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Genetic and Genomic Testing for the Diagnosis and Management of Select Cancers and Genetic Diseases Corporate Medical Policy

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Description

Hereditary breast and ovarian cancer syndrome describe the familial cancer syndromes related to variants in the BRCA genes (BRCA1 located on chromosome 17q21, BRCA2 located on chromosome 13q12-13). The PALB2 gene is located at 16p12.2 and has 13 exons. PALB2 protein assists BRCA2 in DNA repair and tumor suppression. Families with hereditary breast and ovarian cancer syndrome have an increased susceptibility to the following types of cancer: breast cancer occurring at a young age, bilateral breast cancer, male breast cancer, ovarian cancer (at any age), cancer of the fallopian tube, primary peritoneal cancer, prostate cancer, pancreatic cancer, gastrointestinal cancers, melanoma, and laryngeal cancer.

Genetic testing is available for both those with and those at risk for various types of hereditary cancer. This review evaluates genetic testing for hereditary colorectal cancer (CRC) and polyposis syndromes, including familial adenomatous polyposis (FAP), Lynch syndrome (formerly known as hereditary nonpolyposis colorectal cancer), *MUTYH*-associated polyposis (MAP), Lynch syndrome-related endometrial cancer, juvenile polyposis syndrome (JPS), and Peutz-Jeghers syndrome (PJS).

Somatic (acquired) genetic variants in *JAK2*, *MPL*, and *CALR* genes have been implicated as the underlying molecular genetic drivers for the pathogenesis of myeloproliferative neoplasms (MPN). medical policy addresses the use of genetic testing for *JAK2*, *MPL*, and *CALR* genes for diagnosis, prognosis, and treatment selection of patients with MPN.

In the treatment of Philadelphia chromosome-positive leukemias, various nucleic acid-based laboratory methods may be used to detect the *BCR-ABL1* fusion gene for confirmation of the diagnosis; for quantifying mRNA *BCR-ABL1* transcripts during and after treatment to monitor disease progression or remission; and for identification of *ABL* kinase domain (KD) single

nucleotide variants related to drug resistance when there is inadequate response or loss of response to tyrosine kinase inhibitors (TKIs), or disease progression.

Carrier screening is performed to identify individuals at risk of having offspring with inherited recessive single-gene disorders. Carriers are usually not at risk of developing the disease but can pass pathogenic variants to their offspring. Carrier testing may be performed in the prenatal or preconception periods.

Coding Information

Click the links below for attachments, coding tables & instructions.
Attachment I - Coding Table

Policy

Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2)

Individuals With Cancer or With a Personal History of Cancer

Genetic testing for *BRCA1*, *BRCA2*, and *PALB2* variants in cancer-affected individuals may be considered **medically necessary** under any of the following circumstances:

- Individuals with any close blood relative with a known *BRCA1*, *BRCA2*, or *PALB2* pathogenic/likely pathogenic variant (see Policy Guidelines for definitions and for testing strategy).
- Individuals meeting the criteria below but with previous limited testing (*e.g.*, single gene and/or absent deletion duplication analysis)
- Personal history of breast cancer and 1 or more of the following:
    - Diagnosed at age ≤45 years; or
    - Diagnosed at age 46 to 50 years with:
        - An additional breast cancer primary at any age; or
        - ≥1 close relative (see Policy Guidelines) with breast, ovarian, pancreatic, or prostate cancer at any age; or
        - An unknown or limited family history
    - Diagnosed at age ≤60 years with:
        - Triple-negative breast cancer; or
    - Diagnosed at any age with:
        - ≥1 close blood relative with:
            - Breast cancer diagnosed at age ≤50 years; or
            - Ovarian carcinoma; or
            - Metastatic or intraductal/cribriform prostate cancer, or high-risk group or very-high-risk group (see Policy Guidelines) prostate cancer; or
            - Pancreatic cancer; or
        - ≥3 total diagnoses of breast cancer in individual and/or close blood relatives; or
        - Ashkenazi Jewish ancestry
    - Diagnosed at any age with male breast cancer

- Personal history of epithelial ovarian carcinoma (including fallopian tube cancer or peritoneal cancer) at any age
- Personal history of exocrine pancreatic cancer at any age
- Personal history of metastatic or intraductal/cribriform histology prostate cancer at any age; or high-risk group or very-high-risk group prostate cancer at any age
- Personal history of prostate cancer at any age with:
    - ≥1 close blood relative with ovarian carcinoma, pancreatic cancer, or metastatic or intraductal/cribriform prostate cancer at any age, or breast cancer at age ≤50 years; or
    - ≥2 close blood relatives with breast or prostate cancer (any grade) at any age; or
    - Ashkenazi Jewish ancestry
- Personal history of a *BRCA1*, *BRCA2*, or *PALB2* pathogenic/likely pathogenic variant identified on tumor genomic testing that has clinical implications if also identified in the germline.

Individuals Without Cancer or With Other Personal History of Cancer

Genetic testing for *BRCA1, BRCA2,* and *PALB2* variants of cancer-unaffected individuals and individuals with cancer but not meeting the above criteria (including individuals with cancers unrelated to hereditary breast and ovarian cancer syndrome) may be considered **medically necessary** under any of the following circumstances:

- An individual with or without cancer and not meeting the above criteria but who has a 1st- or 2nd-degree blood relative meeting any criterion listed above for Patients With Cancer (except individuals who meet criteria only for systemic therapy decision-making). If the individual with cancer has pancreatic cancer or prostate cancer (metastatic or intraductal/cribriform or high-risk group or very-high-risk group) then only first-degree relatives should be offered testing unless there are other family history indications for testing.
- An individual with any type of cancer (cancer related to hereditary breast and ovarian cancer syndrome but not meeting above criteria, or cancer unrelated to hereditary breast and ovarian cancer syndrome) or unaffected individual who otherwise does not meet the criteria above but has a probability >5% of a *BRCA1/2* or *PALB2* pathogenic variant based on prior probability models (e.g., Tyrer-Cuzick, BRCAPro, Pennll).

See Policy Guidelines: Testing Unaffected Individuals.

Genetic testing for *BRCA*1 and *BRCA2* variants of cancer-affected individuals or cancer-unaffected individuals with a family history of cancer when criteria above are not met is considered **investigational**.

Testing for *PALB2* variants in individuals who do not meet the criteria outlined above is considered **investigational**.

Genetic testing in minors for *BRCA1, BRCA2,* and *PALB2* variants for hereditary breast and ovarian cancer syndrome is considered **investigational** (see Policy Guidelines).

Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

APC Testing

Genetic testing of the *APC* gene may be considered **medically necessary** in the following individuals :

- At-risk relatives (see Policy Guidelines section) of individuals with familial adenomatous polyposis (FAP) and/or a known *APC* variant.
- Individuals with a differential diagnosis of attenuated FAP versus *MUTYH*-associated polyposis (MAP) versus Lynch syndrome. Whether testing begins with *APC* variants or screening for mismatch repair (MMR) variants depends on clinical presentation.

Genetic testing for *APC* gene variants is considered **investigational** for colorectal cancer (CRC) individuals with classical FAP for confirmation of the FAP diagnosis.

Testing for germline *APC* gene variants for inherited CRC syndromes is considered **investigational** in all other situations.

MUTYH Testing

Genetic testing of the *MUTYH* gene may be considered **medically necessary** in the following individuals :

- Individuals with a differential diagnosis of attenuated FAP versus MAP versus Lynch syndrome and a negative result for *APC* gene variants. A family history of no parents or children with FAP is consistent with MAP (autosomal recessive).

Testing for germline *MUTYH* gene variants for inherited CRC syndromes is considered **investigational** in all other situations.

MMR Gene Testing

Genetic testing of MMR genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*) may be considered **medically necessary** in the following individuals :

- Individuals with CRC with tumor testing suggesting germline MMR deficiency or meeting clinical criteria for Lynch syndrome (see Policy Guidelines section).
- Individuals with endometrial cancer with tumor testing suggesting germline MMR deficiency or meeting clinical criteria for Lynch syndrome (see Policy Guidelines section).
- At-risk relatives (see Policy Guidelines section) of individuals with Lynch syndrome with a known pathogenic/likely pathogenic MMR gene variant.
- Individuals with a differential diagnosis of attenuated FAP versus MAP versus Lynch syndrome. Whether testing begins with *APC* variants or screening for MMR genes depends on clinical presentation.
- Individuals without CRC but with a family history meeting the Amsterdam or Revised Bethesda criteria, or documentation of 5% or higher predicted risk of the syndrome on

a validated risk prediction model (e.g. MMRpro, PREMM5 or MMRpredict), when no affected family members have been tested for MMR variants.

Testing for germline MMR gene variants for inherited CRC syndromes is considered **investigational** in all other situations.

EPCAM Testing

Genetic testing of the *EPCAM* gene may be considered **medically necessary** when any 1 of the following 3 major criteria (solid bullets) is met:

- Individuals with CRC, for the diagnosis of Lynch syndrome (see Policy Guidelines section) when:
    - Tumor tissue shows lack of MSH2 protein expression by immunohistochemistry and individual is negative for an *MSH2* germline variant; OR
    - Tumor tissue shows a high level of microsatellite instability and individual is negative for a germline variant in *MLH1*, *MSH2*, *MSH6*, and *PMS2*; OR
- At-risk relatives (see Policy Guidelines section) of individuals with Lynch syndrome with a known pathogenic/likely pathogenic *EPCAM* variant; OR
- Individuals without CRC but with a family history meeting the Amsterdam or Revised Bethesda criteria, or documentation of 5% or higher predicted risk of the syndrome on a validated risk prediction model (e.g. MMRpro, PREMM5 or MMRpredict), when no affected family members have been tested for MMR variants, and when sequencing for MMR variants is negative.

Testing for germline *EPCAM* gene variants for inherited CRC syndromes is considered **investigational** in all other situations.

BRAF V600E or *MLH1* promoter methylation

Somatic genetic testing for *BRAF* V600E or *MLH1* promoter methylation may be considered **medically necessary** to exclude a diagnosis of Lynch syndrome when the MLH1 protein is not expressed in a CRC tumor on immunohistochemical analysis.

Testing for somatic *BRAF V600E* or *MLH1* promoter methylation to exclude a diagnosis of Lynch syndrome is considered **investigational** in all other situations.

SMAD4 and *BMPR1A* Testing

Genetic testing of *SMAD4* and *BMPR1A* genes may be considered **medically necessary** when any 1 of the following major criteria (solid bullets) is met:

- Individuals with a clinical diagnosis of juvenile polyposis syndrome based on the presence of any 1 of the following:
    - at least 5 juvenile polyps in the colon
    - multiple juvenile polyps found throughout the gastrointestinal tract
    - any number of juvenile polyps in a person with a known family history of juvenile polyps.

- At-risk relative of an individual suspected of or diagnosed with juvenile polyposis syndrome.

Testing for germline *SMAD4* and *BMPR1A* gene variants for inherited CRC syndromes is considered **investigational** in all other situations.

STK11 Testing

Genetic testing for *STK11* gene variants may be considered **medically necessary** when any 1 of the following major criteria (solid bullets) is met:

- Individuals with a clinical diagnosis of Peutz-Jeghers syndrome based on the presence of any 2 of the following:
    - presence of 2 or more histologically confirmed Peutz-Jeghers polyps of the gastrointestinal tract.
    - characteristic mucocutaneous pigmentation of the mouth, lips, nose, eyes, genitalia, or fingers
    - family history of Peutz-Jeghers syndrome.
- At-risk relative of an individual suspected of or diagnosed with Peutz-Jeghers syndrome.

Testing for germline *STK11* gene variants for inherited CRC syndromes is considered **investigational** in all other situations.

Other Variants

Genetic testing of all other genes for an inherited CRC syndrome is considered **investigational**.

Genetic Counseling

Pre- and post-test genetic counseling may be considered **medically necessary** as an adjunct to the genetic testing itself.

JAK2, MPL, and CALR Testing for Myeloproliferative Neoplasms

JAK2 testing may be considered **medically necessary** in the diagnosis of individuals presenting with clinical, laboratory, or pathologic findings suggesting polycythemia vera, essential thrombocythemia (ET), or primary myelofibrosis (PMF).

Based on criteria from the World Health Organization and the International Consensus Classification for diagnosis of PV, documentation of a serum erythropoietin level below the reference range for normal is recommended before *JAK2* testing (See Policy Guidelines).

MPL and *CALR* testing may be considered **medically necessary** in the diagnosis of individuals presenting with clinical, laboratory, or pathologic findings suggesting ET or PMF.

JAK2, *MPL*, and *CALR* testing is considered **investigational** in all other circumstances including, but not limited to, the following situations:

- Diagnosis of nonclassic forms of myeloproliferative neoplasms (MPNs)
- Molecular phenotyping of individuals with MPNs
- Monitoring, management, or selecting treatment in individuals with MPNs.

BCR-ABL1 Testing in Chronic Myelogenous Leukemia and Acute Lymphoblastic Leukemia

Chronic Myelogenous Leukemia

BCR-ABL1 qualitative testing for the presence of the fusion gene may be considered **medically necessary** for the diagnosis of chronic myeloid leukemia (see Policy Guidelines section).

BCR-ABL1 testing for messenger RNA transcript levels by quantitative real-time reverse transcription-polymerase chain reaction at baseline before initiation of treatment and at appropriate intervals (see Policy Guidelines section) may be considered **medically necessary** for monitoring of chronic myeloid leukemia treatment response and remission.

Evaluation of *ABL* kinase domain (KD) single nucleotide variants to assess individuals for tyrosine kinase inhibitor resistance may be considered **medically necessary** when there is an inadequate initial response to treatment or any sign of loss of response (see Policy Guidelines section); and/or when there is a progression of the disease to the accelerated or blast phase.

Evaluation of *ABL* KD single nucleotide variants is considered **investigational** for monitoring in advance of signs of treatment failure or disease progression.

Acute Lymphoblastic Leukemia

BCR-ABL1 testing for messenger RNA transcript levels by quantitative real-time reverse transcription-polymerase chain reaction at baseline before initiation of treatment and at appropriate intervals during therapy (see Policy Guidelines section) may be considered **medically necessary** for monitoring of Philadelphia chromosome-positive acute lymphoblastic leukemia treatment response and remission.

Evaluation of *ABL* KD single nucleotide variants to assess individuals for tyrosine kinase inhibitor resistance may be considered **medically necessary** when there is an inadequate initial response to treatment or any sign of loss of response.

Evaluation of *ABL* KD single nucleotide variants is considered **investigational** for monitoring in advance of signs of treatment failure or disease progression.

Carrier Screening for Genetic Diseases

Targeted Risk-Based Carrier Screening

Targeted carrier screening for X-linked and autosomal recessive genetic diseases is considered **medically necessary** for individuals who are pregnant or are considering

pregnancy and are at increased risk of having offspring with an X-linked or autosomal recessive disease when one of the following criteria is met:

- One or both individuals have a first- or second-degree relative who is affected; **OR**
- One individual is known to be a carrier; **OR**
- One or both individuals are members of a population known to have a carrier rate that exceeds a threshold considered appropriate for testing for a particular condition.

AND all of the following criteria are met:

- The natural history of the disease is well understood and there is a reasonable likelihood that the disease is one with high morbidity or early mortality in the homozygous or compound heterozygous state (see Policy Guidelines);
- Alternative biochemical or other clinical tests to definitively diagnose carrier status are not available, or, if available, provide an indeterminate result or are individually less efficacious than genetic testing;
- The genetic test has adequate clinical validity to guide clinical decision-making and residual risk is understood;
- An association of the marker with the disorder has been established;
- If targeted testing is performed by a panel, the panel meets the minimum number of recommended gene variants but does not exceed the maximum, as determined by professional clinical guidelines (see Policy Guidelines). Non-targeted panels can be used instead of targeted testing when the criteria for non-targeted carrier screening are met (see below);
- Previous carrier screening or individual targeted gene testing for the gene variant(s) of interest has not been performed (see Policy Guidelines).

All targeted carrier screening not meeting any of the above criteria is considered **investigational**.

First-degree relatives include a biological parent, brother, sister, or child; second-degree relatives include a biologic grandparent, aunt, uncle, niece, nephew, grandchildren, and half-sibling.

Non-Targeted Carrier Screening

Non-targeted carrier screening panels for autosomal recessive and X-linked genetic disorders may be considered **medically necessary** as an alternative to testing of individual genes (e.g., *SMN1* gene and *CFTR* gene) for individuals who are pregnant or are considering pregnancy at any risk level including high risk and average risk when all of the following criteria are met:

- The natural history of each disease is well understood and there is reasonable likelihood that the disease is one with high morbidity or early mortality in the homozygous or compound homozygous state (see Policy Guidelines);
- Alternative biochemical or other clinical tests to definitively diagnose carrier status are not available, or, if available, provide an indeterminate result or are individually less efficacious than genetic testing;

- The genetic test has adequate clinical validity to guide clinical decision-making and residual risk is understood;
- An association of the markers with the disorders has been established;
- If testing is performed by a panel, the panel meets the minimum number of recommended gene variants but does not exceed the maximum, as determined by professional clinical guidelines (see Policy Guidelines);
- Previous carrier screening has not been performed (see Policy Guidelines).

Non-targeted carrier screening panels are considered **investigational** in all other situations when above criteria are not met (see Policy Guidelines).

Summary of Evidence

Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2)

For individuals who have cancer or a personal or family cancer history and meet criteria suggesting a risk of hereditary breast and ovarian cancer (HBOC) syndrome who receive genetic testing for a *BRCA1* or *BRCA2* variant, the evidence includes a TEC Assessment and studies of variant prevalence and cancer risk. Relevant outcomes are overall survival (OS), disease-specific survival, test validity, and quality of life (QOL). The accuracy of variant testing has been shown to be high. Studies of lifetime risk of cancer for carriers of a *BRCA* variant have shown a risk as high as 85%. Knowledge of *BRCA* variant status in individuals at risk of a *BRCA* variant may impact health care decisions to reduce risk, including intensive surveillance, chemoprevention, and/or prophylactic intervention. In individuals with *BRCA1* or *BRCA2* variants, prophylactic mastectomy and oophorectomy have been found to significantly increase disease-specific survival and OS. Knowledge of *BRCA* variant status in individuals diagnosed with breast cancer may impact treatment decisions. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have other high-risk cancers (e.g., cancers of the fallopian tube, pancreas, prostate) who receive genetic testing for a *BRCA1* or *BRCA2* variant, the evidence includes studies of variant prevalence and cancer risk. Relevant outcomes are OS, disease-specific survival, test validity, and QOL. The accuracy of variant testing has been shown to be high. Knowledge of *BRCA* variant status in individuals with other high-risk cancers can inform decisions regarding genetic counseling, chemotherapy, and enrollment in clinical trials. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with a risk of HBOC syndrome who receive genetic testing for a *PALB2* variant, the evidence includes studies of clinical validity and studies of breast cancer risk, including a meta-analysis. Relevant outcomes are OS, disease-specific survival, and test validity. Evidence supporting clinical validity was obtained from numerous studies reporting relative risks (RRs) or odds ratios (ORs). Study designs included family segregation, kin-cohort, family-based case-control, and population-based case-control. The number of pathogenic variants identified in studies varied from 1 (founder mutations) to 48. The RR for breast cancer associated with a *PALB2* variant ranged from 2.3 to 13.4, with the 2 family-based studies reporting the lowest values. Evidence of preventive interventions in women with *PALB2* variants is indirect, relying on studies of high-risk women and *BRCA* carriers.

These interventions include screening with magnetic resonance imaging, chemoprevention, and risk-reducing mastectomy. Given the penetrance of *PALB2* variants, the outcomes following bilateral and contralateral risk-reducing mastectomy examined in women with a family history consistent with hereditary breast cancer (including *BRCA1* and *BRCA2* carriers) can be applied to women with *PALB2* variants, with the benefit-to-risk balance affected by penetrance. In women at high-risk of hereditary breast cancer who would consider risk-reducing interventions, identifying a *PALB2* variant provides a more precise estimated risk of developing breast cancer compared with family history alone and can offer women a more accurate understanding of benefits and potential harms of any intervention. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

For individuals who are suspected of attenuated familial adenomatous polyposis (FAP), *MUTYH*-associated polyposis (MAP), and Lynch syndrome who receive genetic testing for adenomatous polyposis coli (*APC)*, or are at-risk relatives of patients with FAP who receive genetic testing for *MUTYH* after a negative *APC* test result, the evidence includes a TEC Assessment. Relevant outcomes are overall survival (OS), disease-specific survival, and test accuracy and validity. For patients with an *APC* variant, enhanced surveillance and/or prophylactic treatment will reduce the future incidence of colon cancer and improve health outcomes. A related familial polyposis syndrome, MAP syndrome, is associated with variants in the *MUTYH* gene. Testing for this genetic variant is necessary when the differential diagnosis includes both FAP and MAP because distinguishing between the 2 leads to different management strategies. Depending on the presentation, Lynch syndrome may be part of the same differential diagnosis. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who (1) are suspected of attenuated FAP, MAP, and Lynch syndrome, (2) have colon cancer, (3) have endometrial cancer meeting clinical criteria for Lynch syndrome, (4) are at-risk relatives of patients with Lynch syndrome, (5) are without colon cancer but with a family history meeting Amsterdam or Revised Bethesda criteria, or documentation of 5% or higher predicted risk of the syndrome on a validated risk prediction model, who receive genetic testing for MMR genes, the evidence includes an Agency for Healthcare Research and Quality report, a supplemental assessment to that report by the Evaluation of Genomic Applications in Practice and Prevention Working Group, and an Evaluation of Genomic Applications in Practice and Prevention recommendation for genetic testing in colorectal cancer (CRC). Relevant outcomes are OS, disease-specific survival, and test accuracy and validity. A chain of evidence from well-designed experimental nonrandomized studies is adequate to demonstrate the clinical utility of testing unaffected (without cancer) first- and second-degree relatives of patients with Lynch syndrome who have a known variant in an MMR gene, in that counseling has been shown to influence testing and surveillance choices among unaffected family members of Lynch syndrome patients. One long-term, nonrandomized controlled study and a cohort study of Lynch syndrome family members found significant reductions in CRC among those who followed recommended colonic surveillance. A positive genetic test for an MMR variant can also lead to changes in the management of other Lynch syndrome malignancies. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who warrant Lynch testing, screen negative on MMR testing, but positive for microsatellite instability (MSI) and lack MSH2 protein expression who receive genetic testing

for *EPCAM* variants, the evidence includes variant prevalence studies and case series. Relevant outcomes are OS, disease-specific survival, and test accuracy and validity. Studies have shown an association between *EPCAM* variants and Lynch-like disease in families, and the cumulative risk for CRC is similar to carriers of an *MSH2* variant. Identification of an *EPCAM* variant could lead to changes in management that improve health outcomes. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have CRC in whom MLH1 protein is not expressed on immunohistochemical (IHC) analysis and who receive genetic testing for *BRAF* V600E or *MLH1* promoter methylation, the evidence includes case series. Relevant outcomes are OS, disease-specific survival, and test accuracy and validity. Studies have shown, with high sensitivity and specificity, an association between *BRAF* V600E variant and *MLH1* promoter methylation with sporadic CRC. Therefore, this type of testing could eliminate the need for further genetic testing or counseling for Lynch syndrome. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who (1) are suspected of JPS or PJS or (2) are at-risk relatives of patients suspected of or diagnosed with juvenile polyposis syndrome (JPS) or Peutz-Jeghers syndrome (PJS) who receive genetic testing for *SMAD4*, *BMPR1A*, or *STK11* genes, respectively, the evidence includes multiple observational studies. Relevant outcomes are OS, disease-specific survival, and test accuracy and validity. Studies have shown, with high sensitivity and specificity, an association between *SMAD4* and *BMPR1A* and *STK11* variants with JPS and PJS, respectively. Direct evidence of clinical utility for genetic testing of JPS or PJS is not available. Genetic testing may have clinical utility by avoiding burdensome and invasive endoscopic examinations, release from intensified screening programs resulting in psychological relief, and improving health outcomes by identifying currently unaffected at-risk family members who require intense surveillance or prophylactic colectomy. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

JAK2, MPL, and CALR Testing for Myeloproliferative Neoplasms

For individuals with a suspected myeloproliferative neoplasm (MPN) who receive genetic testing for *JAK2*, the evidence includes case series, retrospective studies, meta-analyses, and randomized controlled trials. Relevant outcomes are overall survival (OS), disease-specific survival, test accuracy and validity, and resource utilization. For patients with suspected Ph-negative MPN, *JAK2* variants are found in nearly 100% of those with polycythemia vera (PV), 60% to 65% of those with essential thrombocythemia (ET), and 60% to 65% of those with primary myelofibrosis (PMF). In individuals with suspected MPN, a positive genetic test for *JAK2* satisfies a major criterion for the International Consensus Classification (2022) and World Health Organization (WHO) 2022 (5th edition) classification for Ph-negative MPNs and eliminates secondary or reactive causes of erythrocytosis and thrombocythemia from the differential diagnosis. The presence of a documented *JAK2* variant may aid in the selection of ruxolitinib, a *JAK2* inhibitor; ruxolitinib, however, is classified as second-line therapy. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with a suspected MPN who receive genetic testing for *MPL*, the evidence includes case series and retrospective studies. Relevant outcomes are OS, disease-specific survival, test accuracy and validity, and resource utilization. For patients with suspected Ph-

negative MPN, *MPL* variants are found in approximately 5% of those with ET and PMF. In individuals with suspected MPN, a positive genetic test for *MPL* satisfies a major criterion for the International Consensus Classification (2022) and WHO (2022, 5th edition) classification for ET and PMF and eliminates secondary or reactive causes of thrombocythemia from the differential diagnosis. The goal of ET treatment is to alleviate symptoms and minimize thrombotic events and bleeding irrespective of *MPL* variant status. For PMF, hematopoietic cell transplantation is the only treatment with curative potential while most other treatment options focus on symptom alleviation. However, in both ET and PMF, establishing the diagnosis through *MPL* genetic testing does not in and of itself result in changes in management that would be expected to improve the net health outcome. Thus, the clinical utility has not been established. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with a suspected MPN who receive genetic testing for *CALR*, the evidence includes case series and retrospective studies. Relevant outcomes are OS, disease-specific survival, test accuracy and validity, and resource utilization. For patients with suspected Ph-negative MPN, *CALR* variants are found in approximately 20% to 25% of those with ET and PMF. For individuals with suspected MPN, a positive genetic test for *CALR* satisfies a major criterion for the International Consensus Classification (2022) and WHO (2022, 5th edition) classification for ET and PMF and eliminates secondary or reactive causes of thrombocythemia from the differential diagnosis. The goal of ET treatment is to alleviate symptoms and minimize thrombotic events and bleeding irrespective of *CALR* variant status. For PMF, hematopoietic cell transplantation is the only treatment with curative potential while most other treatment options focus on symptom alleviation. However, in both ET and PMF, establishing the diagnosis through *CALR* genetic testing does not result in changes in management that would be expected to improve the net health outcome. Thus, the clinical utility has not been established. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

BCR-ABL1 Testing in Chronic Myelogenous Leukemia and Acute Lymphoblastic Leukemia

For individuals who have suspected chronic myelogenous leukemia (CML) who receive *BCR-ABL1* fusion gene qualitative testing to confirm the diagnosis and establish a baseline for monitoring treatment, the evidence includes validation studies. Relevant outcome is test validity. The sensitivity of testing with reverse transcription-polymerase chain reaction is high compared with conventional cytogenetics. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have a diagnosis of CML who receive *BCR-ABL1* fusion gene quantitative testing at appropriate intervals for monitoring treatment response and remission, the evidence includes a systematic review and nonrandomized trials. Relevant outcomes are disease-specific survival, test validity, and change in disease status. Studies have shown high sensitivity of this type of testing and a strong correlation with outcomes, including the risk of disease progression and survival, which may stratify patients to different options for disease management. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have a diagnosis of CML with an inadequate initial response, loss of response, and/or disease progression who receive an evaluation for *ABL* kinase domain (KD) single nucleotide variants to assess for tyrosine kinase inhibitor (TKI) resistance, the evidence includes a systematic review and retrospective cohort study. Relevant outcomes are disease-specific survival, test validity, and medication use. The systematic review and case series evaluated pharmacogenetics testing for TKIs and reported the presence of KD single nucleotide variants detected at imatinib failure. These studies have shown a correlation between certain types of variants, treatment response, and the selection of subsequent treatment options. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have a diagnosis of Philadelphia chromosome (Ph)-positive acute lymphoblastic leukemia (ALL) who receive *BCR-ABL1* fusion gene quantitative testing at baseline before and during treatment to monitor treatment response and remission, the evidence includes prospective and retrospective cohort studies and case series. Relevant outcomes are disease-specific survival, test validity, and change in disease status. As with CML, studies have shown high sensitivity for this type of testing and a strong correlation with outcomes, including the risk of disease progression, which may stratify patients to different treatment options. Also, evidence of treatment resistance or disease recurrence directs a change in medication. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have Ph-positive ALL and signs of treatment failure or disease progression who receive an evaluation for *ABL1* KD single nucleotide variants to assess for TKI resistance, the evidence includes case series. Relevant outcomes are test validity and medication use. Studies have shown that specific imatinib-resistant variants are insensitive to 1 or more of the second-generation TKIs; these variants are used to guide medication selection. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Carrier Screening for Genetic Diseases

For individuals who are asymptomatic but at risk for having offspring with an inherited X-linked or autosomal recessive genetic disorder who receive targeted risk-based carrier screening, the evidence includes studies supporting clinical validity and clinical utility. Relevant outcomes are test validity and changes in reproductive decision making. Results of carrier testing can be used to inform reproductive decisions such as preimplantation genetic diagnosis, in vitro fertilization, not having a child, invasive prenatal testing, adoption, or pregnancy termination. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are either at increased risk or population risk for having offspring with an inherited X-linked or autosomal recessive genetic disorder who receive a non-targeted carrier screening panel, the evidence includes studies supporting clinical validity and clinical utility. Relevant outcomes are test validity and changes in reproductive decision making. Studies have found that non-targeted carrier screening identifies more carriers and more potentially affected fetuses. Many of the genes in carrier screening panels do not meet the American College of Obstetricians and Gynecologists (ACOG) consensus-driven criteria of at least a 1% carrier rate for all ethnic groups. However, non-targeted testing can address the discrepancies between self-reported ethnicity and genetic ancestry in an ethnically mixed population. As panels become larger the likelihood of being identified as a carrier of a rare

genetic disorder increases, leading to an at-risk couple rate of nearly 2% for having an offspring with a recessive or X-linked disorder. Many, though notably not all, of these rare genetic disorders are associated with severe or profound symptoms including shortened lifespan and intellectual or physical disability. With adequate genetic counseling, carrier screening panels can inform reproductive choices, and observational studies have shown that a majority of couples would consider intervention that depends on the severity of the condition. Therefore, non-targeted carrier screening panels for severe recessive and X-linked genetic disorders can have a significant clinical impact. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Policy Guidelines

Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2)

Close Relatives
Close relatives are blood related family members including 1st-, 2nd-, and 3rd-degree relatives on the same side of the family (maternal or paternal).

- 1st-degree relatives are parents, siblings, and children.
- 2nd-degree relatives are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings.
- 3rd-degree relatives are great-grandparents, great-aunts, great-uncles, great-grandchildren, and first cousins.

Prostate Cancer Risk Groups
Risk groups for prostate cancer in this policy include high-risk groups and very-high-risk groups.

- High-risk group: no very-high-risk features and are T3a (American Joint Committee on Cancer staging T3a = tumor has extended outside of the prostate but has not spread to the seminal vesicles); OR Grade Group 4 or 5; OR prostate specific antigen of 20 ng/mL or greater.
- Very-high-risk group: T3b-T4 (tumor invades seminal vesicle(s); or tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall); OR Primary Gleason Pattern 5; OR 2 or 3 high-risk features; OR greater than 4 cores with Grade Group 4 or 5.

Recommended Testing Strategies
Individuals who meet criteria for genetic testing as outlined in the policy statements above should be tested for variants in *BRCA1, BRCA2,* and *PALB2*. Recommended strategies are listed below.

- In individuals with a known familial *BRCA* or *PALB2* variant, targeted testing for the specific variant is recommended.
- In individuals with unknown familial *BRCA* or *PALB2* variant:
    - To identify clinically significant variants, NCCN advises testing a relative who has early-onset disease, bilateral disease, or multiple primaries, because that individual has the highest likelihood of obtaining a positive test result. Unless the affected individual is a member of an ethnic group for which particular founder pathogenic or likely pathogenic variants are known, comprehensive

genetic testing (i.e., full sequencing of the genes and detection of large gene rearrangements) should be performed.
    - If no living family member with breast or ovarian cancer exists, NCCN suggests testing first- or second-degree family members affected with cancer thought to be related to deleterious *BRCA1* or *BRCA2* variants (e.g., prostate cancer, pancreatic cancer, melanoma).
    - If no familial variant can be identified, 2 possible testing strategies are:
        - Full sequencing of *BRCA1* and *BRCA2* followed by testing for large genomic rearrangements (deletions, duplications) only if sequencing detects no variant (negative result). More than 90% of *BRCA* variants will be detected by full sequencing.
        - Alternatively, simultaneous full sequencing and testing for large genomic rearrangements (also known as comprehensive *BRCA* testing; see Comprehensive Variant Analysis below) may be performed as is recommended by NCCN. Comprehensive testing can detect 92.5% of *BRCA1* or *BRCA2* variants.
- Testing for *BRCA1*, *BRCA2*, and *PALB2* through panel testing over serial testing might be preferred for efficiency. Multi-gene panels often include genes of moderate or low penetrance, and genes with limited evidence on which to base management decisions. When considering a gene panel, NCCN recommends use of "tailored panels that are disease-focused and include clinically actionable cancer susceptibility genes".
- Ashkenazi Jewish descent
    - In individuals of known Ashkenazi Jewish descent, one approach is to test for the 3 known founder mutations (185delAG and 5182insC in *BRCA1*; 6174delT in *BRCA2*) first, if testing is negative for founder mutations and if the individual's ancestry also includes non-Ashkenazi ethnicity (or if other *BRCA1/2* testing criteria are met), comprehensive genetic testing should be considered.
- Testing strategy may also include testing individuals not meeting the above criteria who are adopted and have limited medical information on biological family members, individuals with small family structure, and individuals with presumed paternal transmission.

High-Risk Ethnic Groups
Testing of eligible individuals who belong to ethnic populations in which there are well-characterized founder mutations should begin with tests specifically for these variants. For example, founder mutations account for approximately three-quarters of the *BRCA* variants found in Ashkenazi Jewish populations. When testing for founder mutations is negative, a comprehensive variant analysis should then be performed.

Testing Unaffected Individuals
In unaffected family members of potential *BRCA* or *PALB2* variant families, most test results will be negative and uninformative. Therefore, it is strongly recommended that an *affected* family member be tested first whenever possible to adequately interpret the test. Should a *BRCA* or *PALB2* variant be found in an affected family member(s), DNA from an *unaffected* family member can be tested specifically for the same variant of the affected family member without having to sequence the entire gene. Interpreting test results for an unaffected family member without knowing the genetic status of the family may be possible in the case of a positive result for an established disease-associated variant but leads to difficulties in interpreting negative test results (uninformative negative) or variants of

uncertain significance because the possibility of a causative *BRCA or PALB2* variant is not ruled out.

Testing Minors
The use of genetic testing for *BRCA1, BRCA2,* or *PALB2* variants for identifying hereditary breast and ovarian cancer syndrome has limited or no clinical utility in minors, because there is no change in management for minors as a result of knowledge of the presence or absence of a deleterious variant. In addition, there are potential harms related to stigmatization and discrimination. See policy 2.04.128 regarding testing of *BRCA1, BRCA2,* and *PALB2* for Fanconi anemia. See policies 2.04.148, 2.04.151, 2.04.155, and 2.04.156 regarding genetic testing to guide targeted therapy.

Prostate Cancer
Individuals with *BRCA* or *PALB2* variants have an increased risk of prostate cancer, and individuals with known *BRCA* or *PALB2* variants may, therefore, consider more aggressive screening approaches for prostate cancer.

Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

Testing At-Risk Relatives

Due to the high lifetime risk of cancer of most genetic syndromes discussed in this policy, "at-risk relatives" primarily refers to first-degree relatives. However, some judgment must be permitted, e.g., in the case of a small family pedigree, when extended family members may need to be included in the testing strategy. Family history might include at least 2 second-degree relatives with a Lynch syndrome-related cancer, including at least 1 diagnosed before 50 years of age, or at least 3 second-degree relatives with a Lynch syndrome-related cancer, regardless of age.

Targeted Familial Variant Testing

It is recommended that, when possible, initial genetic testing for familial adenomatous polyposis (FAP) or Lynch syndrome be performed in an affected family member, so that testing in unaffected family members can focus on the variant found in the affected family member (see Benefit Application section). If an affected family member is not available for testing, testing should begin with an unaffected family member most closely related to an affected family member.

In many cases, genetic testing for *MUTYH* gene variants should first target the specific variants *Y165C* and *G382D*, which account for more than 80% of variants in white populations, and subsequently, proceed to sequence only as necessary. However, in other ethnic populations, proceeding directly to sequencing is appropriate.

Evaluation for Lynch Syndrome

For patients with colorectal cancer (CRC) or endometrial cancer being evaluated for Lynch syndrome, the microsatellite instability (MSI) test or the immunohistochemical (IHC) test with or without *BRAF* gene variant testing, or methylation testing, should be used as an initial evaluation of tumor tissue before mismatch repair (MMR) gene analysis. Both tests are not

necessary. Proceeding to MMR gene sequencing would depend on the results of MSI or IHC testing. In particular, IHC testing may help direct which MMR gene likely contains a variant, if any, and may also provide additional information if MMR genetic testing is inconclusive. For further information on tumor tissue test results, interpretation, and additional testing options, see the NCCN [National Comprehensive Cancer Network] clinical care guidelines on genetic/familial high-risk assessment: colorectal.

When indicated, genetic sequencing for MMR gene variants should begin with *MLH1* and *MSH2* genes, unless otherwise directed by the results of IHC testing. Standard sequencing methods will not detect large deletions or duplications; when MMR gene variants are expected based on IHC or MSI studies, but none are found by standard sequencing, additional testing for large deletions or duplications is appropriate.

The Amsterdam II Clinical Criteria (all criteria must be fulfilled) are the most stringent for defining families at high risk for Lynch syndrome:

- 3 or more relatives with an associated cancer (CRC, or cancer of the endometrium, small intestine, ureter, or renal pelvis);
- 1 should be a first-degree relative of the other 2;
- 2 or more successive generations affected;
- 1 or more relatives diagnosed before the age of 50 years;
- FAP should be excluded in cases of CRC;
- Tumors should be verified by pathologic examination.
- Modifications:
    - EITHER: very small families, which cannot be further expanded, can be considered to have hereditary nonpolyposis colorectal cancer (HNPCC) with only 2 CRCs in first-degree relatives if at least 2 generations have the cancer and at least 1 case of CRC was diagnosed by the age of 55 years;
    - OR: in families with 2 first-degree relatives affected by CRC, the presence of a third relative with an unusual early-onset neoplasm or endometrial cancer is sufficient.

The Revised Bethesda Guidelines (fulfillment of any criterion meets guidelines) are less stringent than the Amsterdam criteria and are intended to increase the sensitivity of identifying at-risk families. The Bethesda guidelines are also considered more useful in identifying which patients with CRC should have their tumors tested for MSI and/or IHC:

- CRC diagnosed in a patient who is younger than 50 years old;
- Presence of synchronous or metachronous CRC or other HNPCC-associated tumors,[a] regardless of age;
- CRC with high MSI histology diagnosed in a patient younger than 60 years old;
- CRC diagnosed in 1 or more first-degree relatives with a Lynch syndrome-associated tumor, with 1 of the cancers being diagnosed before 50 years of age;
- CRC diagnosed in 2 or more first or second-degree relatives with HNPCC-related tumors,[a] regardless of age.

[a] HNPCC-related tumors include colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, brain (usually glioblastoma as seen in Turcot syndrome), sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome, and carcinoma of the small bowel.

Multiple risk prediction models that provide quantitative estimates of the likelihood of an MMR variant are available such MMRpro, PREMM5, or MMRpredict. National Comprehensive Cancer Network guidelines recommend (category 2A) testing for Lynch syndrome in individuals with a 5% or higher predicted risk of the syndrome on these risk prediction models.

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

JAK2, MPL, and CALR Testing for Myeloproliferative Neoplasms

Testing Strategy
Individuals suspected to have polycythemia vera (PV) should first be tested for the most common finding, *JAK2* V617F. If the testing is negative, further testing to detect other *JAK2* tyrosine kinase variants (e.g., in exon 12) is warranted.

Individuals suspected to have essential thrombocythemia or primary myelofibrosis should first be tested for *JAK2* variants, as noted. If testing is negative, further testing to detect *MPL* and *CALR* variants is warranted.

Criteria for Polycythemia Vera Testing
Based on the World Health Organization (WHO) and International Consensus Classification major and minor criteria (see Table 1), documentation of serum erythropoietin level below the reference range for normal meets a minor criterion for PV. Therefore, serum erythropoietin testing is recommended before *JAK2* testing.

Table 1. World Health Organization 5th Edition and the International Consensus Classification Diagnostic Criteria for Polycythemia Vera

Major Criteria
• Increased hemoglobin level (>16.5 g/dL in men or >16.0 g/dL in women); or • Increased hematocrit (>49% in men or >48% in women); or
• Bone marrow biopsy showing hypercellularity for age with trilineage maturation, including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)

• *JAK2* V617F or *JAK2* exon 12 variant detected
Minor Criterion
• Serum erythropoietin level below the reference range for normal

BCR-ABL1 Testing in Chronic Myelogenous Leukemia and Acute Lymphoblastic Leukemia

Diagnosis of Chronic Myelogenous Leukemia and Acute Lymphoblastic Leukemia
Qualitative molecular confirmation of the cytogenetic diagnosis (i.e., detection of the Philadelphia chromosome) is necessary for accurate diagnosis of chronic myelogenous leukemia (CML). Identification of the Philadelphia chromosome is not necessary to diagnose acute lymphoblastic leukemia (ALL); however, molecular phenotyping is usually performed at the initial assessment (see Determining Baseline RNA Transcript Levels and Subsequent Monitoring subsection).

Distinction between molecular variants (i.e., p190 vs p210) is necessary for accurate results in subsequent monitoring assays.

Determining Baseline RNA Transcript Levels and Subsequent Monitoring

Determination of *BCR-ABL1* messenger RNA transcript levels should be done by quantitative real-time reverse transcription-polymerase chain reaction-based assays and reported results should be standardized according to the International Scale.
For CML, testing is appropriate at baseline before the start of imatinib treatment, and testing is appropriate every 3 months when the individual is responding to treatment. After a complete cytogenetic response is achieved, testing is recommended every 3 months for 2 years, then every 3 to 6 months thereafter during treatment.

Without a complete cytogenetic response, continued monitoring at 3-month intervals during treatment is recommended. It has been assumed that the same time points for monitoring imatinib are appropriate for dasatinib and nilotinib and will likely also be applied to bosutinib and ponatinib.

More frequent monitoring is indicated for individuals diagnosed with CML who are in complete molecular remission and are not undergoing treatment with a tyrosine kinase inhibitor (TKI). For ALL, the optimal timing remains unclear and depends on the chemotherapy regimen used.

Tyrosine Kinase Inhibitor Resistance
For CML, inadequate initial response to TKIs is defined as failure to achieve a complete hematologic response at 3 months, only minor cytogenetic response at 6 months, or major (rather than complete) cytogenetic response at 12 months.

Unlike in CML, ALL resistance to TKIs is less well studied. In individuals with ALL receiving a TKI, a rise in the *BCR-ABL* mRNA level while in hematologic complete response or clinical relapse warrants variant analysis.

Loss of response to TKIs is defined as hematologic relapse, cytogenetic relapse, or 1-log increase in *BCR-ABL1* transcript ratio and therefore loss of major molecular response.

Kinase domain single nucleotide variant testing is usually offered as a single test to identify T315I variant or as a panel (that includes T315I) of the most common and clinically important variants.

Carrier Screening for Genetic Diseases

Carrier screening (targeted or non-targeted) is only medically necessary once per lifetime. Exceptions may be considered if advances in technology support medical necessity for retesting.

Targeted carrier screening for autosomal recessive or X-linked conditions is also called risk-based test or ethnic-based testing. If targeted testing is performed by a panel, the most appropriate panel code available should be used. The panel and the panel billing code should include *CFTR* and *SMN1*.

Non-targeted carrier screening applies to persons of any risk including average risk. Any panel using 81443 for non-targeted carrier screening must include the *CFTR* and *SMN1* genes. Non-targeted carrier screening panels should include the minimum number of genes but not exceed the maximum number of genes recommended by professional guidelines from the American College of Obstetricians and Gynecologists (ACOG; 2-22 conditions) or the American College of Medical Genetics and Genomics (ACMG; 113 genes).

The Committee (reaffirmed in 2023) states that "Ethnic-specific, panethnic, and expanded carrier screening are acceptable strategies for prepregnancy and prenatal carrier screening" and offered the following summary pertaining to expanded carrier screening: "Given the multitude of conditions that can be included in expanded carrier screening panels, the disorders selected for inclusion should meet several of the following consensus-determined criteria: have a carrier frequency of 1 in 100 or greater, have a well-defined phenotype, have a detrimental effect on quality of life, cause cognitive or physical impairment, require surgical or medical intervention, or have an onset early in life. Additionally, screened conditions should be able to be diagnosed prenatally and may afford opportunities for antenatal intervention to improve perinatal outcomes, changes to delivery management to optimize newborn and infant outcomes, and education of the parents about special care needs after birth. Carrier screening panels should not include conditions primarily associated with a disease of adult onset."[ACOG Committee Opinion No. 690; PMID: 28225425]

The ACOG guideline includes a list of 22 conditions deemed reasonable to include in a carrier screening panel (see Table 2). While there is no agreed upon definition of severity across professional societies, these 22 conditions have severity that would be deemed profound or severe per publication based on previous work by ACMG and cited by the most recent ACMG guidelines.[Lazarin et al (2014); PMID: 25494330][Gregg et al (2021); PMID 34285390] All but one condition deemed reasonable by ACOG (alpha-thalassemia) would be classified as profound or severe based on collaborative clinical expert application of a trait-based algorithm; however, in this work it is not clear if the alpha-thalassemia genes *HBA1/HBA2* were classified based on hemoglobin Bart hydrops fetalis syndrome or hemoglobin H disease.[Arjunan et al (2020); PMID: 32474937] Carrier testing of autosomal

recessive genes associated with severe disease with carrier frequency of greater than 1/100 is estimated to identify 82% of at-risk couples.[Guo et al (2019); PMID: 30846881]

In 2021, the ACMG recommended that the phrase "expanded carrier screening" be replaced by "carrier screening" as expanded carrier screening is not well or precisely defined by professional organizations.[Gregg et al (2021); PMID 34285390] Previously, ACMG has defined expanded panels as those that use next-generation sequencing to screen for variants in many genes, as opposed to gene-by-gene screening (e.g., ethnic-specific screening or panethnic testing for cystic fibrosis).

The updated ACMG guideline now recommends a multi-tier approach to carrier screening for autosomal recessive and X-linked conditions, incorporating recommendations from the ACOG Committee Opinion 691 (2017; reaffirmed in 2023),[ACOG Committee Opinion No. 691; PMID: 28225426] to enhance communication and precision while advancing equity in carrier screening (see Table PG1).[Gregg et al (2021); PMID 34285390] The consensus group recognized no accepted standard in defining the severity of various conditions; and, based on previously published work, use the following definitions: (1) profound: shortened lifespan during infancy or childhood, intellectual disability; (2) severe: death in early adulthood, impaired mobility or a [disabling] malformation involving an internal organ; (3) moderate: neurosensory impairment, immune deficiency or cancer, mental illness, dysmorphic features; and (4) mild: not meeting one of those described.[Lazarin et al (2014); PMID: 25494330]

The ACMG consensus group recommends offering Tier 3 carrier screening (≥1/200 carrier frequency + Tier 2; see Table PG1) to all pregnant patients and those planning a pregnancy. Carrier testing of autosomal recessive genes associated with severe disease with carrier frequency greater than 1/100 is estimated to identify 82% of at-risk couples, and identify 93% of at-risk couples when testing for genes with greater than 1/200 carrier frequency.[Guo et al (2019); PMID: 30846881] The ACMG Tier 3 recommendations were based on estimates that moving from Tier 2 (≥1/100 carrier frequency) to Tier 3 (1/200 carrier frequency) provided additional identification of 4-9/10,000 at-risk couples depending on the endogamous population examined. When the population evaluated was weighted by U.S. census data, at-risk couples identified increased by 6 per 10,000 couples when moving from the Tier 2 (≥1/100) carrier frequency to that of Tier 3 (≥1/200). Assuming ~4 million births per year, this translates to an annual increase of identifying 2,400 additional U.S. couples.

The ACMG consensus group specified gene recommendations which include testing for 97 autosomal recessive genes and 16 X-linked genes, all of which associate with disorders of moderate, severe, or profound severity and are of 1/200 or greater carrier frequency. Non-targeted carrier screening panels that test for genes beyond this provide diminishingly small results, and pleiotropy, locus heterogeneity, variant interpretation, and poor genotype-phenotype correlation may disproportionately impact the ability to provide accurate prognostic information.[Gregg et al (2021); PMID 34285390]

Additionally, the recommendations include that male partners of pregnant women and those planning a pregnancy may be offered Tier 3 carrier screening for autosomal recessive conditions when carrier screening is performed simultaneously with their female partner. Tier 4 screening may be offered when a pregnancy stems from a known or possible consanguineous relationship (second cousins or closer) or when family or personal medical history warrants. The ACMG does not recommend offering Tier 1 and/or Tier 2 screening, because these do not

provide equitable evaluation of all racial/ethnic groups, or the routine offering of Tier 4 panels.

Testing Strategy
After testing the proband, targeted testing on the reproductive partner is preferred. Testing only applies to genes meeting criteria outlined above. If a lab does a more extensive test, then testing for other findings in the reproductive partner would not meet criteria. In general, carrier screening can be done once per lifetime. However, if only targeted or limited testing was done previously, then a more general non-targeted panel could be performed, particularly in cases where there is a new reproductive partner. In this case it is likely that genes could be re-tested.

Genetic Counseling
Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods. Carrier screening with appropriate genetic counseling is performed in adults.

Table 2. Example of an Expanded Carrier Screening Panel

Condition	Carrier Frequency in General Population	Carrier Frequency in Specific Ethnic Groups
α-thalassemia	Unknown	African (particularly sub-Saharan): 1 in 3 Mediterranean: 1 in 30 Southeast Asian and Middle Eastern: 1 in 20
ß-thalassemia	Unknown	African American: <1 in 8 Ashkenazi Jewish: Varied Asian: 1 in 20 Mediterranean: 1 in 7
Bloom syndrome	<1 in 500	Ashkenazi Jewish: 1 in 100
Canavan disease	<1 in 150	Ashkenazi Jewish: 1 in 41
Cystic fibrosis	Unknown	African American: 1 in 61 Asian: 1 in 94 Ashkenazi Jewish: 1 in 24 Caucasian: 1 in 25 Hispanic: 1 in 58
Familial dysautonomia	<1 in 500	Ashkenazi Jewish: 1 in 31
Familial hyperinsulinism	<1 in 150	Ashkenazi Jewish: 1 in 52

Condition	Carrier Frequency in General Population	Carrier Frequency in Specific Ethnic Groups
Fanconi anemia C	<1 in 790	Ashkenazi Jewish: 1 in 89
Fragile X syndrome	1 in 259	
Galactosemia	1 in 87	Ashkenazi Jewish: 1 in 127
Gaucher disease	<1 in 100	Ashkenazi Jewish: 1 in 15
Glycogen storage disease type 1A	<1 in 150	Ashkenazi Jewish: 1 in 71
Joubert syndrome	<1 in 500	Ashkenazi Jewish: 1 in 92
Medium-chain acyl-CoA dehydrogenase deficiency	Unknown	Caucasian: 1 in 50
Maple syrup urine disease types 1A and 1B	1 in 240	Ashkenazi Jewish: 1 in 81 (type 1B) Mennonite: 1 in 10 (type 1A- *BCKDHA* p.Y438N)
Mucolipidosis IV	<1 in 500	Ashkenazi Jewish: 1 in 96
Niemann-Pick disease type A	<1 in 500	Ashkenazi Jewish: 1 in 90
Phenylketonuria	Unknown	Caucasian: 1 in 50 Irish: 1 in 34
Sickle cell anemia	Unknown	African American: 1 in 10
Smith-Lemli-Opitz syndrome	Unknown	Caucasian: 1 in 70
Spinal muscular atrophy	Unknown	African American: 1 in 66 Asian: 1 in 53 Ashkenazi Jewish: 1 in 41 Caucasian: 1 in 35 Hispanic: 1 in 117
Tay-Sachs disease	1 in 300	Ashkenazi Jewish: 1 in 30 French Canadian and Cajun: 1 in 30

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Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2)

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JAK2, MPL, and CALR Testing for Myeloproliferative Neoplasms

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Carrier Screening for Genetic Diseases

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Related Policies

Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer

Document Precedence

Blue Cross and Blue Shield of Vermont (Blue Cross VT) Medical Policies are developed to provide clinical guidance and are based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. The applicable group/individual contract and member certificate language, or employer's benefit plan if an ASO group, determines benefits that are in effect at the time of service. Since medical practices and knowledge are constantly evolving, Blue Cross VT reserves the right to review and revise its medical policies periodically. To the extent that there may be any conflict between medical policy and contract/employer benefit plan language, the member's contract/employer benefit plan language takes precedence.

Audit Information

Blue Cross VT reserves the right to conduct audits on any provider and/or facility to ensure compliance with the guidelines stated in the medical policy. If an audit identifies instances of non-compliance with this medical policy, Blue Cross VT reserves the right to recoup all non-compliant payments.

Administrative and Contractual Guidance

Benefit Determination Guidance

Prior approval may be required for services outlined in this policy. Benefits are subject to all terms, limitations and conditions of the subscriber contract.

Incomplete authorization requests may result in a delay of decision pending submission of missing information. To be considered complete, see policy guidelines above.

NEHP/ABNE members may have different benefits for services listed in this policy. To confirm benefits, please contact the customer service department at the member's health plan.

Federal Employee Program (FEP): Members may have different benefits that apply. For further information please contact FEP customer service or refer to the FEP Service Benefit Plan Brochure. It is important to verify the member's benefits prior to providing the service to determine if benefits are available or if there is a specific exclusion in the member's benefit.

Coverage varies according to the member's group or individual contract. Not all groups are required to follow the Vermont legislative mandates. Member Contract language takes precedence over medical policy when there is a conflict.

If the member receives benefits through an Administrative Services Only (ASO) group, benefits may vary or not apply. To verify benefit information, please refer to the member's employer benefit plan documents or contact the customer service department. Language in the employer benefit plan documents takes precedence over medical policy when there is a conflict.

Policy Implementation/Update information

08/11/2025	New Policy
10/17/2025	CPT® code 81479 listed in coding table as suspending for medical review, corrected to requiring prior approval.
08/2026	Adaptive Maintenance Effective 10/01/2026: Added code 0691U to coding table as requiring prior approval. Provider Notification provided during 10/01/2026 Adaptive Maintenance Cycle.
09/2026	Policy Reviewed. References updated. Minor formatting changes for clarity and consistency. No change to policy statement. Added code 0449U to coding table as requiring prior approval, removed code from corporate Investigational Medical policy.

Eligible providers

Qualified healthcare professionals practicing within the scope of their license(s).

Approved by Blue Cross VT Medical Directors

Tom Weigel, MD, MBA
Vice President and Chief Medical Officer

Attachment I – Coding Table

Code Type	Number	Description	Policy Instructions
The following codes will be considered as medically necessary when applicable criteria have been met.			
CPT®	81162	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis (i.e., detection of large gene rearrangements)	Requires Prior Approval
CPT®	81163	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis	Requires Prior Approval
CPT®	81164	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements)	Requires Prior Approval
CPT®	81165	BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis	Requires Prior Approval
CPT®	81166	BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements)	Requires Prior Approval
CPT®	81167	BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements)	Requires Prior Approval
CPT®	81170	ABL1 (ABL proto-oncogene 1, non-receptor tyrosine kinase) (e.g., acquired imatinib tyrosine kinase inhibitor resistance), gene analysis, variants in the kinase domain	Requires Prior Approval
CPT®	81201	APC (adenomatous polyposis coli) (e.g., familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence	Requires Prior Approval

Code Type	Number	Description	Policy Instructions
CPT®	81202	APC (adenomatous polyposis coli) (e.g., familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants	Requires Prior Approval
CPT®	81203	APC (adenomatous polyposis coli) (e.g., familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; duplication/deletion variants	Requires Prior Approval
CPT®	81206	BCR/ABL1 (t(9;22)) (e.g., chronic myelogenous leukemia) translocation analysis; major breakpoint, qualitative or quantitative	Requires Prior Approval
CPT®	81207	BCR/ABL1 (t(9;22)) (e.g., chronic myelogenous leukemia) translocation analysis; minor breakpoint, qualitative or quantitative	Requires Prior Approval
CPT®	81208	BCR/ABL1 (t(9;22)) (e.g., chronic myelogenous leukemia) translocation analysis; other breakpoint, qualitative or quantitative	Requires Prior Approval
CPT®	81210	BRAF (B-Raf proto-oncogene, serine/threonine kinase) (e.g., colon cancer, melanoma), gene analysis, V600 variant(s)	Requires Prior Approval
CPT®	81212	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants	Requires Prior Approval
CPT®	81215	BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant	Requires Prior Approval
CPT®	81216	BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis	Requires Prior Approval
CPT®	81217	BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant	Requires Prior Approval
CPT®	81219	CALR (calreticulin) (e.g., myeloproliferative disorders), gene analysis, common variants in exon 9	Requires Prior Approval
CPT®	81270	JAK2 (Janus kinase 2) (e.g., myeloproliferative disorder) gene analysis, p.Val617Phe (V617F) variant	Requires Prior Approval

Code Type	Number	Description	Policy Instructions
CPT®	81279	JAK2 (Janus kinase 2) (e.g., myeloproliferative disorder) targeted sequence analysis (e.g., exons 12 and 13)	Requires Prior Approval
CPT®	81288	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis	Requires Prior Approval
CPT®	81292	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis	Requires Prior Approval
CPT®	81293	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants	Requires Prior Approval
CPT®	81294	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants	Requires Prior Approval
CPT®	81295	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis	Requires Prior Approval
CPT®	81296	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants	Requires Prior Approval
CPT®	81297	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants	Requires Prior Approval
CPT®	81298	MSH6 (mutS homolog 6 [E. coli]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis	Requires Prior Approval
CPT®	81299	MSH6 (mutS homolog 6 [E. coli]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants	Requires Prior Approval

Code Type	Number	Description	Policy Instructions
CPT®	81300	MSH6 (mutS homolog 6 [E. coli]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants	Requires Prior Approval
CPT®	81301	Microsatellite instability analysis (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (e.g., BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed	Requires Prior Approval
CPT®	81307	PALB2 (partner and localizer of BRCA2) (e.g., breast and pancreatic cancer) gene analysis; full gene sequence	Requires Prior Approval
CPT®	81308	PALB2 (partner and localizer of BRCA2) (e.g., breast and pancreatic cancer) gene analysis; known familial variant	Requires Prior Approval
CPT®	81317	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis	Requires Prior Approval
CPT®	81318	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants	Requires Prior Approval
CPT®	81319	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants	Requires Prior Approval
CPT®	81338	MPL (MPL proto-oncogene, thrombopoietin receptor) (e.g., myeloproliferative disorder) gene analysis; common variants (e.g., W515A, W515K, W515L, W515R)	Requires Prior Approval
CPT®	81339	MPL (MPL proto-oncogene, thrombopoietin receptor) (e.g., myeloproliferative disorder) gene analysis; sequence analysis, exon 10	Requires Prior Approval
CPT®	81401	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)	Requires Prior Approval

Code Type	Number	Description	Policy Instructions
CPT®	81403	Molecular pathology procedure, Level 4 (e.g., analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)	Requires Prior Approval
CPT®	81412	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	Requires Prior Approval
CPT®	81432	Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer, hereditary pancreatic cancer, hereditary prostate cancer), genomic sequence analysis panel, 5 or more genes, interrogation for sequence variants and copy number variants	Requires Prior Approval
CPT®	81435	Hereditary colon cancer-related disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis), genomic sequence analysis panel, 5 or more genes, interrogation for sequence variants and copy number variants	Requires Prior Approval
CPT®	81443	Genetic testing for severe inherited conditions (e.g., cystic fibrosis, Ashkenazi Jewish-associated disorders [e.g., Bloom syndrome, Canavan disease, Fanconi anemia type C, mucolipidosis type VI, Gaucher disease, Tay-Sachs disease], beta hemoglobinopathies, phenylketonuria, galactosemia), genomic sequence analysis panel, must include sequencing of at least 15 genes (e.g., ACADM, ARSA, ASPA, ATP7B, BCKDHA, BCKDHB, BLM, CFTR, DHCR7, FANCC, G6PC, GAA, GALT, GBA, GBE1, HBB, HEXA, IKBKAP, MCOLN1, PAH)	Requires Prior Approval
CPT®	81479	Unlisted molecular pathology procedure	Requires Prior Approval

Code Type	Number	Description	Policy Instructions
CPT®	0016U	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	No Prior Approval Required
CPT®	0017U	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	No Prior Approval Required
CPT®	0027U	JAK2 (Janus kinase 2) (e.g., myeloproliferative disorder) gene analysis, targeted sequence analysis exons 12-15	No Prior Approval Required
CPT®	0040U	BCR/ABL1 (t(9;22)) (e.g., chronic myelogenous leukemia) translocation analysis, major breakpoint, quantitative	No Prior Approval Required
CPT®	0129U	Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis and deletion/duplication analysis panel (ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, and TP53)	Requires Prior Approval
CPT®	0157U	APC (APC regulator of WNT signaling pathway) (e.g., familial adenomatosis polyposis [FAP]) mRNA sequence analysis (List separately in addition to code for primary procedure)	Requires Prior Approval
CPT®	0158U	MLH1 (mutL homolog 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure)	Requires Prior Approval
CPT®	0159U	MSH2 (mutS homolog 2) (e.g., hereditary colon cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure)	Requires Prior Approval
CPT®	0160U	MSH6 (mutS homolog 6) (e.g., hereditary colon cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure)	Requires Prior Approval
CPT®	0161U	PMS2 (PMS1 homolog 2, mismatch repair system component) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) mRNA sequence analysis (List	Requires Prior Approval

Code Type	Number	Description	Policy Instructions
		separately in addition to code for primary procedure)	
CPT®	0162U	Hereditary colon cancer (Lynch syndrome), targeted mRNA sequence analysis panel (MLH1, MSH2, MSH6, PMS2) (List separately in addition to code for primary procedure)	Requires Prior Approval
CPT®	0172U	Oncology (solid tumor as indicated by the label), somatic mutation analysis of BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) and analysis of homologous recombination deficiency pathways, DNA, formalin-fixed paraffin-embedded tissue, algorithm quantifying tumor genomic instability score	Requires Prior Approval
CPT®	0238U	Oncology (Lynch syndrome), genomic DNA sequence analysis of MLH1, MSH2, MSH6, PMS2, and EPCAM, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions	Requires Prior Approval
CPT®	0449U	Carrier screening for severe inherited conditions (e.g., cystic fibrosis, spinal muscular atrophy, beta hemoglobinopathies [including sickle cell disease], alpha thalassemia), regardless of race or self-identified ancestry, genomic sequence analysis panel, must include analysis of 5 genes (CFTR, SMN1, HBB, HBA1, HBA2)	Requires Prior Approval
CPT®	0691U	Carrier screening (cystic fibrosis, spinal muscular atrophy, beta hemoglobinopathies [including sickle cell disease], alpha thalassemia, and Duchenne muscular dystrophy), genomic sequence analysis panel, 6 genes (CFTR, SMN1, HBB, HBA1, HBA2, DMD)	Requires Prior Approval
The following codes will be denied and Not Medically Necessary, Non-Covered, Contract Exclusions or Investigational.			
CPT®	0101U	Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis), genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and	Investigational

Code Type	Number	Description	Policy Instructions
		array CGH, with mRNA analytics to resolve variants of unknown significance when indicated (15 genes [sequencing and deletion/duplication], EPCAM and GREM1 [deletion/duplication only]	
CPT®	0130U	Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis), targeted mRNA sequence analysis panel (APC, CDH1, CHEK2, MLH1, MSH2, MSH6, MUTYH, PMS2, PTEN, and TP53) (List separately in addition to code for primary procedure)	Investigational
CPT®	0400U	Obstetrics (expanded carrier screening), 145 genes by next-generation sequencing, fragment analysis and multiplex ligation-dependent probe amplification, DNA, reported as carrier positive or negative	Investigational