Test Specific Guidelines

Whole Genome Sequencing

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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
Genome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis	81425
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)	81426
Genome (eg, unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained genome sequence (eg, updated knowledge or unrelated condition/syndrome)	81427
Genomic Unity Whole Genome Analysis - Comparator	0213U
Genomic Unity Whole Genome Analysis - Proband	0212U
Praxis Combined Whole Genome Sequencing and Optical Genome Mapping	0267U
Praxis Whole Genome	0265U
RCIGM Rapid Whole Genome Sequencing	0094U

What Is Whole Genome Sequencing?

Definition

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

WGS 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]

Broad genomic testing 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:

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 and 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 preconceptional (utilizing in-vitro fertilization with preimplantation genetic diagnosis) diagnosis options

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

Test Information

Both coding (exons) and noncoding (introns) regions are analyzed by WGS.[10] Often, coding regions are first analyzed by WGS. If no pathogenic mutations are found, the noncoding regions are then analyzed.[10]

Pathogenic variants that can be identified by WGS include missense, nonsense, splice-site, and small deletions or insertions. “Data can also be examined for copy-number variants (CNVs) or structural variants that may either be outside of the coding regions or more easily detected using GS due to increased quantitative accuracy.”[10]

WGS currently is “the most costly technology with the least average depth of coverage, although these limitations are likely to diminish in the future.”[10]

Guidelines and Evidence

American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (ACMG, 2021) published a guideline on the use of exome and genome sequencing in the pediatric population that stated:[11]

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

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

"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.

ACMG (2012) stated the following regarding informed consent for whole exome and whole genome testing:[12]

"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."

"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."

"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."

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

"Patients should be 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."

ACMG (2021) published guidelines for the reporting of incidental findings in clinical exome and genome sequencing that stated:[13,14]

"Variants classified as likely pathogenic and pathogenic variants should be reported. Variants of uncertain significance, likely benign, and benign variants should not be reported as a secondary finding."

This guideline includes a table of "ACMG SF v3.0 genes and associated phenotypes recommended for return from clinical exome and genome sequencing"**.**

Selected Relevant Publications

There is limited evidence regarding the accuracy, reliability, and clinical utility of WGS to identify a genetic basis for suspected genetic disorders in children and young adults with indeterminate findings on conventional diagnostic testing.[15-26] There is also limited, low quality evidence that WGS leads to changes in clinical decision making treatment that significantly improves patient outcomes.[11] Although WGS has the potential to detect multiple classes of genetic variation in a single laboratory procedure, additional well-conducted research is necessary to examine the accuracy, reliability, and clinical utility of WGS before its role can be established in a clinical setting.

Criteria

Introduction

Requests for WGS are reviewed using the following criteria.

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.

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