

## **Clinical Appropriateness Guidelines**

# Genetic Testing for Whole Exome and Whole Genome Sequencing

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## Table of Contents

Scope .....	3
Appropriate Use Criteria .....	3
Whole Exome Sequencing.....	3
Whole Exome Reanalysis.....	4
Whole Genome Sequencing.....	4
Background .....	4
Professional Society Guidelines.....	7
Selected References.....	7
Revision History.....	8

# Scope

This document addresses the diagnostic use of 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 Somatic Tumor Testing Clinical Appropriateness Guidelines).

## Appropriate Use Criteria

### Whole Exome Sequencing

Whole exome sequencing (WES) (81415 and 81416) is medically necessary for a phenotypically-affected individual when all of the following criteria are met:

- 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
- WES results will directly impact clinical decision-making and/or clinical outcome
- A genetic etiology is the most likely explanation for the phenotype as demonstrated by the following:
  - Multiple abnormalities affecting unrelated organ systems or two of the following four criteria:
    - Abnormality affecting a single organ system
    - Significant intellectual disability or severe psychological/psychiatric disturbance (e.g. self-injurious behavior, reversed sleep-wake cycles)
    - Family history strongly implicating a genetic etiology
    - Period of unexplained developmental regression (unrelated to autism or epilepsy)
  - No other causative circumstances (e.g. environmental exposures, injury, 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 that would be recommended in the absence of testing

Prenatal diagnosis or preimplantation testing of an embryo using WES is not medically necessary.

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WES for the purpose of genetic carrier screening is not medically necessary.

## Whole Exome Reanalysis

Reanalysis of previously obtained uninformative whole exome sequence is medically necessary when one 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

## Whole Genome Sequencing

Whole genome sequencing (WGS) is experimental, investigational, and unproven.

Sequencing of the transcriptome (RNA sequencing) is experimental, investigational and unproven.

## CPT Codes

The following codes are associated with the guidelines outlined in this document. This list is not all inclusive.

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)
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)

# Background

Next generation sequencing technology allows high throughput rapid DNA sequencing at a much lower price than previous sequencing methodologies. The evolution of this technology has spurred the development of tests that sequence multiple genes simultaneously, and such testing is expected to

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increasingly enable widespread evaluation of patients' genomes in the clinical setting (Johansen Taber 2014).

Whole exome sequencing (WES) consists of analysis of the protein-coding regions of the human genome, either DNA or RNA. This comprises <2% of the genome and involves the areas currently believed to be the most likely to include mutations that result in clinical phenotypes and disease. Such large-scale genomic sequencing has been proposed for use in scenarios suggesting a single genetic etiology but lacking a clear diagnostic testing path and in which stepwise testing can result in costly and prolonged diagnostic odyssey (ACMG 2012; ACMG 2013; Biesecker 2014).

Determining genetic causality for disease and establishing a molecular diagnosis in clinical practice can aid in confirming or establishing a clinical diagnosis, inform prognosis, help select or discontinuing treatment, reveal mode of inheritance and risk to family members, and/or guide research regarding new therapies or patient management. Overall analytical sensitivity is still being defined for WES.

The American College of Medical Genetics published a statement regarding use of genomic testing that recommends testing be considered in phenotypically affected individuals when (ACMG 2012):

1. 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.
2. 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.
3. A patient presents with a likely genetic disorder but specific genetic tests available for that phenotype have failed to arrive at a diagnosis.
4. 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.
  - a. 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 false positive, false negative, and variants of unknown clinical significance rates. These rates can be expected to be significantly higher than seen when array CGH is used in prenatal diagnosis.

One of the most complex issues surrounding genomic testing is the risk of incidental or secondary findings, where mutations unrelated to the clinical phenotype or variants of uncertain significance are identified. The American College of Medical Genetics and Genomics recommends laboratories who perform WES report on known pathogenic or expected pathogenic variants in 59 medically actionable genes even when unrelated to the primary indication for testing, with the patient's consent (Kalia 2016). While incidental identification of clinically significant mutations pose issues of informed consent, these findings often have clear medical management recommendations (ACMG 2013; Green 2013). However, even amongst the list of 59 genes recommended for the reporting of incidental findings by the American College of Medical Genetics and Genomics, there are challenges in determining the phenotypic consequences of variants identified (Jurgens 2015). The identification of variants of uncertain significance also creates a medical management dilemma, putting the health care provider at risk of under- or over-managing the patient depending on the true underlying clinical implications of the variant. In one study by Shashi et al. (2015), variants of uncertain significance were

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reported in 86% of patients who underwent WES, with 53.7% recommended for follow-up studies, such as additional laboratory tests or genotyping of family members. Due to their uncertain nature, such variants often lead to increased utilization of evaluation, diagnostic, or screening procedures that may be unnecessary, resulting in increased risk of adverse events and costs.

While WES is useful in diagnosing complex phenotypes, targeted testing, when possible, is typically a more cost-effective approach with a lower risk of incidental findings. The Clinical Sequencing Exploratory Research (CSER) program provided an overview of recent advances in genomic medicine, including WES and WGS. They conclude that while there have been many advances, further work is still needed regarding comparative effectiveness and cost-effectiveness. Employing the expertise of clinical genetics specialists facilitates accurate evaluation of patients and assessment of whether targeted testing is likely to produce a more cost-effective and higher yield than WES. Shashi et al. (2014) retrospectively evaluated a cohort of 500 patients who received traditional medical genetics evaluations. Thirty-nine patients were determined to not have a genetic disorder; 212 of the remaining 461 (46%) received a genetic diagnosis, and 72% of those were diagnosed on the first visit. WES would not have contributed to the care of these diagnosed individuals, but it may be clinically and economically useful in some members of the remaining pool of undiagnosed individuals. The authors propose that the clinical utility of genomic testing is greater when testing is applied after an initial clinical genetics evaluation. Experts agree that involvement of trained genetics professionals in consulting with patients is essential prior to and after ordering such tests and can identify the appropriate patients for large multi-gene panels or WES (Kurian 2014; Yang 2013).

In fact, obtaining informed consent and providing pre-test genetic counseling by a trained genetics professional is an essential piece of WES. The ACMG published specific recommendations (ACMG 2012):

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.

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. However, WES is only cost effective if it replaces the need for multiple individual gene tests, and it is not as cost-effective when it is utilized 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 chromosome microarray or multigene panels. Since microarray is most powerful for detecting deletions/duplications involving multiple genes, which typically results in a broad phenotype, medical geneticists should weigh whether a targeted panel or WES may be a more appropriate first-tier test when the patient meets WES testing criteria and the phenotype is more suggestive of a single gene disorder rather than multi-gene deletion or duplication (e.g. skeletal dysplasia).

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Vassy et al (2017) reported on a pilot trial looking at the use of WGS in a healthy adult population and conclude that its use reveals findings of uncertain clinical utility.

# Professional Society Guidelines

American College of Medical Genetics, Board of Directors. Points to consider in the clinical application of genomic sequencing. *Genet Med*. 2012 Aug;14(8):759-61.

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# Revision History

## Clinical Steering Committee Review:

v1.2017 01/25/2017: Approved

## Revisions:

Version	Date	Editor	Description
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, 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

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