Medical Policy

Genetic Testing Guidelines and Pharmacogenetics

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Product Applicability

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Notes:
+ Disclaimer and audit information is located at the end of this document.
◊ The guidelines included in this Plan policy are applicable to members enrolled in Senior Care Options only if there are no criteria established for the specified service in a Centers for Medicare & Medicaid Services (CMS) national coverage determination (NCD) or local coverage determination (LCD) on the date of the prior authorization request. Review the member’s product-specific benefit documents at www.SeniorsGetMore.org to determine coverage guidelines for Senior Care Options.

Policy Summary

The Plan considers genetic testing to be medically necessary for the diagnosis of genetic disease in children and adults, for the determination of future risk of a suspected disease, for the prediction of drug responses, and/or for the detection of risks of specific diseases to future children when medical criteria are met. **Plan prior authorization is required for all molecular and chromosomal genetic testing, except for prenatal genetic screening tests for a member with one of the pregnancy diagnosis codes specified in the Applicable Coding section of this policy when Plan criteria are met.**

Biochemical genetic tests used to study the amount or activity level of proteins to indicate changes to
the DNA require prior authorization only when the test is included in the Applicable Coding section of a Plan genetic testing medical policy.

The Plan supports the National Comprehensive Cancer Network (NCCN) guidelines for genetic counseling for all genetic tests conducted with Plan members; NCCN recommends that adequate pre-test and post-test genetic counseling be provided by a health care professional with expertise in genetics. Genetic counseling provided to a Plan member (and/or guardian if the member is under the age of 18) should be documented in the member’s medical record and conducted by an appropriately trained practitioner with expertise and experience in genetics, including a provider acting within the scope of the practitioner’s license and practice, clinical geneticist, or genetic counselor.

The Plan complies with coverage guidelines for all applicable state-mandated benefits and federally-mandated benefits that are medically necessary for the member’s condition. It will be determined during the prior authorization process if the genetic test is considered medically necessary or experimental and investigational for the requested indication. See the Plan’s medical policy, *Medically Necessary* (policy number OCA 3.14), for the product-specific definitions of medically necessary treatment and the Plan’s *Experimental and Investigational Treatment* medical policy (policy number OCA 3.12), for the product-specific definitions of experimental or investigational treatment. Review the following Plan policies for additional prior authorization guidelines for genetic testing and other related services available at www.bmchp.org for BMC HealthNet Plan members (including Senior Care Options members) and www.wellsense.org for Well Sense Health Plan members:

1. **Chromosomal Microarray Analysis for Unexplained Intellectual Disabilities and/or Multiple Congenital Anomalies**, policy number OCA 3.573

2. **Drug Screening/Testing for Drugs of Abuse and/or Controlled Substances**, policy number OCA 3.98 (for guidelines related to specimen validity testing using DNA authentication in conjunction with drug testing for BMC HealthNet Plan members)

3. **Gene Expression Profiling of Tumor Tissue to Predict Cancer Recurrence and Risk Stratification (Including Oncotype DX™ and Other Tests)**, policy number OCA 3.572

4. **Genetic Testing for Familial Malignant Melanoma**, policy number OCA 3.78

5. **Genetic Testing for Fragile X-Associated Disorders**, policy number OCA 3.571

6. **Genetic Testing for Hereditary Breast and Ovarian Cancer Syndrome**, policy number OCA 3.57

7. **Genetic Testing for Hereditary Colorectal Cancer**, policy number OCA 3.64

8. **Genetic Testing for Hereditary Thrombophilia**, policy number OCA 3.728

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9. **Preimplantation Genetic Testing (Preimplantation Genetic Diagnosis and Pregenetic Screening),** policy number OCA 3.726

**Description of Item or Service**

**Genetic Testing:** Tests that identify changes in chromosomes, genes, and/or proteins to provide information about an individual’s genetic predisposition to certain inherited conditions, diagnosis, carrier status, identification or relationships, and/or expected interaction with therapeutic drugs. Methods of testing include **molecular genetic tests** (or gene tests) to study single genes or short lengths of DNA to identify variations or mutations that lead to a genetic disorder, **chromosomal genetic tests** to analyze whole chromosomes or long lengths of DNA to see if there are large genetic changes that cause a genetic condition, and/or **biochemical genetic tests** to study the amount or activity level of proteins which may indicate changes to the DNA that result in a genetic disorder. Types of genetic testing may include:

1. **Carrier:** Genetic testing that identifies the presence of a carrier state. This type of test is offered to individuals who have a family history of a genetic disorder and to individuals in certain ethnic groups which have an increased risk of specific genetic conditions. Testing both parents provides information about a couple’s risk of having a child with a genetic condition.

2. **Diagnostic:** Genetic testing that confirms or rules out the presence of a specific genetic chromosomal abnormality. Diagnostic testing can be performed before birth or at any time during a person’s life, but diagnostic testing is not available for all genes or for all genetic conditions. This type of test commonly detects a specific gene alteration but is often not able to determine disease severity or age of onset. Diagnostic test results can influence medical management.

3. **Forensic:** Genetic testing that uses DNA sequences to identify an individual for legal purposes. This type of testing can identify crime or catastrophe victims, rule out or implicate a crime suspect, and/or establish biological relationships between people (e.g., paternity). Forensic genetic testing may also include specimen validity testing using DNA authentication in conjunction with drug testing.

4. **Newborn Screening:** According to the American Academy of Pediatrics in 2009, the purpose of newborn screening for genetic disorders is to limit the morbidity and mortality attributable to selected inherited diseases. Testing is normally done early infancy to detect conditions for which early intervention can avoid serious health issues or even death.

5. **Pharmacogenetics/Pharmacogenomics:** Genetic testing to evaluate the interaction between genetics and therapeutic drugs, and classify subtle variations in an individual’s genetic makeup to determine whether a drug is suitable for a particular patient, and if so, what would be the safest and most effective dose. Pharmacogenomics refers to the general study of the many different genes that determine drug behavior, evaluating genetic differences within a

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population that explain certain observed responses to a drug susceptibility to a health problem. Pharmacogenetics refers to the study of inherited differences (variation) in drug metabolism and response, evaluating individual genetic factors that influence how a drug works and analyzing unexpected drug responses to determine a genetic case. The distinction between the two terms, pharmacogenetics and pharmacogenomics, has become somewhat arbitrary in the scientific literature, and they have been used interchangeably.

6. **Predictive:** Genetic testing to determine whether an individual has an increased risk for a particular disease by detecting genetic mutations associated with disorders that have not yet manifested or produced symptoms. Results from this type of test are usually expressed in terms of probability and are therefore less definitive since disease susceptibility may also be influenced by other genetic and non-genetic (e.g. environmental, lifestyle) factors. This type of testing can help individuals who have a family member with a genetic disorder, but have no features of the disorder at the time of testing. Predictive testing results can provide information about an individual’s risk of developing a specific disorder and help with making decisions about medical care.

7. **Prenatal:** Genetic testing that detects changes in fetal genes or chromosomes. This type of testing is done during pregnancy when a fetus has an increased risk for a genetic or chromosomal disorder.

8. **Whole Genome Sequencing and Whole Exome Sequencing:** Genetic testing that examines the entire genome or exome to discover genetic alterations that may be the cause of disease. Currently, this type of test may be used in complex diagnostic cases but is considered experimental and investigational by the Plan (as specified in the Limitations section of this policy). Whole genome sequencing and whole exome sequencing are being explored for use in asymptomatic individuals to predict future disease.

**Medical Policy Statement**

Plan prior authorization is required for ALL molecular and chromosomal genetic testing, except for prenatal genetic screening tests for a member with one of the pregnancy diagnosis codes specified in the Applicable Coding section of this policy when Plan criteria are met. **Biochemical genetic tests** used to study the amount or activity level of proteins to indicate changes to the DNA require prior authorization ONLY when the test is included in the Applicable Coding section of a Plan genetic testing medical policy. See section A below for criteria for genetic testing that requires Plan prior authorization. Review section B below for criteria for genetic testing that does not require Plan authorization. The Summary section of this policy includes a listing of additional Plan medical policies related to genetic testing.
A. **Prior authorization is required** when the member is not pregnant and the following applicable criteria must be met, as specified below in items 1 through 3:

1. **General Genetic Testing Guidelines for ALL Testing:**

   The criteria listed below in items a through e must be met for ALL genetic testing. The Plan considers genetic testing medically necessary when ALL of the following applicable criteria are met and documented in the member’s medical record, as specified below in items a through e:

   a. The test is to be used for the diagnosis or determination of risk for a suspected disease for a member who meets ONE (1) of the following criteria, as specified below in item (1) or item (2):

      (1) Symptomatic (e.g., exhibiting signs and symptoms of a disease), known as diagnostic testing; OR

      (2) Pre-symptomatic, but at an increased risk of disease, as determined by current scientific literature which may be due to family history, ethnicity, or gender, known as predictive testing; AND

   b. The results of the test will be clinically useful to the medical management of the member (i.e., initiate a new course of therapy, alter an existing therapy, determine prognosis or a level of surveillance); AND

   c. A treating provider in the appropriate field who is acting within the scope of the practitioner’s license and practice or a provider with genetic-counseling expertise (including clinical geneticist or genetic counselor) provides documentation (including a letter of medical necessity) supporting the recommendation for testing after reviewing risk factors, clinical scenarios, and family history; AND

   d. The testing is the only and/or most medically appropriate option available to obtain the necessary information to evaluate and treat the member; AND

   e. There is a sufficient amount of evidence in the scientific literature to support the validity and predictive accuracy of the test for the specified indication; AND

2. **Genetic Testing Guidelines by Indication and Test Type:**

   When the indication for testing is not specified below in item A2a (diagnostic and targeted genetic testing or pharmacogenetic testing by medical condition section) or the indication for testing is not included in another Plan genetic testing policy, see item A2b of this section for applicable criteria. (Note: The Limitations section of this policy lists genetic testing categorized

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by medical condition/indication for testing that the Plan considers experimental and investigational.) Review item A2c below for applicable medical necessity criteria for multigene testing.

At least ONE (1) of the following categories of criteria must be met, as specified below in item a, item b, or item c:

a. **Diagnostic and Targeted Genetic Testing or Pharmacogenetic Testing by Medical Condition:**

   The Plan considers targeted genetic testing to be medically necessary when BOTH of the following criteria are met, as specified below in item (1) and item (2):

   (1) The results of the test will be clinically useful to the medical management of the member (e.g., confirm diagnosis to establish appropriate treatment plan or predict response to drug therapy); AND

   (2) ONE (1) of the following genetic tests will be conducted for the specified indication, as listed below in items (a) through (m):

   (a) **Breast Cancer:**

   CISH or FISH testing for the detection of HER2 gene amplification in patients with invasive breast cancer, in order to predict response to Trastuzumab treatment (Herceptin®, Genentech Inc.).

   Other indications for genetic testing for breast cancer may require Plan Medical Director review. See the Limitations section of this policy and other applicable Plan policies.

   (b) **Colorectal Cancer:**

   KRAS gene sequence variant analysis of tumor tissue, either primary tumor or metastasis, at a diagnosis of stage IV colorectal cancer is considered medically necessary for assessment of treatment options for a member of who is a candidate for anti-epidermal growth factor receptor (anti-EGFR) therapy when the analysis will predict the response to treatment with anti-EGFR monoclonal antibodies Cetuximab and Panitumumab. (Note: See the Limitations section for BRAF p.Val600Glu (V600E) and NRAS testing to predict the response to treatment with the anti-EGFR monoclonal antibodies.)
(c) Duchenne Muscular Dystrophy (DMD) or Becker Muscular Dystrophy (BMD):

ONE (1) of the following criteria is met, as specified below in items i through iii:

i. DMD gene variant analysis for diagnostic DMD testing (deletion and duplication analysis with reflex to complete gene sequencing) in members (regardless of gender) exhibiting symptoms of DMD or BMD, when the results are to be used to confirm an equivocal diagnosis or for carrier identification or prenatal diagnosis; OR

ii. For DMD gene variant testing (single-site testing) of a member who is an asymptomatic female relative (including member who is an asymptomatic relative with typical female with two [2] X chromosomes), of an individual with genetically confirmed DMD or BMD, for the purpose of carrier identification; OR

iii. For prenatal testing or PGD (single-site testing) of DMD or BMD for a member in a (biological) family transmitting known DMD variants.

(d) Ehlers-Danlos Syndrome Type IV (EDS IV):

ONE (1) of the following criteria is met, as specified below in item i or item ii:

i. COL3A1 gene testing in a member with clinical symptoms of EDS IV; OR

ii. COL3A1 gene testing to evaluate a member who is an asymptomatic, at-risk first-degree relative of an individual with genetically confirmed EDS IV.

Other indications for COL3A1 gene testing for EDS or additional genetic testing for EDS require Plan Medical Director review. See the Limitations section of this policy.

(e) Gastrointestinal Stromal Tumor (GIST):

ONE (1) of the following criteria is met, as specified below in item i or item ii:

i. For genetic testing of the KIT and PDGFRA genes for predicting resistance to primary treatment with tyrosine kinase inhibitors (TKIs) in patients with advanced metastatic or non-resectable GIST (i.e., primary treatment is the member’s first treatment for GIST with TKIs). See the Limitations section
for genetic testing limitations related to secondary treatment for GIST with TKIs.

ii. Genetic testing for sequence variants in KIT and PDGFRA to confirm a diagnosis of gastrointestinal stromal tumors (GIST) in members who are negative by immunostaining.

The most appropriate patient population for diagnostic testing for sequence variants in KIT and PDGFRA is patients with tumors who have a possible or probable diagnosis of GIST, but have an unclear diagnosis after immunostaining with CD117, CD34, PDGFRA, DOG1, or other antibodies. See below for pharmacogenetics guidelines for GIST treatment. Also, see the Limitations section for genetic testing limitations related to KIT and PDGFRA gene testing for GIST. Other indications for GIST genetic testing require Plan Medical Director review. See the Limitations section of this policy.

(f) Leukemia: 0

Conventional cytogenetic testing and molecular cytogenetic testing (e.g., FISH) to identify chromosomal abnormalities analysis using bone marrow or peripheral blood samples is considered medically necessary for the diagnosis and prognosis of a member with suspected or newly diagnosed primary/de novo (untreated) acute myeloid leukemia (AML) to assist with treatment planning.

∞ Note: Other indications for genetic testing for leukemia require Plan Medical Director review. See the Limitations section of this policy.

(g) Malignant Melanoma:

ONE (1) of the following criteria is met, as specified below in items i through iii:

i. BRAF p.Val600Glu (V600E) testing to predict response to Vemurafenib therapy in malignant melanoma; OR

ii. BRAF p.Val600Glu (V600E) testing to predict response to Dabrafenib monotherapy in advanced/unresectable or malignant melanoma; OR

iii. BRAF p.Val600Glu (V600E) testing to predict response to Trametinib and Dabrafenib combination therapy in advanced/unresectable or malignant melanoma; OR

Evaluation of BRAF p.Val600Glu and p.Val600Lys for purposes of patient qualification for Trametinib and Dabrafenib combination therapy must be
performed using an FDA-approved test for this indication, e.g., the THxID-BRAF kit manufactured by BioMérieux Inc.

(h) Marfan Syndrome:

ONE (1) of the following criteria is met, as specified below in items i through iii:

i. Direct sequence analysis of genes FBN1, TGFBR1, and TGFBR2 in a member who meets the Ghent diagnostic criteria (i.e., criteria used to diagnose Marfan syndrome, as specified in the Definitions section of this policy) for the purpose of obtaining information for reproductive decision making or facilitating the diagnosis of Marfan syndrome in at-risk relatives; OR

ii. Direct sequence analysis of genes FBN1, TGFBR1, and TGFBR2 to facilitate the diagnosis of Marfan syndrome in a member who does not fulfill the Ghent diagnostic criteria (i.e., criteria used to diagnosis the condition) but have one (1) major feature of the condition; OR

iii. Direct sequence analysis of genes FBN1, TGFBR1, and TGFBR2 to evaluate at-risk, first-degree relative (who is a Plan member) of an individual carrying the known disease-causing variants; a member is an at-risk relative when he/she has major involvement (i.e., major feature of the condition) in one (1) body system and minor involvement of a second body system.

Other indications for FBN1, TGFBR1, and/or TGFBR2 gene testing or additional genetic tests for Marfan syndrome require Plan Medical Director review.

(i) Noninvasive Prenatal Testing (NIPT):

NIPT for a pregnant member is considered medically necessary when ordered by the treating provider for testing of aneuploidies involving chromosomes 21 (T21 or Down syndrome), 18 (T18 or Edwards syndrome), 13 (T13 or Patau syndrome), and the sex chromosomes and ONE (1) of the following tests is used: MaterniT21 PLUS (available from Sequenom and Quest Diagnostics Inc.), Harmony Prenatal Test (by Ariosa Diagnostics Inc.), or Panorama Prenatal Test (by ARUP Laboratories). See the Applicable Coding and Limitations sections of this policy for limitations related to this service.
(j) Non-Small Cell Lung Cancer Treatment:

ONE (1) of the following criteria is met, as specified below in item i or item ii:

i. Anaplastic lymphoma kinase (ALK) gene rearrangement testing is considered medically necessary for a member diagnosed with non-small cell lung cancer to predict treatment response to Crizotinib therapy; OR

ii. Genetic testing for epidermal growth factor receptor (EGFR) testing is considered medically necessary to help guide administration of EGFR tyrosine kinase inhibitors (TKIs) in the first-line treatment of a member diagnosed with non-small cell lung cancer to predict treatment response. See the Limitations section for testing in second-line or later treatment.

(k) Ovarian Cancer Treatment:

ONE (1) of the following criteria is met, as specified below in item i or item ii:

i. BRACAnalysis CDx® (Myriad Genetic Laboratories, Inc.) testing is considered medically necessary when used to detect the presences of BRCA1 or BRCA2 gene mutation in ovarian tumor tissue (using blood samples) with a female member (or member born with female reproductive organs and/or with typical female karyotype with two [2] X chromosomes) with advanced ovarian cancer when treatment with Lynparza (olaparib) is being considered, and the member has NOT had previous BRCA mutation testing; OR ¥

ii. Repeat BRCA testing with BRACAnalysis CDx® is considered medically necessary in a female member (or member born with female reproductive organs and/or with typical female karyotype with two [2] X chromosomes) with advanced ovarian cancer when the member had another brand of BRCA test (other than BRACAnalysis® and BRACAnalysis® Large Rearrangement Test or BART™ by Myriad Genetics, Inc.) and who is being considered for treatment with Lynparza (olaparib) after three (3) or more previous lines of chemotherapy. (Comprehensive testing of the BRCA1 and BRCA2 genes for heredity breast and ovarian cancer syndrome is now available from a number of laboratories in the United States, but different methodologies are used in different laboratories.) ¥

¥ Note: The FDA has approved Lynparza (olaparib) when used in combination with BRACAnalysis CDx®, a companion diagnostic test that will detect the presence of mutations in the BRCA genes in blood samples from members with ovarian cancer.

Genetic Testing Guidelines and Pharmacogenetics
(l) Rett Syndrome:

ONE (1) of the following criteria is met, as specified below in item i or item ii:

i. For testing for MECP2 sequence variants in members who have some symptoms of Rett syndrome but do not meet established clinical diagnostic criteria for the condition; OR

ii. For prenatal testing for MECP2 sequence variants in the parents of children with Rett syndrome who meet the established clinical diagnostic criteria and for whom there is evidence that Rett syndrome was inherited rather than occurred sporadically. See the Applicable Coding section of this policy for pregnancy diagnosis codes that do not require prior authorization for genetic testing according to Plan guidelines.

Review the Limitations section of this policy for additional Plan guidelines related to genetic testing for MECP2 sequence variants and genetic testing for Autism Spectrum Disorders, Rett syndrome, and/or Angelman syndrome. Other indications for MECP2 gene testing require Medical Director review when not specified as a medically necessary service in a Plan medical policy.

(m) Thoracic Aortic Aneurysms and Dissections (TAAD):

Sequence variance analysis of genes TGFBR1, TGFBR2, FBN1, MYH11, and ACTA2 is considered medically necessary for an asymptomatic member who is a first-degree blood relative of an individual with genetically confirmed TAAD.

See the Limitations section of this policy for additional Plan guidelines related to genetic testing for TAAD with genes TGFBR1, TGFBR2, FBN1, MYH11, and ACTA2. Other indications for TGFBR1, TGFBR2, FBN1, MYH11, and/or ACTA2 gene testing or additional genetic tests for TAAD require Plan Medical Director review.

See Plan’s Gene Expression Profiling of Tumor Tissue to Predict Cancer Recurrence and Risk Stratification (Including Oncotype DX™ and Other Tests) medical policy (policy number OCA 3.572) for Plan guidelines for gene expression tests of tumor tissue used to predict cancer recurrence or risk stratification.

b. Criteria for Targeted Genetic Testing When Indication Not Specified in a Plan Genetic Testing Policy:

When the indication for testing is not specified above in item A2a (diagnostic and targeted genetic testing or pharmacogenetic testing by medical condition) or the indication for
testing is not included in another Plan genetic testing policy, use criteria in this item A2b. See the Limitations section of this policy for the list of genetic tests categorized by medical condition/indication for testing that the Plan considers experimental and investigational. Review item A2c below rather than this item for applicable medical necessity criteria for multigene testing.

The Plan considers targeted genetic testing to be medically necessary when ALL of the criteria are met with medical record documentation submitted by the treating provider documenting these criteria, as specified below in items (1) through (5):

1. Previous testing performed, and/or other alternatives available to obtain the information; AND

2. Documentation that the member is experiencing signs and symptoms of a disease or that the member is pre-symptomatic and at an increased risk of developing the disease; AND

3. How the results of the test will be clinically useful either diagnostically, therapeutically, prognostically, or preventively; AND

4. Name of provider who completed the member’s pre-test genetic counseling, date of counseling, and provider’s plan for post-test counseling (but this information is NOT required when testing is only for prediction of drug responses); AND

5. Where the specific genetic test will be done and who will interpret the results; OR

c. **Criteria for Multigene Panel Testing (Rather than Targeted Genetic Testing):**

The use of a multigene testing panel may or may NOT be considered medically necessary in addition to, or as an alternative to, disease-specific, targeted genetic testing (including the identification of susceptibility to hereditary cancer syndromes) due to limited data on clinical validity and clinical utility of multigene testing. If the treating provider is recommending multigene panel testing rather than, or in addition to, condition-targeted genetic testing, **Plan Medical Director review is required.** For multigene panel testing to be considered medically necessary, medical record documentation must be submitted to the Plan with the prior authorization request demonstrating that ALL of the following criteria are met (and after approval by a Plan Medical Director), with criteria specified below in items (1) through (7):

1. A recommendation for multigene panel testing for the member by an independent board-certified or board-eligible Medical Geneticist, an American Board of Medical Genetics or American Board of Genetic Counseling-certified Genetic Counselor not employed by a commercial genetic testing laboratory, or a genetic nurse credentialed

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as either a Genetic Clinical Nurse (GCN) or an Advanced Practice Nurse in Genetics (APGN) by either the Genetic Nursing Credentialing Commission (GNCC) or the American Nurses Credentialing Center (ANCC) who is not employed by a commercial genetic testing laboratory; this provider has a documented evaluation of the member which includes a completed 3-generation pedigree and intends to engage in post-test follow-up counseling; AND

(2) Member meets criteria for genetic testing outlined in item A2a above (General Genetic Testing Guidelines for ALL Testing) of this Medical Policy Statement section; AND

(3) All genes included in the multigene panel are relevant to the personal medical history, biological family medical history, and/or treatment plan for the member being tested and there are professional society management guidelines or National Comprehensive National Comprehensive Cancer Network (NCCN) guidelines (with applicable references provided with the prior authorization request) documenting the clinical utility of testing for the members who test positive for any and all genes in the panel; AND

(4) The results of the requested multigene panel will directly impact the treatment plan and clinical decision-making process for the member being tested; AND

× Note: Genotype testing of multiple genes may or may not be considered medically necessary to determine how an individual’s genes affect the individual’s response to drug metabolism and/or adjuvant therapy due to limited data to evaluate the use of testing in clinical practice. According to NCCN guidelines, the use of multigene assays as an alternative to targeted genetic testing to determine clinically appropriate adjuvant therapy may result in a greater chance of identifying variants of uncertain significance for which clinical management is uncertain and mistakenly providing overtreatment or over-screening of these variants and associated medical conditions.

(5) There are no other known causative circumstances or factors (e.g., environmental exposures, injury, infection) that can explain the member’s symptoms or medical condition; AND

(6) Multigene panel testing is more practical testing to diagnose the member’s condition than the separate single gene tests or targeted panels that would be recommended (with supporting documentation provided); AND

(7) The member’s clinical presentation does not fit a well-described syndrome for which single-gene testing, targeted panel testing, or chromosomal microarray analysis is
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1. Forensic genetic testing is NOT covered.

Limitations

Review the member’s applicable benefit document available at www.bmchp.org for a BMC HealthNet Plan member, at www.SeniorsGetMore.org for a Senior Care Options member, or at www.wellsense.org for a Well Sense Health Plan member to obtain the most accurate and up-to-date information on benefit coverage. The following the limitations apply to ALL Plan products, as specified below in items 1 through 9:

1. Forensic genetic testing is NOT covered.

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2. Specimen validity testing using DNA authentication (e.g., ToxProtect by Genotox Laboratories) in conjunction with drug testing is considered experimental and investigational due to insufficient evidence of the clinical utility of DNA authentication (as a component of drug testing for any type of specimen collected, any drug class[es], and for any indication). For BMC HealthNet Plan members, review the Plan’s Drug Screening/Testing (DS/T): Drugs of Abuse reimbursement policy (policy number 4.94) and the Drug Screening/Testing for Drugs of Abuse and/or Controlled Substances medical policy (policy number OCA 3.98) available at www.bmchp.org.

3. Genetic testing that is marketed directly to consumers (direct-to-consumer or DTC) that is ordered by a member without the order of a treating health care provider is not covered.

4. Chromosomal Microarray Testing:

Chromosomal microarray testing used for the diagnosis, prognosis, and/or management of cancers or other diseases requires Plan Medical Director review. Examples include but are not limited to MitoMet or MitoMetPlus testing for mitochondrial disorders. (See Plan policy, Chromosomal Microarray Analysis for Unexplained Intellectual Disabilities and/or Multiple Congenital Anomalies, policy number OCA 3.573, for Plan guidelines for additional indications for testing.)

5. Multigene Panel Testing:

The Plan considers the clinical utility of multigene panel testing for prenatal diagnosis, preimplantation testing of an embryo, and/or when used in the general population to be experimental and investigational. For other indications, review the applicable medical necessity criteria in the Medical Policy Statement section of this policy for multigene panel testing.

6. Tissue of Origin Testing:

Tissue of origin test (TOO) used to identify the primary tissue of origin in patients when there is clinical uncertainty of a tumor’s primary origin is considered experimental and investigational for all indications/conditions. Examples of such testing include but are not limited to ResponseDX (Response Genetics Inc.) and CancerTYPE ID (bioTheranostics Inc.). The TOO is a microarray-based RNA profiling test that compares the RNA expression of formalin-fixed paraffin-embedded (FFPE) tumor tissue from a patient with cancer of unknown primary (CUP) to the expression patterns of a panel of multiple known characterized tumor types (e.g., bladder, breast, colorectal, gastric, hepatocellular, kidney, melanoma, non-Hodgkin’s lymphoma, non-small cell lung, ovarian, pancreas, prostate, sarcoma, testicular germ cell, and thyroid) to identify the most likely primary tissue of origin. According to the National Comprehensive Cancer Network (NCCN) clinical practice guidelines for occult primary cancer,
the clinical benefits of gene expression profiling assays with occult primary cancers have not adequately demonstrated improvement in clinical outcomes. Clinical alternatives to the TOO are standard clinical and pathologic evaluation and further diagnostic tests such as blood tests, endoscopies, and radiological imaging, as appropriate for the individual’s condition.

7. Whole Exome Sequencing:

Whole exome sequencing (WES) is considered experimental and investigational when used for cancer indications, the diagnosis of genetic disorders, prenatal diagnosis, preimplantation testing of an embryo, used in the general population, and/or for any condition due to insufficient data on the analytical validity, clinical validity, and clinical utility of WES as an alternative to targeted genetic testing. Plan Medical Director review is required for all prior authorization requests for WES.

There is limited evidence from large comparative studies of the clinical utility of WES as a preferred clinical alternative to other appropriate screening and diagnostic techniques (even with primary findings from WES). In addition, incidental (secondary) findings from WES may not have high clinical significance, there may be limitations related to the analysis of incidental findings (including reduced technological reliability of the analysis and/or less scientific evidence available to interpret both positive and negative results) and/or interventions may not exist to prevent or ameliorate disease identified with WES. According to The American College of Obstetricians and Gynecologists (Committee Opinion Number 682), the routine use of whole genome or whole exome sequencing for prenatal diagnosis is not recommended outside of the context of clinical trials until sufficient peer-reviewed data and validation studies are published.

8. Whole Genome Sequencing:

Whole genome sequencing (WGS) is considered experimental and investigational when used for cancer indications, the diagnosis of genetic disorders, prenatal testing, used in the general population, and/or for any other indications due to insufficient data on the analytical validity, clinical validity, and clinical utility of WGS as an alternative to targeted genetic testing. Plan Medical Director review is required for all prior authorization requests for WGS.

WGS have been proposed to be more efficient than traditional sequencing methods in discovering the genetic causes of diseases, but there remain issues of error rates due to technical challenges and difficulty interpreting potential causative variants from variants of unknown significance generated for each patient. According to The American College of Obstetricians and Gynecologists (Committee Opinion Number 682), the routine use of whole-genome or whole-exome sequencing for prenatal diagnosis is not recommended outside of the context of clinical trials until sufficient peer-reviewed data and validation studies are published.

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9. Experimental and Investigational Genetic Testing by Medical Condition:

Requests for genetic testing for an indication that does not meet Plan criteria, multigene panels, or genetic testing that the Plan considers experimental and investigational require Plan Medical Director review. The Plan Medical Director will consider individual member medical needs and circumstances (based on the Plan’s Clinical Criteria policy, policy number OCA 3.201) and conduct a review of the applicable National Comprehensive Cancer Care Network (NCCN) guidelines, when appropriate. Genetic testing for ANY of following indications categorized by condition/test type is considered experimental, investigational, or unproven and is NOT covered, as specified below in items a through y:

a. Autism Spectrum Disorders, Rett Syndrome, and/or Angelman Syndrome Genetic Testing:

1. The Plan considers a test using multiple—single nucleotide polymorphisms (SNPs) to identify the risk of autism spectrum disorders to be experimental and investigational due to insufficient data on analytical validity, clinical validity, and clinical utility; an example of such testing includes but is not limited to the ARISk2 Test (IntegraGen Inc.).

2. The Plan considers the Syndromic Autism Panel (developed by Greenwood Genetic Center) using next-generation sequencing (NGS) to evaluate the coding regions and flanking regions of the introns of 83 genes when used for the genetic diagnosis of individuals with autism and other physical features suggestive of a syndrome yet normal chromosomal microarray testing, as a second-tier test for evaluation of Rett syndrome and/or Angelman syndrome, or for any other indication to be experimental and investigational due to limited evidence supporting the clinical validity and clinical utility of testing.

3. Forkhead box protein G1 (FOXG1) gene testing for the congenital variant form of Rett syndrome for confirmation of a diagnosis of congenital Rett syndrome in patients with symptoms compatible with RTT or for prenatal genetic diagnosis in families with a confirmed FOXG1 variant is considered experimental and investigational due to limited evidence supporting the clinical validity and clinical utility of testing. (See the Applicable Coding section of this policy for pregnancy diagnosis codes that do not require prior authorization for genetic testing according to Plan guidelines.)

4. The Plan considers testing for MECP2 sequence variants in disorders other than Rett syndrome, including Angelman syndrome, autism, intellectual disability, X-linked intellectual disability, MECP2 duplication syndrome, schizophrenia, and/or other psychiatric disorders to be experimental and investigational due to limited evidence supporting the clinical validity and clinical utility of testing.
(5) The Plan considers testing for MECP2 sequence variants in members who meet established clinical diagnostic criteria for classic or variant Rett syndrome to not be medical necessary due to its limited clinical utility after a clinical diagnosis of Rett syndrome is made.

Genetic testing indications related to autism spectrum disorders, Rett syndrome, and/or Angelman syndrome that do not meet criteria in the Medical Policy Statement section of this Plan policy require Plan Medical Director review.

b. Breast Cancer Genetic Testing:

(1) Breast cancer Ki-67 (MKI67) proliferation marker testing to prediction treatment response for invasive breast cancer is considered experimental and investigational. Ki-67 testing to predict treatment response for ductal carcinoma in situ (DCIS) or to predict breast cancer recurrence rate as an alternative to the Oncotype DX assay to is considered experimental and investigational.

(2) The CellSearch Circulating Tumor Cell (CTC) Kit (Janssen Diagnostics LLC) is considered experimental and investigational for monitoring metastatic breast cancer (including the evaluation of tumor characteristics, monitoring and prediction of treatment response, and prediction of disease progression and prognosis) and for all other indications.

Genetic testing indications related to breast cancer that do not meet criteria in the Medical Policy Statement section of this policy or another applicable Plan policy require Plan Medical Director review. Review the Plan’s Gene Expression Profiling of Tumor Tissue to Predict Cancer Recurrence and Risk Stratification (Including Oncotype DX™ and Other Tests) medical policy, policy number OCA 3.572, rather than this policy for Plan guidelines related to gene expression analysis using a proprietary risk classifier as a prognostic test and as a predictive test for response to chemotherapy for individuals with breast cancer.

c. Cardiomyopathies and Arrhythmias Genetic Testing:

(1) Plan Medical Director review with individual consideration is required for genetic testing for cardiomyopathies and arrhythmias. The indication for the requested genetic test must meet applicable criteria in the Medical Policy Statement section, and the ordering provider must provide the following additional medical record documentation: Member’s clinical history, expressed electrocardiographic phenotype (i.e., results of diagnostic testing such as electrocardiogram or Holter monitoring), family history of known mutation (if applicable), and type of genetic testing requested with documented clinical utility of testing for the member (i.e., how it will influence
the prognosis or treatment of the member). The member has at least ONE (1) of the following documented medical conditions, as specified below in items (a) through (h):

(a) Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D); OR
(b) Brugada syndrome; OR
(c) Catecholaminergic polymorphic ventricular tachycardia (CPVT)
(d) Dilated cardiomyopathy (DCM); OR
(e) Hypertrophic cardiomyopathy (HCM); OR
(f) Left ventricular non-compaction cardiomyopathy (LVNC): OR
(g) Long QT syndrome (LQTS); OR
(h) Restrictive cardiomyopathy (RCM); OR

(2) The Plan considers genetic testing for atrial fibrillation and/or genetic testing for hereditary cardiac conditions in the general population to be experimental and investigational. Plan Medical Director review is required.

d. CHARGE Syndrome Genetic Testing:

Genetic testing to identify CHARGE syndrome in an individual at risk of having CHARGE syndrome based on a family member who has an identified CHD7 gene variant is considered experimental and investigational. Genetic testing for all indications related to CHARGE syndrome that do not meet criteria in the Medical Policy Statement section of this policy require Plan Medical Director review.

e. Colorectal Cancer (CRC) Genetic Testing:

(1) BRAF p.Val600Glu (V600E) testing is considered experimental and investigational for the assessment of treatment options for a member with colorectal cancer (including metastatic colorectal cancer); this includes testing to predict the response to treatment with anti-epidermal growth factor receptor (anti-EGFR) monoclonal antibodies Cetuximab and Panitumumab (even when the member has previously been shown not to have sequence variants in the KRAS gene). See the Medical Policy statement section for KRAS sequence variant analysis to predict response to treatment with the anti-EGFR monoclonal antibodies.
(2) Neuroblastoma RAS viral oncogene (NRAS) testing is considered experimental and investigational for the assessment of treatment options for a member with colorectal cancer (including metastatic colorectal cancer); this includes testing to predict the response to treatment with anti-epidermal growth factor receptor (anti-EGFR) monoclonal antibodies Cetuximab and Panitumumab (even when the member has previously been shown not to have sequence variants in the KRAS gene). See the Medical Policy statement section for KRAS sequence variant analysis to predict response to treatment with the anti-EGFR monoclonal antibodies.

(3) The NexCourse CRC test (Genoptix Medical Laboratory), testing designed to provide information regarding colorectal cancer prognosis, response to and tolerance of particular therapies, and disease course, is considered experimental and investigational for any indication due to insufficient data to evaluate the use of testing in clinical practice.

(4) ResponseDX: Colon test (Response Genetics Inc.), a multi-gene colorectal cancer genetic test used to predict chemotherapy response, is considered experimental and investigational for any indication because there is currently insufficient evidence to evaluate the impact of the test on patient outcomes.

Genetic testing indications related to colorectal cancer that do not meet criteria in the Medical Policy Statement section of this Plan policy or another applicable Plan policy require Plan Medical Director review.

f. Ehlers-Danlos Syndrome (EDS) Classic Type for Ehlers-Danlos Syndrome Genetic Testing:

(1) COL5A1/COL5A2 gene testing in members with the clinical symptoms of classic EDS (EDS I/II) is considered experimental and investigational due to limited evidence supporting the clinical validity and clinical utility of testing.

(2) COL5A1/COL5A2 gene testing in the asymptomatic family members of patients with genetically confirmed classic EDS (EDS I/II) is considered experimental and investigational due to limited evidence supporting the clinical validity and clinical utility of testing.

(3) Prenatal testing or preimplantation genetic diagnosis of classic EDS (EDS I/II) in families transmitting a known COL5A1/COL5A2 gene variant is considered experimental and investigational due to limited evidence supporting the clinical validity and clinical utility of testing. See the Applicable Coding section of this policy for pregnancy diagnosis codes that do not require prior authorization for genetic testing according to Plan guidelines. See Plan’s Preimplantation Genetic Testing (Preimplantation Genetic Diagnosis and Pregenetic Screening) medical policy, policy

Genetic Testing Guidelines and Pharmacogenetics

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number OCA 3.726, rather than this policy for applicable Plan criteria for preimplantation genetic diagnosis and pregenetic screening.

Other indications for COL5A1/COL5A2 gene testing and/or genetic testing related to EDS require Plan Medical Director review when Plan criteria are not met, as specified in the Medical Policy Statement section of this policy.

g. Gastrointestinal Stromal Tumor (GIST) Genetic Testing:

(1) The Plan considers genetic testing for sequence variants in KIT and PDGFRA to confirm a diagnosis of GIST in patients who are positive by immunostaining to not be medical necessary due to its limited clinical utility after a clinical diagnosis of GIST is made.

(2) Genetic testing for sequence variants in the KIT and PDGFRA genes for the prognosis of patients with gastrointestinal stromal tumors (GIST) is considered experimental and investigational due to limitations in the clinical utility of testing.

(3) Genetic testing of the KIT and PDGFRA genes for monitoring the development of secondary (acquired) resistance or for guiding the treatment choices in patients receiving secondary treatment for gastrointestinal stromal tumors (GIST) with tyrosine kinase inhibitors (TKIs) or for guiding the choice of treatment options that are effective against GIST that has secondary resistance is considered experimental and investigational due to limitations in the clinical utility of testing.

Secondary treatment includes the treatment that follows after the failure of the primary treatment for GIST with TKIs. Genetic testing indications for GIST that are not included in the Medical Policy Statement section of this policy (including primary treatment for GIST and diagnostic testing) require Plan Medical Director review.

h. Hereditary Neuralgic Amyotrophy (HNA) Genetic Testing:

The Plan considers genetic testing for variants in the septin 9 (SEPT9) gene to diagnosis HNA (also known as hereditary brachial plexus neuropathy or neuritis with brachial predilection) to not be medically necessary due to limited documentation of the clinical utility and clinical validity of testing for this indication.

i. Infectious Pathogen Identification with Genetic Testing:

Genetic testing using next-generation sequencing (NGS) technology as an alternative to, or in addition to, phenotypical approaches (cultures) and/or immunological methods (antibody-based approach) to identify particular microbial genes associated with acute or chronic infections for timely diagnosis of the microbial pathogens, to determine the presence or absence of specific drug-resistant genes in the microbes, and/or inform the

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treatment decision-making process using genotype assays to be experimental and investigational due to the overall poor body of evidence documenting the analytical validity and clinical validity of NGS testing for this indication.

j. Kabuki Syndrome Genetic Testing:

(1) The Plan considers genetic testing (including MLL2 variant analysis using direct sequence analysis and/or deletion or duplication analysis) to confirm a diagnosis of Kabuki syndrome (KS) in patients with symptoms compatible with this condition to be experimental and investigational due to limited documentation of the clinical utility, clinical validity, and analytical validity of testing. Alternatives to MLL2 gene analysis for KS include diagnosis based upon evaluation of the clinical characteristics exhibited by the patient.

(2) The Plan considers prenatal genetic diagnosis (including testing for MLL2 variants) in families with a confirmed MLL2 variant or for other indications related to Kabuki syndrome to be experimental and investigational due to limited documentation of the clinical utility, clinical validity, and analytical validity of testing.

k. Leukemia Genetic Testing:

Genetic testing for the diagnosis or prognostic evaluation of acute lymphoblastic leukemia (ALL) and/or non-ALL leukemia through analysis of rearrangements in specific regions of the IG genes immunoglobulin heavy locus (IGH) and immunoglobulin kappa locus (IGK) is considered experimental and investigational due to limitations in the clinical utility of testing. Genetic testing indications related to leukemia that are not included in the Medical Policy Statement section of this Plan policy require Plan Medical Director review.

l. Macular Degeneration Genetic Testing:

The Plan considers the Macula Risk PGx test to be experimental and investigational for any indication due to limited evidence supporting the clinical validity and clinical utility of testing. The Macula Risk PGx test reportedly combines a patient’s current AMD status, data from 15 variants in 12 genes, and non-genetic factors, to predict the patient’s 2-, 5-, and 10-year risk of developing advanced AMD, including choroidal neovascular or geographic atrophy. Genetic testing for all indications related to macular degeneration that do not meet criteria in the Medical Policy Statement section of this policy require Plan Medical Director review.

m. Malignant Melanoma Genetic Testing:

See Plan policy, Genetic Testing for Familial Malignant Melanoma (policy number OCA 3.78), rather than this policy for prior authorization guidelines and limitations related to
genetic testing to determine susceptibility to familial malignant melanoma. Review Plan guidelines in the Medical Policy Statement section of this policy for pharmacogenetics for malignant melanoma treatment; additional indications for genetic testing for melanoma require Plan Medical Director review.

n. Neutropenia Genetic Testing:

The Plan considers elastase, neutrophil expressed (ELANE) gene testing (also known as the ELA2 gene) to be experimental and investigational due to limited evidence supporting the clinical utility of testing. The methods used for ELANE gene testing, which vary depending on the laboratory, may include Sanger sequencing, next-generation sequencing (NGS), polymerase chain reaction (PCR) amplification, primer extension, and microarray analysis to diagnose ELANE-related neutropenia. Two (2) groups of patients may be considered for ELANE gene testing for neutropenia (and both indications are considered experimental and investigational): Individuals with symptoms consistent with ELANE-related neutropenia and prenatal diagnosis in families with a confirmed ELANE variant. Genetic testing for all indications related to neutropenia that do not meet criteria in the Medical Policy Statement section of this policy require Plan Medical Director review.

o. Noninvasive Prenatal Testing (NIPT):

1. The following noninvasive prenatal tests (NIPT) are considered experimental and investigational (even when used with a high-risk, pregnant member) due to insufficient data on the clinical utility and clinical validity of testing: informaSeq (by Integrated Genetics), Verifi Prenatal Test (by Illumina Inc.), VisibiliT (Sequenom), and any additional products not specified in this policy. Medically necessary alternatives for NIPT for high-risk pregnant members may include Harmony Prenatal Test (by Ariosa Diagnostics Inc.), MaterniT21 PLUS (available from Sequenom and Quest Diagnostics Inc.), or Panorama Prenatal Test (by ARUP Laboratories) for testing of aneuploidies involving chromosomes 21 (T21 or Down syndrome), 18 (T18 or Edwards syndrome), 13 (T13 or Patau syndrome), and the sex chromosomes according to the guidelines specified in the Applicable Coding section and this Limitations section.

2. The use of NIPT on multiple-gestation pregnancies is considered experimental and investigational (for all products and chromosomal disorders).

3. The use of NIPT BEYOND the standard testing of aneuploidies involving chromosomes 21, 18, 13, and the sex chromosomes is considered experimental and investigational (for all products); the testing other chromosomal disorders (such as additional trisomies or microdeletions) with NIPT is considered experimental and investigational due to insufficient data on the clinical utility and clinical validity of testing.
(4) The use of NIPT in a pregnant member to test the fetal RHD genotype is considered experimental and investigational for any indication due to insufficient evidence of the clinical utility and clinical validity of this testing for the specified indication. This includes NIPT testing of a pregnant member RhD- negative (i.e., no RhD protein D antigen) with an RhD-positive or unknown RhD status partner as a clinical alternative to the administration of prophylactic anti-D immunoglobulin (at 28 to 30 weeks to prevent formation of antibodies to D antigen) and/or fetal genotyping with invasive methods such as s chorionic villus sampling (CVS) or amniocentesis. An example of an NIPT used to identify rhesus (Rh) status includes but is not limited to the SensiGene Fetal RHD Genotyping Test (by Sequenom Center for Molecular Medicine).

p. Non-Small Cell Lung Cancer (NSCLC) Genetic Testing:

(1) KRAS sequence variant analysis for predicting response to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in the treatment of non-small cell lung cancer is considered experimental and investigational due to limited evidence supporting the clinical validity and clinical utility of testing.

(2) Genetic testing for epidermal growth factor receptor (EGFR) to help guide administration of EGFR tyrosine kinase inhibitors (TKIs) in the second-line or later treatment of a member diagnosed with NSCLC to predict treatment response cancer is considered experimental and investigational due to limited evidence supporting the clinical validity and clinical utility of testing. See the Medical Policy Statement section for Plan guidelines for testing when used in first-line treatment.

(3) Excision repair cross-complementation group 1 protein (ERCC1) gene expression testing for non-small cell lung cancer to assess ERCC1 levels within tumor cells to determine effectiveness of platinum-based chemotherapy regimen is considered experimental and investigational due to limited evidence supporting the clinical validity and clinical utility of testing.

(4) PTEN gene expression testing is considered experimental and investigational for predicting prognosis in patients with NSCLC based on presence or absence of PTEN expression in tumor tissue by immunohistochemistry due to limited evidence supporting the clinical utility of testing.

(5) PTEN gene expression testing is considered experimental and investigational for predicting response to EGFR TKI or other drug therapy in patients with NSCLC based on presence or absence of PTEN expression in tumor tissue by immunohistochemistry due to limited evidence supporting the clinical utility of testing.

(6) VeriStrat (Biodesix Inc.) test is considered experimental and investigational for members with advanced NSCLC who are being considered for treatment with an

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epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) or for any other indication due to limited evidence supporting the clinical utility of testing. The VeriStrat test analyzes a specific protein profile in pretreatment serum obtained from NSCLC patients and assigns a rating. A VeriStrat good result indicates that the patient may respond to treatment with EGFR TKIs, while a VeriStrat poor result indicates that the patient is unlikely to benefit from this type of therapy.

Genetic testing indications related to NSCLC that are not included in the Medical Policy Statement section of this Plan policy require Plan Medical Director review.

q. Pancreatic Cancer Genetic Testing:

(1) Genetic testing for sequence variants in the BRCA2 and PALB2 genes and deletion testing in the PALB2 gene (e.g., Panexia test for hereditary pancreatic cancer developed by Myriad Genetics Inc.) is considered experimental and investigational for individuals with pancreatic cancer to indicate an increased risk of other types of cancer or to predict if an individual is at risk for pancreatic cancer.

(2) Genetic testing with a pancreatic cancer panel (e.g., Pancreatic Cancer Panel by GeneDx Inc. and PancNext Next-Gen Cancer Panel by Ambry Genetics Corp.) using sequencing technology to analyze multiple genes is considered experimental and investigational to identify individuals associated with an increased risk of pancreatic cancer and/or other hereditary cancers.

Genetic testing for all indications related to prostate cancer that do not meet criteria in the Medical Policy Statement section of this policy require Plan Medical Director review.

r. PLP-1 Related Disorders PLP1 Genetic Testing:

(1) PLP1 gene testing is considered experimental and investigational in members exhibiting signs of a PLP1-related disorder, including those with sporadic disease and those with a family history consistent with X-linked inheritance due to limited evidence supporting the clinical validity and clinical utility of testing.

(2) PLP1 gene testing is considered experimental and investigational for asymptomatic family members (who are Plan members) of affected individuals with a genetically confirmed PLP1-related disorder, for the purpose of carrier identification, or presymptomatic diagnosis due to limited evidence supporting the clinical validity and clinical utility of testing.

Genetic testing for all indications related to PLP-1 disorders that do not meet criteria in the Medical Policy Statement section of this policy require Plan Medical Director review.
s. Pitt-Hopkins Syndrome (PTHS) Genetic Testing:

(1) Genetic testing of the transcription factor 4 (TCF4) gene for confirmation of a diagnosis of PTHS in members with symptoms compatible with PTHS is considered experimental and investigational due to limited evidence supporting the clinical validity and clinical utility of testing.

(2) Prenatal genetic diagnosis in families with a confirmed TCF4 variant is considered experimental and investigational due to limited evidence supporting the clinical validity and clinical utility of testing. (See the Applicable Coding section of this policy for pregnancy diagnosis codes that do not require prior authorization for genetic testing according to Plan guidelines.)

Genetic testing for all indications related to PTHS that do not meet criteria in the Medical Policy Statement section of this policy require Plan Medical Director review.

t. Prostate Cancer Genetic Testing:

(1) The Plan considers genetic testing for multiple genes associated with the presence of prostate cancer to be experimental and investigational when used to improve the identification of occult (hidden) prostate cancer in men with negative prostate biopsies yet high-risk, clinicopathologic features; an example of this type of test includes the ConfirmMDx for Prostate Cancer test developed by MDxHealth Inc.

(2) PCA3 detection test for prostate cancer screening in men considering prostate biopsy (i.e., after suspicious digital rectal exam, elevated serum PSA levels, previous negative biopsy, or other risk factor), for prostate cancer screening in the general male population (which may include individuals born with male reproductive organs and/or with typical male karyotype with only one [1] X chromosome), and/or for disease monitoring in prostate cancer patients for whom active surveillance is recommended is considered experimental and investigational due to limited evidence supporting the clinical validity and clinical utility of testing. PCA3 genetic testing in clinical practice focuses on the detection of the PCA3-associated mRNA in blood and urine samples following a digital rectal exam. An example of testing includes but is not limited to the PROGENSA® PCA3 Assay (Gen-Probe Inc.).

(3) The use of protein biomarkers (using diagnostic blood tests, urine tests, or other testing methods such as immunofluorescence and automated quantitative images of biopsy tissue) to predict cancer recurrence or risk stratification based on an established algorithm is considered experimental and investigational due to limited evidence supporting the clinical validity and clinical utility of testing. Examples of this type of testing include but are not limited to the following: 4Kscore Test (OPKO Lab),
Prostarix™ (Metabolon/Bostwick Laboratories), and Promark® (Metamark Genetics, Inc.).

(4) Genetic testing to verify false-negative prostate biopsy by testing existing prostate biopsy tissue from patients with negative biopsy results to differentiate true-negatives from false-negatives are considered experimental and investigational. An example of such testing includes but is not limited to the Prostate Core Mitomic Test (MDNA Life Sciences Inc.). The Prostate Core Mitomic Test uses the presence or absence of a 3.4-kilobase (kb) deletion in the mitochondrial DNA to distinguish between malignant (deletion present) and benign (deletion absent) prostate biopsies. This type of testing (including but not limited to the Prostate Core Mitomic Test) is considered experimental and investigational due to insufficient data supporting the analytical validity, clinical validity, and clinical utility of testing.

Gene-based tests for the screening, detection and management of prostate cancer are considered experimental and investigational. Genetic testing that does not meet criteria in the Medical Policy Statement section of this policy require Plan Medical Director review.

u. PTEN Hematoma Tumor Syndrome (PHTS) Genetic Testing:

PTEN Hamartoma Tumor Syndrome (PHTS) encompasses Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), and Proteus syndrome (PS). PHTS is caused by sequence variants in the tumor suppressor phosphatase and tensin homolog (PTEN) gene.

(1) PTEN gene variant testing in a member suspected of being affected with CS and/or BRRS is considered experimental and investigational due to limited evidence supporting the clinical utility of testing.

(2) PTEN gene variant testing in a member with PS and/or Proteus-like syndrome is considered experimental and investigational due to limited evidence supporting the clinical utility of testing.

(3) PTEN gene variant presymptomatic testing in a relative (who is a Plan member) of an individual with a confirmed PTEN sequence variant is considered experimental and investigational due to limited evidence supporting the clinical utility of testing.

(4) PTEN gene variant testing for prenatal diagnosis or preimplantation genetic diagnosis for PHTS is considered experimental and investigational due to limited evidence supporting the clinical utility of testing. See the Applicable Coding section of this policy for pregnancy diagnosis codes that do not require prior authorization for genetic testing according to Plan guidelines. See Plan’s Preimplantation Genetic Testing (Preimplantation Genetic Diagnosis and Pregenetic Screening) medical policy.
Genetic testing for all indications related to PHTS that do not meet criteria in the Medical Policy Statement section of this policy require Plan Medical Director review.

v. Stickler Syndrome Genetic Testing:

(1) Genetic testing for sequence variants and deletions/duplications in the COL2A1 gene in a member with a suspected diagnosis of Stickler syndrome is considered experimental and investigational due to limited evidence supporting the clinical validity and clinical utility of testing.

(2) Genetic testing for sequence variants and deletions/duplications in the COL11A1, COL11A2, COL9A1, and COL9A2 genes in a member with a suspected diagnosis of Stickler syndrome is considered experimental and investigational due to limited evidence supporting the clinical validity and clinical utility of testing.

(3) Genetic testing for sequence variants and deletions/duplications in the COL2A1, COL11A1, COL11A2, COL9A1, and COL9A2 genes to detect the presence or absence of a familial variant in an at-risk asymptomatic relative (who is a Plan member) of an individual with Stickler syndrome is considered experimental and investigational due to limited evidence supporting the clinical validity and clinical utility of testing.

Genetic testing for all indications related to Stickler syndrome that do not meet criteria in the Medical Policy Statement section of this policy require Plan Medical Director review.

w. Thoracic Aortic Aneurysms and Dissections (TAAD) Genetic Testing:

Genetic testing of members clinically diagnosed with TAAD, with a positive family history of the disorder, and for whom a genetic syndrome has been excluded is considered to not be medically necessary due to its limited clinical utility after a clinical diagnosis of TAAD is made. See the Medical Policy Statement section for medically necessary indications for genetic testing related to TAAD; genetic testing for additional indications related to TAAD that do not meet criteria in the Medical Policy Statement section of this policy require Plan Medical Director review.

x. Thrombophilia Genetic Testing:

See Plan policy, Genetic Testing for Hereditary Thrombophilia (policy number OCA 3.728), rather than this policy for prior authorization guidelines and limitations related to genetic testing to diagnose hereditary thrombophilia.
y. Thyroid Cancer Testing:

(1) BRAF p.Val600Glu (V600E) testing is considered experimental and investigational for individuals with indeterminate thyroid fine-needle aspiration biopsy cytology to diagnosis papillary thyroid carcinoma (PTC) due to limited evidence supporting the clinical validity and clinical utility of testing.

(2) BRAF p.Val600Glu (V600E) testing for members diagnosed with PTC for assessment of patient prognosis is considered experimental and investigational due to limited evidence supporting the clinical validity and clinical utility of testing.

(3) The Plan considers the use of the Afirma Thyroid FNA Analysis Test (Veracyte Inc.), a gene expression test used for the evaluation of patients with thyroid nodules who are being evaluated for the possibility of a thyroid malignancy, to be experimental and investigational for any indication.

(4) The miRInform Thyroid test (Asuragen Inc.) is considered experimental and investigational when used with members with thyroid nodules to evaluate genetic variants that may be associated with a thyroid nodule malignancy or for any other indication.

Genetic testing for all indications related to thyroid cancer that do not meet criteria in the Medical Policy Statement section of this policy require Plan Medical Director review. See the Plan’s policy, *Gene Expression Profiling of Tumor Tissue to Predict Cancer Recurrence and Risk Stratification (Including Oncotype DX™ and Other Tests)*, policy number OCA 3.572, rather than this policy for Plan guidelines related to gene expression analysis using a proprietary risk classifier to categorize indeterminant lesions or tumors, as determined from biopsy specimen (e.g., Afirma Thyroid FNA Analysis by Veracyte Inc. and RosettaGX Reveal by Rosetta Genomics Ltd.). See the Plan’s *Experimental and Investigational Treatment* medical policy, policy number OCA 3.12, for the product-specific definitions of experimental or investigational treatment. Review the Plan’s *Medically Necessary* medical policy, policy number OCA 3.14, for the product-specific definitions of medically necessary treatment. The Plan’s *Preimplantation Genetic Testing (Preimplantation Genetic Diagnosis and Preimplantation Genetic Screening)* medical policy, policy number OCA 3.726, includes applicable clinical criteria for preimplantation genetic testing and associated procedures performed on gametes or embryos; it is important to verify the member’s benefit coverage for these services (e.g., services are excluded from coverage for MassHealth and Senior Care Options products).
Definitions

**CHARGE Syndrome:** CHARGE stands for coloboma, heart defect, atresia choanae (also known as choanal atresia), retarded growth and development, genital abnormality, and ear abnormality. The pattern of malformations varies among individuals with this disorder, and infants often have multiple life-threatening medical conditions. The diagnosis of CHARGE syndrome is based on a combination of major and minor characteristics that affects many areas of the body. The major characteristics of CHARGE syndrome are more specific to this disorder than are the minor characteristics. Many individuals with CHARGE syndrome have missing pieces of tissue in structures that form the eye (coloboma), which forms during early development. A coloboma may be present in one or both eyes and can affect a person's vision, depending on its size and location. Some people also have small eyes (microphthalmia). One or both nasal passages may be narrowed (choanal stenosis) or completely blocked (choanal atresia). Individuals with CHARGE syndrome frequently have cranial nerve abnormalities that can cause swallowing problems, facial paralysis, a sense of smell that is diminished (hyposmia) or completely absent (anosmia), and mild to profound hearing loss. People with CHARGE syndrome also typically have middle and inner ear abnormalities and unusually shaped ears. CHARGE syndrome occurs in approximately 1 in 8,500 to 10,000 individuals. (Source: U.S. Library of Medicine.)

**Chromosomal Microarray Analysis (CMA):** Also known as cytogenomic microarray analysis or cytogenomic constitutional (genome-wide) microarray analysis, CMA is a high-resolution, whole-genome screening used as a diagnostic tool to identify genetic abnormalities not detected with conventional cytogenetic analysis (e.g., karyotyping and FISH); CMA provides more refined testing by detecting smaller deletions and duplications in genomic material, potentially increasing the diagnostic yield in targeted populations. CMA collectively describes two (2) different laboratory techniques, comparative genomic hybridization (CGH) and single nucleotide polymorphism (SNP) arrays.

**Copy Number Variants (CNVs):** An alteration of the DNA of a genome that results in the cell having an abnormal number of copies of one or more sections of the DNA.

**Ehlers-Danlos Syndrome (EDS) Classic Type:** Ehlers-Danlos syndrome (EDS) is a group of heritable connective tissue disorders that is typically divided into 6 major subtypes. The classic type of EDS (which includes earlier classifications of EDS types I and II) is estimated to occur in 1 in 20,000 individuals and is characterized by significant joint laxity, hyperelastic skin, and atrophic scars resulting from tissue fragility. Individuals with classic EDS are likely to experience recurrent joint dislocations, musculoskeletal abnormalities (such as flat feet and spinal curvatures), and easy bruising. Additional features include the presence of molluscod pseudotumors (fleshy lesions associated with scars) and subcutaneous spheroids (small, hard, spherical bodies under the skin that are frequently palpable and mobile). They also have an increased risk for delays in gross motor development, hernias, rectal prolapse, cervical insufficiency, and premature rupture of the amniotic membranes during pregnancy.
Ehlers-Danlos Syndrome Type IV (EDS IV): Ehlers-Danlos syndrome (EDS) is a group of heritable connective tissue disorders that is typically divided into 6 major subtypes. EDS type IV (EDS IV), which is also known as vascular EDS, is the most severe form of the condition and is estimated to account for 5% to 10% of all EDS cases. EDS IV is characterized by a significant risk for arterial and gastrointestinal rupture, as well as an increased risk of uterine rupture during pregnancy. Individuals with EDS IV may also have thin, transparent skin with easy and extensive bruising, and may exhibit characteristic facial features such as thin lips, thin nose, small chin, and prominent eyes. EDS IV is inherited in an autosomal dominant manner resulting from variants in the collagen type III, alpha 1 (COL3A1) gene. It is estimated that up to 98% of patients with a clinical diagnosis of EDS IV have a detectable variant in COL3A1, with approximately half have inherited the disease-causing variant from an affected parent and half have a de novo sequence variant with no family history of EDS.

ELANE-Related Neutropenia: Congenital neutropenia and cyclic neutropenia are severe hematologic disorders of neutrophil production that result in lifelong recurrent fever, and skin and oropharyngeal inflammation. Congenital and cyclic neutropenia were originally thought to be distinct disorders; however, they are now known to be a spectrum of disease due to variants in the ELANE gene (also known as ELA2), collectively called ELANE-related neutropenia.

First-Degree Relative: A blood relative of an individual who shares approximately 50% of the individual’s genes as defined as a parent, full sibling, and children.

Gene Expression Testing: Tests that measure the level of specific RNA in a tissue or bodily fluid at a given point in time to provide information on the individual’s current disease state, predict an individual’s response to treatment, or predict the likelihood of future disease with risk stratification; RNA levels change over time based on pathological conditions and environmental signals. This Plan policy includes guidelines for gene expression testing used to predict response to drug treatment (pharmacogenetics). See Plan policy, Gene Expression Profiling of Tumor Tissue to Predict Cancer Recurrence and Risk Stratification (Including Oncotype DX™ and Other Tests), policy number OCA 3.572, for Plan guidelines for gene expression profiling for other indications.

Genetic Testing: According to U.S. Library of Medicine, genetic testing is defined as a type of medical test that identifies changes in chromosomes, genes, or proteins. The results of a genetic test can confirm or rule out a suspected genetic condition or help determine a person’s chance of developing or passing on a genetic disorder. More than 1,000 genetic tests are currently in use, and more are being developed. Several methods can be used for genetic testing:

1. Molecular genetic tests (or gene tests) study single genes or short lengths of DNA to identify variations or mutations that lead to a genetic disorder.

2. Chromosomal genetic tests analyze whole chromosomes to see if there are large genetic changes, such as an extra copy of a chromosome or missing DNA, that cause a genetic condition.
3. Biochemical genetic tests study the amount or activity level of proteins; abnormalities in either can indicate changes to the DNA that result in a genetic disorder.

**Genome:** The entire set of genetic instructions found in a cell. In humans, the genome consists of 23 pairs of chromosomes, found in the nucleus, as well as a small chromosome found in the cells' mitochondria. These chromosomes, taken together, contain approximately 3.1 billion bases of DNA sequence.

**Ghent Diagnostic Criteria:** Criteria used to diagnose Marfan syndrome. According to Ghent diagnostic criteria, an individual with no family history of Marfan syndrome must have major involvement of two systems and minor involvement of a third in order to be diagnosed with the condition. In those with an affected first-degree relative, a clinical diagnosis requires major involvement of one system and minor involvement of a second. For a diagnosis of neonatal Marfan syndrome, a severe, early-onset form of the condition, an infant must demonstrate significant cardiovascular involvement before 4 weeks of age.

**Hereditary Neuralgic Amyotrophy (HNA):** Also known as hereditary brachial plexus neuropathy or neuritis with brachial predilection, HNA is a rare progressive neurological disorder characterized by sudden onset of severe pain in the shoulder girdle or upper limb that lasts for several weeks, followed by amyotrophy (muscle wasting or atrophy). Variants in the septin 9 (SEPT9) gene have been associated with HNA, but the clinical utility and clinical validity of genetic testing for this indication have not been completely established for this indication due to the rarity of the disorder.

**High-Risk:** Includes members with a personal or family history of an autosomal dominant, autosomal recessive, X-linked recessive, or X-linked dominant condition; or individuals with a family history of a chromosomal abnormality, including chromosomal translocation or inversion.

**Immunohistochemistry (IHC):** A laboratory test that uses antibodies to test for certain antigens in a sample of tissue. The antibody is usually linked to a radioactive substance or a dye that causes the antigens in the tissue to light up under a microscope. Immunohistochemistry is used to help diagnose diseases, such as cancer. It may also be used to help tell the difference between different types of cancer.

**Immunostaining:** Any of several staining techniques that are used to detect specific proteins in a sample.

**Kabuki Syndrome:** Disorder characterized by facial features including arched eyebrows, long eyelashes, long openings of the eyelids with lower lids everted at the outside edges, a flat and broadened tip of the nose, and large protruding earlobes. Individuals with Kabuki syndrome have mild to severe developmental delay and intellectual disability. Affected individuals may also have seizures, microcephaly, hypotonia, nystagmus, strabismus, short stature, and skeletal abnormalities. A wide variety of other health problems may occur in individuals with Kabuki syndrome, including heart abnormalities, otitis media, hearing loss, and early puberty.

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**Marfan Syndrome:** An autosomal dominant connective tissue disorder, primarily involving the skeletal, cardiovascular, and ocular systems. It is estimated to affect 1 in 5000 individuals. Marfan syndrome is typically caused by variants in the fibrillin-1 gene (FBN1), located on chromosome 15 at band q21.1. However, variants in the transforming growth factor beta receptor genes TGFBR1 and TGFBR2 have also been reported in individuals with connective tissue disorders similar to Marfan syndrome. Marfan syndrome gene testing is typically performed by direct sequence analysis of FBN1, TGFBR1, and/or TGFBR2 coding exons and intron-exon junctions.

**Microdeletions:** Small segments of DNA missing from a specific chromosome.

**Microsatellite Instability (MSI):** A change that occurs in the DNA of certain cells (such as tumor cells) in which the number of repeats of microsatellites (short, repeated sequences of DNA) is different than the number of repeats that was in the DNA when it was inherited. The cause of microsatellite instability may be a defect in the ability to repair mistakes made when DNA is copied in the cell.

**Molar Pregnancy/Hydatidiform Mole:** Tumor of the trophoblast of the embryo which under normal conditions develops into the placenta. Molar pregnancy is part of a group of diseases classified as gestational trophoblastic disease (GTD), which originates in the placenta and has the potential to locally invade the uterus and metastasize. The maternal tumor arises from gestational rather than maternal tissue, triggering symptoms of pregnancy. In a complete molar pregnancy, there's no embryo or normal placental tissue. Partial molar pregnancies are rare conceptions characterized by having 69 rather than 46 chromosomes, the additional chromosome complement usually occurring as a result of fertilization of the ovum by two sperm.

**Multigene Panel Tests:** Tests that evaluate more than one (1) gene simultaneously to detect changes in gene expression most commonly associated with certain diseases and other genes that may have limited evidence of an association to the disorder. Multigene panel tests may involve traditional exon-by-exon sequencing of targeted genes to identify genetic variants or use next-generation sequencing. Each laboratory establishes its own set of criteria for selecting the genes represented in a panel, even when panels are used for the same or similar clinical indications. The lack of regulatory oversight of genetic testing means that laboratories can change the components of a panel at any time, making it difficult to evaluate the clinical utility of multigene panel tests. Examples include but are not limited to the following: CancerNext Next-Gen Cancer Panel (Ambry Genetics Corp.), Comprehensive Personalized Medicine Panel (Alpha-Genomix Laboratories), Cytochrome P450 3A4 (CYP3A4) genotype testing (Mayo Medical Laboratories), Genecept Assay (Genomind), MI TumorSeek (Caris Life Sciences), Endometrial Cancer Panel (GeneDx), GYNPlus, High/Moderate Risk Panel, iGene Cancer Panel (ApolloGen Molecular Diagnostics Laboratory), PancNext, Pancreatic Cancer Panel, Preventest, SYMGENE NGS Cancer Panel, and/or VistaSeq Hereditary Cancer Panel.
Next-Generation Sequencing (NGS or Massively Parallel Sequencing): Genetic testing that involves sequencing of millions of DNA fragments using the following three (3) levels of molecular analysis: (1) disease-targeted gene panels to sequence genes with an established role in the targeted disease, (2) exome sequencing of coding regions of the genome to include less common variants associated with the disease (i.e., a coding region is the segment of a gene that contains a protein-coding sequence called an exon in all 22,000 genes of the human genome); and (3) genome sequencing of both the coding and non-coding regions of the genome (i.e., the non-coding regions in between exons are called introns). Multiple sequencing platforms and different processes result in variability in test results among laboratories. Multigene panel tests may involve traditional exon-by-exon sequencing of targeted genes to identify genetic variants or use next-generation sequencing.

Noninvasive Prenatal Testing (NIPT): Also known as noninvasive prenatal screening or NIPS (and previously referred to as noninvasive prenatal diagnosis or NIPD), NIPT is an advanced screening test used to identify fetal aneuploidy (i.e., carrying a fetus with missing or extra chromosomes) in a noninvasive manner using only a maternal blood sample. Most of these aneuploidies involve the presence of an extra chromosome (referred to as trisomy), such as trisomy 21 (T21 or Down syndrome), trisomy 18 (T18 or Edwards syndrome), trisomy 13 (T13 or Patau syndrome), 47, XXY (Klinefelter syndrome), triple X (47,XXX), and 47, XYY syndrome. However, the loss of a single chromosome (monosomy) is also tested (e.g., Turner syndrome, 45,X or monosomy X).

Cell-free fetal DNA (cffDNA) is fetal DNA circulating in maternal blood and constitutes approximately 10% of the DNA in maternal plasma (the cell-free portion of blood). cffDNA can be detected early in pregnancy, allowing NIPT testing to generally performed at 10 weeks gestation or beyond. All NIPT assays use cffDNA in a mother’s blood during pregnancy to assess the chromosome number for the fetus (i.e., an increase/decrease in the representation of the particular chromosome being tested). The methodology and data analysis for NIPT vary by product (and therefore some products may be considered medically necessary by the Plan when applicable criteria are met and other NIPT assays may be considered experimental and investigational). Examples of NIPT assays include the Harmony Prenatal Test (Ariosa Diagnostics Inc.), informaSeq (Integrated Genetics), MaterniT21 PLUS (Sequenom Laboratories), Panorama Prenatal Test (Natera Inc.), Verifi Prenatal Test ([Illumina Inc.], and VisibiliT (Sequenom). Test results are typically received within 8 to 15 days. Most NIPT assays test for aneuploidies involving chromosomes 21, 18, 13, and the sex chromosomes; some products now also offer testing for additional chromosomal disorders.

NIPT is expected to increase the number of prenatal diagnoses of fetal aneuploidy (by serving as a an initial screening tool), decrease the number of unnecessary invasive testing procedures performed, and decrease the number of procedure-related pregnancy losses. The prenatal diagnosis of chromosome abnormalities requires an analysis of fetal cells obtained by either chorionic villus sampling (CVS) or amniocentesis, invasive procedures that are associated with a risk of fetal loss (up to 1 percent). Because of the risk associated with CVS and amniocentesis, most women elect to have a noninvasive screening test (e.g., ultrasound, NIPT, and other blood tests) to better assess their personal risk of carrying a fetus with an aneuploidy before considering invasive testing options.

Genetic Testing Guidelines and Pharmacogenetics

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Pelizaeus-Merzbacher Disease (PMD): A rare X-linked genetic disorder affecting the central nervous system that is associated with abnormalities of the white matter of the brain and spinal cord. PMD typically manifests in infancy or early childhood. Symptoms develop due to lack of myelin sheath of nerve cell fibers. Many areas of the central nervous system may be affected, including the deep portions of the cerebrum (subcortical), cerebellum, brain stem and spinal cord. The findings progress to severe spasticity and ataxia with progressive deterioration of intellectual function. PMD is associated with mutations in the PLP1 gene. Several forms of the disorder have been identified including classic PMD; connatal PMD; transitional PMD; and PLP1 null syndrome. Forms of complicated spastic paraparesis and pure spastic paraparesis (designated SPG2) are also caused by the PLP1 gene. (Source: National Organization for Rare Disorders.)

Pitt-Hopkins syndrome (PTHS): A very rare, severe encephalopathy that has been diagnosed in fewer than 250 individuals worldwide. PTHS is characterized by severe intellectual disability, motor incoordination and speech impairment, and characteristic facial features. Individuals with PTHS commonly have seizures and breathing abnormalities such as hyperventilation and apnea. Other symptoms that may occur with PTHS include clubbing of fingers and toes; constipation; postnatal growth slowing, particularly of the head; stereotypical hand movements; flat feet; a single crease across the palms; small hands and feet; ocular anomalies; short stature; subtle brain abnormalities; and cryptorchidism in males (including individuals born with typical male karyotype with only one (1) X chromosome). Symptoms of PTHS overlap with those of similar intellectual disability disorders such as Angelman (AS), Rett (RTT), and Mowat-Wilson (MWS) syndromes. PTHS is associated with genetic variants in the transcription factor 4 (TCF4) gene.

PLP1-Related Disorder: PLP1-related disorders of central nervous system myelin formation include a range of phenotypes from Pelizaeus-Merzbacher disease (PMD) to spastic paraplegia 2 (SPG2). Life span is shortened with PMD. SPG2 manifests as spastic paraparesis with or without CNS involvement and individual usually have a normal life span.

Rett Syndrome (RTT): A pervasive neurodevelopmental disorder. In the classic form, which is found almost exclusively in phenotypical females (including individuals with typical female with two [2] X chromosomes), growth and development initially appear normal. Starting between 6 and 18 months of age, development and purposeful movement regress, and growth of head and brain slows. Compulsive hand motions are typical, as are breathing and gait abnormalities and small, cold hands and feet. Seizures, spasticity, and scoliosis are frequently noted. The congenital variant of RTT, which is found in both females (including individuals with typical female karyotype with two [2] X chromosomes) and males (including individuals with typical male karyotype with only one [1] X chromosome), has been diagnosed in only a small number of cases of RTT. Congenital RTT is similar to classic RTT, but is characterized by earlier onset, in the first months of life.

Second-Degree Relative: A blood relative of an individual who shares approximately 25% of the individual’s genes as defined as a grandparent, grandchildren, aunt, uncle, nephew, niece, and half-siblings.
**Single Nucleotide Polymorphisms (SNPs):** The most common type of genetic variation among individuals. Each SNP represents a difference in a single DNA building block, called a nucleotide. SNPs occur normally throughout a person’s DNA; normally these variations are found in the DNA between genes. If more than one (1) percent of a population does not carry the same nucleotide at a specific position in the DNA sequence, then this variation can be classified as a SNP. Most SNPs have no effect on health or development. When there is sufficient scientific evidence to support the clinical utility of testing, SNPs may help predict an individual’s response to certain drugs, susceptibility to environmental factors, risk of developing particular diseases, and/or susceptibility to genetic diseases within families.

**Stickler Syndrome:** A multisystem genetic disorder characterized by manifestations in the eyes, hearing ability, facial features, and skeletal system. Abnormalities in the vitreous formation of the eye (the clear gelatinous material that fills the space between the lens and the retina) is characteristic of Stickler syndrome, often causing severe myopia detectable in the newborn period and typically does not progress with age. Stickler syndrome is the most common form of inherited cause of retinal detachment in childhood. Hearing impairment occurs in approximately 40% of cases and is usually mild, but can be progressive. The facial features that are characteristic of Stickler syndrome include a flat facial profile caused by underdevelopment of the bones in the face, a small upturned nose, and micrognathia (small jaw). Stickler syndrome is a disease of collagens. Sequence variants in five (5) genes that encode different collagen proteins have been described in association with Stickler syndrome, including collagen type 2A1 (COL2A1), collagen type 11A1 (COL11A1), collagen type 11A2 (COL11A2), collagen type 9A1 (COL9A1), and collagen type 9A2 (COL9A2).

**Third Degree Relative:** A blood relative of an individual who shares 12.5% of the individual’s genes as defined as a biological first cousin, great grandmother, or great grandfather.

**X-linked Disorder:** A chromosomal abnormality caused by mutations in genes on the X chromosome, one (1) of the two (2) sex chromosomes in each cell. In phenotypical females/individuals with two (2) X chromosomes, a mutation in one (1) of the two (2) copies of the gene in each cell is sufficient to cause an X-linked dominant disorder, and a mutation would have to occur in both copies of the gene to cause an X-linked recessive disorder. Because it is unlikely that phenotypical females (including individuals with typical female karyotype with two [2] X chromosomes) will have two (2) altered copies of this gene, phenotypical males (including individuals with typical male karyotype with only one [1] X chromosome) are affected by X-linked recessive disorders much more frequently than phenotypical females (including individuals with typical female karyotype with two [2] X chromosomes). The high clinical variability in female patients often makes the determination of an X-linked dominant disorder vs. an X-linked recessive disorder difficult. In phenotypical males (including individuals with typical male karyotype with only one [1] X chromosome), a mutation in the only copy of the gene in each cell causes an X-linked disorder. A characteristic of X-linked inheritance is that biological fathers (including biological parents with only one [1] X chromosome) cannot pass X-linked traits to their biological sons (including biological children with only one [1] X chromosome); this results in no phenotypical male-to-phenotypical male transmission. Examples of X-linked disorders include adrenoleukodystrophy, Alport syndrome, choroideremia, Fabry disease, fragile X syndrome, hemophilia A, hemophilia B, Hunter
syndrome, incontinentia pigmenti, Lesch-Nyhan syndrome, muscular dystrophy, and X-linked intellectual disability. (Source: Genetic Home Reference from the U. S. Department of Health & Human Services.)

**Whole Exome Sequencing (WES)/ Whole Genome Sequencing (WGS):** WES captures and sequences at a deep level the protein coding regions (called exons) of an individual's genes using first-generation sequencing techniques or next-generation sequencing to detect disease-causing variants and discover gene targets. 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 affecting the disease. WES has been performed in a number of cancers, whereby comparison between tumor DNA and normal DNA from the same individual allows identification of variants specific to the tumor, which may provide information used for diagnosis and treatment. WES is targeted sequencing of the subset of the human genome that contains functionally important sequences of protein-coding DNA, while whole genome sequencing (WGS) uses next-generation sequencing techniques to sequence both coding and non-coding regions of the genome. Because WES only evaluates the protein-coding regions of the human genome (exons), WES is a more cost-effective alternative to WGS. WES produces a smaller, more manageable data set with faster turnaround time for analyses than WGS. WGS has the ability to detect structural variations located outside of the exome that may be related to many diseases and cannot be identified with WES. WES and WGS have been proposed to be more efficient than traditional sequencing methods in discovering the genetic causes of diseases, but there remain issues of error rates due to technical challenges and difficulty interpreting potential causative variants from variants of unknown significance generated for each patient. Examples of tests include but are not limited to the following: TruGenome tests (Illumina), Endometrial Cancer Panel (GeneDx), ExomeNext and ExomeNext-Rapid (Ambry Genetics), XomeDx™ test (GeneDx), mtSEEK Whole Mitochondrial Genome Analysis (Courtagen Life Sciences Inc.), and/or nucSEEK Comprehensive Sequence Analysis of Nuclear Mitochondrial Exome (Courtagen Life Sciences, Inc.). According to The American College of Obstetricians and Gynecologists (Committee Opinion Number 682), the routine use of whole genome or whole exome sequencing for prenatal diagnosis is not recommended outside of the context of clinical trials until sufficient peer-reviewed data and validation studies are published. **Currently, the Plan considers WES and WGS to be experimental and investigational, as specified in the Limitations sections of this policy.**

**Applicable Coding**

The Plan uses and adopts up-to-date Current Procedural Terminology (CPT) codes from the American Medical Association (AMA), International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) diagnosis codes developed by the World Health Organization and adapted in the United Stated by the National Center for Health Statistics (NCHS) of the Centers for Disease Control under the U.S. Department of Health and Human Services, and the Health Care Common Procedure Coding System (HCPCS) established and maintained by the Centers for Medicare & Medicaid Services (CMS). Because the AMA, NCHS, and CMS may update codes more frequently or at different intervals than Plan policy updates, the list of applicable codes included in this Plan policy is for

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Providers are responsible for obtaining prior authorization for the services specified in the Medical Policy Statement section and Limitation section of this Plan policy for **ALL molecular and chromosomal genetic testing**, even if an applicable code appropriately describing the service that is the subject of this Plan policy is not included in the Applicable Coding section of this Plan policy (except for prenatal genetic screening tests for a member with one of the pregnancy diagnosis codes specified in the coding tables listed below). **Biochemical genetic tests** used to study the amount or activity level of proteins to indicate changes to the DNA require prior authorization ONLY when the test is included in the Applicable Coding section of a Plan genetic testing medical policy. Coverage for services is subject to benefit eligibility under the member’s benefit plan. Please refer to the member’s benefits document in effect at the time of the service to determine coverage or non-coverage as it applies to an individual member. See Plan reimbursement policies for Plan billing guidelines.

Refer to the Medical Policies page of the Provider folder at [www.bmchp.org](http://www.bmchp.org) or [www.wellsense.org](http://www.wellsense.org) for information about additional, condition-specific genetic testing and gene expression profiling policies to estimate cancer recurrence rates. Plan prior authorization is required for all genetic testing, even when the applicable code for the genetic test is not listed in a Plan policy.

It is expected that genetic testing is clinically appropriate for the specified indication and that applicable Plan criteria listed in the Medical Policy Statement and Limitations sections of this Plan policy are met for all genetic testing, even when the prior authorization requirement is waived. (For example, a pregnancy diagnosis is not an indication for gene expression profiling of tumor tissue.) The medical necessity for genetic screening test(s) for the pregnant member (for both population-based screening and targeted population-based screening) must be documented in the member’s medical record; the Plan may validated with medical record audit the medical necessity of genetic testing when the prior authorization requirement is waived.

Prior authorization may or may not be required for medically necessary, non-invasive prenatal genetic screening, as specified below in the following sections when Plan criteria are met: Category 1 (Plan-specified routine and high-risk pregnancy diagnosis codes with corresponding procedure codes that do not require prior authorization when billed according to Plan guidelines), Category 2 (Plan-specified high-risk pregnancy diagnosis codes with corresponding procedure codes that do not require prior authorization when billed according to Plan guidelines), and Category 3 (procedure codes that require Plan authorization), and Category 4 (procedure codes considered experimental and investigational for all diagnosis codes). See the following medical policies for additional prenatal genetic tests which do not require prior authorization according to Plan guidelines: **Chromosomal Microarray Analysis for Unexplained Intellectual Disabilities and/or Multiple Congenital Anomalies**, policy number OCA 3.573, and **Genetic Testing for Fragile X-Associated Disorders**, policy number OCA 3.571.

Genetic Testing Guidelines and Pharmacogenetics

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Category 1: Plan-Specified Routine Pregnancy and High-Risk Pregnancy Diagnosis Codes with Corresponding Procedure Codes with Waived Prior Authorization

<table>
<thead>
<tr>
<th>Plan-Specified, Routine and High-Risk Pregnancy ICD-10 Diagnosis Codes</th>
<th>Description: Prior authorization is NOT required for medically necessary, non-invasive prenatal genetic screening (for CPT codes and HCPCS codes specified below) when one (1) of the following Plan-specified, routine and high-risk pregnancy diagnosis codes is listed as the primary diagnosis code on the submitted claim, Plan criteria are met, and it is a clinically appropriate indication for testing.</th>
</tr>
</thead>
<tbody>
<tr>
<td>O09.00-O09.93</td>
<td>Supervision of high risk pregnancy</td>
</tr>
<tr>
<td>O28.5</td>
<td>Abnormal chromosomal and genetic finding on ante-natal screening of mother</td>
</tr>
<tr>
<td>O35.0xxO - O35.9xx9</td>
<td>Maternal care for known or suspected fetal abnormality and damage</td>
</tr>
<tr>
<td>036.90 - 036.93</td>
<td>Maternal care for fetal problem, unspecified</td>
</tr>
<tr>
<td>Z34.00 - Z34.93</td>
<td>Encounter for supervision of normal pregnancy</td>
</tr>
<tr>
<td>Z36.0-Z36.9</td>
<td>Encounter for antenatal screening</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CPT Codes</th>
<th>Description: Codes covered when medically necessary. Prior authorization is required for these CPT codes UNLESS billed with one (1) of the Plan-specified, routine or high-risk pregnancy ICD-10 diagnosis codes listed above in this section as the primary diagnosis. The following prenatal tests are medically necessary as screening tools for cystic fibrosis:</th>
</tr>
</thead>
<tbody>
<tr>
<td>81220</td>
<td>CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; common variants (e.g., ACMG/ACOG guidelines)</td>
</tr>
<tr>
<td>81221</td>
<td>CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; known familial variants</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
<th>Plan Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>81222</td>
<td>CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; duplication/deletion variants</td>
<td></td>
</tr>
<tr>
<td>81223</td>
<td>CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; full gene sequence</td>
<td>Plan note: According to the American College of Obstetricians and Gynecologists and the American College of Medical Genetics Update on Carrier Screening for Cystic Fibrosis Committee Opinion (number 486, reaffirmed 2014), “complete analysis of the CFTR gene by DNA sequencing is not appropriate for routine carrier screening because it may yield results that can be difficult to interpret. This type of testing is generally reserved for patients with cystic fibrosis (CF), patients with a family history of CF, males with congenital bilateral absence of the vas deferens, or newborns with a positive newborn screening result when mutation testing, using the standard 23-mutation panel, has a negative result. Because carrier screening detects most mutations, sequence analysis should only be considered after discussion with a genetics professional to determine if it will be of value to the evaluation after standard screening has been performed.” Testing may also be conducted on individuals born with male reproductive organs/typical male karyotype with only one (1) X chromosome with congenital bilateral absence of vas deferens.</td>
</tr>
<tr>
<td>81224</td>
<td>CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; intron 8 poly-T analysis (e.g., male infertility)</td>
<td>Plan note: Male infertility includes conditions related to infertility in individuals born with male reproductive organs and/or individuals with typical male karyotype with only one (1) X chromosome.</td>
</tr>
</tbody>
</table>
The following prenatal tests of fetal aneuploidy are medically necessary as screening tools for trisomy 21 (Down syndrome), trisomy 18 (Edwards syndrome) or trisomy 13 (Patau syndrome):

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81420</td>
<td>Fetal chromosomal aneuploidy (e.g., trisomy 21, monosomy X) genomic sequence analysis panel, circulating cell-free fetal DNA in maternal blood, must include analysis of chromosomes 13, 18, and 21</td>
</tr>
</tbody>
</table>

Plan note: Code used for noninvasive prenatal testing (NIPT). All NIPT assays use cell-free fetal DNA (cffDNA) in a mother’s blood during pregnancy to assess the chromosome number for the fetus (i.e., an increase/decrease in the representation of the particular chromosome being tested). The methodology and data analysis for NIPT vary by product (and therefore some products may be considered medically necessary by the Plan when applicable criteria are met and other NIPT assays may be considered experimental and investigational). See the Medical Policy Statement and Limitations sections for a list of products the Plan considers either medically necessary or experimental and investigational and additional limitations related to all NIPT assays.

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
</tr>
</tbody>
</table>

Plan notes:
1. Providers should use HCPCS code G0452 when billing the interpretation and report for this service.
2. See the Limitations section for testing that the Plan considers not medically necessary, experimental and investigational, and/or requires Plan Medical Director review. Review the Medical Policy Statement section for genetic testing the Plan considers medically necessary when applicable Plan criteria are met.
3. Code may be used for BRACAnalysis CDx® when CPT code 81211 is not appropriate according to industry-standard coding guidelines.
4. Review the Plan’s policy, Gene Expression Profiling of Tumor Tissue to Predict Cancer Recurrence and Risk Stratification (Including Oncotype DX™ and Other Tests), policy number OCA 3.572, rather than this policy for Plan guidelines related to gene expression analysis using a proprietary risk classifier to categorize indeterminant lesions or tumors, as determined from biopsy specimen (e.g., Afirma Thyroid FNA Analysis by Veracyte Inc., RosettaGX Reveal by Rosetta Genomics Ltd., and ThyroSeq v.2 Next Generation Sequencing (CBL Path)).
81507  Fetal aneuploidy (trisomy 21, 18, and 13) DNA sequence analysis of selected regions using maternal plasma, algorithm reported as a risk score of each trisomy

Plan note: Code used for noninvasive prenatal testing (NIPT). All NIPT assays use cell-free fetal DNA (cffDNA) in a mother’s blood during pregnancy to assess the chromosome number for the fetus (i.e., an increase/decrease in the representation of the particular chromosome being tested). The methodology and data analysis for NIPT vary by product (and therefore some products may be considered medically necessary by the Plan when applicable criteria are met and other NIPT assays may be considered experimental and investigational). See the Medical Policy Statement and Limitations sections for a list of products the Plan considers either medically necessary or experimental and investigational and additional limitations related to all NIPT assays.

The following prenatal tests are medically necessary as screening tools for Tay–Sachs disease:

81255  HEXA (hexosaminidase A [alpha polypeptide]) (e.g., Tay-Sachs disease) gene analysis, common variants (e.g., 1278insTATC, 1421+1G>C, G269S)

## Category 2: Plan-Specified High-Risk Pregnancy Diagnosis Codes with Corresponding Procedure Codes with Waived Prior Authorization

<table>
<thead>
<tr>
<th>Plan-Specified, High-Risk ICD-10 Diagnosis Codes</th>
<th>Description: Prior authorization is NOT required for medically necessary, noninvasive prenatal genetic screening (for CPT codes and HCPCS codes specified below) when one (1) of the following Plan-specified, high-risk pregnancy diagnosis codes is listed as the primary diagnosis code on the submitted claim, Plan criteria are met, and it is a clinically appropriate indication for testing.</th>
</tr>
</thead>
</table>
| O09.512 - O09.519  Elderly Primigravida | Plan notes:
1. See Plan policies, Genetic Testing for Fragile X-Associated Disorders [policy number OCA 3.571] and Chromosomal Microarray Analysis for Unexplained Intellectual Disabilities and/or Multiple Congenital Anomalies [policy number OCA 3.573], for additional prior authorization guidelines for genetic tests with waived pregnancy diagnosis codes.
2. A mother may include a female member, a member born with female reproductive organs, and/or a member with typical female karyotype with two (2) X chromosomes.
3. See the Medical Policy Statement and Limitations sections for Plan guidelines related to noninvasive prenatal testing (NIPT). |
| O09.521 - O09.529  Elderly Multigravida | |

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<table>
<thead>
<tr>
<th>CPT Codes</th>
<th>Description: Codes covered when medically necessary. Prior authorization is required for these CPT codes UNLESS billed with one (1) of the Plan-specified, high-risk pregnancy ICD-10 diagnosis codes listed above in this section as the primary diagnosis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0009U</td>
<td>Oncology (breast cancer), ERBB2 (HER2) copy number by FISH, tumor cells from formalin fixed paraffin embedded tissue isolated using image-based dielectrophoresis (DEP) sorting, reported as ERBB2 gene amplified or non-amplified</td>
</tr>
<tr>
<td>0015U</td>
<td>Drug metabolism (adverse drug reactions), DNA, 22 drug metabolism and transporter genes, real-time PCR, blood or buccal swab, genotype and metabolizer status for therapeutic decision support</td>
</tr>
<tr>
<td>0016U</td>
<td>Oncology (hematolymphoid neoplasia), RNA, BCR/ABL1 major and minor breakpoint fusion transcripts, quantitative PCR amplification, blood or bone marrow, report of fusion not detected or detected with quantitation</td>
</tr>
<tr>
<td>0017U</td>
<td>Oncology (hematolymphoid neoplasia), JAK2 mutation, DNA, PCR amplification of exons 12-14 and sequence analysis, blood or bone marrow, report of JAK2 mutation not detected or detected</td>
</tr>
<tr>
<td>81161</td>
<td>DMD (dystrophin) (e.g., Duchenne/Becker muscular dystrophy) deletion analysis, and duplication analysis, if performed</td>
</tr>
<tr>
<td>81170</td>
<td>ABL1 (ABL proto-oncogene 1, non-receptor tyrosine kinase) (e.g., acquired imatinib tyrosine kinase inhibitor resistance), gene analysis, variants in the kinase domain</td>
</tr>
<tr>
<td>81200</td>
<td>ASPA (aspartoacylase) (e.g., Canavan disease) gene analysis, common variants (e.g., E285A, Y231X)</td>
</tr>
<tr>
<td>81205</td>
<td>BCKDHB (branched-chain keto acid dehydrogenase E1, beta polypeptide) (e.g., Maple syrup urine disease) gene analysis, common variants (e.g., R183P, G278S, E422X)</td>
</tr>
<tr>
<td>81206</td>
<td>BCR/ABL1 (t9;22)) (e.g., chronic myelogenous leukemia) translocation analysis; major breakpoint, qualitative or quantitative</td>
</tr>
<tr>
<td>81207</td>
<td>BCR/ABL1 (t9;22)) (e.g., chronic myelogenous leukemia) translocation analysis; minor breakpoint, qualitative or quantitative</td>
</tr>
<tr>
<td>81208</td>
<td>BCR/ABL1 (t9;22)) (e.g., chronic myelogenous leukemia) translocation analysis; other breakpoint, qualitative or quantitative</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81209</td>
<td>BLM (Bloom syndrome, RecQ helicase-like) (e.g., Bloom syndrome) gene analysis, 2281del6Ins7 variant</td>
</tr>
<tr>
<td>81210</td>
<td>BRAF (B-Raf proto-oncogene, serine/threonine kinase)(e.g., colon cancer, melanoma), gene analysis, V600 variant(s)</td>
</tr>
<tr>
<td>81218</td>
<td>CEBPA (CCAAT/enhancer binding protein[C/EBP], alpha) (e.g., acute myeloid leukemia), gene analysis, full gene sequence</td>
</tr>
<tr>
<td>81219</td>
<td>CALR (calreticulin) (e.g., myeloproliferative disorders), gene analysis, common variants in exon 9</td>
</tr>
<tr>
<td>81220</td>
<td>CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; common variants (e.g., ACMG/ACOG guidelines)</td>
</tr>
<tr>
<td>81221</td>
<td>CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; known familial variants</td>
</tr>
<tr>
<td>81222</td>
<td>CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; duplication/deletion variants</td>
</tr>
<tr>
<td>81223</td>
<td>CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; full gene sequence</td>
</tr>
</tbody>
</table>

Plan note: According to the American College of Obstetricians and Gynecologists and the American College of Medical Genetics Update on Carrier Screening for Cystic Fibrosis Committee Opinion (number 486, reaffirmed 2014), “complete analysis of the CFTR gene by DNA sequencing is not appropriate for routine carrier screening because it may yield results that can be difficult to interpret. This type of testing is generally reserved for patients with cystic fibrosis (CF), patients with a family history of CF, males with congenital bilateral absence of the vas deferens, or newborns with a positive newborn screening result when mutation testing, using the standard 23-mutation panel, has a negative result. Because carrier screening detects most mutations, sequence analysis should only be considered after discussion with a genetics professional to determine if it will be of value to the evaluation after standard screening has been performed.” Testing may also be conducted on individuals born with male reproductive organs and/or with typical male karyotype with only one (1) X chromosome with congenital bilateral absence of vas deferens. |
| 81224 | CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; intron 8 poly-T analysis (e.g., male infertility) |

Plan note: Male infertility includes conditions related to infertility in individuals born with male reproductive organs and/or with typical male karyotype with only one (1) X chromosome. |
| 81225 | CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *4, *8, *17) |

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<tr>
<th>Code</th>
<th>Description</th>
<th>Variants/Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>81227</td>
<td>CYP2C9 (Cytochrome P450, family 2, subfamily C, polypeptide 9) (e.g., drug metabolism)</td>
<td>gene analysis, common variants (e.g., *2, *3, *5, *6)</td>
</tr>
<tr>
<td>81228</td>
<td>Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants (e.g., Bacterial Artificial Chromosome [BAC] or oligo-based comparative genomic hybridization [CGH] microarray analysis)</td>
<td>Plan note: See Plan policy, <em>Chromosomal Microarray Analysis for Unexplained Intellectual Disabilities and/or Multiple Congenital Anomalies</em>, policy number OCA 3.573, for Plan prior authorization guidelines for microarray analysis for genetic testing for unexplained intellectual disability, developmental delay, multiple congenital anomalies, and/or mental retardation. Use this Plan policy for microarray analysis testing for any indication not specified in policy number OCA 3.573.</td>
</tr>
<tr>
<td>81229</td>
<td>Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities</td>
<td>Plan note: See Plan’s <em>Chromosomal Microarray Analysis for Unexplained Intellectual Disabilities and/or Multiple Congenital Anomalies</em> medical policy, policy number OCA 3.573, for Plan prior authorization guidelines for microarray analysis for genetic testing for unexplained intellectual disability, developmental delay, multiple congenital anomalies, and/or mental retardation. Use this Plan policy for microarray analysis testing for any indication not specified in policy number OCA 3.573.</td>
</tr>
<tr>
<td>81235</td>
<td>EGFR (epidermal growth factor receptor) (e.g., non-small cell lung cancer) gene analysis, common variants (e.g., exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q)</td>
<td></td>
</tr>
<tr>
<td>81240</td>
<td>F2 (prothrombin, coagulation factor II) (e.g., hereditary hypercoagulability) gene analysis, 20210G&gt;A variant</td>
<td></td>
</tr>
<tr>
<td>81241</td>
<td>F5 (coagulation Factor V) (e.g., hereditary hypercoagulability) gene analysis, Leiden variant</td>
<td></td>
</tr>
<tr>
<td>81242</td>
<td>FANCC (Fanconi anemia, complementation group C) (e.g., Fanconi anemia, type C) gene analysis, common variant (e.g., IVS4+4A&gt;T)</td>
<td></td>
</tr>
<tr>
<td>81245</td>
<td>FLT3 (fms-related tyrosine kinase 3) (e.g., acute myeloid leukemia), gene analysis, internal tandem duplication (ITD) variants (i.e., exons 14, 15)</td>
<td></td>
</tr>
<tr>
<td>81246</td>
<td>FLT3 (fms-related tyrosine kinase 3) (e.g., acute myeloid leukemia), gene analysis; tyrosine kinase domain (TKD) variants (e.g., D835, I836)</td>
<td></td>
</tr>
<tr>
<td>81250</td>
<td>G6PC (glucose-6-phosphatase, catalytic subunit) (e.g., Glycogen storage disease, Type 1a, von Gierke disease) gene analysis, common variants (e.g., R83C, Q347X)</td>
<td></td>
</tr>
<tr>
<td>81251</td>
<td>GBA (glucosidase, beta, acid) (e.g., Gaucher disease) gene analysis, common variants (e.g., N370S, 84GG, L444P, IVS2+1G&gt;A)</td>
<td></td>
</tr>
<tr>
<td>81252</td>
<td>GJB2 (gap junction protein, beta 2, 26kDa; connexin 26) (e.g., nonsyndromic hearing loss) gene analysis; full gene sequence</td>
<td></td>
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</table>

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<table>
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<tr>
<th>Code</th>
<th>Gene Name</th>
<th>Variant Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>81253</td>
<td>GJB2 (gap junction protein, beta 2, 26kDa; connexin 26) (e.g., nonsyndromic hearing loss) gene analysis; known familial variants</td>
<td></td>
</tr>
<tr>
<td>81254</td>
<td>GJB6 (gap junction protein, beta 6, 30kDa, connexin 30) (e.g., nonsyndromic hearing loss) gene analysis, common variants (e.g., 309kb [del(GJB6-D13S1830)] and 232kb [del(GJB6-D13S1854)])</td>
<td></td>
</tr>
<tr>
<td>81255</td>
<td>HEXA (hexosaminidase A [alpha polypeptide]) (e.g., Tay-Sachs disease) gene analysis, common variants (e.g., 1278insTATC, 1421+1G&gt;C, G269S)</td>
<td></td>
</tr>
<tr>
<td>81256</td>
<td>HFE (hemochromatosis) (e.g., hereditary hemochromatosis) gene analysis, common variants (e.g., C282Y, H63D)</td>
<td></td>
</tr>
<tr>
<td>81257</td>
<td>HBA1/HBA2 (alpha globin 1 and alpha globin 2) (e.g., alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH Disease), gene analysis, for common deletions or variant (e.g., Southeast Asian, Thai, Filipino, Mediterranean, alpha3.7, alpha4.2, alpha20.5, and Constant Spring)</td>
<td></td>
</tr>
<tr>
<td>81259</td>
<td>IKBKBAP (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein) (e.g., familial dysautonomia) gene analysis, common variants (e.g., 2507+6T&gt;C, R696P)</td>
<td></td>
</tr>
<tr>
<td>81261</td>
<td>IGH@ (Immunoglobulin heavy chain locus) (e.g., leukemias and lymphomas, B-cell), gene rearrangement analysis to detect abnormal clonal population(s); amplified methodology (e.g., polymerase chain reaction)</td>
<td></td>
</tr>
<tr>
<td>81262</td>
<td>IGH@ (Immunoglobulin heavy chain locus) (e.g., leukemias and lymphomas, B-cell), gene rearrangement analysis to detect abnormal clonal population(s); direct probe methodology (e.g., Southern blot)</td>
<td></td>
</tr>
<tr>
<td>81263</td>
<td>IGKBAP (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein) (e.g., familial dysautonomia) gene analysis, common variants (e.g., 2507+6T&gt;C, R696P)</td>
<td></td>
</tr>
<tr>
<td>81264</td>
<td>IGK@ (Immunoglobulin kappa light chain locus) (e.g., leukemia and lymphoma, B-cell), gene rearrangement analysis, evaluation to detect abnormal clonal population(s)</td>
<td></td>
</tr>
<tr>
<td>81270</td>
<td>JAK2 (Janus kinase 2) (e.g., myeloproliferative disorder) gene analysis, P.Val617Phe (V617F) variant</td>
<td></td>
</tr>
<tr>
<td>81272</td>
<td>KIT (v-kit-Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (e.g., gastrointestinal stromal tumor [GIST], acute myeloid leukemia, melanoma), gene analysis, targeted sequence analysis (e.g., exons 8,11,13,17,18)</td>
<td></td>
</tr>
<tr>
<td>81273</td>
<td>KIT(v-kit-Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (e.g., mastocytosis), gene analysis, D816 variant(s)</td>
<td></td>
</tr>
<tr>
<td>81275</td>
<td>KRAS (Kirsten rat sarcoma viral oncogene homolog) (e.g., carcinoma) gene analysis, variants in exon 2 (e.g, codons 12 and 13)</td>
<td></td>
</tr>
<tr>
<td>81276</td>
<td>KRAS (V-Ki-ras2 Kirsten rat sarcoma viral oncogene) (e.g., carcinoma) gene analysis, variants in codons 12 and 13; additional variants(s) (e.g., codon 61, codon 146)</td>
<td></td>
</tr>
<tr>
<td>81287</td>
<td>MGMT (O-6-methylguanine-DNA methyltransferase) (e.g., glioblastoma multiforme), methylation analysis</td>
<td></td>
</tr>
<tr>
<td>81290</td>
<td>MCOLN1 (mucolipin 1) (e.g., Mucolipidosis, type IV) gene analysis, common variants (e.g., IVS3-2A&gt;G, del6.4kb)</td>
<td></td>
</tr>
</tbody>
</table>

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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>81291</td>
<td>MTHFR (5,10-methylenetetrahydrofolate reductase) (e.g., hereditary hypercoagulability) gene analysis, common variants (e.g., 677T, 1298C)</td>
</tr>
</tbody>
</table>

Plan note: See Plan policy, *Genetic Testing for Hereditary Thrombophilia* (policy number OCA 3.728) rather than this policy for prior authorization guidelines for MTHFR testing to determine hereditary thrombophilia.

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81302</td>
<td>MECP2 (methyl CpG binding protein 2) (e.g., Rett syndrome) gene analysis; full sequence analysis</td>
</tr>
<tr>
<td>81303</td>
<td>MECP2 (methyl CpG binding protein 2) (e.g., Rett syndrome) gene analysis; known familial variant</td>
</tr>
<tr>
<td>81304</td>
<td>MECP2 (methyl CpG binding protein 2) (e.g., Rett syndrome) gene analysis; duplication/deletion variants</td>
</tr>
<tr>
<td>81310</td>
<td>NPM1 (nucleophosmin) (e.g., acute myeloid leukemia) gene analysis, exon 12 variants</td>
</tr>
<tr>
<td>81311</td>
<td>NRAS (Neuroblastoma RAS viral [v-ras] oncogene homolog) (e.g., colorectal carcinoma), gene analysis, variants in exon 2 (e.g., codons 12 and 13) and exon 3 (e.g., codon 61)</td>
</tr>
<tr>
<td>81313</td>
<td>PCA3/KLK3 (prostate cancer antigen 3 [non-protein coding]/kallikrein-related peptidase 3 [prostate specific antigen]) ratio (e.g., prostate cancer)</td>
</tr>
<tr>
<td>81314</td>
<td>PDGFRA (platelet-derived growth factor receptor, alpha polypeptide) (e.g., gastrointestinal stromal tumor [GIST]), gene analysis, targeted sequence analysis (e.g., exons 12, 18)</td>
</tr>
<tr>
<td>81315</td>
<td>PML/RARalpha, (t[15;17]), (promyelocytic leukemia/retinoic acid receptor alpha) (e.g., promyelocytic leukemia) translocation analysis; common breakpoints (e.g., intron 3 and intron 6), qualitative or quantitative</td>
</tr>
<tr>
<td>81316</td>
<td>PML/RARalpha, (t[15;17]), (promyelocytic leukemia/retinoic acid receptor alpha) (e.g., promyelocytic leukemia) translocation analysis; single breakpoint (e.g., intron 3, intron 6 or exon 6), qualitative or quantitative</td>
</tr>
<tr>
<td>81321</td>
<td>PTEN (phosphatase and tensin homolog) (e.g., Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis</td>
</tr>
<tr>
<td>81322</td>
<td>PTEN (phosphatase and tensin homolog) (e.g., Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; known familial variant</td>
</tr>
<tr>
<td>81323</td>
<td>PTEN (phosphatase and tensin homolog) (e.g., Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; duplication/deletion variant</td>
</tr>
<tr>
<td>81324</td>
<td>PMP22 (peripheral myelin protein 22) (e.g., Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; duplication/deletion analysis</td>
</tr>
<tr>
<td>81325</td>
<td>PMP22 (peripheral myelin protein 22) (e.g., Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; full sequence analysis</td>
</tr>
<tr>
<td>81326</td>
<td>PMP22 (peripheral myelin protein 22) (e.g., Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; known familial variant</td>
</tr>
<tr>
<td>CPT Code</td>
<td>Description</td>
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</tr>
<tr>
<td>81330</td>
<td>SMPD1 (sphingomyelin phosphodiesterase 1, acid lysosomal) (e.g., Niemann-Pick disease, Type A) gene analysis, common variants (e.g., R496L, L302P, FsP330)</td>
</tr>
<tr>
<td>81331</td>
<td>SNRPN/UBE3A (small nuclear ribonucleoprotein polypeptide N and ubiquitin protein ligase E3A) (e.g., Prader-Willi syndrome and/or Angelman syndrome), methylation analysis</td>
</tr>
<tr>
<td>81332</td>
<td>SERPINA1 (serpin peptidase inhibitor, clade A, alpha-1 antiproteinase, antitrypsin, member 1) (e.g., alpha-1-antitrypsin deficiency), gene analysis, common variants (e.g., *S and *Z)</td>
</tr>
<tr>
<td>81340</td>
<td>TRB@ (T cell antigen receptor, beta) (e.g., leukemia and lymphoma), gene rearrangement analysis to detect abnormal clonal population(s); using amplification methodology (e.g., polymerase chain reaction)</td>
</tr>
<tr>
<td>81341</td>
<td>TRB@ (T cell antigen receptor, beta) (e.g., leukemia and lymphoma), gene rearrangement analysis to detect abnormal clonal population(s); using direct probe methodology (e.g., Southern blot)</td>
</tr>
<tr>
<td>81342</td>
<td>TRG@ (T cell antigen receptor, gamma) (e.g., leukemia and lymphoma), gene rearrangement analysis, evaluation to detect abnormal clonal population(s)</td>
</tr>
<tr>
<td>81350</td>
<td>UGT1A1 (UDP glucuronosyltransferase 1 family, polypeptide A1) (e.g., irinotecan metabolism), gene analysis, common variants (e.g., *28, *36, *37)</td>
</tr>
<tr>
<td>81355</td>
<td>VKORC1 (vitamin K epoxide reductase complex, subunit 1) (e.g., warfarin metabolism), gene analysis, common variants (e.g., -1639G&gt;A, c.173+1000C&gt;T)</td>
</tr>
<tr>
<td>81400</td>
<td>Molecular pathology procedure, Level 1 (e.g., identification of single germline variant [e.g., SNP] by techniques such as restriction enzyme digestion or melt curve analysis) Plan note: This CPT code includes numerous types of tests, including F5 HR2 variant analysis. See CPT® codebook for detailed description of this code. See the Plan’s Genetic Testing for Hereditary Thrombophilia medical policy (policy number OCA 3.728) rather than this policy for Plan authorization guidelines for F5 HR2 testing to determine hereditary thrombophilia.</td>
</tr>
<tr>
<td>81401</td>
<td>Molecular pathology procedure, Level 2 (e.g., 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat) Plan note: This CPT code includes numerous types of tests, including EML4/ALK translocation or inversion analysis (with genetic testing of ALK for non-small cell lung cancer specified in the Medical Policy Statement section of this policy). See CPT® codebook for detailed description of this code. See the Plan’s Genetic Testing for Fragile X-Associated Disorders medical policy (policy number OCA 3.571) and Genetic Testing for Hereditary Colorectal Cancer medical policy (policy number OCA 3.64) rather than this policy for prior authorization guidelines for other applicable tests included in this code.</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
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</tr>
<tr>
<td>81402</td>
<td>Molecular pathology procedure, Level 3 (e.g., &gt;10 SNPs, 2-10 methylated variants, or 2-10 somatic variants [typically using non-sequencing target variant analysis), immunoglobulin and T-cell receptor gene rearrangements, duplication/deletion variants 1 exon, loss of heterozygosity [LOH], uniparental disomy [UPD])</td>
</tr>
<tr>
<td>81403</td>
<td>Molecular pathology procedure, Level 4 (e.g., analysis of single exon by DNA sequence analysis, analysis of &gt;10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)</td>
</tr>
<tr>
<td>81404</td>
<td>Molecular pathology procedure, Level 5 (e.g., analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)</td>
</tr>
<tr>
<td>81405</td>
<td>Molecular pathology procedure, Level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons), regionally targeted cytogenomic array analysis</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
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</tr>
<tr>
<td>81406</td>
<td>Molecular pathology procedure, Level 7 (e.g., analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)</td>
</tr>
<tr>
<td>81407</td>
<td>Molecular pathology procedure, Level 8 (e.g., analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of &gt;50 exons, sequence analysis of multiple genes on one platform)</td>
</tr>
<tr>
<td>81408</td>
<td>Molecular pathology procedure, Level 9 (e.g., analysis of &gt;50 exons in a single gene by DNA sequence analysis)</td>
</tr>
<tr>
<td>81410</td>
<td>Aortic dysfunction or dilation (e.g., Marfan syndrome, Loeys Dietz syndrome, Ehler Danlos syndrome type IV, arterial tortuosity syndrome); genomic sequence analysis panel, must include sequencing of at least 9 genes, including FBN1, TGFBR1, TGFBR2, COL3A1, MYH11, ACTA2, SLC2A10, SMAD3, and MYLK</td>
</tr>
<tr>
<td>81411</td>
<td>Aortic dysfunction or dilation (e.g., Marfan syndrome, Loeys Dietz syndrome, Ehler Danlos syndrome type IV, arterial tortuosity syndrome); duplication/deletion gene analysis panel, must include analyses for TGFBR1, TGFBR2, MYH11, and COL3A1</td>
</tr>
<tr>
<td>81412</td>
<td>Ashkenazi Jewish associated disorders (e.g., Bloom syndrome, Canavan disease, cystic fibrosis, familial dysautonomia, Fanconi anemia group C, Gaucher disease, Tay-Sachs disease), genomic sequence analysis panel, must include sequencing of at least 9 genes, including ASPA, BLM, CFTR, FANCC, GBA, HEXA, IKBKAP, MCOLN1, and SMPD1</td>
</tr>
<tr>
<td>81413</td>
<td>Cardiac ion channelopathies (e.g., Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); genomic sequence analysis panel, must include sequencing of at least 10 genes, including ANK2, CASQ2, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, RYR2, and SCN5A</td>
</tr>
<tr>
<td>81414</td>
<td>Cardiac ion channelopathies (e.g., Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); duplication/deletion gene analysis panel, must include analysis of at least 2 genes, including KCNH2 and KCNQ1</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>------</td>
<td>-------------</td>
</tr>
<tr>
<td>81420</td>
<td>Fetal chromosomal aneuploidy (e.g., trisomy 21, monosomy X) genomic sequence analysis panel, circulating cell-free fetal DNA in maternal blood, must include analysis of chromosomes 13, 18, and 21. Plan noted: Code used for noninvasive prenatal testing (NIPT). All NIPT assays use cell-free fetal DNA (cffDNA) in a mother’s blood during pregnancy to assess the chromosome number for the fetus (i.e., an increase/decrease in the representation of the particular chromosome being tested). The methodology and data analysis for NIPT vary by product (and therefore some products may be considered medically necessary by the Plan when applicable criteria are met and other NIPT assays may be considered experimental and investigational). See the Medical Policy Statement and Limitations sections for a list of products for which the Plan considers either medically necessary or experimental and investigational and additional limitations related to all NIPT assays.</td>
</tr>
<tr>
<td>81430</td>
<td>Hearing loss (e.g., nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); genomic sequence analysis panel, must include sequencing of at least 60 genes, including CDH23, CLRN1, GJB2, GPR98, MTRNR1, MYO7A, MYO15A, PCDH15, OTOF, SLC26A4, TMC1, TMPRSS3, USH1C, USH1G, USH2A, and WFS1.</td>
</tr>
<tr>
<td>81431</td>
<td>Hearing loss (e.g., nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); duplication/deletion analysis panel, must include copy number analyses for STRC and DFNB1 deletions in GJB2 and GJB6 genes.</td>
</tr>
<tr>
<td>81434</td>
<td>Hereditary retinal disorders (e.g., retinitis pigmentosa, Leber congenital amaurosis, cone-rod dystrophy), genomic sequence analysis panel, must include sequencing of at least 15 genes, including ABCA4, CNGA1, CRB1, EYS, PDE6A, PDE6B, PRPF31, PRPH2, RH12, RHO, RP1, RP2, RPE65, RPRGR, and USH2A.</td>
</tr>
<tr>
<td>81437</td>
<td>Hereditary neuroendocrine tumor disorders (e.g., medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paragaglioma), genomic sequence analysis panel, must include sequencing of at least 6 genes, including MAX, SDHB, SDHC, SDHD, TMEM127 and VHL.</td>
</tr>
<tr>
<td>81438</td>
<td>Hereditary neuroendocrine tumor disorders (e.g., medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paragaglioma), genomic sequence analysis panel, must include sequencing of at least 6 genes, including MAX, SDHB, SDHC, SDHD, TMEM127 and VHL; duplication/deletion analysis panel, must include analyses for SDHB, SDHC, SDHD and VHL.</td>
</tr>
<tr>
<td>81439</td>
<td>Inherited cardiomyopathy (e.g., hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy) genomic sequence analysis panel, must include sequencing of at least 5 genes, including DSG2, MYBPC3, MYH7, PKP2, and TTNI.</td>
</tr>
<tr>
<td>81440</td>
<td>Nuclear encoded mitochondrial genes (e.g., neurologic or myopathic phenotypes), genomic sequence panel, must include analysis of at least 100 genes, including BCS1L, C10orf2, COQ2, COX10, DGUOK, MPV17, OPA1, PDSS2, POLG, POLG2, RRM2B, SCO1, SCO2, SLC25A4, SUCLA2, SUCLG1, TAZ, TK2, and TYMP.</td>
</tr>
</tbody>
</table>
### Noonan spectrum disorders (e.g., Noonan Syndrome, cardio-facio-cutaneous syndrome, Costello Syndrome, LEOPARD syndrome, Noonan-like syndrome), genomic sequence analysis panel
- Must include sequencing of at least 12 genes, including BRAF, CBL, HRAS, KRAS, MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, RIT1, SHOC2, and SOS1.

### Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, 5-50 genes
- Must include sequencing of at least 12 genes, including BRAF, CBL, HRAS, KRAS, MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, RIT1, SHOC2, and SOS1.

### Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, DNA analysis, 5-50 genes
- Must include sequencing of at least 12 genes, including BRAF, CBL, HRAS, KRAS, MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, RIT1, SHOC2, and SOS1.

### Whole mitochondrial genome
- Must include sequencing of the entire mitochondrial genome with heteroplasmacy detection.

### X-linked intellectual disability (XLID)
- Must include analysis of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, and SLC16A2.

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<table>
<thead>
<tr>
<th>81479</th>
<th>Unlisted molecular pathology procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Plan notes:</td>
</tr>
<tr>
<td></td>
<td>1. Providers should use HCPCS code G0452 when billing the interpretation and report for this service.</td>
</tr>
<tr>
<td></td>
<td>2. See the Limitations section for testing that the Plan considers not medically necessary, experimental and investigational, and/or requires Plan Medical Director review. Review the Medical Policy Statement section for genetic testing the Plan considers medically necessary when applicable Plan criteria are met.</td>
</tr>
<tr>
<td></td>
<td>3. Code may be used for BRACAnalysis CDx® when CPT code 81211 is not appropriate according to industry-standard coding guidelines.</td>
</tr>
<tr>
<td></td>
<td>4. Review the Plan’s <em>Gene Expression Profiling of Tumor Tissue to Predict Cancer Recurrence and Risk Stratification (Including Oncotype DX™ and Other Tests)</em> medical policy (policy number OCA 3.572) rather than this policy for Plan guidelines related to gene expression analysis using a proprietary risk classifier to categorize indeterminate lesions or tumors, as determined from biopsy specimen (e.g., Afirma Thyroid FNA Analysis by Veracyte Inc., RosettaGX Reveal by Rosetta Genomics Ltd., and ThyroSeq v.2 Next Generation Sequencing (CBL Path)).</td>
</tr>
</tbody>
</table>

| 81490 | Autoimmune (rheumatoid arthritis), analysis of 12 biomarkers using immunoassays, utilizing serum, prognostic algorithm reported as a disease activity score |
| 81493 | Coronary artery disease, mRNA, gene expression profiling by real-time RT-PCR of 23 genes, utilizing whole peripheral blood, algorithm reported as a risk score |
| 81507 | Fetal aneuploidy (trisomy 21, 18, and 13) DNA sequence analysis of selected regions using maternal plasma, algorithm reported as a risk score of each trisomy |

Plan note: Code used for noninvasive prenatal testing (NIPT). All NIPT assays use cell-free fetal DNA (cffDNA) in a mother’s blood during pregnancy to assess the chromosome number for the fetus (i.e., an increase/decrease in the representation of the particular chromosome being tested). The methodology and data analysis for NIPT vary by product (and therefore some products may be considered medically necessary by the Plan when applicable criteria are met and other NIPT assays may be considered experimental and investigational). See the Medical Policy Statement and Limitations sections for a list of products the Plan considers either medically necessary or experimental and investigational and additional limitations related to all NIPT assays.

<p>| 81535 | Oncology (gynecologic), live tumor cell culture and chemotherapeutic response by DAPI stain and morphology, predictive algorithm reported as a drug response score; first single drug or drug combination |
| 81536 | Oncology (gynecologic), live tumor cell culture and chemotherapeutic response by DAPI stain and morphology, predictive algorithm reported as a drug response score; each additional single drug or drug combination (List separately in addition to code for primary procedure) |</p>
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81538</td>
<td>Oncology (lung), mass spectrometric 8-protein signature, including amyloid A, utilizing serum, prognostic and predictive algorithm reported as good versus poor overall survival</td>
</tr>
<tr>
<td>81545</td>
<td>Oncology (thyroid), gene expression analysis of 142 genes, utilizing fine needle aspirate, algorithm reported as a categorical result (e.g., benign or suspicious)</td>
</tr>
<tr>
<td>81595</td>
<td>Cardiology (heart transplant), mRNA, gene expression profiling by real-time quantitative PCR of 20 genes (11 content and 9 housekeeping), utilizing sub fraction of peripheral blood, algorithm reported as a rejection risk score</td>
</tr>
</tbody>
</table>
|        | Plan note: For Senior Care Options members only, review the National Coverage Determination (NCD) for Heartsbreath Test for Heart Transplant Rejection (260.10) for coverage guidelines; criteria may be accessed at: [https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=325&ncdver=1&DocID=260.10&SearchType=Advanced&bc=IAAAABAAAAAA&](https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=325&ncdver=1&DocID=260.10&SearchType=Advanced&bc=IAAAABAAAAAA&)
<p>| 81599  | Unlisted multianalyte assay with algorithmic analysis |
|        | Plan note: Review the Plan’s Gene Expression Profiling of Tumor Tissue to Predict Cancer Recurrence and Risk Stratification (Including Oncotype DX™ and Other Tests) medical policy (policy number OCA 3.572) rather than this policy for Plan guidelines related to gene expression analysis using a proprietary risk classifier to categorize the affected individual’s prognosis and risk of relapse (e.g., MyPRS developed by Signal Genetics LLC to test plasma cells from bone marrow aspirate of an individual with multiple myeloma or Prosigna Breast Cancer Prognostic Gene Signature Assay developed NanoString Technologies Inc. to test tumor tissue of an individual with breast cancer). |
| 88230  | Tissue culture for non-neoplastic disorders; lymphoctye |
| 88233  | Tissue culture for non-neoplastic disorders; skin or other solid tissue biopsy |
| 88235  | Tissue culture for non-neoplastic disorders; amniotic fluid or chorionic villus cells |
| 88237  | Tissue culture for neoplastic disorders; bone marrow, blood cells |
| 88239  | Tissue culture for neoplastic disorders; solid tumor |
| 88240  | Cryopreservation, freezing and storage of cells, each cell line |
| 88241  | Thawing and expansion of frozen cells, each aliquot |
| 88245  | Chromosome analysis for breakage syndromes; baseline Sister Chromatid Exchange (SCE), 20-25 cells |</p>
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>88248</td>
<td>Chromosome analysis for breakage syndromes; baseline breakage, score 50-100 cells, count 20 cells, 2 karyotypes (e.g., for ataxia telangiectasia, Fanconi anemia, fragile X) Plan note: Review the following medical policies for additional Plan prior authorization guidelines: Genetic Testing for Fragile X-Associated Disorders (policy number OCA 3.571) and Chromosomal Microarray Analysis for Unexplained Intellectual Disabilities and/or Multiple Congenital Anomalies (policy number OCA 3.573).</td>
</tr>
<tr>
<td>88249</td>
<td>Chromosome analysis for breakage syndromes; score 100 cells, clastogen stress (e.g., diepoxybutane, mitomycin C, ionizing radiation, UV radiation)</td>
</tr>
<tr>
<td>88261</td>
<td>Chromosome analysis; count 5 cells, 1 karyotype, with banding</td>
</tr>
<tr>
<td>88262</td>
<td>Chromosome analysis; count 15-20 Cells, 2 karyotypes, with banding</td>
</tr>
<tr>
<td>88263</td>
<td>Chromosome analysis; count 45 cells for mosaicism, 2 karyotypes, with banding</td>
</tr>
<tr>
<td>88264</td>
<td>Chromosome analysis; analyze 20-25 cells</td>
</tr>
<tr>
<td>88267</td>
<td>Chromosome analysis, amniotic fluid or chorionic villus, count 15 cells, 1 karyotype, with banding</td>
</tr>
<tr>
<td>88269</td>
<td>Chromosome analysis, in situ for amniotic fluid cells, count cells from 6-12 colonies, 1 karyotype, with banding</td>
</tr>
<tr>
<td>88271</td>
<td>Molecular cytogenetics; DNA probe, each (e.g., FISH)</td>
</tr>
<tr>
<td>88272</td>
<td>Molecular cytogenetics; chromosomal in situ hybridization, analyze 3-5 cells (e.g., for derivatives and markers)</td>
</tr>
<tr>
<td>88273</td>
<td>Molecular cytogenetics; chromosomal in situ hybridization, analyze 10-30 cells (e.g., for microdeletions)</td>
</tr>
<tr>
<td>88274</td>
<td>Molecular cytogenetics; interphase in situ hybridization, analyze 25-99 cells</td>
</tr>
<tr>
<td>88275</td>
<td>Molecular cytogenetics; interphase in situ hybridization, analyze 100-300 cells</td>
</tr>
<tr>
<td>88280</td>
<td>Chromosome analysis; additional karyotypes, each study</td>
</tr>
<tr>
<td>88283</td>
<td>Chromosome analysis; additional specialized banding technique (e.g., NOR, C-band)</td>
</tr>
<tr>
<td>88285</td>
<td>Chromosome analysis; additional cells counted, each study</td>
</tr>
<tr>
<td>88289</td>
<td>Chromosome analysis; additional high resolution study</td>
</tr>
<tr>
<td>88291</td>
<td>Cytogenetics and molecular cytogenetics, interpretation and report</td>
</tr>
<tr>
<td>88299</td>
<td>Unlisted cytogenetic study</td>
</tr>
</tbody>
</table>

**HCPCS Codes**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>S3800</td>
<td>Genetic testing for amyotrophic lateral sclerosis (ALS)</td>
<td></td>
</tr>
<tr>
<td>S3840</td>
<td>DNA analysis for germline mutations of the RET proto-oncogene for susceptibility to multiple endocrine neoplasia type 2</td>
<td></td>
</tr>
<tr>
<td>S3841</td>
<td>Genetic testing for retinoblastoma</td>
<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>S3842</td>
<td>Genetic testing for Von Hippel-Lindau disease</td>
</tr>
<tr>
<td>S3844</td>
<td>DNA analysis of the connexin 26 gene (GJB2) for susceptibility to congenital, profound deafness</td>
</tr>
<tr>
<td>S3845</td>
<td>Genetic testing for alpha-thalassemia</td>
</tr>
<tr>
<td>S3846</td>
<td>Genetic testing for hemoglobin E beta-thalassemia</td>
</tr>
<tr>
<td>S3849</td>
<td>Genetic testing for Niemann-Pick disease</td>
</tr>
<tr>
<td>S3850</td>
<td>Genetic testing for sickle cell anemia</td>
</tr>
<tr>
<td>S3852</td>
<td>DNA analysis for APOE epsilon 4 allele for susceptibility to Alzheimer’s disease</td>
</tr>
<tr>
<td>S3853</td>
<td>Genetic testing for myotonic muscular dystrophy</td>
</tr>
<tr>
<td>S3861</td>
<td>Genetic testing, sodium channel, voltage-gated, type V, alpha subunit (SCN5A) and variants for suspected Brugada Syndrome</td>
</tr>
<tr>
<td>S3865</td>
<td>Comprehensive gene sequence analysis for hypertrophic cardiomyopathy</td>
</tr>
<tr>
<td>S3866</td>
<td>Genetic analysis for a specific gene mutation for hypertrophic cardiomyopathy (HCM) in an individual with a known HCM mutation in the family</td>
</tr>
<tr>
<td>S3870</td>
<td>Comparative genomic hybridization (CGD) microarray testing for developmental delay, autism spectrum disorder and/or intellectual disability</td>
</tr>
</tbody>
</table>

### Category 3: Procedure Codes that Require Plan Authorization for All Diagnosis Codes

<table>
<thead>
<tr>
<th>CPT Codes and HCPCS Codes</th>
<th>Description: Codes covered when medically necessary.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1 Codes and Category 2 Codes</td>
<td>All medically necessary CPT codes and HCPCS codes specified in Category 1 and Category 2 require prior authorization for all diagnosis codes (unless a pregnancy waiver applies, as stated above). Codes may be considered medically necessary according to the guidelines specified in the Medical Policy Statement and Limitations sections of this Plan policy and must be clinically appropriate for the specified indication.</td>
</tr>
</tbody>
</table>

### Category 4: Procedure codes considered experimental and investigational for all diagnosis codes.

<table>
<thead>
<tr>
<th>CPT Codes</th>
<th>Description: Codes considered experimental and investigational for all diagnosis codes.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0004U</td>
<td>Infectious disease (bacterial), DNA, 27 resistance genes, PCR amplification and probe hybridization in microarray format (molecular detection and identification of AmpC, carbapenemase and ESBL coding genes), bacterial culture colonies, report of genes detected or not detected, per isolate</td>
</tr>
</tbody>
</table>

Plan note: See the Limitations section of this Plan policy for applicable criteria (specified as Experimental and Investigational Genetic Testing by Medical Condition: Infectious Pathogen Identification with Genetic Testing).
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0005U</td>
<td>Oncology (prostate) gene expression profile by real-time RT-PCR of 3 genes (ERG, PCA3, and SPDEF), urine, algorithm reported as risk score Plan note: See the Limitations section of this Plan policy for applicable criteria. Gene-based tests for the screening, detection and management of prostate cancer are considered experimental and investigational. The use of protein biomarkers (using diagnostic blood tests, urine tests, or other testing methods such as immunofluorescence and automated quantitative images of biopsy tissue) to predict prostate cancer recurrence or risk stratification based on an established algorithm is considered experimental and investigational.</td>
</tr>
<tr>
<td>0007U</td>
<td>Drug test(s), presumptive, with definitive confirmation of positive results, any number of drug classes, urine, includes specimen verification including DNA authentication in comparison to buccal DNA, per date of service Plan note: See the Limitations section of this Plan policy for applicable criteria. This is a non-payable code for all Plan products.</td>
</tr>
<tr>
<td>0008U</td>
<td>Helicobacter pylori detection and antibiotic resistance, DNA, 16S and 23S rRNA, gyrA, ppb1, rdxA and rpoB, next generation sequencing, formalin-fixed paraffin embedded or fresh tissue, predictive, reported as positive or negative for resistance to clarithromycin, fluoroquinolones, metronidazole, amoxicillin, tetracycline and rifabutin</td>
</tr>
<tr>
<td>0010U</td>
<td>Infectious disease (bacterial), strain typing by whole genome sequencing, phylogenetic-based report of strain relatedness, per submitted isolate</td>
</tr>
<tr>
<td>0012U</td>
<td>Germline disorders, gene rearrangement detection by whole genome next-generation sequencing, DNA, whole blood, report of specific gene rearrangement(s)</td>
</tr>
<tr>
<td>0013U</td>
<td>Oncology (solid organ neoplasia), gene rearrangement detection by whole genome next-generation sequencing, DNA, fresh or frozen tissue or cells, report of specific gene rearrangement(s)</td>
</tr>
<tr>
<td>0014U</td>
<td>Hematology (hematolymphoid neoplasia), gene rearrangement detection by whole genome next-generation sequencing, DNA, whole blood or bone marrow, report of specific gene rearrangement(s)</td>
</tr>
<tr>
<td>81415</td>
<td>Exome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis Plan notes: 1. The Plan considers exome sequence analysis to be experimental and investigational, as specified in the Limitations section. Plan Medical Director review is required for all prior authorization requests. 2. According to The American College of Obstetricians and Gynecologists (Committee Opinion Number 682), the routine use of whole-exome sequencing for prenatal diagnosis is not recommended outside of the context of clinical trials until sufficient peer-reviewed data and validation studies are published.</td>
</tr>
<tr>
<td>Code</td>
<td>Service Description</td>
</tr>
<tr>
<td>-------</td>
<td>-------------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| 81416 | Exome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator exome (e.g., parents, siblings) (List separately in addition to code for primary procedure) | 1. The Plan considers exome sequence analysis to be medically necessary ONLY when applicable criteria are met, as specified in the Medical Policy Statement section. Limitations for whole exome sequencing are included in the Limitations section. Plan Medical Director review is required.  
2. According to The American College of Obstetricians and Gynecologists (Committee Opinion Number 682), the routine use of whole exome sequencing for prenatal diagnosis is not recommended outside of the context of clinical trials until sufficient peer-reviewed data and validation studies are published. |
| 81417 | Exome (e.g., unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained exome sequence (e.g., updated knowledge or unrelated condition/syndrome) | 1. The Plan considers exome sequence analysis to be medically necessary ONLY when applicable criteria are met, as specified in the Medical Policy Statement section. Limitations for whole exome sequencing are included in the Limitations section. Plan Medical Director review is required.  
2. According to The American College of Obstetricians and Gynecologists (Committee Opinion Number 682), the routine use of whole-exome sequencing for prenatal diagnosis is not recommended outside of the context of clinical trials until sufficient peer-reviewed data and validation studies are published. |
<p>| 81422 | Fetal chromosomal microdeletion(s) genomic sequence analysis (e.g., DiGeorge syndrome, Cri-du-chat syndrome), circulating cell-free fetal DNA in maternal blood | Plan note: See the Limitations section of this Plan policy for applicable criteria. The use of NIPT BEYOND the standard testing of aneuploidies involving chromosomes 21, 18, 13, and the sex chromosomes is considered experimental and investigational; this includes the testing other chromosomal disorders (such as additional trisomies or microdeletions) with NIPT. |</p>
<table>
<thead>
<tr>
<th>Code</th>
<th>Service Description</th>
<th>Plan Notes</th>
</tr>
</thead>
</table>
| 81425  | Genome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis | 1. The Plan considers whole genome sequence analysis to be experimental and investigational for any indication, as specified in the Limitations section. Plan Medical Director review is required for all prior authorization requests.  
2. According to The American College of Obstetricians and Gynecologists (Committee Opinion Number 682), the routine use of whole-genome sequencing for prenatal diagnosis is not recommended outside of the context of clinical trials until sufficient peer-reviewed data and validation studies are published. |
| 81426  | Genome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator genome (e.g., parents, siblings) (List separately in addition to code for primary procedure) | 1. The Plan considers whole genome sequence analysis to be experimental and investigational for any indication, as specified in the Limitations section. Plan Medical Director review is required for all prior authorization requests.  
2. According to The American College of Obstetricians and Gynecologists (Committee Opinion Number 682), the routine use of whole-genome sequencing for prenatal diagnosis is not recommended outside of the context of clinical trials until sufficient peer-reviewed data and validation studies are published. |
| 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) | 1. The Plan considers whole genome sequence analysis to be experimental and investigational for any indication, as specified in the Limitations section.  
2. According to The American College of Obstetricians and Gynecologists (Committee Opinion Number 682), the routine use of whole-genome sequencing for prenatal diagnosis is not recommended outside of the context of clinical trials until sufficient peer-reviewed data and validation studies are published. |
Clinical Background Information

Genetic testing is a type of medical test that identifies changes in chromosomes, genes, or proteins and is used to find changes that are associated with inherited disorders. The results of a genetic test can confirm or rule out a suspected genetic condition or help determine a person’s chance of developing or passing on a genetic disorder. Several hundred genetic tests are currently in use, and more are being developed. Identifying patients who will benefit from certain treatment strategies utilizing pharmacogenetic testing is vital to ensuring better clinical outcomes.

The Food and Drug Administration (FDA) only regulates genetic tests sold as kits and has practiced enforcement discretion for laboratory-developed tests (LDTs), which represent the majority of genetic tests marketed in the United States. While the Centers of Medicare & Medicaid Services (CMS) does regulate the clinical laboratories in which LDTs are performed, CMS does not evaluate whether the genetic tests are clinically meaningful.

The American College of Medical Genetics and Genomics (ACMG) does not recommend the self-ordering of direct-to-consumer (DTC) genetic tests by patients without the involvement of a treating healthcare provider. DTC tests might include carrier tests for common genetic diseases, predisposition tests for chronic conditions, and/or pharmacogenetic testing that provide information about how an individual’s genes may response to pharmacotherapy. According to the ACMG, the potential harms include inappropriate test utilization, misinterpretation of test results, lack of necessary follow-up, and other adverse consequences. The accuracy of DTC genetic tests or the reporting of the test results may also be questionable. The Centers for Disease Control and Prevention (CDC) Office of Public Health Genomics (OPHG) supports the process for evaluating scientific data on emerging genetic tests with the ACCE Model Project and the Evaluation of Genomic Applications in Practice and Prevention.

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(EGAPP™) initiative. Genetic tests and the applications of genomic technology must be evaluated based on analytic validity, clinical validity, clinical utility, and associated ethical, legal and social implications.

At the time of the Plan’s most recent policy review, the Centers for Medicare & Medicaid Services (CMS) has implemented the following national coverage determinations (NCDs) related to genetic tests: NCD for Colorectal Cancer Screening Tests (210.3) for coverage of immunoassay and guaiac fecal occult blood tests and the Cologuard™ - Multitarget Stool DNA (sDNA) test when CMS applicable criteria are met, NCD for Pharmacogenomic Testing for Warfarin Response (90.1) for medically necessary indications for testing as determined by CMS, and NCD for Cytogenetic Studies (190.3) for coverage based on CMS guidelines. Medicare uses a combination of national and local coverage determinations for making coverage decisions for genetic tests. Medicare administrative contractors (MAC) may implement local coverage determinations (LCDs) that apply only within their own jurisdictions. Verify if applicable CMS criteria are in effect (through an NCD, LCD, or other CMS guidelines) for the specified genetic test, product name, site-specific gene analysis, and the indication for testing on the date of the prior authorization request for a Senior Care Options member.

References


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Genetic Testing Guidelines and Pharmacogenetics

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Centers for Medicare & Medicaid Services (CMS). National Coverage Determination (NCD) for Colorectal Cancer Screening Tests (210.3). Effective Date October 9, 2014. Implementation Date September 8, 2015. Accessed at: https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=281&ncdver=5&CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=Massachusetts&KeyWord=colorectal+cancer&KeyWordLookUp=Title&KeyWordSearchType=And&bc=gAAAAABAAAAA%3d%3d%

Centers for Medicare & Medicaid Services (CMS). National Coverage Determination (NCD) for Cytogenetic Studies (190.3). July 16, 1998. Accessed at: https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=198&ncdver=1&CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=Massachusetts&KeyWord=cytogenetic&KeyWordLookUp=Title&KeyWordSearchType=And&lcd_id=24308&lcd_version=26&basket=lcda%242424308*3a%24246*3a%24Genetic+Testing*3a%24MAC+-+Part+B*3a%24Noridian+Administrative+Services%257C%257ChlL(03102)*3a%24&bc=gAAAAACAAAAAAA&

Centers for Medicare & Medicaid Services (CMS). National Coverage Determination (NCD) for Pharmacogenomic Testing for Warfarin Response (90.1). August 3, 2009. Accessed at: https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=333&ncdver=1&CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=Massachusetts&KeyWord=warfarin&KeyWordLookUp=Title&KeyWordSearchType=And&lcd_id=24308&lcd_version=26&basket=lcda%242424308*3a%24246*3a%24Genetic+Testing*3a%24MAC+-+Part+B*3a%24Noridian+Administrative+Services%257C%257ChlL(03102)*3a%24&bc=gAAAAACAAAAAAA&


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Hayes Genetic Test Evaluation Overview. BRAF p.Val600Glu (V600E) and p.Val600Lys (V600K) Testing to Predict Response to Trametinib and Dabrafenib Combination Therapy in Melanoma for Malignant Melanoma (Multiple Manufacturers). Winifred Hayes, Inc. February 12, 2015.


Hayes Genetic Test Evaluation Overview. Prostate Core Mitomic Test for Prostate Cancer Diagnosis (MDNA Life Sciences, Inc.). Winifred Hayes, Inc. April 23, 2015.


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Hayes GTE Report. BRAF p.Val600Glu Testing in Papillary Thyroid Carcinoma. Winifred Hayes, Inc.


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Hayes GTE Synopsis. Combined Cardiac Pan (GeneDx Inc.) Winifred Hayes, Inc. January 21, 2016.


Hayes GTE Synopsis. MI TumorSeek (Caris Life Sciences). Winifred Hayes, Inc. March 17, 2016.


Genetic Testing Guidelines and Pharmacogenetics

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Hayes Search & Summary. 4Kscore Test (OPKO Lab) for Prostate Cancer. Winifred Hayes, Inc. March 3, 2016.


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<table>
<thead>
<tr>
<th>Original Approval Date</th>
<th>Original Effective Date* and Version Number</th>
<th>Policy Owner</th>
<th>Original Policy Approved by</th>
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<tr>
<td>Regulatory Approval: N/A</td>
<td>12/01/11 Version 1</td>
<td>Medical Policy Manager as Chair of MPCTAC</td>
<td>MPCTAC and QIC</td>
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<td>Internal Approval: 08/17/11: Medical Policy, Criteria, and Technology Assessment Committee (MPCTAC) 09/28/11: Quality Improvement Committee (QIC)</td>
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*Effective Date for the BM HealthNet Plan Commercial Product(s): 01/01/12
*Effective Date for the Well Sense Health Plan New Hampshire Medicaid Product(s): 01/01/13
*Effective Date for the Senior Care Options Product(s): 01/01/16

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<th>Policy Revisions History</th>
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<tr>
<td><strong>Review Date</strong></td>
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<tr>
<td>07/29/12</td>
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<tr>
<td>01/30/14</td>
<td>Review for effective date 04/01/14. Added ICD10 diagnosis code equivalents of existing ICD9 diagnosis codes.</td>
<td>04/01/14</td>
<td>01/27/14: MPCTAC 01/30/14: QIC</td>
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<td>07/01/14</td>
<td>Review for effective 10/01/14. Updated Summary section. Added CPT code 81507 and HCPCS code S3870 to the applicable code list.</td>
<td>10/01/14</td>
<td>07/21/14: MPCTAC (electronic vote) 07/24/14: QIC (electronic vote)</td>
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<td>11/01/14 and 12/01/14</td>
<td>Review for effective date 03/01/15. Revised Summary, Description of Item or Service, Definitions, and References sections. Revised criteria in the Medical Policy Statement and Limitations section. Updated applicable code list.</td>
<td>03/01/15</td>
<td>11/19/14: MPCTAC 12/02/14: MPCTAC (electronic vote) 12/10/14: QIC</td>
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<td>11/25/15</td>
<td>Review for effective date 01/01/16. Updated template with list of applicable products and notes. Revised language related to applicable products in the Limitations section without changing criteria. Revised language in the Applicable Coding section.</td>
<td>01/01/16</td>
<td>11/18/15: MPCTAC 11/25/15: MPCTAC (electronic vote) 12/09/15: QIC</td>
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<tr>
<td>01/01/16</td>
<td>Review for effective date 05/01/16. Revised language and list of waived pregnancy diagnosis codes and corresponding procedure codes in the Applicable Coding section. Revised list of procedure codes according to industry-standard 2016 code changes. Updated Summary, Description of Item or Service, Definitions, Clinical Background Information, and References sections. Revised criteria in the Medical Policy Statement and Limitations sections.</td>
<td>05/01/16</td>
<td>01/20/16: MPCTAC 02/10/16: QIC</td>
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<td>09/01/16 and 09/28/16</td>
<td>Review for effective date 11/01/16. Administrative changes made to the Summary, Description of Item or Service, Medical Policy Statement, and Applicable Coding sections to clarify the types of genetic testing that require Plan prior authorization. No changes</td>
<td>11/01/16</td>
<td>09/21/16: MPCTAC 09/30/16: MPCTAC (electronic vote) 10/12/16: QIC</td>
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### Policy Revisions History

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<tr>
<th>Date</th>
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<th>Version</th>
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<tr>
<td>12/05/16</td>
<td>Industry-wide code change with the addition of 2017 applicable codes effective 01/01/17. Administrative changes made to clarify language related to gender. Added definitions.</td>
<td>01/01/17</td>
<td>11</td>
<td>Not applicable because industry-wide code revisions.</td>
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<tr>
<td>01/01/17</td>
<td>Review for effective date 05/01/17. Revised ICD-10 pregnancy diagnosis codes and updated CPT codes in the Applicable Coding section. Updated criteria in the Medical Policy Statement and Limitations sections. Revised Summary, Definitions, Clinical Background Information, References, and Reference to Applicable Laws and Regulations sections. Added Plan notes to Applicable Coding section.</td>
<td>05/01/17</td>
<td>12</td>
<td>01/18/17: MPCTAC 02/08/17: QIC</td>
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<td>06/01/17</td>
<td>Review for effective date 07/01/17. Industry-wide code changes made to the Applicable Coding section. Administrative changes made to the Summary, Applicable Coding, and References sections. Updated Limitations section to be consistent with industry-wide code addition.</td>
<td>07/01/17</td>
<td>13</td>
<td>06/21/17: MPCTAC.</td>
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<tr>
<td>08/09/17 and 09/08/17</td>
<td>Revision effective 10/01/17. Industry-wide updates to the ICD-10 diagnosis and HCPCS codes included in the Applicable Coding section.</td>
<td>10/01/17</td>
<td>14</td>
<td>Not applicable because CMS industry wide changes to HCPCS and ICD10 Diagnosis codes.</td>
</tr>
<tr>
<td>09/20/17</td>
<td>Review for effective date 12/01/17. Revised criteria in the Limitations section. Updated Policy Summary, Description of Item or Service, References, and Other Applicable Policies sections. Revised the applicable code list and administrative changes made to the Applicable Coding section.</td>
<td>12/01/17</td>
<td>15</td>
<td>09/20/17: MPCTAC.</td>
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### Last Review Date

09/20/17

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Next Review Date

01/01/18

Authorizing Entity

MPCTAC

Other Applicable Policies

Administrative Policy - Clinical Review Criteria, policy number OCA 3.201
Medical Policy - Chromosomal Microarray Analysis for Unexplained Intellectual Disabilities and/or Multiple Congenital Anomalies, policy number OCA 3.573
Medical Policy - Drug Screening/Testing for Drugs of Abuse and/or Controlled Substances, policy number OCA 3.98
Medical Policy - Experimental and Investigational Treatment, policy number OCA 3.12
Medical Policy - Gene Expression Profiling of Tumor Tissue to Predict Cancer Recurrence and Risk Stratification (Including Oncotype DX™ and Other Tests), policy number OCA 3.572
Medical Policy - Genetic Testing for Familial Malignant Melanoma, policy number OCA 3.78
Medical Policy - Genetic Testing for Fragile X-Associated Disorders, policy number OCA 3.571
Medical Policy - Genetic Testing for Hereditary Breast and Ovarian Cancer Syndrome, policy number OCA 3.57
Medical Policy - Genetic Testing for Hereditary Colorectal Cancer, policy number OCA 3.64
Medical Policy - Genetic Testing for Hereditary Thrombophilia, policy number OCA 3.728
Medical Policy - Medically Necessary, policy number OCA 3.14
Medical Policy - Preimplantation Genetic Testing (Preimplantation Genetic Diagnosis and Pregenetic Screening), policy number OCA 3.726

Reference to Applicable Laws and Regulations


Disclaimer Information: *

Medical Policies are the Plan’s guidelines for determining the medical necessity of certain services or supplies for purposes of determining coverage. These Policies may also describe when a service or supply is considered experimental or investigational, or cosmetic. In making coverage decisions, the Plan uses these guidelines and other Plan Policies, as well as the Member’s benefit document, and when appropriate, coordinates with the Member’s health care Providers to consider the individual Member’s health care needs.

Plan Policies are developed in accordance with applicable state and federal laws and regulations, and accrediting organization standards (including NCQA). Medical Policies are also developed, as appropriate, with consideration of the medical necessity definitions in various Plan products, review of current literature, consultation with practicing Providers in the Plan’s service area who are medical experts in the particular field, and adherence to FDA and other government agency policies. Applicable state or federal mandates, as well as the Member’s benefit document, take precedence over these.

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guidelines. Policies are reviewed and updated on an annual basis, or more frequently as needed. Treating providers are solely responsible for the medical advice and treatment of Members.

The use of this Policy is neither a guarantee of payment nor a final prediction of how a specific claim(s) will be adjudicated. Reimbursement is based on many factors, including member eligibility and benefits on the date of service; medical necessity; utilization management guidelines (when applicable); coordination of benefits; adherence with applicable Plan policies and procedures; clinical coding criteria; claim editing logic; and the applicable Plan – Provider agreement.