

Whole Exome and Whole Genome Sequencing

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Whole exome sequencing (WES) is defined as targeted sequencing of the subset of the human genome that contains functionally important sequences of protein-coding DNA. Whole genome sequencing (WGS) uses next-generation sequencing techniques to sequence both coding- and non-coding regions of the genome. WES and WGS have been proposed to be more efficient than traditional sequencing methods in discovering the genetic causes of diseases and other indications.

MEDICAL POLICY CRITERIA

Whole exome sequencing and whole genome sequencing is considered **investigational** for all indications, including but not limited to:

- A. diagnosis in patients with suspected genetic disorders
- B. population-based screening
- C. cancer testing to identify targeted therapies
- D. preimplantation genetic diagnosis and screening
- E. invasive prenatal (fetal) testing
- F. products of conception and pregnancy loss

G. testing for chromosomal rearrangements

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. [Preimplantation Genetic Testing](#), Genetic Testing, Policy No. 18
2. [Genetic and Molecular Diagnostic Testing](#), Genetic Testing, Policy No. 20
3. [Chromosomal Microarray Analysis \(CMA\) and Next-generation Sequencing Panels for the Genetic Evaluation of Patients with Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, or Congenital Anomalies](#), Genetic Testing, Policy No. 58
4. [Evaluating the Utility of Genetic Panels](#), Genetic Testing, Policy No. 64
5. [Invasive Prenatal \(Fetal\) Diagnostic Testing Using Chromosomal Microarray Analysis \(CMA\)](#), Genetic Testing, Policy No. 78
6. [Chromosomal Microarray Analysis \(CMA\) for the Evaluation of Products of Conception and Pregnancy Loss](#), Genetic Testing, Policy No. 79

BACKGROUND

Human Genome Variation Society (HGVS) nomenclature^[1] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term “variant” is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as “mutation.” Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance (VUS).

Currently available clinical assays designed for the molecular diagnosis of rare Mendelian diseases are incomplete. This is due to genetic heterogeneity, the presence of unknown causative genes, and because only a portion of the known genes and variants can be efficiently tested using conventional molecular methods. Recently, next-generation sequencing (NGS) technologies have become more accessible in terms of cost and speed and have been adopted by a growing number of molecular genetic clinical laboratories.

Depending on the disorder and the degree of genetic and clinical heterogeneity, the current diagnostic pathway for patients with suspected genetic disorders accompanied by multiple anomalies may depend on various combinations of low-yield radiographic, electrophysiological, biochemical, biopsy, and targeted genetic evaluations.^[2] The search for a diagnosis may thus become a time-consuming and expensive process. When a disease-causing gene(s) is established, assays based on polymerase chain reaction (PCR) technology, for example, can be designed to specifically detect known variants for clinical diagnosis. When many different single-nucleotide variants (SNVs) in a gene are possible, Sanger sequencing, the current gold standard for detecting unknown SNVs, can be employed to determine the entire sequence of the coding and intron/exon splice sites of gene regions where variants are most likely to be found. However, when genes are large and variants are possible in many or all exons (protein-coding regions of the gene), and when there is genetic (locus) heterogeneity, comprehensive Sanger sequencing may be prohibitively laborious and costly.

WES using NGS technology is a relatively new approach to obtaining a genetic diagnosis in patients more efficiently compared with traditional methods. Exome sequencing has the capacity to determine an individual’s exomic variation profile in a single assay. This profile is

limited to most of the protein coding sequence of an individual (approximately 85%), is composed of about 20,000 genes and 180,000 exons, and constitutes approximately 1% of the whole genome. It is believed that the exome contains about 85% of heritable disease-causing variants.

Published studies have shown that exome sequencing can be used to detect previously annotated pathogenic variants and reveal new likely pathogenic variants in known and unknown genes. A limited number of studies have reported that the diagnostic yield of exome sequencing appears to be significantly increased above that of traditional Sanger sequencing, while also being faster and more efficient relative to Sanger sequencing of multiple genes.

WGS uses similar techniques to WES, but involves the sequencing of noncoding DNA in addition to the protein-coding segments of the genome.

LIMITATIONS OF WES AND WGS

At this time, the limitations of WES and WGS include technical and implementation challenges. There are issues of error rates due to uneven sequencing coverage, gaps in exon capture prior to sequencing, and difficulties with narrowing the large initial number of variants to manageable numbers without losing likely candidate variants. It is difficult to filter and interpret potential causative variants from the large number of variants of unknown significance (VUS) generated for each patient. Variant databases are poorly annotated, and algorithms for annotating variants will need to be automated. Existing databases that catalog variants and putative disease associations are known to have significant entry error rates.

Approaches for characterizing the functional impact of rare and novel variants (i.e., achieving full-genome clinical interpretations that are scientifically sound and medically relevant) have to be improved. The variability contributed by the different platforms and procedures used by different clinical laboratories offering exome sequencing as a clinical service is unknown, and detailed guidance from regulatory and professional organizations is still under development. Finally, exome sequencing has some similar limitations as Sanger sequencing; e.g., it will not identify the following: intronic sequences or gene regulatory regions; chromosomal changes; large deletions, duplications or rearrangements within genes; nucleotide repeats; or epigenetic changes. WGS address some of these limitations, but is limited by the need for increased analytic power and the likelihood of greater identification of VUS.

There are also ethical questions about reporting incidental findings such as identifying medically relevant variants in genes unrelated to the diagnostic question, sex chromosome abnormalities, and non-paternity when family studies are performed. Standards for the required components of informed consent before WES/WGS is performed have been proposed and include a description of confidentiality and a description of how incidental findings will be managed.^[3] Methods of reporting findings from WES/WGS are in development. For example, McLaughlin et al, reporting on the MedSeq Project which is testing methods for evaluating and reporting WES/WGS data, described the development of a genome report that highlights results significant to the indication being evaluated.^[4]

RESULTS OF TESTING WITH WES/WGS^[5]

1. A variant known to cause human disease is identified. This is also known as a pathogenic variant.

- This is a sequence variant that has been shown through prior genetic and clinical research to cause a disease.
2. A variant suspected to cause human disease is identified. This is also known as a pathogenic variant.
 - Most variants detected by WES sequencing are uncharacterized and some are novel (i.e., never known to have been observed in a human sample). Some variants allow for relatively easy and accurate clinical interpretation; however, for most there is little data on which to base an assessment of causality. Tools to facilitate the assessment of causality include bioinformatic analyses, predicted structural changes, and others. While these tools may be useful, their predictive power is highly variable. In addition, each clinical laboratory offering WES/WGS testing have their own “in-house” algorithm to facilitate assessment and classification of these variants.
 3. A variant of uncertain significance (VOUS/VUS) is identified.
 - Among the known 30,000 to 40,000 variants that reside in the protein-coding portions of the genome, the typical subject will have three to eight actionable variants. (Most relate to reproductive risks, i.e., heterozygous carrier alleles.) But the remaining thousands are either highly likely to be benign or of uncertain clinical significance. It can be equally as challenging to prove that a variant is benign as it is to prove it is pathogenic. Currently, nearly all variants among the tens of thousands must be considered of uncertain significance.

AVAILABLE TESTING SERVICES

WES

Examples of some laboratories offering exome sequencing as a clinical service and their indications for testing are summarized in the table below.

Laboratory	Laboratory indications for testing
Ambry Genetics	“The patient’s clinical presentation is unclear/atypical disease and there are multiple genetic conditions in the differential diagnosis.”
GeneDx	“a patient with a diagnosis that suggests the involvement of one or more of many different genes, which would, if even available and sequenced individually, be prohibitively expensive”
Baylor College of Medicine	“used when a patient’s medical history and physical exam findings strongly suggest that there is an underlying genetic etiology. In some cases, the patient may have had an extensive evaluation consisting of multiple genetic tests, without identifying an etiology.” Baylor also offers a prenatal WES test.
University of California Los Angeles Health System	“This test is intended for use in conjunction with the clinical presentation and other markers of disease progression for the management of patients with rare genetic disorders.”

EdgeBio	Recommended “In situations where there has been a diagnostic failure with no discernible path . . . In situations where there are currently no available tests to determine the status of a potential genetic disease . . . In situations with atypical findings indicative of multiple disease[s]”
Children’s Mercy Hospitals and Clinics	Provided as a service to families with children who have had an extensive negative work-up for a genetic disease; also used to identify novel disease genes.
Emory Genetics Laboratory	“Indicated when there is a suspicion of a genetic etiology contributing to the proband’s manifestations.”
Knight Diagnostic Laboratory	“diagnosing rare hereditary diseases, inconclusive results from targeted panel tests, presentation of multiple phenotypes or when a patient presents an unknown or novel phenotype.”

WGS

Although WGS has been used as a research tool, it is less well-developed as a clinical service. Several laboratories offer WGS as a clinical service.

REGULATORY STATUS

No U.S. Food and Drug Administration (FDA)-cleared genotyping tests were found. Thus, genotyping is offered as a laboratory-developed test. Clinical laboratories may develop and validate tests in-house (“home-brew”) and market them as a laboratory service. Such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The laboratory offering the service must be licensed by CLIA for high-complexity testing.

EVIDENCE SUMMARY

Validation of the clinical use of any genetic test focuses on three main principles:

1. The analytic validity of the test, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent;
2. The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. The clinical utility of the test, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

The focus of the literature search was on evidence related to the ability of genetic test results to:

- Guide decisions in the clinical setting related to either treatment, management, or prevention, and
- Improve health outcomes as a result of those decisions.

ANALYTIC VALIDITY

Whole Exome Sequencing

There is relatively little data specific to the analytic validity of whole exome sequencing (WES). The next-generation sequencing (NGS) techniques used for WES are generally expected to have high accuracy for variant detection, NGS platforms differ in terms of the depth of sequence coverage, methods for base calling and read alignment, and other factors. These factors contribute to potential variability across the different platforms and procedures used by different clinical laboratories offering exome sequencing as a clinical service. The American College of Medical Genetics (ACMG) has clinical laboratory standards for NGS, including WES.^[6] The guidelines outline the documentation of test performance measures that should be evaluated for NGS platforms, and note that typical definitions of analytic sensitivity and specificity do not apply for NGS.

Depending on the platform and variant call method used, WES may not accurately detect large insertions and deletions, large copy number variants (CNVs), and structural chromosome rearrangements due to the short sequence read lengths.^[6] For these types of large genetic variants, WES is currently less sensitive than high-resolution microarray testing.^[7] NGS also has poorer coverage for A/T-rich, G/C rich, and pseudogene regions, and homopolymer stretches.^[8,9]

Whole Genome Sequencing

Whole genome sequencing (WGS) is subject to the same considerations related to potential variability in technical performance as WES. Dewey (2014) published an evaluation of the coverage and concordance of clinically relevant genetic variation provided by WGS technologies in 12 healthy adult volunteers.^[10] All subjects underwent WGS sequencing with the Illumina platform; nine subjects also underwent WGS by the Complete Genomics platform to evaluate reproducibility of sequence data. Genome sequences were compared with several reference standards. Depending on the sequencing platform, a median of 10% (Illumina Inc.; range, 5% to 34%) to 19% (Complete Genomics Inc.; range, 18% to 21%) of genes associated with inherited disease and a median of 9% (Illumina Inc.; range, 2% to 27%) to 17% (Complete Genomics Inc.; range, 17% to 19%) of American College of Medical Genetics (ACMG)-reportable genes were not covered at a minimum threshold for genetic variant discovery. The genotype concordance between sequencing platforms was high for common genetic variants, for single nucleotide variants in protein coding regions of the genome, and among candidate variants for inherited disease risk. However, genotype concordance between sequencing platforms for small insertion/deletion variants was moderate overall (median, 57%; range, 53% to 59%) and in protein coding regions of the genome (median, 66%; range, 64% to 70%) but was substantially lower among genetic variants that were candidates for inherited disease risk (median, 33%; range, 10% to 75%).

WES/WGS for Preimplantation

Peters (2015) reported on the results of WGS performed on three 5- to 10-cell biopsies from two blastocyst-stage embryos in order to detect single base de novo variants and small insertions and deletions.^[11] Both parents and paternal grandparents were also analyzed in order to measure false-positive and false-negative error rates. Overall, >95% of each genome was called. Experimentally derived haplotypes were used to detect up to 82% of de novo SNVs with a false-positive rate of about one error per gigabase, resulting in fewer than 10 errors per embryo. The authors state that this represents an approximately 100-fold lower error rate than previously published from 10-cell embryos, and it is the first demonstration that WGS

can be used to accurately identify de novo variants in spite of the thousands of false-positive errors introduced by the extensive DNA amplification required for deep sequencing.

WES/WGS for Pregnancy Loss

Qiao (2016) evaluated the use of whole exome sequencing identify genetic causes of idiopathic recurrent early pregnancy loss (RPL), assessing seven euploid miscarriages from four families with RPL.^[12] The study identified compound heterozygous pathogenic variants of *DYNC2H1* and *ALOX15* in two out of four families with RPL. Although the authors concluded that CNVs, individual SNVs and pool of deleterious gene variants identified by exome sequencing could contribute to RPL, they acknowledge that the study has limitations, mainly the small sample cohort is small and that functional analysis of the candidate variants must be evaluated to determine whether the variants are causative.

CLINICAL VALIDITY AND UTILITY

The clinical validity of WES and WGS is related to the diagnostic performance of these technologies, while the clinical utility lies in the influence of the results on medical decision making and patient outcomes. In order for clinical utility to be established, evidence would be needed of the ability of WES or WGS to provide the following improvements over other sequencing methods:

- Ability to establish a definitive diagnosis by detection of additional variants not found by other testing methods and leading to management changes that improve outcomes and/or eliminate the need for additional testing
- Equivalent or superior accuracy attained with superior efficiency of workup (e.g., diagnosis obtained more quickly) compared with other methods of sequencing.

Systematic Reviews

A 2013 BlueCross BlueShield Association Technology Evaluation Center (TEC) Special Report on WES in patients with suspected genetic disorders, found no published studies that systematically examined potential outcomes of interest such as changes in medical management (including revision of initial diagnoses), and changes in reproductive decision making after a diagnosis of a Mendelian disorder by WES.^[13] The evidence was limited to a small number of studies of patient series and a larger number of very small series or family studies that reported anecdotal examples of medical management and reproductive decision-making outcomes of exome sequencing in patients who were not diagnosed by traditional methods. These studies showed that, over and above traditional molecular and conventional diagnostic testing, exome sequencing could lead to a diagnosis that influenced patient care and/or reproductive decisions, but gave no indication of the proportion of patients for which this was true. The report noted that publication of a large number of small diagnostic studies with positive results but few with negative results raise the possibility of publication bias, the impact of which is unknown.

Nonrandomized Studies

Since the publication of the 2013 TEC Special Report, numerous studies were identified which demonstrate that WES and WGS can be used to identify novel genetic variants in a range of clinical conditions. Typically, the populations included in these studies have suspected rare genetic disorders, although the specific patient populations vary.^[7,14-33] However, evidence

related to the use of WES or WGS test results in changes in medical management or reproductive decision making is limited.

WES/WGS in Clinical Practice

Since the publication of the 2013 TEC Special Report, several studies have been published that address the use of either WES or WGS in clinical practice.

A study by Vissers (2017) compared WES with the standard diagnostic pathway in 150 complex pediatric neurology patients suspected of having a genetic disorder.^[34] Both diagnostic pathways were performed in parallel on all patients separately, then compared after completion. The standard diagnostic pathway provided a conclusive diagnosis in 11 (7.3%) of the patients, while WES provided a conclusive diagnosis in 44 (29.3%) of patients. Standard genetic analysis revealed three pathogenic variants that were not detected by WES. The impact of the testing on treatment decisions was not evaluated.

A study comparing WGS with panel testing for patients with hypertrophic cardiomyopathy was published by Cirino (2017).^[35] The study included 41 patients who had undergone targeted genetic testing with either a panel test or a targeted genetic test for a familial variant, who subsequently underwent WGS. The panel testing identified 20 variants as pathogenic, likely pathogenic, or uncertain significance. WGS identified 19 of these 20 variants, as well as a pathogenic variant and several VUS in genes that had been implicated in hypertrophic cardiomyopathy, but were not included in the genetic panel test. Additionally, WGS uncovered 84 secondary findings, many of which indicated that the patients were carriers for gene variants associated with autosomal recessive diseases.

Ellingford (2016) compared the efficacy of WGS with targeted NGS panel testing in the diagnosis of inherited retinal disease (IRD).^[36] All 46 individuals had been phenotypically assessed in a single institution, represented a complete suite of possible clinical outcomes, and underwent both targeted panel testing (105 genes) as well as WGS testing with targeted analysis. For each individual, the investigators assessed whether the panel and WGS identified the same clinically relevant variants and achieved the same clinical outcome. Across known disease-causing genes, the panel and WGS achieved similar levels of sensitivity and specificity for SNV detection. However, WGS also identified 14 clinically relevant genetic variants through WGS that had not been identified by the 105-gene panel for the 46 individuals with IRD. 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 panel testing. Calculating weighted estimates, accounting for population structure, the investigators suggest that WGS methods could result in an overall 29% (95% confidence interval [CI] 15 to 45) uplift in diagnostic yield for inherited retinal disease.

Farwell (2015) tested an inheritance model-based analysis approach to WES in 500 patients with undiagnosed genetic conditions.^[37] In this study, exome sequencing was performed, along with inheritance-based model filtering, medical review, cosegregation analysis, and novel gene analysis. In 152 patients (30%), positive or likely positive changes in a characterized gene were found. Changes in novel genes were seen in 31 patients (7.5%). Patients with ataxia, epilepsy, and multiple congenital anomalies were most likely to have a diagnosis made. WES in family trios resulted in a higher diagnostic rate compared to patient-only WES.

Sawyer (2015) investigated the diagnostic yield of WES for a cohort of patients suspected to have a genetic disorder who had already received standard-of-care genetics evaluation (either

single gene testing, occasional small gene panels or and chromosome microarray) and diagnostic testing as part of the Finding Of Rare Disease GENes (FORGE) Canada research study.^[38] Of 362 families submitted to FORGE for WES, the investigators identified disease-causing variants in known genes for 105 families (29%). The success rate ranged from 12% (immunological disorders) to 44% (ciliopathies).^[39] There were six of the 105 families (26%) in this study whose medical management changed dramatically subsequent to a diagnosis through WES; three had their therapy adjusted and three had specific therapy initiated.

Tammimies (2015). reported on the results of CMA and WES in a sample of children with autism spectrum disorders (ASD).^[40] The patient cohort included 258 consecutively enrolled patients, stratified into three groups based on the presence of major congenital abnormalities and minor physical anomalies (n = 168, 37, and 53 considered essential, equivocal, and complex, respectively). All probands underwent CMA testing. WES was performed for 95 proband-parent trios. Among the 95 patients undergoing WES, eight children (nine variants) were received an ASD-related molecular diagnosis (8.4%, 95% CI 3.7% to 15.9%). Incidental or medically actionable findings were reported in 8 of 95 (8.4%) probands tested with WES.

Nolan and Carlson (2016) reviewed medical charts of patients that were seen at a pediatric neurology clinic between 2011 and 2015.^[41] WES was recommended for 135 of these patients, and was performed for 53 of them. Use of WES improved the diagnostic rate from 25% to 48%. Lack of insurance coverage was the most common barrier to WES.

Allen (2016) used WES to help diagnose children with early onset epileptic encephalopathies in a single-center study.^[42] There were 50 patients in the study, which targeted 137 epilepsy-associated genes. Pathogenic variants were identified in 11 of the patients (22%) and VUS were found in two patients. Of these, 11 variants were determined to be de novo and paternal testing was not possible for one patient.

Lee (2014) reported on a large (n = 814) single-center cohort of patients with undiagnosed, suspected genetic conditions who underwent WES.^[43] The investigators used a “trio-CES [clinical exome sequencing]” technique that involves sequencing of the proband and two family members, typically unaffected parents. For the first approximately 300 cases, all reported variants were confirmed by Sanger sequencing with more than 99% confirmation. After that, variants were evaluated with a QUAL score, a scaled probability of a variant existing at a given site, and only clinically significant variants with a QUAL score lower than 500 were confirmed. Variants found were annotated to provide information about their effect on protein function, allele frequency in the general population, and prior evidence of disease causality, and subsequently filtered to select likely pathogenic DNA variants. For variants in probands with family member testing available, variants were categorized as de novo (usually heterozygous in the patient and potentially causing an autosomal dominant condition), homozygous, compound heterozygous, and inherited variants. Variants were evaluated in the context of a “primary gene list,” which was determined based on phenotypic key words included in referring clinician notes. Of the 814 patients included, 520 patients (64%) were children, and 254 of those were younger than five years at testing. The most common clinical indication for testing was developmental delay in the entire population and in the childhood group (37% and 53%, respectively). In the adult group, ataxia was the most common indication for testing (26%). Overall, a molecular diagnosis with a causative variant in a well-established clinical gene was provided for 213 of 814 cases (26%, 95% CI 23% to 29%). Of the 264 variants reported in 213 cases, 188 were reported as “likely pathogenic” and 73 were reported as “pathogenic” variants.

Yang (2013) reported results from the first 250 patients who underwent WES at a single institution.^[44] Most patients (80%) were children presenting with phenotypes consistent with a neurologic disorder. Sixty-two patients were identified to have 86 mutated alleles that satisfied criteria for a molecular diagnosis for an overall rate of a positive molecular diagnosis of 25%. Thirty-nine of the patients with a molecular diagnosis had rare genetic diagnoses. In addition to diagnostic findings, 30 patients had medically actionable incidental findings in a total of 16 genes, and 13 had carrier-status variants in genes from the ACMG-recommended population-screening panel. This study suggests that WES can have a high diagnostic yield in an appropriately-selected population. However, rates of incidental findings were also high, and the impact of these findings upon clinical outcomes is unknown. A 2014 update to this study included 504 patients and reported similar findings to the original study with high rates of incidental findings.^[45]

Wortmann (2015) performed WES in 109 patients suspected of having a mitochondrial disorder.^[46] Initially, WES data were filtered and analyzed for genes that were known to be associated with mitochondrial disease, and if these results were negative, the whole exome was examined. Diagnosis were made in 39% of the cohort, with a higher proportion of diagnoses (57%) in those with the highest suspicion of mitochondrial disease.

The diagnostic yield of WES in adults was reported by Posey (2016), who retrospectively reviewed 486 consecutive WES results for adults from a diagnostic laboratory.^[47] In this group, 85 (17.5%) received a molecular diagnosis, and diagnosis rates were higher in those between ages 18 and 30 years, compared to patients above age 30 (23.9% vs. 10.4%, respectively, $p=0.0001$).

Several recent studies have reported on the use of WGS to assess chromosomal rearrangements.^[48-51] In general, these studies have evaluated this technology in small numbers of patients with known or suspected chromosomal structural variations. For example, Liang (2017) used next-generation sequencing to detect balanced chromosomal translocations in parents of eight prenatal cases of unbalanced translocations.^[48] Low-coverage WGS detected five balanced translocations, compared to three detected by G-banding analysis and two detected by fluorescence in situ hybridization, and identified six disrupted genes in four apparently healthy individuals. Nilsson (2017) published a report on the use of low-coverage mate-pair WGS in 22 carriers of translocations, which identified gene disruptions in 48% of chromosome breakpoints, including disruptions in seven candidate disease genes in five carriers with neurocognitive disabilities.^[49] The clinical utility of this approach has not been assessed

Additional studies have been performed to assess the diagnostic yield of WES and WGS in certain populations, such as critically ill newborns (diagnostic yield 30%),^[52] and individuals with specific types of inherited diseases, including mitochondrial disease,^[46] limb-girdle muscular dystrophy.^[53] Diagnosis rates in these studies were 39% and 45% for limb-girdle muscular dystrophy and mitochondrial disease, respectively.

Changes in Patient Management with WES/WGS

Since the publication of the 2013 TEC Special Report, several studies have reported on potential benefits, in terms of medical management changes or avoidance of alternative testing, following WES/WGS.

Leinøe (2017) evaluated the use of WES to direct functional testing and diagnosis of 156 Scandinavian patients with rare, inherited bleeding disorders.^[54] WES analysis was focused on 87 genes associated with bleeding disorders. There were 353 germline variants were identified, eight of which were known pathogenic variants. Computational analysis predicted that 99 of the 353 previously unknown variants were significant, which was reduced to 59 significant variants after filtering by inheritance pattern. Functional platelet testing based on genetic variants identified 20 of the 59 variants as novel class 4 or 5 variants. The impact of WES on patient management was not assessed beyond the selection of functional platelet testing.

Valencia (2015) examined the clinical utility of WES in a retrospective study of 40 pediatric patients referred for sequencing at Cincinnati Children's Hospital.^[55] The majority of these patients had either multiple congenital anomalies (30%) or phenotypes related to mitochondrial (25%), neurological (22%), or immunodeficiency (17%) disorders. Genetic defects were identified in 12 (30% of the patients), and 47% of the variants were previously unreported. There were 36 patients (90%) that elected to receive secondary findings, and three of these patients had medically actionable secondary findings. The authors reported that WES results led to medical management changes in patients with identified variants, however medical management was defined very broadly, and included ending the diagnostic odyssey and genetic counseling. Only five of the patients had documented changes to their treatment plan as a result of the findings.

Soden (2014) reported on the use of WGS and/or WES in parent-child trios for 119 children with neurodevelopmental disorders.^[56] A definitive molecular diagnosis of an established genetic disorder was identified in 45 of the 100 families with children affected by neurodevelopmental disorders (53/119 affected children). Chart reviews and interviews with referring physicians were used to assess changes in short-term management following WES/WGS, and changed patient management and/or clinical impression was reported in 22 of 45 families (49%).

Iglesias (2014) reported on clinical changes that occurred after WES/WGS in a broader population of 115 patients with a genetically undefined disorder.^[57] The most common indications for WES evaluation were birth defects, developmental delay, and seizures, in 24.3%, 25.2%, and 14% of patients, respectively. A definitive diagnosis was made in 37 cases (32.2%). The clinical implications of testing are described qualitatively for patients with a genetic diagnosis. In six cases, it was noted that genetic information was used for reproductive planning; in 11 cases, patients were noted to have a change in medical management or surveillance or testing for related conditions.

Stark (2016) evaluated the diagnostic and clinical utility of WES as a first-tier test in 80 infants suspected of having a monogenic disease.^[58] Standard evaluations, including targeted genetic testing, were performed in parallel during this study. There were 46 infants that received a diagnosis from WES, compared with 11 in the same group that received diagnoses from standard testing. Clinical management was changed in 15 of the 46 patients with a diagnosis, 28 couples were identified as having a high risk for recurrence in future offspring, and 12 relatives of patients received a genetic diagnosis through cascade testing.

In a retrospective study of 78 children with neurodevelopmental disorders with a prior unrevealing workup who underwent WES, Srivastava (2014) reported a presumptive diagnostic testing rate of 41%.^[59] Results of WES changed patient management in all cases,

most often related to reproductive planning (n = 27), along with additional disease monitoring in four cases, further workup for systemic involvement in six cases, and seven medication changes.

A study by Mackley (2017) explored stakeholder views on secondary findings in WES/WGS in a systematic review that included 44 articles.^[60] While stakeholders generally supported the return of “actionable” findings, the definitions of “actionable” were varied. According to the authors, “Stakeholder views on SF disclosure exist along a spectrum: potential WES/WGS recipients' views were largely influenced by a sense of rights, whereas views of genomics professionals were informed by a sense of professional responsibility. Experience with genetic illness and testing resulted in greater caution about SF, suggesting that truly informed decisions require an understanding of the implications and limitations of WES/WGS and possible findings.”

WES/WGS for Testing of Cancers to Identify Targeted Therapies

Comparison of cancer variants with matched normal tissue can provide evidence about whether variants are truly somatic cancer variants or whether they are incidental variants that do not have meaningful biologic activity. Jones (2015) performed comprehensive variant testing on 815 pairs of tumor tissue and matched normal tissue from patients with 15 different tumor types.^[61] Each sample was analyzed by both targeted sequencing and whole exome sequencing. A total of 105,672 somatic alterations were identified. After filtering for variants present in normal tissue, there was an average of 4.34 variants per patient on targeted analysis and 135 variants per patient on whole exome sequencing. After additional filtering using the COSMIC (Catalog of Somatic Mutations in Cancer) database, the authors estimated that 38% of the variants identified by targeted analysis were true positives and 62% were false positives; on whole exome analysis, 10% of variants were true positives and 90% were false positives.

PRACTICE GUIDELINE SUMMARY

AMERICAN COLLEGE OF MEDICAL GENETICS

- In 2015, ACMG published a policy statement updating their 2013 their recommendations for analysis and reporting of secondary/incidental findings in whole genome and whole exome sequencing.^[62,63]
 - The panel states that patients must be made aware, at the time of consent, that laboratories routinely analyze the sequence of a set of genes deemed to be highly medically actionable so as to detect pathogenic variants that may predispose to a severe but preventable disease.
 - Although patients have the choice to opt out of receiving these results, that they should be made aware of the ramifications of doing so.
 - Due to the inherent difficulty of counseling patients about the features of each disorder and every gene deemed actionable by the ACMG, analysis and reporting of secondary findings should apply to the entire list of medically actionable genes, and not a subset.
- A 2012 consensus-based Policy Statement from the American College of Medical Genetics (ACMG) noted the following potential indications and disadvantages for genomic sequencing:^[64]

- Diagnostic testing with WES (and whole genome sequencing [WGS]) should be considered in the clinical diagnostic assessment of a phenotypically affected individual when:
 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.
- WGS/WES for screening:
 1. WGS/WES may be considered in preconception carrier screening using a strategy to focus on genetic variants known to be associated with significant phenotypes in homozygous or hemizygous progeny.
 2. WGS/WES should not be used at this time as an approach to prenatal screening, or as a first-tier approach for newborn screening.
- Disadvantages of WGS/WES
 1. WES may miss some clinically significant mutations due to inefficient capture of certain exons.
 2. Overall analytical sensitivity is still being defined for both WES and WGS.
 3. WGS/WES are highly likely to reveal secondary findings (also called incidental or unanticipated findings) such as finding a previously unsuspected high risk of future disease or an unrecognized disorder in an asymptomatic patient. “When interpreting secondary findings, or results that are generated in the course of screening asymptomatic individuals, it is critical that the standards for what is reportable be high to avoid burdening the health care system and consumers with what could be very large numbers of false positive results.”
- In March 2013, an ACMG board finalized approval of their recommendations for reporting incidental findings in whole genome and whole exome sequencing.^[63] A working group determined that reporting some incidental findings would likely have medical benefit for the patients and families of patients undergoing clinical sequencing and recommended that when a report is issued for clinically indicated exome and genome sequencing, a minimum list of conditions, genes and variants should be routinely evaluated and reported to the ordering clinician.

SUMMARY

There is not enough research to determine whether whole exome sequencing (WES) or whole genome sequencing (WGS) can be used to improve patient health outcomes. In addition, there are technical limitations such as the lack of standardized laboratory

procedures, gaps in interpreting ancillary information, and the detection of variants of uncertain significance. Therefore, the use of WES or WGS is considered investigational for all indications.

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CODES

Codes	Number	Description
CPT	0012U	Germline disorders, gene rearrangement detection by whole genome next-generation sequencing, DNA, whole blood, report of specific gene rearrangement(s)
	0013U	Oncology (solid organ neoplasia), gene rearrangement detection by whole genome next-generation sequencing, DNA, fresh or frozen tissue or cells, report of specific gene rearrangement(s)
	0014U	Hematology (hematolymphoid neoplasia), gene rearrangement detection by whole genome nextgeneration sequencing, DNA, whole blood or bone marrow, report of specific gene rearrangement(s)
	0036U	Exome (ie, somatic mutations), paired formalin-fixed paraffin-embedded tumor tissue and normal specimen, sequence analyses
	0056U	Hematology (acute myelogenous leukemia), DNA, whole genome next-generation sequencing to detect gene rearrangement(s), blood or bone marrow, report of specific gene rearrangement(s)
	81415	Exome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis
	81416	;sequence analysis, each comparator exome (eg, parents, siblings) (List separately in addition to code for primary procedure)
	81417	;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	;sequence analysis, each comparator genome (eg, parents, siblings) (List separately in addition to code for primary procedure)
	81427	;re-evaluation of previously obtained genome sequence (eg, updated knowledge or unrelated condition/syndrome)
	81479	Unlisted molecular pathology procedure
HCPCS	None	

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