

**Policy: MP280**

**Section: Medical Benefit Policy**

**Subject: Exome and Genome Sequencing**

**Applicable line of business:**

<b>Commercial</b>	<b>x</b>	<b>Medicaid</b>	<b>x</b>
<b>Medicare</b>	<b>x</b>	<b>ACA</b>	<b>x</b>
<b>CHIP</b>	<b>x</b>		

**I. Policy:** Exome and Genome Sequencing

**II. Purpose/Objective:**

To provide a policy of coverage regarding exome and 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.

**Commercial**

Geisinger Health Plan may refer collectively to health care coverage sponsors Geisinger Health Plan, Geisinger Quality Options, Inc., and Geisinger Indemnity Insurance Company, unless otherwise noted. Geisinger Health Plan is part of Geisinger, an integrated health care delivery and coverage organization.

**Medicare**

Geisinger Gold Medicare Advantage HMO, PPO, and HMO D-SNP plans are offered by Geisinger Health Plan/Geisinger Indemnity Insurance Company, health plans with a Medicare contract. Continued enrollment in Geisinger Gold depends on contract renewal. Geisinger Health Plan/Geisinger Indemnity Insurance Company are part of Geisinger, an integrated health care delivery and coverage organization.

**CHIP**

Geisinger Health Plan Kids (GHP Kids) is a Children's Health Insurance Program (CHIP) offered by Geisinger Health Plan in conjunction with the Pennsylvania Department of Human Services (DHS). Geisinger Health Plan is part of Geisinger, an integrated health care delivery and coverage organization.

**Medicaid**

Geisinger Health Plan Family (GHP Family) is a Medical Assistance (Medicaid) insurance program offered by Geisinger Health Plan in conjunction with the Pennsylvania Department of Human Services (DHS). Geisinger Health Plan is part of Geisinger, an integrated health care delivery and coverage organization.

**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:**

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.

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. Genome has the potential to detect deep intronic, non-coding, and structural variants not assayed with exome sequencing. Repeat expansion disorders are also detectable through genome with high sensitivity, but this has not been formally validated. Genome sequencing (GS) has emerging clinical utility at this time and is offered at few clinical laboratories.

Rapid whole-genome testing rGS 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, rGS 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.

Genomics societies are moving away from the terminology “whole exome” and “whole genome,” in favor of calling these tests exome sequencing (ES) and genome sequencing (GS).

### **INDICATIONS: REQUIRES PRIOR AUTHORIZATION by a Plan Medical Director or Designee**

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
  - Developmental Pediatrician
  - 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, cardiologist)

**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; or
    - non-syndromic developmental delay, cerebral palsy, loss of developmental milestones, intellectual disability, or a cognitive disability; or
    - One or more structural congenital anomalies or malformation(s); or
    - Two or more dysmorphic features not specific to a well delineated genetic syndrome; or
    - Suspected Mendelian condition in which multiple genes could potentially account for the phenotype; or
    - Complex Unexplained epilepsy, or epileptic encephalopathy where an infectious etiology has been ruled out; or
    - Primary hypotonia in a neonate

**Or**

- b. An **adult** who exhibits at least one of the following:
  - Any one of the following neurological disorders:
    - Intellectual disability or non-syndromic developmental delay with onset < 18y, or
    - Unexplained epilepsy or epileptic encephalopathy with onset < 18y , where an infectious etiology has been ruled out
    - 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
  - One or more structural anomalies, or
  - Increased nuchal thickness or thickened nuchal fold
- d. A member is eligible for a repeated (update) exome or genome test in the following scenarios:
  - The above clinical criteria have been satisfied for medical necessity, and
  - The first exome was non-diagnostic, and
  - The first exome test was performed prior to 2017 OR substantial advances to the test methodology have been incorporated by the performing laboratory since the original analysis

**Parental Testing as part of ES:**

Inclusion of one or more parental, or biologic relative samples, for duo or trio testing is considered medically necessary for exome sequencing of an affected child's or second degree biological relatives if the criteria is met and ANY of the following clinical situations:

- The index member'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

### **Exome Sequencing (ES) Re-Analysis**

Requests for the re-analysis of a previously approved 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 altered the phenotype assessed during the original 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.

There is a maximum limit of 5 reanalysis given advances in technology that may warrant update testing.

### **Genome Sequencing (GS) - REQUIRES PRIOR AUTHORIZATION BY A PLAN MEDICAL DIRECTOR OR DESIGNEE**

Requests for coverage of GS will be evaluated on a case-by-case basis given the emerging utility.

Whole-Genome sequencing may be considered when the following criteria have been met:

- Exome sequencing with at least one reanalysis has been performed >5 years ago AND was non-diagnostic; or
- ES has not yet been performed, AND
- Single gene testing and/or targeted panel testing has been completed and is uninformative, AND
- Clinical criteria points 1 through 4 above are satisfied

### **Rapid Exome Sequencing (rES) and Rapid Genome Sequencing (rGS)**

Rapid exome sequencing (rES) or rapid genome sequencing (rGS), 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 or neurologic 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 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 ES/GS on health outcomes when compared to established tests or technologies for the following applications:

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

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

- healthy pregnancy
- isolated ultrasound soft marker(s), (eg. echogenic bowel, intracardiac echogenic focus, choroid plexus cysts)
- indications other than fetal structural anomalies

The Plan does **NOT** provide coverage for the use of ES/GS 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 ES/GS on health outcomes when compared to established molecular profiling tests or technologies.

Rapid-exome sequencing (rES) or rapid genome sequencing (rGS) 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 ES and GS 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](http://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 formalin-fixed 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
- 0425U Genome (eg, unexplained constitutional or heritable disorder or syndrome), rapid sequence analysis, each comparator genome (eg, parents, siblings)
- 0426U Genome (eg, unexplained constitutional or heritable disorder or syndrome), ultra-rapid sequence analysis
- 0094U Genome (e.g., unexplained constitutional or heritable disorder or syndrome), rapid sequence analysis
- 0507U Oncology (ovarian), DNA, whole-genome sequencing with 5-hydroxymethylcytosine (5hmC) enrichment, using whole blood or plasma, algorithm reported as cancer detected or not detected
- Current Procedural Terminology (CPT®) © American Medical Association: Chicago, IL

#### 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); 9/24 (revise criteria)

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

**CMS UM Oversight Committee Approval:** 12/23; 11/8/24

Geisinger Health Plan may refer collectively to health care coverage sponsors Geisinger Health Plan, Geisinger Quality Options, Inc., and Geisinger Indemnity Insurance Company, unless otherwise noted. Geisinger Health Plan is part of Geisinger, an integrated health care delivery and coverage organization.

Coverage for experimental or investigational treatments, services and procedures is specifically excluded under the member's certificate with Geisinger Health Plan. Unproven services outside of an approved clinical trial are also specifically excluded under the member's certificate with Geisinger Health Plan. This policy does not expand coverage to services or items specifically excluded from coverage in the member's certificate with Geisinger Health Plan. Additional information can be found in MP015 Experimental, Investigational or Unproven Services.

Prior authorization and/or pre-certification requirements for services or items may apply. Pre-certification lists may be found in the member's contract specific benefit document. Prior authorization requirements can be found at <https://www.geisinger.org/health-plan/providers/ghp-clinical-policies>

Please be advised that the use of the logos, service marks or names of Geisinger Health Plan, Geisinger Quality Options, Inc. and Geisinger Indemnity Insurance Company on a marketing, press releases or any communication piece regarding the contents of this medical policy is strictly prohibited without the prior written consent of Geisinger Health Plan. Additionally, the above medical policy does not confer any endorsement by Geisinger Health Plan, Geisinger Quality Options, Inc. and Geisinger Indemnity Insurance Company regarding the medical service, medical device or medical lab test described under this medical policy.