Clinical Policy Title: Whole genomic sequencing (WGS) and whole exome sequencing (WES)

Clinical Policy Number: 02.01.17

Effective Date: January 1, 2016
Initial Review Date: October 16, 2015
Most Recent Review Date: October 19, 2016
Next Review Date: October 2017

Related policies:

CP# 02.01.02 Genetic testing for breast and ovarian cancer
CP# 02.01.03 Genetic testing for primary autosomal recessive microcephaly
CP# 02.01.08 Familial polyposis gene testing
CP# 02.01.09 Genetic testing, rare diseases
CP# 04.01.02 Genetic testing for long QT syndrome (LQTS)
CP# 11.04.02 Genetic testing for autism spectrum disorder
CP# 13.01.01 Genetic testing for prostate cancer prognosis

ABOUT THIS POLICY: Keystone First has developed clinical policies to assist with making coverage determinations. Keystone First’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by Keystone First when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Keystone First’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Keystone First’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Keystone First will update its clinical policies as necessary. Keystone First’s clinical policies are not guarantees of payment.

Coverage policy

Keystone First considers the once-per-lifetime use of whole genomic sequencing (WGS) testing and whole exome sequencing (WES) testing, either done alone or in combination with other genetic testing, to be clinically proven and, therefore, medically necessary when all of the following criteria are met:

- Test results will directly impact management (i.e., as a result of the test, effective treatment may be offered that will alter the course of disease or outcomes).
• Test is an analytically and clinically valid test (i.e., supported by peer-reviewed published research).
• Test results will be discussed with the patient or guardian (including the limitations of the testing method, the risks and benefits of either continuing or stopping the therapy based on the test, and current cancer management guidelines).
• There is a care-coordinating, multidisciplinary team available for genetic and behavioral counseling for a tiered evaluation. This team includes a primary care provider and a geneticist (who is a physician or a licensed genetic counselor).
• Patient or guardian desire for engagement with the integrated multidisciplinary team is documented in the clinical record.
• Consideration has been given to standard diagnostic evaluation and use of tiered panel or targeted test sequence for a minimal number of genes to establish the diagnosis.

Limitations:

Keystone First considers the use of all other WGS testing and WES testing to be investigational and, therefore, not medically necessary.

Keystone First considers the repetitive testing of WGS and WES to be investigational and, therefore, not medically necessary.

Alternative covered services:

A primary care physician, specialist medical expert, or qualified geneticist may evaluate a patient for genetic conditions with alternative covered services, including routine office consultation and clinical investigation (i.e., laboratory, imaging, functional testing, and diagnostic procedures, specifically G-band karyotyping).

Background

Current-generation WGS and WES are important tools of genetic diagnosis in a rapidly moving field that boasts as much as 95 percent single nucleotide polymorphism (SNP) detection sensitivity for genetic variation. -generation WGS has now been supplanted by longer sequencing reads and the addition of “paired-end” analysis, which add further to test accuracy and applicability in disease detection. Costs have fallen commensurate with the advancing utility of the technology, now estimated at $1,000 – $1,500 per testing kit to determine one individual’s genomic map.

The technology is highly effective at identifying SNPs and small insertions and deletions of the genetic code that constitute mutations and differences manifest as clinical findings of disease. On the down side, there are still shortcomings, such as the likelihood of polymerase chain reaction (PCR) amplification and its negative impact on SNP detection sensitivity. As costs for the clinical application of this
technology have fallen, demand has greatly increased for this high-tech application to map the individual genome.

WGS is to be distinguished from WES, a substantially reduced analytic tool of analysis for the protein-coding portion of the genome, with a requirement of 20-fold less raw sequence data compared to WGS. WES is an attractive alternative to WGS, costing roughly 30 percent less than WGS, but not all of the information available in the genome is detected by this methodology. Moreover, studies have identified a marked unevenness of capture from one region to another in exome capture based on such factors as exon size and guanine-cytosine (GC) context.

The merits of WGS for genomic variant testing include uniform analysis of whole regions of the human genome and an intrinsically richer data depth for understanding gene polymorphisms of clinical significance. WGS can also detect genomic rearrangements that are outside coding regions examined by individual sequencing techniques alone. In its scope and productivity per test, WGS has supplanted targeted capture and sequenced nucleotide studies.

**Searches**

Keystone First searched PubMed and the databases of:
- UK National Health Services Center for Reviews and Dissemination.
- Agency for Healthcare Research and Quality's National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on September 30, 2016. Search terms were: "whole exome sequencing (MeSH)," "whole genome sequencing (MeSH)," and "genetic tests (MeSH)."

We included:
- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews.**
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

Yang, et al. (2013), presented data on the first 250 subjects referred by clinicians for whole-WES analysis. Approximately 80 percent of the patients were children with clinically diagnosed neurologic derangements. The authors reported a 25 percent success rate at reaffirming the clinical neurologic
diagnosis with WGS, identifying autosomal dominant, autosomal recessive, and X-linked disease. As a comparator, conventional G-band karyotyping is associated with a positive diagnostic rate of 5 percent – 15 percent. Finally, the group offered an assessment of WGS in the clinical workplace, adding: “Questions about cost-effectiveness, accuracy, yield, and effective integration of genome-based diagnosis in medical care must be addressed in future studies and will require prospective study designs.”

Yang’s work built on the findings of previous studies (de Ligt 2012, Rauch 2012) in which over 50 percent of patients with nonsyndromic, sporadic cases of intellectual disability were identified. In an impressive showing of a cohort of pediatric patients from the German Mental Retardation Network, genetic variations totaling 79 different mutations in 53 of 100 patients with all-inclusive intellectual disability (ID); and 13 percent of those with severe ID (13 of 100) were assigned a specific molecular diagnosis by WGS. Both de Ligt and Rauch remarked that the phenotypic description of the cases they examined were incomplete when examined with the additional input of genomic testing to assess for sporadic non-syndromic intellectual disability.

Speaking of the “state of the art,” Parla, et al. (2011), noted the field had undergone “rapid progress in its development and usage,” but noted both strengths and limitations at that time, describing it as “transitional” at capturing genomic variation. In particular, coverage limitations of exome capture prevented its application to a number of disease entities of interest; which in turn led to expansion of the WES technology into WGS. The authors also noted that exome targeted capture’s future may lie not in broad screening for genetic disease, but instead for more specialized applications like multiplexed custom capture of specific regions of the genome.

Policy updates:

Ellingford (2016) compared the efficacy of WGS with targeted next-generation sequencing (NGS) in the diagnosis of inherited retinal disease (IRD) in a total of 562 patients diagnosed with IRD. The authors retrospectively reviewed the findings from a diagnostic NGS deoxyribonucleic acid (DNA) test for 562 patients with IRD. A subset of 46 of 562 patients (encompassing potential clinical outcomes of diagnostic significance) also underwent WGS, and were compared as to mutation detection rates and molecular diagnostic yields. The authors also compared the sensitivity and specificity of the two techniques to identify known single nucleotide variants (SNVs) using six control samples with publicly available genotype data. Across known disease-causing genes, targeted NGS and WGS achieved similar levels of sensitivity and specificity for SNV detection. However, WGS also identified 14 clinically relevant genetic variants that had not been identified by NGS diagnostic testing for the 46 individuals with IRD. These variants included large deletions and variants in noncoding regions of the genome. Identification of these variants confirmed a molecular diagnosis of IRD for 11 of the 33 individuals referred for WGS who had not obtained a molecular diagnosis through targeted NGS testing. Weighted estimates, accounting for population structure, suggest that WGS methods could result in an overall 29 percent (95 percent confidence interval, 15 – 45) uplift in diagnostic yield. The authors concluded that WGS methods can
detect disease-causing genetic variants missed by current NGS diagnostic methodologies for IRD and thereby demonstrate the clinical utility and additional value of WGS.

Szego (2016) in a narrative review compared whole genome sequencing to chromosomal microarray as a frontline genetic for autism disorder (AD) and related developmental conditions. The authors posited that WGS will in time replace chromosomal microarray as the diagnostic standard of care test for AD, and encouraged consistency among guidelines regarding what genomic information should be made available to patients and their families. The authors also promoted creation of an infrastructure to share clinical WGS data with other researchers in a systematic and ethically defensible manner.

Mafucci (2016) in a cohort study demonstrated that WES can succeed in dissecting the genetic etiology of common variable immunodeficiency (CVID) disease. The authors identified, using WES, causative genetic defects in 50 subjects who had at least one of the following criteria: 1) early onset, autoimmune/inflammatory manifestations, 2) low B lymphocytes, or 3.) familial history of hypogammaglobulinemia. The authors found 17 probable disease-causing mutations in 15 patients (30 percent). These variations were rare or private and included monoallelic mutations in NFKB1, STAT3, CTLA4, PIK3CD, and IKZF1, and biallelic mutations in LRBA and STXBP2. Forty-two other damaging variants were found but were not considered likely disease-causing based on the mode of inheritance and/or patient phenotype. The authors concluded that WES analysis of immunodeficiency-associated genes is a cost-effective approach to identify disease-causing mutations in CVID patients with severe phenotypes.

Brewer (2016) in a prospective study followed two large, distantly related families that mapped to the Charcot-Marie-Tooth neuropathy CMTX3 locus at chromosome Xq26.3-q27.3. WGS found a large DNA interchromosomal insertion within the CMTX3 locus that originated from chromosome 8q24.3, segregated fully within the disease in the two families, that is absent from the general population. The authors opined that the CMTX3 insertion represents an understudied pathogenic mechanism for inherited peripheral neuropathies and highlights the diagnostic importance in detecting rare disease of WGS technology.

Gray (2016) conducted surveys and interviews to determine oncologists’ attitudes about WES and to identify lung and colorectal cancer patients’ preferences for learning WES findings in 167 patients (85 percent white, 58 percent female, mean age 60 years) and 27 oncologists (22 percent female). Although oncologists had extensive experience ordering somatic tests (median 100/year), they had little experience ordering germline tests. Oncologists intended to disclose most WES results to patients but anticipated numerous challenges in using WES. Patients had moderately low levels of genetic knowledge (mean 4 correct of 7). Most patients chose to learn results that could help select a clinical trial, pharmacogenetic and positive prognostic results, and results suggesting inherited predisposition to cancer and treatable non-cancer conditions (all ≥ 95 percent). Fewer chose to receive negative prognostic results (84 percent) and results suggesting predisposition to untreatable non-cancer conditions (85 percent). The authors concluded that the majority of patients want most cancer-related
and incidental WES results. Patients' low levels of genetic knowledge and oncologists’ inexperience with large-scale sequencing presage challenges to implementing paired WES in practice.

**Summary of clinical evidence:**

<table>
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<tbody>
<tr>
<td>Gray (2016)</td>
<td><strong>Key points:</strong></td>
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| Oncologists’ and Cancer Patients’ Views on Whole-Exome Sequencing and Incidental Findings: Results from the CanSeq Study | - Survey of attitudes about WES in 167 patients (85% white, 58% female, mean age 60 years) and 27 oncologists (22% female).  
- Oncologists’ cumulative experience ordering somatic tests was a median 100/year, but had little experience ordering germline tests.  
- Oncologists intended to disclose most WES results to patients, but anticipated numerous challenges in using WES.  
- Patients had moderately low levels of genetic knowledge (mean 4 correct of 7) and chose to learn results that could help select a clinical trial, pharmacogenetic and positive prognostic results, and results suggesting inherited predisposition to cancer and treatable non-cancer conditions (all ≥ 95%).  
- Fewer chose to receive negative prognostic results (84%) and results suggesting predisposition to untreatable non-cancer conditions (85%).  
- The authors concluded that the majority of patients want most cancer-related and incidental WES results.  
- Patients' low levels of genetic knowledge and oncologists' inexperience with large-scale sequencing presage challenges to implementing paired WES in practice. |
| Ellingford (2016) | **Key points:** |
| Whole Genome Sequencing Increases Molecular Diagnostic Yield Compared with Current Diagnostic Testing for Inherited Retinal Disease. | - Retrospective review of WGS compared to NGS in the diagnosis of IRD in a total of 562 patients.  
- Authors compared the sensitivity and specificity of the two techniques to identify known SNVs and across known disease-causing genes.  
- NGS and WGS achieved similar levels of sensitivity and specificity for SNV detection. WGS also identified 14 clinically relevant genetic variants that had not been identified by NGS diagnostic testing.  
- Identification of these variants confirmed a molecular diagnosis of IRD for 11 of the 33 individuals referred for WGS who had not obtained a molecular diagnosis through targeted NGS testing.  
- WGS yielded in an overall 29% (95% confidence interval, 15 – 45) uplift in diagnostic yield. The authors concluded that WGS methods can detect disease-causing genetic variants missed by current NGS diagnostic methodologies. |
| Maffucci (2016) | **Key points:** |
| Genetic Diagnosis Using Whole Exome Sequencing in Common Variable Immunodeficiency | - Cohort study of WES to determine the genetic etiology of CVID.  
- The authors identified causative genetic defects in 50 subjects who had at least one of the following criteria: 1) early onset, autoimmune/inflammatory manifestations; 2) low B lymphocytes; and/or 3) familial history of hypogammaglobulinemia. |
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<td>Szego (2016)</td>
<td>Whole Genome Sequencing as a Genetic Test for Autism Spectrum Disorder: From Bench to Bedside and Then Back Again</td>
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<td>Yang (2013)</td>
<td>Clinical Whole-Exome Sequencing for the Diagnosis of Mendelian Disorders</td>
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<tr>
<td>de Ligt (2012)</td>
<td>Diagnostic exome sequencing in persons with severe intellectual disability</td>
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| Rauch (2012) | Range of genetic mutations associated with severe nonsyndromic sporadic intellectual disability: an exome sequencing | **Key points:** Examined ID in a pediatric cohort of the German Mental Retardation Network. Found nonsyndromic, sporadic cases of ID by exome sequencing in 45% – 55% of participants. De novo variants were etiologic in nearly a third (16 of 51) of those undergoing
Glossary

Exome — An exome refers to the portion of the human genome that contains functionally important regions of the nucleic acids (i.e., DNA) that direct the body to make proteins essential for the body to function properly. These regions of DNA are referred to as exons. There are approximately 180,000 exons in the human genome, which represents about 3 percent of the genome.

Whole exome sequencing (WES) — A test to sequence nucleotide by nucleotide, various portions of the human exome of an individual to a depth of coverage necessary to build a consensus sequence with high accuracy. This consensus sequence is then compared to reference of what is normal in the population, identifying variations in an individual's DNA sequence that can be related back to the individual's medical disorder.

Whole genomic sequencing (WGS) — A test to analyze a patient's DNA as a causative or pertinent co-factor in the patient’s medical concerns. In contrast to ES tests that analyze one gene or small groups of related genes at a time, the WGS analyzes the exons (or coding regions) of thousands of genes simultaneously.

References

Professional society guidelines/other:


Peer-reviewed references:


**Clinical trials:**

Searched clinicaltrials.gov on September 30, 2016, using terms “whole exome sequencing” and “whole genome sequencing” | Open Studies. Four studies found, three relevant.


National Cancer Institute (NCI).. Molecular Profiling in Tissue Samples From Patients With Cancer Who Are Exceptional Responders to Treatment. ClinicalTrials.gov website.


**CMS National Coverage Determinations (NCDs):**

No NCDs identified as of the writing of this policy.

**Local Coverage Determinations (LCDs):**

There are multiple LCDs regarding genetic testing identified as of the writing of this policy. The reader is referred to the CMS.gov website for the complete listing of these tests: https://www.cms.gov/medicare-coverage-database/search/search-results.aspx?CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=All&KeyWord=genetic+test &KeyWordLookUp=Title&KeyWordSearchType=And&bc=gAAAAAIAAAAAA%3d%3d=&. Accessed September 28, 2016.

**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill in accordance with those manuals.

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