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Clinical Appropriateness Guidelines

Genetic Testing

Appropriate Use Criteria: Hereditary Cancer Testing

Key to Revisions	Indicates
<u>Blue underline</u>	Insertion
Red strikethrough	Deletion

Proprietary

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Table of Contents

Description and Application of the Guidelines	3
General Clinical Guideline	4
Clinical Appropriateness Framework	4
Simultaneous Ordering of Multiple Diagnostic or Therapeutic Interventions	4
Repeat Diagnostic Intervention	4
Repeat Therapeutic Intervention	5
Hereditary Cancer Testing	6
General Recommendations	6
Genetic Counseling	6
Clinical Indications	7
General Requirements	7
Germline pathogenic variants not otherwise specified*	7
Condition-Specific Requirements	8
Adenomatous polyp syndromes	8
Hamartomatous polyposis syndromes	10
Serrated polyposis syndrome (SPS)	12
Hereditary mixed polyposis syndrome (GREM1-associated mixed polyposis)	13
Lynch syndrome	13
Li-Fraumeni syndrome	15
Hereditary breast, ovarian, and pancreatic cancer (HBOP)	17
Melanoma	22
Nevoid basal cell carcinoma syndrome	23
Endocrine neoplasms	24
Kidney cancer	25
Prostate cancer	26
References	27
Codes	29
History	32

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. As used by Carelon, the Guidelines establish objective and evidence-based criteria for medical necessity determinations where possible. In the process, multiple functions are accomplished:

- To establish criteria for when services are medically necessary (i.e., in general, shown to be effective in improving health outcomes and considered the most appropriate level of service)
- 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 advocate for 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 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. Relevant citations are included in the References section attached to each Guideline. Carelon reviews all of its Guidelines at least annually.

Carelon makes its Guidelines publicly available on its website twenty-four hours a day, seven days a week. Copies of the Carelon Clinical Appropriateness Guidelines are also available upon oral or written request. 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.

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. If requested by a health plan, Carelon will review requests based on health plan medical policy/guidelines in lieu of the Carelon Guidelines.

Pharmaceuticals, radiotracers, or medical devices used in any of the diagnostic or therapeutic interventions listed in the Guidelines must be FDA approved or conditionally approved for the intended use. However, 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 should outweigh any potential harms that may result (net benefit).
- Current literature and/or standards of medical practice should support that the recommended intervention offers the greatest net benefit among competing alternatives.
- Based on the clinical evaluation, current literature, and standards of medical practice, there exists a reasonable likelihood that the intervention will change management and/or lead to an improved outcome for the patient.

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 supersede the requirements set forth above. During the peer-to-peer conversation, factors such as patient acuity and setting of service may also be taken into account.

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.

Hereditary Cancer Testing

General Recommendations

Genetic Counseling

~~Genetic c~~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](#)
- ~~Interpretation of family and medical histories to assess the probability of 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

~~Post-test counseling for any positive screening test~~

[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~~ ~~clia~~ 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. (Burke, 2014, #1). ~~(Kneb, 2010, #2)~~ [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.](#) (Resta, 2006, #3)

[It is also recognized that the 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.](#) (CDC, 2020, #4)

[Genomic technologies generate large amounts of data, and this increases the potential for uncertainty in managing and adapting to this information.](#) (Borno, 2020, #5) [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.](#) (Borno, 2020, #5, Patch, 2018, #6) [Uncovering incidental findings and being overwhelmed with information are important barriers to genetic testing, particularly among vulnerable patient subgroups.](#) (Borno, 2020, #5) [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.](#)

~~Genetic counselors provide a patient-centered contribution to the care of individuals who are undergoing genetic testing. Genetic counseling is a communication process aimed at helping people understand and adapt to the medical, psychological, and familial implications of genetic contributions to disease. (Patch, 2018, #6) Genetic counselors have advanced training in medical genetics and counseling which helps guide and support patients seeking more information about how inherited diseases and conditions might affect them or their families. This expertise is also applied to interpret genetic test results based on an individual's personal and family history. Genetic counselors are often specialized in oncology.~~

The current literature demonstrates the clinical value of genetic counselor involvement in service delivery, including improvements in clinical management and positive psychological impact along with increased patient engagement. Physicians have varying levels of knowledge on how to interpret genetic and genomic information, and often express low confidence and high uncertainty in counseling about genetic testing findings.(Gray, 2014, #7) Professional genetic counselors add unique value to the existing care team. For example, a study of the accuracy of routine prenatal genetic screening in patients referred for genetic counseling found that genetic history obtained by the referring provider was missing detail in over half, and of these approximately 40% had their clinical care changed by discovery of this information by a genetic counselor.(Gilstrop Thompson, 2020, #8) Similarly, rates of family history documentation and referral to genetic testing in a multidisciplinary breast cancer clinic have been shown to significantly improve with the addition of a genetic counselor.(Kishan, 2016, #9) Moreover, genetic counseling for breast cancer patients has been shown to impact beneficial changes in cancer-related knowledge, distress, and decisional conflict.(Christie, 2012, #10) In the gastrointestinal cancer risk assessment setting, genetic counseling has been shown to improve patient engagement in the realms of commitment, navigation, and informed choice.(Zakas, 2019, #11) In regards to newborn screening, the unique and valuable services of genetic counselors have been shown to add efficiency to the diagnostic resolution process.(Langfelder-Schwind, 2019, #12) And in the pediatric setting, even when a medical geneticist is involved in the care, the addition of a genetics counselor significantly improves adherence to medical management.(Rutherford, 2014, #13) These are only a small sample of the literature that exists clearly demonstrating the value of genetic counseling.

In the past decade, there has been explosive growth in the number of genetic tests available, the number and types of companies involved in providing these tests, diversity of the business models involved, and the diverse settings where genetic tests are accessed by consumers. There is access to some kinds of testing through direct-to-consumer channels, but most of the healthcare-associated testing is from full-service commercial laboratories, for-profit specialized laboratories, or not-for-profit laboratories, such as those associated with academic medical centers.(Scheuner, 2021, #14) While laboratory business models vary widely, there is increasing interest in use of de-identified data from genetic testing for use in research and discovery and other business purposes beyond the application to individual patient care. These other uses of genetic information have partly fueled a trend for broader indications for testing and testing of larger panels of genes. Furthermore, while genetic counselors have traditionally been trained to counsel patients in healthcare settings prior to germline testing for diseases with a Mendelian inheritance pattern, their education and skills can also be readily adapted to other settings. Genetic testing services are now delivered both in person and via telehealth, and counselors may be employed not only by healthcare institutions but also by laboratories working under various distinct business models.

Genomic technologies generate large amounts of data, and this increases the potential for uncertainty in managing and adapting to this information. 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.(Pollard, 2019, #15) Uncovering incidental findings and being overwhelmed with information are important barriers to somatic testing, particularly among vulnerable patient subgroups.(Borno, 2020, #5) Genetic counseling is an invaluable resource for patients undergoing germline or somatic genetic testing, but there are practical limitations because of the scarcity of genetic counselors relative to the current need. Clinicians are often required to stretch their skillsets and play a role in providing basic counseling about genetic testing and will need more training and skills to do so effectively. Further research is needed regarding the use of clinical practice tools to enhance patient care and uphold the clinical and ethical ideals of medical care in this complicated realm of care delivery.

The use of genetic counseling by professionals not employed by testing laboratories is strongly recommended for a wide variety of common clinical scenarios across all realms of medicine. Genetic counseling is considered mandatory for a subset of clinical scenarios related to germline or somatic testing where the stakes are predictably high in terms of the potential medical and psychological consequences of the testing process. The specific scenarios for which genetic counseling is mandatory and the minimum expected qualifications for genetic counseling providers may vary by health plan.

Clinical Indications

General 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) or suspected to have a known genetic condition [or is known to have been inadequately tested for a suspected genetic condition](#)
- Scientific literature has established that one or more genes have pathogenic variability associated with the genetic condition
- A biochemical or alternative test has been performed but the results are indeterminate, **OR** the genetic disorder cannot be identified through biochemical or other testing
- 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

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.(Berwick, 2021, #16)

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.(Hayes, 2021, #17) The term clinical utility was elaborated by ACCE project that was carried out by the Foundation for Blood Research with support from the CDC.(Grosse, 2006, #18) 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.(Grosse, 2006, #18) 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.(Hayes, 2021, #17) While there are no strict definitions for clinical utility in tumor biomarker testing, common study designs used to establish a basis for clinical utility are prospective clinical trials that directs patient management (the gold standard) and sometimes prospective/retrospective studies with archived specimens.

Condition-Specific Requirements

Adenomatous polyp syndromes

Germline genetic testing of the APC gene and/or MUTYH gene variants for susceptibility to invasive cancer due to adenomatous polyp syndromes is considered **medically necessary** when **EITHER** of the following criteria are met:

- The individual has a personal history of more than 10 cumulative colorectal adenomas
- The individual's family history and/or clinical findings are suggestive of an inherited polyposis syndrome

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.(Macaron, 2015, #19) The adenomatous polyposis syndromes comprise familial adenomatous polyposis (FAP), MUTYH-associated polyposis (MAP). The 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. (Boland, 2022, #20)

Adenomatous polyp syndromes

The American Society of Colon and Rectal Surgeons (ASCRS) Clinical Practice Guidelines for the Management of Inherited Polyposis Syndromes recommends that polyposis syndromes should typically be considered in patients with greater than 20 lifetime adenomas, patients with a personal history of desmoid tumor or other extracolonic manifestations of FAP, or family members of individuals with known FAP, AFAP, or MAP. This is a strong recommendation based on low-quality evidence. (Herzig, 2017, #21) 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 the 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). The clinical question to answer is the threshold of cumulative adenoma numbers at which genetic testing should be sought. 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 use a lower threshold for germline genetic testing recommending that patients with multiple colorectal adenomas (>10) should be considered for panel germline genetic testing.

Major guidelines addressing the thresholds for testing and relevant genes to be included 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 mutation analysis." (Syngal, 2015, #22)

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]" (Stjepanovic, 2019, #23)

"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]" (Stjepanovic, 2019, #23)

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." (National Comprehensive Cancer Network (NCCN), #24)

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)." (Tomita, 2021, #25)

ASCRS: "The diagnosis of MAP should be considered in patients presenting with colorectal polyposis (>20 lifetime adenomas). Grade of Recommendation: Strong recommendation based on low-quality evidence, 1C." (Herzig, 2017, #21)

"The number of polyps may not correlate with the prevalence of biallelic MYH mutations as well as it does with APC mutations, making it difficult to recommend screening for MAP based on a specific number of polyps. Although many reports cite a threshold of 10 polyps as an indication for genetic testing, the National Comprehensive Cancer Network guidelines have moved to a threshold of 20 polyps.^{2-6,13,47,50} While acknowledging the limited evidence supporting a specific polyp number cutoff, consideration for genetic testing for MAP should be given in most patients with >20 lifetime adenomas." (Herzig, 2017, #21)

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.”(Hampel, 2015, #26)

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:

- Three 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
- Individual is a first- or second-degree relative of a patient suspected of having or diagnosed with juvenile polyposis syndrome

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 small intestine
- Characteristic mucocutaneous pigmentation of the mouth, lips, nose, eyes, genitalia, or fingers
- Family history of Peutz-Jeghers syndrome

Cowden syndrome

Genetic testing for PTEN pathogenic variants to evaluate for Cowden syndrome is considered **medically necessary** when **BOTH** of the following criteria are met:

- **EITHER** of the following pathognomonic criteria are present:
 - Adult Lhermitte-Duclos disease (cerebellar tumors)
 - Multiple mucocutaneous lesions including **ANY** of the following:
 - Three or more trichilemmomas, at least one of which is biopsy-proven
 - 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
- **THREE** (3) or more of the following conditions are present:
 - Breast cancer
 - Fibrocystic disease of the breast
 - Non-medullary thyroid cancer
 - Thyroid adenoma or multinodular goiter
 - Endometrial cancer
 - Genitourinary tumors

- Genitourinary malformations or testicular lipomatosis
- 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 ($\geq 97^{\text{th}}$ percentile: 58 cm for adult women, 60 cm for adult men)
- Macular pigmentation of the glans penis

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), Peutz-Jeghers syndrome (PJS), and the PTEN-hamartoma tumor syndrome (PHTS). The PHTS includes Cowden syndrome (in adults) and Bannayan-Riley-Ruvalcaba syndrome (BRRS) in pediatric populations, both sharing a common etiology of germline PTEN pathogenic variant (Tan, 2011, #27) and Proteus syndrome. 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. Peutz-Jeghers syndrome (PJS) is caused by mutations in the STK11 gene and is characterized by mucocutaneous hyperpigmentation of the mouth, lips, nose, eyes, genitalia, or fingers; multiple hamartomatous polyps in the GI tract; and increased risks for colorectal (39% between ages 15 and 64), pancreatic (36%), gastric (29%), and small intestinal (13%) cancers. In addition, there are increased risks for breast cancer (54%), ovarian sex cord tumors with annular tubules (21%), and adenoma malignum of the cervix (10%) and the testes, especially Sertoli cell tumors (9%). PJ polyps are hamartomatous with glandular epithelium supported by smooth muscle cells contiguous with the muscularis mucosa." (Hampel, 2015, #26)

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

NCCN (National Comprehensive Cancer Network (NCCN), #24): 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.
- 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.
- NCCN recommends evaluation for Cowden/PTEN hamartoma tumor syndrome in patients with 2 or more hamartomatous polyps.

ACMG/NSGC (Hampel, 2015, #26): "JPS testing should be considered for any individual with a personal history of or first-degree relative with

- three to five cumulative histologically proven juvenile GI polyps
- any number of juvenile GI polyps with a positive family history of juvenile polyposis syndrome; or
- multiple juvenile polyps located throughout the GI tract.”

Danish Guidelines(Jelsig, 2021, #28): “Referral criteria for genetic work-up and counseling – number of polyps is the cumulative number. Hamartomatous polyps (including Peutz-Jeghers – and juvenile polyps):

- a personal history of 1 or more Peutz-Jeghers polyp(s)
- a personal history of 2 or more juvenile polyps
- a family history of Peutz-Jeghers Syndrome or Juvenile Polyposis Syndrome
- a history of 1 or more hamartomatous polyps and one or more extraintestinal manifestation(s), e.g. macrocephaly, mucocutaneous pigmentations, telangiectasias, epistaxis, thoracic aortic dilation, trichilemmomas, papillomatous lesions, acral keratoses, breast-, thyroid-, and/or endometrial cancer”

ACG(Syngal, 2015, #22): Indications for PJS genetic testing:

- “Individuals with perioral or buccal pigmentation and/or two or more histologically characteristic GI hamartomatous polyp(s) or a family history of PJS should be evaluated for PJS.”
- “Genetic evaluation of a patient with possible PJS should include testing for STK11 mutations.”
- “Individuals with five or more juvenile polyps in the colorectum or any juvenile polyps in other parts of the GI tract should undergo evaluation for PJS.”

Patients at risk for JPS are defined as **ANY** of the following:

- 5 or more colorectal juvenile polyps
- Any juvenile polyps in parts of the GI tract other than the colon or rectum
- Any number of juvenile polyps in an individual with a family history of JPS
- Individuals with a family history of JPS

“Individuals with multiple GI hamartomas or ganglioneuromas should be evaluated for CS [Cowden syndrome] and related conditions.”(Syngal, 2015, #22)

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.(Meester, 2020, #29)

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(National Comprehensive Cancer Network (NCCN), #24)

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.(Meester, 2020, #29) 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.”(National Comprehensive Cancer Network (NCCN), #24)

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 mutations may be considered for SPS patients with concurrent adenomas and/or a family history of adenomas.(Syngal, 2015, #22)

ACMG/NSGC: No causative mutations 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.(Hampel, 2015, #26)

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.(Lieberman, 2017, #30) 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.(National Comprehensive Cancer Network (NCCN), #24)

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.”(Syngal, 2015, #22)

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.”(Hampel, 2015, #26)

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:

- Known Lynch syndrome pathologic variant in a first- or second-degree relative
- Personal history of a tumor with MMR deficiency based on somatic testing of MLH1, MSH2, MSH6, PMS2, or EPCAM genes

- 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 validated predictive models (e.g., MMRpro, PREMM, MMRpredict)
- Personal history of colorectal or endometrial 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
 - Family history of Lynch syndrome-related cancer in **EITHER** of the following scenarios:
 - At least one first- or second-degree relative diagnosed before age 50 years
 - Two or more first- or second-degree relatives diagnosed at any age
- 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 relative with colorectal or endometrial cancer and another Lynch syndrome-related cancer
 - Two or more first- or second-degree relatives with Lynch syndrome-related cancers, with at least one diagnosed before 50
 - Three or more first- or second-degree relatives with Lynch syndrome-related cancers

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. (Sinicrope, 2018, #31) 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.

MMR testing through immunohistochemistry (IHC) or microsatellite instability (MSI) is consistently recommended for all newly diagnosed patients with colorectal cancer by multiple, high-quality evidence-based and consensus-based guidelines.

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 \geq 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." (Giardiello, 2014, #32)

ACG: "All newly diagnosed colorectal cancers (CRCs) should be evaluated for mismatch repair deficiency." (Syngal, 2015, #22)

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. (Stoffel, 2015, #33)

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. (Holter, 2022, #34)

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). (Sinicrope, 2018, #31, Stoffel, 2015, #33) 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.” (National Comprehensive Cancer Network (NCCN), #24)

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 $\geq 5\%$ chance of LS based on risk prediction models should undergo genetic evaluation for LS.” (Syngal, 2015, #22)

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).” (Stoffel, 2015, #33)

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.”](#) (National Comprehensive Cancer Network (NCCN), #24) “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” (National Comprehensive Cancer Network (NCCN), #24)

[Also of note, as it relates to the use of PREMM5 score thresholds, typically accepted at \$\geq 5\%\$, when lower thresholds are accepted \(e.g., \$\geq 2.5\%\$ \), 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.” (Hampel, 2015, #26)

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 (National Comprehensive Cancer Network (NCCN), #24) recommend testing focused on the specific pathogenic variant.

Li-Fraumeni syndrome

Testing for pathogenic or likely pathogenic variants of TP53 is considered **medically necessary** for individuals at risk based on **ANY** of the following (per the Chompret criteria, updated in 2015):

- Breast cancer diagnosed at age 30 or younger
- Breast cancer diagnosed at age 45 or younger 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 age 45 or younger 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 age 45 or younger
- Personal history of adrenocortical carcinoma, choroid plexus carcinoma, or embryonal anaplastic rhabdomyosarcoma
- Patient who has had a pathogenic or likely pathogenic variant of TP53 identified on tumor genomic testing
- [Individuals with at least one first-, second-, or third-degree relative with a known TP53 variant](#)

Rationale

The transcription factor p53 (TP53) acts as a guardian of the genome (Frebourg, 2020, #35) 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 variants in the tumor suppressor gene TP53 (McGee, 2018, #36) 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. (Mai, 2017, #37)

The prevalence of TP53 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. (Schrader, #38, de Andrade, 2017, #39) However, affected individuals are at very high risk of malignancy. In an observational cohort study was done in 480 carriers of pathogenic or likely pathogenic germline 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), with the highest comparative incidence from childhood to 30 years of age. The overall cancer incidence remained 10.3 (95% CI 7.9-13.2) times higher than that of the general population after age 50 years. (de Andrade, 2019, #40) Because the TP53 gene is currently included in broad panels used in genetic testing, the number of TP53 tests performed in non-suggestive clinical situations has significantly increased. Whereas the interpretation of TP53 variants predicted to result in loss of function, such as nonsense or frameshift deletions or insertions, is usually obvious, the interpretation of missense variants, representing the majority, is often challenging and requires specific expertise. (Frebourg, 2020, #35)

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. 5-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 ($p=0.0132$). (Villani, 2016, #41) A substantial proportion of tumors identified by surveillance were low-grade or premalignant lesions. It is not clear whether or not 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 ~~criteria, called~~ the Chompret criteria, for LFS to cover the different clinical presentations associated with germline TP53 pathogenic variants and to facilitate its clinical recognition. (Chompret, 2001, #42) These criteria have since been updated in 2009 and 2015. The most recent series, involving 1730 French patients selected on the basis of existing clinical criteria suggestive of LFS, showed that it is possible to distinguish different classes of 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.(Bougeard, 2015, #43)

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 guidelines:

NCCN: In the NCCN guidelines for [Hereditary eColorectal eCancer](#), no specific recommendations are made regarding testing for LFS. While there is a well-established increased risk of CRC in LFS, the core malignancies associated with LFS include non-Ewing sarcoma, adrenocortical cancer, breast cancer, and choroid plexus cancer.(National Comprehensive Cancer Network (NCCN), #24) [Within the Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic Practice Guidelines, testing criteria for LFS are made, to include already-mentioned criteria above, in addition to individuals "...from a family with a known TP53 P/LP variant."](#)(National Comprehensive Cancer Network (NCCN), 2023, #44)

ACMG/NSGC: A consensus-based guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors recommends consideration of LFS in patients with colorectal cancer and one additional tumor associated with LFS, one diagnosed at age 45 or younger.(Hampel, 2015, #26)

Hereditary breast, ovarian, and pancreatic cancer (HBOP)

BRCA1 and BRCA2

[Germline genetic testing for known familial pathogenic variants of BRCA1 or BRCA2 is considered **medically necessary** in the following scenarios:](#)

- [Any first-, second-, or third-degree relative who has a known BRCA1 or BRCA2 pathogenic variant, where the results will influence reproductive decision-making or decision-making about cancer screening](#)

Germline genetic testing panels ([see multi-gene panel testing*](#)) that include BRCA1 and BRCA2 are considered **medically necessary** to aid in current systematic therapy and surgical decision-making in the following scenarios:

- Personal history of cancer in [individuals assigned female sex at birth](#)~~women~~ with **ANY** of the following:
 - Epithelial ovarian cancer
 - Pancreatic adenocarcinoma
 - Breast cancer and **ANY** of the following:
 - [Diagnosis at age 50 years or younger](#)
 - Triple negative breast cancer
 - ~~Bilateral breast cancer~~[Multiple primary breast cancers \(synchronous or metachronous\)](#)
 - [Lobular breast cancer concomitant with personal or family history of hereditary diffuse gastric cancer](#)
 - ~~Diagnosis at age 50 years or younger~~
 - Ashkenazi Jewish ethnicity
 - [At least ~~One or more~~ first- or second-degree relatives](#) with epithelial ovarian cancer
 - [At least one first-degree relative with metastatic prostate cancer or high risk localized prostate cancer](#)
 - Two or more first- or second-degree relatives on the same side of the family with breast cancer

- ~~At least One or more~~ first- or second-degree relative with breast cancer diagnosed at age 50 years or younger
- ~~At least One or more~~ first- or second-degree male relative with breast cancer
- ~~One or more first-, second-, or third-degree relative with a known BRCA1 or BRCA2 pathogenic variant~~
- Two or more first- or second-degree relatives on the same side of the family with pancreatic adenocarcinoma
- ~~At least One or more~~ first- or second-degree relatives with bilateral breast cancer or two breast primaries
- Personal history of breast or pancreatic cancer in individuals assigned male sex at birth ~~men~~
- Individuals assigned female sex at birth ~~Women~~ with **ANY** of the following risk profiles:
 - Inherited cancer susceptibility as determined by a validated BRCA1 or BRCA2 mutation assessment tool, including any of the following tools: Ontario Family History Assessment Tool; Manchester Scoring System; Referral Screening Tool; Pedigree Assessment Tool; 7-Question Family History Screening Tool; International Breast Cancer Intervention Study Instrument [Tyrer-Cuzick]; or BRCAPRO [brief version]
 - ~~At least One or more~~ first-degree relatives with breast cancer diagnosed at age 50 years and younger
 - ~~At least One or more~~ first- or second-degree relative with epithelial ovarian, fallopian tube, or primary peritoneal cancer
 - ~~At least One or more~~ first-degree relatives with ~~bilateral breast cancer~~ multiple primary breast cancers (metachronous or synchronous)
 - ~~At least One or more~~ male first- or second-degree relatives with breast cancer
 - ~~One or more first- or second-degree relatives with both breast and epithelial ovarian cancer~~
 - ~~One or more first-, second-, or third-degree relatives with a known BRCA1 or BRCA2 pathogenic variant~~
 - ~~One or more first- or second-degree relatives on the same side of the family with breast cancer AND one or more first- or second-degree relatives on the same side of the family with epithelial ovarian cancer~~
 - Two or more first- or second-degree relatives on the same side of the family with breast cancer, one of whom was diagnosed at age 50 years and younger
 - Two or more first- or second-degree relatives on the same side of the family with breast cancer or prostate cancer with Gleason grade group 2 or higher
 - Three or more first- or second-degree relatives on the same side of the family with breast cancer
 - ~~Three or more first- or second-degree relatives from the same side of the family with breast or high-grade prostate cancer~~
 - Ashkenazi Jewish descent **AND** ~~one or more~~ at least one first-degree relatives with breast cancer
 - Ashkenazi Jewish descent **AND** two or more second-degree relatives on the same side of the family with breast or epithelial ovarian cancer
 - ~~Men~~ with **EITHER** of the following risk profiles:
 - ~~Two or more first-degree relatives with pancreatic cancer~~

- ~~Any first-, second-, or third-degree relative who has a known BRCA1 or BRCA2 pathogenic variant, where the results will influence reproductive decision-making~~
- Individuals with at least ~~familial pancreatic cancer (defined as having two or more first-degree relatives with pancreatic cancer)~~
- Individuals with at least one first- or second-degree relative with epithelial ovarian cancer
- Confirmatory testing of persons with positive BRCA1/BRCA2 variants on 23andMe Personal Genome Service (PGS) Genetic Health Risk Report ~~(single site testing only)~~ or other commercial entities demonstrating genetic susceptibility based on findings in high penetrance genes related to breast, ovarian, or pancreatic cancer

Note: A positive BRCA1/BRCA2 pathogenic variant identified by 23andMe PGS (or similar commercial direct-to-consumer test) in any individual or first-degree relative requires diagnostic confirmation to be considered.

- Focused confirmatory testing for germline genomic analysis demonstrating genetic susceptibility based on specific findings of pathogenic variants found the **context of somatic testing for malignancy** related to genes (noted in Tables 1, 2, and 3) associated with breast, ovarian, or pancreatic cancer
- Confirmatory testing for germline genomic analysis demonstrating genetic susceptibility based on pathogenic variants found related to breast, ovarian, or pancreatic cancer (noted in Tables 1, 2, and 3) when the findings are discovered in the **context of IRB-approved clinical research** in which the individual being tested has consented to be performed
- Current candidates for poly (ADP-ribose) polymerase (PARP) therapy if found to have pathogenic variants in BRCA1 or BRCA2
- Diagnosis of Li-Fraumeni syndrome or Cowden syndrome (PTEN Hamartoma tumor syndrome) with or without a personal history of cancer

***Multi-Gene Panel Testing**

Germline genetic testing which includes additional pathogenic variants related to breast, ovarian, or pancreatic cancer (see Tables 1, 2, and 3, respectively, for details) 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 pathological variants associated with significantly increased risk for breast and/or associated cancers along with established management implications
- Genes included in the panel are associated with clear treatment and or surveillance options

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

Table 1. Genetic testing for genes associated with elevated risk of breast carcinoma

<u>Gene – Breast Carcinoma</u>	<u>Cancer / Syndrome</u>
ATM	Breast, <u>Ovarian</u> , <u>Pancreatic</u>
<u>BARD1</u>	<u>Breast</u>
BRCA1 and BRCA2	Breast, Ovarian, Pancreatic
CDH1	Hereditary diffuse gastric cancer, <u>Breast</u>
CHEK2	Breast
PALB2	Breast (male and female), Ovarian, Pancreatic
PTEN	PTEN hamartoma tumor syndrome, <u>Breast</u>
<u>RAD51C, RAD51D</u>	<u>Breast</u> , <u>Ovarian</u>
STK11	Peutz-Jeghers syndrome, <u>Breast</u> , <u>Pancreatic</u>
TP53	Li-Fraumeni syndrome, <u>Breast</u> , <u>Pancreatic</u>

Table 2. Genetic testing for genes associated with elevated risk of epithelial ovarian cancer

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

Table 3. Genetic testing for genes associated with elevated risk of pancreatic adenocarcinoma

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

~~Table 1. Genetic testing for genes associated with risk of breast cancer~~

Gene	Cancer / Syndrome
ATM	Breast
BRCA1 and BRCA2	Breast / Ovarian / Pancreatic
CDH1	Hereditary diffuse gastric cancer
CHEK2	Breast

Gene	Cancer / Syndrome
PALB2	Breast (male and female) / Ovarian / Pancreatic
PTEN	PTEN hamartoma tumor syndrome
STK11	Peutz-Jeghers syndrome
TP53	Li-Fraumeni syndrome

Rationale

Overall, there are 13 genes associated with elevated lifetime risks of hereditary breast and ovarian cancer. (Sessa, 2023, #45) 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. (Kuchenbaecker, 2017, #46) Pathogenic variants in these genes carry increased risks of male-breast, pancreatic, and stomach cancers; in addition, male BRCA2 carriers are also at increased prostate cancer risk. There were no strong associations found with risks of other cancers. (Li, 2022, #47) 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. (Domchek, 2010, #48) 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. (Hartmann, 2016, #49) 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. (Liu, 2022, #50) Overall, about 6% of breast cancer patients harbor pathogenic variants in hereditary breast and ovarian cancer (HBOC) genes. 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. (Sessa, 2023, #45) 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 also PALB2 carriers with estrogen receptor negative invasive breast cancer. (Yadav, 2023, #51) Such findings influence the screening and surveillance approach to affected individuals.

Germline genetic testing has become an integral part of the care of patients with breast and ovarian cancer for over 20 years, and testing guidelines have evolved as key patient subgroups such as triple-negative breast cancer, pancreatic cancer, and selected patients with prostate cancer. (Kurian, 2019, #52) 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. (Guzauskas, 2023, #53) Moreover, germline BRCA1/2 pathogenic variants have been found to be a valid predictive biomarker of response to there are now data driving specific therapy with use of poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitor therapy indicated specifically for patients with germline BRCA1/2 pathogenic variants. For example, in the OlympiA study, a large phase 3, double-blind, randomized controlled trial, patients with HER2-negative early breast cancer with BRCA1 or BRCA2 germline pathogenic or likely pathogenic 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. (Tutt, 2021, #54) 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 (Henry, 2022, #55), 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. (Andre, 2022, #56)

Despite the importance of knowing BRCA status, multiple studies have demonstrated that there is substantial undertesting of BRCA1 and BRCA2. (Kurian, 2019, #52, Cham, 2022, #57, Childers, 2017, #58) 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. (Owens, 2019, #59) 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. In regards to 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 (Robson M, PMID #10464625). Of note, founder mutations can also be found in other populations too, including in Latin America (Ossa CA, PMID #27286788), the Bahamas (Akbari MR, PMID # 23458327), Nepal (Mehta A, PMID #356987740), 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%-95%) 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 males 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 8-additional genes (~~BRCA1, BRCA2~~, PALB2, BARD1, RAD51C, RAD51D, ATM, and CHEK2, PTEN, STK11, BRIP1, CDH1, and P53) have been found to have significant association with breast cancer based on ~~two large~~ case-control studies that analyzed the associations between a number of cancer susceptibility genes and breast cancer risk. (Sessa, 2023, #45, Dorling, 2021, #60, Hu, 2021, #61) 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. (Narod, 2021, #62) 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. (Yang, 2020, #63) 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. (Lowry, 2022, #64) 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. (Desmond, 2015, #65) 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. (Lowry, 2022, #64) 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. (Thompson, 2016, #66) The frequency of variants in most breast cancer panel genes among individuals selected for possible hereditary breast cancer is low, and oversized large gene panels have been shown to have the potential to provide clinical misinformation and harm at the individual level. (Thompson, 2016, #66)

Melanoma

Testing for CDKN2A and/or BAP1 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 of 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

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. (Soura, 2016, #67) Although many new loci have been implicated in hereditary melanoma, including BAP1, CDKN2A

mutations remain the most common.(Toussi, 2020, #68) There are conditional recommendation for genetic counseling for CDKN2A/p16 testing by evidence-based guidelines. While there is no data regarding alterations in management or outcomes, there are some management changes suggested by some consensus guidelines.

[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.”(Hampel, 2015, #26)

NCCN: “Consider genetic counseling referral for p16/CDKN2A mutation testing in the presence of 3 or more invasive cutaneous melanomas, or a mix of invasive melanoma, pancreatic cancer, and/or astrocytoma diagnoses in an individual or family. 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.” 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, “general melanoma risk management is appropriate, such as annual full-body skin examination and minimizing UV exposure.”(National Comprehensive Cancer Network (NCCN), 2022, #69)

Nevoid basal cell carcinoma syndrome

Focused genetic testing that may include testing for PTCH variants ([including associated downstream variants, such as SMO and SUFU](#)) are 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 minor criteria, OR THREE (3) minor criteria.**

- **Major criteria**
 - Lamellar calcification of the falx cerebri in an individual age 19 or younger
 - Jaw keratocyst
 - Palmar or plantar pits
 - Multiple basal cell carcinomas (more than 5 in a lifetime) or a basal cell carcinoma diagnosed before age 30 (excluding basal cell carcinomas that develop after radiotherapy)
 - First-degree relative with nevoid basal cell carcinoma syndrome
- **Minor criteria**
 - Childhood medulloblastoma (primitive neuroectodermal tumor)
 - Lymphomesenteric or pleural cysts
 - Macrocephaly (occipital frontal circumference > 97th percentile)
 - Cleft lip 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)

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 as follows: Gorlin–Goltz syndrome, Rombo syndrome, and Bazex-Dupré-Christol syndrome. 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.](#) (Schierbeck, 2019, #70)

[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 mutations in the PTCH1 gene, PTCH2 gene, or the suppressor of fused \(SUFU\) gene. Approximately 90% of sporadic basal cell carcinomas have identifiable mutations in at least one allele of PTCH1, and an additional 10% have activating mutations in the downstream smoothened \(SMO\) protein, which presumably render SMO resistant to inhibition by PTCH1.](#) (Epstein, 2008, #71) [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.](#)

The following professional medical societies have made the following 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.”](#) (Hampel, 2015, #26)

[NCCN: “In certain patients at high risk for multiple primary tumors \(eg, Gorlin syndrome, xeroderma pigmentosum, history of RT\), increased surveillance and consideration of prophylactic measures may be indicated. Consider referring patients with suspected Gorlin syndrome or xeroderma pigmentosum for genetic evaluation.”](#) (National Comprehensive Cancer Network (NCCN), 2022, #69)

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 gastrinoma
- Type 2 gastric neuroendocrine tumor
- Multifocal pancreatic neuroendocrine tumors
- Medullary thyroid cancer
- Parathyroid adenoma, diffuse hyperplasia, or primary hyperparathyroidism before age 30
- Multiple parathyroid adenomas or recurrent primary hyperparathyroidism
- 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 and clinical features suspicious of a hereditary condition

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 on chromosome 12. 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, which encodes a 610 amino acid protein, menin. (Brandi, 2021, #72) 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 on chromosome 10. It has a frequency of roughly 1 in 35,000. (Crosbie, 2019, #73) It has two distinct variants, MEN2A 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. (Lewis, 2020, #74) MEN2A accounts for 80% of hereditary MTC syndromes. As many as 25% of unselected

individuals with MTC have a RET pathogenic variant. Individual series found that 4–11% of individuals with isolated MTC have a RET pathogenic variant. (Hampel, 2015, #26) 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.

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. (Neumann, 2019, #75) In 85-90% of cases, these are pheochromocytomas and they are sometimes detected by a classic symptoms related to catecholamine-producing tumors (headache, diaphoresis, tachycardia, and sometimes refractory hypertension) and often found through incidental imaging. (Lewis, 2020, #74) The most clinically relevant syndromes involved with pheochromocytomas and paragangliomas are (Neumann, 2019, #75):

- MEN-2, caused by germline mutations of the RET proto-oncogene;
- von Hippel–Lindau disease, caused by mutations in the VHL tumor suppressor genes;
- neurofibromatosis type 1, caused by mutations in the NF1 tumor-suppressor gene;
- paraganglioma syndromes 1 through 5, caused by mutations 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 mutations in the genes encoding transmembrane protein 127 (TMEM127) and MYC-associated factor X (MAX)

Kidney cancer

Germline genetic testing for a single gene **OR** a [targeted panel](#) ~~of up to 20 genes~~ is considered **medically necessary** for hereditary kidney cancer syndromes in individuals with a personal history of **ANY** of the following:

- Renal cell carcinoma diagnosed at age 46 or younger
- Bilateral or multifocal renal tumors
- At least one first- or second-degree relative with renal cell carcinoma

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-Dube[®] (BHD), hereditary leiomyomatosis and RCC (HLRCC), succinate dehydrogenase kidney cancer (SDH-RCC), tuberous sclerosis complex (TSC), Cowden syndrome, and microphthalmia associated transcription factor (MITF). 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 found at or below the bottom age decile cutoff of <46 years. (Shuch, 2014, #76) 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. (Lui, 2019, #77) [Per Bukavina et al., examples—although not limited to—of variants, prevalence, and risk of developing RCC are listed by condition in the table below:](#) (Bukavina, 2022, #78)

Condition	Gene/Translocation	Prevalence	Risk of RCC
VHL Syndrome	VHL	1.4 : 100,000	30% to 40%
BHD Syndrome	FLCN	2 : 1,000,000	30%
Chromosome 3 Translocation	3:6, 3:8, 3:11	Variable	30%
Hereditary Papillary Renal Cell Cancer	MET	1 : 1,500,000	100%
HLRCC	FH	1.4 : 100,000	15% to 32%

BRCA1-Associated Protein-1 (BAP1) Tumor Predisposition Syndrome	BAP1	1 : 26,837	9% to 13%
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Prostate cancer

(Also see [Lynch syndrome](#) and [HBOP](#))

Germline genetic testing of [a focused set of 20 or fewer](#) specific genes which may include HOXB13, BRCA2, BRCA1, CHEK2, [PALB2](#), ~~and ATM~~, [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/very-high risk localized](#) prostate cancer
 - [Intermediate risk prostate cancer with intraductal or cribriform histology or Ashkenazi descent by family history](#)
 - [Prostate cancer diagnosed before age 60 AND at least one first-degree relative with prostate cancer diagnosed before age 60](#)
 - [One or more pathogenic variants found by tumor somatic testing of ANY of the following genes:](#)
 - [BRCA2, BRCA1, CHEK2, ATM, PALB2, MLH1, MSH2, MSH6, PMS2, or EPCAM](#)
 - [Low or intermediate risk localized prostate cancer concomitant with a personal history of breast, pancreatic, melanoma, intestinal \(colorectal or small bowel\), or upper tract urothelial cancer\(s\)](#)
- [Family history of ANY of the following:](#)
 - ~~Two~~ [three](#) or more first-degree relatives with prostate cancer
- ~~High-risk* localized prostate cancer and EITHER of the following:~~
 - ~~Ashkenazi Jewish ancestry~~
 - ~~Two or more first-degree relatives with breast, ovarian, or pancreatic cancer or Lynch syndrome spectrum cancer in any relatives on the same side of the family~~
- ~~Personal history of prostate cancer diagnosed before age 60 AND at least one first-degree relative with prostate cancer diagnosed before age 60~~
 - [One or more first-degree relatives with prostate cancer diagnosed before age 60 or who died of prostate cancer](#)
- ~~Personal history of one or more pathogenic variants found by tumor somatic testing of any of the following genes: BRCA2, BRCA1, CHEK2, or ATM~~

~~*Includes NCCN high or very high-risk localized disease, or intraductal or cribriform histology~~

Rationale

Germline testing for inherited mutations 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 (Lee, 2022, #79), approximately 12% of unselected men with metastatic prostate cancer have been reported to carry germline mutations in DNA repair genes, most frequently BRCA2 (5.3%), ATM (1.6%), CHEK2 (1.9%), and BRCA1 (0.9%). (Pritchard, 2016, #80, Marino, 2022, #81) Men with specific genetic mutations can have a 2-fold to 10-fold increased risk of prostate cancer. Men with germline BRCA2 mutations have been associated with not only increased prostate cancer risk, but also higher mortality and younger age of diagnosis. (Page, 2019, #82) 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](#). (Russo, 2022, #83, Giri, 2022, #84) Various consensus guidelines have addressed criteria for germline testing in prostate cancer, including: Philadelphia Prostate Cancer Consensus Conference 2019, European Advanced Prostate Cancer Consensus, American Urological Association/American Society for Radiation Oncology/Society of Urologic Oncology Guideline, American Society of Clinical Oncology Policy

Statement Update, and American College of Medical Genetics and Genomics and National Society of Genetic Counselors Practice Guideline.(Giri, 2022, #84) [While genetic testing in prostate cancer is routinely recommended and numerous guidelines exist, there is still considerable lack of consensus regarding who should be tested and how they should be tested, and the overall quality of evidence is low.](#)(Clark, 2022, #85, Tuffaha, 2023, #86) [There are various, focused multi-gene panels in common use, with a typical upper limit of 20 genes or fewer.](#)(Marino, 2022, #81, Giri, 2022, #84, Selvarajah, 2022, #87)

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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

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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
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
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
81309	PIK3CA (phosphatidylinositol-4, 5-bisphosphate 3-kinase, catalytic subunit alpha) (eg, colorectal and breast cancer) gene analysis, targeted sequence analysis (eg, exons 7, 9, 20)
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
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)
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); genomic sequence analysis panel, must include sequencing of at least 10 genes, always including <i>BRCA1</i> , <i>BRCA2</i> , <i>CDH1</i> , <i>MLH1</i> , <i>MSH2</i> , <i>MSH6</i> , <i>PALB2</i> , <i>PTEN</i> , <i>STK11</i> , and <i>TP53</i> [for breast cancer testing of less than 51 genes and when genes <i>ATM</i> , <i>BARD1</i> , <i>CHEK2</i> , <i>RAD51C</i> , and <i>RAD51D</i> are also included]
81433	Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); duplication/deletion analysis panel, must include analyses for <i>BRCA1</i> , <i>BRCA2</i> , <i>MLH1</i> , <i>MSH2</i> , and <i>STK11</i> [for breast cancer testing of less than 51 genes and when genes <i>ATM</i> , <i>BARD1</i> , <i>CHEK2</i> , <i>PALB2</i> , <i>RAD51C</i> , and <i>RAD51D</i> are also included]
81435	Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); genomic sequence analysis panel, must include sequencing of at least 10 genes, including <i>APC</i> , <i>BMPR1A</i> , <i>CDH1</i> , <i>MLH1</i> , <i>MSH2</i> , <i>MSH6</i> , <i>MUTYH</i> , <i>PTEN</i> , <i>SMAD4</i> , and <i>STK11</i> [for Lynch syndrome testing of less than 51 genes and when genes <i>EPCAM</i> and <i>PMS2</i> are also included]
81436	Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); duplication/deletion analysis panel, must include analysis of at least 5 genes including <i>MLH1</i> , <i>MSH2</i> , <i>EPCAM</i> , <i>SMAD4</i> , and <i>STK11</i> [for Lynch syndrome testing of less than 51 genes and when genes <i>MSH6</i> and <i>PMS2</i> are also included]
81437	Hereditary neuroendocrine tumor disorders (eg, medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); genomic sequence analysis panel, must include sequencing of at least 6 genes, including <i>MAX</i> , <i>SDHB</i> , <i>SDHC</i> , <i>SDHD</i> , <i>TMEM127</i> , and <i>VHL</i>
81438	Hereditary neuroendocrine tumor disorders (eg, medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); duplication/deletion analysis panel, must include analyses for <i>SDHB</i> , <i>SDHC</i> , <i>SDHD</i> , and <i>VHL</i>
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 <i>BRCA2</i> , <i>BRIP1</i> , <i>DKC1</i> , <i>FANCA</i> , <i>FANCB</i> , <i>FANCC</i> , <i>FANCD2</i> , <i>FANCE</i> , <i>FANCF</i> , <i>FANCG</i> , <i>FANCI</i> , <i>FANCL</i> , <i>GATA1</i> , <i>GATA2</i> , <i>MPL</i> , <i>NHP2</i> , <i>NOP10</i> , <i>PALB2</i> , <i>RAD51C</i> , <i>RPL11</i> , <i>RPL35A</i> , <i>RPL5</i> , <i>RPS10</i> , <i>RPS19</i> , <i>RPS24</i> , <i>RPS26</i> , <i>RPS7</i> , <i>SBDS</i> , <i>TERT</i> , and <i>TINF2</i>
81479	Unlisted molecular pathology procedure
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], <i>EPCAM</i> and <i>GREM1</i> [deletion/duplication only])
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], <i>EPCAM</i> [deletion/duplication only])

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)
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)
0131U	Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), targeted mRNA sequence analysis panel (13 genes)
0132U	Hereditary ovarian cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), targeted mRNA sequence analysis panel (17 genes)
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)
0135U	Hereditary gynecological cancer (eg, hereditary breast and ovarian cancer, hereditary endometrial cancer, hereditary colorectal cancer), targeted mRNA sequence analysis panel (12 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)
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 <i>MLH1</i> , <i>MSH2</i> , <i>MSH6</i> , <i>PMS2</i> , and <i>EPCAM</i> , 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

ICD-10 Diagnosis

Refer to the ICD-10 CM manual

History

Status	Review Date	Effective Date	Action
Revised	10/23/2023	06/30/2024	Independent Multispecialty Physician Panel (IMPP) review. Expanded indications for Li-Fraumeni syndrome, HBOP cancer (including multi-gene 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.
Revised	04/12/2023	11/05/2023	Independent Multispecialty Physician Panel (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.