WHOLE EXOME AND GENOME SEQUENCING

Policy Number: 2015M0057A  Effective Date: June 1, 2015

INSTRUCTIONS:

“Medical Policy assists in administering UCare benefits when making coverage determinations for members under our health benefit plans. When deciding coverage, all reviewers must first identify enrollee eligibility, federal and state legislation or regulatory guidance regarding benefit mandates, and the member specific Evidence of Coverage (EOC) document must be referenced prior to using the medical policies. In the event of a conflict, the enrollee’s specific benefit document and federal and state legislation and regulatory guidance supersede this Medical Policy. In the absence of benefit mandates or regulatory guidance that govern the service, procedure or treatment, or when the member’s EOC document is silent or not specific, medical policies help to clarify which healthcare services may or may not be covered. This Medical Policy is provided for informational purposes and does not constitute medical advice. In addition to medical policies, UCare also uses tools developed by third parties, such as the InterQual Guidelines®, to assist us in administering health benefits. The InterQual Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice. Other Policies and Coverage Determination Guidelines may also apply. UCare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary and to provide benefits otherwise excluded by medical policies when necessitated by operational considerations.”
POLICY DESCRIPTION:

Genetic tests are laboratory studies of human deoxyribonucleic acid (DNA), chromosomes, genes or gene products to diagnose the presence of a genetic variation associated with a high risk of having or transmitting a specific inherited disorder.

This policy describes the use of:

- Whole Exome Sequencing (WES), a laboratory process utilized to determine the arrangement (sequence) of the subset of an individual’s entire genome that contains functionally important sequences of protein-coding DNA, at a single time. WES involves obtaining blood samples from the individual and/or family members for the identification of mutations in the genome without having to target a gene or chromosome region based upon an individual’s personal or family history.

- Whole genome sequencing (WGS) is a laboratory procedure which seeks to determine an individual's entire DNA sequence, specifying the order of every base pair within the genome at a single time. This process involves obtaining a DNA sample from an individual's hair, saliva, epithelial cells or bone marrow. WGS may also be referred to as full genome sequencing, complete genome sequencing or entire genome sequencing.

COVERAGE RATIONALE / CLINICAL CONSIDERATIONS:

- Whole Exome Sequencing test is considered EXPERIMENTAL AND/OR INVESTIGATIONAL and NOT MEDICALLY NECESSARY for all applications.

- Whole Genoma Sequencing test is considered EXPERIMENTAL AND/OR INVESTIGATIONAL and NOT MEDICALLY NECESSARY for all applications.

Published evidence of well-designed studies in peer-reviewed journals is insufficient to determine whether the use of whole exome and whole genome sequencing tests improve health outcomes.

Clinical Considerations:

Whole exome sequencing (WES) using next-generation sequencing has been recently introduced as a diagnostic clinical laboratory test. A potential major indication for use is molecular diagnosis of patients with a phenotype that is suspicious for a genetic disorder or for patients with known genetic disorders that have a large degree of genetic heterogeneity involving substantial gene complexity. Such patients may be left without a clinical diagnosis of their disorder despite a lengthy diagnostic workup involving a variety of
traditional molecular and other types of conventional diagnostic tests. For some of these patients, WES, after initial conventional testing has failed to make the diagnosis, may return a likely pathogenic variant.

However, at this time, there are many technical limitations to WES that prohibit its use in routine clinical care. The limited experience with WES on a population level leads to gaps in understanding and interpreting ancillary information and variants of uncertain significance. As a result, the risk/benefit ratio of WES testing is poorly defined. Therefore, the use of WES is considered investigational for all indications.

**BACKGROUND:**

The exome refers to the portion of the human genome that contains functionally important sequences of 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 1% of the genome. These 180,000 exons are arranged in about 22,000 genes. It is known that most of the errors that occur in DNA sequences that then lead to genetic disorders are located in the exons. Therefore, sequencing of the exome is thought to be an efficient method of analyzing a patient’s DNA to discover the genetic cause of diseases or disabilities.

**WHOLE EXOME SEQUENCING (WES)**

The WES test involves sequencing all of the protein-coding regions of an individual’s genes. While exons represent only 1% of the genome, they account for approximately 85% of disease-causing variants. Through identification of variants across the exome, WES avoids the need to run multiple single-gene tests, which require prior information about variants that may be causing a disease or condition. WES has been performed in a wide variety of disorders, including Mendelian (caused by variants in a single gene) and multifactorial (affected by variants in many genes as well as environmental factors) disorders to identify de novo variants (e.g., new genetic variants in the tested individual) or inherited variants. A majority of WES studies have been conducted for rare conditions with Mendelian inheritance patterns, whereby a single gene affects the condition and a variant is usually rare with a large effect. On the other hand, analysis of multifactorial disorders (whereby variants in many genes generally each have small effects) has been conducted in some neurological disorders, but is limited for other conditions. WES has primarily been used for 2 purposes—discovery and diagnosis. Discovery refers to identification of novel or previously identified variants that may have a protein-altering function on the disease being studied. WES has generally been used as a diagnostic tool in individual cases. Identification of protein-altering (and possibly deleterious) variants using WES may provide information on potential new avenues for diagnosis and treatment. Additionally, the WES includes mitochondrial genome sequencing. Mitochondria are structures within cells that convert the energy from food into a form that cells can use. Although most DNA is packaged in chromosomes within the nucleus, mitochondria also have a small amount of their own DNA. This genetic material is known as mitochondrial DNA or mtDNA. In humans, mitochondrial DNA represents a small fraction of the total DNA in cells. Many genetic conditions are related to changes in particular mitochondrial genes.
The principle of the test is to sequence nucleotide by nucleotide, 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 standards and references of what is normal in the population and the result is interpreted by board-certified laboratory directors and clinicians. By sequencing the exome of a patient and comparing it to normal reference sequence, variations in an individual's DNA sequence can be identified and related back to the individual's medical concerns in an effort to discover the cause of the medical disorder.

A number of clinical laboratories in the United States offer WES testing. Typical sample requirements are whole blood samples. In WES, exons across the entire genome are specifically targeted and selected, followed by sequencing of these selected exons.

Patient populations that may be considered for WES testing include:
• Patients with negative results from prior genetic testing.
• Absence of availability of genetic testing for a given condition.
• Individuals with no clear clinical diagnosis for their condition.
• Individuals with a family history of a condition for which the genetic basis is not understood.

WHOLE GENOME SEQUENCING (WGS)

The WGS test is a laboratory procedure which seeks to determine an individual's entire DNA sequence, specifying the order of every base pair within the genome at a single time. This process involves obtaining a DNA sample from an individual’s hair, saliva, epithelial cells or bone marrow. WGS research continues to determine what role it has in the clinical setting to accurately predict the development or to minimize a particular disease in asymptomatic individuals.

ROLE OF GENETIC COUNSELING

Cancer and noncancer disorders can be Mendelian or multifactorial. These can be inherited or acquired during a person’s lifetime, depending on the type of disorder. In addition, the mode of inheritance can be recessive, dominant, or the disorder may have multiple modes of inheritance. Genetic counseling may be beneficial to a patient planning WES, especially if a condition is present in family members. A counselor can provide guidance on the interpretation of WES results, informing the patient of risk of being affected, or the possibility of the results not providing a functional role of variants identified. In addition, patients may benefit from counseling about incidental findings and the implications of these types of results (ACMG Board of Directors, 2012; Green et al., 2013).

CLINICAL LABORATORIES IN THE UNITED STATES

A number of clinical laboratories in the United States offer WES testing for noncancer indications, but just 1 laboratory (Baylor College of Medicine Medical Genetics Laboratories) offers tests specific for cancer. Typical sample requirements include a tumor sample (blood or biopsy) and a sample of normal tissue from the patient for comparison. In WES, exons across the entire genome are specifically targeted and selected, followed by sequencing of these selected exons.

Patient populations that may be considered for WES testing include patients with a specific cancer for the purposes of treatment planning, and patients with a cancer of unknown etiology to aid in diagnosis and treatment.

Whole exome sequencing (WES) is offered by several laboratories, including, but not limited to, those listed below. All of the laboratories provided in the following table have current CLIA certifications.

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Laboratory Indication for Testing</th>
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<tbody>
<tr>
<td>Ambry Genetics, Aliso Viejo, CA</td>
<td>The patient’s clinical presentation is unclear/atypical disease and there are multiple genetic conditions in the differential diagnosis</td>
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<tr>
<td>GeneDx, Gaithersburg, MD</td>
<td>A patient with a diagnosis that suggests the involvement of one or more of many different genes, which would, even if available and sequencing individually, be prohibitively expensive</td>
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<tr>
<td>Institution</td>
<td>Description</td>
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<tr>
<td>Baylor College of Medicine, Houston, TX</td>
<td>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</td>
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<tr>
<td>University of California Los Angeles Health System, CA</td>
<td>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</td>
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<tr>
<td>EdgeBio, Gaithersburg, MD</td>
<td>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)”</td>
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<tr>
<td>Children’s Mercy Hospitals and Clinics, Kansas City, KS</td>
<td>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</td>
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<tr>
<td>Emory Genetics Laboratory, Atlanta, GA</td>
<td>Indicated when there is a suspicion of a genetic etiology contributing to the probands manifestations</td>
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**REGULATORY STATUS:**

1. **U.S. FOOD AND DRUG ADMINISTRATION (FDA):**

   No approvals for WES were identified on the FDA website on July 5, 2013 (search 510(k) Premarket Notification using keyword exome). Genetic tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA) of 1988. All of the laboratories that provide whole exome sequencing have current CLIA certifications, including Ambry Genetics Corp., ARUP Laboratories, Baylor College of Medicine Medical Genetics Laboratories, Emory Genetics Laboratory, and GeneDx Inc.

2. **CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS):**

   There is no CMS National Coverage Determination (NCD) or Local Coverage Determination (LCD) for whole exome/genome sequencing testing.

3. **MINNESOTA DEPARTMENT OF HUMAN SERVICES (DHS):**

   Minnesota DHS does not have a policy statement regarding whole exome or whole genome sequencing in its Provider Manual or other specific provider references.

   MHCP covers cytogenetic testing performed on an MHCP recipient. Documentation in the medical record must reflect the medical necessity for the testing. All claims submitted for payment of cytogenetic testing must contain the specific diagnosis related to the tests being performed. Use the most specific procedure code available with the genetic coding modifier and number of units. (Some cytogenetic tests require authorization.)

   - BRCA Genetic Mutation Testing for Breast & Ovarian Cancer Susceptibility
   - Single-Mutation Analysis
MHCP does not cover cytogenetic testing for:

- Legal, paternity, or informational purposes, unless it is medically necessary for the recipient to receive cytogenetic testing
- Family members who are not MHCP recipients
- Fetus testing

4. STATE MANDATES:

The National Newborn Screening and Genetics Resource Center (NNSGRC) provides information on
state mandates for both genetic and nongenetic newborn screening. The state of Minnesota does not have a newborn screening or genetic program for early identification and treatment of infants who are affected by certain heritable disorders and genetic disease.

CLINICAL EVIDENCE:

SUMMARY:
A number of studies have assessed the clinical evidence for WES in cancer; however, analytical validity studies of WES have been mostly conducted using noncancer samples. Furthermore, a majority of clinical validity studies have only assessed the genetic landscape of tumors when compared to normal samples. No definitive evidence for clinical utility is available, but studies have suggested the potential for clinical utility in some instances.

Analytical validity has been evaluated by 4 studies, with 3 studies in healthy individuals and 1 in cancer patients. Each study compared multiple platforms used for exome enrichment, including Agilent, NimbleGen, Illumina, and Raindance platforms. All studies showed high genotype concordance (> 98%) with previously detected variant information. In addition, 1 study showed that genotype sensitivity (defined as the probability that the technology being used is able to accurately detect a variant) varied between platforms, estimated at 64% to 85% for the Agilent platform and 72% to 91% for the NimbleGen platforms.

Clinical validity studies mainly addressed the genetic landscape of tumors compared with normal tissue. Breast cancer has been the most extensively studied, with 5 studies in unrelated individuals and 2 studies in families. In addition, colon and rectal cancer, prostate cancer, leukemia and lymphoma, endometrial and ovarian cancer, lung-related cancers, and head and neck squamous cell carcinoma (HNSCC) have each been evaluated by at least 2 studies. The different cancers showed varying variant rates, with the lowest estimated for chronic lymphocytic leukemia (CLL) (average of 0.72 per megabase [Mb] of DNA sequence analyzed) and highest for colon cancer (average of 47 per Mb of DNA sequence analyzed). In all cases, previously identified and novel genes were detected that exhibited high frequencies of variants with potential effect on the cancer being studied. For example, the following were identified in breast cancer: mitogen-activated protein kinase, E3 ubiquitin protein ligase (MAP3K1); tumor protein p53 (TP53); Bloom syndrome, RecQ helicase-like (BLM); and Fanconi anemia, complementation group C (FANCC). Splicing factor 3b, subunit 1, 155kDa (SF3B1) in CLL patients were identified. Furthermore, SF3B1 variants were associated with shorter time to disease progression and lower 10-year survival rate in CLL.

Evidence of clinical utility of WES in cancer is very limited. While none of the reviewed studies provided definitive evidence for clinical utility, they showed the potential for utility. In a breast cancer study, followup analyses showed enrichment of GATA-binding protein 3 (GATA3) variants (identified by WES) in samples showing a decline in proliferation-related Ki-67 antigen (commonly referred to simply as Ki-67) levels postsurgery, which is a marker for response to aromatase inhibitor treatment. A second study showed that when the number of variants exceeded a specified cutoff (referred to as “somatic hypermutation” in several studies), this was not only a risk factor for determining platinum-based
chemotherapy response in ovarian cancer treatment, but was also statistically significantly associated with longer overall survival and progression-free survival. A third study identified 5'-nucleotidase, cytosolic II (NT5C2) variants that were associated with acute myeloid leukemia (AML) relapse even when receiving treatment, suggesting NT5C2

APPLICABLE CODES:

The Current Procedural Terminology (CPT®) codes and HCPCS codes listed in this policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is a covered or non-covered health service. The inclusion of a code does not imply any right to reimbursement or guarantee claims payment. Other medical policies and coverage determination guidelines may apply.

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<td>Unlisted molecular pathology procedure</td>
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<tr>
<td>81599</td>
<td>Unlisted multianalyte assay with algorithmic analysis</td>
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may be a potential marker to identify individuals who may experience AML relapse despite chemotherapy treatment.

REFERENCES:

29. Gudgeon JM, McClain MR, Palomaki GE, Williams MS. Rapid ACCE: experience with a rapid and structured

40. Kono M, Sugiura K, Suganuma M, et al. Whole-exome sequencing identifies ADAM10 mutations as a cause of


**Clinical & Quality Management**

**MEDICAL POLICY**

<table>
<thead>
<tr>
<th>Date</th>
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<td>04/24/2014</td>
<td>Reviewed and approved by the Quality Improvement Advisory and Credentialing Committee (QIACC).</td>
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<td>05/01/2014</td>
<td>Published to UCare.org</td>
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<tr>
<td>07/01/2015</td>
<td>Policy Update:</td>
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<td>• Added applicable CPT codes 81415, 81416, 81417, 81425, 81426, 81427 and ICD-9/ICD-10 codes to the Coding Section.</td>
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<td>• No change to policy statements. References and rationale updated.</td>
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<td>• Policy identification number updated to 2015M0057A.</td>
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