


MEDICAL POLICY	Genetic Testing: Whole Exome, Whole Genome and Proteogenomic Testing (All Lines of Business Except Medicare)
Effective Date: 1/1/2022  1/1/2022	Medical Policy Number: 219 Medical Policy Committee Approved Date: 3/19; 5/19; 11/19, 8/2020; 9/2020; 4/2021; 08/2021; 09/2021; 11/2021
Medical Officer Date	

See Policy CPT CODE section below for any prior authorization requirements

SCOPE:

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

APPLIES TO:

All lines of business except Medicare

BENEFIT APPLICATION

Medicaid 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.

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

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- 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

POLICY CRITERIA

Whole Exome Sequencing (WES)

- I. Whole exome sequencing (WES) may be considered **medically necessary and covered** for the evaluation of unexplained congenital or neurodevelopmental disorders in children < 18 years of age when **all** of the following criteria (A. - F.) are met:
 - A. The genetic counseling requirements above (criterion I.) have been met; **and**
 - B. **Either** of the two following criteria are documented:
 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**
 - C. A genetic etiology is considered the most likely explanation for the phenotype, and **both** of the following are met:
 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**
 - D. A diagnosis cannot be made by standard clinical and laboratory work-up, excluding invasive procedures such as muscle biopsy; **and**
 - E. 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:
 - 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**
- F. Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection).

Notes: Whole exome sequencing is limited to once per lifetime. Tests that are potentially covered per the above policy criteria are listed in the [Policy Guidelines](#), below.

- II. WES of a comparator exome(s) of a first-degree relative(s) (e.g., parents, siblings) may be considered **medically necessary and covered** when criteria for WES of the affected child above (I. and II.) are met.
- III. WES is considered **investigational and not covered*** for any other indication, including but not limited to:
 - A. When the above criteria (I. and II.) are not met
 - B. Adults (≥ 18 years) not meeting criteria above
 - C. For oncologic indications, including but not limited to:
 1. evaluation of hereditary cancer syndromes
 2. identification of genetic targets for therapeutic management (e.g., EXaCT-1 Whole Exome Testing)
 - D. Screening of asymptomatic individuals

Note: See [Policy Guidelines](#) for test names relevant to this criteria

Whole Genome Sequencing (WGS)(see [Policy Guidelines](#) for test names relevant to this criteria)**

- IV. Whole genome sequencing (WGS) is considered **investigational and not covered** for all indications, including but not limited to the evaluation, diagnosis or management of:
 - A. Hereditary conditions
 - B. Oncologic indications
 - C. Reproductive planning and prenatal testing

Proteogenomic Testing*

- V. Proteogenomic testing (e.g., GPS Cancer®) is considered **investigational and not covered** for all indications, including but not limited to informing therapeutic management for oncologic indications. **Note:** See [Policy Guidelines](#) for test names relevant to this criteria.

Link to [Policy Summary](#)

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POLICY GUIDELINES

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

*Always Not-Covered WES/WGS and Proteogenomic Tests

Tests that do not meet the medical necessity criteria above (II. and III.) are always investigational and not covered regardless of indication and include but are not limited to the following:

- CNGnome® Test (PerkinElmer Genomics)²
- GPS Cancer™ (NantOmics)³
- Praxis Whole Genome Sequencing
- Praxis Somatic Whole Genome Sequencing
- Praxis Somatic Optical Mapping
- Praxis Combined Whole Genome Sequencing and Optical Genome Mapping
- Praxis Somatic Combined Whole Genome Sequencing and Optical Genome Mapping

CPT CODES

All Lines of Business Except Medicare	
Prior Authorization Required	
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)
Not Covered	
0012U	Germline disorders, gene rearrangement detection by whole genome next-generation sequencing, DNA, whole blood, report of specific gene rearrangement(s)
0013U	Oncology (solid organ neoplasia), gene rearrangement detection by whole genome next-generation sequencing, DNA, fresh or frozen tissue or cells, report of specific gene rearrangement(s)

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0014U	Hematology (hematolymphoid neoplasia), gene rearrangement detection by whole genome next-generation sequencing, DNA, whole blood or bone marrow, report of specific gene rearrangement(s)
0036U	Exome (ie, somatic mutations), paired formalin-fixed paraffin-embedded tumor tissue and normal specimen, sequence analyses
0056U	Hematology (acute myelogenous leukemia), DNA, whole genome next-generation sequencing to detect gene rearrangement(s), blood or bone marrow, report of specific gene rearrangement(s)
0094U	Genome (eg, unexplained constitutional or heritable disorder or syndrome), rapid sequence analysis
0209U	Cytogenomic constitutional (genome-wide) analysis, interrogation of genomic regions for copy number, structural changes and areas of homozygosity for chromosomal abnormalities
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)
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

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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
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)
Unlisted Codes All unlisted codes will be reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is billed related to services addressed in this policy then prior-authorization is required.	
81479	Unlisted molecular pathology procedure
81599	Unlisted multianalyte assay with algorithmic analysis

Medicare Only

Prior Authorization Required

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
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)

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0014U	Hematology (hematolymphoid neoplasia), gene rearrangement detection by whole genome next-generation sequencing, DNA, whole blood or bone marrow, report of specific gene rearrangement(s)
0036U	Exome (ie, somatic mutations), paired formalin-fixed paraffin-embedded tumor tissue and normal specimen, sequence analyses
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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)
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Unlisted Codes
 All unlisted codes will be reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is billed related to services addressed in this policy then **prior-authorization is required.**

81479	Unlisted molecular pathology procedure
81599	Unlisted multianalyte assay with algorithmic analysis

DESCRIPTION

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 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.⁴

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.⁴

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.⁵ 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.⁵

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).⁶ 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.⁷

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). Currently, 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. The test compares the information from DNA, RNA and protein between a patient's tumor tissue and blood in an effort to identify genetic and protein markers which may be able to direct patients to a particular Food and Drug Administration (FDA)-approved therapy or active clinical trial, identify potential tumor-resistant therapies to be avoided.⁸

REVIEW OF EVIDENCE

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 July of 2021. 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

Whole Exome Sequencing for Hereditary Conditions

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).⁹ 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 2019, 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.¹⁰ The review reported diagnostic rates in this population between 24% to 48%.

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.¹¹ The analysis found 37 studies published between 2011 and 2017, totalling 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 limitations. 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 < 3years¹²: WES = 33%, NGS panel = 27%, karyotyping = 44%, microarray = 27%.
 - Children with drug-resistant epilepsy¹³: WES = 17%, clinical exome = 45%, panel = 33%.
 - Complex pediatric neurological disorders¹⁴⁻¹⁸: 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)¹⁹: WES = 8.4%, CMA = 9.3%.
 - Children/infants with a suspected monogenic condition (predominantly congenital abnormalities, dysmorphic features and/or neurometabolic indications):²⁰⁻²² WES = range: 52% to 58%, standard genetic testing (single gene (s) or panels) = 14%.
 - Hearing loss in children²³: WES = 37%, panels = 16%.
 - Patients with developmental delay/intellectual disability (cohort was 87% children)²⁴: WES = 30%, WGS = 22%. The study also found that 11% of the affected patients had VUSs.
 - Adult patients with neurological disorders:²⁵ 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).²⁶
- **Non-Comparative studies:**
 - Rare diseases (mixed pediatric and adult-onset conditions)²⁷: 226/802 patients; 28.2%.
 - Adult genetic conditions²⁸: 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%.²⁹ Among 13 studies, average 34.4% for trio exome sequencing; among 7 studies, 26.6% for singleton exome sequencing.³⁰ 38/106; 36%.³¹
 - Chronic kidney disease (adults)³²: 22/92 patients; 24%.
 - Undiagnosed genetic conditions (mixed populations with between 78% to 85% children)³³⁻³⁵: 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 encephalopathy³⁶: 11/50 patients; 22%. VUS rate of 4%.
 - Limb-girdle muscular dystrophy (63% of cohort were children)³⁷: 27/60 families; 45%, with higher yields for trios [60%].
 - Intellectual developmental disorder and unexplained metabolic phenotypes (cohort 80% children):³⁸ 28/41 probands (68%).

WES in the Prenatal Setting

There are limited data on WES in prenatal genetic diagnostic testing. 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.

Whole Genome Sequencing for Hereditary Conditions

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.³⁹ 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 cardiomyopathy⁴⁰: WGS = 31%, panel = 31%. VUS rate was 17% for both WGS and panel.
 - Inherited retinal diseases (phenotypically heterogeneous cohorts)^{41,42}: 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)⁴³: rapid WGS (rWGS) = 31%, standard WGS = 24%, CMA = 6%, panels = 18%, WES = 33%, methylation testing = 13%. It 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^{44,45}: rWGS = 43% to 57%, standard genetic testing = 9% to 10%.
 - Pediatric patients with congenital malformations and/or neurodevelopmental disorders (n=100)⁴⁶: WGS = 34%, CMA = 8%, CMA plus targeted gene sequencing = 13%.
 - Patients with a suspected genetic condition with previous negative results (108 patients)⁴⁷: 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)⁴⁸
 - Pediatric patients with unsolved leukodystrophies: WGS = 5/9 (56%), SOC = 5/23 (22%)⁴⁹

- Non-Comparative studies:
 - Developmental delay/intellectual disability (n=244 patients):²⁴ 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 seizures⁵⁰ (diagnostic yield = 32%, and 84% of these were de novo mutations)
 - Pediatric neurodevelopmental disorders¹⁷: 11/15 critically ill children who underwent rapid WGS (73%).
 - Patients with a suspected genetic condition with previous negative results (156 patients):⁵¹ 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

WES/WGS for Targeted Therapy Identification for Oncologic Indications

Pediatric Populations

In 2016, Parsons et al. published a study which determined the prevalence of somatic and germline mutations in children with solid tumors.⁵² 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.⁵³ 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.⁵⁴ 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 20⁵⁵. 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.⁵² 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)⁵⁶ (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)⁵⁷: 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)⁵⁸: 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)⁵⁹: 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)⁶⁰: 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.⁵⁹ 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 2016, 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.¹⁰ 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)³²: 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 epilepsy¹³: 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 conditions²⁹: 5/12 children (42%) who were diagnosed by WES had changes in treatment plans.
- Pediatric neurodevelopmental disorders (2 studies):
 - Soden et al.¹⁷: 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.¹⁸: 32/32 patients positive for pathogenic variants underwent changes in management.
- Undiagnosed genetic conditions (mixed cohort with 78% children):³⁴ 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:²⁰ (predominantly congenital abnormalities, dysmorphic features and/or neurometabolic indications):²⁰ 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):²² 6/ 23 (26%) patients had altered clinical management.
 - Rapid WES (median turnover time = 16 days):²¹ 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):³⁸ 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.

Whole Genome Sequencing for Hereditary Conditions

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)⁴⁴: 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):⁴⁵ 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.

WES/WGS for Targeted Therapy Identification for Oncologic Indications

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)⁶¹: 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)⁵⁷: 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)⁵⁸: 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.⁸ 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.

CLINICAL PRACTICE GUIDELINES

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,⁷ 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 2012, the ACMG published a position statement that recommended the following regarding exome and genome sequencing for diagnostic purposes:⁶²

“WGS/WES should be considered in the clinical diagnostic assessment of a phenotypically affected individual when:

- 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.
 - i. [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, ACOG/SMFM published joint guidelines on the use of next-generation sequencing in prenatal diagnosis,⁶³ 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.”

CENTERS FOR MEDICARE & MEDICAID

As of July 25, 2021, no Centers for Medicare & Medicaid (CMS) coverage guidance was identified which addresses exome, genome or proteogenomic testing for any indication.

POLICY 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 for whom there is a strong suspicion of a condition of genetic etiology that is unable to be diagnosed using clinical, laboratory or targeted genetic testing. The body of evidence consists of a large number of moderate to large observational studies that report diagnostic yields typically between 25-50% and report no less than 25% of patients who undergo management changes as a result of WES. The use of WES to arriving at the correct diagnoses in these patients not only provides relief after diagnostic odysseys but also avoids further diagnostic investigations, enables informed patient management, and facilitates accurate genetic counseling and risk assessments, along with providing families with prenatal options. In addition, clinical practice guidelines published by the American Society of Human Genetics and the American College of Medical Genetics and Genomics support the use of WES in this population.

The use of WES in adult patients has not been as well-studied. There is a paucity of studies that have been published evaluating the clinical validity and utility of WES strictly in adult patients. In addition, studies that have included adults as part of a mixed cohort have reported small numbers of included adults (typically less than 20% of the overall patient cohort). The few studies that have evaluated diagnostic yield by age have reported significantly lower diagnostic yields in adult patients compared to children.

Whole Genome Sequencing (WGS) for Hereditary Conditions

Although the diagnostic yield for WGS appears to be similar to that of WES, there are far fewer publications on the use of WGS in a clinical setting than WES for the evaluation of hereditary conditions. Therefore, the clinical validity of WGS has not been firmly established in this setting. In addition, there is insufficient evidence that the use of WGS leads to changes in management and that these changes lead

to improved health outcomes. In addition, the use of WGS in this patient population has limitations that are unique to WGS compared to WES, including but not limited to significantly increased detection of variants of uncertain significance (VUSs), longer turn-around times, and more complex and less standardized data analysis methods.

WES/WGS for Oncologic Indications

There is insufficient evidence that the use of WES or WGS for oncologic indications, including the evaluation of hereditary cancer syndromes and the identification of genetic targets for therapeutic management, leads to improved diagnostic yields or changes in patient management. There is a paucity of studies published evaluating the use of WES or WGS for hereditary cancers. Regarding the use of WES and WGS as a tool to aid in cancer care, including identification of variants that are known therapeutic targets, there are a limited number of studies that have reported on actual changes in management as a result of WES or WGS testing. In addition, the use of WES and WGS in this setting have limitations unique to oncologic indications, including poor sample quality, small sample quantity and low tumor yield; all of which can reduce the analytical sensitivities of these tests to below the cut-offs required for clinical laboratories.

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.

INSTRUCTIONS FOR USE

Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Companies reserve the right to determine the application of Medical Policies and make revisions to Medical Policies at any time. Providers will be given at least 60-days notice of policy changes that are restrictive in nature.

The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement.

REGULATORY STATUS

Mental Health Parity Statement

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

MEDICAL POLICY CROSS REFERENCES

- Genetic Counseling
- Genetic Testing: Non-Covered Genetic Panel Tests (All Lines of Business Except Medicare)
- Genetic Testing: Non-Covered Genetic Panel Tests (Medicare Only)
- Genetic Testing: Pharmacogenetic Testing (All Lines of Business Except Medicare)
- Genetic Testing: Pharmacogenetic Testing (Medicare Only)
- Genetic Testing: Reproductive Planning and Prenatal Testing (All Lines of Business Except Medicare)
- Genetic Testing: Reproductive Planning and Prenatal Testing (Medicare Only)

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