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Clinical Appropriateness Guidelines

Genetic Testing

Appropriate Use Criteria: Hereditary Cancer Testing

Proprietary

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Description and Application of the Guidelines

The Carelon Clinical Appropriateness Guidelines (hereinafter “the Carelon Clinical Appropriateness Guidelines” or the “Guidelines”) are designed to assist providers in making the most appropriate treatment decision for a specific clinical condition for an individual. The Guidelines establish objective and evidence-based criteria for medical necessity determinations, where possible, that can be used in support of the following:

- To establish criteria for when services are medically necessary
- To assist the practitioner as an educational tool
- To encourage standardization of medical practice patterns
- To curtail the performance of inappropriate and/or duplicate services
- To address patient safety concerns
- To enhance the quality of health care
- To promote the most efficient and cost-effective use of services

The Carelon guideline development process complies with applicable accreditation and legal standards, including the requirement that the Guidelines be developed with involvement from appropriate providers with current clinical expertise relevant to the Guidelines under review and be based on the most up-to-date clinical principles and best practices. Resources reviewed include widely used treatment guidelines, randomized controlled trials or prospective cohort studies, and large systematic reviews or meta-analyses. Carelon reviews all of its Guidelines at least annually.

Carelon makes its Guidelines publicly available on its website. Copies of the Guidelines are also available upon oral or written request. Additional details, such as summaries of evidence, a list of the sources of evidence, and an explanation of the rationale that supports the adoption of the Guidelines, are included in each guideline document.

Although the Guidelines are publicly available, Carelon considers the Guidelines to be important, proprietary information of Carelon, which cannot be sold, assigned, leased, licensed, reproduced or distributed without the written consent of Carelon. Use of the Guidelines by any external AI entity without the express written permission of Carelon is prohibited.

Carelon applies objective and evidence-based criteria, and takes individual circumstances and the local delivery system into account when determining the medical appropriateness of health care services. The Carelon Guidelines are just guidelines for the provision of specialty health services. These criteria are designed to guide both providers and reviewers to the most appropriate services based on a patient’s unique circumstances. In all cases, clinical judgment consistent with the standards of good medical practice should be used when applying the Guidelines. Guideline determinations are made based on the information provided at the time of the request. It is expected that medical necessity decisions may change as new information is provided or based on unique aspects of the patient’s condition. The treating clinician has final authority and responsibility for treatment decisions regarding the care of the patient and for justifying and demonstrating the existence of medical necessity for the requested service. The Guidelines are not a substitute for the experience and judgment of a physician or other health care professionals. Any clinician seeking to apply or consult the Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient’s care or treatment.

The Guidelines do not address coverage, benefit or other plan specific issues. Applicable federal and state coverage mandates take precedence over these clinical guidelines, and in the case of reviews for Medicare Advantage Plans, the Guidelines are only applied where there are not fully established CMS criteria. If requested by a health plan, Carelon will review requests based on health plan medical policy/guidelines in lieu of the Carelon Guidelines. Use of an FDA-approved or conditionally approved product does not constitute medical necessity or guarantee reimbursement by the respective health plan.

The Guidelines may also be used by the health plan or by Carelon for purposes of provider education, or to review the medical necessity of services by any provider who has been notified of the need for medical necessity review, due to billing practices or claims that are not consistent with other providers in terms of frequency or some other manner.

General Clinical Guideline

Clinical Appropriateness Framework

Critical to any finding of clinical appropriateness under the guidelines for a specific diagnostic or therapeutic intervention are the following elements:

- Prior to any intervention, it is essential that the clinician confirm the diagnosis or establish its pretest likelihood based on a complete evaluation of the patient. This includes a history and physical examination and, where applicable, a review of relevant laboratory studies, diagnostic testing, and response to prior therapeutic intervention.
- The anticipated benefit of the recommended intervention is likely to outweigh any potential harms, including from delay or decreased access to services that may result (net benefit).
- Widely used treatment guidelines and/or current clinical literature and/or standards of medical practice should support that the recommended intervention offers the greatest net benefit among competing alternatives.
- There exists a reasonable likelihood that the intervention will change management and/or lead to an improved outcome for the patient.

Providers may be required to submit clinical documentation in support of a request for services. Such documentation must a) accurately reflect the clinical situation at the time of the requested service, and b) sufficiently document the ordering provider's clinical intent.

If these elements are not established with respect to a given request, the determination of appropriateness will most likely require a peer-to-peer conversation to understand the individual and unique facts that would justify a finding of clinical appropriateness. During the peer-to-peer conversation, factors such as patient acuity and setting of service may also be taken into account to the extent permitted by law.

Genetic tests not specifically mentioned in the guidelines are considered not medically necessary.

Simultaneous Ordering of Multiple Diagnostic or Therapeutic Interventions

Requests for multiple diagnostic or therapeutic interventions at the same time will often require a peer-to-peer conversation to understand the individual circumstances that support the medical necessity of performing all interventions simultaneously. This is based on the fact that appropriateness of additional intervention is often dependent on the outcome of the initial intervention.

Additionally, either of the following may apply:

- Current literature and/or standards of medical practice support that one of the requested diagnostic or therapeutic interventions is more appropriate in the clinical situation presented; or
- One of the diagnostic or therapeutic interventions requested is more likely to improve patient outcomes based on current literature and/or standards of medical practice.

Repeat Diagnostic Intervention

In general, repeated testing of the same anatomic location for the same indication should be limited to evaluation following an intervention, or when there is a change in clinical status such that additional testing is required to determine next steps in management. At times, it may be necessary to repeat a test using different techniques or protocols to clarify a finding or result of the original study.

Repeated testing for the same indication using the same or similar technology may be subject to additional review or require peer-to-peer conversation in the following scenarios:

- Repeated diagnostic testing at the same facility due to technical issues

- Repeated diagnostic testing requested at a different facility due to provider preference or quality concerns
- Repeated diagnostic testing of the same anatomic area based on persistent symptoms with no clinical change, treatment, or intervention since the previous study
- Repeated diagnostic testing of the same anatomic area by different providers for the same member over a short period of time

Repeat Therapeutic Intervention

In general, repeated therapeutic intervention in the same anatomic area is considered appropriate when the prior intervention proved effective or beneficial and the expected duration of relief has lapsed. A repeat intervention requested prior to the expected duration of relief is not appropriate unless it can be confirmed that the prior intervention was never administered. Requests for ongoing services may depend on completion of previously authorized services in situations where a patient's response to authorized services is relevant to a determination of clinical appropriateness.

Hereditary Cancer Testing

General Recommendations

Genetic Counseling

Counseling is strongly recommended prior to hereditary cancer screening that involves genetic testing and should include **ALL** of the following components:

- Interpretation of family and medical histories to provide a risk assessment for disease occurrence or recurrence
- Education about inheritance, genetic testing, disease management, prevention, risk reduction, and resources
- Counseling to promote informed choices and adaptation to the risk or presence of a genetic condition
- Counseling should include the following details:
    - Limitations of the testing used
    - A negative result does not indicate heritable risk is zero or low.
    - Identification of inconclusive results called variants of uncertain significance is possible.
    - Modifications to genetic variants' pathogenicity interpretations can occur and patients may be recontacted with reclassified results in the future
- Counseling for the psychological aspects of genetic testing

Note: Post-test counseling should be performed for any diagnostic genetic test result.

Rationale

Genetic testing is a procedure that involves risk that accompanies its potential benefits. The clinical team and the patient should consider the balance of risks and potential benefits before testing is pursued through informed consent. As with any procedure, the clinical utility of the genetic test must be considered along with its psychological and sociologic implications.[1] Counseling, either by a genetic counselor and/or team clinician, provides a patient-centered approach to the care of individuals who are undergoing a diagnostic genetic test.[2]

It is also recognized that accessibility to genetic counselors is limited by available resources as well as other social determinants of health. Therefore, as it relates to screening, the importance should be placed on counseling in a general sense, such as informed consent, as noted above.[3]

Genomic technologies generate large amounts of data, and this increases the potential for uncertainty in managing and adapting to this information.[4] Clinicians are tasked with accurately interpreting and communicating information about test validity and the reliability of test results, as well as the probability for individual patient benefit.[4, 5] Uncovering incidental findings and being overwhelmed with information are important barriers to genetic testing, particularly among vulnerable patient subgroups. Genetic counseling is an invaluable resource for patients undergoing genetic testing, but there are practical limitations because of the scarcity of genetic counselors relative to the current need, as noted above.

Clinical Indications

General Requirements

Germline hereditary genetic testing may be performed **only once per lifetime** for a given gene except when the individual is known to have been inadequately tested.

Germline testing should be performed in a CLIA-approved lab with established experience in germline testing.

Prior to using any germline findings for medical management, it is important to establish whether the reported findings were obtained from a laboratory that is certified by both the College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendments (CLIA) to issue a report of germline findings directly to ordering health care providers. Some states (e.g., New York) may have additional reporting requirements.

Germline pathogenic variants not otherwise specified*

**To be used only when a specific indication is not available.*

Genetic testing is considered **medically necessary** when **ALL** the following criteria are met:

- The individual to be tested is either at significant risk for a genetic disorder (for example, based on family history), suspected to have a known genetic condition, or is known to have been inadequately tested for a suspected genetic condition
    - This may include, but is not limited to, a personal history of a tumor (somatic) pathogenic variant in one or more of these genes: BRCA1, BRCA2, BRIP1, MLH1, MSH2, MSH6, MUTYH, PALB2, PMS2, RAD51C, RAD51D, RET, SDHAF2, SDHB, SDHC, SDHD, TMEM127, TSC2, or VHL
    - For individuals younger than age 30, this may include a personal history of a pathogenic variant in one or more of these genes: APC, PTEN, RB1, or TP53
- Scientific literature has established that one or more genes have pathogenic variants associated with the genetic condition
- The genetic test has established clinical utility such that a positive or negative result of the genetic test will significantly impact clinical management and will likely result in a net improvement in health outcomes

Confirmatory clinical germline genetic testing of the identified variant(s) is considered **medically necessary** if **ALL** of the criteria above are met **AND EITHER** of the following apply:

- An individual identified to have a pathogenic or likely pathogenic (P/LP) germline variant in genes with established clinical utility based on FDA approved direct-to-consumer genetic testing
- An individual identified to have a P/LP variant in genes with established clinical utility based on results of IRB approved clinical research studies

Germline genetic testing for known familial P/LP variants is considered **medically necessary** in the following scenarios:

- Any first-, second- or third-degree relative who has a known P/LP variant, where the results have established clinical utility

Rationale

Clinicians might consider germline genetic testing in 3 situations: 1) to establish a diagnosis in symptomatic persons (diagnostic testing), 2) to assess predisposition for disease in asymptomatic persons who have increased risk due to family history or personal characteristics (predisposition or predictive testing), or 3) to use a genetic biomarker to assess risk categorization, screening, differential diagnosis, prognosis, prediction, or monitoring. Diagnostic testing is currently the most common type of genetic testing medical practice and includes targeted Sanger sequencing for suspected monogenic disorders and focused panel sequencing of genes for hereditary cancer and other hereditary conditions. Patient centeredness enters the diagnostic process in various ways, including pursuit of relevant knowledge, temperance in the pursuit of diagnosis, and interpretability of test results.[6]

Evidence-based guidelines on the use of genetic tests require a systematic assessment of the usefulness of the test in patient care. A screening or diagnostic genetic test or genetic biomarker alone does not have inherent utility. Whereas it is unlikely that clinical utility would exist if the genetic test does not have clinical validity, clinical validity does not equate to clinical utility.[7] The term clinical utility was elaborated by ACCE project that was carried out by the Foundation for Blood Research with

support from the CDC.[8] The key components of the process, as detailed by the ACCE framework, are analytical validation, clinical validation, clinical utility and consideration of the ethical, legal and social implications of the test. Clinical utility is the term used to reference patient-centered usefulness, the ability of the genetic test to prevent or ameliorate key health outcomes through the adoption of efficacious treatments based on the results of the test.[8] The ability to inform clinical practice and to influence outcomes not directly related to health status may also be important. For example, diagnostic thinking, therapeutic choice, and societal impacts may also be considered. A pragmatic determination of clinical utility is dependent on several factors, including what end point is considered, how large the difference in that end point must be to apply the genetic test, the level of evidence that exists to support the decision to apply the genetic test, and the risk tolerance of the relevant stakeholders involved in the process.[7] The American Society of Clinical Oncology (ASCO) indicates in the germline genetic testing guideline that when a pathogenic variant is identified with tumor testing, there are specific genes that should trigger germline genetic testing.[9]

Condition-Specific Requirements

Adenomatous Polyp Syndromes

Germline genetic testing for any of the following genes—APC, MUTYH, NTHL1, AXIN, MSH3, POLE, POLD1—for susceptibility to invasive cancer due to adenomatous polyp syndromes is considered **medically necessary** when **ANY** of the following criteria are met:

- The individual has a personal history of more than 10 cumulative colorectal adenomas
- The individual has multifocal or bilateral congenital hypertrophy of retinal pigment epithelium (CHRPE)
- The individual has a personal history of cribriform-morular thyroid cancer
- The individual has a first-, second- or third-degree relative with a known pathogenic variant in a gene associated with the adenomatous polyp syndromes
- The individual has a first-, second- or third-degree relative with clinical findings suggestive of an inherited polyposis syndrome
- Individuals with gastrointestinal cancers presenting under the age of 50 years
- In individuals with any cancer with a P/LP APC variant identified on somatic tumor genomic testing, germline testing should be considered in **EITHER** of the following scenarios:
    - Those meeting one or more of the adenomatous testing criteria above after reevaluation of personal and family history
    - Those diagnosed less than 30 years of age with any cancer

Rationale

Inherited colorectal polyposis syndromes are associated with early age of onset of colorectal cancer, multiple first- or second-degree relatives affected, and multiple lifetime cumulative polyps.[10] The adenomatous polyposis syndromes comprise familial adenomatous polyposis (FAP), MUTYH-associated polyposis (MAP) and can involve other genes. Gastrointestinal hamartomatous polyposis syndromes are rare, autosomal dominant disorders associated with an increased risk of benign and malignant intestinal and extraintestinal tumors. They include Peutz-Jeghers syndrome (STK11 associated), juvenile polyposis syndrome (SMAD4 or BMPR1A associated), the PTEN hamartoma tumor syndrome (including Cowden's syndrome and Bannayan-Riley-Ruvalcaba syndrome), and hereditary mixed polyposis syndrome.[11]

The American Society of Colon and Rectal Surgeons (ASCRS) Clinical Practice Guidelines for the Management of Inherited Polyposis Syndromes recommend that polyposis syndromes should typically be considered in patients with greater than 10 lifetime adenomas, colorectal cancer diagnosed at an age younger than 50 years, personal history of desmoid disease, other extracolonic manifestations of polyposis syndromes, or family members of individuals with known FAP, or MAP. This is a strong recommendation based on moderate-quality evidence.[12] A clinical diagnosis of FAP is generally agreed upon when >100 adenomas are found, and germline testing of the APC gene is recommended for these individuals, because this facilitates screening for the pathogenic variant in family members and may have predictive value for extracolonic

manifestations. Although most probands with >100 adenomas will have a detectable pathogenic variant or deletion in APC, there is a small proportion of cases where no pathogenic variant can be found. For patients with fewer than 100 adenomas, clarifying the diagnosis can be difficult. The recent development of next-generation DNA sequencing and multigene panel testing allows these patients to be tested for all known colorectal cancer genes with a single blood test. This is helpful because many syndromes have been associated with attenuated adenomatous polyposis (AFAP, MAP, polymerase proofreading associated polyposis, Lynch syndrome). In addition to APC and MUTYH, NTHL1, AXIN, MSH3 genes should be considered in a multigene panel looking at adenomatous polyp syndromes. Guidelines recommend genetic testing for individuals with greater than 10 to 20 cumulative lifetime adenomas as patients with more than 20 adenomas have a more than 10% risk of carrying a genetic pathologic variant.[12] At-risk family members of a patient with an identified pathogenic variant are screened for the variant. The ESMO and ACG guidelines for hereditary gastrointestinal cancers recommend that patients with multiple colorectal adenomas (>10) should be considered for panel germline genetic testing.

Major guidelines addressing the thresholds and relevant genes for testing are summarized below:

ACG: “Individuals who have a personal history of >10 cumulative colorectal adenomas, a family history of one of the adenomatous polyposis syndromes, or a history of adenomas and FAP-type extracolonic manifestations (duodenal/ampullary adenomas, desmoid tumors (abdominal > peripheral), papillary thyroid cancer, congenital hypertrophy of the retinal pigment epithelium, epidermal cysts, osteomas) should undergo assessment for the adenomatous polyposis syndromes. Genetic testing of patients with suspected adenomatous polyposis syndromes should include APC and MUTYH gene analysis.”[13]

ESMO: “Patients with multiple colorectal adenomas (>10) should be considered for panel germline genetic testing that includes APC, MUTYH, POLE, POLD1 and NTHL1 genes. APC analysis should include large rearrangements [III, A].”[14]

“Biallelic MUTYH mutations should be suspected in cases of AFAP or FAP with a recessive pattern of inheritance, diagnosis before the age of 50 years, and multiple colonic polyps. A multigene single analysis of APC, MUTYH (all exons), POLE, POLD1 and NTHL1 is recommended [V, B].”[14]

NCCN: “Genetic testing for adenomatous polyposis is recommended when an individual has a personal history of ≥20 cumulative adenomas. Some studies have suggested genetic testing with a threshold of ≥10 cumulative adenomas. Genetic testing is also recommended when an individual has a family history of a known P/LP variant in polyposis genes.”[15]

JSCCR (Japanese Society for Cancer of the Colon/Rectum): “Genetic testing in patients with clinically diagnosed FAP is weakly recommended for treatment selection and surveillance reference and differentiation from other types of adenomatous polyposis (Recommendation 2/Evidence level C).”[16]

ASCRS: “Polyposis syndromes should typically be considered in patients with greater than 10 lifetime adenomas, colorectal cancer diagnosed at an age younger than 50 years, personal history of desmoid disease, or other extracolonic manifestations of polyposis syndromes, or family members of individuals with known FAP or MAP. This is a strong recommendation based on moderate-quality evidence. In addition to APC and MUTYH, NTHL-1, AXIN, MSH3 genes should be included in a multigene panel.”[12]

ACMG/NSGC: “Individuals with FAP are also at increased risk for duodenal (4–12%), pancreatic (~2%), and papillary thyroid (cribriform morular variant) (1–2%) cancers, as well as hepatoblastoma by age 5 (1–2%) and medulloblastoma (<1%). Extracolonic manifestations can include congenital hypertrophy of the retinal pigmented epithelium, osteomas, dental abnormalities, benign cutaneous lesions such as epidermoid cysts and fibromas, and desmoid tumors. APC mutations are found in 80% of patients with 1,000 or more adenomas, 56% of patients with 100–999 adenomas, 10% of patients with 20–99 adenomas, and 5% of patients with 10–19 adenomas. …MUTYH-associated polyposis is a recessive condition caused by biallelic mutations in the MUTYH gene and is characterized by an increased risk for adenomatous colon polyps and colorectal cancer (80%). Individuals with MUTYH associated polyposis can develop only a few adenomatous colon polyps or they can have >100 adenomatous colon polyps. As a result, this condition can overlap with FAP, attenuated FAP, and LS. Testing is often ordered for both APC and MUTYH at the same time for patients with ≥10 adenomatous colon polyps.”[17]

CCO: Guidelines for testing include ≥20 colorectal adenomas,10-19 colorectal adenomas ≤60 years of age, personal history of any of the following suspicious extracolonic tumors: Cribiform-morular variant of papillary thyroid cancer, hepatoblastoma, desmoid <40 years of age, retinal pigment epithelium (RPE) hamartomas associated with FAP17 (RPEH-FAP).[18]

Hamartomatous Polyposis Syndromes

Juvenile polyposis syndrome

Genetic testing for SMAD4 and BMPR1A gene variants to evaluate for juvenile polyposis syndrome is considered **medically necessary** when **ANY** of the following criteria are met:

- Five or more juvenile polyps in the colon
- Multiple juvenile polyps in other parts of the gastrointestinal tract
- Any number of juvenile polyps in a person with a known family history of juvenile polyps
- The individual is a first- or second-degree relative of a patient suspected of having or diagnosed with juvenile polyposis syndrome
- The individual has a first-, second- or third-degree relative with a known pathogenic variant in SMAD4 or BMPR1A

Peutz-Jeghers syndrome

Genetic testing for STK11 gene variants to evaluate for Peutz-Jeghers syndrome is considered **medically necessary** when **ANY** of the following criteria are met:

- Two 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
- The individual has a first-, second- or third-degree relative with a known pathogenic variant in STK11

PTEN-hamartoma tumor syndrome (including Cowden syndrome)

Genetic testing for PTEN pathogenic variants to evaluate for PTEN-hamartoma tumor syndrome (PHTS) is considered **medically necessary** when **EITHER of the following criteria are met**:

- **ONE or more** of the following criteria are met:
    - Adult Lhermitte-Dulcos disease (cerebellar tumors)
    - Bannayan-Riley-Ruvalcaba syndrome
    - Autism spectrum disorder **AND** macrocephaly (≥ 97th percentile: 58 cm for adult women, 60 cm for adult men)
    - Multiple cutaneous lesions including **ANY** of the following:
        - Two or more biopsy-proven trichilemmomas
        - Three or more acral keratoses (palmoplantar keratotic pits and/or acral hyperkeratotic papules)
        - Three or more mucocutaneous neuromas
        - Three or more oral papillomas (particularly on tongue and gingivae) which are biopsy-proven or diagnosed by a dermatologist
    - The individual has a first-, second- or third-degree relative with a known pathogenic variant in PTEN

OR

- **THREE (3) or more** of the following criteria are met:
    - Breast cancer
    - Fibrocystic disease of the breast
    - Non-medullary thyroid cancer
    - Thyroid adenoma or multinodular goiter
    - Endometrial cancer

- Renal cell carcinoma
- Colorectal cancer
- Genitourinary malformations
- Testicular lipomatosis
- Three or more esophageal glycogenic acanthoses
- Lipomas
- Uterine fibroids
- Any GI hamartomas or ganglioneuromas
- Autism spectrum disorder
- Intellectual disability with IQ ≤ 75
- Biopsy-proven trichilemmoma
- Multiple palmoplantar keratoses
- Multifocal cutaneous facial papules
- Macular pigmentation of the glans penis
- Vascular anomalies (including multiple intracranial developmental venous anomalies)
- Macrocephaly (≥ 97th percentile: 58 cm for adult women, 60 cm for adult men)

See multigene panel testing for hereditary breast, ovarian, or pancreatic carcinoma under Hereditary Breast, Ovarian, and Pancreatic Cancer (HBOP) for additional criteria if a gene panel includes PTEN and STK11.

Rationale

The hamartomatous polyposis syndromes account for less than 1% of cases of colon cancer in North America. These syndromes include juvenile polyposis syndrome (JPS) caused by germline pathogenic variants in BMPR1A and SMAD4, Peutz-Jeghers syndrome (PJS) caused by germline pathogenic variants in STK11, and the PTEN-hamartoma tumor syndrome (PHTS) caused by germline pathogenic variants in PTEN.[11] The PHTS includes Cowden syndrome (in adults) and Bannayan-Riley-Ruvalcaba syndrome (BRRS) in pediatric populations.[19] Malignancies associated with JPS include colorectal, gastric, duodenal and pancreatic cancers.[11] Malignancies associated with PJS include colorectal cancer, as well as cancers of the stomach, small bowel, breast, ovary, cervix (adenoma malignum), uterus, pancreas, testis (Sertoli cell tumor), and lung. Malignancies associated with PHTS are breast, thyroid, endometrial, renal, and colorectal.[11, 20]

[17]Due to this increased risk of multiple malignancies, genetic testing of patients at risk for hamartomatous polyposis syndromes is recommended by multiple guidelines:

NCCN[20]

JPS

A clinical diagnosis of JPS is considered in an individual who meets at least one of the following criteria:

- ≥ 5 juvenile polyps of the colon
- Multiple juvenile polyps found throughout the GI tract
- Any number of juvenile polyps in an individual with a family history of JPS

Clinical genetic testing is recommended for any patient meeting the above criteria or with a family history of JPS. Approximately 50% of patients meeting clinical criteria for JPS will have pathogenic variants detected in the BMPR1A or SMAD4 genes.

PJS

A clinical diagnosis of PJS can be made when an individual has two or more of the following features:

- Two or more Peutz-Jeghers-type hamartomatous polyps of the GI tract
- Mucocutaneous hyperpigmentation of the mouth, lips, nose, eyes, genitalia, or fingers
- Family history of PJS

Clinical genetic testing is recommended for any patient meeting the above criteria or with a family history of PJS. The majority of cases occur due to the pathogenic variants in the STK11 (LKB1) gene. Somatic STK11 P/LP variants are common in many tumor types in absence of a germline P/LP variant.

Cowden/PHTS

NCCN [21] recommends evaluation for Cowden/PHTS in patients meeting any of the following:

- Clinical diagnostic criteria[22]
- Personal history of Bannayan-Riley-Ruvalcaba syndrome
- Adult Lhermitte-Duclos disease
- Autism spectrum disorder and macrocephaly
- Two or more biopsy-proven trichilemmomas
- Two or more major clinical diagnostic criteria (one must be macrocephaly)
- Three major clinical diagnostic criteria, without macrocephaly
- One major and ≥3 minor clinical diagnostic criteria
- Four or more minor clinical diagnostic criteria

U.S. Multi-Society Task Force on CRC[11]

JPS

- 5 or more juvenile polyps of the colon or rectum
- 2 or more juvenile polyps in other parts of the gastrointestinal tract
- Any number of juvenile polyps and 1 or more first-degree relatives with juvenile polyposis syndrome

PJS

- 2 or more histologically confirmed Peutz-Jeghers polyps
- Any number of Peutz-Jeghers polyps in an individual who has a family history of PeutzJeghers syndrome in a first-degree relative
- Characteristic mucocutaneous pigmentation in a person with a family history of Peutz-Jeghers syndrome
- Any number of Peutz-Jeghers polyps in a person with the characteristic mucocutaneous pigmentation of Peutz-Jeghers syndrome

Cowden/PHTS

- Individuals with multiple gastrointestinal hamartomas or ganglioneuromas [13]

ASCO[9]

ASCO recommends the following genes be included on gene panels with the specified cancer types below when germline genetic testing is indicated. *The authors specify that JPS, PJS and PHTS are rare, though, and some providers/patients may or may not choose to include the associated genes if personal and family history do not support the syndrome phenotype.*

JPS

SMAD4 and BMPR1A:

- Colorectal
- Gastric

PJS

STK11:

- Breast
- Colorectal
- Endometrial
- Gastric
- Non-small cell lung cancer—if EGFR tumor pathogenic variant (such as p.T790M) found with no previous EGFR-TKI therapy
- Pancreatic adenocarcinoma

PHTS

PTEN:

- Breast
- Endometrial
- Renal cell carcinoma
- Colorectal (less strongly recommended)
- Cutaneous melanoma (less strongly recommended)

Serrated Polyposis Syndrome (SPS)

Genetic testing for serrated polyposis syndrome (SPS) is considered **not medically necessary** for any indication.

Rationale

Colorectal serrated polyps are a pathologically diverse group of lesions that includes sessile serrated polyps (SSPs), also known as sessile serrated adenomas or lesions; traditional serrated adenomas, and hyperplastic polyps.[23]

A clinical diagnosis of serrated polyposis syndrome is considered in an individual who meets at least one of the following criteria:

- ≥ 5 serrated lesions/polyps proximal to the rectum, all being ≥ 5 mm in size, with ≥ 2 being ≥ 10 mm in size
- > 20 serrated lesions/polyps of any size distributed through the large bowel, with ≥ 5 being proximal to the rectum[15]

The prevalence of SSPs are less than 5% on average, and differences in prevalence with age and among different locations, and long-term cancer risk are still unclear.[23] Because a discrete genetic cause is not yet identified, there is no net benefit for genetic testing and such testing is not recommended in multiple evidence-based guidelines.

Guideline recommendations are discussed further below:

NCCN: “For the majority of patients with SPS, no cause is identifiable. Pathogenic variants in RNF43 have been identified as a rare cause, as have biallelic pathogenic variants in MUTYH. Several studies have observed SPS occurring in patients who were previously treated for Hodgkin lymphoma and other childhood or young adulthood cancers. Genetic testing may be favored based on patient preference, family history of colorectal cancer, or presence of features (such as adenomas) that could overlap with other hereditary colorectal cancer syndromes. SPS is commonly grouped with the HPSs but does not appear to be inherited in a simple Mendelian fashion. Some studies link PVs in RNF43 to SPS; however, studies of larger cohorts suggest that RNF43 only explains a small proportion of cases.”[15]

ACG: A clear genetic etiology has not yet been defined for SPS, and therefore genetic testing is currently not routinely recommended for SPS patients; testing for MUTYH pathogenic/likely pathogenic (P/LP) variants may be considered for SPS patients with concurrent adenomas and/or a family history of adenomas.[13]

ACMG/NSGC: No causative P/LP variants in BMPR1A, SMAD4, PTEN, MUTYH, or GREM1 were found in a series of 65 individuals with serrated polyposis syndrome; it is likely that this condition is caused by novel genes that have yet to be discovered. Although genetic testing may not be useful at present, a genetics referral is indicated because the diagnosis will affect future management, and other polyposis syndromes should be ruled out.[17]

Hereditary Mixed Polyposis Syndrome (GREM1-associated mixed polyposis)

Genetic testing for hereditary mixed polyposis syndrome, to include the GREM1 variant **OR** any other genes, is considered **not medically necessary** for any indication.

Rationale

Hereditary mixed polyposis syndrome is a rare colon cancer predisposition syndrome caused by a duplication of a noncoding sequence near the gremlin 1, DAN family BMP antagonist gene (GREM1) originally described in Ashkenazi Jews.[24] There is no clear phenotype in affected patients. The clinical presentation is multiple colorectal polyps of mixed histology, including hyperplastic, juvenile, and adenomatous polyps. The incidence of the condition is unknown, though it is reported to be extremely rare. There is some association with a 40-kb upstream duplication involving the GREM1 gene, but this is rare and is not reported in all cases of hereditary mixed polyposis syndrome. Some cases are also associated with pathogenic variants in the BMPR1A gene. Overall, genetic testing is not definitively recommended by guidelines, due to lack of a clear phenotype or definitive etiology, and lack of data regarding relative risk of hereditary colorectal carcinoma.

Guideline recommendations are discussed further below:

NCCN: The association of the upstream duplication involving GREM1 has been noted only in patients of Ashkenazi Jewish ancestry, and the evidence linking this genetic variant with HMPS is not well established. In addition, the relative risk of colorectal cancer in patients with this variant is reported to be uncertain. NCCN further states that there are duplications other than the 40kb one in Ashkenazi Jewish patients with HMPS, but the cancer risk of these other duplications remains unclear as well.[15]

ACG: “Even though HMPS linked to a locus on chromosome 15q13.3–q14 in a number of families, which includes the CRAC1 gene, the etiology remains elusive. Recently, a duplication 40 kb upstream of the GREM1 gene locus at chromosome 15 was found in two individuals with HMPS. The authors hypothesized that this duplication interacts with the GREM1 promoter causing increased GREM1 expression, resulting in a predisposition to multiple colorectal polyps. Genetic testing for GREM1 mutation and expression might be considered in families with adenomatous and hamartomatous polyposis in which an etiology cannot be determined.”[13]

ACMG/NSGC: Consensus-based guidelines from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors recommend that referral be considered in patients with a personal history or first-degree relative with 10 or more colorectal polyps with mixed histology, but further state: “The major gene(s) responsible for hereditary mixed polyposis syndrome have not been identified; however, some cases are caused by mutations in the BMPR1A gene. Also, a founder mutation involving the GREM1 gene was identified in Ashkenazi Jewish patients with hereditary mixed polyposis syndrome.”[17]

Lynch Syndrome

Germline genetic testing of MLH1, MSH2, MSH6, PMS2 or EPCAM genes to evaluate for Lynch syndrome (a mismatch repair deficiency syndrome) is considered **medically necessary** in **ANY** of the following scenarios:

- Personal history of a tumor with MMR deficiency based on somatic testing using PCR, NGS, or IHC
- Immunohistochemistry (IHC) testing of colorectal cancer, endometrial cancer, or any other Lynch syndrome-associated cancer showing loss of expression of MSH2 or MSH6 (or both), or loss of expression of PMS2; or loss of expression of MLH1 and PMS2 without evidence of BRAF V600E pathogenic variant or MLH1 promoter methylation
- Evidence of microsatellite instability (MSI-high) based on testing of colorectal cancer, endometrial cancer, or any other Lynch syndrome-associated cancer, and IHC testing showing loss of expression of MLH1 and PMS2 without evidence of BRAF V600E pathogenic variant or MLH1 promoter methylation
- 5% or higher lifetime risk of Lynch syndrome based on a validated predictive model
- Personal history of colorectal or endometrial cancer or any other Lynch syndrome-related cancer in **ANY** of the following scenarios:
    - Individual is age 49 years or younger at diagnosis
    - Presence of synchronous or metachronous colorectal cancer

    - Known additional Lynch syndrome-related cancer (colorectal, endometrial, gastric, ovarian, pancreatic, urothelial, CNS glioma, biliary tract, small intestine, sebaceous adenomas or carcinomas, keratoacanthomas, or breast carcinomas with medullary features)
- Personal history of a P/LP variant identified on tumor genomic testing that has clinical implications if also identified in the germline
- Family history which includes **ANY** of the following:
    - At least one first-degree relative with colorectal or endometrial cancer diagnosed before age 50
    - At least one first-degree or second-degree relative with colorectal or endometrial cancer and another Lynch syndrome-related cancer (colorectal, endometrial, gastric, ovarian, pancreatic, urothelial, CNS glioma, biliary tract, small intestine, sebaceous adenomas or carcinomas, keratoacanthomas, or breast carcinomas with medullary features)
    - Two or more first- or second-degree relatives on the same side of the family with Lynch syndrome-related cancers, with at least one diagnosed before age 50
    - Three or more first- or second-degree relatives on the same side of the family with Lynch syndrome-related cancers

Known familial genetic testing for Lynch syndrome

Genetic testing of a single high-risk gene is **medically necessary** for individuals who have a first-, second- or third-degree relative with a known pathogenic variant in that gene.

Rationale

Colorectal cancers with deficient somatic mismatch repair (MMR) are associated with an earlier stage at diagnosis and a lower propensity for metastases than proficient mismatch repair tumors.[25] The Lynch syndrome (LS) phenotype involves a predominance of right colon cancers, poor tumor differentiation, increased risk for endometrial cancer and other malignancies, and hypermutation due to deficient mismatch repair. It is the most common inherited syndrome associated with colorectal cancers, accounting for about 3% of diagnoses.

Multiple high-quality evidence-based and consensus-based guidelines consistently recommend MMR testing through immunohistochemistry (IHC) or microsatellite instability (MSI) for all newly diagnosed patients with colorectal cancer. The Lynch-spectrum tumor types also extend to carcinomas of the endometrium, small bowel, ureter, renal pelvis, ampulla of Vater, stomach, ovary, pancreas, brain, and breast carcinomas with medullary features as well.[26]

US Multi-Society Task Force on Colorectal Cancer: “Individuals who have a personal history of a tumor showing evidence of MMR deficiency (without evidence of MLH1 promoter methylation); uterine cancer diagnosed at younger than age 50 years; a known family MMR gene mutation; fulfill Amsterdam criteria or revised Bethesda guidelines; and/or have a personal risk of ≥ 5% chance of LS based on prediction models should undergo genetic evaluation for LS. This guideline is a strong recommendation, with evidence level III, and GRADE moderate-quality evidence.”[27]

ACG: “All newly diagnosed colorectal cancers (CRCs) should be evaluated for mismatch repair deficiency.”[13]

ESMO (endorsed by ASCO): Tumor testing for DNA mismatch repair (MMR) deficiency with immunohistochemistry for MMR proteins and/or MSI should be assessed in all CRC patients. As an alternate strategy, tumor testing should be carried out in individuals with CRC younger than 70 years, or those older than 70 years who fulfill any of the revised Bethesda guidelines.[28]

NSGC/CGA-IGC: A consensus-based practice resource from the National Society of Genetic Counselors and the Collaborative Group of the Americas on Inherited Gastrointestinal Cancer states that universal tumor screening for Lynch syndrome is recommended for all patients with CRC or endometrial cancer, regardless of age. MMR immunohistochemistry or microsatellite instability (MSI) can be used for universal screening; the authors state that testing for both MMR IHC and MSI can be considered when suspicion for LS is high.[29]

Based on the results of initial testing for MMR, germline NGS testing for germline pathogenic variants is sometimes indicated. For example, ASCO guidelines recommend that if loss of MLH1/PMS2 protein expression is observed in the tumor, analysis of BRAF V600E pathogenic variant or analysis of methylation of the MLH1 promoter should be carried out first to rule out a sporadic case. If tumor is MMR deficient and somatic BRAF variant is not detected or MLH1 promoter methylation is not identified, testing for germline pathogenic variants is indicated. And if there is loss of any of the other proteins (MSH2, MSH6, PMS2) is observed, germline genetic testing should be carried out for the genes corresponding to the absent proteins (e.g.,

MSH2, MSH6, EPCAM, PMS2, or MLH1).[25, 28] The benefit of this approach is endorsed by multiple evidence-based and consensus-based guidelines.

NCCN: "The panel recommends tumor screening for MMR deficiency for all CRC and endometrial cancers regardless of age at diagnosis." NCCN also recommends evaluation for Lynch syndrome in patients with "personal history of a tumor with MMR deficiency determined by PCR, NGS, or IHC at any age."[20]

ACG: "Individuals who have a personal history of a tumor showing evidence of mismatch repair deficiency (and no demonstrated BRAF mutation or hypermethylation of MLH1), a known family mutation associated with LS, or a risk of ≥5% chance of LS based on risk prediction models should undergo genetic evaluation for LS."[13]

ESMO (endorsed by ASCO): "If loss of MLH1/PMS2 protein expression is observed in the tumor, analysis of BRAF V600E mutation or analysis of methylation of the MLH1 promoter should be carried out first to rule out a sporadic case. If tumor is MMR deficient and somatic BRAF mutation is not detected or MLH1 promoter methylation is not identified, testing for germline mutations is indicated. If loss of any of the other proteins (MSH2, MSH6, PMS2) is observed, germline genetic testing should be carried out for the genes corresponding to the absent proteins (e.g., MSH2, MSH6, EPCAM, PMS2, or MLH1)."[28]

Regardless of the results of standard MMR or MSI testing, patients may be found to have increased risk for Lynch syndrome on the basis of family history obtained through genetic counseling. The net benefit of genetic testing on this basis is recommended by multiple high-quality evidence-based guidelines:

NCCN: LS-related cancers include "…colorectal, endometrial, gastric, ovarian, pancreatic, urothelial, brain (usually glioblastoma), biliary tract, and small intestine, as well as sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas as seen in Muir-Torre syndrome."[20] "If an individual has a personal or family history of a Lynch syndrome-related cancer, the panel has summarized criteria under three domains that can be used to select patients for the evaluation of Lynch syndrome:

- Personal history of a tumor with MMR deficiency determined by PCR, NGS, or IHC at any age
- Personal history of colorectal, endometrial, or other Lynch syndrome-associated cancer
- An individual at increased risk based on family history or model-predicted risk for Lynch syndrome"[15]

Also of note, as it relates to the use of PREMM5 score thresholds, typically accepted at ≥ 5%, when lower thresholds are accepted (e.g., ≥ 2.5%), sensitivity will increase but at the expense of decreased specificity.

ACMG/NSGC: "Individuals with a family history of three or more LS-associated cancers should also be referred…LS is characterized by increased lifetime risks for colorectal (40–80%), endometrial (25–60%), ovarian (4–24%), and gastric (1–13%) cancers. Individuals with LS can also have an increased risk for urothelial carcinoma, glioblastoma, and sebaceous, biliary, small bowel, and pancreatic adenocarcinomas. The lifetime risks for cancer are lower in individuals with MSH6 and PMS2 mutations."[17]

Sometimes, a patient has a known family history of a pathogenic or likely pathogenic variant in the MLH1, MSH2, MSH6, PMS2, or EPCAM genes. In this case, consensus guidelines[15] recommend testing focused on the specific pathogenic variant.

EHTG-ESCP (European Hereditary Tumor Group-European Society of Coloproctology): "Germline multigene panel testing (for CRC and polyposis syndromes) should be undertaken in patients with gastrointestinal cancers presenting under the age of 50 years."[30]

CCO: "Personal history of a IHC deficient tumor (exception of sebaceous neoplasm), personal history of a IHC deficient sebaceous neoplasm plus ≥1 of the following: diagnosed ≤60 years of age, multiple primary sebaceous neoplasms, personal and/or close relative(s) diagnosed with LS cancer."[18]

Hereditary Diffuse Gastric Cancer (HDGC)

Germline genetic testing of CDH1 is considered **medically necessary** in **ANY** of the following scenarios:

- Individual with a known CDH1 pathogenic variant (P/LP) in a first-, second- or third-degree relative
- Individual with diffuse gastric cancer (DGC) at any age (signet ring morphology)
- Individual with bilateral lobular breast cancer, diagnosed at age <70 years
- Individual <50 years of age with gastric in situ signet ring cells or pagetoid spread of signet ring cells
- Family history of ≥2 first-degree or second-degree relatives with gastric cancer with at least one diagnosed at age ≤50 years or at least one confirmed to be DGC at any age

- Family history of ≥1 first-degree or second-degree relatives with DGC at any age, and ≥1 case of lobular breast cancer at age <70 years in different family members
- Family history of ≥2 first-degree or second-degree relatives with lobular breast cancer in family members <50 years of age

See multigene panel testing for hereditary breast, ovarian, or pancreatic carcinoma under Hereditary Breast, Ovarian, and Pancreatic Cancer (HBOP) for additional criteria if a gene panel includes CDH1.

Rationale

Hereditary diffuse gastric carcinoma is an autosomal dominant cancer susceptibility syndrome associated with pathologic variants in the CDH1 gene. The CDH1 gene encodes E-Cadherin, a cell adhesion protein. Pathogenic variants in CDH1 are a major cause of HDGC with a prevalence of 1/5000 to 1/8000 in unselected population studies. Pathologic variants in the CDH1 gene are associated with gastric signet ring cell carcinoma and lobular breast carcinoma. Neoplastic transformation requires somatic inactivation of the second CDH1 allele.[20, 31] Diffuse gastric carcinoma has a histologic appearance referred to as signet-ring cell carcinoma and has a gross appearance characterized by diffuse thickening and hardening of the stomach wall leading to a "leather bottle" appearance also known as linitis plastica.[20]

Intramucosal signet ring cell carcinoma (pT1a) is the histologic lesion associated with CDH1 pathologic variant. A high rate of carriers of CDH1 pathologic variants will have at least intramucosal signet ring cell carcinoma stage pT1a. The rate of progression of pT1a lesions to higher stage advanced diffuse gastric carcinoma is uncertain. Because of the relatively low incidence of HDGC, randomized clinical trial data specific to HDGC are scarce. In patients with a CDH1 PV who underwent prophylactic gastrectomy, most specimens with signet ring cell carcinoma are stage pT1a. The prevalence of greater than or equal to stage pT1b is 2%-3% in gastrectomy specimens.[20] Given the low rates of progression, management can consist of either prophylactic gastrectomy or endoscopic surveillance. The pros and cons of gastrectomy versus endoscopic surveillance require careful discussion between physicians and patients given the surgical risks and indeterminate rate of tumor progression. Further management updates will be monitored in this condition. The NCCN, CCO, and IGCLC contain genetic testing recommendations for HDGC. ACG recognizes the CDH1 association with HDGC but states in a table footnote that common germline gene variant syndromes are important regarding the biology; however, to date, they are not clinically actionable.[32] ASCO states that CDH1 testing may be considered in germline assessment of gastric carcinoma.

IGCLC: "2020 hereditary diffuse gastric cancer (HDGC) genetic testing criteria CDH1 testing is recommended when one of the following criteria have been met (see Panel 1: 2020 hereditary diffuse gastric cancer (HDGC) genetic testing criteria) and cancer diagnoses have been confirmed. When a criterion involves two or more cancers, at least one cancer should have confirmed histology. Where possible, other relevant cancers should also be confirmed. Histologically confirmed intestinal-type gastric cancer and non-lobular breast cancer cases should not be used to fulfil testing criteria, because these cancers are not part of HDGC. Individuals who fulfill criteria for genetic testing but are found to be negative for a CDH1 variant should subsequently be considered for CTNNA1 analysis."[33]

CCO: "Gastric panel criteria are based on the International Gastric Cancer Linkage Consortium (IGCLC) 2020 guidelines, with additional criteria to incorporate other hereditary gastric and gastroesophageal junction cancers. "[18]

ACG: "Common germline gene variant syndromes are important regarding the biology; however, to date, they are not clinically actionable."

ASCO: CDH1 gene testing can be considered in multigene panel testing in gastric carcinoma with a note that this gene is associated with a higher relative risk of cancer associated with a specific syndrome. Because of the rarity of pathogenic variants in this gene, some providers/patients may or may not choose to include syndrome-related genes if personal history and family history do not support the syndrome phenotype.

Li-Fraumeni Syndrome

Testing for pathogenic or likely pathogenic (P/LP) variants of TP53 is considered **medically necessary** for individuals at risk based on **ANY** of the following (referencing the Chompret [34, 35] criteria, last updated in 2015):

- Personal history of breast cancer diagnosed at or before age 30
- Personal history of breast cancer diagnosed at or before age 45 and **EITHER** of the following:
    - At least one first- or second-degree relative with a Li-Fraumeni syndrome spectrum tumor other than breast diagnosed before age 56
    - At least one first- or second-degree relative with multiple primary cancers at any age

- Personal history of a Li-Fraumeni syndrome spectrum tumor other than breast cancer (soft tissue sarcoma, osteosarcoma, CNS tumor) diagnosed at or before age 45 and **EITHER** of the following:
    - At least one first- or second-degree relative with a Li-Fraumeni syndrome spectrum tumor before age 56
    - At least one first- or second-degree relative with multiple primary cancers at any age
- Personal history of multiple tumors (other than multiple tumors of the breast), of which two belong to the Li-Fraumeni syndrome spectrum **AND** at least one was diagnosed at or before age 45
- Personal history of adrenocortical carcinoma, choroid plexus carcinoma, embryonal anaplastic rhabdomyosarcoma, or pediatric hypodiploid acute lymphoblastic leukemia
- Individual has at least one first-, second- or third-degree relative with a documented TP53 P/LP germline variant **AND** the affected family member meets at least **ONE of the above personal history criteria** for Li-Fraumeni syndrome
- Individual has had a P/LP variant of TP53 identified on tumor somatic testing **AND ONE** of the following applies:
    - The individual meets one or more of the personal history criteria above
    - The individual was diagnosed at or before age 29 with any cancer

See multigene panel testing for hereditary breast, ovarian, or pancreatic carcinoma under Hereditary Breast, Ovarian, and Pancreatic Cancer (HBOP) for additional criteria if a gene panel includes TP53.

Rationale

The transcription factor p53 (TP53) acts as a guardian of the genome[36] and responds to diverse cellular stresses to regulate target genes that induce cell cycle arrest, apoptosis, senescence, DNA repair, or changes in metabolism. Li-Fraumeni syndrome (LFS) is a rare, variably penetrant cancer predisposition syndrome associated with germline pathogenic or likely pathogenic (P/LP) variants in the tumor suppressor gene TP53[37] and associated with various early-onset tumors, consisting predominantly of sarcoma, breast cancer, brain tumors, leukemia, and adrenocortical carcinoma. However, the LFS spectrum has expanded as more cohort studies are performed and show higher risk of other prevalent tumors including melanoma, prostate cancer, and colorectal cancer.[38] The Li-Fraumeni spectrum based on an International Germline TP53 Variant Data Set introduced attenuated LFS, defined by the presence of a germline TP53 P/LP gene variant in a person with any cancer who does not meet LFS genetic testing criteria and has no cancer diagnosed before age 18 years. There is known to be variation in the disease risk and cancer spectrum associated with individual TP53 variants.[39]

The prevalence of germlineTP53 pathogenic variants in adults with cancer is low. In two large database series of adult cancer patients (without selection based on family history), about 0.2% (1 in 500) were found to be associated with TP53 variants.[40, 41] However, affected individuals are at very high risk of malignancy. In an observational cohort study was done in 480 carriers of germline (P/LP) TP53 variants enrolled in the National Cancer Institute's referral-based longitudinal Li-Fraumeni syndrome study between Aug 1, 2011, and March 24, 2020, individuals with LFS had a nearly 24 times higher incidence of any cancer than the general population (standardized incidence ratio 23.9; 95% CI 21.9-26.0); the highest comparative cancer incidence occurring from childhood to age 30. The overall cancer incidence remained 10.3 (95% CI 7.9-13.2) times higher than that of the general population after age 50.[42] Because the TP53 gene is currently included in broad panels used in germline genetic testing, the number of TP53 tests performed in non-suggestive clinical situations has significantly increased. Caution must be taken when germline P/LP TP53 variants are identified in healthy adults with family histories not suggestive of LFS because of the possibility of clonal hematopoiesis. Clonal hematopoiesis means a somatic hematopoietic stem cell produces blood cells with an *acquired* P/LP variant.[43] Acquired P/LP TP53 variants can be detected in blood and saliva through germline testing. When there is no evidence of a hematologic malignancy, this phenomenon is referred to as clonal hematopoiesis of indeterminate potential (CHIP). If CHIP is misinterpreted as LFS, unnecessary surveillance and interventions may be advised.[44]

Because of the significant elevated risk of malignancy associated with LFS, surveillance protocols for carriers bearing disease-causing TP53 variants have been proposed. A prospective observational study of one surveillance protocol using physical examination and frequent biochemical and imaging studies (consisting of whole-body MRI, brain MRI, breast MRI, mammography, abdominal and pelvic ultrasound, and colonoscopy) was introduced at three tertiary care centers in Canada and the USA on Jan 1, 2004, with follow-up through July 1, 2015. This study identified 89 carriers of TP53 pathogenic variants in 39 unrelated families, of whom 40 (45%) agreed to surveillance and 49 (55%) declined surveillance. Nineteen (21%) patients crossed over from the non-surveillance to the surveillance group, giving a total of 59 (66%) individuals undergoing surveillance for a median of 32 months. Five-year overall survival was 88.8% (95% CI 78.7–100) in the surveillance group and

59.6% (47.2–75.2) in the non-surveillance group (p=0.0132).[45] A substantial proportion of tumors identified by surveillance were low-grade or premalignant lesions. It is not clear whether these lesions would transform, but the rate of transformation in those with TP53 germline pathogenic variants may not be the same as those with sporadic cases in non-carriers. Of note, LFS is associated with heightened radiosensitivity, and thus definitive radiotherapy is discouraged for treatment of skin cancers such as cutaneous squamous cell carcinoma or basal cell carcinoma. Limitations of this non-randomized observational study include the non-randomized design, inherent possibility of lead-time bias, and the lack of data about the psychological impacts of intense surveillance.

In 2001 the French LFS working group introduced the Chompret criteria for LFS to cover the different clinical presentations associated with germline TP53 pathogenic variants and to facilitate its clinical recognition.[35] These criteria have since been updated in both 2009 and 2015. The most recent series, involving 1730 French patients selected based on existing clinical criteria suggestive of LFS, showed that it is possible to distinguish different classes of TP53 alterations according to their clinical severity. The most severe pathogenic variants are the dominant negative missense variants: they are significantly associated with earlier tumor onset, and they represent the predominant germline alterations in carriers who tend to develop childhood cancers. The less severe alterations correspond to loss of function pathogenic variants, such as nonsense variants, frameshift variants, or genomic rearrangements; these alterations are associated with later tumor onset and were mostly found in pedigrees characterized by cancers occurring in adults.[34] It is important to recognize that somatic variants identified in tumor specimens are common in TP53 especially when testing is performed in older adults. Somatic TP53 variants may not indicate the need for germline testing unless the clinical/family history is consistent with LFS.[46]

Colorectal cancer in the absence of other malignancies in the LFS spectrum (osteosarcoma, soft tissue sarcoma, adrenocortical cancer, breast cancer, choroid plexus cancer) does not indicate this syndrome, and LFS testing is not recommended by the following guidelines:

NCCN: The NCCN recognizes colorectal cancer, gastric cancer, prostate cancer, and melanoma as associated with LFS; however, they list only the core malignancies associated with LFS in their testing criteria which include soft tissue sarcoma, osteosarcoma, adrenocortical cancer, breast cancer, and central nervous system tumors.[44]

The National Society of Genetic Counselors (NSGC) listed the following malignancies as associated with Li-Fraumeni syndrome: soft-tissue sarcoma, osteosarcoma, brain, breast, adrenocortical, bronchoalveolar, colorectal, and leukemia, and recommends consideration of LFS in patients diagnosed with either colorectal cancer or leukemia and one additional tumor associated with LFS, one diagnosed at or before age 45.[17]

Colorectal, gastric, and prostate cancer in the absence of other malignancies in the LFS spectrum (osteosarcoma, soft tissue sarcoma, adrenocortical cancer, breast cancer, choroid plexus cancer) does not indicate this syndrome, and LFS testing is not recommended.

Hereditary Breast, Ovarian, and Pancreatic Cancer (HBOP)

Hereditary breast cancer

Individuals age ≤ 65 years when diagnosed with breast carcinoma

Germline genetic testing using a multigene panel that includes BRCA1 and BRCA2 is considered **medically necessary** for individuals with a personal history of breast cancer diagnosed ≤ 65 years.

See multigene panel testing for hereditary breast, ovarian, or pancreatic carcinoma* for details about the scope of panel testing.

Individuals age > 65 years when diagnosed with breast carcinoma

Germline genetic testing using a multigene panel that includes BRCA1 and BRCA2 is considered **medically necessary** for individuals with a personal history of breast cancer diagnosed > 65 years with **ANY** of the following criteria:

- Individuals assigned male sex at birth
- Triple-negative breast cancer
- Multiple primary breast cancers (synchronous or metachronous)
- Lobular breast cancer concomitant with personal or family history of hereditary diffuse gastric cancer

- Ashkenazi Jewish or other similarly high-risk ancestry
- Currently a candidate for PARP inhibitor therapy

See multigene panel testing for hereditary breast, ovarian, or pancreatic carcinoma* for details about the scope of panel testing.

Individuals with no current or prior diagnosis of breast carcinoma

Germline genetic testing using a multigene panel that includes BRCA1 and BRCA2 is considered **medically necessary** for individuals without a current or prior diagnosis of breast cancer with **ANY** of the following criteria:

- Personal or family history suggests the possibility of a pathogenic variant with **ANY** of the following:
    - Personal history of epithelial ovarian cancer or pancreatic adenocarcinoma
    - Risk of a P/LP variant in BRCA1 or BRCA2 is ≥5% based on a validated predictive model
    - At least one first-, second- or third-degree blood relative with breast cancer diagnosed at or before age 50
    - At least one first-, second- or third-degree blood relative with epithelial ovarian, fallopian tube, or primary peritoneal cancer
    - At least one first- or second-degree blood relative with multiple primary breast cancers (metachronous or synchronous)
    - At least one first-, second- or third-degree blood relative with breast cancer in an individual assigned male sex at birth
    - At least one first-, second- or third-degree blood relative with metastatic prostate cancer, or high or very high-risk grade group of localized or locally advanced prostate cancer
    - Three or more first-, second- or third-degree blood relatives on the same side of the family with invasive breast and/or prostate cancer
    - Individuals with at least one first-degree blood relative with pancreatic cancer
    - Ashkenazi Jewish or other similarly high-risk ancestry **AND** at least one first-degree blood relative with breast cancer
    - Ashkenazi Jewish or other similarly high-risk ancestry **AND** two or more second-degree blood relatives on the same side of the family with breast cancer

See multigene panel testing for hereditary breast, ovarian, or pancreatic carcinoma* for details about the scope of panel testing.

Hereditary epithelial ovarian cancer

Individuals with personal history of invasive epithelial ovarian carcinoma

Germline genetic testing using a multigene panel that includes BRCA1 and BRCA2 is considered **medically necessary** for individuals with a personal history of invasive epithelial ovarian cancer (including fallopian tube cancer or primary peritoneal cancer) at any age to aid in therapy and surgical decision-making and/or for personal and family risk assessment.

See multigene panel testing for hereditary breast, ovarian, or pancreatic carcinoma* for details about the scope of panel testing.

Individuals with no current or prior diagnosis of epithelial ovarian carcinoma

Germline genetic testing using a multigene panel that includes BRCA1 and BRCA2 is considered **medically necessary** for individuals without a current or prior diagnosis of epithelial ovarian cancer with personal or family history suggests the possibility of a pathogenic variant with **ANY** of the following:

- At least one first-, second- or third-degree blood relative with epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer at any age
- Risk of a P/LP variant in BRCA1 or BRCA2 is ≥5% based on a validated predictive model

See multigene panel testing for hereditary breast, ovarian, or pancreatic carcinoma* for details about the scope of panel testing.

Hereditary pancreatic ductal adenocarcinoma

Individuals with personal history of invasive exocrine pancreatic cancer (pancreatic ductal adenocarcinoma)

Germline genetic testing using a multigene panel that includes BRCA1 and BRCA2 is considered **medically necessary** for individuals with a personal history of invasive exocrine pancreatic cancer at any age to aid in therapy and surgical decision-making and/or for personal and family risk assessment.

See multigene panel testing for hereditary breast, ovarian, or pancreatic carcinoma* for details about the scope of panel testing.

Individuals with no current or prior diagnosis of exocrine pancreatic cancer (pancreatic ductal adenocarcinoma)

Germline genetic testing using a multigene panel that includes BRCA1 and BRCA2 is considered **medically necessary** for individuals without a current or prior diagnosis of exocrine pancreatic cancer with personal or family history suggests the possibility of a pathogenic variant with **ANY** of the following:

- First-degree blood relative with exocrine pancreatic cancer (pancreatic ductal adenocarcinoma)
- Risk of a P/LP variant in BRCA1 or BRCA2 is ≥5% based on validated predictive models

See multigene panel testing for hereditary breast, ovarian, or pancreatic carcinoma* for details about the scope of panel testing.

*Multigene panel testing for hereditary breast, ovarian, or pancreatic carcinoma

A multigene germline panel of 20 genes or less (including BRCA1 or BRCA2) related to breast, ovarian, or pancreatic cancer is considered **medically necessary** when **ALL** of the following criteria are met:

- Panels are targeted to the personal and family history of the individual
- Genes included in the panel have known P/LP germline variants associated with significantly increased risks for breast and/or associated cancers along with established management implications

See Tables 1, 2, and 3, for detailed examples of genes that **should** be tested based on an individual's clinical presentation related to one or more of breast, ovarian, and pancreatic cancers, respectively.

Note: Individuals who meet criteria for single gene testing and tested negative with previous limited testing sometime in the past (e.g., single gene and/or absent deletion duplication analysis) may be considered for multigene panel testing in this scenario. This does not imply that single gene testing is currently necessary before proceeding to multigene testing.

Known familial genetic testing for hereditary breast, ovarian, or pancreatic carcinoma

Genetic testing of a single high-risk gene (listed in Tables 1, 2, and 3 below) is **medically necessary** for individuals who have a first-, second- or third-degree relative with a known pathogenic variant in that gene.

Individuals requiring confirmatory testing

Individuals requiring confirmatory clinical high-risk germline testing based on findings of P/LP germline variants found in other testing contexts including **ANY** of the following:

- 23andMe PGS (or similar FDA approved commercial direct-to-consumer testing)
- Somatic testing for malignancy
- IRB approved clinical research

Table 1. Genetic testing for genes associated with a higher relative risk of breast carcinoma or highly actionable

Gene – Breast Carcinoma	Cancer / Syndrome
BRCA1 and BRCA2	Breast, Ovarian, Pancreatic
CDH1	Hereditary diffuse gastric cancer, Breast
PALB2	Breast (male and female), Ovarian, Pancreatic
PTEN	PTEN hamartoma tumor syndrome, Breast
STK11	Peutz-Jeghers syndrome, Breast, Pancreatic
TP53	Li-Fraumeni syndrome, Breast, Pancreatic

Table 2. Genetic testing for genes associated with a higher relative risk of ovarian carcinoma or highly actionable

Gene – Epithelial Ovarian Cancer	Cancer / Syndrome
ATM	Breast, Ovarian, Pancreatic
BRCA1 and BRCA2	Breast, Ovarian, Pancreatic
BRIP1	Ovarian
MLH1, MSH2, MSH6, PMS2, and EPCAM	Ovarian, Pancreatic
PALB2	Breast (male and female), Ovarian, Pancreatic
RAD51C, RAD51D	Breast, Ovarian

Table 3. Genetic testing for genes associated with a higher relative risk of pancreatic carcinoma or highly actionable

Gene – Pancreatic Adenocarcinoma	Cancer / Syndrome
ATM	Pancreatic
BRCA1 and BRCA2	Breast, Ovarian, Pancreatic
CDK2NA and CDK4	Pancreatic
MLH1, MSH2, MSH6, PMS2, and EPCAM	Ovarian, Pancreatic
PALB2	Breast (male and female), Ovarian, Pancreatic
STK11	Peutz-Jeghers syndrome, Breast, Pancreatic
TP53	Li-Fraumeni syndrome, Breast, Pancreatic

Rationale

Germline genetic testing has become an integral part of the care of patients with breast, ovarian, and pancreatic cancer for over 20 years, and testing guidelines have evolved in key patient subgroups such as triple-negative breast cancer, pancreatic cancer, and selected patients with prostate cancer.[47] Variant prevalence, adherence to preventive interventions, and age at the time of screening are highly influential parameters for evaluating the benefits of germline genetic testing at the population level.[48] Overall, there are 13 genes associated with elevated lifetime risks of hereditary breast and ovarian cancer.[49] Most importantly, pathogenic variants in BRCA1 or BRCA2 genes are associated with a high risk of both breast and ovarian cancer. From a prospective cohort of 9856 pathogenic variant carriers, the cumulative breast cancer risk to age 80 years was 72% for BRCA1 and 69% for BRCA2 carriers; the cumulative ovarian cancer risk to age 80 years was 44% for BRCA1 and 17% for BRCA2 carriers.[50] Pathogenic variants in these genes carry increased risks of breast, pancreatic, and stomach cancers; in addition, male BRCA2 carriers are at increased prostate cancer risk. There were no strong associations found with risks of other cancers.[51]

In the general population, BRCA1/2 P/LP variants account for 5% to 10% of breast cancer and 15% of ovarian cancer cases.[52] The detection of significant pathogenic variants in BRCA1 or BRCA2 can improve medical management through early detection or risk reduction strategies. The use of risk-reducing mastectomy was associated with a lower risk of breast cancer; risk-reducing salpingo-oophorectomy was associated with a lower risk of ovarian cancer, first diagnosis of breast cancer, all-cause mortality, breast cancer-specific mortality, and ovarian cancer-specific mortality.[53] Although these risk-reducing surgeries may provide considerable benefits in terms of cancer prevention for women with BRCA1 or BRCA2 pathogenic variants, they can be associated with adverse physical and psychosexual effects, thus requiring shared decision-making discussions of management options in affected women.[54] For women with pathogenic variants in other, moderate-penetrance genes where the degree of risk for breast and/or ovarian cancer is less precisely defined, the role of risk reducing surgery is less precisely defined and thus more controversial.[55] However, there are further studies exploring the clinical utility of acting upon pathogenic variants in moderate penetrance genes other than BRCA1 or BRCA2. Whereas roughly 3% of breast cancer patients have pathogenic variants of high penetrance genes (BRCA1, BRCA2, and PALB2), other moderate penetrance genes account for another 3% of breast cancers and another 4% are due to a combination of genetic and environmental factors.[49] The clinical utility of acting on these findings continues to evolve. For example, the risk of contralateral breast cancer is significantly higher in individuals with pathogenic CHEK2 variants and PALB2 carriers with estrogen receptor negative invasive breast cancer.[56] Such findings influence the screening and surveillance approach to affected individuals.

In 2023, the American Society of Clinical Oncology (ASCO) and the Society of Surgical Oncology (SSO) jointly developed a guideline for germline testing in patients with invasive breast cancer.[57] This ASCO-SSO guideline was not evidence-based; rather, it was based on formal consensus (modified Delphi process) and followed the ASCO methodological standards for guideline development. The most significant recommendation was that all individuals age 65 or under newly diagnosed with breast cancer should be offered BRCA1 and BRCA2 testing. This consensus recommendation moves in the direction taken in guidelines related to ovarian cancer [58] and pancreatic cancer [59] where BRCA and BRCA2 testing is generally recommended. The ASCO-SSO guideline for germline testing in breast cancer also recommended that all patients with recurrent breast cancer (local or metastatic) who are candidates for PARP inhibitor therapy should be offered BRCA 1 and BRCA2 testing regardless of family history. This latter recommendation is also recommended in NCCN guidelines[44] and is based on data showing that germline BRCA1/2 pathogenic variants have been found to be a valid predictive biomarker of response to poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitor therapy.[52] For example, in the OlympiA study, a large phase III, double-blind, randomized controlled trial, patients with HER2-negative early breast cancer with BRCA1 or BRCA2 germline pathogenic or likely pathogenic (P/LP) variants and high-risk clinicopathological factors who had received local treatment and neoadjuvant or adjuvant chemotherapy were randomly assigned to 1 year of oral olaparib or placebo with the patients receiving olaparib found to have significantly longer survival free of invasive or distant disease than was placebo.[60] Moreover, in the OlympiAD phase III trial, both overall survival and progression-free benefits were established for individuals with BRCA mutated HER2-negative metastatic breast cancer treated in the first-line setting with a PARP inhibitor (olaparib) compared to treatment of physicians choice.[61] In contrast, PALB2, another high penetrance gene associated with pathogenic germline variants, is not currently recommended by professional guidelines for use as a biomarker for systemic therapy of breast cancer [62], and the general strategy of using targeted therapy matched to genomic findings have not been shown to improve progression-free survival in metastatic breast cancer except for the established genes (such as BRCA) with high levels of evidence to support actionability.[63]

Despite the importance of knowing BRCA status, multiple studies have demonstrated that there is substantial undertesting of BRCA1 and BRCA2.[47, 64, 65] The U.S. Preventive Services Task Force (USPSTF) issued an updated recommendation in 2019 regarding risk assessment and genetic testing for BRCA1 and BRCA2 gene pathogenic variants.[52] The recommendation now applies to women with a previous diagnosis of cancer (but who have never been tested for BRCA1/2 pathogenic variants), and more explicitly considers ancestry as a risk factor for carrying a BRCA1/2 gene variant (previously, the recommendation only applied to women with a family history associated with an increased risk – based on cancer). The USPSTF recommends that women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or who have an ancestry associated with BRCA1/2 gene variants should be assessed with an appropriate risk assessment tool. Regarding ancestry risk, Ashkenazi Jewish people have high risk of pathogenic variants in BRCA1 or BRCA2 due to the high penetrance of some specific germline BRCA variants in their ancestry—in particular, c.185delA/5382insC for BRCA1 and c.6174delT for BRCA2.[66] Of note, founder mutations can also be found in other populations, including Sephardi Jewish, certain populations in Greenland[67], Latin America[68], the Bahamas[69], Nepal[70], and other populations. This highlights the importance of careful assessment of family history. Women with a positive result should receive genetic counseling, and, if indicated after counseling, genetic testing. The USPSTF explicitly recommends against routine risk assessment, genetic counseling, or genetic testing in all other women. Most women with breast or ovarian cancer (approximately 90%) do not have a hereditary form of the condition, and their risk of cancer is believed to be related to a wide variety of environmental factors such as smoking, obesity, hormone use and other lifestyle factors. For example, women diagnosed with breast cancer at age over 60 with no close relatives with breast, ovarian, pancreatic, or prostate cancer have a low probability (<2.5%) of having a high penetrance gene associated with breast or ovarian carcinoma.[44] For individuals assigned male sex at birth, specific cancer risks include breast and prostate cancer. The most compelling pathogenic variant in males is BRCA2, with increased risk for male breast cancer noted for nearly all HBOC genes and for prostate cancer ATM is also particularly important.

In addition to BRCA pathogenic variants, 11 additional genes (PALB2, BARD1, RAD51C, RAD51D, ATM, CHEK2, PTEN, STK11, BRIP1, CDH1,and P53) have been found to have significant association with breast cancer based on case-control studies that analyzed the associations between a number of cancer susceptibility genes and breast cancer risk.[71-73] In these case-control studies, the distribution of pathogenic variants among women with breast cancer was different from the distribution among unaffected women, with this difference being a consequence of the relative penetrance of variants in BRCA1, BRCA2, and PALB2, which are associated with a high risk of breast cancer with odds ratios ranging from 5.0 to 10.6.[74] In particular, an analysis of data from 524 families across 21 countries with PALB2 pathogenic variants a substantial association between germline PALB2 PVs and ovarian, pancreatic, and male breast cancers.[75] Moreover, moderate risk of breast cancer has been recognized in individuals with pathogenic variants of ATM and CHEK2, each of which increases breast cancer risk by at least 2-fold, and collectively they are identified in 2% to 3% of women with a diagnosis of breast cancer.[76] Testing for additional moderate risk genes plus Lynch syndrome genes has been found to identify additional findings that may influence clinical management in another 3-4% of patients who are evaluated for hereditary breast or ovarian cancer.[77] In a modeling analysis to estimate lifetime breast cancer mortality reduction and other key endpoints associated with different screening strategies applied to women with PALB2, ATM, or CHEK2 pathogenic variants, the findings suggest that annual MRI screening starting at 30 to 35 years followed by annual MRI and mammography at 40 years may reduce breast cancer mortality by more than 50% for women with these particular findings.[76] The American Society of Clinical Oncology (ASCO) indicates in the germline genetic testing guideline that the most strongly recommended genes in a multigene panel for breast cancer are BRCA1, BRCA2, PALB2, CDH1, PTEN, STK11, and TP53.[9] Clinical genetic testing has evolved such that commercial breast and ovarian cancer multigene panels are being used in the clinical diagnostic setting, but these are most often panels that test dozens of genes, many relating to genes of unknown significance.[78] The frequency of variants in most breast cancer panel genes among individuals selected for possible hereditary breast cancer is low, and oversized gene panels have been shown to have the potential to provide clinical misinformation and harm at the individual level.[78]

An area of discordance in guidelines exists regarding the question of whether or not BRCA testing is also relevant for individuals diagnosed with ductal carcinoma in situ (DCIS) as their sole risk factor for a BRCA pathogenic variant, despite DCIS traditionally being considered a precancerous, non-invasive form of breast cancer. The NCCN guideline regarding testing criteria for high penetrance breast cancer susceptibility genes includes a footnote that states that for the purposes of these NCCN guidelines, invasive and ductal carcinoma of the breast should be included.[21] This is in distinction to the ASCO and ESMO guidelines and the USPSTF statement which does not include such expansion to DCIS.[9, 49, 52] Note also that the US National Cancer Institute conducts research in DCIS in an entirely separate branch (the Division of Cancer Prevention) compared to research related to invasive breast cancer (the Division of Cancer Treatment and Diagnosis), highlighting that DCIS is typically not conflated with invasive breast cancer. For those with DCIS and no other established risk factors for BRCA P/LP variant, the prevalence estimate of pathogenic BRCA variants is around 2% (less than the 5% threshold typically used for BRCA testing). Available, validated online tools that can aid in this evaluation about BRCA-related risks include CanRisk (https://www. canrisk.org/).[79] The CanRisk tool is explicit in stating that neither history of DCIS nor treatment are considered in the BOADICEA/CanRisk model, and DCIS should not be included in the risk calculations. Moreover, in a retrospective study aimed to determine which of the following three scenarios, related to DCIS entry into the only BRCAPRO tool, predicted BRCA pathogenic variant status more accurately (1) DCIS as an invasive breast cancer (IBC) entered using the actual age of diagnosis, (2) DCIS as IBC entered with 10 years added to the actual age of diagnosis, and (3) DCIS entered as no cancer. In terms of accuracy of BRCA positivity, there was no statistically significant difference between DCIS at age at diagnosis, DCIS at 10 years later than age at diagnosis, and DCIS entered as no cancer (AUC = 0.77, 0.784, 0.75, respectively: p = 0.60).[80] This is consistent with other data to suggest that, taken alone, DCIS is not an independent factor that elevates the likelihood of BRCA mutation. As noted earlier however, the NCCN includes DCIS with invasive breast cancer as testing criteria for high-penetrance breast cancer susceptibility genes including BRCA1 and BRCA2.

Melanoma

Germline genetic testing of a focused set of 20 or fewer specific genes which may include CDKN2A, BAP1, and CDK4 pathogenic variants are considered **medically necessary** for persons at risk for familial melanoma, familial atypical multiple mole melanoma-pancreatic cancer syndromes, or familial atypical multiple mole melanoma syndrome (FAMMM) as defined by **ANY** of the following diagnostic criteria:

- Personal history of three (3) or more melanomas
- Personal history of melanoma and pancreatic cancer (exocrine type)
- Personal history of melanoma and a personal or family history in two or more first-degree relatives with mesothelioma or clear cell renal carcinoma or basal cell carcinoma (BAP-1 associated cancers)
- Personal history of melanoma and astrocytoma

- Three or more first- or second-degree relatives with melanoma or pancreatic cancer
- Personal history of invasive cutaneous melanoma who have a first-degree relative diagnosed with pancreatic cancer (exocrine type)
- Both melanoma and astrocytoma in two or more first-degree relatives

Known familial genetic testing for familial melanoma, familial atypical multiple mole melanoma-pancreatic cancer syndromes or FAMMM

Genetic testing of a single high-risk gene is **medically necessary** for individuals who have a first-, second- or third-degree relative with a known pathogenic variant in that gene.

Rationale

About 10%-15% of melanoma patients report a family history of melanoma; however, individuals with features of true hereditary melanoma (i.e., unilateral lineage, multigenerational, multiple primary lesions, and early onset of disease) are rare.[81] Although many new loci have been implicated in hereditary cutaneous melanoma, including BAP1, CDK4, MC1R, BRCA2, TERT, MITF, and PTEN variants, CDKN2A pathogenic/likely pathogenic (P/LP) variants remain the most common.[82] There are limited data suggesting that monoallelic MBD4 pathogenic variants may explain some cases of familial uveal melanoma, but further data are needed to confirm the associations.[83] There are conditional recommendations for genetic counseling for CDKN2A/p16 testing by evidence-based guidelines. While there is no data regarding alterations in management or outcomes, there are management changes suggested by some consensus guidelines. The American Society of Clinical Oncology (ASCO) indicates in the germline genetic testing guideline that the most strongly recommended genes in a multigene panel for melanoma for cutaneous melanoma are CDKN2A and CDK4 and for uveal melanoma BAP1 is strongly recommended.[83]

Guideline recommendations are discussed further below:

ACMG/NSGC: “Hereditary melanoma is caused by mutations in the CDKN2A/ARF gene, which encodes p16 and p14ARF, and the CDK4 gene. Hereditary melanoma is characterized by multiple melanocytic nevi (usually >50) and a family history of melanoma. Individuals with hereditary melanoma have a 17% risk for pancreatic cancer by age 75 (ref. 82). The penetrance for melanoma in families with CDKN2A mutations is at least 28%, although it is perhaps as high as 91% in families with multiple cases.”[17]

NCCN: “Consider genetic counseling referral for p16/CDKN2A mutation testing if a family or personal history of either 3 or more invasive cutaneous melanomas, or a mix of invasive melanoma, pancreatic cancer, and/or astrocytoma diagnoses. Multigene panel testing that includes CDKN2A is also recommended for patients with invasive cutaneous melanoma who have a first degree relative diagnosed with pancreatic cancer. Testing for other genes that may harbor melanoma-predisposing mutations may be warranted, depending on personal or family history of at least two noncutaneous cancers, such as pancreatic, renal, bladder, GI, and/or breast.” For CDKN2A variants, NCCN notes strong evidence of an absolute risk for melanoma of 28-76% depending on other genetic modifiers as well as other risk factors such as geographic location and family history. They further indicate that comprehensive skin examination by a dermatologist, supplemented with total body photography and dermoscopy is recommended every 6 months for individuals with confirmed CDKN2A P/LP variants.[21]

Nevoid Basal Cell Carcinoma Syndrome

(also called Gorlin-Goltz syndrome, basal cell nevus syndrome)

Focused genetic testing of PTCH1 and SUFU is considered **medically necessary** for persons at risk for nevoid basal cell carcinoma syndrome based on the following diagnostic criteria. The individual must meet **ANY** of the following: **TWO (2) major criteria, ONE major criterion AND TWO (2) minor criteria**, **OR THREE (3) minor criteria**.

- **Major criteria**
    - Multiple basal cell carcinomas (out of proportion to prior sun exposure and skin type) or one basal cell carcinoma diagnosed before age 30 (excluding basal cell carcinomas that develop after radiotherapy)
    - Lamellar calcification of the falx cerebri
    - Odontogenic keratocyst

  - Palmar or plantar pitting
  - First-degree relative with nevoid basal cell carcinoma syndrome
- **Minor criteria**
  - Childhood medulloblastoma (primitive neuroectodermal tumor)
  - Lymphomesenteric or pleural cysts
  - Macrocephaly
  - Cleft lip and/or cleft palate
  - Vertebral or rib anomalies observed on x-ray
  - Preaxial or postaxial polydactyly
  - Ovarian or cardiac fibromas
  - Ocular anomalies (cataract, developmental defects, and pigmentary changes of the retinal epithelium)

Known familial genetic testing for nevoid basal cell carcinoma syndrome

Genetic testing of a single high-risk gene is **medically necessary** for individuals who have a first-, second- or third-degree relative with a known pathogenic variant in that gene.

Rationale

A small group of patients are genetically predisposed to hereditary non-melanoma skin cancers. These hereditary conditions, called genodermatoses, are often clustered with multiple family members showing symptoms. The most common syndromes associated with basal cell carcinoma are Gorlin-Goltz, Rombo, and Bazex-Dupré-Christol syndromes. Multiple squamous cell carcinomas can be related to xeroderma pigmentosum, Ferguson-Smith, Muir-Torre syndrome, Mibelli-type porokeratosis, keratitis-ichthyosis-deafness syndrome, Rothmund-Thomson syndrome, Bloom syndrome, and epidermodysplasia verruciformis.[84, 85]

Gorlin-Goltz syndrome (OMIM 109400) is an autosomal dominant basal cell carcinoma syndrome characterized by multiple nevoid basal cell epitheliomas, jaw cysts and bifid rib syndrome caused by pathogenic variants in the PTCH1 gene, or the suppressor of fused (SUFU) gene.[86] Approximately 90% of sporadic basal cell carcinomas have identifiable pathogenic/likely pathogenic (P/LP) variants in at least one allele of *PTCH1*, and an additional 10% have activating P/LP variants in the downstream smoothened (SMO) protein, which presumably render SMO resistant to inhibition by PTCH1.[87] Affected individuals have unusual facial appearances (mandibular prognathia, lateral displacement of the inner canthus, frontal and biparietal bossing), dental cysts, palmar pits and a predisposition for BCC. Other cardinal features are calcification of the falx cerebri, medulloblastoma, kyphoscoliosis, rib anomalies, cleft lip/palate, eye anomalies, milia and syndactyly. Proposed diagnostic criteria include a set of major criteria and minor criteria.[88] Meeting two major or one major and two minor criteria fulfills the diagnostic criteria.

The following professional medical societies have made these recommendations:

ACMG/NSGC: “Referral should be considered for any individual with a personal history of or first-degree relative with any two criteria from the major or minor diagnostic criteria lists.”[17]

NCCN: “In certain patients at high risk for multiple primary tumors (e.g., Gorlin syndrome, xeroderma pigmentosum, history of RT), increased surveillance and consideration of prophylactic measures may be indicated. Consider referring patients with suspected Gorlin syndrome or xeroderma pigmentosum for genetic evaluation.”[89]

Endocrine Neoplasms

Germline genetic testing for a single gene or a panel focused on the set of genes reasonably needed to assess the suspected condition is considered **medically necessary** in individuals with a personal history of **ANY** of the following:

- Adrenocortical carcinoma (ACC)

- Paraganglioma or pheochromocytoma
- Duodenal or pancreatic neuroendocrine tumor
- Type 2 gastric neuroendocrine tumor
- Gastrointestinal stroma tumors (GIST) diagnosed before age 30
- Medullary thyroid cancer
- Parathyroid adenoma, diffuse hyperplasia, or primary hyperparathyroidism before age 30
- Multiple parathyroid adenomas or recurrent primary hyperparathyroidism
- Sporadic pituitary adenoma diagnosed in childhood or adolescence
- Sporadic, functioning pituitary adenoma diagnosed in adults age 29 or younger *(except for microprolactinomas in individuals assigned female at birth)* **OR** a non-functioning pituitary adenoma >1 cm
- MEN2-related features including lip mucosal neuromas resulting in thick vermilion of the upper and lower lip, mucosal neuromas of the lips and tongue, medullated corneal nerve fibers, marfanoid habitus.
- Family history of neuroendocrine tumors or associated conditions (including primary hyperparathyroidism, duodenal or pancreatic neuroendocrine tumor, pituitary adenoma, or carcinoid tumor of bronchial, thymic, or gastric origin) in a first-, second- or third-degree relative and clinical features in the individual suspicious of a hereditary condition

Known familial genetic testing for hereditary endocrine neoplasms

Genetic testing of a single high-risk gene (listed in Tables 4-8 below) is **medically necessary** for individuals who have a first-, second- or third-degree relative with a known pathogenic variant in that gene.

See Tables 4-8 below for scope of genes that should be tested based on the underlying type of endocrine neoplasm.

Table 4. Genetic testing for genes associated with elevated risk of pheochromocytomas and paragangliomas

Gene – Pheochromocytomas and Paragangliomas
FH
MAX
RET
SDHA
SDHB
SDHC
SDHD
TMEM127
NF1
VHL

Table 5. Genetic testing for genes associated with elevated risk of gastrointestinal stromal tumors (GIST)

Gene – Gastrointestinal Stromal Tumors
KIT

Gene – Gastrointestinal Stromal Tumors
PDGFRA
NF1 (if the somatic test shows NF1 P/LP variant)
SDHA, SDHAF2, SDHB, SDHC, SDHD (if SDH-deficient or SDH mutant tumor)

Table 6. Genetic testing for genes associated with elevated risk of medullary thyroid carcinoma

Gene – Medullary Thyroid Carcinoma
RET

Table 7. Genetic testing for genes associated with elevated risk of adrenocortical tumors

Gene – Adrenocortical Tumors
APC
EPCAM
MEN1
MLH1
MSH2
MSH6
PMS2
TP53

Table 8. Genetic testing for genes associated with elevated risk of pancreatic neuroendocrine tumors

Gene – Pancreatic Neuroendocrine Tumors
MEN1
VHL

Rationale

Neuroendocrine tumors are rare and associated with a variety of endocrine syndromes including multiple endocrine neoplasia (MEN) types 1, 2A, 2B, and 4. MEN4 is particularly rare and arises from pathogenic variants of CDKN1B.[90] MEN1 and MEN2 are the more common neuroendocrine syndromes.

MEN1 or Wermer's syndrome (OMIM *131100) has a prevalence 3-20/100,000 and is a highly penetrant autosomal dominant disorder caused by germline pathogenic variants in the tumor suppressor gene MEN1.[91] Primary hyperparathyroidism is by far the most prevalent feature of this condition, but it also affects the anterior pituitary, the exocrine pancreas, and may also cause cutaneous lesions and adrenal tumors.

MEN2 is also an autosomal dominant syndrome caused by a pathogenic variant of the RET proto-oncogene. It has a frequency of roughly 1 in 35,000.[92] It has two distinct variants, MEN2A or Sipple syndrome and MEN2B. Medullary thyroid cancer (MTC) and pheochromocytoma are shared aspects of the MEN2 syndromes, but classical MEN2A features hyperparathyroidism whereas patients with MEN2B have a Marfanoid body habitus and a tendency to develop mucosal neuromas.[93] MEN2A accounts for 80% of hereditary MTC syndromes. As many as 25% of unselected individuals with MTC have a germline RET pathogenic variant. Individual series found that 4%–11% of individuals with isolated MTC have a germline RET pathogenic variant.[17] RET testing is not indicated in apparently sporadic hyperparathyroidism in the absence of other clinical suspicion for MEN2. Families with MTC and no other MEN2-associated tumors are referred to as having familial medullary thyroid cancer and all patients diagnosed with MTC are considered candidates for germline RET pathogenic variant based on various professional guidelines.

MEN4 is a rare autosomal dominant syndrome that has significant clinical overlap with MEN1.[90, 94] MEN4 has a milder phenotype and later age of onset than MEN1. Primary hyperparathyroidism and pituitary adenoma are the main features and neuroendocrine tumors are rare. Penetrance estimates and surveillance recommendations are not available for MEN4.[95]

Hereditary paraganglioma-pheochromocytoma syndromes are rare with an incidence of about 0.6 cases per 100,000 person years and are characterized by paragangliomas (tumors that arise from neuroendocrine tissues distributed along the paravertebral axis). Pheochromocytoma is an adrenal tumor, and paraganglioma is an extra-adrenal tumor; since the two tumor types cannot be differentiated on the basis of histologic findings.[96] In 85%-90% of cases, these are pheochromocytomas and they are sometimes detected by a classic symptom related to catecholamine-producing tumors (headache, diaphoresis, tachycardia, and sometimes refractory hypertension) and often found through incidental imaging.[93] The most clinically relevant syndromes involved with pheochromocytomas and paragangliomas are listed below[96]:

- MEN-2, caused by germline pathogenic/likely pathogenic (P/LP) variants of the RET proto-oncogene;
- von Hippel–Lindau disease, caused by P/LP variants in the VHL tumor suppressor genes;
- neurofibromatosis type 1, caused by P/LP variants in the NF1 tumor-suppressor gene;
- paraganglioma syndromes 1 through 5, caused by P/LP variants of the succinate dehydrogenase genes SDHD (syndrome 1), SDHAF2 (syndrome 2), SDHC (syndrome 3), SDHB (syndrome 4), and SDHA (syndrome 5);
- hereditary pheochromocytoma syndromes caused by P/LP variants in the genes encoding transmembrane protein 127 (TMEM127) and MYC-associated factor X (MAX)

The American Society of Clinical Oncology (ASCO) indicates in the germline genetic testing guideline a list of genes most strongly recommended genes in a multigene panel when personal or family history indicates endocrine neoplasms such as pheochromocytomas or paragangliomas, gastrointestinal stromal tumors, medullary thyroid carcinoma, or adrenocortical tumors.[9]

Hereditary Myeloid Neoplasms

Germline genetic testing* with a single gene **OR** a targeted panel (up to 50 genes) for hereditary myeloid neoplasms is considered **medically necessary** for individuals when **ANY** of the following criteria are met:

Personal history of a myeloid malignancy (AML, MDS) **AND at least one** of the following:

- Diagnosed at or before age 49
- Hypocellular MDS
- New diagnosis of aplastic anemia
- Personal history of one additional primary cancer
- Personal history of **ANY** of the following:
    - Congenital anomalies such as microcephaly, short stature or skeletal abnormalities (thumbs, arms, etc.)
    - Inborn errors of immunity such as poor stem cell mobilizer, unexplained cytopenias (i.e., thrombocytopenia) or macrocytosis, immune deficiency/dysregulation
    - Pulmonary and/or liver fibrosis
- Somatic NGS panel result is suggestive of a germline predisposition to myeloid neoplasm with at least **ONE** of the following:
    - Somatic variant allele fraction of 30% or greater
    - Somatic variant ins CHEK2, I200T, or a truncating DDX41 variant
- A first- or second-degree relative AML or MDS
- Member of a family with known germline pathogenic variant in a myeloid neoplasm predisposition gene

Allogeneic related donor hematopoietic cell transplantation candidates for individuals with a suspected hereditary myeloid neoplasm:

- **Genetic testing of a single high-risk gene** is **medically necessary** for individuals who have a first-, second- or third-degree relative with a known pathogenic variant in that gene

*__*Note*__:

Skin biopsy for fibroblast culture is the preferred specimen in individuals affected with hematopoietic disease.

Rationale

The prevalence of hereditary myeloid neoplasms, which include conditions such as myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML), is estimated to be up to 10% of all myeloid neoplasms.[97] Hereditary myeloid neoplasms can be associated with various predisposition genes, including those involving pathogenic/likely pathogenic (P/LP) variants in genes such as DDX41, CEBPA, RUNX1, ANKRD26, and ETV6. Hereditary myeloid neoplasms may present with or without pre-existing hematologic abnormalities or other organ dysfunctions.[97-100] Germline predisposition alleles that confer risk to lymphoid malignancies are emerging and often overlap with the myeloid malignancy risk genes.[99, 101]

A 2025 prospective cohort study by Tesi et al. evaluated the diagnostic yield and clinical utility of the Nordic guidelines for germline genetic investigation in patients with myeloid neoplasms (MNs), including AML, MDS, and related disorders.[102] Among 85 patients meeting the Nordic criteria (based on suggestive medical/family history or somatic findings) P/LP germline variants were identified in 35% of cases. Suggestive medical/family history criteria included patients with a family history of myeloid neoplasms, other hematologic malignancies, or cancers in first- or second-degree relatives, as well as those with a family history of cancers or clinical findings consistent with inherited bone marrow failure syndromes or other hereditary cancer predisposition syndromes. P/LP variants were identified in DDX41, TERT, RTEL1, ETV6, PARN, SAMD9 most commonly. The diagnostic yield was highest (52%) in those selected by somatic cytogenetic/molecular findings, and lowest (6%) in those selected by family history alone.[103]

Several professional societies have published clinical criteria for germline predisposition to myeloid neoplasms.

European Leukemia Net (ELN) for acute myeloid leukemia: Germline testing should be considered in patients a personal history of two or more cancers, one of which is a hematopoietic malignancy (regardless of order); a personal history of a hematopoietic malignancy plus either another relative within two generations with another hematopoietic malignancy, another relative within two generations with a solid tumor diagnosed at age 50 or younger, or another relative within two generations with other hematopoietic abnormalities; the presence of a deleterious gene variant in tumor profiling that could be a germline allele, especially if that variant is present during remission; diagnosis of a hematopoietic malignancy at an earlier age than average (for example, myelodysplastic syndrome diagnosed at age 40 or younger).[101]

NCCN: Germline genetic testing should be considered in patients with MDS who have a personal history of MDS, acute myeloid leukemia AML, or other hematologic malignancy diagnosed at a young age (<50 years); a family history of two or more first- or second-degree relatives with MDS, AML, or other hematologic malignancy; personal or family history of physical findings or clinical features suggestive of an inherited bone marrow failure syndrome or other hereditary cancer predisposition syndrome (e.g., abnormal skin pigmentation, nail dystrophy, short stature, congenital anomalies, pulmonary fibrosis, lymphedema, immunodeficiency); unexplained persistent cytopenias or bone marrow failure, especially in younger patients; detection of a pathogenic or likely pathogenic variant in a gene known to be associated with germline predisposition to myeloid neoplasms (e.g., DDX41, CEBPA, RUNX1, GATA2, ETV6, ANKRD26, SRP72, Fanconi anemia genes) during somatic diagnostic workup, particularly if the variant allele frequency is high or the mutation is present in the absence of typical somatic drivers; or prior to allogeneic hematopoietic cell transplantation when a related donor is being considered.[104]

NSGC: Germline genetic testing for myeloid malignancies should be considered in individuals with personal history of two or more cancers, one of which is a hematopoietic malignancy (order does not matter); personal history of a hematopoietic malignancy plus another relative within two generations with another hematopoietic malignancy, or another relative within two generations with a solid tumor diagnosed at age 50 or younger, or another relative within two generations with other hematopoietic abnormalities; presence of a deleterious gene variant in tumor profiling that could be a germline allele, especially if that variant is present during remission; age of diagnosis of hematopoietic malignancy at an earlier age than average (for example, myelodysplastic syndrome diagnosed at age 40 or younger); and confirmation of germline status of a variant by its presence in DNA derived from a tissue source not likely to undergo somatic mutation frequently (such as cultured skin fibroblasts or hair follicles) and at a variant allele frequency consistent with the germline (generally considered between 30% and 60%), or its presence in at least two relatives at a variant allele frequency consistent with the germline. [105]

Professional societies also recommend multigene panels to evaluate for hereditary myeloid neoplasms. The gene panels vary in size, gene content, and may be further tailored based on additional clinical findings. However, ELN, NCCN, ESMO, and NSGC agree on a core five non-syndromic germline gene associations: CEBPA, DDX41, RUNX1, ANKRD26 and ETV6. Please see those society publications detailing germline genes associated with myeloid neoplasms and other clinical

findings.[101, 104-106] The NCCN also recommends initial, non-molecular laboratory tests to help clinicians determine which relevant syndromes and germline gene panels to target.[104] The initial tests include flow cytometry or paroxysmal nocturnal hemoglobinuria, telomere length by flow FISH chromosomal breakage study [Fanconi anemia], serum pancreatic isoamylase and serum isoamylase [Schwachman-Diamond syndrome], erythrocyte adenosine deaminase [Diamond-Blackfan anemia], additional bone marrow testing: cytogenetic analysis/chromosomal microarray analysis. In addition, germline testing should be performed using non-hematopoietic tissue (e.g., cultured skin fibroblasts or buccal swab) to avoid confounding by somatic P/LP variants.[101, 104, 105]

Hereditary Brain Tumors

Germline genetic testing for a targeted panel (up to 20 genes) is considered **medically necessary** for hereditary brain malignancy syndromes for **individuals with a personal history of a primary malignant brain tumor AND ANY** of the following:

- Diagnosed in childhood through young adulthood
- Personal history of an additional primary cancer
- Two or more first- or second-degree blood relatives with a brain malignancy and/or associated cancers (Li-Fraumeni syndrome tumors, Muir-Torre syndrome tumors, soft tissue tumors, etc.) on the same side of the family

Known familial genetic testing for a hereditary brain tumor

Genetic testing of a single high-risk gene is **medically necessary** for individuals who have a first-, second- or third-degree relative with a known pathogenic variant in that gene.

Rationale

Hereditary brain tumors are relatively rare; however, they are associated with several well-characterized tumor predisposition syndromes. The prevalence of hereditary brain tumors varies depending on tumor histology, age of onset, syndrome and germline gene. Germline genetic testing in children (birth up to 18 years of age) with brain tumors is indicated to identify underlying cancer predisposition syndromes present in a significant proportion of pediatric brain tumors and can directly impact clinical management and surveillance.[107]

The American Association for Cancer Research (AACR) Cancer Predisposition Working Group recommends germline testing for all children diagnosed with brain tumors as treatment decisions (e.g., radiotherapy, chemotherapy) and long-term surveillance may be altered by the presence of a germline pathogenic variant. Up to 50% of children with a brain tumor and a cancer predisposition syndrome are the first affected in their family and reliance solely on family history is insufficient. At minimum, AACR recommends testing to include all tumor-associated genes and for tumors with multiple associated genes, such as medulloblastoma, broad multigene or CNS tumor-targeted panels are preferred for efficiency and cost-effectiveness. AACR lists pediatric brain tumor types by associated gene (Table 9).[107]

NCCN provides general germline genetic testing recommendations for pediatric diffuse high-grade gliomas, “In the pediatric population, dedicated germline testing should be strongly considered in the appropriate clinical context, recognizing that not all sequencing assays readily distinguish between germline and somatic variants” and for adult central nervous system cancers, “when to consider genetic testing … For Li-Fraumeni syndrome, Lynch syndrome…, For FAP…For patients with personal/family history suggestive of other cancer predisposition syndromes…”[108, 109]

The NCCN explicitly recommends genetic testing for children diagnosed with medulloblastoma. They do not provide a specific germline gene list; however, they enumerate genetic syndromes and genes associated with pediatric medulloblastoma, including:[109]

- **APC**: Associated with familial adenomatous polyposis
- **PTCH1** and **SUFU**: Associated with nevoid basal cell carcinoma syndrome
- **TP53**: Li-Fraumeni syndrome
- **MLH1, MSH2, MSH6**, and **PMS2**: Constitutional Mismatch Repair Genes
- **BRCA2** (biallelic and monoallelic) and **PALB2** (monoallelic): homologous recombination repair deficiency[110]
- **GPR161**: Overlapping phenotype with nevoid basal cell carcinoma syndrome
- **ELP1**: Recently associated with certain medulloblastoma cases

- **CREBBP** and **EP300**: Associated with Rubinstein-Taybi syndrome (autosomal dominant)

Cancer Care Ontario provides personal and family history criteria as well as a 20-gene central nervous system germline testing list, applicable to various tumor types in adults. The clinical criteria are Personal history of a brain tumor with either multiple tumors and/or cancers in one person (e.g., brain, soft tissue, Lynch syndrome cancers) OR ≥2 close relatives with brain tumors and/or associated cancers (Lynch syndrome cancer, Li-Fraumeni syndrome tumors, soft tissue, etc.) on the same side of the family. Gene list: APC, EPCAM, LZTR1, MLH1, MSH2, MSH6, NF1, NF2, PMS2, POLE, POT1, PTCH1, PTEN, SMARCB1, SMARCE1, SUFU, TP53, TSC1, TSC2, VHL.[18]

Table 9. Childhood brain tumors and germline gene associations[OBJ;107, 110]

CNS Tumor Type	Key Germline Genes	Associated Syndrome(s)/ Clinical Context	Clinical Notes
Medulloblastoma	APC	Familial adenomatous polyposis (FAP)	Associated with WNT subgroup
	PTCH1, SUFU	Gorlin syndrome (nevoid basal cell carcinoma syndrome)	Associated with SHH subgroup
	TP53	Li-Fraumeni syndrome	Associated with SHH subgroup
	BRCA2, PALB2	Fanconi anemia (biallelic)	Test only if family history, skeletal/neurologic anomalies, or severe/unexpected chemotherapy toxicity. Medulloblastoma risk in heterozygous carriers presumed low
Rhabdoid tumors (AT/RT)	SMARCB1	Rhabdoid tumor predisposition syndrome	Atypical teratoid/rhabdoid tumor and extracranial malignant rhabdoid tumor
	SMARCA4	Rhabdoid tumor predisposition syndrome 2	Rare
Low-grade glioma (incl. optic glioma)	NF1	Neurofibromatosis type 1	Bilateral optic pathway gliomas highly suggestive
Dysplastic gangliocytoma (Lhermitte-Duclos)	PTEN	PTEN hamartoma tumor syndrome (Cowden syndrome)	Major diagnostic criterion
High-grade glioma	TP53	Li-Fraumeni syndrome	Association
	PMS2, MSH6, MSH2, MLH1, POLE	Constitutional mismatch repair deficiency (CMMRD)	Consider in high-grade glioma
	POT1	POT1-tumor predisposition syndrome	Rare
Subependymal giant cell astrocytoma	TSC1, TSC2	Tuberous sclerosis complex	Pathognomonic for TSC
Cerebral astrocytoma	CDKN2A/B	Familial melanoma–astrocytoma syndrome	Rare
Spinal ependymoma (brain)	NF2	Neurofibromatosis type 2	Association
Meningioma & Schwannomatosis	BAP1, DGCR8, LZTR1, NF2, PTEN, SMARCB1, SMARCE1, SUFU	Various	Association with both tumor types
Clear cell-type meningioma	SMARCE1	SMARCE1-related meningioma	Strong association with clear cell-type
Chordoma	TBXT (Brachyury)	Familial chordoma	Gene duplication
	TSC1, TSC2	Tuberous sclerosis complex	Rare association
Choroid plexus carcinoma	TP53	Li-Fraumeni syndrome	Strong association

CNS Tumor Type	Key Germline Genes	Associated Syndrome(s)/ Clinical Context	Clinical Notes
CNS Hemangioblastoma	VHL	Von Hippel-Lindau disease	One third cases have VHL
Pineoblastoma	DICER1	DICER1 syndrome	Single report
	RB1	Hereditary retinoblastoma	Association
Pituitary blastoma	DICER1	DICER1 syndrome	Rare, but pathognomonic

SHH – sonic hedgehog

Kidney Cancer

Germline genetic testing for a single gene **OR** a targeted panel (up to 20 genes) which may include BAP1, FH, FLCN, MET, SDHA, SDHAF2, SDHB, SDHC, SDHD, PTEN, TSC1, TSC2, or VHL is considered **medically necessary** for hereditary kidney cancer syndromes in individuals with **ANY** of the following:

- Personal history of renal cell carcinoma with **ANY** of the following clinical or histologic criteria:
    - Diagnosis at age 46 or younger
    - Bilateral or multifocal tumors
    - At least one first- or second-degree relative with renal cell carcinoma
    - Evidence of syndromic presentation (e.g., seizures, pneumothorax)
    - Multifocal papillary histology
    - Birt-Hogg-Dubé syndrome-related histology (multiple chromophobe, oncocytoma, or oncocytic hybrid tumors)
    - Hereditary leiomyomatosis-associated renal cell carcinoma (HLRCC)
    - Renal cell carcinoma with fumarate hydratase deficiency or other features associated with HLRCC
    - Succinate dehydrogenase (SDH)-deficient RCC histology
    - Angiomyolipomas of the kidney and one additional tuberous sclerosis complex criterion in the same individual
    - Personal/family history of associated tumors (e.g., hemangioblastoma, leiomyomas)
- Unaffected individuals with family history of renal cell carcinoma in two or more first- or second-degree relatives (on the same side of the family)

Known familial genetic testing for hereditary kidney cancer syndromes

Genetic testing of a single high-risk gene is **medically necessary** for individuals who have a first-, second- or third-degree relative with a known pathogenic variant in that gene.

Rationale

Hereditary renal cell carcinoma (RCC) may account for 5% to 8% or more of kidney cancers and includes a variety of syndromes including von Hippel-Lindau (VHL), hereditary papillary renal cell carcinoma (HPRC), Birt-Hogg-Dubé (BHD), hereditary leiomyomatosis and RCC (HLRCC), succinate dehydrogenase kidney cancer (SDH-RCC), tuberous sclerosis complex (TSC), Cowden syndrome, and microphthalmia associated transcription factor (MITF). A retrospective analysis of 321 patients with RCC who underwent genetic evaluation showed that the most frequent germline mutations were FLCN (n = 10, 3.1%), SDHB (n = 4, 1.2%), VHL (n = 4, 1.2%), MLH1 (n = 3, 0.9%), and CHEK2 (n = 4, 1.2%).[111] In an analysis of the age distribution of RCC cases in the SEER-17 program and in an institutional hereditary kidney cancer population, the age distributions were compared by sex, race, histology, and hereditary cancer syndrome. Investigators found that 70% of the hereditary cases were at or below the bottom age decile cutoff of <46 years.[112] Multigene panel tests allow testing for multiple

genes currently associated with hereditary RCC and for patients who lack distinguishing clinical features of a classic hereditary cancer syndrome.[113] Per Bukavina et al., examples (although not limited to) of variants, prevalence, and risk of developing RCC are listed by condition in the following table:[114]

Table 10. Genetic testing for genes associated with elevated risk of hereditary kidney cancer syndromes [115]

Condition	Gene/Translocation	Prevalence	Risk of RCC
Von Hippel-Lindau (VHL) syndrome	VHL	1.4:100,000	30%–40%
Birt-Hogg-Dubé (BHD) syndrome	FLCN	2:1,000,000	30%
Chromosome 3 translocation	3:6, 3:8, 3:11	Variable	30%
Hereditary papillary renal cell cancer (HPRC)	MET	1:1,500,000	100%
Hereditary leiomyomatosis and renal cell cancer (HLRCC)	FH	1.4:100,000	15%–32%
BRCA1-associated protein-1 (BAP1) tumor predisposition syndrome	BAP1	1:26,837	9%–13%
Tuberous sclerosis complex (TSC)	TSC1/TSC2	1:6,000–1:10,000	2%–5%

More recently a retrospective analysis of 997 kidney tumors composed of 790 clear cell RCC and 207 non-clear cell RCC cases collected through the Ontario tumor bank underwent genetic testing examining 19 RCC-related and 27 cancer predisposition genes. This study was performed to evaluate the incidence of pathologic variants genes in nonsyndromic, sporadic cases of RCC within Canada in comparison with cancer-free controls. The results were then combined with those reported for patients from Japan, the United Kingdom, and the United States to investigate PV variations in different populations. 39 germline PVs in 56 patients (5.8%) from the Canadian cohort were identified. Compared with cancer-free controls, PVs in CHEK2 (odds ratio [OR], 4.8 [95% CI, 2.7 to 7.9], P = 3.94 X 10^{-5}) and ATM (OR, 4.5 [95% CI, 2.0 to 8.7], P = .016) were significantly enriched in patients with clear cell carcinoma, whereas PVs in FH (OR, 215.1 [95% CI, 64.4 to 597.8], P = 6.14 X 10^{-9}) were enriched in patients with non-clear cell RCCs. PVs in BRCA1, BRCA2, and ATM were associated with metastasis (P = .003). Comparative analyses showed an enrichment of TP53 PVs in patients from Japan, of CHEK2 and ATM in patients from Canada, the United States and the United Kingdom, and of FH and BAP1 in the United States.[116] The results of this study suggest that the genetic etiology of sporadic RCC may be underestimated based on lack of testing for these genes in most syndromic hereditary RCC panels. Testing for these genes is currently not recommended by professional society guidelines.

The American Society of Clinical Oncology (ASCO) indicates in the germline genetic testing guideline that the most strongly recommended genes in a multigene panel for renal cancer are BAP1, FH, FLCN, MET, SDHA, SDHAF2, SDHB, SDHC, SDHD, PTEN, or VHL.[9] Addition of TSC1 and TSC2 genes associated with tuberous sclerosis may also be considered per NCCN guidelines,[117] ERKNet Working Group for Autosomal Dominant Structural Kidney Disorders and the ERA Genes & Kidney Working Group, Cancer Care Ontario evidence guidelines,[18, 118] 2024 ASCO guideline on Selection of Germline Genetic Testing Panels in Patients With Cancer, and 2024 CUA-KCRNC Expert Report: Management of non-clear cell renal cell carcinoma.

Prostate Cancer

(Also see Lynch syndrome and HBOP)

Germline genetic testing of a focused set of 20 or fewer specific genes with a higher relative risk of prostate cancer or highly actionable should include BRCA1, BRCA2, HOXB13, MLH1, MSH2, MSH6, PMS2, and EPCAM to inform assessment of hereditary risk of prostate cancer is considered **medically necessary** for individuals with a history of **ANY** of the following:

- Personal history of **ANY** of the following:
    - Metastatic, locally advanced, or high-risk localized prostate cancer with high-risk localized disease defined as T3 or higher staging, grade group 4 or 5 (Gleason Score 8 to 10), lymph node involvement, and/or PSA ≥20 ng/ml
    - Prostate cancer diagnosed before age 60 **AND** at least one first-degree relative with prostate cancer diagnosed before age 60
    - Low- or intermediate-risk localized prostate cancer concomitant with **ANY** of the following:

        - A personal history of breast, pancreatic, gastric, brain, melanoma, intestinal (colorectal or small bowel), or upper tract urothelial cancer(s)
        - A family history of pancreatic, gastric, brain, melanoma, intestinal cancer (colorectal or small bowel), or endometrial cancer diagnosed at or before age 50
        - A family history of upper tract urothelial cancer(s) in first- or second-degree relatives
- Family history suggests the possibility of a pathogenic variant related to increased risk of prostate cancer with **ANY** of the following:
    - Risk of a P/LP variant in BRCA1 or BRCA2 is ≥5% based on a validated predictive model
    - One or more first-, second- or third-degree blood relative with metastatic prostate cancer, or high or very high-risk grade group of localized or locally advanced prostate cancer
    - One or more first- or second-degree relatives with prostate cancer diagnosed before age 60 or who died of prostate cancer
    - Two or more first-degree relatives with prostate cancer regardless of age or stage
    - One or more first-, second- or third-degree blood relative with breast cancer diagnosed at or before age 50
    - One or more first-degree, second- or third-degree blood relative with multiple primary breast cancers (metachronous or synchronous)
    - One or more first-, second- or third-degree blood relatives with breast cancer in an individual assigned male sex at birth
    - One or more first-, second- or third-degree blood relative with epithelial ovarian, fallopian tube, or primary peritoneal cancer
    - Individuals with at least two first-degree blood relatives with pancreatic cancer
    - Two or more first-, second- or third-degree blood relatives on the same side of the family with invasive breast, ovarian, and/or prostate cancer regardless of age or stage
    - Ashkenazi Jewish descent or other similarly high ancestry-related risk **AND** at least one first-degree blood relative with breast cancer
    - Ashkenazi Jewish descent or other similarly high ancestry-related risk **AND** two or more second-degree blood relatives on the same side of the family with breast cancer or epithelial ovarian cancer

Known familial genetic testing for hereditary prostate cancer

Genetic testing of a single high-risk gene is medically necessary for individuals who have a first-, second- or third-degree relative with a known pathogenic variant in that gene.

Individuals requiring confirmatory testing

Individuals requiring confirmatory clinical germline testing of a specific gene or genes based on findings of BRCA1, BRCA2, CHEK2, PALB2, HOXB13, MLH1, MSH2, MSH6, PMS2, or EPCAM pathogenic or likely pathogenic germline variants found in other testing contexts including **ANY** of the following:

- 23andMe PGS (or similar FDA approved commercial direct-to-consumer testing)
- Somatic testing for malignancy
- IRB approved clinical research

Rationale

Germline testing for inherited pathogenic/likely pathogenic (P/LP) variants is important for selected individuals with prostate cancer to estimate cancer risks above the estimated 11% risk in the general population. Whereas ~5%–7% of men with early-stage prostate cancer are carriers[119], approximately 12% of unselected men with metastatic prostate cancer have been reported to carry germline P/LP variants in DNA repair genes, most frequently BRCA2 (5.3%), ATM (1.6%), CHEK2 (1.9%), and BRCA1 (0.9%).[120-122] Men with specific genetic P/LP variants can have a 2-fold to 10-fold increased risk of prostate cancer.[123] Men with germline BRCA2 P/LP variants have been associated with not only increased prostate cancer risk, but also higher mortality and younger age of diagnosis.[124] The major hereditary cancer syndromes linked to prostate cancer are hereditary breast and ovarian cancer, Lynch syndrome, and hereditary prostate cancer associated with HOXB13, but other less common cancer associations have also been described.[125] Various consensus guidelines have addressed criteria for germline testing in prostate cancer, including: ASCO 2025 Guidelines on Germline and Somatic Genomic Testing for Metastatic Prostate Cancer, EAU EANM ESTRO ESUR ISUP SIOG Guidelines on Prostate Cancer 2025, Cancer Care Ontario Hereditary Cancer Testing Eligibility Criteria 2024, the NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate, Version 3.2025, and others.[122, 126-128] Guideline statements with recommendations for germline testing include the AUA/SUO guideline[129], the Canadian Urological Association guideline[130], and the NCCN Genetic/Familial High-Risk Assessment guideline.[44] While germline genetic testing in prostate cancer is routinely recommended for selected individuals at elevated risk hereditary prostate cancer[131, 132], there remains uncertainty regarding which individuals should be tested and how they should be tested, and the overall quality of evidence is low.[133, 134] There are various focused multigene panels in common use, with a typical upper limit of 20 genes or fewer.[121, 126, 132, 135] The American Society of Clinical Oncology (ASCO) indicates in the germline genetic testing guideline that the most strongly recommended genes in a multigene panel for prostate cancer are BRCA1, BRCA2, EPCAM, HOXB13, MLH1, MSH2, MSH6, and PMS2.[9]

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Codes

The following code list is not meant to be all-inclusive. Authorization requirements will vary by health plan. Please consult the applicable health plan for guidance on specific procedure codes.

Specific CPT codes for services should be used when available. Nonspecific or not otherwise classified codes may be subject to additional documentation requirements and review.

CPT/HCPCS

May Be Medically Necessary When Criteria are Met

Code	May Be Medically Necessary When Criteria are Met
81162	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis (ie, detection of large gene rearrangements)
81163	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81164	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
81165	BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis

Code	May Be Medically Necessary When Criteria are Met
81166	BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
81167	BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
81201	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence
81202	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants
81203	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; duplication/deletion variants
81212	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated (eg, hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants
81215	BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant
81216	BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81217	BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant
81218	CEBPA (CCAAT/enhancer binding protein [C/EBP], alpha) (eg, acute myeloid leukemia), gene analysis, full gene sequence
81242	FANCC (Fanconi anemia, complementation group C) (eg, Fanconi anemia, type C) gene analysis, common variant (eg, IVS4+4A>T)
81288	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis
81292	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81293	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81294	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81295	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81296	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81297	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81298	MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81299	MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81300	MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81307	PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer) gene analysis; full gene sequence
81308	PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer) gene analysis; known familial variant
81310	NPM1 (nucleophosmin) (eg, acute myeloid leukemia) gene analysis, exon 12 variants
81317	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81318	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81319	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81321	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis
81322	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; known familial variant
81323	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; duplication/deletion variant
81334	RUNX1 (runt related transcription factor 1) (eg, acute myeloid leukemia, familial platelet disorder with associated myeloid malignancy) gene analysis, targeted sequence analysis (eg, exons 3-8)

Code	May Be Medically Necessary When Criteria are Met
81338	MPL (MPL proto-oncogene, thrombopoietin receptor) (eg, myeloproliferative disorder) gene analysis; common variants (eg, W515A, W515K, W515L, W515R)
81339	MPL (MPL proto-oncogene, thrombopoietin receptor) (eg, myeloproliferative disorder) gene analysis; sequence analysis, exon 10
81345	TERT (telomerase reverse transcriptase) (eg, thyroid carcinoma, glioblastoma multiforme) gene analysis, targeted sequence analysis (eg, promoter region)
81351	TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; full gene sequence
81352	TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; targeted sequence analysis (eg, 4 oncology)
81353	TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; known familial variant
81401	Molecular pathology procedure, Level 2 (eg, 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)
81403	Molecular pathology procedure, Level 4 (eg, 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)
81404	Molecular pathology procedure, Level 5 (eg, 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)
81405	Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)
81408	Molecular pathology procedure, Level 9 (eg, analysis of >50 exons in a single gene by DNA sequence analysis)
81432	Hereditary breast cancer-related disorders (eg, 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
81435	Hereditary colon cancer-related disorders (eg, 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
81437	Hereditary neuroendocrine tumor-related disorders (eg, medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma), genomic sequence analysis panel, 5 or more genes, interrogation for sequence variants and copy number variants
81441	Inherited bone marrow failure syndromes (IBMFS) (eg, Fanconi anemia, dyskeratosis congenita, Diamond-Blackfan anemia, Shwachman-Diamond syndrome, GATA2 deficiency syndrome, congenital amegakaryocytic thrombocytopenia) sequence analysis panel, must include sequencing of at least 30 genes, including BRCA2, BRIP1, DKC1, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, GATA1, GATA2, MPL, NHP2, NOP10, PALB2, RAD51C, RPL11, RPL35A, RPL5, RPS10, RPS19, RPS24, RPS26, RPS7, SBDS, TERT, and TINF2
81479	Unlisted molecular pathology procedure
0129U	Hereditary breast cancer-related disorders (eg, 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)
0235U	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions
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
S3840	DNA analysis for germline mutations of the RET proto-oncogene for susceptibility to multiple endocrine neoplasia type 2
S3841	Genetic testing for retinoblastoma
S3842	Genetic testing for von Hippel-Lindau disease

Not Medically Necessary

Code	Not Medically Necessary
0101U	Hereditary colon cancer disorders (eg, Lynch syndrome, *PTEN* hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis), genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and 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])

Code	Not Medically Necessary
0102U	Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and array CGH, with MRNA analytics to resolve variants of unknown significance when indicated (17 genes [sequencing and deletion/duplication])
0103U	Hereditary ovarian cancer (eg, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and array CGH, with MRNA analytics to resolve variants of unknown significance when indicated (24 genes [sequencing and deletion/duplication], *EPCAM* [deletion/duplication only])
0130U	Hereditary colon cancer disorders (eg, 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)
0133U	Hereditary prostate cancer–related disorders, targeted mRNA sequence analysis panel (11 genes)
0134U	Hereditary pan cancer (eg, hereditary breast and ovarian cancer, hereditary endometrial cancer, hereditary colorectal cancer), targeted mRNA sequence analysis panel (18 genes)
0136U	ATM (ataxia telangiectasia mutated) (eg, ataxia telangiectasia) mRNA sequence analysis
0137U	PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer) mRNA sequence analysis
0138U	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) mRNA sequence analysis
0157U	APC (APC regulator of WNT signaling pathway) (eg, familial adenomatosis polyposis [FAP]) mRNA sequence analysis
0158U	MLH1 (mutL homolog 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) mRNA sequence analysis
0159U	MSH2 (mutS homolog 2) (eg, hereditary colon cancer, Lynch syndrome) mRNA sequence analysis
0160U	MSH6 (mutS homolog 6) (eg, hereditary colon cancer, Lynch syndrome) mRNA sequence analysis
0161U	PMS2 (PMS1 homolog 2, mismatch repair system component) (eg, hereditary nonpolyposis colorectal cancer, Lynch syndrome) mRNA sequence analysis
0162U	Hereditary colon cancer (Lynch syndrome), targeted mRNA sequence analysis panel (MLH1, MSH2, MSH6, PMS2)
0474U	Hereditary pan-cancer (eg, hereditary sarcomas, hereditary endocrine tumors, hereditary neuroendocrine tumors, hereditary cutaneous melanoma), genomic sequence analysis panel of 88 genes with 20 duplications/deletions using next-generation sequencing (NGS), Sanger sequencing, blood or saliva, reported as positive or negative for germline variants, each gene
0475U	Hereditary prostate cancer-related disorders, genomic sequence analysis panel using next-generation sequencing (NGS), Sanger sequencing, multiplex ligation-dependent probe amplification (MLPA), and array comparative genomic hybridization (CGH), evaluation of 23 genes and duplications/deletions when indicated, pathologic mutations reported with a genetic risk score for prostate cancer

ICD-10 Diagnosis

Refer to the ICD-10 CM manual

History

Status	Review Date	Effective Date	Action
Revised	07/17/2025	04/04/2026	Independent Multispecialty Physician Panel (IMPP) review. Revised indications for adenomatous polyp syndromes (expansive), Peutz-Jeghers syndrome (expansive), Cowden syndrome – renamed to PTEN-hamartoma tumor syndrome, includes Cowden syndrome (expansive), Lynch syndrome (expansive), hereditary diffuse gastric cancer (new section), Li-Fraumeni syndrome (expansive), hereditary breast cancer (expansive), multigene panel for HBOP (specify 20 or fewer genes), endocrine neoplasms (expansive), hereditary myeloid neoplasms (expansive new section), hereditary brain tumors (expansive new section), kidney cancer (expansive), prostate cancer (restrictive). Added CPT codes 81218, 81310, 81334, 81338, 81339, and 81345 (MNWCM) and moved 81441 and 81242 from NMN to MNWCM list.
Updated codes 01/01/2026	n/a	Unchanged	CPT code update: removed termed codes 0131U, 0132U, 0135U (NMN).
Revised	01/30/2025, 07/16/2024	03/23/2025	IMPP review. Expanded criteria for confirmatory genetic testing, removed requirement that alternate biochemical tests not available. Revised indications for adenomatous polyp syndromes (expansive), juvenile polyposis syndrome (restrictive), Cowden syndrome (expansive), Lynch syndrome (expansive), Li-Fraumeni syndrome (expansive/ restrictive); HBOP criteria divided into categories by disease, clarified statement about BRCA risk models, personal history distinguished from family history, hereditary breast cancer (expansive), multigene panel for HBOP (expansive/restrictive); melanoma (expansive), nevoid basal cell syndrome (expansive), endocrine neoplasms (expansive), kidney cancer (expansive), prostate (expansive/restrictive). Clarifications throughout. Added references.
Updated codes 01/01/2025	n/a	Unchanged	CPT code update: removed termed codes 81433, 81436, 81438 (MNWCM). Revised long descriptions for 81432, 81435, 81437.
Updated codes 10/01/2024	n/a	Unchanged	Added CPT codes 81403 and 81479 (MNWCM).
Revised	10/23/2023	06/30/2024 (new codes 07/01/2024)	IMPP review. Expanded indications for Li-Fraumeni syndrome, HBOP cancer (including multigene panel testing), melanoma, and prostate cancer. Clarified testing is not medically necessary for serrated polyposis syndrome (SPS) and hereditary mixed polyposis syndrome (GREM1-associated mixed polyposis). Updated references. Added CPT code 0129U (MNWCM). Added new CPT codes effective 07/01/2024: 0474U, 0475U (NMN).
Updated codes 03/17/2024	n/a	Unchanged	Split code list into those considered medically necessary when criteria are met (MNWCM) and not MN. Added HCPCS codes S3841 and S3842 (MNWCM). Removed CPT codes 81309 and 81403. Added required language to General Clinical Guideline per new Medicare regulations.
Revised	04/12/2023	11/05/2023	IMPP review. Adenomatous polyp syndromes – clarified criteria. HBOP cancer, BRCA1/2 testing – for women, added mutation assessment tools; raised age of breast cancer diagnosis to 50 for first-degree relatives; additional clarifications to criteria for men. Added reference.
Created	08/29/2022	02/12/2023	IMPP review. Original effective date.