342562<br>"*The time to diagnosis was significantly shorter in the immediate-GS. **The overall diagnostic efficacy of combined GS and SoC approaches 76.5% in <4 months**, greater than historical norms (without WGS) of <50% over 5 years.*" | The Vanderver et al study was included in the HTA report. We inadvertently omitted data on time to diagnosis that was reported by authors; this has been corrected and added to Appendix D Evidence Tables, and has been added to the results in Section 3.3.1. However, this addition does not change our overall certainty of evidence rating for clinical utility given these results were from 1 study, with limited precision (i.e. small sample size), and some concerns for bias. |
| **3. WGS access landscape is transforming to accommodate patient, physician, and payer views.**<br>Over the last three years, access to WGS has increased globally; there has been a pronounced increase in the number of national, regional, and commercial policies that endorse WGS testing.[8,13] As WGS becomes more accessible in the outpatient setting, physicians, patients, and payers reevaluate WGS value. | No changes required to report. We did not evaluate access to WGS so cannot comment further. |
| Jobanputra, V., Schroeder, B., Rehm, H.L. *et al.* Advancing access to genome sequencing for rare genetic disorders: recent progress and call to action. *Npj Genom. Med.* **9**, 23 (2024). https://doi.org/10.1038/s41525-024-00410-2<br><br>"With these changes, the total number of covered lives in the US now exceeds 50 M. A request in the Fiscal Year 2023 Omnibus Appropriations Bill that the Centers for Medicare and Medicaid Services (CMS) develop guidance for state health officials on best practices for incorporating GS and other genetic testing technologies into their Medicaid and Children's Health Insurance Program (CHIP), and to investigate how such testing fits into the Early and Periodic Screening, Diagnostic and Treatment (EPSDT) benefit, may further improve both coverage and access for Medicaid patients." | This article is a narrative review concerning access to WGS; it is not within the scope of this HTA which was focused on effectiveness, safety, and cost. |
| Notably, many commercial insurers and their Medicaid books of business already cover WGS independent of the Early and Periodic Screening, Diagnostic and Treatment (EPSDT) benefit. In Washington, two of the five Medicaid health plans have affirmative coverage for whole genome sequencing (see table below). This is likely reflected in Table 1 in the | We have updated the payor coverage policy section to reflect policies from the 5 Medicaid Managed Care plans mentioned in the comment. Though they offer relevant perspectives for the HTCC in making a coverage decision, the 2 |

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| evidence report draft. Further, Molina Healthcare has approved coverage for WGS under the EPSDT benefit.<br><br>Managed Medicaid Membership, Health Plan, Coverage status<br>142363, Amerigroup Real Solutions, Not covered<br>110875, Centene Corporation/Coordinated Care of Washington, Covered<br>521386, Molina Healthcare, Not covered<br>159025, United Healthcare of Washington, Covered<br>Community Health Plan of Washington, Not covered]<br><br>Physicians should have the autonomy to select the most suitable genetic tests for their patients, while also considering the workload of their care teams in the outpatient clinical setting. In these settings, coordinating care often becomes a stressor across different care sites, and the complexity of this process can particularly impact rare disease patients, who are frequently overlooked in referral processes.15<br><br>Pasquier, L. et al. How do non-geneticist physicians deal with genetic tests? A qualitative analysis. Eur J Hum Genet 30, 320–331 (2022). https://doi.org/10.1038/s41431-021-00884-z<br>**"this intersection between care by a specialist and management of genetic testing reveals tensions that clinical physicians face with regard to their reflective work. In both specialities investigated in our study, the main sources of stress for professionals are as follows: coordination and cooperation between specialists and organization of care as a team"**<br><br>Physicians, who have used WGS in their clinical practice, felt that clinical genome sequencing will lead to improved diagnoses for patients with rare diseases by making the path to diagnosis more efficient, making it more likely patients will get a diagnosis with fewer tests needed.15 By fostering physician choice and broadening access to WGS, we can pave the way for a more equitable and effective approach to patient care.2,6<br><br>Hill M, et al. Delivering genome sequencing for rapid genetic diagnosis in critically ill children: parent and professional views, experiences and challenges. Eur J Hum Genet. 2020 Nov;28(11):1529-1540. Doi: 10.1038/s41431-020-0667-z.<br>"I think the main benefit is that the differential diagnosis is very wide and broad...you can test for many things with one test, you can cast your net wide, you don't have to be as specific andthe timeframe in which you can get the results back is quite impressive. – Professional-7, medical doctor trainee" | studies cited in the rest of the comment are not applicable to the scope of the HTA. |
| Finally, patients value genetic diagnosis, especially those who have been living with no diagnosis.16 After a genetic diagnosis, patients and families experience less anxiety, as it helps them accept their conditions, become part of a patient community, and organize their interactions with physicians, as well as independent e\orts outside of the hospital.16<br><br>Peter M, et al. Participant experiences of genome sequencing for rare diseases in the 100,000 Genomes Project: a mixed methods study. Eur J Hum Genet. 2022 May;30(5):604-610. doi: 10.1038/s41431-022-01065-2.<br>“For those who had been struggling with the uncertainty of not having a diagnosis, being able to attribute a cause for their or their child’s condition | We acknowledged that outcomes like this were not included in the HTA because they are likely contained in qualitative research studies, which were not in the scope of this HTA. |

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| could be helpful practically by facilitating access to specialist equipment and educational and social support." | |
| In conclusion, while we recognize the significance of the evidence presented in this report, we assert that it does not adequately convey the full benefits of WGS. The report itself admits to limitations in the current standard of targeted genetic testing. The comprehensive nature of WGS provides a potent means for early diagnosis and enhancing patient outcomes. Moreover, limited access to WGS only intensifies healthcare disparities. We urge a reevaluation of the evidence with a more thorough interpretation that underscores our support for the broader use of WGS. | We agree the full benefits of WGS may not be fully represented in the HTA report. This is partially because of how the HTA was scoped, but more importantly because of limitations of the evidence base itself. No changes to the report are required. |
| **Seattle Childrens Hopsital PLUGS** | |
| We want to thank the Director for agreeing to review WGS during this session. As stated in the Whole Genome Sequencing Draft Evidence Report, the report is intended, "to help the State of Washington's independent Health Technology Clinical Committee make well-informed coverage determinations" and is not intended as "a substitute for the application of clinical judgment." We have reviewed the Draft Evidence Report in its entirety and consider it to be comprehensive in response to the key questions. Our feedback here is intended to highlight several points made in the report and to share our clinical perspective, which is informed by our internal practice at Seattle Children's and through our national laboratory stewardship collaboration, PLUGS®. We hope you will consider the following perspective when considering coverage and criteria development. | No changes to report required. We note that the purpose of this comment is not on the report but to share a perspective on coverage. |
| As a brief introduction, we represent the laboratory stewardship program at Seattle Children's Hospital and PLUGS®, a non-profit national laboratory stewardship collaboration that we founded in 2013. The mission of PLUGS® is to improve laboratory test access, ordering, result retrieval, interpretation, and reimbursement. To that end, one of our primary initiatives relates to insurance alignment. We have established positive relationships with local and national payers to encourage adoption of coverage policies for medically appropriate tests and to improve administrative processes that present barriers to providers, patients, and payers. We have a particular interest in supporting policies and improvements in rare disease, given the paucity of coverage policies, challenges with meeting evidence thresholds, and rapid evolution of technologies. Our long-standing laboratory stewardship program at Seattle Children's Hospital guides utilization of medically appropriate laboratory tests, including genetic tests. We shared our expertise during the 2019 HTA program review of whole exome sequencing (WES) and collaborated with the HCA Medical Director to draft coverage criteria. We are grateful for the expansion of WES coverage since that time and have seen the positive impact of this diagnostic tool for many of our patients. Since that time, genetic testing has continued to evolve. Until recently, we followed a stepwise process, one test at a time, working to align with existing payer policies. This process is often lengthy and timeconsuming, and cumulative costs can be impactful to individuals, hospitals, and payers. Further, a diagnosis may remain elusive either because we are unable to complete all recommended tests (navigating the process is challenging for patients and providers!) or because we are unable to access the optimal test, due to variable insurance coverage policies. WGS combines many tests into one and offers the best available diagnostic option for many individuals with undiagnosed rare disease, particularly when used as a first-line test in specific clinical circumstances. | No changes to the report required. We note that the purpose of this comment is not on the report but to share a perspective on coverage. |

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| The report highlights the challenges with capturing the best available evidence in this patient population and as such, we offer our clinical perspective on evolving standards of care utilizing WGS for rare disease patients in Washington. The authors comment on the variation in rigor and completeness of outcome ascertainment and lack of standard outcome definitions to quantitatively assess clinical utility. They also state that by the time long-term comparative studies assessing health benefits and harms are completed, the technology and approaches used will have evolved. We know that the standard of care and evidence-based medicine overlap, but are not identical.1 The standard of care is used as both a medical and legal term and has a range of definitions.2 A composite definition of the standard of care is the expectation of the average provider to diagnose, treat, monitor, and communicate about a health condition. Standards of care in laboratory testing are often based on weaker evidence from small case control studies, observational studies, or a consensus of academically-oriented, board-certified medical specialists. Larger well-controlled studies and randomized control trials are less common, and tend to be restricted to the highest volume tests for common diseases. In practice, the legal standard of care comes from experts, and their opinion is based on peer-reviewed research; guidelines, practice updates, and other educational documents from professional societies and the government; textbooks and online information from medical publishers; and historical practice patterns. The Draft Report aligns with the level of evidence we would expect for WGS in a rare disease population and it is our assessment that the evidence supports clinical adoption of WGS in specific circumstances. | No changes to the report required. The commenter supports our characterization of the challenges in this body of research and our assessment of the methodological quality of this research. The rest of the comment is around perspectives on coverage. |
| We encourage adoption of coverage of WGS, with inclusion criteria, because we deem WGS to be the best tool to end the diagnostic odyssey in specific clinical circumstances based on available evidence. WES and WGS are similar diagnostic tools in the evaluation of individuals with rare disease, but there are clear technical advantages of WGS that support increased diagnostic yield and reduce time-todiagnosis. As access to WGS increases, WGS will supplant WES to become the preferred diagnostic test. Over the past year, we have supported the transition from WES to WGS in the Seattle Children's clinical practice, expanding adoption of WGS for specific clinical indications with guidance from our specialists. | No changes to the report required. We note that the purpose of this comment is not on the report but to share a perspective on coverage. |
| We would like to submit our PLUGS expert-drafted genome sequencing medical policy to use as guidance. It includes optimal conditions for coverage of medically appropriate genome sequencing. Please find a copy of our current policy attached. It is also available at https://www.schplugs.org/wpcontent/uploads/Genomic-Sequencing-in-Rare-Disease_2023_FINAL.pdf. | No changes to the report required. We note that the purpose of this comment is not on the report but to share a perspective on coverage. |
| Lastly, we want to comment on the cost-effectiveness of WGS. We reviewed the current WA Medicaid FFS rate for WGS (CPT codes 81425 and 81426) and as currently priced, adoption of WGS coverage would be impractical when compared to the current fees for WES + CMA (chromosomal microarray). We note the variable conversion from the CLFS for WES (CPT codes 81415 and 81416) compared to WGS and recommend that the HCA review and consider a cost adjustment to better align WGS fees to a rate that is more comparable to current fees of WES + CMA. | No changes to the report required. We note that the purpose of this comment is not on the report but to share a perspective on coverage specific to current reimbursement rates. |
| **Clinical Perspective**: Seattle Children's Hospital, along with the national non-profit laboratory stewardship collaboration, PLUGS®, offers insights into laboratory test utilization. They advocate for insurance alignment, | No changes to the report required. We note that the purpose of this comment is not on the report but to share a perspective on coverage. |

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| particularly in rare diseases, aiming to improve rational access and reimbursement for medically appropriate tests. | |
| **Experience with WES and WGS**: Seattle Children's Hospital has previously contributed to the HTA review of Whole Exome Sequencing (WES) and collaborated with WA Medicaid on coverage criteria development. We have witnessed the positive impact of WES and support the transition to WGS for specific clinical indications. • | No changes to the report required. We note that the purpose of this comment is not on the report but to share a perspective on coverage. |
| **Challenges and Benefits of WGS**: WGS offers advantages over stepwise testing approaches, potentially reducing costs and time-to-diagnosis. The report acknowledges challenges in evidence capture and outcome ascertainment but supports clinical adoption of WGS in specific circumstances | No changes to the report required. We note that the purpose of this comment is not on the report but to share a perspective that they believe the findings of the report support coverage. |
| **Policy Recommendation**: Seattle Children's Hospital proposes adoption of WGS coverage with inclusion criteria based on available evidence and technical advantages. We provide the PLUGS® expert-drafted genome sequencing medical policy for consideration. | No changes to the report required. We note that the purpose of this comment is to support coverage. |
| **Cost Considerations**: While advocating for WGS adoption, we highlight cost-effectiveness concerns, suggesting a review of Medicaid fee rates to ensure alignment with current practicesand costs. | No changes to the report required. We note that the purpose of this comment is not on the report but to share concerns about current reimbursement rates. |