Whole Exome, Whole Genome, and Proteogenomic Sequencing and Genetic Testing for Mitochondrial Disorders

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SCOPE: Providence Health Plan, Providence Health Assurance, and Providence Plan Partners as applicable (referred to individually as “Company” and collectively as “Companies”).

PLAN PRODUCT AND BENEFIT APPLICATION

☒ **Commercial** ☐ **Medicaid/OHP*** ☐ **Medicare****

*Medicaid/OHP Members

Oregon: Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

PHP follows Guideline Notes 172 and 173 of the OHP Prioritized List of Health Services for guidance on New and Emerging Technology. In the absence of OHP guidance, PHP will follow this policy.

**Medicare Members

This *Company* policy may be applied to Medicare Plan members only when directed by a separate *Medicare* policy. Note that investigational services are considered **"not medically necessary"** for Medicare members.

COVERAGE CRITERIA

Whole Exome Sequencing (WES)

I. Whole exome sequencing (WES) may be considered **medically necessary** in patients with congenital anomalies, developmental delay or intellectual disability when **all** of the following criteria (A. - F.) are met:

   A. Either of the following are met (1.-2.):
      1. Patient is 18 years of age or younger; **or**
      2. Patient is aged 18-21 and both of the following are met (a.-b.):
         a. The congenital anomaly, developmental delay, or intellectual disability had onset prior to age 18; **and**
         b. A genetic evaluation consistent with pediatric criteria was initiated but not completed prior to age 18; **and**
   B. Genetic counseling requirements outlined in the Medical Policy "Genetic Counseling (Company)" have been met; **and**
   C. **Either** of the following are documented (1.-2.):
      1. Multiple congenital abnormalities affecting unrelated organ systems; **or**
      2. **Two or more** of the following criteria are met:
         a. Abnormality affecting at minimum a single organ system;

b. Significant developmental delay, intellectual disability, symptoms of a complex neurodevelopmental disorder (e.g., self-injurious behavior, reverse sleep-wake cycles, dystonia, hemiplegia, spasticity, epilepsy, muscular dystrophy), and/or symptoms of a severe neuropsychiatric condition (e.g., schizophrenia, bipolar disorder, Tourette syndrome);
c. Family history strongly suggestive of a genetic etiology, including consanguinity;
d. Period of unexplained developmental regression; **and**

D. A genetic etiology is considered the most likely explanation for the phenotype, and **either** of the following are met (1.-2.):
1. Clinical presentation is nonspecific and does not fit a well-described syndrome; **or**
2. Previous genetic testing has failed to yield a diagnosis; **and**

E. A diagnosis cannot be made by standard clinical and laboratory work-up, excluding invasive procedures such as muscle biopsy; **and**

F. WES is predicted to have an impact on health outcomes, including **one or more** of the following:
1. Reducing diagnostic uncertainty (e.g., eliminating lower-yield testing and additional screening testing that may later be proven unnecessary once a diagnosis is achieved); **or**
2. Guiding prognosis and improving clinical decision-making, which can improve clinical outcome by any of the following:
a. initiation of specific treatments and/or avoidance of contraindicated treatments;
b. surveillance for later-onset comorbidities;
c. initiation of palliative care;
d. withdrawal of care; **or**
3. For persons planning a pregnancy, informing genetic counseling related to recurrence risk and prenatal diagnosis options; **and**

G. Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection).

Note: Reanalysis of previously obtained whole exome sequencing data may be considered medically necessary when new gene-disease associations, updated variant interpretation standards, or evolution of the member's clinical phenotype are reasonably expected to affect diagnostic yield or clinical management. Tests that are potentially covered per the above policy criteria are listed in the Policy Guidelines, below.

II. Trio exome sequencing (sequencing of the proband and both biological parents) is considered **medically necessary** when criterion I. for WES of the affected child above is met, and parental samples are available.

III. WES of a comparator exome(s) of a first-degree relative(s) (e.g., parents, siblings) may be considered **medically necessary** when trio testing is not feasible and criterion I. for WES of the affected child above is met.

IV. Rapid WES or WGS may be considered **medically necessary** in critically ill infants when timely diagnosis impacts management.

Mitochondrial Disorder Genetic Testing

V. Genetic testing, including single gene, multi-gene, and whole mitochondrial genome sequencing panels, may be considered medically necessary for the diagnosis of primary mitochondrial disorders (see Policy Guidelines) when both of the following criteria are met (A.-B.):

A. Signs and symptoms of a mitochondrial disorder are present (see Policy Guidelines); **and**
B. At least one of the following is met (1.-2.):
   1. A clinical diagnosis cannot be made without additional testing, and a muscle or liver biopsy has not been performed; **or**
   2. For persons planning a pregnancy, informing genetic counseling related to recurrence risk and prenatal diagnosis options.

VI. WES is considered **not medically necessary** for any other indication, including but not limited to the following:

A. When the above criteria are not met
B. For oncologic indications, including but not limited to (1.-2.):
   1. Evaluation of hereditary cancer syndromes
   2. Identification of genetic targets for therapeutic management (e.g., EXaCT-1 Whole Exome Testing)
C. Screening of asymptomatic individuals
D. Reproductive planning for unaffected individuals
E. Prenatal testing

VII. Whole mitochondrial genome sequencing is considered **not medically necessary** when criteria III. is not met.

VIII. Repeat testing of the same germline genetic content, for the same genetic information, is considered **not medically necessary**.

Whole Genome Sequencing (WGS)

IX. Whole genome sequencing (WGS) may be considered **medically necessary** when all of the following criteria are met (A.-G.):

A. The patient 21 years of age or younger; **and**
B. The patient has not previously undergone exome sequencing or exome sequencing is unlikely to adequately detect the suspected variant type; **and**
C. The patient has not previously undergone genome sequencing; **and**
D. Genetic counseling requirements outlined in the Medical Policy "Genetic Counseling (Company)" have been met; **and**
E. Results are expected to inform clinical management, prognosis, or family counseling; **and**
F. A diagnosis cannot be made by standard clinical work-up, excluding invasive procedures such as muscle biopsy; **and**

G. Either of the following are met (1.-2.)
   1. Patient has **any** of the following (a.-d.):
      a. Unexplained epileptic encephalopathy with onset before three years of age and no prior epilepsy multigene panel testig performed; **or**
      b. Global developmental delay identified through formal assessment; **or**
      c. Moderate, severe, or profound intellectual disability diagnosed prior to age 18; **or**
      d. Multiple congenital anomalies affecting unrelated organ systems; **or**
   2. Patient has at least **two** of the following (a.-g.):
      a. Major abnormality affecting at minimum a single organ system; **or**
      b. Formal diagnosis of autism with additional neurologic, congenital, or developmental features; **or**
      c. Symptoms of a complex neurodevelopmental disorder (e.g., epilepsy, self-injurious behavior, reverse sleep-wake cycles, dystonia, ataxia, alternating
      d. Hemiplegia, neuromuscular disorder, cerebral palsy) ; **or**
      e. Severe neuropsychiatric condition (e.g., schizophrenia, bipolar disorder, Tourette syndrome); **or**
      f. Period of unexplained developmental regression; **or**
      g. Laboratory findings suggestive of an inherited metabolic disorder.

X. Whole genome sequencing (WGS) is considered **not medically necessary** when criterion IX. above is not met.

Proteogenomic Testing

XI. Proteogenomic testing (e.g., GPS Cancer®) is considered **not medically necessary** for all indications, including but not limited to informing therapeutic management for oncologic indications.

Link to Evidence Summary

POLICY CROSS REFERENCES

- Genetic Counseling, MP316
- Non-Covered Genetic Panel Tests, MP213
- Genetic Testing for Reproductive Planning and Prenatal Testing, MP78

The full Company portfolio of current Medical Policies is available online and can be accessed here.

POLICY GUIDELINES

DOCUMENTATION REQUIREMENTS

In order to determine the clinical utility of a genetic test, the following documentation must be provided at the time of the request. Failure to submit complete documentation may affect the outcome of the review.

- Specific gene, trade or proprietary name of the test, or if a custom built test, include every gene(s) and/or component of the test
- Name of laboratory where the testing is being conducted or was conducted
- Clinical notes to include the following:
  - Documentation of genetic counseling as required in the policy criteria below which includes how test results will impact clinical decision making
  - Reason (indication) for performing test, including the suspected condition
  - Existing signs and/or symptoms related to reason for current test request
  - Prior test/laboratory results related to reason for current test request
  - Family history, if applicable
  - How results from current test request will impact clinical decision making
- All relevant CPT/HCPCS codes billed

DEFINITIONS

WES Tests

Whole exome sequencing tests that are potentially covered per the above policy criteria include but are not limited to the following:

- NextStepDx PLUS (Lineagen)[1]

Primary Mitochondrial Disorders

Examples of Primary Mitochondrial Disorders[2]
(Not all-inclusive)

- Alpers (aka Alpers-Huttenlocher) syndrome
- Barth syndrome
- Chronic progressive external ophthalmoplegia (CPEO)
- Coenzyme Q10 deficiency
- Growth retardation, amino aciduria, cholestasis, iron overload, lactic acidosis, and early death (GRACILE) syndrome
- Infantile-onset spinocerebellar ataxia (IOSCA)
- Kearns-Sayre syndrome
- Leber hereditary optic neuropathy (LHON)
- Leigh syndrome
- Maternally inherited deafness and diabetes (MIDD)
- Mitochondrial DNA depletion syndrome; mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS)
- Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)
- Mitochondrial recessive ataxia syndrome (MIRAS)

- Myoclonus epilepsy with ragged red fibers (MERFF)
- Neuropathy, ataxia, and retinitis pigmentosa (NARP)
- Pearson syndrome
- Sensory ataxia neuropathy, dysarthria, ophthalmoplegia (SANDO)

Signs and Symptoms of Mitochondrial Disorders[2]

Primary mitochondrial disorders can have a variety of presentations, depending on the molecular cause. They are often multisystem disorders, and may include (not all-inclusive):

- skeletal muscle myopathy
- cardiomyopathy
- encephalopathy
- ophthalmoplegia
- neuropathy
- hypotonia/muscle weakness
- seizures
- developmental delay
- ataxia
- deafness
- short stature

BACKGROUND

Whole Genome Sequencing (WGS)

The genome is an individual's complete set of DNA, including all of its genes. Each genome contains all of the information needed to build and maintain that individual. A copy of the entire genome is contained in in each human cell within the body. Whole genome sequencing (WGS), also called genomic sequencing, is a genetic testing strategy that may be used to determine the order of all the nucleotides in an individual's DNA and can determine variations in both the coding (exons) and non-coding portions (introns) of the genome.[3]

Whole Exome Sequencing (WES)

WES provides the base pair sequence for all the protein-coding regions in the genome, the exons. WES allows the detection of coding changes within almost any gene in the human genome. Because most known mutations that cause disease occur in exons, WES is purported to be a more efficient method to identify possible disease-causing mutations compared to single gene or genetic panel testing.[3]

Both WES and WGS may be used clinically to detect pathogenic single nucleotide changes or small insertions or deletions and may be used as a diagnostic test when a patient's clinical presentation does not point to a specific genetic disorder.[4] Although WES is usually used to detect single base pair substitutions or duplications or deletions of a few base pairs, it can also theoretically identify larger deletions or duplications, also referred to as copy number variants (CNVs) with the reported sensitivity of medium-resolution chromosomal microarrays (CMAs). WES has been reported as having lower sensitivity for the identification of CNVs than whole genome sequencing or high-resolution CMAs due to limitations of exon capture methods and a lack of standard bioinformatics for this purpose.[4]

Ethical and Legal Implications of WES and WGS for Hereditary Conditions

According to the American College of Medical Genetics and Genomics (ACMG), untargeted massively paralleled genetic testing methods like WES and WGS inevitably identify variants of uncertain significance (VUSs). The identification of VUSs is not unique to WES and WGS, but the likelihood of their detection increases as the amount of genes and non-coding genetic data increases based on the test methodology. The protocol for reporting out VUSs varies by laboratory and the relaying of this information to the patient must be considered with caution, as their "actionability" is not known.

In addition, WES and WGS can identify pathogenic variants in regions of the genome not considered for assessment based on the patient's clinical presentation. These secondary findings present an ethical dilemma for medical professionals who may feel obligated to share these results with patients (and/or their parents).[5] The reporting of secondary findings becomes more complex when the patient being tested is a pediatric patient. Recommendations around reporting secondary findings have been made by several professional associations. (See Clinical Practice Guidelines section below)

Several additional important ethical, legal, and psychosocial issues are unique to the use of WES and WGS in pediatric patients. These include their inability to provide informed consent, such that decisions are made through parents or guardians, concern for maintaining a child's autonomy, and the appropriateness of testing for adult-onset disorders (optionally reported out as secondary findings) when there may not be a treatment or intervention that can begin in childhood.[6]

WES/WGS for Targeted Therapy Identification for Oncologic Indications

Large-scale sequencing efforts comparing tumor and normal tissue are currently under investigation in an effort to provide personalized therapeutic options to patients diagnosed with a number of different malignancies. However, integration of WES/WGS into cancer care suffers from unique limitations, including but not limited to:

- Samples are often small in size, of poor quality and contain low tumour purity.
- Sample preparation techniques and computational approaches required to detect the spectrum of genes and mutations for cancer care have not been extensively validated in research settings, let alone clinical settings.
- The ability of the test to identify actionable mutations at an acceptable analytical sensitivity has not been established at this time.

Proteogenomic Testing

Proteogenomic testing is a comprehensive approach that combines WGS with the large-scale evaluation of protein expression (called proteomics). This approach may also incorporate large-scale expression of RNA from all the genes in the genome (called transcriptomics). There is one test currently marketed commercially, the GPS Cancer test (NantHealth), which uses all three approaches to help guide personalized treatment options for patients with various types of oncologic conditions. This test analyzes DNA, RNA, and protein from a patient's tumor and blood to identify markers that can guide FDA-approved therapies or clinical trials, and avoid potential tumor-resistant treatments.[7]

Mitochondrial Disorders

Primary mitochondrial disorders are one of the most common inborn errors of metabolism, impacting the structure or function of the mitochondria as a result of either nuclear DNA (nDNA) or mitochondrial DNA (mtDNA) mutations.[8] The clinical expression of mitochondrial diseases are manifest by a wide range of clinical presentations. Tissues relying (primarily/mostly) on aerobic metabolism—such as (those/the tissues) comprising the central nervous system, the cardiovascular system, and skeletal muscle—are preferentially affected. [9] The prevalence of these disorders has risen over the last two decades as the pathophysiology and clinical manifestations have been better characterized. It is currently estimated that the minimum prevalence of primary mitochondrial diseases is at least 1 in 5000.[8]

REGULATORY STATUS

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Approval or clearance by the Food and Drug Administration (FDA) does not in itself establish medical necessity or serve as a basis for coverage. Therefore, this section is provided for informational purposes only.

CLINICAL EVIDENCE AND LITERATURE REVIEW

EVIDENCE REVIEW

The focus of the following review is on evidence related to the clinical validity and clinical utility of whole exome sequencing (WES) and whole genome sequencing (WGS). In the present context, the clinical validity of WES and WGS is related to the diagnostic performance of these technologies. The clinical utility of WES and WGS may be established by evaluating the following components of the test:

- Ability to establish a definitive diagnosis in a patient whose clinical presentation does not point to a specific condition, thereby eliminating the need for further clinical workup or invasive testing
- Leads to changes in clinical management of the condition that improve outcomes
- Leads to discontinuation of interventions that are unnecessary and/or ineffective
- Leads to changes in medication management that are likely to improve outcomes
- Provides prognostic information not revealed by standard laboratory, genetic and/or clinical testing that reclassifies patients into clinically relevant prognostic categories for which there are different treatment strategies.

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of WES and WGS for a variety of indications. Below is a summary of the available evidence identified through April 2026. Of note, studies with fewer than 25 patients were not included in the review below, since these studies are not statistically powered to yield significant results.

Clinical Validity

<u>Whole Exome Sequencing for Hereditary Conditions</u>

In 2021, Stefanski and colleagues published a systematic review with meta-analyses of clinical sequencing studies that utilized next-generation sequencing (NGS) to diagnose individuals with neurodevelopmental disorders (NDDs).[10] One hundred and three clinical studies evaluating individuals for the following disorders were included: epilepsy, autism spectrum disorder (ASD), or intellectual disability (ID) (epilepsy, N = 72; ASD, N = 14; ID, N = 21), including 32,331 individuals. Targeted gene panel sequencing was used in 73, and exome sequencing in 36 cohorts. Overall, highly selected patient cohorts resulted in diagnostic yields of 17.1% for ASD, 24% for epilepsy, and 28.2% for ID (23.7% overall). The diagnostic yield for exome sequencing was higher than for panel sequencing, even though not statistically significant (27.2% vs 22.6%, P = .071).

In 2023, Hayes published a review of the clinical utility of WES/WGS for previously undiagnosed pediatric neurodevelopmental disorders.[11] The review reported diagnostic rates in this population between 24% to 48%. This report identified twelve studies that met inclusion criteria, with diagnostic yields ranging from 24% to 73%, changes in clinical management reported in 3% to 44% of cases, and improved outcomes in 2% to 22% of patients. The studies varied in quality and design, and outcome reporting was inconsistent. Nonetheless, Hayes found that WES, and to a lesser extent WGS, may have clinical utility in pediatric patients with complex or unexplained neurodevelopmental presentations, particularly when standard testing has failed. The body of evidence was considered promising but not definitive, and the overall utility was rated as "uncertain."

In 2018, a meta-analysis was published on the diagnostic and clinical utility of WGS, WES, and chromosomal microarray (CMA) in children with suspected genetic diseases.[12] The analysis found 37 studies published between 2011 and 2017, totaling 20,068 children. Diagnostic utility of WGS was 41%, WES was 36%, and CMA was 10%), with no significant differences found between WGS and WES, and significantly less diagnostic utility in CMA compared to WGS and WES. Clinical utility of WGS (27%) and WES (17%) were higher than CMA (6%) as well. This analysis had a number of limitation. Among the included studies, only one was a randomized controlled trial, the diagnostic rates utilized from the included studies were not reclassified according to strength of evidence of gene-disease relationships, and there was great heterogeneity in pooled averages of the published data.

Additional studies reporting on the diagnostic yield of WES have been published for a number of conditions, including the following:

- Comparative studies:
    - Epilepsy with an onset at < 3years[13]: WES = 33%, NGS panel = 27%, karyotyping = 44%, microarray = 27%.
    - Children with drug-resistant epilepsy[14]: WES = 17%, clinical exome = 45%, panel = 33%.
    - Complex pediatric neurological disorders[15-19]: WES = range 25% to 48%, standard care pathway (imaging, muscle biopsy or lumbar puncture, and/or sequential gene testing) = range 7% to 25%.
    - Children with Autism spectrum disorders (ASD)[20]: WES = 8.4%, CMA = 9.3%.
    - Children/infants with a suspected monogenic condition (predominantly congenital abnormalities, dysmorphic features and/or neurometabolic indications):[21-23] WES = range: 52% to 58%, standard genetic testing (single gene (s) or panels) = 14%.
    - Hearing loss in children[24]: WES = 37%, panels = 16%.
    - Patients with developmental delay/intellectual disability (cohort was 87% children)[25]: WES = 30%, WGS = 22%. The study also found that 11% of the affected patients had VUSs.

- Adult patients with neurological disorders:[26] WES = 25%, panels = 25%, 1-2 genes = 50%, CMA = 45%Infants with serious illness of unknown etiology: n=94, rapid WES = 20% (19/95); rapid WGS = 19% (19/94).[27]

- Non-Comparative studies:
  - Rare diseases (mixed pediatric and adult-onset conditions)[28]: 226/802 patients; 28.2%.
  - Adult genetic conditions[29]: 85/486 of adults; 17.5%, with a higher rate [23.9%] for those 18-30 years of age compared to patients older than 30 years [10.4%].
  - Pediatric genetic conditions: 12/40 children; 30%.[30] Among 13 studies, average 34.4% for trio exome sequencing; among 7 studies, 26.6% for singleton exome sequencing.[31] 38/106; 36%.[32]
  - Chronic kidney disease (adults)[33]: 22/92 patients; 24%.
  - Undiagnosed genetic conditions (mixed populations with between 78% to 85% children)[34-36]: range: 30% to 32%. The highest diagnostic rates were observed among patients with ataxia (44%), multiple congenital anomalies (36% to 54%), and epilepsy (35%), intellectual disability/developmental delay (34%). VUS rate reported at 25%. Two of the three studies evaluated diagnostic rates by age, reporting no difference between pediatric and adult patients. One study reported adult diagnostic rate of 19% and pediatric diagnostic rate of 31%.
  - Unexplained early onset epileptic encephalopathy[37]: 11/50 patients; 22%. VUS rate of 4%.
  - Limb-girdle muscular dystrophy (63% of cohort were children)[38]: 27/60 families; 45%, with higher yields for trios [60%].
  - Intellectual developmental disorder and unexplained metabolic phenotypes (cohort 80% children):[39] 28/41 probands (68%).

<u>WES in the Prenatal Setting</u>

- In 2017, Fu et al. evaluated a number of technologies in the prenatal setting, including 196 CMA- and karyotype-negative fetuses that underwent WES. Overall, 47 (24%) had a pathogenic variant identified that could potentially explain the phenotype. The incidence of VUS and secondary findings was 12% and 6%, respectively.

- In 2022, Hayes conducted a systematic review assessing the clinical utility of prenatal whole genome sequencing and prenatal whole exome sequencing.[40] Four studies were identified reporting clinical action taken as a result of data from prenatal WES. All 4 studies aimed to evaluate the clinical impact of exome sequencing in fetuses with abnormalities detected by ultrasound. A total of 202 patients were evaluated in the 4 studies; however, only 66 pregnancies met the inclusion criteria outlined for this report. All studies evaluated WES and 2 studies focused on specific clinically relevant genomic regions (Pangalos et al., 2016; Chandler et al., 2018). Studies reported that pregnancy management decisions were made as a result of molecular diagnosis provided by WES and when WES did not detect any known pathogenic variants. Data from these 4 small studies suggest that prenatal WES may have clinical utility when standard genetic tests are negative and there is strong clinical suspicion of an abnormality. Although the data are limited, this evidence suggests that WES may inform pregnancy management decisions in cases where fetal abnormalities have been detected by ultrasound and lower-tier genetic testing failed to provide a diagnosis. All studies were of very poor quality and the overall quality of the body of evidence is very low. Thus, there is insufficient evidence to suggest that prenatal WES has broad clinical value.

Whole Genome Sequencing for Hereditary Conditions

In 2024, Hayes conducted a systematic review assessing the clinical utility of whole genome sequencing (WGS) and whole exome sequencing (WES) for pediatric patients with intellectual disability (ID) as the primary phenotype.[41] The review found no peer-reviewed studies that met inclusion criteria demonstrating that WGS or WES directly impacted clinical management or improved health outcomes in this population. While some studies reported diagnostic yield, none provided sufficient evidence of actionability or changes in care resulting from sequencing results. As a result, Hayes concluded that there is insufficient evidence to support the use of WGS or WES for ID alone, and the overall quality of the evidence was rated as low.

In 2019, Hayes updated a review of the clinical utility of WGS for neonatal and pediatric patients to identify or confirm the genetic etiology of a known or unknown disorder in clinically affected patients and as a method of newborn screening, including six studies including between 21-1696 patients.[42] Three of the included studies evaluated the use of WGS in patients with autism, developmental delay, and/or structural malformations; two studies evaluated WGS performed in an acute setting (neonatal intensive unit [NICU] and/or postoperative intensive care unit [PICU]) for the purpose of diagnosis; and one study compared the use of WGS for a subset of genes related to newborn screening (NBS) to traditional NBS methods. The review reported diagnostic rates that ranged from 34% to 73%, with the highest yields obtained through family-based WGS of patients (testing of trios).

Additional studies reporting on the diagnostic yield of WGS have been published for a number of conditions, including the following:

- Comparative studies:
    - Hypertrophic cardiomyopathy[43]: WGS = 31%, panel = 31%. VUS rate was 17% for both WGS and panel.
    - Inherited retinal diseases (phenotypically heterogeneous cohorts)[44,45]: WGS = 51% to 52%, WES = 50%, panel = 28%.
    - Neonates <4 months old with illnesses suggestive of a genetic condition but were of unknown etiology (n=65 neonates)[46]: rapid WGS (rWGS) = 31%, standard WGS = 24%, CMA = 6%, panels = 18%, WES = 33%, methylation testing = 13%. In was noted that rWGS would not have identified 33% of diagnoses, as four were structural variants and one was a change in DNA methylation not identifiable by rWGS.
    - Acutely/critically ill infants[47,48]: rWGS = 43% to 57%, standard genetic testing = 9% to 10%.
    - Pediatric patients with congenital malformations and/or neurodevelopmental disorders (n=100)[49]: WGS = 34%, CMA = 8%, CMA plus targeted gene sequencing = 13%.
    - Patients with a suspected genetic condition with previous negative results (108 patients)[50]: WGS = 37%, WES = 30%. Of note, 4% of positive results were missed by WGS, and 3% of were missed by WES. Limitations of this study include the small sample size and the high rate of consanguinity, which may have inflated the diagnostic yield for both WES and WGS.
    - Patients ≤18 years old with clinical phenotype suggestive underlying genetic disorder: WGS= 41% (42/103), panel = 24% (25/103)[51]
    - Pediatric patients with unsolved leukodystrophies: WGS = 5/9 (56%), SOC = 5/23 (22%)[52]

- Non-Comparative studies:

- Developmental delay/intellectual disability (n=244 patients):[25] 22.1% (pathogenic or likely pathogenic variant) for single nucleotide changes and indels, and a 2.2% yield for larger copy number variants (CNVs).The overall rate of VUSs was 11.2% for WGS.
- Developmental and epileptic encephalopathy pharmaco-resistant seizures[53] (diagnostic yield = 32%, and 84% of these were de novo mutations)
- Pediatric neurodevelopmental disorders[18]: 11/15 critically ill children who underwent rapid WGS (73%).
- Patients with a suspected genetic condition with previous negative results (156 patients):[54] Overall, 21% of cases were diagnosed based on WGS, with the proportion increasing to 34% (23/68) for Mendelian disorders and 57% (8/14) in family trios.

Limitations of these studies include one or more of the following:

- Retrospective study design
- Heterogeneous patient populations (in terms of age and phenotype)
- Observational and not comparative to other genetic testing techniques
- Small sample size tested and/or small numbers of patients with a positive result
- Different sequencing platforms used and different data analysis methodologies
- Prior genetic testing results not disclosed or not available
- Reporting of pathogenic variants being missed by wgs but detected by conventional sequential gene testing (e.g., deletions or duplications)
- High rates of incidental findings in pediatric cohorts
- High rates of variants of uncertain significance (vuss) compared to other genetic testing methods
- Lack of evaluation diagnostic yields and/or outcomes in a single patient population between wgs sequencing platforms/data analysis methodologies

<u>WES/WGS for Targeted Therapy Identification for Oncologic Indications</u>

Pediatric Populations

In 2016, Parsons et al. published a study which determined the prevalence of somatic and germline mutations in children with solid tumors.[55] Tumor samples were available for WES in 121 patients. In this group, somatic mutations with established clinical utility were found in four patients (3%), and mutations with *possible* clinical utility were found in 29 patients (24%).

In 2018, Østrup et al. reported on the clinical impact of molecular profiling technologies, including WES, RNA sequencing, transcriptome arrays, and single nucleotide polymorphism (SNP) arrays, on pediatric tumors in children with refractory cancer. Fifty-one of the samples from 48 children were evaluated by WES.[56] The highest yield for actionable findings was from WES (39%). Overall, 20/51 samples (39%) were reported as having actionable findings, but WES variants were not analyzed separately from variants found using other methodologies.

In 2018, Rusch et al. performed WGS, WES and transcriptome (RNA-Seq) sequencing of tumors and normal tissue from 78 pediatric cancer patients.[57] The samples were made up of the following: hematologic (n=36), solid tumor (n=26), and brain tumor (n=16). Overall, 240 pathogenic variants were reported across all cases, including 84 of 86 known from previous diagnostic testing (98% sensitivity).

Combined three-platform sequencing (WES/WGS and transcriptome analyses) achieved 98% sensitivity, but independently, WGS , WES and transcriptome sequencing only achieved sensitivities of 89%, 62% and 18%, respectively.

In 2015, Zhang et al. reported the prevalence of cancer pre-disposition germline mutations in children and adolescents with cancer in 1120 patients under the age of 20[58]. Whole exomes were sequenced in 456 patients, whole genomes were sequenced in 595, and both WES and WGS were performed in 69. Patient exomes were compared to population controls from the 1000 Genomes project and from sequencing from an autism study. Overall, germline mutations were found in 95 children with cancer (8.5%), as compared to only 0.6 to 1.1% of controls. Diagnostic yields were not reported separately for WES and WGS. Changes in management as a result of WES and/or WGS were not reported.

In 2016, Parsons et al. published a study which determined the prevalence of somatic and germline mutations in children with solid tumors.[55] Diagnostic germline mutations, assayed by WES on blood, related to the child's clinical presentation were found in 15/150 patients (10%). Nearly all patients (98%) had variants of unknown significance in known cancer genes, drug response genes, and genes known to be associated with recessive disorders.

Adults

Several studies have been published that have evaluated the use of WES or WGS to characterize tumors and aid in the selection of targeted therapies in adult cohorts, including the following:

- Comparative Studies:
    - Mixed tumor types (Jones et al., 2015)[59] (WES and panel testing on 815 tumor-normal paired samples from patients of 15 tumor types):
        - Overall 75% of cases had somatic alterations in genes associated with known therapies or current clinical trials and 3% of patients had germline alterations in cancer-predisposing genes. However, WES and targeted panel results were not separately reported.
        - tumor only WES was unable to identify germline mutations
        - false-positive findings were higher for WES (65%) than panel testing (31%)
- Noncomparative:
    - Advanced cancer (78 patients, predominantly adults) (Laskin et al., 2015)[60]: Overall, 55 patients (71%) received results that were considered "actionable". No actual changes in management were reported.
    - Metastatic and treatment-resistant cancers (19 tumor types) (Beltran et al., 2015)[61]: WES provided informative results in 91/97 patients (94%), including alterations for which there is an approved drug, there are therapies in clinical or preclinical development, or they are considered drivers and potentially actionable. No actual changes in management were reported.
    - Mixed primary and metastatic tumors, using the EXaCT-1 WES assay (Rennert et al., 2016)[62]: Prospective analysis of 337 tumor samples from patients with advanced disease. Mutations were identified in 168 unique genes out of the 558 cancer genes analysed (30%). Among these, 72 mutations were Tier 1 (40 unique mutations in 15 genes) and 475 were Tier 2 (338 unique variations in 153 genes), accounting for 13% and 69% of the cases, respectively. No actual changes in management were reported.

- Follicular thyroid cancer (Nicolson et al., 2018)[63]: WES on 39 tumors of three different subtypes. Overall, 14/39 samples (36%) had mutations in known cancer- or FTC-specific driver genes and 8/39 samples (20.5%) had mutations in RAS family genes. No actual changes in management were reported.

Note on analytical validity: One important limitation of the use of WES in cancer care is that it has been reported that up to 25% of the captured regions in clinically relevant genes did not achieve the required minimum depth of coverage for accurate negative-mutation calls, leading to unacceptably high false-negative results.[62] This limitation is of particular importance for tumour suppressor genes, where deleterious mutations could potentially occur anywhere along the entire length of the coding region and the inability to detect these mutations may preclude treatment with effective therapies.

Clinical Utility

Whole Exome Sequencing for Hereditary Conditions

In 2021, Hayes published a review of the clinical utility of WES for non-autism-related neurological conditions in pediatric populations after standard diagnostic and genetic tests failed to provide a definitive diagnosis, including 8 studies evaluating between 42 and 2000 patients.[11] The review excluded studies that included adults (even if clinical onset was in childhood), potentially erroneously reducing clinical utility for any given neurological condition The review reported that diagnosis by WES directly changed patient management in 45.3% to 76.9% of patients in three studies and 3.4% in one study.

Of note, in the initial publication of the Hayes review, the clinical utility of WES in this population was graded as a "C". However, in the 2018 update, over 450 unique studies were identified, and Hayes indicated that "new study(s) that have data on the clinical utility of genetic testing may have an impact on the Hayes Rating(s)." However, a review of these new studies was not reported.

Additional clinical utility of WES has been reported for a number of other indications, including:

- Chronic kidney disease (adults)[33]: 16/19 patients with actionable mutations; 68%, including but not limited to avoidance of immunosuppressants [4 patients], referral for transplant [3 patients], additional testing of other symptoms [4 patients], initiation of new medication therapies [4 patients].
- Children with drug resistant epilepsy[14]: 34/86 patients diagnosed by WES accepted changes in management and 91% of these either reported reduced or no seizures at follow-up.
- Pediatric genetic conditions[30]: 5/12 children (42%) who were diagnosed by WES had changes in treatment plans.
- Pediatric neurodevelopmental disorders (2 studies):
    - Soden et al.[18]: 22/45 patients diagnosed by either WES or rapid WGS [49%] changed patient management). Drug or dietary treatments were started 10 children and in two there was a reported favorable response to the treatment including reduction of seizures. Three diagnoses enabled discontinuation of unnecessary treatments, and nine prompted evaluation for possible disease complications.
    - Srivastava et al.[19]: 32/32 patients positive for pathogenic variants underwent changes in management.

- Undiagnosed genetic conditions (mixed cohort with 78% children):[35] 21/37 patients who were diagnosed had reported changes in management, including screening for additional manifestations (n=8 patients), altered management (n=14), novel therapy (n=2), identification of other familial mutation carriers (n=5), and reproductive planning (n=6). WES results triggered changes in reproductive planning (n = 27), disease monitoring initiation (n = 4), investigation of systemic involvement of the disorder(s) (n = 6), changing of prognosis (n = 10), medication changes (n = 7), and clinical trial education (n = 3)".
- Children/ Infants with a suspected monogenic condition (3 studies, 2 by the same group)
    - Standard WES in infants:[21] (predominantly congenital abnormalities, dysmorphic features and/or neurometabolic indications):[21] 15/ 46 patients diagnosed through WES (32.6%) had a change in clinical management, including but not limited to modifications to existing treatment regimens (n=8), additional surveillance for known complications of their condition (n=9), and one was discharged from surveillance based on an erroneous clinical diagnosis.
    - Standard WES in children (2 to 18 years of age):[23] 6/ 23 (26%) patients had altered clinical management.
    - Rapid WES (median turnover time = 16 days):[22] 21/21 patients diagnosed through rapid WES (57%) had changes in clinical management, including the provision of lifesaving treatment, avoidance of invasive biopsies, and palliative care guidance.
- Intellectual developmental disorder and unexplained metabolic phenotypes (cohort 80% children):[39] 18/28 (64%) of patients with a positive results from WES had changes in management, including but not limited to incorporation of new preventive measures (e.g., screening for cancer and avoidance of disease triggers), initiation of immune-modulating therapies, initiation of more precise symptomatic treatments (e.g., supplementation with 5-hydroxytryptophan, levodopa, carbidopa, serine, or folinic acid), and treatments targeting the identified abnormality at a cellular or molecular level.

<u>Whole Genome Sequencing for Hereditary Conditions</u>

In 2016, Hayes published a review of the clinical utility of WGS for neonatal and pediatric patients to identify or confirm the genetic etiology of a known or unknown disorder in clinically affected patients and as a method of newborn screening, including six studies including between 21-1696 patients. Three of the included studies evaluated the use of WGS in patients with autism, developmental delay, and/or structural malformations; two studies evaluated WGS performed in an acute setting (neonatal intensive unit [NICU] and/or postoperative intensive care unit [PICU]) for the purpose of diagnosis; and one study compared the use of WGS for a subset of genes related to newborn screening (NBS) to traditional NBS methods. The review reported the following:

- The impact of WGS on clinical management was reported in four studies and ranged from 19% to 85% in pediatric patients.
- Limitations included, but were not limited to the following:
    - No studies reported on long-term improved impact on health outcomes in either pediatric or neonate populations.
    - WGS in neonates for NBS: only one study to consider, deemed of very low quality. Additional studies are needed that compare WGS with traditional NBS methods, evaluate the change in patient management resulting from WGS, and assess the impact on short- and long-term patient outcomes. The review stated "When WGS is used as a

method of NBS, complications arise in interpreting the disease risk of some variants identified in a (initially) healthy patient."
    - Overall the body of evidence was of low quality for changing pediatric patient management based on WGS.

Of note, in the initial publication of the Hayes review, the clinical utility of WES in this population was graded as a "C" for pediatric populations and "D2" for newborn screening. However, in the 2018 update, over 800 additional studies were identified, and Hayes indicated "new study(s) that have data on the clinical utility of genetic testing may have an impact on the Hayes Rating(s)." However, a review of these new studies was not reported.

Additional reports of the clinical utility of WGS have been published for various indications, including:

- Acutely ill infants (n=29 infants)[47]: The rate of clinical utility of rWGS (31%, thirteen of 42 infants) was significantly greater than for standard genetic tests (2%, one of 42; P = .0015). Eleven (26%) infants with diagnostic rWGS avoided morbidity, one had a 43% reduction in likelihood of mortality, and one started palliative care.
- Critically ill infants (n=35 patients):[48] Impact on clinical management was noted in 13 (65%) of 20 infants diagnosed by rWGS, four (20%) had diagnoses that led to a clinical intervention and six (30%) were started on palliative care.

<u>WES/WGS for Targeted Therapy Identification for Oncologic Indications</u>

Several studies have been published that have evaluated the use of WES or WGS to aid in the selection of targeted therapies in adult cohorts, including the following:

- Noncomparative:
    - Ovarian cancer (Sohn et al., 2012)[64]: Retrospective analysis of WES data on 174 women with high grade ovarian serous cancer (HG-OSC). Authors reported that 62 mutations or more per patient was a predictive factor for determining platinum-based chemotherapy response and was also statistically significantly associated with longer overall survival and progression-free survival.
    - Advanced cancer (78 patients, predominantly adults) (Laskin et al., 2015)[60]: Overall, 23 of the 55 patients that received actionable results (42%) received treatment that was driven by WGS results. Overall, 14 patients (25%) showed clinical /radiographic improvement as a result of the WGS-directed treatment. However, the authors reported that there were limited treatment options available based on results, including even when considering available clinical trials.
    - Metastatic and treatment-resistant cancers (19 tumor types) (Beltran et al., 2015)[61]: WES provided informative results in 91/97 patients (94%); however, treatment was guided in only five patients (5%).

There are a limited number of studies that have reported on the actual clinical utility of WES or WGS for cancer care. These studies all suffer from small patient numbers, heterogeneity with-in and between studies in terms of patient population, and overall low proportions of patients having actual management changes based on WGS/WES test results. Only two studies were identified that reported on whether the changes in management resulted in changes in patient health outcomes. Several

additional studies have reported on the potential/perceived clinical utility of WES or WGS based on the pathogenicity of variants identified. However, these latter studies did not report actual changes in management.

Proteogenomic Testing

In 2017, Hayes published a review of the GPS Cancer proteogenomic test but was unable to identify any studies reporting on the analytical validity, clinical validity, or clinical utility of the test.[7] Therefore, Hayes gave the GPS test a D2 rating.

The clinical validity of proteogenomic tests, including but not limited to the GPS Cancer test, is undefined and no inferences can be made regarding the clinical utility of these tests.

Mitochondrial Disorder Genetic Testing

No randomized studies on clinical utility were identified. Clinical utility for genetic testing for mitochondrial disorders is therefore determined on its ability to confirm diagnosis, reduce further testing, and act as a tool for family planning. No evidence review was conducted. Criteria is based on clinical practice guidelines.

CLINICAL PRACTICE GUIDELINES

American Academy of Pediatrics (AAP)

In 2025, the AAP published a clinical practice guideline addressing the genetic evaluation of children with intellectual disability or global developmental delay.[65] In the guideline, authors endorse a tiered, phenotype-driven and agnostic diagnostic approach to children with GDD/ID. The AAP recommends exome or genome sequencing as a first-tier test in most cases, citing superior diagnostic yield and cost-effectiveness when pursued earlier in the diagnostic process. Genome sequencing is described as preferable when available because of its broader capacity to detect intronic, noncoding, copy-number, and structural variants, although access and resource considerations are acknowledged. The report stresses that genetic testing should be selected based on clinical complexity and anticipated impact on management rather than exhaustive exclusion of alternative etiologies before testing.

American Society of Human Genetics (ASHG) / American College of Medical Genetics and Genomics (ACMG)

In 2015, the ASHG/ACMG jointly published a statement on genetic testing in children and adolescents,[6] recommending the following regarding whole-exome and whole-genome sequencing:

- "When clinically indicated, the scope of genetic testing should be limited to single-gene analysis or targeted gene panels based on the clinical presentation of the patient.
- Targeted testing using genome-scale sequencing, but restricting analysis to a limited set of genes relevant to the clinical indication, is an acceptable alternative to a single-gene analysis or targeted gene panel in certain circumstances.

- When genome-scale sequencing is performed but the analysis is restricted to a limited set of targeted genes, ASHG finds it ethically acceptable for the laboratory to limit the analysis to the genes of clinical interest.
- ASHG recommends that, in the context of diagnostic testing for a child with a most likely genetic disorder, genome-scale sequencing is appropriate when prior, more limited genetic testing failed to identify a causative mutation.
- At the present time, genome-scale sequencing **is not indicated** for screening in healthy children.
- Genome-scale sequencing **is not indicated** for the purposes of clinical newborn screening at this time."

American College of Medical Genetics and Genomics (ACMG)

In 2021, the ACMG published a clinical practice guideline for the use of WES and WGS in pediatric patients.[66] Authors made the following recommendation: "We strongly recommend ES and GS as a first-tier or second-tier test (guided by clinical judgment and often clinician-patient/family shared decision making after CMA or focused testing) for patients with one or more [congenital anomalies] prior to one year of age or for patients with [developmental delay/intellectual disability] with onset prior to 18 years of age."

In 2015, ACMG published a policy statement updating their 2013 their recommendations for analysis and reporting of secondary/incidental findings in whole genome and whole exome sequencing.[67] The ACMG Board of Directors made the following statements:

- The panel states that patients must be made aware, at the time of consent, that laboratories routinely analyze the sequence of a set of genes deemed to be highly medically actionable so as to detect pathogenic variants that may predispose to a severe but preventable disease.
- Although patients have the choice to opt out of receiving these results, that they should be made aware of the ramifications of doing so.
- Due to the inherent difficulty of counseling patients about the features of each disorder and every gene deemed actionable by the ACMG, analysis and reporting of secondary findings should apply to the entire list of medically actionable genes, and not a subset.

In 2012, the ACMG published a position statement that recommended the following regarding exome and genome sequencing for diagnostic purposes:[68]

> "WGS/WES should be considered in the clinical diagnostic assessment of a phenotypically affected individual when:
>
> - 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.
> - 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.
> - A patient presents with a likely genetic disorder but specific genetic tests available for that phenotype have failed to arrive at a diagnosis.

- 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.
    - [However] prenatal diagnosis by genomic (i.e., next-generation whole exome- or whole genome-) sequencing has significant limitations. The current technology does not support short turn-around times which are often expected in the prenatal setting. There are high false positive, false negative, and variants of unknown clinical significance rates. These can be expected to be significantly higher than seen when array CGH is used in prenatal diagnosis."

ACMG has recommended that for screening purposes:

- "WGS/WES *may be considered* in preconception carrier screening, using a strategy to focus on genetic variants known to be associated with significant phenotypes in homozygous or hemizygous progeny.
- WGS/WES **should not be used** at this time as an approach to prenatal screening.
- WGS/WES **should not be used** as a first-tier approach for newborn screening."

American College of Obstetricians and Gynecologists / Society for Maternal Fetal Medicine (ACOG/SMFM)

In 2016 (reaffirmed in 2023), ACOG/SMFM published joint guidelines on the use of next-generation sequencing in prenatal diagnosis,[69] recommending the following:

> "The routine use of whole-genome or whole-exome sequencing for prenatal diagnosis is not recommended outside of the context of clinical trials until sufficient peer-reviewed data and validation studies are published."

Mitochondrial Medicine Society

The Mitochondrial Medicine Society (2015) published a consensus statement on the diagnosis and management of mitochondrial disease.[8] Most evidence was grade III or less (case control, low-quality cohort studies, or expert opinion without an explicit critical appraisal) using the Oxford Centre for Evidence-Based Medicine criteria. Consensus recommendations were reported using the Delphi method. A subset of the consensus recommendations for DNA testing are as follows:

- "Massively parallel sequencing/NGS [next-generation sequencing] of the mtDNA [mitochondrial DNA] genome is the preferred methodology when testing mtDNA and should be performed in cases of suspected mitochondrial disease instead of testing for a limited number of pathogenic point mutations.

- mtDNA deletion and duplication testing should be performed in cases of suspected mitochondrial disease via NGS of the mtDNA genome, especially in all patients undergoing a diagnostic tissue biopsy.

    - If a single small deletion is identified using polymerase chain reaction-based analysis, then one should be cautious in associating these findings with a primary mitochondrial disorder.

    - When multiple mtDNA deletions are noted, sequencing of nuclear genes involved in mtDNA biosynthesis is recommended.
- When considering nuclear gene testing in patients with likely primary mitochondrial disease, NGS methodologies providing complete coverage of known mitochondrial disease genes is preferred. Single-gene testing should usually be avoided because mutations in different genes can produce the same phenotype. If no known mutation is identified via known NGS gene panels, then whole exome sequencing should be considered.

EVIDENCE SUMMARY

Whole Exome Sequencing (WES) for Hereditary Conditions

There is sufficient evidence of clinical validity and utility for the use of whole exome sequencing (WES) for the evaluation of pediatric patients as a first- or second-tier treatment for whom there is a strong suspicion of a condition of congenital anomalies, and/or developmental or intellectual disabilities. The published evidence base consists primarily of moderate to large observational studies demonstrating diagnostic yields commonly ranging from approximately 25% to 50%, with a substantial subset of patients experiencing clinically meaningful management changes following diagnosis. These changes include modifications to treatment or surveillance, avoidance of additional invasive or low-yield diagnostic testing, and improved prognostic clarity. Establishing a molecular diagnosis through WES also facilitates accurate genetic counseling, recurrence risk assessment, and informed reproductive planning for families.

Professional society guidelines published by the American Academy of Pediatrics (AAP) and the American College of Medical Genetics and Genomics (ACMG) strongly support the use of WES in pediatric patients with congenital anomalies, developmental delay, or intellectual disability, either as a first-tier test or following more targeted evaluation. These guidelines emphasize phenotype-driven test selection and the expectation that results will inform management rather than rigid sequencing algorithms.

The use of WES in adult patients has been less extensively studied. Available evidence frequently includes adults as a minority within mixed-age cohorts, and limited age-stratified analyses suggest lower diagnostic yields in adults compared with children. As a result, the evidence supporting routine use of WES in broader adult populations—outside of narrowly defined clinical scenarios—remains more limited.

Whole Genome Sequencing (WGS) for Hereditary Conditions

Whole genome sequencing (WGS) has demonstrated diagnostic performance comparable to WES in pediatric patients with suspected hereditary conditions and offers incremental advantages in detecting copy-number changes, structural variants, and noncoding variants that may not be reliably captured by exome-based approaches. Although the evidence base for WGS is smaller than that for WES, available studies and guideline reviews support its use in selected pediatric patients with complex or multisystem neurodevelopmental phenotypes, particularly when genome-wide analysis is expected to provide clinically actionable information.

Current professional guidelines from the AAP and ACMG recognize WGS as an appropriate first- or second-tier diagnostic option in pediatric patients with congenital anomalies or developmental delay/intellectual disability when clinical judgment indicates that broader genomic interrogation is warranted. Demonstrated clinical utility is most consistent in phenotypically complex cases where results inform medical management, surveillance, prognosis, or family counseling.

Limitations of WGS include increased interpretive complexity, higher rates of variants of uncertain significance, and greater analytic and resource requirements compared with WES. Accordingly, routine use of WGS outside of carefully selected pediatric indications is not supported, and its application should be limited to clinical scenarios in which genome-wide testing is reasonably expected to influence care.

WES/WGS for Oncologic Indications

There is insufficient evidence to support the routine use of germline whole exome or whole genome sequencing for oncologic indications, including the evaluation of hereditary cancer syndromes or tumor-directed therapeutic decision-making, compared with established targeted genetic testing strategies. Published studies examining WES or WGS specifically for hereditary cancers are limited, and available evidence does not demonstrate consistent improvements in diagnostic yield or patient management.

In the context of cancer care more broadly, limitations such as variable sample quality, tumor heterogeneity, and reduced analytical sensitivity further constrain the utility of WES and WGS compared with validated, tumor-specific next-generation sequencing assays. As a result, the use of germline WES or WGS for oncologic indications is not considered medically necessary outside of select, nonstandard circumstances.

WES/WGS for Reproductive Purposes and Prenatal Testing

There is a paucity of evidence on the use of WES or WGS for reproductive planning and in the prenatal setting. The long turnaround times for these tests, typically 4-8 weeks, make them unfeasible and impractical in these settings. New techniques that allow for rapid detection and reporting of WES and WGS tests are exclusively being studied in research settings at this time. In addition, clinical practice guidelines published by the American College of Obstetricians and Gynecologists, the Society for Maternal Fetal Medicine, and the American College of Medical Genetics and Genomics.

Proteogenomic Testing

At this time, no studies were identified that reported on the analytical validity, clinical validity, or clinical utility of proteogenomic tests for any indication. Therefore, the clinical validity of proteogenomic tests, including but not limited to the GPS Cancer test, is undefined and no inferences can be made regarding the clinical utility of these tests.

Mitochondrial Disorder Genetic Testing

There is enough research to show that diagnostic genetic testing for primary mitochondrial diseases can improve health outcomes for certain patients. Primary mitochondrial diseases are multisystem diseases

that arise from dysfunction in the mitochondrial protein complexes involved in oxidative metabolism. Although there are no specific treatments for these disorders, they can be difficult to diagnose, and genetic testing may allow patients to avoid more invasive muscle or liver biopsies. Genetic testing also has the potential to inform reproductive testing and decision-making. Therefore, diagnostic genetic testing may be considered medically necessary when policy criteria are met.

HEALTH EQUITY CONSIDERATIONS

The Centers for Disease Control and Prevention (CDC) defines health equity as the state in which everyone has a fair and just opportunity to attain their highest level of health. Achieving health equity requires addressing health disparities and social determinants of health. A health disparity is the occurrence of diseases at greater levels among certain population groups more than among others. Health disparities are linked to social determinants of health which are non-medical factors that influence health outcomes such as the conditions in which people are born, grow, work, live, age, and the wider set of forces and systems shaping the conditions of daily life. Social determinants of health include unequal access to health care, lack of education, poverty, stigma, and racism.

The U.S. Department of Health and Human Services Office of Minority Health calls out unique areas where health disparities are noted based on race and ethnicity. Providence Health Plan (PHP) regularly reviews these areas of opportunity to see if any changes can be made to our medical or pharmacy policies to support our members obtaining their highest level of health. Upon review, PHP creates a Coverage Recommendation (CORE) form detailing which groups are impacted by the disparity, the research surrounding the disparity, and recommendations from professional organizations. PHP Health Equity COREs are updated regularly and can be found online here.

BILLING GUIDELINES AND CODING

CODES*		
CPT	0036U	Exome (ie, somatic mutations), paired formalin-fixed paraffin-embedded tumor tissue and normal specimen, sequence analyses
	0094U	Genome (eg, unexplained constitutional or heritable disorder or syndrome), rapid sequence analysis
	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 variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, proband
	0213U	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, each comparator genome (eg, parent, sibling)
	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, proband
	0215U	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 (eg, parent, sibling)
	0260U	Rare diseases (constitutional/heritable disorders), identification of copy number variations, inversions, insertions, translocations, and other structural variants by optical genome mapping
	0264U	Rare diseases (constitutional/heritable disorders), identification of copy number variations, inversions, insertions, translocations, and other structural variants by optical genome mapping
	0265U	Rare constitutional and other heritable disorders, whole genome and mitochondrial DNA sequence analysis, blood, frozen and formalin-fixed paraffin-embedded (FFPE) tissue, saliva, buccal swabs or cell lines, identification of single nucleotide and copy number variants
	0267U	Rare constitutional and other heritable disorders, identification of copy number variations, inversions, insertions, translocations, and other structural variants by optical genome mapping and whole genome sequencing
	0297U	Oncology (pan tumor), whole genome sequencing of paired malignant and normal DNA specimens, fresh or formalin-fixed paraffin-embedded (FFPE) tissue, blood or bone marrow, comparative sequence analyses and variant identification
	0299U	Oncology (pan tumor), whole genome optical genome mapping of paired malignant and normal DNA specimens, fresh frozen tissue, blood, or bone marrow, comparative structural variant identification
	0300U	Oncology (pan tumor), whole genome sequencing and optical genome mapping of paired malignant and normal DNA specimens, fresh tissue, blood, or bone marrow, comparative sequence analyses and variant identification
	0318U	Pediatrics (congenital epigenetic disorders), whole genome methylation analysis by microarray for 50 or more genes, blood
	0331U	Oncology (hematolymphoid neoplasia), optical genome mapping for copy number alterations and gene rearrangements utilizing DNA from blood or bone marrow, report of clinically significant alterations
	0335U	Rare diseases (constitutional/heritable disorders), whole genome sequence analysis, including small sequence changes, copy number variants, deletions, duplications, mobile element insertions, uniparental disomy (UPD), inversions, aneuploidy, mitochondrial genome sequence analysis with heteroplasmy and large deletions, short tandem repeat (STR) gene expansions, fetal sample, identification and categorization of genetic variants
	0336U	Rare diseases (constitutional/heritable disorders), whole genome sequence analysis, including small sequence changes, copy number variants, deletions, duplications, mobile element insertions, uniparental disomy (UPD), inversions, aneuploidy, mitochondrial genome sequence analysis with heteroplasmy and large deletions, short tandem repeat (STR) gene expansions, blood or saliva, identification and categorization of genetic variants, each comparator genome (eg, parent)

	0410U	Oncology (pancreatic), DNA, whole genome sequencing with 5-hydroxymethylcytosine enrichment, whole blood or plasma, algorithm reported as cancer detected or not detected
	0413U	Oncology (hematolymphoid neoplasm), optical genome mapping for copy number alterations, aneuploidy, and balanced/complex structural rearrangements, DNA from blood or bone marrow, report of clinically significant alterations
	0417U	Rare diseases (constitutional/heritable disorders), whole mitochondrial genome sequence with heteroplasmy detection and deletion analysis, nuclear-encoded mitochondrial gene analysis of 335 nuclear genes, including sequence changes, deletions, insertions, and copy number variants analysis, blood or saliva, identification and categorization of mitochondrial disorder–associated genetic variants
	0425U	Genome (eg, unexplained constitutional or heritable disorder or syndrome), rapid sequence analysis, each comparator genome (eg, parents, siblings)
	0426U	Genome (eg, unexplained constitutional or heritable disorder or syndrome), ultra-rapid sequence analysis
	0454U	Rare diseases (constitutional/heritable disorders), identification of copy number variations, inversions, insertions, translocations, and other structural variants by optical genome mapping
	0507U	Oncology (ovarian), DNA, whole-genome sequencing with 5hydroxymethylcytosine (5hmC) enrichment, using whole blood or plasma, algorithm reported as cancer detected or not detected
	0532U	Rare diseases (constitutional disease/hereditary disorders), rapid whole genome and mitochondrial DNA sequencing for single-nucleotide variants, insertions/deletions, copy number variations, peripheral blood, buffy coat, saliva, buccal or tissue sample, results reported as positive or negative
	0567U	Rare diseases (constitutional/heritable disorders), whole-genome sequence analysis combination of short and long reads, for single-nucleotide variants, insertions/deletions and characterized intronic variants, copy-number variants, duplications/deletions, mobile element insertions, runs of homozygosity, aneuploidy, and inversions, mitochondrial DNA sequence and deletions, short tandem repeat genes, methylation status of selected regions, blood, saliva, amniocentesis, chorionic villus sample or tissue, identification and categorization of genetic variants
	0582U	Rare diseases (constitutional disease/hereditary disorders), rapid whole genome DNA sequencing for single-nucleotide variants, insertions/deletions, copy number variations, blood, saliva, tissue sample, variants reported
	0583U	Rare diseases (constitutional disease/hereditary disorders), rapid whole genome comparator DNA sequencing for single-nucleotide variants, insertions/deletions, copy number variations, blood, saliva, tissue sample, variants reported with proband results (List separately in addition to code for primary procedure)
	0653U	Nephrology (inherited kidney disorders), DNA, analysis of approximately 700 genes associated with inherited kidney diseases by exome sequencing, using whole blood, saliva, or nail clipping, reported as an interpretive clinical report classifying pathogenic and likely pathogenic variants

	0654U	Inborn error of metabolism (primary mitochondrial disease), mitochondrial analysis of 1 enzyme complex by western blot analysis, using cultured skin fibroblasts, diagnostic qualitative result
	0655U	Inborn error of metabolism (primary mitochondrial disease), mitochondrial analysis of 1 enzyme complex by spectrophotometric kinetic assay, using cultured skin fibroblasts, diagnostic quantitative result
	0656U	Inborn error of metabolism (primary mitochondrial disease), mitochondrial analysis of 1 enzyme complex by radioactive activity assay, using cultured skin fibroblasts, diagnostic quantitative result
	0657U	Rare diseases (constitutional/heritable disorders), rapid whole genome sequence analysis of comparator nuclear and mitochondrial DNA by next-generation sequencing (NGS), using blood or buccal sample, relevant variants reported with proband results
	0658U	Rare diseases (constitutional/heritable disorders), rapid whole genome sequence analysis of nuclear and mitochondrial DNA by next-generation sequencing (NGS) for singlenucleotide variants (SNVs), insertions/deletions, copy number variants, uniparental disomy, and repeat expansions, using blood or buccal sample, identification and categorization of genetic variants
	0659U	Rare diseases (constitutional/heritable disorders), ultrarapid whole genome sequence analysis of nuclear and mitochondrial DNA by next-generation sequencing (NGS) for singlenucleotide variants (SNVs), insertions/deletions, copy number variants, uniparental disomy, and repeat expansions, using blood or buccal sample, identification and categorization of genetic variants
	81401	Molecular pathology procedure, Level 2 (e.g., 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
	81403	Molecular pathology procedure, level 4 (e.g. analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons
	81404	Molecular pathology procedure, level 5 (e.g., analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 Page 17 of 20 MP215 exons, or characterization of a dynamic mutation disorder /triplet repeat by southern blot analysis
	81405	Molecular pathology procedure, level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons)
	81406	Molecular pathology procedure, Level 7 (e.g., analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)
	81415	Exome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis
	81416	Exome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator exome (eg, parents, siblings) (List separately in addition to code for primary procedure)

	81417	Exome (eg, unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained exome sequence (eg, updated knowledge or unrelated condition/syndrome)
	81425	Genome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis
	81426	Genome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator genome (eg, parents, siblings) (List separately in addition to code for primary procedure)
	81427	Genome (eg, unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained genome sequence (eg, updated knowledge or unrelated condition/syndrome)
	81440	Nuclear encoded mitochondrial genes (eg, neurologic or myopathic phenotypes), genomic sequence panel, must include analysis of at least 100 genes, including BCS1L, C10orf2, COQ2, COX10, DGUOK, MPV17, OPA1, PDSS2, POLG, POLG2, RRM2B, SCO1, SCO2, SLC25A4, SUCLA2, SUCLG1, TAZ, TK2, and TYMP
	81460	Whole mitochondrial genome (eg, Leigh syndrome, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes [MELAS], myoclonic epilepsy with ragged-red fibers
	81465	Whole mitochondrial genome large deletion analysis panel (eg, Kearns-Sayre syndrome, chronic progressive external ophthalmoplegia), including heteroplasmy detection, if performed
	81479	Unlisted molecular pathology procedure
	81599	Unlisted multianalyte assay with algorithmic analysis

***Coding Notes:**

- The above code list is provided as a courtesy and may not be all-inclusive. Inclusion or omission of a code from this policy neither implies nor guarantees reimbursement or coverage. Some codes may not require routine review for medical necessity, but they are subject to provider contracts, as well as member benefits, eligibility and potential utilization audit.
- All unlisted codes are reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is submitted for non-covered services addressed in this policy then it will be **denied as not covered**. If an unlisted code is submitted for potentially covered services addressed in this policy, to avoid post-service denial, **prior authorization is recommended**.
- **See the non-covered and prior authorization lists on the Company Medical Policy, Reimbursement Policy, Pharmacy Policy and Provider Information website for additional information.**
- HCPCS/CPT code(s) may be subject to National Correct Coding Initiative (NCCI) procedure-to-procedure (PTP) bundling edits and daily maximum edits known as "medically unlikely edits" (MUEs) published by the Centers for Medicare and Medicaid Services (CMS). This policy does not take precedence over NCCI edits or MUEs. Please refer to the CMS website for coding guidelines and applicable code combinations.

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POLICY REVISION HISTORY

DATE	REVISION SUMMARY
2/2023	Converted to new policy template.
8/2023	Annual update. Changed denial from investigational to not medically necessary. Removed OncoMap Extra from list of non-covered panels and added PGxome Prenatal test.
10/2023	Q4 2023 code set update. Added criteria for mitochondrial genome testing.
11/2023	Interim update. No changes to criteria.
12/2023	Interim update. Added panels to list of non-covered Whole Genome tests

	Q1 2024 code set update. Added 2 codes.
5/2024	Interim update. Title Change, expanding scope of policy to include genetic testing for mitochondrial disorders
6/2024	Annual update. No changes to coding or criteria.
7/2024	Q3 2024 code set update.
10/2024	Q4 2024 code set update.
4/2025	Q2 2025 code set update.
6/2025	Annual update. Clarifying language
7/2025	Q3 2025 codes set update. One code added.
10/2025	Interim update. Additional medical necessity criteria. Q4 2025 code set update. 2 codes added.
12/2025	Interim update. Clarified language in criterion VI.E
7/2026	Annual update. Liberalize several medical necessity criteria. Q3 2026 code set update.