Whole Exome Sequencing

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

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What is whole exome sequencing

Definition

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

- WES 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, electrophysiologic, and targeted genetic testing such as a chromosomal microarray, single-gene analysis, and/or a targeted gene panel.\(^1\)
- WES is typically not an appropriate first-tier test, but can be appropriate if initial testing is unrevealing, or if there is no single-gene or panel test available for the particular condition.\(^2\)
- Identifying a molecularly confirmed diagnosis in a timely manner for an individual with a rare genetic condition can have a variety of health outcomes,\(^2,9\) including:
o 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

o 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)

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

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

Test information

• WES 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.

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

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

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

• WES 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.10
Guidelines and evidence

American College of Medical Genetics and Genomics

- The American College of Medical Genetics (ACMG, 2012) states the following regarding the clinical application of whole exome and whole genome testing:
  - “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 whole-genome) 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:
    - “Pretest counseling should be done by a medical geneticist or an affiliated genetic counselor and should include a formal consent process.”
    - “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.”
    - “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, 2012) states the following regarding informed consent for whole exome and whole genome testing:
o “Before initiating GS/ES, counseling should be performed by a medical geneticist or an affiliated genetic counselor and should include written documentation of consent from the patient.”

o “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.”

o “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.”

o “GS/ES is not recommended before the legal age of majority except for:”
  - “Phenotype-driven clinical diagnostic uses;”
  - “Circumstances in which early monitoring or interventions are available and effective; or”
  - “Institutional review board–approved research.”

o “As part of the pretest counseling, a clear distinction should be made between clinical and research-based testing.”

o “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.”

o “Patients should be informed of policies regarding re-contact of referring physicians as new knowledge is gained about the significance of particular results.”

• The American College of Medical Genetics (ACMG, Updated 2016) published guidelines for the reporting of incidental findings in clinical exome and genome sequencing.\(^{13,14}\) They state the following:

  o “We continue to support the reporting of known or expected pathogenic variants, but we do not recommend reporting variants of uncertain significant as secondary findings (SFs).”

  o This 2016 ACMG guideline includes a table of “ACMG SF v2.0 genes and associated phenotypes recommended for return of secondary findings in clinical sequencing.”

• Evidence for the clinical utility of WES 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. WES 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.\textsuperscript{7,15,16}

- The average diagnostic yield of WES is 20-40% depending on the individual’s age, phenotype, previous workup, and number of comparator samples analyzed.\textsuperscript{5,15,17}

Among individuals with a pathogenic or likely pathogenic findings by WES, 5-7% received a dual molecular diagnosis (i.e., two significant findings associated with non-overlapping clinical presentations).\textsuperscript{15,17}

- The use of family trio WES reduces the rate of uncertain findings, adds to the clinical sensitivity with regard to the interpretation of clinically novel genes, and increases the diagnostic utility of WES. For example, in three publications the positive rate ranges from 31-37% in patients undergoing trio analysis compared to 20-23% positive rate among proband-only WES.\textsuperscript{15,18,19}

- Re-evaluation of previously obtained exome sequence has the potential for additional diagnostic yield because of constant expansions of existing variant databases, as well as periodic novel gene discovery.\textsuperscript{20}

**American College Obstetricians and Gynecologists and Society for Maternal Fetal Medicine**

In a joint statement, the American College of Obstetricians and Gynecologists and the Society for maternal Fetal Medicine (2016) state the following regarding prenatal WES:\textsuperscript{21}

- “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**

A joint statement from the International Society for Prenatal Diagnosis, the Society for Maternal Fetal Medicine, and the Perinatal Quality Foundation on prenatal WES states:\textsuperscript{22}

- “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.”

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

Peer Reviewed Literature

- The clinical utility of prenatal exome is currently lacking. According to one review, although analyses of the clinical utility of prenatal WES are beginning to be published, it is too soon to “determine the extent to which prenatal genomic sequencing results actually alter perinatal care and result in benefits or harm to families.”

- Potential promises of fetal WES include early diagnosis for informed decision-making, potential in utero or early perinatal treatment or therapy, and improved knowledge of prenatal presentations and development.

- 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.

- Technical issues prenatal WES include gaps in sequence coverage, the extended time required when secondary methods are used to fill these gaps, and the inability to detect copy number variations, trinucleotide repeat mutations, or low level mosaicism.

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

Criteria

- Whole exome sequencing (WES) 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
    - A clinical letter detailing the evaluation by a Geneticist is provided which includes ALL of the following information:
      - Differential diagnoses, and
      - Testing algorithm, and
      - Previous tests performed and results, and
• A genetic etiology is the most likely explanation, and
• Recommendation that whole exome sequencing is the most appropriate test, and
• Predicted impact on member's plan of care, AND

o Patient is <21 years of age, AND
o A genetic etiology is considered the most likely explanation for the phenotype, based on EITHER of the following:
  ▪ Multiple congenital abnormalities defined by ONE of the following:
    • Two or more major anomalies affecting different organ systems*, or
    • One major and two or more minor anomalies affecting different organ systems*, OR
  ▪ 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
    • biochemical findings suggestive of an inborn error of metabolism, AND

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

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

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

o 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.

**Prenatal diagnosis by whole 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**

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

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

**Billing and reimbursement**

- WES 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).

- WES 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 whole exome sequence, rather than a targeted set of
genes. At a minimum, genes associated with the clinical presentation and those constitutional mutations in genes listed on the ACMG minimum list entitled “Conditions, genes, and variants recommended for return of incidental findings in clinical sequencing” 13, when requested, should be reported by the laboratory to the ordering clinician, regardless of the indication for which the exome sequence was ordered.

- 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.

- Re-evaluation of a previously obtained exome due to updated 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


