Geisinger

Geisinger Health Plan Policies and Procedure Manual

Policy: MP280

Section: Medical Benefit Policy

Subject: Whole Exome and Whole Genome Sequencing

Applicable Lines of Business

Commercial	**X**	**CHIP**	**X**
Medicare	**X**	**ACA**	**X**
Medicaid	**X**		

I. Policy: Whole Exome and Whole Genome Sequencing

II. Purpose/Objective:

To provide a policy of coverage regarding whole exome and whole genome sequencing

III. Responsibility:

A. Medical Directors
B. Medical Management

IV. Required Definitions

1. Attachment – a supporting document that is developed and maintained by the policy writer or department requiring/authoring the policy.
2. Exhibit – a supporting document developed and maintained in a department other than the department requiring/authoring the policy.
3. Devised – the date the policy was implemented.
4. Revised – the date of every revision to the policy, including typographical and grammatical changes.
5. Reviewed – the date documenting the annual review if the policy has no revisions necessary.

V. Additional Definitions

Medical Necessity or Medically Necessary means Covered Services rendered by a Health Care Provider that the Plan determines are:

a. appropriate for the symptoms and diagnosis or treatment of the Member's condition, illness, disease or injury;
b. provided for the diagnosis, and the direct care and treatment of the Member's condition, illness disease or injury;
c. in accordance with current standards of good medical treatment practiced by the general medical community.
d. not primarily for the convenience of the Member, or the Member's Health Care Provider; and
e. the most appropriate source or level of service that can safely be provided to the Member. When applied to hospitalization, this further means that the Member requires acute care as an inpatient due to the nature of the services rendered or the Member's condition, and the Member cannot receive safe or adequate care as an outpatient.

Medicaid Business Segment

Medically Necessary — A service, item, procedure, or level of care that is necessary for the proper treatment or management of an illness, injury, or disability is one that:

- Will, or is reasonably expected to, prevent the onset of an illness, condition, injury or disability.
- Will, or is reasonably expected to, reduce or ameliorate the physical, mental or developmental effects of an

illness, condition, injury or disability.
- Will assist the Member to achieve or maintain maximum functional capacity in performing daily activities, taking into account both the functional capacity of the Member and those functional capacities that are appropriate for Members of the same age

DESCRIPTION:

Whole exome sequencing is a strategy to selectively sequence the coding regions of the genome. Exons are short, functionally important sequences of DNA which represent the coding regions of genes. In the human genome there are about 180,000 exons which represents about 1% of the human genome. The goal of this approach is to focus on the 1% of the genome that corresponds to functional variation responsible for both Mendelian and common diseases, rather than examining DNA sequence from the whole genome, the majority of which has not yet been linked to clinically relevant information.

Whole genome sequencing is the process of determining the entirety, or nearly the entirety, of the DNA sequence of an organism's genome. This entails sequencing all of an organism's chromosomal DNA as well as DNA contained in the mitochondria.

Rapid whole genome testing rWGS precludes the need for multiple tests (eg: chromosomal microarray, whole exome, triplet repeat disorder studies) that evaluate for different types of genetic diseases. This eliminates the need for prioritizing certain studies and formation of a complex differential diagnosis. By identifying an underlying genetic etiology of presentations at birth, rWGS can enable individual tailoring of management, including prognostic determination and screening for complications. In addition, Improvements in outcome of critically ill infants through rapid genomic sequencing have been well documented.

INDICATIONS: <u>REQUIRES PRIOR AUTHORIZATION by a Plan Medical Director or Designee</u>

Whole exome sequencing will be considered for coverage when **all of** the following criteria are met:

1. Test is ordered by one of the following provider types:
   - Medical Geneticist
   - Genetics Nurse Practitioner
   - Licensed and/or Certified Genetic Counselor with a provider involved in patient evaluation or follow up of results (examples: neurologist, neonatologist, psychiatrist)
   - Neurologist in collaboration with a medical geneticist or certified genetic counselor
   - Developmental Pediatrician
   - Psychiatrist in collaboration with a medical geneticist or certified genetic counselor

   and

2. The test would confirm or establish a diagnosis that may lead to changes in medical management in any of the following ways:
   Guide specific clinical management, decision-making, preventive surveillance, or outcomes specified by the ordering provider
   Apply specific treatments, or withhold of contraindicated treatments,
   Surveillance for later-onset comorbidities,
   Initiation of palliative care or withdrawal of care versus continued treatment,

   and

3. The member or parents/legal guardians have been appropriately counseled about the testing's benefits and limitations by a qualified professional who is not employed by or contracted with a commercial genetic testing laboratory.

   and

4. The member is:
   a. A **child** (defined as under the age of 21) who exhibits at least one of the following:
      - Autism spectrum disorder;
      - non-syndromic developmental delay, cerebral palsy, loss of developmental milestones, intellectual disability, or a cognitive disability
      - One or more structural congenital anomalies or malformation(s),
      - Two or more dysmorphic features not specific to a well delineated genetic syndrome
      - Suspected Mendelian condition in which multiple genes could potentially account for the phenotype
      - Complex epilepsy, or epileptic encephalopathy

Or

b. An **adult** who exhibits at least one or more of the following:
   - Any one of the following neurological disorders:
     - Intellectual disability or non-syndromic developmental delay with onset < 18y, or
     - Complex epilepsy or epileptic encephalopathy with onset < 18y
     - Progressive neurodegenerative disorder, or
     - Neuropsychiatric disorder,

   - Clinical presentation is strongly suggestive of a genetic etiology due to involvement of two or more organ systems AND the phenotype warrants evaluation of multiple genes, where:
     - WES/WGS is more practical than ordering separate single gene tests or two panels based on the differential diagnosis. For example, the patient's phenotype is suggestive of two or more syndromes identifiable through two separate panels
     - WES/WGS may preclude the need for multiple invasive procedures in the absence of this testing (eg avoid muscle biopsy)
   - The member's family history is suggestive of two or more syndromes where two diagnostic or predictive panels would be ordered for the member. For example, the patient's paternal family warrants panel testing for HBOC evaluation whereas the maternal family warrants panel testing for cardiomyopathy.

c. A **fetus** when all of the following criteria are met:
   - Testing is performed on direct amniotic fluid or amniotic fluid/chorionic villi, cultured cells from amniotic fluid/chorionic villi or DNA extracted from fetal blood or tissue AND
   - Standard diagnostic testing by chromosomal microarray or karyotype is complete and uninformative AND
   - Two or more structural anomalies, or
   - One structural fetal anomaly with family history of disease suggesting shared etiology

WES Trio testing:

Testing is considered medically necessary for exome sequencing of an affected child's biological mother and/or father if the criteria is met and ANY of the following clinical situations:

- The index Individual's medical history and physical exam strongly suggest that there is an underlying genetic etiology; or
- Identification of a gene variant or mutation in an individual with a previously undiagnosed genetic syndrome; or
- Reoccurrence risk assessment

Whole Exome Sequencing Re-Analysis

Requests for the re-analysis of a previously approved whole exome sequence will be considered to be medically necessary when one of the following criteria are met:

- A minimum of 12 months has elapsed from the date of original analysis; and
- The re-analysis is being done through the original sequencing lab; and
  - Additional symptoms or clinical signs have broadened the phenotype assessed during the original exome evaluation; or
  - The birth and/or the diagnosis of a similarly affected first-degree relative has added to the pedigree analysis
  - Studies have identified new genes applicable to the disease phenotype.
  - Rapid, proband-only testing was performed, and relatives are now available for duo or trio analysis.

Whole Genome Sequencing (WGS) - <u>REQUIRES PRIOR AUTHORIZATION BY A PLAN MEDICAL DIRECTOR OR DESIGNEE</u>

Whole genome has limited clinical utility at this time and is not recommended as a first line test. Whole genome sequencing may be a more cost-effective approach to diagnostic genetic testing when ordered in place of both chromosomal microarray AND whole exome sequencing. If either test has been ordered, consideration of requests for WGS will be done on a "per-case" basis.

Whole genome may be considered when ALL of the following criteria have been met:

- WES has not been performed, AND
- Single gene testing and/or targeted panel testing has been completed and is uninformative, AND
- Points 1 through 4 above are satisfied

Rapid Whole Exome Sequencing (rWES) and Rapid Whole Genome Sequencing (rWGS

Rapid whole exome sequencing (rWES) or rapid whole genome sequencing (rWGS), are considered medically necessary for the evaluation of

- Any critically ill infant in neonatal or pediatric intensive care; and
- The clinical presentation cannot otherwise be attributed to a non-genetic etiology; and one or more of the following:
    - The child exhibits one or more congenital anomalies, malformations, or dysmorphic features; or
    - The child exhibits clinical features suggestive of a genetic disease or complex metabolic phenotype or
    - The child exhibits an abnormal laboratory test suggestive of a genetic disease or complex metabolic phenotype

Recommend duo or trio testing whenever possible. Proband only testing is permissible so as not to delay timeline for result.

EXCLUSIONS:
The Plan does NOT provide coverage for the use of whole exome sequencing for indications other than those listed above because it is considered experimental, investigational or unproven.

There is currently insufficient evidence in the peer-reviewed published medical literature to establish the effectiveness of WES/WGS on health outcomes when compared to established tests or technologies for the following applications:

Whole exome or whole genome sequencing in the general population is considered unproven and not medically necessary, and therefore **NOT COVERED.**

Testing using whole exome or whole genome sequencing is considered unproven and not medically necessary, and therefore **NOT COVERED** for ANY of the following indications:

- Any testing using cell-free DNA
- Preimplantation testing of an embryo
- Carrier screening
- Diagnosis or prognosis of cancer

Testing of a fetus using whole exome or whole genome sequencing is considered unproven and not medically necessary, and therefore **NOT COVERED** for ANY of the following indications:

- healthy pregnancy
- isolated ultrasound soft marker(s), (eg. echogenic bowel, intracardiac echogenic focus, choroid plexus cysts)
- isolated neural tube defect, or increased nuchal translucency
- indications other than fetal structural anomalies

The Plan does **NOT** provide coverage for the use of WES/WGS for diagnosis or prognosis of cancer because it is considered experimental, investigational or unproven. There is currently insufficient evidence in the peer-reviewed published medical literature to establish the effectiveness of WES/WGS on health outcomes when compared to established molecular profiling tests or technologies.

Rapid whole exome sequencing (rWES) or rapid whole genome sequencing (rWGS) are not covered in cases of isolated prematurity, identified infectious etiology, health issues related to known maternal condition or exposure (eg: illicit drugs, viral, diabetes, etc), or a confirmed genetic diagnosis has already been established that explains all present diagnoses.

MEDICARE BUSINESS SEGMENT:
Per Decision Memo CAG-00450R, next generation sequencing is covered only for the diagnosis of germline (inherited) breast and ovarian cancer. Generally, exome sequencing is not covered for this indication.

MEDICAID Business Segment:
Requests for WES requires a Program Exception for the Medicaid Business segment.

Any requests for services, that do not meet criteria set in the PARP, may be evaluated on a case by case basis.

Note: A complete description of the process by which a given technology or service is evaluated and determined to be experimental, investigational or unproven is outlined in MP 15 - Experimental Investigational or Unproven Services or Treatment.

CODING ASSOCIATED WITH:

The following codes are included below for informational purposes and may not be all inclusive. Inclusion of a procedure or device code(s) does not constitute or imply coverage nor does it imply or guarantee provider reimbursement. Coverage is determined by the member specific benefit plan document and any applicable laws regarding coverage of specific services. Please note that per Medicare coverage rules, only specific CPT/HCPCS Codes may be covered for the Medicare Business Segment. Please consult the CMS website at www.cms.gov ***or the local Medicare Administrative Carrier (MAC) for more information on Medicare coverage and coding requirements.***

81349 Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities, interrogation of genomic regions for copy number and loss of heterozygosity variants, low-pass sequencing analysis
81415 Exome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis
81416 Exome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator exome (eg, parents, siblings)
81417 Exome (eg, unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained exome sequence (eg, updated knowledge or unrelated condition/syndrome)
81425 Genome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis
81426 Genome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator genome (e.g., parents, siblings)
81427 Genome (e.g., unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained genome sequence (e.g., updated knowledge or unrelated condition/syndrome)
0036U Exome (ie, somatic mutations), paired formalin-fixed paraffin-embedded tumor tissue and normal specimen, sequence analyses [EXaCT-1 Whole Exome Testing]
0260U Rare diseases (constitutional/heritable disorders), identification of copy number variations, inversions, insertions, translocations, and other structural variants by optical genome mapping (Augusta Optical Genome Mapping)
0264U Rare diseases (constitutional/heritable disorders), identification of copy number variations, inversions, insertions, translocations, and other structural variants by optical genome mapping (Praxis Optical Genome Mapping)
0265U Rare constitutional and other heritable disorders, whole genome and mitochondrial DNA sequence analysis, blood, frozen and formalin-fixed paraffin-embedded (FFPE) tissue, saliva, buccal swabs or cell lines, identification of single nucleotide and copy number variants (Praxis Whole Genome Sequencing)
0266U Unexplained constitutional or other heritable disorders or syndromes, tissue-specific gene expression by whole-transcriptome and next-generation sequencing, blood, formalin-fixed paraffin-embedded (FFPE) tissue or fresh frozen tissue, reported as presence or absence of splicing or expression changes (Praxis Transcriptome)
0267U Rare constitutional and other heritable disorders, identification of copy number variations, inversions, insertions, translocations, and other structural variants by optical genome mapping and whole genome sequencing (Praxis Combined Whole Genome Sequencing and Optical Genome Mapping)
0297U Oncology (pan tumor), whole genome sequencing of paired malignant and normal DNA specimens, fresh or formalinfixed paraffin-embedded (FFPE) tissue, blood or bone marrow, comparative sequence analyses and variant identification
0298U Oncology (pan tumor), whole transcriptome sequencing of paired malignant and normal RNA specimens, fresh or formalin-fixed paraffin-embedded (FFPE) tissue, blood or bone marrow, comparative sequence analyses and expression level and chimeric transcript identification
0299U Oncology (pan tumor), whole genome optical genome mapping of paired malignant and normal DNA specimens, fresh frozen tissue, blood, or bone marrow, comparative structural variant identification
0300U Oncology (pan tumor), whole genome sequencing and optical genome mapping of paired malignant and normal DNA specimens, fresh tissue, blood, or bone marrow, comparative sequence analyses and variant identification
0094U Genome (e.g., unexplained constitutional or heritable disorder or syndrome), rapid sequence analysis

LINE OF BUSINESS:

Eligibility and contract specific benefits, limitations and/or exclusions will apply. Coverage statements found in the line of business specific benefit document will supersede this policy. For Medicare, applicable LCD's and NCD's will supercede this policy. For PA Medicaid Business segment, this policy applies as written.

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This policy will be revised as necessary and reviewed no less than annually.

Devised: 1/14

Revised: 1/16 (added indications), 2/18 (added indication); 11/18 (expand indications); 12/19 (add reanalysis); 12/20 (add trio testing criteria, expand reanalysis); 6/21 (revise title, add information and exclusions); 4/22 (clarify MA Program exception requirement); 4/23 (revise indications, exclusions); 9/23 (add rWES and rWGS criteria)

Reviewed: 2/15**,** 2/17