Clinical Appropriateness Guidelines

Chromosomal Microarray Analysis, Whole Exome and Whole Genome Sequencing

EFFECTIVE SEPTEMBER 4, 2022

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GEN07-0922.2

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Scope

This document addresses the diagnostic use of chromosomal microarray analysis (CMA) and whole exome sequencing (WES) in the evaluation of rare disease. It does not address the use of WES as a technology for tumor profiling (see Clinical Appropriateness Guidelines for Molecular Testing of Solid and Hematologic Tumors and Malignancies). This document also addresses whole genome sequencing (WGS) as well as other broad scale profiling, e.g., whole transcriptome analysis and genome mapping. All tests listed in these guidelines may not require prior authorization or may have separate coverage criteria; please refer to the health plan.

Genetic Counseling Requirement

Genetic testing, i.e., whole exome sequencing, included in these guidelines is covered when:

1. The patient meets coverage criteria outlined in the guidelines
2. A recommendation for genetic testing has been made by one of the following:
    - An independent board-certified or board-eligible medical geneticist not employed by a commercial genetic testing laboratory*
    - An American Board of Medical Genetics or American Board of Genetic Counseling-certified genetic counselor not employed by a commercial genetic testing laboratory*
    - A genetic nurse credentialed as either a Genetic Clinical Nurse (GCN) or an Advanced Practice Nurse in Genetics (APGN) by either the Genetic Nursing Credentialing Commission (GNCC) or the American Nurses Credentialing Center (ANCC) who is not employed by a commercial genetic testing laboratory*

    Who:

    - Has evaluated the case and performed pre-test genetic counseling with the patient or the patient's legal guardian
    - Has completed a three-generation pedigree
    - Intends to engage in post-test follow-up counseling with the patient or the patient's legal guardian

**A physician, genetic counselor or genetic nurse employed by a laboratory that operates within an integrated, comprehensive healthcare delivery system is not considered to be an employee of a commercial genetic testing laboratory for the purpose of these guidelines.*

Appropriate Use Criteria

Whole Exome Sequencing

Whole exome sequencing (WES) (81415 with or without 81416) is medically necessary for any of the following clinical scenarios when all of the general criteria for WES testing (below) are also met.

Phenotype Suspicious for a Genetic Diagnosis

Testing is ordered after an individual has been evaluated by a board-certified medical geneticist or other board-certified specialist physician with specific expertise in the conditions being tested for and relevant genes, AND any of the following:

- Individual with multiple major structural or functional congenital anomalies affecting unrelated organ systems (including major metabolic disorders), OR
- Individual with one major structural or functional congenital anomaly and two or more minor structural anomalies, OR
- Individual with one major structural congenital anomaly and a family history strongly implicating a genetic etiology OR
- Individual with known or suspected developmental and epileptic encephalopathy (onset before three years of age) for which likely non-genetic causes of epilepsy (e.g., environmental exposures; brain injury secondary to complications of extreme prematurity, infection, trauma) have been excluded, OR
- Individual diagnosed with global developmental delay* following formal assessment by a developmental pediatrician or neurologist, OR
- Individual diagnosed with moderate/severe/profound intellectual disability** following formal assessment by a developmental pediatrician or neurologist, OR
- Individual with confirmed congenital bilateral sensorineural hearing loss of unknown etiology

*Global developmental delay is defined as significant delay in younger children, <5 years of age, in at least two of the major developmental domains: gross or fine motor; speech and language; cognition; social and personal development; and activities of daily living.

**Moderate/severe/profound intellectual disability as defined by DSM-5 criteria diagnosed by 18 years of age.

Fetal Testing

- Standard diagnostic genetic testing (chromosomal microarray analysis (CMA) and/or karyotype) of the fetus has been performed and is uninformative **AND**
- Testing is ordered in conjunction with a board-certified medical geneticist or genetic counselor **AND**

- Testing is performed on direct amniotic fluid/chorionic villi, cultured cells from amniotic fluid/chorionic villi or DNA extracted from fetal blood or tissue **AND**
- At least one of the following is present:
  - Multiple fetal structural anomalies affecting unrelated organ systems
  - Fetal hydrops of unknown etiology
  - A fetal structural anomaly affecting a single organ system (please note exclusions below) **AND** family history strongly suggests a genetic etiology
    - Isolated anomalies excluded from coverage:
      - Isolated increased nuchal translucency
      - Isolated talipes (clubfeet)
      - Isolated neural tube defect
      - Isolated congenital heart defects
      - Isolated cleft lip and/or palate
      - Isolated congenital diaphragmatic hernia

Fetal WES is not medically necessary for any of the following indications:

- Healthy pregnancies
- Indications other than fetal structural anomalies
- Ultrasound soft markers of aneuploidy (e.g., choroid plexus cysts, echogenic bowel, intracardiac echogenic focus)

General Criteria for WES Testing

(*All of the following criteria are necessary to pursue WES testing in the clinical scenarios above*):

- WES results will directly impact clinical decision-making and/or clinical outcome
- No other causative circumstances (e.g., environmental exposures, injury, prematurity, infection) can explain symptoms
- Clinical presentation does not fit a well-described syndrome for which single-gene or targeted panel testing is available
- The differential diagnosis list and/or phenotype warrant testing of multiple genes, and at least one of the following:
  - WES is more practical than the separate single gene tests or panels that would be recommended based on the differential diagnosis

- WES results may preclude the need for multiple and/or invasive procedures, follow-up, or screening ("diagnostic odyssey") that would be recommended in the absence of testing

WES is not medically necessary in the following scenarios:

- Testing using cell-free DNA
- Preimplantation testing of an embryo
- Genetic carrier screening
- Asymptomatic screening
- Oncology indications
- Isolated mild intellectual disability
- Isolated autism spectrum disorder

Whole Exome Reanalysis

Reanalysis of previously obtained uninformative whole exome sequence (81417) is medically necessary when any of the following criteria is met:

- There has been onset of additional symptoms that broadens the phenotype assessed during the original exome evaluation
- There has been the birth or diagnosis of a similarly affected first-degree relative that has expanded the clinical picture
- New scientific knowledge suggests a previously unknown link between the patient's findings and specific genes/pathogenic or likely pathogenic variants AND at least 18 months have passed since the last analysis

Chromosomal Microarray Analysis

Chromosomal microarray analysis (CMA) is medically necessary for any of the following indications:

- Non-syndromic autism spectrum disorder
- Non-syndromic global developmental delay or intellectual disability*
- Individual with multiple major structural or functional congenital anomalies affecting unrelated organ systems (including major metabolic disorders)*
- Known or suspected developmental and epileptic encephalopathy (onset before three years of age) for which likely non-genetic causes of epilepsy (e.g., environmental exposures; brain injury secondary to complications of extreme prematurity, infection, trauma) have been excluded*

*CMA is intended for use in the detection of chromosomal duplications and deletions only and is therefore indicated when the possibility of microdeletion or microduplication syndromes/conditions are suspected. It cannot detect other common variant types (e.g., sequence variants). If sequence variants are high on the differential diagnosis, please see whole exome sequencing criteria above.

For oncologic indications, please see Clinical Appropriateness Guidelines for Molecular Testing of Solid and Hematologic Tumors and Malignancies.

For reproductive indications, please see Clinical Appropriateness Guidelines for Genetic Testing for Reproductive Carrier Screening and Prenatal Diagnosis.

Whole Genome Sequencing

Whole genome sequencing (WGS) is not medically necessary*.

Whole genome sequencing of the transcriptome (RNA sequencing) and genome mapping are not medically necessary.

*Please refer to the health plan for exceptions.

CPT Codes

The following codes are associated with the guidelines outlined in this document. This list is not all inclusive. Medical plans may have additional coverage policies that supersede these guidelines.

Covered when medical necessity criteria are met:

81228	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number variants, comparative genomic hybridization [CGH] microarray analysis
81229	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants, comparative genomic hybridization (CGH) microarray analysis
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)

Considered not medically necessary:

(Proprietary tests that do not meet criteria are considered not medically necessary when submitted with their specific assigned code listed below or any less specific coding.)

81349	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and loss-of-heterozygosity variants, low-pass sequencing analysis
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
0094U (Rady® RCIGM)	Genome (eg, unexplained constitutional or heritable disorder or syndrome), rapid sequence analysis
0209U (CNGnome®)	Cytogenomic constitutional (genome-wide) analysis, interrogation of genomic regions for copy number, structural changes and areas of homozygosity for chromosomal abnormalities
0212U (Genomic Unity® Whole Genome Analysis Proband)	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 (Do not report 0212U in conjunction with 81425)
0213U (Genomic Unity® Whole Genome Analysis Comparator)	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) (Do not report 0213U in conjunction with 81426)
0214U (Genomic Unity® Exome Plus Analysis Proband)	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 (Do not report 0214U in conjunction with 81415)
0215U	Rare diseases (constitutional/heritable disorders), whole exome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short

(Genomic Unity® Exome Plus Comparator)	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) (Do not report 0215U in conjunction with 81416)
0260U (Augusta Optical Genome Mapping)	Rare diseases (constitutional/heritable disorders), identification of copy number variations, inversions, insertions, translocations, and other structural variants by optical genome mapping
0264U (Praxis Optical Genome Mapping)	Rare diseases (constitutional/heritable disorders), identification of copy number variations, inversions, insertions, translocations, and other structural variants by optical genome mapping
0265U (Praxis Whole Genome Sequencing)	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
0266U (Praxis Transcriptome)	Unexplained constitutional or other heritable disorders or syndromes, tissue specific gene expression by whole transcriptome and next-generation sequencing, blood, formalin-fixed paraffin embedded (FFPE) tissue or fresh frozen tissue, reported as presence or absence of splicing or expression changes
0267U (Praxis Combined Whole Genome Sequencing and Optical Genome Mapping)	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

Background

Whole exome sequencing (WES) is a method of analyzing the protein coding regions, also called the exome, which comprise 1-2% of the entire genome. With the ability to screen all genes, WES theoretically captures at least 85% of the genetic variants associated with human Mendelian disorders (Rabbani et al. 2014). Limitations of WES do exist and currently include reduced ability to detect copy number variants, reduced coverage depth for select genes and the potential for variants of uncertain significance and secondary findings (Zou et al. 2020; Srivastava et al. 2019). These mitigating factors have not precluded the technology from increasingly becoming a common molecular diagnostic test for individuals with suspected rare genetic disorders. WES is most appropriate when used for patients whose phenotype is strongly suggestive of a genetic disorder, but targeted testing has either been negative or is impractical due to a wide or uncertain differential diagnosis (ACMG 2012).

Several large studies have demonstrated the diagnostic utility of WES, in which diagnosis rates have ranged between 22-57% (Clark et al. 2018; Yang et al. 2014; Lee et al. 2014). Though diagnostic utility does not always directly correlate with clinical utility, providing a molecularly confirmed diagnosis can often shorten the diagnostic odyssey, improve disease management, allow for targeted treatments and surveillance for later-onset comorbidities for a subset of patients, and inform genetic counseling with respect to recurrence risks and prenatal diagnosis options for families (Sawyer et al. 2016; Malinowski et al. 2020). Even in cases for which treatments are not available, using WES to confirm a lethal diagnosis in acutely ill pediatric patients allows for the avoidance of invasive biopsies, additional workup, and appropriate implementation of palliative care (Stark et al. 2018).

Rationale for Genetic Counseling for WES

Pre-test genetic counseling provides individuals seeking genetic testing the opportunity to make informed decisions about their genetic testing and subsequent medical management options. Genetic counseling combines expertise in obtaining and interpreting family history information, the ability to identify the most beneficial individual in a family to initiate testing, identification of the most appropriate testing options, experience in obtaining informed consent for testing and proficiency in genetic variant interpretation, in order to maximize the genetic testing experience for patients and their healthcare providers. The genetic counseling informed consent process also educates and empowers patients to consider the psychological, financial, employment, disability, and insurance implications of genetic testing and results (Al-Khatib et al. 2018). Patients who receive genetic counseling report increased knowledge, understanding, and satisfaction regarding their genetic testing experience (Armstrong et al. 2015; Harvey et al. 2007).

The advent of multi-gene panels and genome-scale sequencing have increased the complexity of the genetic testing landscape. Misuse of genetic testing increases the risk for adverse events and patient harm, including missed opportunities for diagnosis and disease prevention (Bellcross et al. 2011; Plon et al. 2011). Genetic information requires expert interpretation and ongoing re-evaluation to ensure the most accurate interpretation is utilized to inform medical management decision making. The multitude of genetic testing options as well as the complex information revealed by genetic testing can make choosing the most appropriate test and interpretation of results difficult for non-genetics healthcare providers (Ray 2011). Involvement of a clinical genetics provider has been shown to ensure the correct test is ordered, limit result misinterpretation and allow patients to make informed, evidence-based medical decisions with their healthcare providers (Cragun et al. 2015).

Genetic counseling not only improves patient outcomes but also reduces unnecessary healthcare spending. Pre-test genetic counseling has been shown to reduce inappropriate test ordering and prevent unnecessary medical procedures and interventions that follow from inaccurate result interpretation (DHHS 2011). While genetic testing is now available for almost all clinical specialties, correct use and interpretation is necessary to prevent adverse outcomes. While genetic counseling may benefit any patient considering or undergoing genetic testing, tests that offer predictive information or have a higher chance of identifying variants of uncertain significance often carry stronger recommendations in the form of consensus guidelines and professional statements recommending genetic counseling by trained genetics professionals.

There is consensus that genetic counseling by trained genetics professionals represents best practice prior to and after ordering such tests and can identify the most appropriate tests (e.g., multi-gene panels or WES) and the most appropriate testing candidates (Yang et al. 2013).

Obtaining informed consent and providing pre-test genetic counseling by a trained genetics professional is an essential component of WES. The American College of Medical Genetics (ACMG) published specific recommendations (ACMG Board of Directors 2013):

1. Pre-test counseling should be done by a medical geneticist or an affiliated genetic counselor and should include a formal consent process
2. Prior to initiating WGS/WES, participants should be counseled regarding the expected outcomes of testing, the likelihood and type of incidental results that could be generated, and what results will or will not be disclosed
3. As part of the pre-test counseling, a clear distinction should be made between clinical and research-based testing. In many cases, findings will include variants of unknown significance that might be the subject for research; in such instances a protocol approved by an institutional review board must be in place and appropriate prior informed consent obtained from the participant

Variants of uncertain significance and incidental or secondary findings not only complicate genetic counseling but also interpretation of WES results, and they carry a risk of harm to the patient if misinterpreted by an inexperienced clinician. Incidental or secondary findings, where variants unrelated to the clinical phenotype are identified, pose issues of informed consent but often have clear medical management recommendations (ACMG 2013; Green 2013). Jurgens (2015) commented on the ongoing challenges in determining the phenotypic consequences of variants identified even among the list of 59 genes recommended, at the time of his publication, by the American College of Medical Genetics and Genomics for the reporting of the secondary findings. This list has now increased to 73 genes underscoring the continued importance of genetic counseling.

Whole Exome Sequencing

Phenotype Suspicious of a Genetic Diagnosis

WES is useful in diagnosing complex phenotypes. The expertise of clinical genetics specialists allows them to accurately evaluate patients and determine whether WES would be more useful in diagnosing their complex phenotype over more targeted testing. Shashi et al. (2014) retrospectively evaluated a cohort of 500 patients who received traditional medical genetics evaluations and concluded that the clinical utility of genomic testing is greater when testing is applied after an initial clinical genetics evaluation. To further this point, Baldridge, et al (2017) performed a retrospective analysis of 155 patients who underwent WES as part of their Exome Clinic. They report that after medical genetics evaluation, prior test results/clinical exam, and use of additional diagnostic modalities, their clinic's diagnostic yield was 43%. They further note that clinical management was altered in 12% of diagnosed cases.

In addition to the diagnostic power of WES, the cost-effectiveness of such testing is a compelling reason to consider its use in clinical practice. WES has been shown to reduce healthcare costs by limiting downstream medical interventions, regardless of whether a molecular diagnosis is confirmed (Vrijenhoek et al. 2018). However, WES is only cost effective if it replaces the need for multiple individual tests, and it is not as cost-effective when it is used after performing and receiving uninformative results from multiple other genetic tests. For this reason, genetics providers should consider when WES should be performed prior to more traditional testing, such as chromosomal microarray or targeted panels. Recommendations from the Clinical Genetics Think Tank, an association

of American and Canadian geneticists, suggest that a targeted gene panel should be utilized if available as first-tier testing when the patient's clinical presentation is specific to a known genetic condition, and WES should only be considered as a next step if the previous panel is outdated, the patient's phenotype is atypical or has evolved, or there is clinical urgency.

Whole Exome Sequencing for Global Developmental Delay (gDD)/Intellectual Disability (ID)

The diagnostic yield for WES has been shown in multiple studies to range from 27-50% (Anazi et al. 2017; Nolan et al. 2016). While mitigating factors such as consanguinity and difficulty separating other phenotypic features from gDD/ID is a pervasive limitation in the current evidence, the diagnostic yield has been consistently documented. Visser et al. (2017) provide supplemental data revealing a 31% diagnostic yield in 24/78 patients described with isolated intellectual disability. Kukri et al. (2019) revealed a diagnostic yield of 19% when subjects lacking reported facial dysmorphism with moderate to profound ID were analyzed.

There is evidence of utility for the use of WES in individuals with gDD/ID. Salient outcomes from whole exome sequencing considered as evidence of clinical utility include changes in management (targeted workup for systemic involvement, further disease monitoring as well as obviating the need for further testing), ending the diagnostic odyssey, and family-focused outcomes such as cascade genetic testing (Manickam et al. 2021). The ACMG performed a systematic evidence review which included a meta-analysis of 25 studies and reported a rate of change in short-term clinical management (defined as modifications to medications, procedures or treatments) of 8% (95% CI 6,11) for all patients receiving exome/genome sequencing. The Ontario Health Technology Assessment (OHTA) reported a rate of 5.9% for exome sequencing (Ontario Health Quality 2020). In a separate meta-analysis of 19 studies, the reported rate of change for long-term clinical management (defined as referral to specialists, surveillance or life-style changes) was 10% (95% CI 7, 15) with the OHTA reporting this rate of change as 17.2% (Ontario Health Quality 2020).

Clinical utility also includes reproductive-focused outcomes following WES in individuals with gDD/ID (Manickam et al. 2021; Srivastava et al. 2014; Nolan et al. 2016). When the threshold for diagnostic yield of testing is high, reproductive decision-making holds greater clinical utility; the risk for an affected child is a known factor (potentially as high as 25-50%) and not theoretical.

Whole Exome Sequencing in Developmental and Epileptic Encephalopathy

There is evidence of utility for the use of WES in individuals with early onset epilepsies. Sheidley et al. (2018) discussed possible utility of genetic testing for epilepsy includes avoidance of treatment (i.e., epilepsy surgery) and invasive diagnostic tests (lumbar puncture, muscle biopsy, frequency of brain imaging). Additionally, there are a number of specific genetic epilepsy diagnoses that lead to immediate and specific treatment recommendations. Diagnostic criteria for developmental and epileptic encephalopathy have traditionally been made based on observations on EEG, imaging, and seizure semiology. However, there is significant clinical and genetic heterogeneity in this group of conditions. Varying electroclinical syndromes are defined by ILAE and many have overlapping or heterogeneous genetic causes (Palmer et al. 2018). In this population a rapid diagnosis can significantly impact treatment options (i.e., GLUT1 deficiency of B6 dependent early onset epilepsy) or referral to other specialties or palliative care (Myers et al. 2018). Additionally, 40-50% remain undiagnosed after first tier assessment (neurological, neuroimaging, evaluation, screening for metabolic disorders, CMA and targeted genetic testing) (Palmer et al. 2018).

Vissers et al. (2017) examined 150 patients with neurological disorders (including 5 with epilepsy and 39 patients with Intellectual Disability (ID)+epilepsy or ID+movement disorder) and found that WES identified significantly more conclusive diagnoses (29.3%) than the standard care pathway (7.3%) without incurring higher costs. Nolan et al. (2016) found a diagnostic rate for WES, through a retrospective chart review, increased from 25% - 48%. Howell et al. (2018) reported an increased diagnostic yield of 67% with WES in 114 patients with severe epilepsies of infancy (SEI). Myers et al. (2018) compiled studies that utilized WGS and WES studies in epilepsy and encephalopathy and found that the diagnostic rate ranged from 12.5-77% for patients with various forms of early life epilepsies.

Whole Exome Sequencing for Sensorineural Hearing Loss

Approximately 80% of congenital hearing loss is due to genetic variants with roughly 20% of genetic diagnoses involving one of over 400 genetic syndromes and 80% being classified as nonsyndromic (Korver et al, 2017). Due to this heterogeneous etiology, next-generation sequencing panels are commonly used to assess large numbers of genes for diagnosis of sensorineural hearing loss (SNHL), however this approach is limited given that a majority of cases of hereditary deafness are due to rare genes and there is broad heterogeneity between families and across ethnicities. Panels differ in covered region, sequence-capturing methodology and data-analyzing pipe-line, making the sequencing results generally not compatible for cross-platform re-analysis and comparison (Zou et al. 2020).

In recent years, WES has been used to expedite identification of new genes and variants associated with hearing loss and has increased the rate of genetic diagnosis for infants with congenital hearing impairment (Downie et al. 2019; Bademci et al. 2016; Zou et al. 2020). Downie et al. (2019) reported a 56% rate of genetic diagnosis for infants with congenital bilateral hearing impairment using whole exome with clarification by microarray. In addition, the opportunity for early diagnosis of individuals who may not yet have developed syndromic features, and are too young to know if their hearing loss is stable or progressive, is significant. Confirmation of syndromic SNHL provides an opportunity for earlier screening and access to treatment and/or clinical trials. For example, individuals with Usher syndrome may have an opportunity to participate in clinical trials to prevent vision loss. Downie et al. (2019) found that (54/59) 92% of participants in their study who received a diagnosis had some change in their medical management.

Early confirmation of nonsyndromic hearing loss can also alleviate the need for additional screening. Downie et al. (2019) reports that 37/106 (36%) of infants with bilateral SNHL in their cohort were discharged from further screening and surveillance after nonsyndromic P/LP variants were identified, reducing the burden on the family and alleviating the unnecessary utilization of healthcare resources. Stark et al. (2019) found that for the infants' families in their cohort, the major impact of early genomic diagnosis was the restoration of parental reproductive confidence. Studies are also underway to address the question of secondary findings from WES.

Whole Exome Sequencing in the Prenatal Setting

Data has demonstrated clinical utility for WES in the prenatal population after uninformative standard diagnostic testing, i.e., karyotype and/or microarray. Diagnostic yields are generally quoted as ranging from 10-57% and are dependent on associated ultrasound findings (Abou Tayoun and Mason-Suares 2019; Lord et al. 2019; Petrovski et al. 2019). Fu and colleagues (2018) reported a definitive diagnosis using WES following a normal karyotype and microarray in 22.3% of fetuses with a single malformation and 30.8% in those with multiple malformations. In addition, a high diagnostic yield (9-47%) has been reported using WES in fetuses with hydrops (Yates et al. 2017; Drury et al. 2015)

providing an alternative to current commercially available panels which may not contain newly discovered pathogenic variants.

Conversely, several studies have revealed a low diagnostic yield for monogenic disorders using WES in fetuses with isolated sonographic soft markers, i.e., increased nuchal translucency, choroid plexus cysts, echogenic foci in the heart or bowel, thickened nuchal fold, absent nasal bone, single umbilical artery, or persistent right umbilical vein (Fu et al. 2017; Lord et al. 2019; Abou Tayoun and Mason-Suares 2019). Diagnostic yield has also been determined to be proportional to the severity of the ultrasound findings, i.e., higher for fetuses with more than two anomalies (Monaghan et al. 2020; Lord et al. 2019). There is also concern about difficulties in interpreting WES results for isolated findings such as complex cardiac defects (Pasipoularides 2018). Therefore, when pursuing testing for isolated congenital anomalies it should only be considered in those with demonstrated informative results and high diagnostic yield.

The American College of Medical Genetics (ACMG) has recently published considerations for the use of WES in the prenatal setting (Monaghan et al. 2020). While ACMG has suggested consideration of WES for fetuses likely to have a genetic disorder when other investigations have not yielded a diagnosis, it is important to remain cognizant of the limitations in the prenatal setting. Identification of fetal structural anomalies using ultrasonography limits the ability for clinicians to ascertain the full phenotypic spectrum which may impact the interpretation of WES (Aarabi et al. 2018). The relatively long turnaround time of WES has historically been a limitation for its use in a prenatal setting, especially when ultrasound findings are not detected until later gestational ages (Daum et al. 2019). However, emerging technologies allow for more rapid completion of test results (Felice et al. 2019). Prenatal WES may also be considered in the context of research in cases that do not meet clinical criteria for testing.

Whole Exome Reanalysis

There may be scenarios in which reanalysis of previously uninformative whole exome sequence data is medically necessary. This includes the onset of additional symptoms that broaden the phenotype assessed during the original exome evaluation, or the birth or diagnosis of a similarly affected first-degree relative that has expanded the clinical picture. In addition, due to the rapid increase in knowledge surrounding disease genes and phenotypes, WES reanalysis can be helpful at future time intervals. Reanalysis of exome data has shown to increase the diagnostic yield by 11-16% when performed one to three years after initial testing (Alfares et al. 2018; Ewans et al. 2018; Hiatt et al. 2018). Reanalysis can also help re-classify previously detected variants of uncertain significance.

Chromosomal Microarray Analysis

Chromosomal microarray (CMA) or comparative genomic hybridization (CGH) detects microduplications and microdeletions of chromosomal DNA. Many studies have validated this technology as a more sensitive alternative to traditional cytogenetic karyotyping. CMA is now recommended as a first-tier test in place of karyotyping for multiple indications, although the technology cannot detect balanced rearrangements (e.g., balanced reciprocal translocations). SNP arrays are a specific type of oligonucleotide array that targets alternative alleles at SNPs within the genome. SNP array offers the ability to analyze a sample at a higher resolution than metaphase cytogenetics for DNA copy number alterations (duplications and deletions), copy number polymorphisms, and loss of heterozygosity (LOH).

The ACMG recommends CMA as a first-tier test in the initial postnatal evaluation of individuals with multiple anomalies not specific to a well-delineated genetic syndrome, apparently non-syndromic developmental delay/intellectual disability, and autism spectrum disorders (Manning et al. 2020; Shao et al. 2021).

In addition, if a specific syndrome is not readily identified, then chromosomal microarray would be a reasonable first line diagnostic measure for those with developmental and epileptic encephalopathies. Chromosomal microarray has been found to have diagnostic yields in the approximately 5–30% range in various studies in epilepsy (Noh et al. 2012). Specific to epileptic encephalopathies, array comparative hybridization (aCGH) has been reported to identify copy number variants in ~4-13% with further confirmed de novo and pathogenic variants in 2.9-13% (Epilepsy Phenome/Genome Project & Epi4K Consortium 2015; Mercimek-Mahmutoglu et al. 2015). Another study found that in patients presenting with early life epilepsies 32/188 (17%) had diagnostic/pathogenic findings on CMA (Berg et al. 2017). Other groups have found similar yields (Allen et al. 2015; Poduri 2017; Mefford et al. 2011; Olson et al. 2014; Tumiene et al. 2018). This rate is similar to diagnostic rates for autism spectrum disorders as noted by ACMG (Schaefer and Mendelsohn 2013).

See the Reproductive Carrier Screening and Prenatal Diagnosis Guideline for use of microarray in the reproductive setting.

Evaluation of Regions of Homozygosity (ROH)

In addition to identifying copy number variants, SNP arrays can identify areas of the genome with allelic homozygosity. These regions of homozygosity are identified in approximately 6% of individuals undergoing SNP array for clinical reasons (Wang et al. 2015). Most of these are caused by consanguinity, others are caused by uniparental disomy or ancestral homozygosity. With ROH, there is a concern for pathology caused by imprinting, such as Angelman or Prader Willi syndromes, or for recessive conditions as there is a higher likelihood of having homozygous P/LP variants in genes found within the ROH. No guidelines exist for how to approach further evaluation of ROH after they have been identified. If the ROH is found within a region known to be imprinted, UPD studies should be considered. To evaluate for recessive conditions, the preferred approach would be to search genes in the region associated with disease and identify candidate genes based on clinical symptoms. Sequencing of the entire region may be considered in select cases if no candidate gene is identified but increases the chance of identifying a variant of uncertain significance or P/LP variants in genes that are not clinically actionable.

Understanding the Clinical Relevance of Copy Number Variants

Inter-laboratory interpretation of copy number variants across technologies, e.g., CMA or NGS platforms, is complex and evolving but must be consistent. The American College of Medical Genetics and Genomics (ACMG) and the Clinical Genome Resource (ClinGen) recommend a uniform five-tier CNV variant classification system outlined in the ACMG/AMP sequence variant interpretation guidelines (Richards et al. 2015; Riggs et al. 2020). Utilizing evidence at a given point in time supporting or refuting a particular variant's pathogenicity, regardless of patient-specific factors, will produce necessary consistency and clarity in establishing potential clinical impact (Riggs et al. 2020).

Professional Society Guidelines

American College of Medical Genetics and Genomics (ACMG)

ACMG Clinical Practice Resource. Array-Based Technology and Recommendations for Utilization in Medical Genetics Practice for Detection of Chromosomal Abnormalities.
Manning M, Hudgins L. 2020 Dec;22(12):2126. PubMed PMID: 32514088.

ACMG Clinical Guideline. Exome and Genome Sequencing for Pediatric Patients with Congenital Anomalies or Intellectual Disability.
Manickam K, McClain MR, Demmer LA, et al.; ACMG Board of Directors. Genet Med. 2021 Jul 1. PubMed PMID: 34211152.

ACMG Points to Consider Statement. DNA-Based Screening and Population Health.
Murray M, Giovanni M, Doyle D, et al. Genet Med. 2021 Jun;23(6):989-995. PubMed PMID: 33727704.

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Revision History

Medical Advisory Board Review:

v2.2022 03/17/2022: Approved

v1.2022 09/20/2021: Approved

v2.2021 03/12/2021: Approved

v1.2021 11/13/2020: Approved

v2.2020 05/08/2020: Reviewed

v1.2020 11/04/2019: Reviewed

v2.2019 05/23/2019: No Criteria Changes

v1.2019 11/07/2018: Reviewed

v1.2018 03/31/2018: Reviewed

Clinical Steering Committee Review:

v2.2022 02/14/2022: Approved

v1.2022 08/23/2021: Approved

v2.2021 02/22/2021: Approved

v1.2021 10/13/2020: Approved

v2.2020 04/06/2020: Approved

v1/2020 10/11/2019: Approved

v2.2019 04/03/2019: Approved

v1.2019 10/03/2018: Approved

v1.2018 02/28/2018: Approved

v1.2017 01/25/2017: Approved

Revisions:

Version	Date	Editor	Description
v2.2022 *GEN07-0922.2*	02/18/2022	Carrie Langbo, MS, CGC	Semi-annual update. Criteria for WES was updated. The background, professional society guidelines, CPT codes and references were updated.
v1.2022 *GEN07-0322.1*	08/16/2021	Carrie Langbo, MS, CGC, Heather Dorsey, MS, CGC and Amanda	Semi-annual update. CMA criteria and content incorporated with no changes in coverage stance. WES criteria updated to include testing for gDD and moderate/severe/profound ID. WES not medically necessary list was updated. The background,

		Archbold, MS, CGC	professional society guidelines, CPT codes and references were updated.
v2.2021 *GEN07-0921.1*	02/15/2021	Carrie Langbo, MS, CGC	Semi-annual update. Neurological features for WES criteria were clarified and epilepsy criteria was updated to reflect new terminology for developmental and epileptic encephalopathies. The background, professional society guidelines and references were updated.
v1.2021	9/11/2020	Heather Dorsey, MS, CGC	Semi-annual update. Genetic counseling requirements were updated as well as criteria across WES testing for phenotype suspicious of a genetic disorder, epilepsy, hearing loss and reanalysis. CPT codes, professional society guidelines and the background were updated.
v2.2020	03/13/2020	Carrie Langbo, MS, CGC	Whole exome sequencing criteria was updated to include coverage criteria for fetal testing, and individuals with hearing loss. CPT codes, professional society guidelines, background and references were updated.
v1.2020	9/11/2019	Samantha Freeze, MS, CGC	Semi-annual review. No criteria changes.
v2.2019	04/03/2019	Laura Rebek, MS, CGC	Semi-annual review. No criteria changes. Updated references.
v1.2019	10/03/2018	Heather Dorsey, MS, CGC	Semi-annual review. Additional criteria for early-onset epilepsy added. Background, professional society guidelines and references updated. Administrative change to genetic counseling requirement - moved from client policy to guidelines. CPT code list reformatted. PMID added.

v1.2018	03/31/2018	Heather Dorsey, MS, CGC	Semi-annual review. No criteria changes. Disclaimer sentence added to scope. Background, professional society guidelines and references updated.
v1.2017	10/27/2017	Heather Dorsey, MS, CGC	Quarterly review. No criteria changes. Updated references.
v1.2017	09/11/2017	Megan Czarniecki, MS, CGC	Formatted references to NLM style. Moved methodological considerations to appropriate use criteria and background. Updated associated CPT codes. Removed genetic counseling recommendation. Approved by Policy Lead.
v1.2017	07/03/2017	Heather Dorsey, MS, CGC	Quarterly review. No criteria changes. Added statement to clarify that WES for carrier screening is not included in coverage criteria. Updated references. Approved by Policy Lead.
v1.2017	04/25/2017	Gwen Fraley, MS, CGC	Quarterly review. No criteria changes. Updated references.
v1.2017	12/20/2016	Heather Dorsey, MS, CGC	Quarterly review. No criteria changes. Updated references and renumbered to 2017.
v1.2016	10/03/2016	Gwen Fraley, MS, CGC	Added criteria for exome reanalysis. Updated references.
v1.2015	08/27/2015	Gwen Fraley, MS, CGC	Original version

Original Effective Date: 08/27/2015

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