Washington State Health Care Authority

July 26, 2024 Meeting Materials
Health Technology Clinical Committee

Previous meeting business

Contents

Washington State Health Care Authority

Health Technology Clinical Committee

Date: June 14, 2024
Time: 8:00 a.m. – 12:30 p.m.
Location: Webinar
Adopted: Pending

Meeting materials and transcript are available on the **HTA website.**

HTCC Minutes

Members present: John Bramhall, MD, PhD; Clinton Daniels, DC, MS; Janna Friedly, MD, MPH; Chris Hearne, DNP, MPH; Conor Kleweno, MD; Christoph Lee, MD, MS; Laurie Mischley, ND, MPH, PhD; Sheila Rege, MD; Jonathan Sham, MD; Tony Yen, MD
Clinical experts: Amy Yuen, MD

HTCC Formal Action

1. **Welcome and Chair remarks:** Dr. Rege, chair, called the meeting to order; members present constituted a quorum.
2. **HTA program updates:** Josh Morse, program director, presented HTCC meeting protocols and guidelines, and an overview of the HTA program.
3. **Previous meeting business:**

   May 17, 2024 meeting minutes: Draft minutes reviewed. Motion made and seconded to approve the minutes as written.

   Action: 10 committee members approved the May 17, 2024 meeting minutes.

   Vote on spinal cord stimulation draft findings and decision: Public comments and draft findings reviewed.

   Action: Ten committee members voted to finalize spinal cord stimulation draft findings and decision.

   Vote on bariatric surgery draft findings and decision: Public comments and draft findings reviewed.

   Action: Ten committee members voted to finalize bariatric surgery draft findings and decision.
4. **Tumor treating fields**

   HTCC reviewed petition and supplemental materials.

   Action: Ten committee members voted that the evidence presented would not change the previous determination
5. **Whole genome sequencing (WGS)**

   HTCC discussion and action:

   Discussion

The committee drafted coverage criteria for use of WGS. Based on the deliberations of key health outcomes, the committee decided that it had the most complete information: a comprehensive and current evidence report, public comments, and state agency utilization information. The committee discussed and voted separately on the evidence for the use of WGS. The committee decided that the current evidence on WGS is sufficient to determine coverage with conditions. The committee considered the evidence, public comment and expert input, and gave greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.

Based on these findings, the committee voted to cover WGS with conditions.

	Not covered	Covered under certain conditions	Covered unconditionally
Whole genome sequencing	0	9	0

Discussion

The committee reviewed and discussed the available studies for use of WGS. Members drafted coverage criteria for the use of WGS and voted on a draft findings and decision. Details of study design, inclusion criteria, outcomes, cost, cost-effectiveness, and other factors affecting study quality were discussed as well as clinical application.

Decision

Limitations of coverage:

Whole genome sequencing (WGS) is a covered benefit with conditions for the evaluation of unexplained congenital or neurodevelopmental or neurodegenerative disorders in a phenotypically affected individual when **ALL of the following** criteria are met:

1. 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), who is not employed by a commercial genetic testing laboratory, has evaluated the patient and family history, and recommends and/or orders the test; and

2. A genetic etiology is considered the most likely explanation for the phenotype, based on **EITHER of the following**;

   - Multiple abnormalities affecting unrelated organ systems, (e.g. multiple congenital anomalies); or
   - **TWO of the following criteria are met:**
     - Significant abnormality affecting at minimum, a single organ system,
     - Unexplained cognitive changes in adulthood,
     - Profound global developmental delay[1], or intellectual disability[2] as defined below,
     - Family history strongly suggestive of a genetic etiology, including consanguinity,
     - Period of unexplained developmental regression (unrelated to autism or epilepsy),
     - Biochemical findings suggestive of an inborn error of metabolism where targeted testing is not available; and

3. Other circumstances (e.g. environmental exposures, injury, infection) do not reasonably explain the constellation of symptoms; and
4. 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
5. The differential diagnosis list and/or phenotype warrant testing of multiple genes and **ONE of the following**:
    - WGS 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); or
    - WGS results may preclude the need for invasive procedures or screening that would be recommended in the absence of testing (e.g. muscle biopsy); and
6. A standard clinical work-up has been conducted and did not lead to a diagnosis; and
7. Results will impact clinical decision-making for the individual being tested; and
8. Pre- and post-test counseling is performed by an American Board of Medical Genetics or American Board of Genetic Counseling certified genetic counselor.

Non-covered indicators:

WGS is not covered for:

- Carrier testing for "at risk" relatives.
- Prenatal or pre-implantation testing.

Definitions:

[1] **Global developmental delay (GDD)** is used to categorize children who are younger than five years of age.

GDD is defined as a significant delay[2] in two or more developmental domains, including gross or fine motor, speech/language, cognitive, social/personal, and activities of daily living and is thought to predict a future diagnosis of ID. Such delays require accurate documentation by using norm-referenced and age appropriate standardized measures of development administered by experienced developmental specialists, or documentation of profound delays based on age appropriate developmental milestones are present.

Reference: *Comprehensive Evaluation of the Child With Intellectual Disability or Global Developmental Delays Pediatrics 2014;134:e903–e918. Page e905*

Significant delay is typically defined as performance two standard deviations or more below the mean on age-appropriate, standardized, normal-referenced testing.

[2] **Intellectual disability (ID)** is a life-long disability diagnosed at or after age five when intelligence quotient (IQ) testing is considered valid and reliable. The Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association (DSM-V), defines patients with ID as having an IQ less than 70, onset during childhood, and dysfunction or impairment in more than two areas of adaptive behavior or systems of support.

Action

The committee checked for availability of a Centers for Medicare and Medicaid Services (CMS) national coverage decision (NCD). Based on the information provided in the systematic review, there is no NCD for whole genome sequencing.

The committee discussed clinical guidelines identified from the following organizations:

- Medical Genome Initiative (MGI), 2024, Evidence review and consideration for use of first-line genome sequencing to diagnose rare genetic disorders
- National Society of Genetic Counselors (NSGC), 2023, Genetic testing and counseling for the unexplained epilepsies: an evidence-based practice guideline
- National Institute of Health and Care Excellence (NICE), 2022, Epilepsies in children, young people, and adults
- EuroGentest, 2022, Recommendations for WGS in diagnostics for rare diseases
- American College of Medical Genetics and Genomics (ACMG), 2021, Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability evidence-based guideline
- Canadian College of Medical Geneticists, 2015, The clinical application of genome-wide sequencing for monogenic diseases in Canada

The recommendations of the guidelines vary. The committee's determination is consistent with the noted guidelines.

HTA staff will prepare a findings and decision document on use of spinal cord stimulation for the treatment of selected conditions for public comment to be followed by consideration for final approval at the next committee meeting.

6. Meeting adjourned

Washington State Health Care Authority

Revised bariatric surgery

Draft findings and decision
Timeline, overview and comments

Timeline

Phase	Date	Public Comment Days
Selected technologies published	July 7, 2023	
Public comments	July 7 to August 7, 2023	**31**
Draft key questions published	October 19, 2023	
Public comments	October 19 to November 1, 2023	**14**
Final key questions published	November 15, 2023	
Draft report published	March 1, 2024	
Public comments	March 1 to April 1, 2024	**31**
Final report published	April 23, 2024	
Public meeting	May 17, 2024	
Draft findings & decision published	May 21, 2024	
Public comments	June 26 to July 10, 2024	**15**

Overview

Category	Comment Period *May 21 to June 3, 2024*	Cited Evidence
Patient, relative, and citizen	0	-
Legislator and public official	0	-
Health care professional	0	-
Industry & manufacturer	0	-
Professional society & advocacy organization	0	-
Total	**0**	

Washington State Health Care Authority

Health Technology Clinical Committee
DRAFT Findings and Decision

Topic: Bariatric surgery
Meeting date: May 17, 2024
Final adoption: Pending

Number and coverage topic:
20240517B – Bariatric surgery

HTCC coverage determination:
Bariatric surgery is a **covered benefit with conditions.**

HTCC reimbursement determination:
Limitations of coverage:

- **Adults**
  - Adults with body mass index (BMI) ≥35 (non-Asian descent) OR BMI ≥32.5 (Asian descent),

  OR
  - Adults with type 2 diabetes mellitus (T2DM) AND BMI ≥30 (non-Asian descent) OR BMI ≥27.5 (Asian descent)

  AND
  - Performed by a center with Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program (MBSAQIP) accreditation
- **Adolescents**
  - Adolescents (13+) with bone maturity AND BMI ≥40 OR BMI ≥35 with one obesity-related complication

  AND
  - Procedure is sleeve gastrectomy or Roux-en-Y gastric bypass

  AND
  - Performed by a center with Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program (MBSAQIP) accreditation
- **Approved procedures include:**
  - Adjustable gastric banding
  - Sleeve gastrectomy
  - Endoscopic sleeve gastroplasty
  - Roux-en-Y gastric bypass
  - Biliopancreatic diversion with or without duodenal switch
  - Single-anastomosis duodenal ileostomy with sleeve gastrectomy (SADI-S)
  - One-anastomosis gastric bypass (OAGB)

Non-covered indicators:

- Intragastric balloons are not a covered benefit

Related documents:

- Final key questions
- Final evidence report

- Meeting materials and transcript

Agency contact information:

Agency	Phone Number
Labor and Industries	1-800-547-8367
Public and School Employees Health Plan	1-800-200-1004
Washington State Medicaid	1-800-562-3022

HTCC coverage vote and formal action:

Committee decision

Based on the deliberations of key health outcomes, the committee decided that it had the most complete information: a comprehensive and current evidence report, public comments, and state agency utilization information. The committee discussed and voted separately on the evidence for the use of adjustable gastric banding, sleeve gastrectomy, endoscopic sleeve gastroplasty, Roux-en-Y gastric bypass, biliopancreatic diversion with or without duodenal switch, single-anastomosis duodenal ileostomy with sleeve gastrectomy, and one-anastomosis gastric bypass for adults and adolescents. The committee decided that the current evidence on adjustable gastric banding, sleeve gastrectomy, endoscopic sleeve gastroplasty, Roux-en-Y gastric bypass, biliopancreatic diversion with or without duodenal switch, single-anastomosis duodenal ileostomy with sleeve gastrectomy, and one-anastomosis gastric bypass for use in adults, and sleeve gastrectomy and Roux-en-Y gastric bypass in adolescents is sufficient to determine coverage with conditions. The committee considered the evidence, public comment and expert input, and gave greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.

Based on these findings, the committee voted to cover with conditions adjustable gastric banding, sleeve gastrectomy, endoscopic sleeve gastroplasty, Roux-en-Y gastric bypass, biliopancreatic diversion with or without duodenal switch, single-anastomosis duodenal ileostomy with sleeve gastrectomy, and one-anastomosis gastric bypass for use in adults and sleeve gastrectomy and Roux-en-Y gastric bypass in adolescents. Separately, the committee voted not to cover intragastric balloons for adults or adolescents.

	Not covered	Covered under certain conditions	Covered unconditionally
Adjustable gastric bands, sleeve gastrectomy, endoscopic sleeve gastroplasty, Roux-en-Y gastric bypass, biliopancreatic diversion with or without duodenal switch, single anastomosis duodenal ileostomy with sleeve gastrectomy, and one-anastomosis gastric bypass in adults	0	9	0
Sleeve gastrectomy and Roux-en-Y gastric bypass in adolescents	0	9	0

Discussion

The committee reviewed and discussed the available studies for use of adjustable gastric banding, sleeve gastrectomy, endoscopic sleeve gastroplasty, Roux-en-Y gastric bypass, biliopancreatic diversion with or without duodenal switch, single-anastomosis duodenal ileostomy with sleeve gastrectomy, and one-anastomosis gastric bypass for adults and adolescents. Conditions for

coverage were discussed, drafted, and voted on. All committee members present supported the conditions of coverage of adjustable gastric banding, sleeve gastrectomy, endoscopic sleeve gastroplasty, Roux-en-Y gastric bypass, biliopancreatic diversion with or without duodenal switch, single-anastomosis duodenal ileostomy with sleeve gastrectomy, and one-anastomosis gastric bypass for adults and sleeve gastrectomy and Roux-en-Y gastric bypass for adolescents. Details of study design, inclusion criteria, outcomes, cost, cost-effectiveness, and other factors affecting study quality were discussed as well as clinical application.

Decision

Bariatric surgery is covered with conditions for the following:

- **Approved procedures include:**
    - Adjustable gastric banding
    - Sleeve gastrectomy
    - Endoscopic sleeve gastroplasty
    - Roux-en-Y gastric bypass
    - Biliopancreatic diversion with or without duodenal switch
    - Single-anastomosis duodenal ileostomy with sleeve gastrectomy
    - One-anastomosis gastric bypass
- **Adults**
    - Adults with body mass index (BMI) ≥35 (non-Asian descent) OR BMI ≥32.5 (Asian descent),

  OR
    - Adults with type 2 diabetes mellitus (T2DM) AND BMI ≥30 (non-Asian descent) OR BMI ≥27.5 (Asian descent)

  AND
    - Performed by a center with Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program (MBSAQIP) accreditation
- **Adolescents**
    - Adolescents (13+) with bone maturity AND BMI ≥40, OR ≥35 with one obesity-related complication

  AND
    - Procedure is sleeve gastrectomy or Roux-en-Y gastric bypass[1]

  AND
    - Performed by a center with Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program (MBSAQIP) accreditation

Bariatric surgery is not a covered benefit for the use of intragastric balloons in adults or adolescents.

Action

The committee checked for availability of a Centers for Medicare and Medicaid Services (CMS) national coverage decision (NCD). Based on the information provided in the systematic review, there is an NCD for bariatric surgery:

- **Centers for Medicare and Medicaid Services (CMS) National Coverage Determination**

[1] *Highlighted portions amended to include HTCC's original draft language during May 17, 2024 meeting.*

In 2006, the Centers for Medicare & Medicaid Services (CMS) issued a National Coverage Determination (NCD) limiting Medicare coverage to accredited centers[154]; subsequently, by 2010 almost 90% of MBS procedures were performed in accredited centers.[150,153] Although CMS ultimately reversed the facility accreditation requirement in 2013, citing inconsistent outcomes at bariatric centers of excellence and concern regarding access limitations, participation in national accreditation has remained high.[150,153,155-157]

The committee discussed clinical guidelines identified from the following organizations:

- American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings: Co-Sponsored by the American Association for the Study of Liver Diseases (2022)
- Referral of Adults with Obstructive Sleep Apnea for Surgical Consultation: An American Academy of Sleep Medicine Clinical Practice Guideline (2021)
- American Gastroenterological Association (AGA) Clinical Practice Guidelines on Intragastric Balloons in the Management of Obesity (2021)
- VA/DoD Clinical Practice Guideline for the Management of Adult Overweight and Obesity (2020)
- Clinical Practice Guidelines for the Perioperative Nutrition, Metabolic, and Nonsurgical Support of Patients Undergoing Bariatric Procedures - 2019 Update: Cosponsored by American Association of Clinical Endocrinologists/ American College of Endocrinology, The Obesity Society, American Society for Metabolic and Bariatric Surgery, Obesity Medicine Association, and American Society of Anesthesiologists (2020)
- 2022 American Society for Metabolic and Bariatric Surgery and International Federation for the Surgery of Obesity and Metabolic Disorders Indications for Metabolic and Bariatric Surgery (2023)
- American Society for Metabolic and Bariatric Surgery Updated Statement on Single-Anastomosis Duodenal Switch (2020)
- American Society for Metabolic and Bariatric Surgery position statement on one-anastomosis gastric bypass (2024)
- Evaluation and Treatment of Obesity and Its Comorbidities: 2022 Update of Clinical Practice Guidelines for Obesity by the Korean Society for the Study of Obesity (2023)
- Metabolic Surgery in Treatment of Obese Japanese Patients with Type 2 Diabetes: A Joint Consensus Statement from the Japanese Society for Treatment of Obesity, the Japan Diabetes Society, and the Japan Society for the Study of Obesity (2022)
- European Guideline on Obesity Care in Patients with Gastrointestinal and Liver Diseases - Joint European Society for Clinical Nutrition and Metabolism / United European Gastroenterology Guideline (2022)
- IFSO Update Position Statement on One Anastomosis Gastric Bypass (OAGB) (2021)
- Single Anastomosis Duodenal-Ileal Bypass with Sleeve Gastrectomy/One Anastomosis Duodenal Switch (SADI-S/OADS) IFSO Position Statement-Update 2020 (2021)
- Clinical Practice Guidelines of the European Association for Endoscopic Surgery (EAES) on Bariatric Surgery: Update 2020. Endorsed by IFSO-EC, EASO and ESPCOP

- Clinical Practice Guidelines for Childbearing Female Candidates for Bariatric Surgery, Pregnancy, and Post-partum Management After Bariatric Surgery (2019)
- Obesity Canada and the Canadian Association of Bariatric Physicians and Surgeons Clinical Practice Guidelines: Bariatric Surgery: Surgical Options and Outcomes (2020)
- Remission of Type 2 Diabetes: Diabetes Canada Clinical Practice Guidelines Expert Working Group (2022)
- Ministry of Public Health Qatar National Clinical Guideline: Bariatric & Metabolic Surgery in Adults (2021)
- NICE Guideline: Overweight and Obesity Management: Draft for Consultation (*Expected 2024*)
- NICE Interventional Procedures Guidance: Endoscopic Sleeve Gastroplasty for Obesity (2024)
- European Association for Endoscopic Surgery Rapid Guideline: Systematic Review, Network Meta-Analysis, CINeMA and GRADE assessment, and European Consensus on Bariatric Surgery-Extension 2022

The recommendations of the guidelines vary. The committee's determination is consistent with the noted guidelines.

HTA staff will prepare a findings and decision document on use of bariatric surgery for public comment to be followed by consideration for final approval at the next committee meeting.

Health Technology Clinical Committee Authority:

Washington State's legislature believes it is important to use a science-based, clinician-centered approach for difficult and important health care benefit decisions. Pursuant to chapter 70.14 RCW, the legislature has directed the Washington State Health Care Authority (HCA), through its Health Technology Assessment (HTA) program, to engage in an evaluation process that gathers and assesses the quality of the latest medical evidence using a scientific research company that takes public input at all stages.

Pursuant to RCW 70.14.110, a Health Technology Clinical Committee (HTCC) composed of eleven independent health care professionals reviews all the information and renders a decision at an open public meeting. The Washington State HTCC determines how selected health technologies are covered by several state agencies (RCW 70.14.080-140). These technologies may include medical or surgical devices and procedures, medical equipment, and diagnostic tests. HTCC bases its decisions on evidence of the technology's safety, efficacy, and cost effectiveness. Participating state agencies are required to comply with the decisions of the HTCC. HTCC decisions may be re-reviewed at the determination of the HCA Director.

Washington State Health Care Authority

Whole genome sequencing

Draft findings and decision
Timeline, overview and comments

Timeline

Phase	Date	Public Comment Days
Selected technologies published	July 7, 2023	
Public comments	July 7 to August 7, 2023	**31**
Draft key questions published	October 18, 2023	
Public comments	October 18 to October 31, 2023	**14**
Final key questions published	November 15, 2023	
Draft report published	April 4, 2024	
Public comments	April 4 to May 6, 2024	**32**
Final report published	May 22, 2024	
Public meeting	June 14, 2024	
Draft findings & decision published	June 26, 2024	
Public comments	June 26 to July 10, 2024	**14**

Overview

Category	Comment Period *May 21 to June 3, 2024*	Cited Evidence
Patient, relative, and citizen	0	-
Legislator and public official	0	-
Health care professional	0	-
Industry & manufacturer	1	Yes
Professional society & advocacy organization	2	Yes
Total	**3**	

Comments

	Respondents	Representing	Cited Evidence
☐ 1.	Ty Jones	Cambia Health Services	Yes
☐ 2.	Sarah Cowles Candadai	PLUGS	Yes
☐ 3.	Max Brown	NW Rare Disease Coalition	No

From: [redacted]
To: HCA ST Health Tech Assessment Prog
Subject: Public Comments for HTCC 20240614A Whole Genome Sequencing DRAFT Findings and Decision
Date: Monday, July 8, 2024 9:44:38 AM

External Email

The Final Evidence Report cites that 3 of the 12 payors reviewed preauthorize WGS. I see that those three payors have combined their WES and WGS policies, and the WGS part of each policy has a criterion that includes WES testing status. I see that the limitations of coverage in the draft for new HTCC are identical to HTCC 20191122A Whole Exome Sequencing. Have you considered combining the WES (https://www.hca.wa.gov/assets/program/wes-final-findings-decision-20200515.pdf) and WGS HTCC Decisions, and/or calling out WES testing in the WGS limitations of coverage?

The WGS policy criteria that addresses WES testing status from those policies is listed below.

a. Cigna[1]: "Concurrent whole exome and whole genome sequencing is considered not medically necessary."

b. Centene[2]: "Criteria A. The member/enrollee previously had uninformative whole exome sequencing (WES), AND 1. WES reanalysis is not possible."

c. United Health[3]: "Neither CMA nor WES have been performed;"

Cited sources:

1. Cigna. Medical Coverage Policy. Whole exome and whole genome sequencing for noncancer indications. Whole Exome and Whole Genome Sequencing for Non-Cancer Indications (cigna.com). Published 2023. Updated January 15, 2024. Accessed June 6, 2024.
2. Centene Corporation. Concert Genetic Testing: Exome and Genome Sequencing For The Diagnosis of Genetic Disorders. https://www.coordinatedcarehealth.com/content/dam/centene/Coordinated%20Care/policies/clinical-policies/corp-WA-eff-dates/CG_Exome_and_Genome_Sequencing_for_Dx.pdf. Published 2023. Updated March 1, 2023. Accessed June 6, 2024.
3. United Health Care. Medical Management Guideline. Whole exome and whole genome sequencing (Non-Oncology Conditions). Whole Exome and Whole Genome Sequencing (Non-Oncology Conditions) – Commercial and Individual Exchange Medical Policy (uhcprovider.com). Published 2024. Updated January 1, 2024. Accessed June 6, 2024.

Ty Jones, MD, CAQSM, CPPS, CPHQ (he/him)
Health Care Authority Medical Director
Cambia Health Solutions
[redacted]

[redacted]

From: [redacted]
To: HCA ST Health Tech Assessment Prog
Cc: [redacted]
Subject: Feedback on HTCC Draft Coverage Criteria for WGS
Date: Monday, July 8, 2024 2:51:47 PM
Attachments: HTA Draft Coverage Criteria feedback_SCHPLUGS_07.08.24.pdf

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External Email

To Whom It May Concern,

On behalf of PLUGS (Patient-centered Laboratory Utilization Guidance Services), we would like to share the following feedback with the HTCC regarding the proposed coverage criteria for whole genome sequencing.

Jessie Conta (Licensed Genetic Counselor, Laboratory Stewardship Consultant, PLUGS® Co-founder) is copied here, and both she and I can serve as primary points of contact for questions.

Thank you for your consideration and please let us know if we can provide additional information.

Sincerely,
Sarah Clowes Candadai

Sarah Clowes Candadai, MS, CGC
Pronouns: She/Her

Program Manager II, PLUGS
Licensed Genetic Counselor
Department of Laboratories & PLUGS (Patient-centered Laboratory Utilization Guidance Services)
[redacted]

[redacted]

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To Whom It May Concern,

We want to thank the Director and HTCC for the thoughtful review of whole genome sequencing (WGS). We attended the June 14th Committee meeting and appreciated the opportunity to provide public comment. We reviewed the HTCC report from that meeting and would like to share specific feedback on the proposed criteria. This feedback is based on our clinical experience supporting genomic testing at Seattle Children's hospital, our national perspective on access barriers from our leadership position within PLUGS, and our specific expertise in medical policy development for molecular testing.

1. **Clinical Coverage Criteria:**
   Briefly, 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. The inclusion criteria at that time were based on the PLUGS Whole Exome Sequencing Policy, version 2, published in October 2019. Since that time, the policy was updated to the PLUGS Genomic Testing in Rare Disease policy and covers both exome and genome sequencing (version 1, published June 2022, revised in July 2023) and we're the process of completing our annual review of this policy. As was discussed during the Committee meeting, genomic testing evolves rapidly, and these policies have also changed considerably since 2019. For these reasons, we encourage review of the current PLUGS Genomic Testing in Rare Disease policy and utilization of this resource to guide the inclusion criteria for whole genome sequencing (WGS). A copy of the current policy is attached and can also be accessed here: https://www.schplugs.org/wp-content/uploads/Genomic-Sequencing-in-Rare-Disease_2023_FINAL.pdf.

   The PLUGS policy specifically aligns with existing professional society guidelines reviewed by the HTCC, including clinical guidelines from ACMG and NSGC regarding clinical populations that benefit from genomic testing.

   Specifically, these guidelines support WGS for individuals with the following isolated features:

   - Epilepsy of unexplained etiology with onset at any age (PLUGS policy references 55-58)
   - Confirmed bilateral sensorineural hearing loss of unknown etiology and panel testing is unrevealing (PLUGS policy reference 59)
   - Intellectual disability (ID), following formal assessment by a developmental pediatrician or neurologist, defined as moderate/severe/profound by Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria, diagnosed by 18 years of age (PLUGS policy references 38, 53-54)
   - Global developmental delay (DD), following formal assessment by a developmental pediatrician or neurologist, defined as significant delay in younger children, under age five years, in at least two of the major developmental domains: gross or fine motor; speech and language; cognition; social and personal development; and activities of daily living (PLUGS policy references 38, 53-54)

   The PLUGS policy incorporates these recommendations as stand-alone inclusion criteria, which we recommend incorporating as a solution to HTCC discussion points for final coverage decisions.

2. Provider Specialty Requirement:

The draft decision includes a requirement for a medical geneticist to evaluate the patient; however, this is a significant access barrier. Historically, payer policies included explicit requirements regarding ordering and/or evaluating providers, often limiting to a board-certified/board-eligible geneticist. Our original PLUGS policy was one of these and our rationale for including this requirement at that time was to prevent misutilization of a new technology. Since 2019, medical practice and our approach has evolved out of necessity to prevent unnecessary access barriers and based on our clinical utilization experience at Seattle Children's and among our national PLUGS peers.

There is a critical shortage of medical geneticists in the United States with estimates of 2 medical geneticists per 500,000 people and medical geneticists accounting for <1% of physician workforce.[1-3] Nationally, available medical geneticists are clustered in metropolitan areas leading to limited or no access for people who reside in rural areas.[3] Lack of access can result in socioeconomic status-based inequities and differences in health outcomes for underserved populations.[3] Additionally, waiting time for specialist evaluation including geneticists may be lengthy, further delaying access to testing and care.[2,4]

In Washington, we see similar findings with variable wait times to see a medical geneticist. Through personal communications with genetics clinics across the state, we know that while some clinics have wait times of 3-4 months for new patients, most patients may wait upwards of a year to be seen for some indications. For adult patients, options are even more limited. Referral indications for test coordination from specialists are increasingly common, due to payer policy requirements.

More recent guidelines and statements recognize the importance and role of non-geneticists in providing access to genetic testing including WGS as part of the care for their patients.[5-7] For example, the 2021 ACMG ES/GS practice guideline explicitly states the guideline is intended to assist nongenetic professionals "to appropriately use and interpret ES/GS".[8]

The HTCC draft coverage criteria includes a requirement to involve a genetic counselor which provides the appropriate safety net to support alignment with the inclusion criteria, appropriate utilization, and most importantly, informed consent and counseling. Genetic counselors play a critical role in guiding testing strategy and assessing the utility of genetic testing in individuals with rare disease, as well as supporting informed consent. Practice guidelines outline the role of genetic counselors in consent and result disclosure/interpretation for WGS.[9] Genetic counselors are trained to assess appropriate testing strategies and prevent order errors.[10,11] Genetic counselors can bridge access gaps between medical geneticists and other specialists, ensuring appropriate utilization of genomic sequencing in individuals with rare disease.[10,11] For these reasons, Seattle Children's Hospital and other PLUGS member sites empower specialists to recommend and order WGS testing as long as pre- and post- test genetic counseling is provided by a Genetic Counselor.

In the absence of clear inclusion criteria, it is logical to require that the patient be seen by a trusted expert who can steward limited resources and use WGS appropriately. However, when the inclusion criteria for use of WGS are detailed and explicit, as drafted and with our additional recommendations, requiring a medical geneticist evaluation puts an unnecessary barrier to access and will result in additional disparities of care.

We therefore recommend revising criterion 1 from:

1. *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), who is not employed by a commercial genetic testing laboratory, has evaluated the patient and family history, and recommends and/or orders the test;

to:

1. ***The patient and the patient's family history have been evaluated by a board-certified/board-eligible specialist with expertise in the conditions and genes for which testing is being considered.***

and keeping criterion 8 as written (*Pre- and post-test counseling is performed by an American Board of Medical Genetics or American Board of Genetic Counseling certified genetic counselor*).

3. Consider how WGS coverage criteria impacts existing WES coverage

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 efficiencies as was highlighted in the evidence review and HTCC discussion. As such, WGS will likely supplant WES to become the preferred diagnostic test, particularly as access to WGS increases; however, this will likely take many years.[12] The final version of the HTCC coverage criteria for WGS will most likely differ from the criteria that exists for WES that was approved by the Committee in 2020. PLUGS opted to combine the technologies into a single policy for use until WGS fully replaces WES.

Considering the updated review of WGS, we encourage the HTCC to provide guidance on how to utilize both policies in practice and recommend reviewing the PLUGS policy example.

Thank you for your consideration. Please contact us if you have additional questions.

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

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Appendix:

PLUGS POLICY GENOMIC SEQUENCING FOR RARE DISEASE

Genomic Sequencing for Rare Disease

Executive Summary:

This health insurance policy describes using advanced genetic testing methods, known as exome sequencing (ES) and genome sequencing (GS), to help people with rare genetic diseases. Rare diseases affect around 1 in 10 Americans. Many of these conditions come from our genes.

ES and GS are powerful tools that doctors use to figure out what's causing these rare genetic diseases in individuals. They're much better at diagnosing these conditions, which can lead to better medical care and even save money. These tests are recommended for people who fit certain criteria, like when doctors don't know the genetic cause of a disease and have ruled out other possibilities.

The policy highlights how helpful ES and GS can be in various conditions such as birth defects, brain and nerve disorders, epilepsy, hearing loss, and certain inherited metabolism problems. GS is favored over ES because it has technical advantages, and using samples from not just the individual but their family too can make the diagnosis even better. Also, going back and reanalyzing genetic data that was collected before can give us more insights for diagnosis.

The policy also underlines the importance of talking to qualified genetic counselors before and after getting these tests done. These experts can provide valuable guidance and support to understand the results and make informed decisions about healthcare.

Background:

Approximately 1 in 10 Americans, an estimated 30 million individuals, are affected by rare disease. It is estimated that 71.9% of rare diseases have identified genetic origins.[2] The average time to get an accurate diagnosis is 4.8 years.[1] The diagnostic evaluation of an individual suspected of having a rare genetic condition may include combinations of radiographic, biochemical, electrophysiologic, and genetic testing. Genetic testing strategies include targeted approaches, such as single-gene analysis, and/or a targeted gene panel, chromosomal microarrays, as well as broad genomic sequencing, including exome sequencing (ES) and genome sequencing (GS). ES/GS are particularly useful for evaluating genetic conditions that demonstrate a high degree of genetic heterogeneity. When compared to serial genetic testing strategies, ES/GS are superior due to broader coverage, reduced cost and improved efficiencies.[3-8]

Identifying a molecularly confirmed diagnosis in a timely manner for an individual with a rare genetic condition can have a variety of health outcomes including but not limited to:[7,9-20]

- guiding prognosis and improving clinical decision-making via
    - application of specific treatments, as well as withholding of contraindicated treatments for certain rare genetic conditions
    - planning or avoidance of surgical interventions
    - surveillance for comorbidities
    - initiation of palliative care
    - withdrawal of care
- reducing the psychological and financial 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 for other living relatives (i.e., siblings), as well as recurrence risk counseling and prenatal diagnosis options for the family

Genomic Sequencing for Rare Disease

Technical Information:

Genomic sequencing technologies currently utilized in clinical practice include exome sequencing and short-read genome sequencing. ES and GS are similar diagnostic tools in the evaluation of individuals with rare disease, but there are clear technical advantages of GS that support increased diagnostic yield and efficiencies as outlined below. As such, GS will likely supplant ES to become the preferred diagnostic test, particularly as access to GS increases.[21]

Exome sequencing (ES) is a capture-based method that targets the DNA sequence of coding regions (exons) and flanking intronic regions of 1% of the genome. ES is associated with technical and analytical variability, including uneven sequencing coverage and gaps in exon capture before sequencing. In contrast, genome sequencing (GS) involves shearing and sequencing all intergenic and intragenic regions, eliminating the need for a capture step, which increases efficiency and minimizes PCR-based artifacts. Both ES and GS can identify the following categories of pathogenic variants: missense, nonsense, splice-site, and small deletions or insertions. GS is advantageous as a diagnostic tool due to uniformity of coverage, including GC-rich regions, as well as the ability to detect variants that may be missed by ES, such as copy-number variants (CNV), mid-size insertions and deletions (ca. 10-500 bp), nucleotide repeat expansion mutations, deeper intronic mutations, structural variants (e.g., translocations, inversions), and variants that result in methylation defects and uniparental disomy.[13,15,22-26]

Several studies have compared ES to GS and demonstrate improved diagnostic yield with GS. Lionel et al examined a cohort of participants (N=70) who received both GS and ES.[6] In this cohort, GS had a diagnostic yield of 50% compared to 37% for ES. GS detected all diagnostic variants found by ES in addition to revealing several diagnostic variants not apparent in ES data. Examples of variants "missed" by ES included deep intronic SNVs, small CNVs, and SNVs in noncoding RNA. Wang et al showed that, in comparison to GS, a significant number of pathogenic variant types would have gone undetected by ES, CMA, and ES + CMA. Variant types that were undetected by ES included large CNVs, small deletions and structural variants.[17]

Addition of CNV calling to small variant calling pipelines improves diagnostic efficacy and efficiency in patients with rare genetic disease. GS is a unified testing platform that can be used in place of combined or sequential ES and chromosomal microarray (CMA).[6,26] In a prospective comparative study in which 100 patients with suspected genetic diseases received GS and CMA, GS identified genetic variants meeting clinical diagnostic criteria in 34% of cases, representing a fourfold increase in diagnostic rate over CMA (8%; P value = 1.42E − 05), and identified all CNVs detected by CMA.[10]

In addition, GS has shown incremental diagnostic yield in individuals with non-diagnostic ES. In a cohort of heavily pre-investigated patients, GS was able to provide a diagnosis in 13% of patients in whom ES results were inconclusive.[27] Another study of 50 patients with severe intellectual disability and non-diagnostic CMA ES demonstrated that GS had a diagnostic yield of 42%.[22] Bertoli-Avella et al showed that up to 29.6% of ES negative cases could benefit from GS testing (14.5% with pathogenic or likely pathogenic results, and 15.1% with VUS).[28] The majority of genetic diagnoses made by GS in ES negative cases could be attributed to its superior technical performance; GS detected 79 noncoding variants, 41 of which were classified as pathogenic/likely pathogenic.

The use of family trio samples in genomic sequencing analysis helps reduces the time to diagnosis, the rate of uncertain findings, and improves the clinical sensitivity and efficiency with regard to the

interpretation of clinically novel genes, and increases the diagnostic yield of ES/GS.[12,15,29,30] As part of a meta-analysis, five studies that conducted within-cohort comparisons of diagnostic utility of singleton and trio ES/GS found the pooled odds of diagnosis for trios was twice that of singletons (P<0.0001).[31]

Periodic reanalysis of previously obtained exome or genome sequence has the potential for additional diagnostic yield because of expanding variant databases, as well as periodic novel gene discovery and publication.[25,32-34] A review of twenty-seven peer-reviewed articles revealed a median new diagnosis rate via reanalysis of 15% and median reanalysis timeframe of 22 months.[34] The authors suggest that an interval of greater than 18 months from the original report may be optimal for reanalysis. The majority of new diagnoses from re-analysis of ES result from newly discovered genes, with additional diagnostic yield from expanded phenotypic spectrum and upgraded classification of variants in previously known genes.[35] Reanalysis can be improved by thorough clinical reassessment and systematic reevaluation of the patient by the ordering provider.[36]

Guidelines and Evidence:

The American College of Medical Genetics and Genomics (ACMG) has several relevant policy statements that offer guidance on: the clinical application of ES/GS,[37,38] informed consent for ES/GS,[39] technical standards to ensure quality results and the interpretation and reporting of variants,[40] reporting of secondary findings in clinical ES/GS,[41,42] and re-analysis.[44]

A statement from the ACMG includes the following indications for diagnostic testing using ES/GS in assessment of phenotypically affected individuals when:[37]

> "a. The phenotype or family history data strongly implicate a genetic etiology, but the phenotype does not correspond with a specific disorder for which a genetic test targeting a specific gene is available on a clinical basis."
> "b. A patient presents with a defined genetic disorder that demonstrates a high degree of genetic heterogeneity, making WES or WGS analysis of multiple genes simultaneously a more practical approach."
> "c. A patient presents with a likely genetic disorder, but specific genetic tests available for that phenotype have failed to arrive at a diagnosis."
> "d. A fetus with a likely genetic disorder in which specific genetic tests, including targeted sequencing tests, available for that phenotype have failed to arrive at a diagnosis."

The ACMG issued an evidence-based clinical practice guideline for the use of exome sequencing and genome sequencing (ES/GS) in 2021.[38] The guideline supports the clinical utility of ES/GS as a first- or second-tier test for individuals with one or more congenital anomalies with onset prior to age 1 year, or developmental delay, or intellectual disability with onset prior to 18 years. ES/GS has a higher diagnostic yield compared with standard genetic testing and may be more cost-effective when ordered earlier in the diagnostic evaluation.

In 2021, the ACMG Secondary Findings Working Group published an updated policy statement with recommendations for reporting of secondary findings in clinical ES and GS.[41] This policy statement provides guidance on consenting, scope of secondary finding reporting based on test type, and proposes a framework for annual updates to the secondary findings list. The goal of the secondary finding gene list is to provide updated guidance to clinical laboratories on which medically actionable genes unrelated to the indication for testing should be evaluated as part of clinical ES/GS.[42] Included in this list are several genes associated with heritable cardiovascular disease. The American Heart Association

published a consensus statement to guide clinicians regarding counseling for incidentally identified genetic variants in monogenic cardiovascular disease genes and to assist them in the interpretation and clinical application of variants.[43]

Recommendations for obtaining informed consent for clinical ES/GS, including secondary findings, have also been outlined by the ACMG.[39] A medical geneticist or genetic counselor should perform pre-test counseling and consent documentation.

The ACMG Laboratory Quality Assurance Committee issued points to consider in the reevaluation and reanalysis of genomic test results,[44] including general considerations, considerations for variant-level reevaluation and case-level reanalysis, and reporting. This statement also suggests considerations for reanalysis versus retesting using new methodologies, including:

- Time elapsed since the previous testing occurred
- Improvements in technology/chemistry (e.g., new methods for DNA capture and sequencing)
- Bioinformatics advancements
- New information regarding the genetic etiology of a condition
- Additional patient phenotypes or family history that developed in the interim

ES/GS are powerful diagnostic tools for individuals with rare genetic conditions in which the specific genetic etiology is unclear or unidentified by standard clinical evaluation. While the diagnostic yield of ES/GS varies depending upon the individual's age, phenotype, previous workup, and inclusion of comparators, the efficacy is well established. Further, the diagnostic yield of ES/GS is higher when used earlier in the diagnostic work-up.[45] A review of publications from 2009-2017 revealed median diagnostic yield of ES/GS in aggregate analyses was 33.2%, but varied by broad clinical categories and test type.[14] The 100,000 Genomes Project demonstrated that GS had an overall diagnostic yield of 25% in 2183 probands—many of whom were heavily pre-tested.[46] Notably, diagnostic yields for intellectual disability, hearing disorders, and vision disorders ranged from 40 to 55%; diagnostic yield for individuals with dysmorphic or congenital anomalies was 21%. Based on the results, the National Health Service implemented GS as the first-tier test for 25+ different clinical conditions. Use of GS/ES also reveals dual molecular diagnoses that contribute to complex phenotypes (i.e., two significant findings associated with non-overlapping clinical presentations).[10]

Evidence for the clinical utility of ES/GS in individuals suspected of having rare genetic disease includes numerous retrospective and prospective case series, and randomized controlled trials. Relevant outcomes include improved clinical decision-making (e.g., initiation of specific treatments, withholding of contraindicated treatments, changes to surveillance, changes in reproductive decision making, and resource utilization.[7,10,13,14,16-19,27,30,47,48] An impact on medical management has been clearly demonstrated in both rapid ES/GS and non-rapid ES/GS cohorts.

A meta-analysis of relevant articles published between 2011 and 2021 compared the diagnostic rate and clinical utility of ES and GS across pediatric and adult populations, as well as the number of variants of uncertain significance (VUS) and health economic outcomes associated with these technologies.[49] Based on nine studies that compared ES and GS within the cohorts, the odds of a diagnosis by GS was 1.2 times greater than that of ES. Pooled clinical utility of GS (61%) was higher than that of ES (48%) and the rate of VUS by ES and GS did not differ significantly.

Genomic Sequencing for Rare Disease

ES/GS has been shown to positively impact healthcare utilization through cost-savings compared to serial genetic testing strategies, as well as reduced lengths of stay and reduced professional and facility fees.[4,8,12,19,45] Several health economic studies have been published that demonstrate that GS is the most efficient approach to the diagnosis of children with rare and undiagnosed genetic conditions compared to previous standard of care.[8,50] If GS is unavailable, ES represents the next most efficient option compared with standard of care. Other strategies provided the same or fewer diagnoses at a higher incremental cost per diagnosis.

Genetic counselors play a critical role in guiding testing strategy and assessing the utility of genetic testing in individuals with rare disease, as well as supporting informed consent. Practice guidelines outline the role of genetic counselors in consent and result disclosure/interpretation for ES/GS.[37] Genetic counselors are trained to assess appropriate testing strategies and prevent order errors.[51,52] Genetic counselors can bridge access gaps between medical geneticists and other specialists, ensuring appropriate utilization of genomic sequencing in individuals with rare disease.[51,52]

Congenital Anomalies

Many congenital anomalies have an underlying genetic etiology, and may occur in isolation, or in conjunction with other features. ES/GS have demonstrated diagnostic utility in individuals with multiple congenital anomalies, particularly when ordered early in the diagnostic evaluation.[46,48] The ACMG evidence-based clinical practice guideline supports the use of ES/GS as a first- or second-tier test for individuals with one or more congenital anomalies with onset prior to age 1 year.[38] Clinical utility includes short-term active clinical management changes (modifications to medications, procedures, or treatment) and long-term clinical management (referral to specialists and surveillance for disease-related conditions, or lifestyle changes).

Neurodevelopmental Disorders

Neurodevelopmental disorders, including global developmental delay, intellectual disability, and/or autism spectrum disorder, are a heterogeneous group of conditions that impact brain development and affect various aspects of daily functioning. A meta-analysis investigating the diagnostic yield of ES in neurodevelopmental disorders (NDD) showed that ES outperformed chromosomal microarray, with an overall diagnostic yield of 36% (31% for isolated NDD, and 53% for NDD plus associated conditions).[53] In another study of 100 individuals with intellectual disability, use of GS as a first-line genetic test yielded a diagnostic rate of 27%, more than doubled compared to clinical microarray (12%), including identification of structural variants, single nucleotide variants, uniparental disomy, and short tandem repeats.[54] The ACMG evidence-based clinical practice guideline supports the use of ES/GS as a first- or second-tier test for individuals with developmental delay (DD) or intellectual disability (ID) with onset prior to age 18 years.[38] Isolated autism without ID or congenital malformation was formally out of scope for the practice guideline, but evaluation of ES/GS in this population is ongoing.

Epilepsy

Epilepsy is a neurological disorder that causes recurrent, unprovoked seizures. While the cause of epilepsy is unknown in approximately 50% of cases, it can be caused by genetic factors, head trauma, structural brain abnormalities, stroke, infections, autoimmune conditions, metabolic conditions, tumors, or prenatal injury.[55] It is estimated that 30% of all epilepsies have a genetic cause.[56] A genetic diagnosis changed treatment in 12-80% of epilepsy patients including optimal anti-seizure medication, dietary treatment, and epilepsy surgical decisions.[57] A genetic diagnosis also informs recurrence risk estimations used in family planning. A practice guideline on genetic testing for epilepsy was published in 2022,

adopted by the National Society of Genetic Counselors (NSGC), and endorsed by the American Epilepsy Society (AES).[58] The guideline recommends genetic testing for individuals of any age with unexplained epilepsy to include exome/genome sequencing and/or a multi-gene panel (>25 genes) as first-tier testing followed by chromosomal microarray, with exome/genome sequencing conditionally recommended over multi-gene panel.

Hearing Loss

The ACMG Professional Practice Guidelines Committee presented updated recommendations for the evaluation and etiologic diagnosis of hearing loss.[59] Hearing loss is genetically heterogeneous, supporting the value of panels and ES/GS in the diagnostic evaluation. Identifying the etiology of hearing loss may affect clinical management, particularly for syndromic hearing loss, improve prognostic accuracy, and guide recurrence risk counseling. The guideline includes an updated algorithm (Figure 1) that integrates pre-test genetic counseling and initial testing using single-gene tests and comprehensive hearing loss gene panels, as well as congenital CMV testing using newborn bloodspots. If the initial testing is unrevealing, ES/GS can be considered.

Inherited Metabolic Disorders

Inherited metabolic disorders (IMDs) are rare genetic or inherited disorders resulting from an enzyme defect in biochemical and metabolic pathways affecting metabolism of proteins, fats, or carbohydrates or impaired organelle function.[60] IMDs can have complex clinical presentations and often impact multiple organ systems. Diagnosis typically involves a complex combination of biochemical and molecular analyses. Age of presentation can vary, with more severe forms appearing in early childhood accompanied by significant morbidity and mortality. Appropriate acute illness protocols and specific supportive therapies are necessary for individuals diagnosed with an IMD. Mitochondrial diseases are a subset of IDMs, with clinical and genetic heterogeneity that present diagnostic, clinical management, and therapeutic challenges. [60] Pathogenic variants in nuclear-encoded genes account for the majority of pediatric mitochondrial disease (70-80%) with 20-25% of cases due to pathogenic variants in the mitochondrial genome. Mitochondrial genome variants are more frequently responsible for mitochondrial disease in adults (75%).[61] GS is advantageous in the diagnostic work-up of mitochondrial disease because of coverage of both the nuclear and mitochondrial genomes in a single test, and ability to detect heteroplasmy levels as low as 1%. GS identified both mitochondrial and non-mitochondrial diagnoses in individuals with suspected mitochondrial disorders, preventing the need for invasive tests such as a muscle biopsy.[61,62]

Genomic Sequencing for Rare Disease

Criteria:

Exome Sequencing or Genome Sequencing:

Exome sequencing or genome sequencing (ES/GS) is considered medically necessary when ALL of the following criteria are met:

1. The etiology of the patient's features is not known, and a genetic etiology is considered a likely explanation for the phenotype, based on ONE of the following, AND
    a) Epilepsy of unexplained etiology with onset at any age, OR
    b) Confirmed bilateral sensorineural hearing loss of unknown etiology and panel testing is unrevealing, OR
    c) Intellectual disability, following formal assessment by a developmental pediatrician or neurologist, defined as moderate/severe/profound by Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria, diagnosed by 18 years of age, OR
    d) Global developmental delay, following formal assessment by a developmental pediatrician or neurologist, defined as significant delay in younger children, under age five years, in at least two of the major developmental domains: gross or fine motor; speech and language; cognition; social and personal development; and activities of daily living, OR
    e) Multiple congenital anomalies affecting unrelated organ systems, OR
    f) At least TWO of the following criteria are met:
        - abnormality affecting at minimum a single organ system
        - autism
        - severe neuropsychiatric condition (e.g., schizophrenia, bipolar disorder, Tourette syndrome, self-injurious behavior, reverse sleep-wake cycles)
        - symptoms of a complex neurological condition (e.g., dystonia, hemiplegia, spasticity, hypotonia, myopathy, muscular dystrophy)
        - family history strongly suggestive of a genetic etiology, including consanguinity
        - period of unexplained developmental regression (unrelated to epilepsy or autism)
        - laboratory findings suggestive of an inherited metabolic disorder
2. Alternate etiologies have been considered and ruled out, when possible (e.g., MRI abnormalities/brain malformations, environmental exposure, injury, infection, isolated prematurity), AND
3. Clinical presentation does not fit a well-described syndrome for which more targeted testing is available.

Exclusions:

- ES/GS is considered not medically necessary for the diagnosis of genetic disorders in individuals who do not meet the above criteria.
- ES/GS is considered experimental/investigational for screening for genetic disorders in asymptomatic or pre-symptomatic individuals.

Other Considerations:

- While ES and GS are similar diagnostic tools in the evaluation of individuals with rare disease, there are clear technical advantages of GS that support increased diagnostic yield and efficiencies. As such, if given a choice, GS is the preferred diagnostic test in individuals who meet the above criteria.

Genomic Sequencing for Rare Disease

- GS is preferred when a mitochondrial disorder is suspected, due to analysis of both the nuclear and mitochondrial genome.
- Pre- and post-test counseling by an appropriate provider, such as an American Board of Medical Genetics and Genomics or American Board of Genetic Counseling-certified Genetic Counselor, is strongly recommended.
- The patient and the patient's family history have been evaluated by a board-certified/board-eligible specialist with expertise in the conditions and genes for which testing is being considered.
- Trio samples are preferred for ES/GS. Use of family trio samples in genomic sequencing analysis helps reduces the time to diagnosis, the rate of uncertain findings, and improves the clinical sensitivity and efficiency regarding the interpretation of clinically novel genes, and increases the diagnostic yield of ES/GS
- Re-analysis of previously obtained exome or genome sequence has the potential for additional diagnostic yield because of expanding variant databases, as well as periodic novel gene discovery and publication. Re-analysis could be considered prior to additional genomic sequencing, particularly if there has been onset or identification of additional symptoms that broadens the clinical phenotype assessed during the original ES/GS analysis, and/or there has been a change in the family history that expands the clinical picture, such as the birth or diagnosis of a similarly affected first-degree relative.
- ES/GS in the setting of prenatal genetic diagnosis or screening is not addressed in this policy.
- Ideal sample type should be considered based on the clinical presentation (e.g., mosaicism is suspected based on pigmentary anomalies, consider skin fibroblast as ideal sample type).
- Rapid genome sequencing (rGS), defined as return of preliminary positive results in <7 days and final report in <14 days, may be indicated for acutely ill individuals. Criteria for rGS testing can be found in the Rapid Genome Sequencing Policy.

CPT Codes:

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
Genome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis	81425
Sequence analysis, each comparator genome (e.g., parent(s), sibling(s))	81426
Genome (e.g., unexplained constitutional or heritable disorder or syndrome), rapid sequence analysis (e.g., RCIGM Rapid Whole Genome Sequencing; Rady Children's Institute for Genomic Medicine)	0094U
Rare diseases (constitutional/heritable disorders), whole genome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, proband	0212U
Rare diseases (constitutional/heritable disorders), whole genome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and	0213U

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variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, each comparator genome (e.g., parent, sibling)	
Rare diseases (constitutional/heritable disorders), whole exome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, proband	0214U
Rare diseases (constitutional/heritable disorders), whole exome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, each comparator exome (e.g., parent, sibling)	0215U

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Update details:
Inclusion criteria was revised to align with the PLUGS Epilepsy Genetic Testing Policy and simplified for clarity. All references were reviewed, and additional references were included. Updated Executive Summary was added.

From: [redacted]
To: HCA ST Health Tech Assessment Prog
Subject: NW Rare Disease Coalition Draft Decision Comments - 7.10
Date: Wednesday, July 10, 2024 2:27:11 PM
Attachments: image001.png
7.9 HTCC draft decision wgs access.docx

External Email

Hello, I'm reaching out to share the attached letter from the NW Rare disease coalition, reflecting on the HTCC's draft decision regarding whole genome sequencing. We're very enthusiastic about the direction of the decision, but wanted to offer a minor suggestion to the "Provider Specialty Requirement" section to ensure equitable access to WGS is available across Washington state. Thank you very much your time and consideration of this submission.

Max Brown
Vice President of Public Affairs
[redacted]

Desimone
CONSULTING GROUP

July 10th, 2024

Dear Chair Rege, Vice Chair Friedly, and members of the Health Technology Clinical Committee,

Thank you for your thorough consideration of whole genome sequencing on June 14th. It was a privilege to have the opportunity to hear the very thoughtful presentation and discourse throughout the meeting. After review of the HTCC report, we hope to provide additional commentary to positively shape the already encouraging direction the HTCC is pursuing to expand access to more comprehensive testing technologies to rare disease patients across Washington state.

Our comments reflect on the "Provider Specialty Requirement" section of the draft decision – which would limit patient evaluations to be performed only by medical geneticists. For many communities, medical geneticists can be difficult to access. While urban communities with better resourced clinical systems might retain medical geneticists who could administer WGS evaluation in compliance with the draft decision, their presence in exurban or rural communities is increasingly sparse. For many young patients afflicted with rare diseases, time is of the essence to achieve diagnosis, and long wait times to access specialty care could negatively impact a lifetime of healthcare outcomes.

We'd urge the Committee to consider an expanded role that Genetic Counselors could play in helping to address potential WGS access disparities between communities in concert with other specialty clinicians. Genetic Counselors are trained to recommend appropriate testing options, scan for any ordering errors, and liaise between other specialties, providing a critical link between patients and the network of physicians that serve them. Clinical settings are increasingly empowering different clinical specialists to recommend and order WGS testing if Genetic Counselors are involved in providing counseling services to patients before and after testing.

We are concerned that the draft decision grants exclusive evaluation authority solely to medical geneticists, which will create an access barrier that will be difficult to overcome in more rural parts of the state. We hope you consider modification to the "Provider Specialty Requirement" section of the draft decision to open the aperture of evaluating specialists beyond medical geneticists, insofar as Genetic Counselors remain involved in both pre-and-post-test evaluation. Thank you very much for your time and continued consideration.

Sincerely,

Northwest Rare Disease Coalition Co-Founders

Carolina Sommer Joshua Henderson Max Brown

Washington State Health Care Authority

Health Technology Clinical Committee
DRAFT Findings and Decision

Topic: Whole genome sequencing
Meeting date: June 14, 2024
Final adoption: Pending

Number and coverage topic:
20240614A – Whole genome sequencing

HTCC coverage determination:
Whole genome sequencing is a **covered benefit with conditions.**

HTCC reimbursement determination:
Limitations of coverage:
Whole genome sequencing (WGS) is a covered benefit with conditions for the evaluation of unexplained congenital or neurodevelopmental or neurodegenerative disorders in a phenotypically affected individual when **ALL of the following** criteria are met:

1. 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), who is not employed by a commercial genetic testing laboratory, has evaluated the patient and family history, and recommends and/or orders the test; and

2. A genetic etiology is considered the most likely explanation for the phenotype, based on **EITHER of the following**;

   - Multiple abnormalities affecting unrelated organ systems, (e.g. multiple congenital anomalies); or

   - **TWO of the following criteria are met:**

     — Significant abnormality affecting at minimum, a single organ system,
     — Unexplained cognitive changes in adulthood,
     — Profound global developmental delay[1], or intellectual disability[2] as defined below,
     — Family history strongly suggestive of a genetic etiology, including consanguinity,
     — Period of unexplained developmental regression (unrelated to autism or epilepsy),
     — Biochemical findings suggestive of an inborn error of metabolism where targeted testing is not available; and

3. Other circumstances (e.g. environmental exposures, injury, infection) do not reasonably explain the constellation of symptoms; and

4. 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

5. The differential diagnosis list and/or phenotype warrant testing of multiple genes and **ONE of the following**:

- WGS 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); or
- WGS results may preclude the need for invasive procedures or screening that would be recommended in the absence of testing (e.g. muscle biopsy); and

6. A standard clinical work-up has been conducted and did not lead to a diagnosis; and
7. Results will impact clinical decision-making for the individual being tested; and
8. Pre- and post-test counseling is performed by an American Board of Medical Genetics or American Board of Genetic Counseling certified genetic counselor.

Non-covered indicators:

WGS is not covered for:

- Carrier testing for "at risk" relatives.
- Prenatal or pre-implantation testing.

Definitions:

[1] **Global developmental delay (GDD)** is used to categorize children who are younger than five years of age.

GDD is defined as a significant delay[2] in two or more developmental domains, including gross or fine motor, speech/language, cognitive, social/personal, and activities of daily living and is thought to predict a future diagnosis of ID. Such delays require accurate documentation by using norm-referenced and age appropriate standardized measures of development administered by experienced developmental specialists, or documentation of profound delays based on age appropriate developmental milestones are present.

Reference: *Comprehensive Evaluation of the Child With Intellectual Disability or Global Developmental Delays Pediatrics 2014;134:e903–e918. Page e905*

Significant delay is typically defined as performance two standard deviations or more below the mean on age-appropriate, standardized, normal-referenced testing.

[2] **Intellectual disability (ID)** is a life-long disability diagnosed at or after age five when intelligence quotient (IQ) testing is considered valid and reliable. The Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association (DSM-V), defines patients with ID as having an IQ less than 70, onset during childhood, and dysfunction or impairment in more than two areas of adaptive behavior or systems of support.

Related documents:

- Final key questions
- Final evidence report
- Meeting materials and transcript

Agency contact information:

Agency	Phone Number

Labor and Industries	1-800-547-8367
Public and School Employees Health Plan	1-800-200-1004
Washington State Medicaid	1-800-562-3022

HTCC coverage vote and formal action:

Committee decision

Based on the deliberations of key health outcomes, the committee decided that it had the most complete information: a comprehensive and current evidence report, public comments, and state agency utilization information. The committee discussed and voted on the evidence for the use of whole genome sequencing. The committee decided that the current evidence on whole genome sequencing is sufficient to determine coverage with conditions. The committee considered the evidence, public comment and expert input, and gave greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.

Based on these findings, the committee voted to cover with conditions whole genome sequencing.

	Not covered	Covered under certain conditions	Covered unconditionally
Whole genome sequencing	0	9	0

Discussion

The committee reviewed and discussed the available studies for use of whole genome sequencing. Conditions for coverage were discussed, drafted, and voted on. All committee members present supported the conditions of coverage of whole genome sequencing. Details of study design, inclusion criteria, outcomes, cost, cost-effectiveness, and other factors affecting study quality were discussed as well as clinical application.

Decision

Whole genome sequencing is covered with conditions for the following:

Whole genome sequencing (WGS) is a covered benefit with conditions for the evaluation of unexplained congenital or neurodevelopmental or neurodegenerative disorders in a phenotypically affected individual when **ALL of the following** criteria are met:

1. 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), who is not employed by a commercial genetic testing laboratory, has evaluated the patient and family history, and recommends and/or orders the test; and

2. A genetic etiology is considered the most likely explanation for the phenotype, based on **EITHER of the following**; and

    - Multiple abnormalities affecting unrelated organ systems, (e.g. multiple congenital anomalies); or

- **TWO of the following criteria are met:**
  - Significant abnormality affecting at minimum, a single organ system,
  - Unexplained cognitive changes in adulthood,
  - Profound global developmental delay[1], or intellectual disability[2] as defined below,
  - Family history strongly suggestive of a genetic etiology, including consanguinity,
  - Period of unexplained developmental regression (unrelated to autism or epilepsy),
  - Biochemical findings suggestive of an inborn error of metabolism where targeted testing is not available;

3. Other circumstances (e.g. environmental exposures, injury, infection) do not reasonably explain the constellation of symptoms; and
4. 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
5. The differential diagnosis list and/or phenotype warrant testing of multiple genes and **ONE of the following**:
   - WGS 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); or
   - WGS results may preclude the need for invasive procedures or screening that would be recommended in the absence of testing (e.g. muscle biopsy); and
6. A standard clinical work-up has been conducted and did not lead to a diagnosis; and
7. Results will impact clinical decision-making for the individual being tested; and
8. Pre- and post-test counseling is performed by an American Board of Medical Genetics or American Board of Genetic Counseling certified genetic counselor.

WGS is not a covered benefit for carrier testing for 'at risk' relatives and prenatal or pre-implantation testing.

Definitions:

[1] **Global developmental delay (GDD)** is used to categorize children who are younger than five years of age.

GDD is defined as a significant delay[2] in two or more developmental domains, including gross or fine motor, speech/language, cognitive, social/personal, and activities of daily living and is thought to predict a future diagnosis of ID. Such delays require accurate documentation by using norm-referenced and age appropriate standardized measures of development administered by experienced developmental specialists, or documentation of profound delays based on age appropriate developmental milestones are present.

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Action

The committee checked for availability of a Centers for Medicare and Medicaid Services (CMS) national coverage decision (NCD). Based on the information provided in the systematic review, there is no NCD for whole genome sequencing.

The committee discussed clinical guidelines identified from the following organizations:

- Medical Genome Initiative (MGI), 2024, Evidence review and consideration for use of first-line genome sequencing to diagnose rare genetic disorders
- National Society of Genetic Counselors (NSGC), 2023, Genetic testing and counseling for the unexplained epilepsies: an evidence-based practice guideline
- National Institute of Health and Care Excellence (NICE), 2022, Epilepsies in children, young people, and adults
- EuroGentest, 2022, Recommendations for WGS in diagnostics for rare diseases
- American College of Medical Genetics and Genomics (ACMG), 2021, Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability evidence-based guideline
- Canadian College of Medical Geneticists, 2015, The clinical application of genome-wide sequencing for monogenic diseases in Canada

The recommendations of the guidelines vary. The committee's determination is consistent with the noted guidelines.

HTA staff will prepare a findings and decision document on use of stereotactic body radiation therapy for the treatment of selected conditions for public comment to be followed by consideration for final approval at the next committee meeting.

Health Technology Clinical Committee Authority:

Washington State's legislature believes it is important to use a science-based, clinician-centered approach for difficult and important health care benefit decisions. Pursuant to chapter 70.14 RCW, the legislature has directed the Washington State Health Care Authority (HCA), through its Health Technology Assessment (HTA) program, to engage in an evaluation process that gathers and assesses the quality of the latest medical evidence using a scientific research company that takes public input at all stages.

Pursuant to RCW 70.14.110, a Health Technology Clinical Committee (HTCC) composed of eleven independent health care professionals reviews all the information and renders a decision at an open public meeting. The Washington State HTCC determines how selected health technologies are covered by several state agencies (RCW 70.14.080-140). These technologies may include medical or surgical devices and procedures, medical equipment, and diagnostic tests. HTCC bases its decisions on evidence of the technology's safety, efficacy, and cost effectiveness. Participating state agencies are required to

comply with the decisions of the HTCC. HTCC decisions may be re-reviewed at the determination of the HCA Director.

Washington State Health Care Authority

HTCC final approval of coverage decision

Next step: proposed findings and decision and public comment

At the next public meeting the committee will review the proposed findings and decision and consider any public comments as appropriate prior to a vote for final adoption of the determination.

1) Based on public comment was evidence overlooked in the process that should be considered?
2) Does the proposed findings and decision document clearly convey the intended coverage determination based on review and consideration of the evidence?

Next step: final determination

Following review of the proposed findings and decision document and public comments:

Final vote

Does the committee approve the Findings and Decisions document with any changes noted in discussion?

If yes, the process is concluded.

If no, or an unclear (i.e., tie) outcome chair will lead discussion to determine next steps.