

Test Specific Guidelines



Exome Sequencing

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Introduction

Exome sequencing is addressed by this guideline.

Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

Procedures addressed by this guideline	Procedure codes
Exome Sequencing (e.g., unexplained constitutional or heritable disorder or syndrome)	<u>81415</u>
Exome Sequencing, Comparator (e.g., parent(s), sibling(s))	<u>81416</u>
Exome Sequencing Re-evaluation (e.g., updated knowledge or unrelated condition/syndrome)	<u>81417</u>
<u>Genomic Unity Exome Plus Analysis -</u> Comparator	<u>0215U</u>
<u>Genomic Unity Exome Plus Analysis -</u> <u>Proband</u>	<u>0214U</u>

What Is Exome Sequencing?

Definition

Exome sequencing (ES/WES) utilizes DNA-enrichment methods and massively parallel nucleotide sequencing to identify disease-associated variants throughout the human genome.

ES has been proposed for diagnostic use in individuals who present with complex genetic phenotypes suspected of having a rare genetic condition, who cannot be diagnosed by standard clinical workup, or when features suggest a broad differential diagnosis that would require evaluation by multiple genetic tests. The standard approach to the diagnostic evaluation of an individual suspected of having a rare genetic condition may include combinations of radiographic, biochemical, electrophysiological, and targeted genetic testing such as a chromosomal microarray, single-gene analysis, and/or a targeted gene panel.¹

ES may be appropriate if initial testing is unrevealing, or if there is no single-gene or panel test available for the particular condition, or if a rapid diagnosis for a critically-ill child is indicated.²⁻⁵

<u>Identifying a molecularly confirmed diagnosis in a timely manner for an individual</u> with a rare genetic condition can have a variety of health outcomes,²⁻¹² including:

guiding prognosis and improving clinical decision-making, which can improve clinical outcome by

application of specific treatments as well as withholding of contraindicated treatments for certain rare genetic conditions

surveillance for later-onset comorbidities

initiation of palliative care

withdrawal of care

reducing the financial & psychological impact of diagnostic uncertainty and the diagnostic odyssey (e.g., eliminating lower-yield testing and additional screening testing that may later be proven unnecessary once a diagnosis is achieved)

informing genetic counseling related to recurrence risk and prenatal or preconception (utilizing in-vitro fertilization with preimplantation genetic diagnosis) diagnosis options

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

Test Information

Introduction

Exome sequencing is limited to the DNA sequence of coding regions (exons) and flanking intronic regions of the genome, which is estimated to contain 85% of heritable disease-causing variants. Results of testing with ES include known pathogenic variants definitely associated with disease or a variant of uncertain significance (VUS).^{13,14}

Pathogenic variants that can be identified by ES include missense, nonsense, splice-site, and small deletions or insertions.

At the present time, ES typically fails to detect certain classes of disease-causing variants, such as structural variants (e.g., translocations, inversions), abnormal chromosome imprinting or methylation, some mid-size insertions and deletions (ca. 10-500 bp), trinucleotide repeat expansion mutations, deeper intronic

<u>mutations, and low-level mosaicism. The current evidence base evaluating ES to</u> <u>specifically identify deletions/duplications for any disease or condition is very</u> <u>limited, consisting mostly of small case reports ¹⁵⁻¹⁹ and case reviews or small</u> <u>uncontrolled studies.^{20,21}</u>

ES has the advantage of decreased turnaround time and increased efficiency relative to Sanger sequencing of multiple genes.

ES is associated with technical and analytical variability, including uneven sequencing coverage, gaps in exon capture before sequencing, as well as variability in variant classification based on proprietary filtering algorithms and potential lack of critical clinical history or family samples.²²

Guidelines and Evidence

Introduction

This section includes relevant guidelines and evidence pertaining to exome sequencing.

American College of Medical Genetics and Genomics

<u>The American College of Medical Genetics (ACMG, 2012) stated the following</u> regarding the clinical application of exome and genome testing:²³

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

"The phenotype or family history data strongly implicate a genetic etiology, but the phenotype does not correspond with a specific disorder for which a genetic test targeting a specific gene is available on a clinical basis."

"A patient presents with a defined genetic disorder that demonstrates a high degree of genetic heterogeneity, making WES or WGS analysis of multiple genes simultaneously a more practical approach."

"A patient presents with a likely genetic disorder, but specific genetic tests available for that phenotype have failed to arrive at a diagnosis."

"A fetus with a likely genetic disorder in which specific genetic tests, including targeted sequencing tests, available for that phenotype have failed to arrive at a diagnosis."

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

The following are recommended pretest considerations:

<u>"Pretest counseling should be done by a medical geneticist or an affiliated genetic counselor and should include a formal consent process."</u>

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<u>"Before 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."</u>

"As part of the pretest 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."

The American College of Medical Genetics (ACMG, 2013) stated the following regarding informed consent for exome and genome testing:²⁴

<u>"Before initiating GS/ES, counseling should be performed by a medical geneticist</u> or an affiliated genetic counselor and should include written documentation of consent from the patient."

"Incidental/secondary findings revealed in either children or adults may have high clinical significance for which interventions exist to prevent or ameliorate disease severity. Patients should be informed of this possibility as a part of the informed consent process."

"Pretest counseling should include a discussion of the expected outcomes of testing, the likelihood and type of incidental results that may be generated, and the types of results that will or will not be returned. Patients should know if and what type of incidental findings may be returned to their referring physician by the laboratory performing the test."

<u>"Patients should be counseled regarding the potential benefits and risks of GS/ES, the limitations of such testing, potential implications for family members, and alternatives to such testing."</u>

"GS/ES is not recommended before the legal age of majority except for

Phenotype-driven clinical diagnostic uses;

<u>Circumstances in which early monitoring or interventions are available and effective; or</u>

Institutional review board-approved research."

<u>"As part of the pretest counseling, a clear distinction should be made between clinical and research-based testing."</u>

"Patients should be informed as to whether individually identifiable results may be provided to databases, and they should be permitted to opt out of such disclosure." "Patients should be informed of policies regarding re-contact of referring physicians as new knowledge is gained about the significance of particular results."

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<u>The American College of Medical Genetics (ACMG, 2021) published an updated</u> <u>guideline for the reporting of secondary findings (SF) in clinical exome and</u> <u>genome sequencing. They stated:²⁵</u>

"The overall goal of the SFWG [Secondary Findings Working Group] is to recommend a minimum list of genes that places limited excess burden on patients and clinical laboratories while maximizing the potential to reduce morbidity and mortality when ES/GS is being performed."

"Variants of uncertain significance should not be reported in any gene."

"It is important to reiterate here that use of the SF results should not be a replacement for indication-based diagnostic clinical genetic testing."

A table of "ACMG SF v3.0 gene and associated phenotypes recommended for return as secondary findings from clinical exome and genome sequencing" was provided

"Given the increase in uptake of clinical ES/GS, the ACMG SFWG and BOD [Board of Directors] have agreed the list of recommended genes should now be updated annually."

The American College of Medical Genetics and Genomics (ACMG, 2020) issued an educational Points to Consider Statement addressing good process, benefits, and limitations of using exome sequencing in the prenatal setting.²⁶

Evidence for the clinical utility of ES in individuals with multiple congenital anomalies and/or a neurodevelopmental phenotype includes numerous large case series. Relevant outcomes include improved clinical decision making (e.g., application of specific treatments, withholding of contraindicated treatments, changes to surveillance), changes in reproductive decision making, and resource utilization. ES serves as a powerful diagnostic tool for individuals with rare genetic conditions in which the specific genetic etiology is unclear or unidentified by standard clinical workup.^{10,27-32}

<u>The average diagnostic yield of ES is 20-40% depending on the individual's age,</u> <u>phenotype, previous workup, and number of comparator samples</u> <u>analyzed.^{8,11,27,33} Among individuals with a pathogenic or likely pathogenic</u> <u>findings by ES, 5-7% received a dual molecular diagnosis (i.e., two significant</u> <u>findings associated with non-overlapping clinical presentations).^{27,33}</u>

<u>The use of family trio ES reduces the rate of uncertain findings, adds to the</u> <u>clinical sensitivity with regard to the interpretation of clinically novel genes, and</u> <u>increases the diagnostic utility of ES. For example, in three publications the</u> <u>positive rate ranges from 31-37% in patients undergoing trio analysis compared</u> to 20-23% positive rate among proband-only ES.^{5,27,34,35} <u>Re-evaluation of previously obtained exome sequence has the potential for</u> <u>additional diagnostic yield because of constant expansions of existing variant</u> <u>databases, as well as periodic novel gene discovery.³⁶⁻³⁸</u>

<u>A 2020 systematic evidence-based review by the ACMG on "outcomes from</u> <u>exome and genome sequencing for pediatric patients with congenital anomalies</u> <u>or intellectual disability" stated:³⁹</u>

"There is evidence that ES/GS for patients with CA/ DD/ID informs clinical and reproductive decision-making, which could lead to improved outcomes for patients and their family members. Further research is needed to generate evidence regarding health outcomes to inform robust guidelines regarding ES/GS in the care of patients with CA/DD/ID."³⁹

ACMG (2021) published a clinical guideline on the use of exome and genome sequencing in the pediatric population that stated:⁴⁰

"We strongly recommend ES [exome sequencing] and GS [genome sequencing] as a first-tier or second-tier test (guided by clinical judgment and often clinicianpatient/family shared decision making after CMA or focused testing) for patients with one or more CAs prior to one year of age or for patients with DD/ID with onset prior to 18 years of age."

<u>"Consistent with existing guidelines/recommendations/position statements, patients with clinical presentations highly suggestive of a specific genetic diagnosis should undergo targeted testing first."</u>

"Isolated autism without ID or congenital malformation is formally out of scope for this recommendation but evaluation of exome/genome studies is ongoing."

Diagnostic yield of genome-wide sequencing was determined to be outside the scope of the systematic evidence review.

American College of Obstetricians and Gynecologists

<u>The American College of Obstetricians and Gynecologists (ACOG, 2018) stated</u> <u>the following in a technology assessment for modern genetics in obstetrics and</u> <u>gynecology:⁴¹</u>

"The American College of Medical Genetics and Genomics recommends considering whole-exome sequencing when specific genetic tests available for a phenotype, including targeted sequencing tests, have failed to arrive at a diagnosis in a fetus with multiple congenital anomalies suggestive of a genetic disorder."

The 2020 guidelines for management of stillbirth stated:42

"Microarray is the preferred method of evaluation for these reasons but, due to cost and logistic concerns, karyotype may be the only method readily available for some patients. In the future, whole exome sequencing or whole genome



sequencing may be part of the stillbirth workup, but it is not currently part of the standard evaluation."

American College Obstetricians and Gynecologists and Society for Maternal Fetal Medicine

<u>A joint statement, the American College of Obstetricians and Gynecologists</u> (ACOG, 2016) and the Society for Maternal Fetal Medicine (SMFM, 2016) stated the following regarding prenatal ES.⁴³

"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."

International Society for Prenatal Diagnosis, Society for Maternal Fetal Medicine, and Perinatal Quality Foundation

<u>A joint statement from the International Society for Prenatal Diagnosis (ISPD, 2018), the Society for Maternal Fetal Medicine (SMFM, 2018), and the Perinatal Quality Foundation (PQF, 2018) on prenatal ES stated:⁴⁴</u>

"The routine use of prenatal [genome wide] sequencing as a diagnostic test cannot currently be supported due to insufficient validation data and knowledge about its benefits and pitfalls. Prospective studies with adequate population numbers for validation are needed.... Currently, it is ideally done in the setting of a research protocol. Alternatively, sequencing may be performed outside a research setting on a case-by-case basis when a genetic disorder is suspected for which a confirmatory genetic diagnosis can be obtained more quickly and accurately by sequencing. Such cases should be managed after consultation with and under the expert guidance of genetic professionals working in multidisciplinary teams with expertise in the clinical diagnostic application of sequencing, including interpretation of genomic sequencing results and how they translate to the prenatal setting, as well as expertise in prenatal imaging and counseling."

<u>"There is currently limited genotype-phenotype correlation for the genetic</u> <u>disorders identified in the fetal period because ultrasound imaging is frequently</u> <u>limited, and the fetal phenotypes of many conditions have not been well</u> <u>described."</u>

Selected Relevant Publications

<u>The clinical utility of prenatal exome is currently lacking. According to one review,</u> <u>although analyses of the clinical utility of prenatal ES are beginning to be</u> <u>published, it is too soon to "determine the extent to which prenatal genomic</u> <u>sequencing results actually alter perinatal care and result in benefits or harm to</u> <u>families."</u> ⁴⁵ Potential promises of fetal ES include early diagnosis for informed decisionmaking, potential in utero or early perinatal treatment or therapy, and improved knowledge of prenatal presentations and development.⁴⁶

Potential pitfalls include the need for extensive pre- and post-test counseling, long turn-around times and the need for a well-defined phenotype to provide the most informative and rapid results, difficulty in interpreting variants of uncertain clinical significance in the context of a phenotype defined by prenatal ultrasound findings, and the ethical issues inherent in discovering secondary and incidental findings in the prenatal period.⁴⁶

<u>Technical issues of prenatal ES include gaps in sequence coverage, the extended</u> <u>time required when secondary methods are used to fill these gaps, and the</u> <u>inability to detect copy number variations, trinucleotide repeat mutations, or low</u> <u>level mosaicism.⁴⁶</u>

It is essential that additional data on the clinical utility and risks of prenatal ES be collected.⁴⁵

<u>Criteria</u>

Introduction

Requests for exome sequencing are reviewed using these criteria.

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

The patient and family history have been evaluated by a Board-Certified or Board-Eligible Medical Geneticist, AND

<u>A clinical letter detailing the evaluation by a Geneticist is provided which includes</u> <u>ALL of the following information:</u>

Differential diagnoses, and

Testing algorithm, and

Previous tests performed and results, and

A genetic etiology is the most likely explanation, and

Recommendation that exome sequencing is the most appropriate test, and

Predicted impact on member's plan of care, AND

Patient is <21 years of age, AND

A genetic etiology is considered the most likely explanation for the phenotype, based on ONE of the following:

Multiple congenital abnormalities defined by ONE of the following:

Two or more major anomalies affecting different organ systems*, or

<u>One major and two or more minor anomalies affecting different organ systems*,</u> <u>or</u>

<u>Unexplained epileptic encephalopathy (onset before three years of age) and no</u> <u>prior epilepsy multigene panel testing performed, OR</u>

TWO of the following criteria are met:

major abnormality affecting at minimum a single organ system*, and/or

formal diagnosis of autism, significant developmental delay, or intellectual disability (e.g., characterized by significant limitations in both intellectual functioning and in adaptive behavior), and/or

symptoms of a complex neurodevelopmental disorder (e.g., self-injurious behavior, reverse sleep-wake cycles, dystonia, ataxia, alternating hemiplegia, neuromuscular disorder), and/or

severe neuropsychiatric condition (e.g., schizophrenia, bipolar disorder, Tourette syndrome), and/or

period of unexplained developmental regression, and/or

laboratory findings suggestive of an inborn error of metabolism, AND

<u>Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection), AND</u>

<u>Clinical presentation does not fit a well-described syndrome for which first tier</u> <u>testing (e.g., single gene testing, comparative genomic hybridization</u> [CGH]/chromosomal microarray analysis [CMA]) is available, AND

Multiple targeted panels are appropriate based on the member's clinical presentation, AND

There is a predicted impact on health outcomes including:

Application of specific treatments, or

Withholding of contraindicated treatments, or

Surveillance for later-onset comorbidities, or

Initiation of palliative care, or

Withdrawal of care, AND

A diagnosis cannot be made by standard clinical work-up, excluding invasive procedures such as muscle biopsy

* Major structural abnormalities are generally serious enough as to require medical treatment on their own (such as surgery) and are not minor developmental variations that may or may not suggest an underlying disorder.

Genomic Unity Exome Plus Analysis (CPT: 0214U and 0215U)

The member meets the above criteria for exome sequencing, AND

<u>The member meets criteria for whole mtDNA sequencing based on current</u> <u>eviCore guideline *Mitochondrial Genetic Testing* AND</u>

The member has not had previous whole mtDNA sequencing analysis performed

Prenatal Diagnosis by Exome Sequencing

This test is considered investigational and/or experimental.

Investigational and experimental (I&E) molecular and genomic (MolGen) tests refer to assays involving chromosomes, DNA, RNA, or gene products that have insufficient data to determine the net health impact, which typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity), significantly improves health outcomes (clinical utility), and/or performs better than an existing standard of care medical management option. Such tests are also not generally accepted as standard of care in the evaluation or management of a particular condition.

In the case of MolGen testing, FDA clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight and FDA clearance often does not assess clinical utility.

Exclusions and Other Considerations

Exome deletion/duplication analysis (typically billed with 81228 or 81229) is considered experimental/investigational and therefore, not reimbursable.

ES is considered experimental/investigational for screening for genetic disorders in asymptomatic or pre-symptomatic individuals.

Billing and Reimbursement

ES will be considered for reimbursement when it is deemed more efficient and economical than the separate single-gene tests or panels that would be recommended based on the differential diagnosis (e.g., genetic conditions that demonstrate a high degree of genetic heterogeneity).

ES will be considered for reimbursement only when billed with an appropriate CPT code:

81415 should be billed for the proband. 81415 should only be billed when analyzing the entire exome sequence, rather than a targeted set of genes. At a minimum, genes associated with the clinical presentation and those



<u>constitutional mutations in genes listed on the ACMG minimum list entitled</u> <u>"Conditions, genes, and variants recommended for return of incidental findings</u> <u>in clinical sequencing"</u>²⁸, when requested, should be reported by the laboratory <u>to the ordering clinician, regardless of the indication for which the exome</u> <u>sequence was ordered.</u>

81416 should be billed when a comparator exome is performed. A trio of the proband and both parents is generally preferred, although other family members may be more informative based on the clinical presentation. A maximum of two units of 81416 will be considered for reimbursement.

81415 is not reimbursable for a targeted exome analysis (e.g. XomeDxSlice custom gene panel completed on a single exome platform). The appropriate GSP panel code, unlisted code (e.g. 81479), or Tier 1 or Tier 2 code(s) must be billed.

81415 will be reimbursable once per lifetime.

When a single exome platform is used for more than one test (e.g., XomeDxSlice reflex to full exome analysis), all tests reported from the same exome analysis may be:

Billed together under one unit of 81415, or

Billed separately, but 81415 cannot be used. When billed separately, studies may be billed using Tier 1 codes, Tier 2 codes, or 81479 at an amount that does not exceed the cost of full exome analysis.

81417 is not an appropriate code for reflex from targeted to full exome.

<u>Re-evaluation of a previously obtained exome due to updated clinical information</u> or expanded scientific knowledge or for the purpose of evaluating a patient for an unrelated condition/syndrome on a different date of service will be considered for reimbursement only when billed using 81417.

References

Introduction

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