Test Specific Guidelines

Hereditary Cancer Syndrome Multigene Panels

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Introduction

Hereditary cancer syndrome multigene panel testing is addressed by this guideline.

Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

Procedures addressed by this guideline	Procedure codes
BRCAplus	0129U
BreastNext	0102U
Chromosomal Microarray [BAC], Constitutional	81228
Chromosomal Microarray [SNP], Constitutional	81229
Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and loss-of-heterozygosity variants, low-pass sequencing analysis	81349
ColoNext	0101U
CustomNext + RNA: APC	0157U
CustomNext + RNA: MLH1	0158U
CustomNext + RNA: MSH2	0159U
CustomNext + RNA: MSH6	0160U
CustomNext + RNA: PMS2	0161U
CustomNext + RNA: Lynch (MLH1, MSH2, MSH6, PMS2)	0162U

Procedures addressed by this guideline	Procedure codes
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 BRCA1, BRCA2,CDH1, MLH1, MSH2, MSH6, PALB2, PTEN, STK11, and TP53	81432
Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); duplication/deletion analysis panel, must include analyses for BRCA1, BRCA2, MLH1, MSH2, and STK11	81433
Hereditary cancer syndrome multigene gene panel	81479
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 APC, BMPR1A, CDH1, MLH1, MSH2, MSH6, MUTYH, PTEN, SMAD4, and STK11	81435
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 MLH1, MSH2, EPCAM, SMAD4, and STK11	81436
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 MAX, SDHB, SDHC, SDHD, TMEM127, and VHL	81437
Hereditary neuroendocrine tumor disorders (eg, medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); duplication/deletion analysis panel, must include analyses for SDHB, SDHC, SDHD, and VHL	81438
OvaNext	0103U
+RNAinsight for ATM	0136U
+RNAinsight for BRCA1/2	0138U
+RNAinsight for BreastNext	0131U
+RNAinsight for CancerNext	0134U
+RNAinsight for ColoNext	0130U
+RNAinsight for GYNPlus	0135U
+RNAinsight for OvaNext	0132U

Procedures addressed by this guideline	Procedure codes
+RNAinsight for PALB2	0137U
+RNAinsight for ProstateNext	0133U

What Are Hereditary Cancer Syndromes?

Definition

When a mutation in a single gene causes a significantly increased risk for certain cancers, it is called a hereditary cancer syndrome. Hereditary cancer syndromes are usually characterized by a pattern of specific cancer types occurring together in the same family, younger cancer diagnosis ages than usual, and/or other co-existing non-cancer conditions.

Prevalence

Most cancer is sporadic and believed to be caused by a mix of behavioral or lifestyle, environmental, and inherited risk factors. However, about 5-10% of cancers are believed to have a major inherited component.[1]

Hereditary Cancer Syndromes

There are more than 50 hereditary cancer syndromes.[1] Some of the most common are listed below with associated cancers.[2]

Hereditary breast and ovarian cancer syndrome (HBOC): breast, ovarian/fallopian tube/primary peritoneal cancer, pancreatic, prostate cancers

Lynch syndrome: colorectal, endometrial, small bowel, stomach, ovarian, pancreatic, ureteral and renal pelvis, biliary tract, brain, sebaceous adenoma, and keratoacanthoma tumors

Familial adenomatous polyposis: colorectal and other gastrointestinal cancers, gastrointestinal tract polyps (adenomas, fundic gland), osteomas, desmoids, thyroid cancer and hepatoblastoma

MUTYH-associated polyposis: colorectal and other gastrointestinal cancers, adenomas, hyperplastic polyps

Cowden syndrome: benign and malignant tumors of the breast, endometrium, and thyroid; cancer and polyps (hamartomas) in the colon and rectum

Li-Fraumeni syndrome: soft tissue sarcoma, osteosarcoma, leukemia, melanoma, and cancer of the breast, pancreas, colon, adrenal cortex, stomach, esophagus and brain

Peutz-Jeghers syndrome: polyps (hamartomas) in the stomach, small intestine and colon, and pancreas, lung, breast, uterine and non-epithelial ovarian cancer

Many hereditary cancer syndromes can include the same types of cancer and therefore have overlapping clinical findings. For example, breast cancer is a feature of HBOC, Li-Fraumeni syndrome, Cowden syndrome, and other hereditary cancer syndromes. The pattern of cancers in the family or pathognomonic features may help determine the underlying syndrome. However, in many cases it can be difficult to reliably diagnose hereditary cancer syndromes based on clinical and family history alone.

Genes Associated With Hereditary Cancer Syndromes

The NCCN suggested specific genes that may contribute to hereditary cancers.[3-5] They are provided in the table below.

Hereditary cancer type	Associated genes
Breast cancer	ATM, BARD1, BRCA1, BRCA2, CDH1, CHEK2, NF1, PALB2, PTEN, STK11, TP53
Colon cancer / polyposis	APC, AXIN2, BMPR1A, CHEK2, EPCAM, GREM1, MLH1, MLH3, MSH2, MSH3, MSH6, MUTYH, NTHL1, PMS2, POLD1, POLE, PTEN, SMAD4, STK11, TP53
Ovarian cancer	BRCA1, BRCA2, BRIP1, MLH1, MSH2, MSH6, PMS2, EPCAM, RAD51C, RAD51D, and STK11
Pancreatic cancer	ATM, BRCA1, BRCA2, CDKN2A, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2, STK11, TP53
Prostate cancer	ATM, BRCA1, BRCA2, CHEK2, MLH1, MSH2, MSH6, PALB2, PMS2

Test Information

Introduction

Testing for hereditary cancer syndromes may include multigene panel testing.

Multi-Gene Testing Panels

The efficiency of NGS has led to an increasing number of large, multi-gene testing panels. NGS panels that test several genes at once are particularly well-suited to conditions caused by more than one gene or where there is considerable clinical overlap between conditions making it difficult to reliably narrow down likely causes. Additionally, tests should be chosen to maximize the likelihood of identifying mutations in the genes of interest, contribute to

alterations in patient management, and/or minimize the chance of finding variants of uncertain clinical significance.

Guidelines and Evidence

Introduction

This section includes relevant guidelines and evidence pertaining to hereditary cancer syndrome multigene panel testing.

American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (ACMG has published several statements or standards that offer general guidance on the clinical application of large-scale sequencing, including recommendations regarding counseling around unexpected results, variants of unknown significance, and minimum requirements for reporting apply to many NGS applications.[6-8]

ACMG (2021) published a technical standard for use of NGS in the clinical laboratories which stated:[7]

"Choosing an appropriate NGS-based test is the responsibility of the ordering health-care provider. Given the large number of tests (https://www.ncbi.nlm.nih.gov/gtr/) available to the clinician, the clinical laboratory often provides critical advice in test selection. Ordering providers must weigh considerations of sensitivity, specificity, cost, and turnaround time for each clinical situation."

"Test development must consider the variant types that will be detected in the genes or regions of the genome interrogated."

In a 2020 technical standard on gene sequencing panels, ACMG stated:[8]

"Gene sequencing panels are a powerful diagnostic tool for many clinical presentations associated with genetic disorders. Advances in DNA sequencing technology have made gene panels more economical, flexible, and efficient."

"Due to differences in decision-making processes in the absence of clear professional standards, genes included on similar disease-focused panels vary between laboratories. With the ability to sequence multiple genes simultaneously, it is imperative to evaluate critically the validity of gene–disease associations prior to test design."

"Transparency is imperative when performing a gene sequencing panel so that ordering providers know what the test includes and what it does not."

Gene panels should:

"Maximize clinical specificity by limiting or excluding GUSs [genes of uncertain significance], thereby minimizing detection of VUS [variants of uncertain significance]"

"Employ auxiliary assays for genes/regions that cannot be interrogated with current sequencing technology to maximize the clinical utility."

In a 2020 statement on whether all individuals with breast cancer should receive BRCA1/2 testing, ACMG stated:[9]

"With the advances in sequencing technologies and increasing access to and expanding indications for genetic testing, it remains critical to ensure that implementation of testing is based on evidence. Currently, there is insufficient evidence to recommend genetic testing for BRCA1/2 alone or in combination with multi-gene panels for all breast cancer patients."

American College of Obstetricians and Gynecologists

In a Committee Opinion, the American College of Obstetricians and Gynecologists (ACOG, 2019) stated:[10]

"If a hereditary cancer risk assessment suggests an increased risk of a hereditary cancer syndrome, referral to a specialist in cancer genetics or a health care provider with expertise in genetics is recommended for expanded gathering of family history information, risk assessment, education, and counseling, which may lead to genetic testing and tailored cancer screening or risk reduction measures, or both."

"Genetic testing may be performed using a panel of multiple genes through next-generation sequencing technology. This multigene testing process increases the likelihood of finding variants of unknown significance, and it also allows for testing for pathogenic and likely pathogenic variants in multiple genes that may be associated with a specific cancer syndrome or family cancer phenotype (or multiple phenotypes)."

American Society of Breast Surgeons

The American Society of Breast Surgeons (2019) published a consensus guideline on genetic testing for hereditary breast cancer. They stated the following:[11]

"Breast surgeons, genetic counselors, and other medical professionals knowledgeable in genetic testing can provide patient education and counseling and make recommendations to their patients regarding genetic testing and arrange testing. When the patient's history and/or test results are complex, referral to a certified genetic counselor or genetics professional may be useful. Genetic testing is increasingly provided through multi-gene panels. There are a wide variety of panels available, with different genes on different panels. There is a lack of consensus among experts regarding which genes should be tested in

different clinical scenarios. There is also variation in the degree of consensus regarding the understanding of risk and appropriate clinical management of mutations in some genes."

"Genetic testing should be made available to all patients with a personal history of breast cancer. Recent data support that genetic testing should be offered to each patient with breast cancer (newly diagnosed or with a personal history). If genetic testing is performed, such testing should include BRCA1/BRCA2 and PALB2, with other genes as appropriate for the clinical scenario and family history. For patients with newly diagnosed breast cancer, identification of a mutation may impact local treatment recommendations (surgery and potentially radiation) and systemic therapy. Additionally, family members may subsequently be offered testing and tailored risk reduction strategies."

"Genetic testing should be made available to all patients with a personal history of breast cancer. Every patient being seen by a breast surgeon, who had genetic testing in the past and no pathogenic variant was identified, should be re-evaluated and updated testing considered. In particular, a patient who had negative germline BRCA1 and 2 testing, who is from a family with no pathogenic variants, should be considered for additional testing. Genetic testing performed prior to 2014 most likely would not have had PALB2 or other potentially relevant genes included and may not have included testing for large genomic rearrangements in BRCA1 or BRCA2."

"Genetic testing should be made available to patients without a history of breast cancer who meet NCCN guidelines. Unaffected patients should be informed that testing an affected relative first, whenever possible, is more informative than undergoing testing themselves. When it is not feasible to test the affected relative first, then the unaffected family member should be considered for testing if they are interested, with careful pre-test counseling to explain the limited value of "uninformative negative" results. It is also reasonable to order a multi-gene panel if the family history is incomplete (i.e., a case of adoption, patient is uncertain of exact type of cancer affecting family members, among others) or other cancers are found in the family history, as described above."

American Society of Clinical Oncology

The American Society of Clinical Oncology (ASCO, 2020) published the following recommendations after a consensus conference on germline testing in prostate cancer:[12]

"For men with metastatic PCA, broader panel testing may be appropriate, particularly if considering treatment or clinical trial options."

Recommended priority genes for individuals with metastatic prostate cancer include BRCA1/2 and mismatch repair genes.

Recommended priority gene for individuals with nonmetastatic prostate cancer is BRCA2.

Additional genes can be considered in either group depending upon personal or family history.

“Reflex testing may be considered for all patients, but especially for men with nonmetastatic disease considering AS or men without PCA for early detection, which allows for initial testing of genes that inform management.”

National Comprehensive Cancer Network (NCCN)

The National Comprehensive Cancer Network (NCCN) made the following general recommendations for using multi-gene panels in evaluating risk for breast and ovarian cancer and now includes this option in some management algorithms:[3-5]

“Multi-gene testing is a new and rapidly growing field, but there is currently a lack of evidence regarding proper procedure and risk management strategies that should follow testing, especially when pathogenic or likely pathogenic variants are found for moderate-penetrance genes and when a VUS is found. For this reason, the NCCN panel recommends that multi-gene testing be offered in the context of professional genetic expertise, with pre- and post-test counseling being offered.” [4]

“Consider comprehensive testing of patient with multi-gene panel or if unaffected, attempt, if possible, to test family member with highest likelihood of a pathogenic/likely pathogenic variant before testing an unaffected individual”.[3]

"An individual's personal and/or family history may be explained by more than one inherited cancer syndrome; thus, phenotype-directed testing based on personal and family history through a tailored multi-gene panel test is often more efficient and cost-effective and increases the yield of detecting a pathogenic/likely pathogenic variant in a gene that will impact medical management for the individual or their at-risk family members."[3]

"There may also be a role for multi-gene testing in individuals who have tested negative for a single syndrome, but whose personal or family history remains suggestive of an inherited susceptibility."[3]

“Because commercially available tests differ in the specific genes analyzed, variant classification, and other factors (eg methods of DNA/RNA analysis or option to reflex from a narrow to a larger panel; provision of financial assistance for cascade testing of relatives), it is important to consider the indication for testing and expertise of the laboratory when choosing the specific laboratory and test panel.” [3]

“Multi-gene testing can include "intermediate" penetrant (moderate-risk) genes. For many of these genes, there are limited data on the degree of cancer risk, and there may currently be no clear guidelines on risk management for carriers of pathogenic/likely pathogenic variants. Not all genes included on available multi-gene tests are necessarily clinically actionable.” If a moderate risk gene mutation

is identified, “gene carriers should be encouraged to participate in clinical trials or genetic registries.” [3]

“Pathogenic/likely pathogenic variants in many breast, ovarian, pancreatic, and prostate cancer susceptibility genes involved in DNA repair may be associated with rare autosomal recessive conditions, thus posing risks to offspring to offspring if the partner is also a carrier.” [3]

“As more genes are tested, there is an increased likelihood of finding variants of unknown significance (VUS), mosaicism, and clonal hematopoiesis of indeterminate potential (CHIP).” [3]

“Multi-gene panel testing increases the likelihood of finding pathogenic/likely pathogenic variants without clear clinical significance.” [3]

NCCN Practice Guidelines for Genetic/Familial High-Risk Assessment: Colorectal (2022) stated the following regarding genetic testing:[4]

“The introduction of multi-gene testing for hereditary forms of cancer has rapidly altered the clinical approach to testing at-risk patients and their families. Based on NGS technology, these tests simultaneously analyze a set of genes that are associated with a specific family cancer phenotype or multiple phenotypes.”

"When more than one gene can explain an inherited cancer syndrome, multigene testing is more efficient than single-gene testing, or sequential single syndrome testing."

"Chances of finding a VUS or pathogenic variant with uncertain clinical management increase as the number of genes included in the multigene panel increase."

“There is also a role for multi-gene testing in individuals who have tested negative (indeterminate) for a single syndrome, but whose personal or family history remains strongly suggestive of an inherited susceptibility.”

“As is the case with high-risk genes, it is possible that the risks associated with moderate-risk genes may not be entirely due to that gene alone, but may be influenced by gene/gene or gene/environment interactions. In addition, certain pathogenic variants in a gene may pose higher or lower risk than other pathogenic variants in that same gene. Therefore, it may be difficult to use a known pathogenic variant alone to assign risk for relatives.”

"Multi-gene testing may be preferred, particularly for patients with a strong family history or if the age of CRC diagnosis is less than 50 years."

Germline multigene testing that “includes all polyposis and colorectal cancer genes” is preferred for the following individuals when there is no known pathogenic variants in any polyposis gene in the family:

“Personal history of >20 cumulative adenomas”

“Multifocal/bilateral congenital hypertrophy of retinal pigment epithelium (CHERPE)”

“Consider testing if a personal history of between 10-19 cumulative adenomas, desmoid tumor, hepatoblastoma, cribriform-morular variant of papillary thyroid cancer, unilateral CHRPE,or if individual meets criteria for SPS [Serrated Polyposis Syndrome] with at least some adenomas.”

NCCN Practice Guidelines for Prostate Cancer (2022) stated the following regarding genetic testing:[5]

"Germline testing, when performed, should include MLH1, MSH2, MSH6, and PMS2 (for Lynch syndrome) and the homologous recombination genes BRCA1, BRCA2, ATM, PALB2, and CHEK2. Additional genes may be appropriate depending on clinical context."

Germline genetic testing is recommended for all men with high-risk, very-high-risk, regional, or metastatic prostate cancer.

NCCN Practice Guidelines for Cutaneous Melanoma (2022) stated the following regarding genetic testing:[13]

“Multigene panel testing that includes CDKN2A is recommended for patients with invasive cutaneous melanoma who have a first degree relative diagnosed with pancreatic cancer.”

“Testing other genes that can harbor melanoma-predisposing mutations may be warranted.”

Criteria

Introduction

Requests for hereditary cancer syndrome panel testing are reviewed using these criteria.

Hereditary Cancer Multi-Syndrome Panels

This guideline applies only to testing performed as a multi-syndrome panel for hereditary cancer. For information on single gene or single syndrome requests, please refer to a test-specific policy, if available, as this testing is not addressed here. If none is available, please refer to the clinical use guideline *Genetic Testing for Cancer Susceptibility and Hereditary Cancer Syndromes*.

Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

No known cancer-predisposing mutation in the family, AND

No previous hereditary cancer syndrome multi-gene panel testing, AND

No previous hereditary cancer syndrome testing for any gene on the panel, AND

One of the following is met:

Member has a personal diagnosis of cancer consistent with the hereditary cancer syndrome that is suspected in the family, or

Member is not affected with cancer but is the most informative person in the family to test and an affected family member cannot proceed with testing. If the member is not the most informative person to test, documentation in the medical record* provided by the ordering physician's office must be provided and clearly document that it is impossible to test the most informative family member, AND

One of the following is met:

Member has a personal history of invasive cutaneous melanoma and a first degree biological relative diagnosed with pancreatic cancer (multi-syndrome panel must include CDKN2A), or

Member meets criteria for BRCA Analysis based on current eviCore guideline *BRCA Analysis*, or

Member meets criteria for Lynch Syndrome Genetic Testing based on current eviCore guideline *Lynch Syndrome Genetic Testing*, or

Member meets criteria for Familial Adenomatous Polyposis Syndrome Genetic Testing based on current eviCore guideline *Familial Adenomatous Polyposis Syndrome Genetic Testing*, or

Member meets criteria for MUTYH Associated Polyposis Genetic Testing based on current eviCore guideline *MUTYH Associated Polyposis Genetic Testing*, or

Member meets criteria for two other separate hereditary cancer syndromes based on eviCore guidelines that are included on the panel, AND

Rendering laboratory is a qualified provider of service per the Health Plan policy.

Note ***Documentation describing the reason the unaffected member is the most informative person to test for a hereditary cancer syndrome must be provided by the ordering health care provider as part of the medical record of the member. The laboratory test request form is not sufficient for this purpose.**

Deletion/Duplication Analysis

Paragraph

Member meets criteria for sequencing above, AND

Previous sequencing panel, if applicable, was performed and no mutations identified.

RNA Testing

This test is considered investigational and/or experimental

Investigational and experimental (I&E) molecular and genomic (MolGen) tests refer to assays involving chromosomes, DNA, RNA, or gene products that have insufficient data to determine the net health impact, which typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity), significantly improves health outcomes (clinical utility), and/or performs better than an existing standard of care medical management option. Such tests are also not generally accepted as standard of care in the evaluation or management of a particular condition.

In the case of MolGen testing, FDA clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight and FDA clearance often does not assess clinical utility.

Hereditary Cancer Testing Reflex or Update Panels (e.g. MyRisk Update) Will Be Reimbursed When the Following Criteria Are Met:

Paragraph

Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

No known cancer-causing mutation in the family, AND

No previous hereditary cancer syndrome multi-gene panel testing, AND

Testing for one condition, for which the member meets eviCore criteria, was performed and billed separately. A multi-gene panel is now being considered and will be billed at a rate comparable to single syndrome pricing, AND

Member meets medical necessity criteria for at least one additional condition included in the panel that was not already tested (e.g., hereditary breast and ovarian cancer was already performed, but Lynch syndrome criteria are also met). Please refer to test-specific guidelines for details.

Although not a complete list, the following are considered separate conditions:

Hereditary breast cancer - this includes both BRCA1/2 and PALB2 (Note that if BRCA1/2 testing was already performed and PALB2 criteria are now met, PALB2 testing alone would be reimbursable and not an update panel.)

Lynch syndrome

Li-Fraumeni syndrome

Familial adenomatous polyposis

Cowden syndrome

Peutz-Jeghers syndrome

MUTYH-associated polyposis

Billing and Reimbursement Considerations

Testing will only be considered when billed with an appropriate panel code. When multiple CPT codes are billed for components of a panel, eviCore will redirect to the appropriate panel code(s).

Genetic testing is only necessary once per lifetime.

A single gene included in a panel or a multi-gene panel may not be reimbursed if testing has been performed previously. Exceptions may be considered if technical advances in testing demonstrate significant advantages that would support a medical need to retest.

If a panel was previously performed and an updated, larger panel is being requested, only testing for the medically necessary, previously untested genes will be reimbursable. Therefore, only the most appropriate procedure codes for those additional genes will be considered for reimbursement.

Only one multi-syndrome hereditary cancer panel will be reimbursed.

References

Introduction

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