Washington State Health Care Authority

Whole Exome Sequencing

Public comment on draft evidence report

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Health Technology Assessment Program (HTA)

Washington State Health Care Authority

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This document was created in response to 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

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Public Comments and Responses

The draft evidence report was posted for public comment from September 5, 2019 to October 4, 2019. One public comment was submitted. The names and affiliations of those submitting the comment are summarized in ***Table 1.***

Table 1. Individuals or Organizations Submitting Public Comments on the Draft Evidence Report

Name	Title/Affiliation
Michael Astion, MD, PhD	Medical Director, Department of Laboratories, Seattle Children's Hospital Clinical Professor of Laboratory Medicine, Dept of Laboratory Medicine, University of Washington Co-Founder, Patient-centered Laboratory Utilization Guidance Services (PLUGS)
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Public comments and responses to comments are detailed in ***Table 2***. Complete copies of the comments submitted by individuals follow the table.

Table 2. Public Comments on Draft Evidence Report and Specific Responses

Name (#)	Public Comment	Response
Seattle Children's Hospital & PLUGS (1)	We have reviewed the Draft Evidence Report in its entirety and consider it to be comprehensive and fair in response to the key questions.	Thank you.
Seattle Children's Hospital & PLUGS (2)	We would like to submit our PLUGS expert-drafted exome sequencing medical policy to use as guidance. It has been adopted, in some cases word-for-word, by both commercial payers (for example, Aetna http://www.aetna.com/cpb/medical/data/100_199/0140.html), and third-party benefits management companies, including eviCore. It includes optimal conditions for coverage of medically appropriate exome sequencing. Please find a copy of our current policy attached. It is also available at http://www.schplugs.org/insurance-alignment/.	Thank you for sharing this guidance.
Seattle Children's Hospital & PLUGS (3)	This policy references the value of family trios in exome sequencing analysis. Family trios optimize interpretation of the variants detected in the patient. Family trio testing can improve patient safety by reducing the rate of uncertain findings, adding to the clinical sensitivity with regard to the interpretation of clinically novel genes, and increasing the diagnostic yield of exome sequencing. The current CMS rate for the patient's exome CPT code 81415 (Exome, sequence analysis) is $4,780. The current CMS rate for each comparator family member's exome CPT code 81416 (sequence analysis, each comparator exome (e.g., parents, siblings) is $12,000. It is not logical for the comparator sample charges to be higher than the patient's. This comparator rate is inappropriately high and as such, could make trio exome sequencing for patients in our state cost-prohibitive. A rate of $1,200 would be more normative for 81416 and help ensure the increased value of comparator samples submitted as part of exome sequencing could be realized for patients in Washington State.	Thank you for sharing this information.

Abbreviations:

CMS = Center for Medicare & Medicaid Services;
CPT = Current Procedural Terminology;
PLUGS = Patient-centered Laboratory Utilization Guidance Services.

Feedback on Draft Evidence Report: Whole Exome Sequencing

From the Seattle Children's Hospital Department of Laboratories Leadership and Patient-centered Laboratory Utilization Guidance Services (PLUGS®)

As stated in the **Whole Exome Sequencing** Draft Evidence Report, the report is intended, "to help the Washington HCA make well-informed coverage determinations and thereby improve the quality of health care services." The report states as its purpose, "to review efficacy, safety and cost of whole exome sequencing (WES)."

We have reviewed the Draft Evidence Report in its entirety and consider it to be comprehensive and fair in response to the key questions. We have the following feedback that we hope you will incorporate when considering coverage and criteria development.

The mission of PLUGS® is to improve laboratory test ordering, retrieval, interpretation and reimbursement. To that end, one of our primary initiatives relates to insurance alignment. We have established positive relationships with local payers to improve efficiencies around test review and have developed coverage policies for medically appropriate lab tests which are shared freely, in the hopes of insurance plan adoption. Ultimately, this supports patients and payers.

We would like to submit our PLUGS expert-drafted exome sequencing medical policy to use as guidance. It has been adopted, in some cases word-for-word, by both commercial payers (for example, Aetna http://www.aetna.com/cpb/medical/data/100_199/0140.html), and third-party benefits management companies, including eviCore. It includes optimal conditions for coverage of medically appropriate exome sequencing. Please find a copy of our current policy attached. It is also available at http://www.schplugs.org/insurance-alignment/.

This policy references the value of family trios in exome sequencing analysis. Family trios optimize interpretation of the variants detected in the patient. Family trio testing can improve patient safety by reducing the rate of uncertain findings, adding to the clinical sensitivity with regard to the interpretation of clinically novel genes, and increasing the diagnostic yield of exome sequencing. The current CMS rate for the patient's exome CPT code 81415 (Exome, sequence analysis) is $4,780. The current CMS rate for each comparator family member's exome CPT code 81416 (sequence analysis, each comparator exome (e.g., parents, siblings) is $12,000. It is not logical for the comparator sample charges to be higher than the patient's. This comparator rate is inappropriately high and as such, could make trio exome sequencing for patients in our state cost-prohibitive. A rate of $1,200 would be more normative for 81416 and help ensure the increased value of comparator samples submitted as part of exome sequencing could be realized for patients in Washington State.

Thank you for your consideration. Please contact us if you have additional questions, (206) 987-3353.

Signed by leadership within Seattle Children's Hospital Department of Laboratories and Patient-centered Laboratory Utilization Guidance Services (PLUGS®)

[redacted]

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Whole Exome Sequencing (WES)

Procedure(s) addressed by this policy:	Procedure Code(s)
Exome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis	81415
Sequence analysis, each comparator exome (e.g., parent(s), sibling(s))	81416
Re-evaluation of previously obtained exome sequence (e.g., updated knowledge or unrelated condition/syndrome)	81417

What Is Whole Exome Sequencing?

- Whole exome sequencing (WES) utilizes DNA-enrichment methods and massively parallel nucleotide sequencing to identify disease-associated variants throughout the human genome.
- WES has been proposed for diagnostic use in individuals who present with complex genetic phenotypes suspected of having a rare genetic condition, who cannot be diagnosed by standard clinical workup, or when features suggest a broad differential diagnosis that would require evaluation by multiple genetic tests.
- The standard approach to the diagnostic evaluation of an individual suspected of having a rare genetic condition may include combinations of radiographic, biochemical, electrophysiologic, and targeted genetic testing such as a chromosomal microarray, single-gene analysis, and/or a targeted gene panel.[1]
- WES is typically not an appropriate first-tier test, but can be appropriate if initial testing is unrevealing, or if there is no single-gene or panel test available for the particular condition.[2]
- Identifying a molecularly confirmed diagnosis in a timely manner for an individual with a rare genetic condition can have a variety of health outcomes[2,3,4,5,6,7,8,9], including:
    - guiding prognosis and improving clinical decision-making, which can improve clinical outcome by
        - application of specific treatments as well as withholding of contraindicated treatments for certain rare genetic conditions
        - surveillance for later-onset comorbidities
        - initiation of palliative care
        - withdrawal of care
    - reducing the financial & psychological impact of diagnostic uncertainty and the diagnostic odyssey (e.g., eliminating lower-yield testing and additional screening testing that may later be proven unnecessary once a diagnosis is achieved)
    - informing genetic counseling related to recurrence risk and prenatal diagnosis options

- allowing for more rapid molecular diagnosis than a sequential genetic testing approach

Test Information

- WES is limited to the DNA sequence of coding regions (exons) and flanking intronic regions of the genome, which is estimated to contain 85% of heritable disease-causing variants.
- Pathogenic variants that can be identified by WES include missense, nonsense, splice-site, and small deletions or insertions.
- At the present time, WES will typically miss certain classes of disease-causing variants, such as structural variants (e.g., translocations, inversions), abnormal chromosome imprinting or methylation, copy-number variants, some mid-size insertions and deletions (ca. 10-500 bp), trinucleotide repeat expansion mutations, deeper intronic mutations, and low-level mosaicism.
- WES has the advantage of decreased turnaround time and increased efficiency relative to Sanger sequencing of multiple genes.
- WES is associated with technical and analytical variability, including uneven sequencing coverage, gaps in exon capture before sequencing, as well as variability in variant classification based on proprietary filtering algorithms and potential lack of critical clinical history or family samples.[10]

Guidelines and Evidence

- The American College of Medical Genetics and Genomics, Association for Molecular Pathology, and College of American Pathologists convened a workgroup that developed standard terminology for describing sequence variants. The guidelines describe criteria for classifying sequence variants into five categories (pathogenic, likely pathogenic, uncertain significance, likely benign, and benign) based on criteria using typical types of variant evidence (e.g., population data, computational data, functional data, segregation data).[11]
- The American College of Medical Genetics has three relevant policy statements that offer guidance on: 1) the clinical application of whole exome and whole genome testing,[12] 2) informed consent for genome/exome sequencing,[13] and 3) reporting of incidental findings in clinical exome and genome sequencing.[14,15]
- Evidence for the clinical utility of WES in individuals with multiple congenital anomalies and/or a neurodevelopmental phenotype includes numerous large case series. Relevant outcomes include improved clinical decision-making (e.g., application of specific treatments, withholding of contraindicated treatments, changes to surveillance), changes in reproductive decision making, and resource utilization. WES serves as a powerful diagnostic tool for individuals with rare genetic conditions in which the specific genetic etiology is unclear or unidentified by standard clinical workup.[7,16,17]

- The average diagnostic yield of WES is 20-40% depending on the individual's age, phenotype, previous workup, and number of comparator samples analyzed.[5,16,18] Among individuals with a pathogenic or likely pathogenic findings by WES, 5-7% received a dual molecular diagnosis (i.e., two significant findings associated with non-overlapping clinical presentations).[16,18]
- The use of family trio WES reduces the rate of uncertain findings, adds to the clinical sensitivity with regard to the interpretation of clinically novel genes, and increases the diagnostic utility of WES. For example, in three publications the positive rate ranges from 31-37% in patients undergoing trio analysis compared to 20-23% positive rate among proband-only WES.[16,19,20]
- Re-evaluation of previously obtained exome sequence has the potential for additional diagnostic yield because of constant expansions of existing variant databases, as well as periodic novel gene discovery and publication.[21]

Criteria

- Whole exome sequencing (WES) is considered medically necessary for the evaluation of unexplained congenital or neurodevelopmental disorder in children <21years of age when ALL of the following criteria are met:
    - The patient and family history have been evaluated by a Board-Certified or Board-Eligible Medical Geneticist, or an Advanced Practice Nurse in Genetics (APGN) credentialed by either the Genetic Nursing Credentialing Commission (GNCC) or the American Nurses Credentialing Center (ANCC), and
    - A genetic etiology is considered the most likely explanation for the phenotype, based on EITHER of the following, and
        - multiple congenital abnormalities affecting unrelated organ systems
        - TWO of the following criteria are met:
            - abnormality affecting at minimum a single organ system
            - significant developmental delay, intellectual disability (e.g., characterized by significant limitations in both intellectual functioning and in adaptive behavior), symptoms of a complex neurodevelopmental disorder (e.g., self-injurious behavior, reverse sleep-wake cycles, dystonia, hemiplegia, spasticity, epilepsy, muscular dystrophy), and/or severe neuropsychiatric condition (e.g., schizophrenia, bipolar disorder, Tourette syndrome)
            - family history strongly suggestive of a genetic etiology, including consanguinity
            - period of unexplained developmental regression
            - biochemical findings suggestive of an inborn error of metabolism
    - Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection), and

- Clinical presentation does not fit a well-described syndrome for which single-gene or targeted panel testing (e.g., comparative genomic hybridization [CGH]/chromosomal microarray analysis [CMA]) is available, and
- WES is more efficient and economical than the separate single-gene tests or panels that would be recommended based on the differential diagnosis (e.g., genetic conditions that demonstrate a high degree of genetic heterogeneity), and
- A diagnosis cannot be made by standard clinical work-up, excluding invasive procedures such as muscle biopsy, and
- Predicted impact on health outcomes, as above, and
- Pre- and post-test counseling by an appropriate provider (as deemed by the Health Plan policy), such as an American Board of Medical Genetics or American Board of Genetic Counseling-certified Genetic Counselor

Exclusions and Other Considerations:

- WES is considered experimental/investigational for the diagnosis of genetic disorders in individuals <21 years of age who do not meet the above criteria.
- WES is considered experimental/investigational for screening for genetic disorders in asymptomatic or pre-symptomatic individuals.
- Ideal sample type should be considered based on the clinical presentation (e.g., suspect mosaicism based on pigmentary anomalies, consider skin fibroblast as ideal sample type).

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