



# Louisiana

## Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

**Policy #** 00389

**Original Effective Date:** 11/20/2013

**Current Effective Date:** 12/20/2017

*Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.*

*Note: Genetic Testing for the Diagnosis of Inherited Peripheral Neuropathies is addressed separately in medical policy 00378.*

*Note: Genetic Testing for Facioscapulohumeral Muscular Dystrophy is addressed separately in medical policy 00392.*

*Note: Genetic Testing for Epilepsy is addressed separately in medical policy 00401.*

*Note: Genetic Testing for Limb-Girdle Muscular Dystrophies is addressed separately in medical policy 00489.*

*Note: Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies is addressed separately in medical policy 00536.*

### **When Services May Be Eligible for Coverage**

*Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:*

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider whole exome sequencing (WES) for the evaluation of unexplained congenital or neurodevelopmental disorder in children to be **eligible for coverage**.

### **Patient Selection Criteria**

Coverage eligibility will be met for whole exome sequencing (WES) for the evaluation of unexplained congenital or neurodevelopmental disorder in children when ALL of the following criteria are met:

- The patient has been evaluated by a clinician with expertise in clinical genetics and counseled about the potential risks of genetic testing; and
- There is potential for a change in management and clinical outcome for the individual being tested; and
- A genetic etiology is considered the most likely explanation for the phenotype despite previous genetic testing (e.g., chromosomal microarray analysis and /or targeted single-gene testing), OR when previous genetic testing has failed to yield a diagnosis and the affected individual is faced with invasive procedures or testing as the next diagnostic step (e.g., muscle biopsy).

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### **When Services Are Considered Investigational**

*Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

Based on review of available data, the Company considers whole exome sequencing (WES) for the diagnosis of genetic disorders in all other situations to be **investigational**.\*

Based on review of available data, the Company considers whole genome sequencing (WGS) for the diagnosis of genetic disorders to be **investigational**.\*

Based on review of available data, the Company considers whole exome sequencing (WES) and whole genome sequencing (WGS) for screening for genetic disorders to be **investigational**.\*

### **Background/Overview**

#### **WHOLE EXOME SEQUENCING AND WHOLE GENOME SEQUENCING**

WES is targeted next-generation sequencing (NGS) of the subset of the human genome that contains functionally important sequences of protein-coding deoxyribonucleic acid (DNA), while WGS uses NGS techniques to sequence both coding and noncoding regions of the genome. WES and WGS have been proposed for use in patients presenting with disorders and anomalies not explained by standard clinical workup. Potential candidates for WES and WGS include patients who present with a broad spectrum of suspected genetic conditions.

Given the variety of disorders and management approaches, there are a variety of potential health outcomes from a definitive diagnosis. In general, the outcomes of a molecular genetic diagnosis include (1) impacting the search for a diagnosis, (2) informing follow-up that can benefit a child by reducing morbidity, and (3) affecting reproductive planning for parents and potentially the affected patient.

The standard diagnostic workup for patients with suspected Mendelian disorders may include combinations of radiographic, electrophysiologic, biochemical, biopsy, and targeted genetic evaluations. The search for a diagnosis may thus become a time-consuming and expensive process.

#### **WES and WGS Technology**

WES or WGS using NGS technology can facilitate obtaining a genetic diagnosis in patients efficiently. WES is limited to most of the protein-coding sequence of an individual ( $\approx 85\%$ ), is composed of about 20,000 genes and 180,000 exons (protein-coding segments of a gene), and constitutes approximately 1% of the genome. It is believed that the exome contains about 85% of heritable disease-causing mutations. WES has the advantage of speed and efficiency relative to Sanger sequencing of multiple genes. WES shares some limitations with Sanger sequencing. For example, 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 uses techniques similar to WES, but includes noncoding regions. WGS has greater ability to detect large deletions or duplications in protein-coding regions compared with WES, but requires greater data analytics. Technical aspects of WES and WGS are

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evolving, including the development of databases such as the National Institutes of Health’s ClinVar database (<http://www.ncbi.nlm.nih.gov/clinvar/>) to catalog variants, uneven sequencing coverage, gaps in exon capture before sequencing, and difficulties with narrowing the large initial number of variants to manageable numbers without losing likely candidate mutations. The variability contributed by the different platforms and procedures used by different clinical laboratories offering exome sequencing as a clinical service is unknown.

In 2013, the American College of Medical Genetics and Genomics, Association for Molecular Pathology, and College of American Pathologists convened a workgroup to develop standard terminology for describing sequence variants. Guidelines developed by this workgroup, published in 2015, describe criteria for classifying pathogenic and benign sequence variants based on 5 categories of data: pathogenic, likely pathogenic, uncertain significance, likely benign, and benign.

### WES and WGS Testing Services

Several laboratories offer WES and WGS as a clinical service. Illumina offers 3 TruGenome tests: the TruGenome Undiagnosed Disease Test (indicated to find the underlying genetic cause of an undiagnosed rare genetic disease of single-gene etiology), the TruGenome™<sup>+</sup> Predisposition Screen (indicated for healthy patients interested in learning about their carrier status and genetic predisposition toward adult-onset conditions), and the TruGenome Technical Sequence Data (WGS for labs and physicians who will make their own clinical interpretations). Ambry Genetics offers 2 WGS tests, the ExomeNext and ExomeNext-*Rapid*, which sequence both the nuclear and the mitochondrial genomes. GeneDx offers WES with its XomeDx™<sup>+</sup> test. Medical centers may also offer WES and WGS as a clinical service.

Examples of laboratories offering WES as a clinical service and their indications for testing are summarized in Table 1.

**Table 1. Examples of Laboratories Offering Whole Exome Sequencing as a Clinical Service**

Laboratory	Laboratory Indications for Testing
Ambry Genetics (Aliso Viejo, CA)	“The patient’s clinical presentation is unclear/atypical disease and there are multiple genetic conditions in the differential diagnosis.”
GeneDx (Gaithersburg, MD)	“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 (Houston, TX)	“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.”
Illumina (San Diego, CA)	The TruGenome Undiagnosed Disease Test is indicated to find the underlying genetic cause of an undiagnosed rare genetic disease of single-gene etiology.
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 (Gaithersburg, MD)	Recommended “In situations where there has been a diagnostic failure with no

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	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 (Kansas City, MO)	Provided as a service to families with children who have had an extensive negative workup for a genetic disease; also used to identify novel disease genes.
Emory Genetics Laboratory (Atlanta, GA)	“Indicated when there is a suspicion of a genetic etiology contributing to the proband’s manifestations.”

Note that this evidence review does not address the use of WES and WGS for preimplantation genetic diagnosis or screening, prenatal (fetal) testing, or for testing of cancer cells.

### **FDA or Other Governmental Regulatory Approval**

U.S. Food and Drug Administration (FDA)

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Whole exome or genome sequencing tests as a clinical service are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. FDA has chosen not to require any regulatory review of this test

Centers for Medicare and Medicaid Services (CMS)

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

### **Rationale/Source**

This review was informed in part by a 2013 Technology Evaluation Center (TEC) Special Report on exome sequencing for patients with suspected genetic disorders.

Validation of the clinical use of any genetic test focuses on 3 main principles: (1) analytic validity, 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) clinical validity, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and (3) clinical utility (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).

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# Louisiana

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Policy # 00389

Original Effective Date: 11/20/2013

Current Effective Date: 12/20/2017

## **WHOLE EXOME SEQUENCING IN PATIENTS WITH MULTIPLE CONGENITAL ANOMALIES OR A NEURODEVELOPMENTAL DISORDER**

### **Clinical Context and Test Purpose**

The purpose of WES in patients who have multiple unexplained congenital anomalies or a neurodevelopmental disorder is to establish a molecular diagnosis. The criteria under which diagnostic testing for a genetic or heritable disorder may be considered clinically useful are as follows:

- A definitive diagnosis cannot be made based on history, physical examination, pedigree analysis, and/or standard diagnostic studies or tests;
- The clinical utility of a diagnosis has been established (e.g., by demonstrating that a definitive diagnosis will lead to changes in clinical management of the condition, changes in surveillance, or changes in reproductive decision making, and these changes will lead to improved health outcomes); and
- Establishing the diagnosis by genetic testing will end the clinical workup for other disorders.

The question addressed in this evidence review is: Does WES improve health outcomes when used for the diagnosis of patients with multiple unexplained congenital anomalies or a neurodevelopmental disorder?

The following PICOTS were used to select literature to inform this review.

### ***Patients***

The relevant population of interest is patients presenting with multiple unexplained congenital anomalies or a neurodevelopmental disorder that is suspected to have a genetic basis but are not explained by standard clinical workup.

### ***Intervention***

The relevant intervention of interest is WES.

### ***Comparators***

The relevant comparator of interest is standard clinical workup without WES.

### ***Outcomes***

The general outcomes of interest are the accuracy of NGS compared with Sanger sequencing, the sensitivity and specificity and positive and negative predictive value for the clinical condition, and improvement in health outcomes. Health outcomes include a reduction in morbidity due to appropriate treatment and surveillance, the end of the diagnostic odyssey, and effects on reproductive planning for parents and potentially the affected patient.

False-positive test results can lead to misdiagnosis and inappropriate clinical management. False-negative test results can lead to a lack of a genetic diagnosis and continuation of the diagnostic odyssey.

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### **Timing**

These tests are performed when standard clinical workup has failed to arrive at a diagnosis.

### **Setting**

These tests are offered commercially through various manufacturers.

### **Analytic Validity**

There are relatively few data specific to the analytic validity of WES. NGS techniques used for WES are expected to have high accuracy for mutation detection. However, NGS platforms differ regarding the depth of sequence coverage, methods for base calling and read alignment, and other factors. These factors contribute to potential variability across the platforms and procedures used by different clinical laboratories offering exome sequencing as a clinical service. The American College of Medical Genetics and Genomics has clinical laboratory standards for NGS, including WES. 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, and structural chromosome rearrangements due to the short sequence read lengths. WES may be less sensitive for the detection of copy number variants than high-resolution microarray testing. NGS also has poorer coverage for A/T-rich, G/C-rich, and pseudogene regions, as well as homopolymer stretches.

### **Clinical Validity**

A number of studies have reported on the use of WES in clinical practice (see Table 2). Typically, the populations included in these studies have suspected rare genetic disorders, although the specific populations vary.

Series have been reported with as many as 2000 patients. The largest reason for referral to a tertiary care center was an unexplained neurodevelopmental disorder. Many patients had been through standard clinical workup and testing without identification of a genetic variant to explain their condition. Diagnostic yield in these studies, defined as the proportion of tested patients with clinically relevant genomic abnormalities, ranged from 25% to as many as 48%. Because there is no reference standard for the diagnosis of patients who have exhausted alternative testing strategies, clinical confirmation may be the only method for determining false-positive and false-negative rates. No reports were identified of incorrect diagnoses, and how often they might occur is unclear.

When used as a first-line test in infants with multiple congenital abnormalities and dysmorphic features, diagnostic yield may be as high as 58%. Testing parent-child trios has been reported to increase diagnostic yield, to identify an inherited variant from an unaffected parent and be considered benign, or to identify a de novo variant not present in an unaffected parent. First-line trio testing for children with complex neurologic disorders was shown to increase the diagnostic yield (29%, plus a possible diagnostic finding in 27%) compared with a standard clinical pathway (7%) performed in parallel in the same patients.

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Policy # 00389

Original Effective Date: 11/20/2013

Current Effective Date: 12/20/2017

### Clinical Utility

Cohort studies following children from presentation to outcomes have not been reported. There are considerable challenges conducting studies of sufficient size given the underlying genetic heterogeneity, and including follow-up adequate to observe final health outcomes. Studies addressing clinical utility have reported mainly diagnostic yield and management changes. Thus, it is difficult to quantify lower or upper bounds for any potential improvement in the net health outcome owing in part to the heterogeneity of disorders, rarity, and outcome importance that may differ according to identified pathogenic variants. Actionable items following testing in the reviewed studies (see Table 2) included family planning, change in management, change or avoidance of additional testing, surveillance for associated morbidities, prognosis, and ending the diagnostic odyssey.

The evidence reviewed here reflects the accompanying uncertainty, but supports a perspective that identifying a pathogenic variant can (1) impact the search for a diagnosis, (2) inform follow-up that can benefit a child by reducing morbidity and rarely potential mortality, and (3) affect reproductive planning for parents and later potentially the affected child. When recurrence risk can be estimated for an identified variant (e.g., by including parent testing), future reproductive decisions can be affected. Early use of WES can reduce the time to diagnosis and reduce the financial and psychological burdens associated with prolonged investigation.

**Table 2. Diagnostic Yields of WES for Congenital Anomalies or a Neurodevelopmental Disorder**

Study (Year)	Patient Population	N	Design	Yield, n (%)	Additional Information
Yang et al (2013)	Suspected genetic disorder (80% neurologic)	250 (1% fetus; 50% <5 y; 38% 5-18 y; 11% adults)	Consecutive patients at single center	62 (25)	Identification of atypical phenotypes of known genetic diseases and blended phenotypes
Yang et al (2014)	Suspected genetic disorder (88% neurologic or developmental)	2000 (45% <5 y; 42% 5-18 y; 12% adults)	Consecutive patients at single center	504 (25)	Identification of novel variants. End of the diagnostic odyssey and change in management
Lee et al (2014)	Suspected rare Mendelian disorders (57% of children had developmental delay; 26% of adults had ataxia)	814 (49% <5 y; 15% 5-18 y; 36% adults)	Consecutive patients at single center	213 (26)	Trio (31% yield) vs proband only (22% yield)
Iglesias et al (2014)	Birth defects (24%); developmental delay (25%); seizures (32%)	115 (79% children)	Single-center tertiary clinic	37 (32)	Discontinuation of planned testing, changed medical management, and family planning
Soden et al (2014)	Children with unexplained neurodevelopmental disorders	119 (100 families)	Single-center database <sup>a</sup>	53 (45)	Change in clinical care or impression in 49% of families
Srivastava et al (2014)	Children with unexplained neurodevelopmental disorders	78	Pediatric neurogenetics clinic	32 (41)	Changed medical management, prognostication, and family planning
Farwell et al (2015)	Unexplained neurologic disorders (65% pediatric)	500	WES laboratory	152 (30)	Trio (37.5% yield) vs proband only (20.6%)

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Study (Year)	Patient Population	N	Design	Yield, n (%)	Additional Information
Nolan and Carlson (2016)	Children with unexplained neurodevelopmental disorders	50	Pediatric neurology clinic	41 (48)	yield); 31 (7.5% de novo) Changed medication, systemic investigation, and family planning
Allen et al (2016)	Patients with unexplained early-onset epileptic encephalopathy	50 (95% <1 y)	Single center	11 (22)	2 VUS for follow-up, 11 variants identified as de novo
Stark et al (2016)	Infants ( $\leq 2$ y) with suspected monogenic disorders with multiple congenital abnormalities and dysmorphic features	80	Prospective comparative study at a tertiary center	46 (58)	First-line WES increased yield by 44%, changed clinical management and family planning
Vissers et al (2017)	Children with complex neurologic disorders of suspected genetic origin	150	Prospective comparative study at a tertiary center	<ul style="list-style-type: none"> <li>• 44 (29) conclusive</li> <li>• 41 (27) possible</li> </ul>	First-line WES had 29% yield vs 7% yield for standard diagnostic workup <sup>b</sup>

VUS: variants of uncertain significance; WES: whole exome sequencing.

<sup>a</sup> Included both WES and whole genome sequencing.

<sup>b</sup> Standard diagnostic workup included an average of 23.3 physician-patient contacts, imaging studies, muscle biopsies or lumbar punctures, other laboratory tests, and an average of 5.4 sequential gene by gene tests.

### Section Summary: Whole Exome Sequencing in Patients With Multiple Congenital Anomalies or a Neurodevelopmental Disorder

The evidence on WES in patients who have multiple congenital anomalies or a developmental disorder with a suspected genetic etiology includes case series. These series have reported diagnostic yields of WES ranging from 22% to 58%, depending on the individual's age, phenotype, and previous workup. Comparative studies have reported an increase in diagnostic yield compared with standard testing strategies. Thus, for individuals who have a suspected genetic etiology but for whom the specific genetic alteration is unclear or unidentified by standard clinical workup, WES may return a likely pathogenic variant. A genetic diagnosis for these patients is reported to change management, including medication changes, discontinuation of or additional testing, ending the diagnostic odyssey, and family planning.

### WES IN PATIENTS WITH A SUSPECTED GENETIC DISORDER OTHER THAN MULTIPLE CONGENITAL ANOMALIES OR A NEURODEVELOPMENTAL DISORDER

#### Clinical Context and Test Purpose

Most of the literature on WES is on neurodevelopmental disorders in children; however, other potential indications for WES have been reported (see Table 3). These include limb-girdle muscular dystrophy, inherited retinal disease, and other disorders including mitochondrial, endocrine, and immunologic disorders. The yield for unexplained limb-girdle muscular dystrophy and retinal disease is high, but a limited number of patients have been studied to date.

The purpose of WES in patients who have a suspected genetic disorder other than multiple unexplained congenital anomalies or a neurodevelopmental disorder is to establish a molecular diagnosis. The criteria

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# Louisiana

## Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

Policy # 00389

Original Effective Date: 11/20/2013

Current Effective Date: 12/20/2017

under which diagnostic testing for a genetic or heritable disorder may be considered clinically useful are as above.

The question addressed in this evidence review is: Does WES improve health outcomes when used for the diagnosis of a suspected genetic condition?

The following PICOTS were used to select literature to inform this review.

### ***Patients***

The relevant population of interest is patients presenting with a disorder other than multiple unexplained congenital anomalies or a neurodevelopmental disorder that is suspected to have a genetic basis but is not explained by standard clinical workup.

### ***Intervention***

The relevant intervention of interest is WES.

### ***Comparators***

The relevant comparator of interest is standard clinical workup without WES.

### ***Outcomes***

The general outcomes of interest are the accuracy of NGS compared with Sanger sequencing, the sensitivity and specificity and positive and negative predictive value for the clinical condition, and clinical health outcomes. Health outcomes include a reduction in morbidity due to appropriate treatment and surveillance, the end of the diagnostic odyssey, and effects on reproductive planning for parents and potentially the affected patient.

### ***Timing***

The test is performed when standard clinical workup has failed to arrive at a diagnosis.

### ***Setting***

These tests are offered commercially through various manufacturers.

### ***Analytic Validity***

As described above for use of WES in patients with multiple congenital anomalies or a neurodevelopmental disorder.

### ***Clinical Validity***

Studies have assessed WES for a broad spectrum of disorders. The diagnostic yield in patient populations restricted to specific phenotypes ranges from 3% for colorectal cancer to 60% for unexplained limb-girdle muscular dystrophy. Some studies used a virtual gene panel that is restricted to genes that are associated with the phenotype, while others have examined the whole exome, either initially or sequentially. An advantage of WES over individual gene or gene panel testing is that the stored data allows reanalysis as

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## Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

Policy # 00389

Original Effective Date: 11/20/2013

Current Effective Date: 12/20/2017

new genes are linked to the patient phenotype. WES has also been reported to be beneficial in patients with atypical presentations.

**Table 3. Diagnostic Yields of WES for Conditions Other Than Multiple Congenital Anomalies or a Neurodevelopmental Disorder**

Study (Year)	Patient Population	N	Design	Yield, n (%)	Additional Actions
Neveling et al (2013)	Unexplained disorders: blindness, deafness, movement disorders, mitochondrial disorders, hereditary cancer	186	Outpatient genetic clinic; post hoc comparison with Sanger sequencing	3%-52%	WES increased yield vs Sanger sequencing. Highest yield for blindness and deafness
Ghaoui et al (2015)	Unexplained limb-girdle muscular dystrophy	60 families	Prospective study of patients identified from a specimen bank	27 (60)	Trio (60% yield) vs proband only (40% yield)
Valencia et al (2015)	Unexplained disorders: congenital anomalies (30%), neurologic (22%), mitochondrial (25%), endocrine (3%), immunodeficiencies (17%)	40 (<17 y)	Consecutive patients in a single center	12 (30)	Altered management including genetic counseling and ending diagnostic odyssey
Wortmann et al (2015)	Suspected mitochondrial disorder	109	Patients referred to a single center	42 (39)	57% yield in patients with high suspicion of mitochondrial disorder
Posey et al (2016)	Adults (overlap of 272 patients reported by Yang et al, 2014), includes neurodevelopmental and other phenotypes	486 (53% 18-30 y; 47% >30 y)	Review of lab findings in adults	85 (18)	Yield in patients 18-30 y (24%) vs those >30 y (10.4%)
Walsh et al (2017)	Peripheral neuropathy in patients ranging from 2-68 y	<ul style="list-style-type: none"> <li>• 23 children</li> <li>• 27 adults</li> </ul>	Research study at tertiary pediatric and adult centers	19 (38)	Initial targeted analysis with virtual gene panel, followed by WES
Miller et al (2017)	Craniosynostosis in patients who tested negative on targeted genetic testing	40	Research study of referred patients <sup>a</sup>	15 (38)	Altered management and reproductive decision making

WES: whole exome sequencing.

<sup>a</sup> Included both WES and whole genome sequencing.

### Clinical Utility

A genetic diagnosis for an unexplained disorder can alter management in several ways: such a diagnosis may lead to including genetic counseling and ending the diagnostic odyssey, and may affect reproductive decision making.

### Section Summary: WES in Patients with a Suspected Genetic Disorder Other Than Multiple Congenital Anomalies or a Neurodevelopmental Disorder

There are increasing reports of WES being used to identify a molecular basis for disorders other than multiple congenital anomalies or neurodevelopmental disorders. The diagnostic yields in these studies ranged from 3% for colorectal cancer to 60% for trio (parents and child) analysis of limb-girdle muscular dystrophy. One concern with WES is the possibility of incidental findings. Some studies report on the use of



# Louisiana

## Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

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a virtual gene panel with restricted analysis of disease-associated genes, and the authors noted that WES data allows reanalysis as new genes are linked to the patient phenotype. Overall, there are a limited number of patients that have been studied for any specific disorder, and study of WES in these disorders is at an early stage.

### **WHOLE GENOME SEQUENCING IN PATIENTS WITH A SUSPECTED GENETIC DISORDER**

The purpose of WGS in patients who have a suspected genetic disorder is to establish a molecular diagnosis from either the coding or noncoding regions of the genome. The criteria under which diagnostic testing for a genetic or heritable disorder may be considered clinically useful are as above.

The question addressed in this evidence review is: Does WGS improve health outcomes when used for the diagnosis of a suspected genetic disorder?

The following PICOTS were used to select literature to inform this review.

#### ***Patients***

The relevant population of interest is patients presenting with any of a variety of disorders and anomalies that are suspected to have a genetic basis but are not explained by standard clinical workup.

#### ***Intervention***

The relevant intervention of interest is WGS.

#### ***Comparators***

The relevant comparator of interest is standard clinical workup without WGS.

#### ***Outcomes***

As described above for use of WES in patients with multiple congenital anomalies or a neurodevelopmental disorder.

#### ***Timing***

As described above for use of WES in patients with multiple congenital anomalies or a neurodevelopmental disorder.

#### ***Setting***

As described above for use of WES in patients with multiple congenital anomalies or a neurodevelopmental disorder.

#### ***Analytic Validity***

WGS can detect structural variants and variants in regulatory regions. However, it is subject to many of the same considerations for potential variability in technical performance as WES. In 2014, Dewey et al reported the coverage and concordance of clinically relevant genetic variations provided by WGS technologies in 12 healthy adult volunteers. All subjects underwent WGS with the Illumina platform; 9

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Original Effective Date: 11/20/2013

Current Effective Date: 12/20/2017

subjects also underwent WGS by the Complete Genomics (Mountain View, CA) platform to evaluate the reproducibility of sequence data. Genome sequences were compared with several reference standards. Depending on the sequencing platform, a median of 10% (Illumina; range, 5%-34%) to 19% (Complete Genomics; range, 18%-21%) of genes associated with inherited disease and a median of 9% (Illumina; range, 2%-27%) to 17% (Complete Genomics; range, 17%-19%) of American College of Medical Genetics and Genomics-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 or deletion variants was moderate overall (median, 57%; range, 53%-59%) and in protein-coding regions of the genome (median, 66%; range, 64%-70%), but was substantially lower among genetic variants that were candidates for inherited disease risk (median, 33%; range, 10%-75%).

WGS may have improved coverage compared with WES, particularly in GC-rich regions, structural variants, and intronic variants.

### Clinical Validity

Studies have shown that WGS can detect more pathogenic variants than WES, due to an improvement in detecting copy number variants, insertions and deletions, intronic single-nucleotide variants, and exonic single-nucleotide variants in regions with poor coverage on WES. In some studies the genes examined were those that had previously been associated with the phenotype, while other studies were research-based and conducted more exploratory analysis (see Table 4). It has been noted that genomes that have been sequenced with WGS are available for future review when new variants associated with clinical diseases are discovered.

**Table 4. Diagnostic Yields With WGS**

Study (Year)	Patient Population	N	Design	Yield, n (%)	Additional Actions
Taylor et al (2015)	Broad spectrum of suspected genetic disorders	217	Multicenter series	46 (21)	34% yield in Mendelian disorders; 57% yield in trios
Ellingford et al (2016)	Unexplained inherited retinal disease	46	WGS in patients referred to a single center	24 (52)	Estimated 29% increase in yield vs NGS
Carss et al (2017)	Unexplained inherited retinal disease	605	NIHR-BioResource Rare Diseases Consortium	331 (55)	Compared with a detection rate of 50% with WES (n=117)
Lionel et al (2017)	Well-characterized but genetically heterogeneous cohort that had undergone targeted gene sequencing	103	Trio test for patients recruited from pediatric nongenetic subspecialists	42 (41)	Compared with a yield of 24% with standard diagnostic testing and a 25% increase in yield from WES

NGS: next-generation sequencing; NIHR: National Institute for Health Research; WGS: whole genome sequencing; WES: whole exome sequencing.

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# Louisiana

## Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

Policy # 00389

Original Effective Date: 11/20/2013

Current Effective Date: 12/20/2017

### Clinical Utility

The effect on health outcomes based on WGS results are the same as those with WES, with a possible change in surveillance, management and/or reproductive planning. A reduction in invasive testing and an end of the diagnostic odyssey are also considered to be significant health outcomes.

### Section Summary: Whole Exome Sequencing in Patients With a Suspected Genetic Disorder

WGS has increased coverage and diagnostic yield compared with WES, but the technology is limited by the amount of data generated and greater need for storage and analytic capability. Several authors have proposed that, as WGS becomes feasible on a larger scale, it may in the future become the standard first-tier diagnostic test.

### SUMMARY OF EVIDENCE

For individuals who have multiple unexplained congenital anomalies or a neurodevelopmental disorder who receive WES, the evidence includes large case series and within-subject comparisons. Relevant outcomes are test accuracy and validity, functional outcomes, changes in reproductive decision making, and resource utilization. Patients who have multiple congenital anomalies or a developmental disorder with a suspected genetic etiology, but whose specific genetic alteration is unclear or unidentified by standard clinical workup, may be left without a clinical diagnosis of their disorder, despite a lengthy diagnostic workup. For a substantial proportion of these patients, WES may return a likely pathogenic variant. Several large and smaller series have reported diagnostic yields of WES ranging from 25% to 60%, depending on the individual's age, phenotype, and previous workup. One comparative study found a 44% increase in yield compared with standard testing strategies. Many of the studies have also reported changes in patient management, including medication changes, discontinuation of or additional testing, ending the diagnostic odyssey, and family planning. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have a suspected genetic disorder other than multiple congenital anomalies or a neurodevelopmental disorder who receive WES, the evidence includes small case series and prospective research studies. Relevant outcomes are test accuracy and validity, functional outcomes, changes in reproductive decision making, and resource utilization. There are increasing reports of use of WES to identify a molecular basis for disorders other than multiple congenital anomalies or neurodevelopmental disorders. The diagnostic yields in these studies range from as low as 3% to 60%. One concern with WES is the possibility of incidental findings. Some studies have reported on the use of a virtual gene panel with restricted analysis of disease-associated genes, and WES data allows reanalysis as new genes are linked to the patient phenotype. Overall, there are a limited number of patients who have been studied for any specific disorder, and clinical use of WES for these disorders is at an early stage. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with a suspected genetic disorder who receive WGS, the evidence includes case series. Relevant outcomes are test accuracy and validity, functional outcomes, changes in reproductive decision making, and resource utilization. WGS has increased coverage and diagnostic yield compared with WES, but the technology is limited by the amount of data generated and greater need for storage and analytic

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# Louisiana

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Policy # 00389

Original Effective Date: 11/20/2013

Current Effective Date: 12/20/2017

capability. Several authors have proposed that as WGS becomes feasible on a larger scale, it may in the future become the standard first-tier diagnostic test. At present, there is limited data on the clinical use of WGS. The evidence is insufficient to determine the effects of the technology on health outcomes.

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# Louisiana

## Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

Policy # 00389

Original Effective Date: 11/20/2013

Current Effective Date: 12/20/2017

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### Policy History

Original Effective Date: 11/20/2013

Current Effective Date: 12/20/2017

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|------------|--|
| 11/07/2013 | Medical Policy Committee review  |
| 11/20/2013 | Medical Policy Implementation Committee approval. New policy.  |
| 12/04/2014 | Medical Policy Committee review  |
| 12/17/2014 | Medical Policy Implementation Committee approval. Title changed from "Whole Exome Sequencing" to "Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders." The policy investigational section was revised to clarify that the intent of the policy is limited to the diagnosis of genetic disorders. |
| 08/03/2015 | Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.  |
| 12/03/2015 | Medical Policy Committee review  |
| 12/16/2015 | Medical Policy Implementation Committee approval. No change to coverage eligibility.   |
| 12/01/2016 | Medical Policy Committee review  |
| 12/21/2016 | Medical Policy Implementation Committee approval. Added eligibility statement for WES with criteria and INV statement for WES and WGS in screening for genetic disorders.  |
| 01/01/2017 | Coding update: Removing ICD-9 Diagnosis Codes  |
| 08/01/2017 | Coding update  |
| 12/07/2017 | Medical Policy Committee review  |
| 12/20/2017 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged.  |

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# Louisiana

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Policy # 00389

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Current Effective Date: 12/20/2017

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Code Type	Code
CPT	81415, 81416, 81417, 81425, 81426, 81427, 81479 New code eff 8/1/17: 0012U
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

\*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
  - 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
  - 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
  - 3. Reference to federal regulations.

\*\*Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;

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# Louisiana

## Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

Policy # 00389

Original Effective Date: 11/20/2013

Current Effective Date: 12/20/2017

- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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