Peutz-Jeghers Syndrome Genetic Testing

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Introduction

Peutz-Jeghers syndrome (PJS) genetic testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
STK11 deletion/duplication analysis	81404
STK11 known familial mutation analysis	81403
STK11 sequencing	81405

Criteria

Introduction

Requests for Peutz-Jeghers syndrome (PJS) genetic testing are reviewed using the following criteria.

STK11 Known Familial Mutation Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous STK11 gene testing that would detect the familial mutation, AND
- Diagnostic and Predisposition Testing:

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  - Known family mutation in the STK11 gene identified in 1st degree relative(s). (Note: 2nd or 3rd degree relatives may be considered when 1st degree relatives are unavailable or unwilling to be tested), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

STK11 Sequencing

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous STK11 gene sequencing, and
  - No known familial STK11 mutation, AND
- Diagnostic Testing for Symptomatic Individuals:
  - A clinical diagnosis of PJS based on at least two of the following features:
    - At least two PJS-type hamartomatous polyps of the gastrointestinal tract, or
    - Mucocutaneous hyperpigmentation of the mouth, lips, nose, eyes, genitalia, or fingers, or
    - A family history of PJS, OR
- Predisposition Testing for Presymptomatic/Asymptomatic Individuals:
  - Member is a 1st degree relative of someone with a clinical diagnosis of PJS who has had no previous genetic testing (Note that testing in the setting of a more distant affected relative will only be considered if the 1st degree relative is unavailable or unwilling to be tested), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

STK11 Deletion/Duplication Testing

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous STK11 deletion/duplication analysis has been performed, and
  - Above criteria for STK11 full gene sequencing are met, and
  - STK11 sequencing was previously performed and no mutations were found, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Other Considerations

PJS testing may be performed as part of a multigene, multisyndrome panel. For information on multigene, multisyndrome panel testing, please refer to the guideline *Hereditary Cancer Syndrome Multigene Panels* as this testing is not addressed here.

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What is Peutz-Jeghers syndrome?

Peutz-Jeghers syndrome (PJS) is a genetic disorder characterized by the development of polyps (hamartomas) in the gastrointestinal (GI) tract, most commonly the small intestine. Polyps can also occur in the stomach and colon and on occasion in the renal pelvis, urinary bladder, ureters, lungs, nares, and gallbladder.[1] Individuals with PJS also have characteristic mucocutaneous pigmentation and an increased risk to develop cancer.[2]

Prevalence

The prevalence is not well established with estimates ranging from 1/25,000 to 1/280,000.[1] PJS can occur in any racial or ethnic group.

Symptoms

Approximately a third of affected individuals present with polyps by age 10, and by age 20, about half have clinical signs and symptoms.[2] Affected individuals also typically have mucocutaneous pigmented lesions — lip freckling is classic, but pigmentation may also develop in the mouth, gums, nose, perianal area, and on the fingers and toes.[1,2] Mucocutaneous pigmentation typically becomes pronounced in children before age five, but may fade in puberty and adulthood. In addition to an increased risk for gastrointestinal polyps and cancer, people with PJS have an increased risk for other cancers, including those of the pancreas, lung, breast, uterus, cervix, ovaries, and testes.[1,2]

Cancer Risks[3]

Type of Cancer	Risk
Breast (female)	32-54%
Colon	39%
Stomach	29%
Small intestine	13%
Pancreas	11-36%
Ovary (typically benign sex cord/Sertoli cell tumors)	at least 20%
Cervix (typically minimal deviation adenocarcinoma)	at least 10%
Uterus	9%

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Type of Cancer	Risk
Testes (typically sex cord/Sertoli cell tumors)	9%
Lung	7-17%

Cause

PJS is caused by mutations in the STK11 gene, which is a tumor suppressor gene. Its normal role is to control growth and development of cells. Mutations in STK11 cause cells to grow and divide uncontrollably, leading to the development of polyps and an increased risk for cancer.[1] Over 200 distinct STK11 gene mutations or deletions have been identified in people with PJS. Ninety-four to 96% of individuals with PJS will have an STK11 pathogenic mutations.[4,5] The detection rate in familial versus sporadic cases is 87% and 97.8%, respectively.[5]

Inheritance

PJS is inherited as an autosomal dominant disorder.

Autosomal dominant inheritance

In autosomal dominant inheritance, individuals have 2 copies of the gene and only one mutation is required to cause disease. When a parent has a mutation, each offspring has a 50% risk of inheriting the mutation. Males and females are equally likely to be affected.

"In large series, 60-78% of individuals with PJS had affected relatives. ...17-40% of probands represent apparently simplex cases. In a separate study, between 30%-45% of probands represent simplex cases."[1] The proportion of a new (de novo) mutation is unclear due to variable expressivity and the frequency of subtle signs in parents is unknown.[1]

Diagnosis

A clinical diagnosis can be established in an individual who has one of the following:[1]

- "Two or more histologically confirmed PJS-type hamartomatous polyps.
- Any number of PJS-type polyps detected in one individual who has a family history of PJS in at least one close relative.
- Characteristic mucocutaneous pigmentation in an individual who has a family history of PJS in at least one close relative.
- Any number of PJS-type polyps in an individual who also has characteristic mucocutaneous pigmentation."

The molecular diagnosis of PJS is established in an individual with suggestive findings and a heterozygous mutation in the SKT11 gene. Suggestive findings include two or more PJS-type hamartomatous polyps of the GI tract, characteristic mucocutaneous pigmentation, gynecomastia in males as a result of estrogen-producing Sertoli cell testicular tumors, and history of intussusception.[1]

Approximately 80-85% of individuals with PJS will have a mutation detected by next generation sequencing.[1]

Approximately 15-20% of individuals with PJS will have a mutation detected by deletion/duplication analysis.[1]

Management

Screening and prevention options are available to specifically address the increased risk for the development of polyps and cancers in an individual with a STK11 pathogenic mutation [1-3,6] Some of these screening tests will begin in childhood while others start in adulthood.

Survival

In one study of 54 individuals with PJS and a median follow-up of 7 years, 30% (16 individuals) of affected individuals were deceased at a median age of 51 years.[7] The cause of death was unknown in 4 individuals but otherwise the cause of death was from malignancies and most commonly metastatic gynecologic cancer. “Given the morbidities associated with repeated operations and the risk for cancer-related mortality in the long-term, efforts should focus on minimizing the need for surgical intervention and optimizing cancer detection, treatment and prevention."[7]

Test information

Introduction

Testing for PJS may include known familial mutation analysis, next generation sequencing, and/or deletion/duplication analysis.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

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Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

Guidelines and evidence

American Society of Clinical Oncologists

The American Society of Clinical Oncologists (ASCO, 2010) position statement on genetic testing stated the following:[8]

- "Tests for high-penetrance mutations in appropriate populations have clinical utility, meaning that they inform clinical decision making and facilitate the prevention or amelioration of adverse health outcomes."

The American Society of Clinical Oncologists (ASCO, 2015) position statement on genetic testing recommended the evaluation of clinically relevant genes and addressed the use of multigene panels:[9]

- "It is sufficient for cancer risk assessment to evaluate genes of established clinical utility that are suggested by the patient's personal and/or family history. Because of the current uncertainties and knowledge gaps, providers with particular expertise in cancer risk assessment should be involved in the ordering and interpretation of multigene panels that include genes of uncertain clinical utility and genes not suggested by the patient's personal and/or family history. ASCO encourages research to delineate the optimal use of panel-based testing, development of evidence-based practice guidelines as data emerges, and education of providers regarding challenges in the use of these tests."

The American Society of Clinical Oncologists (ASCO, 2024) guidelines on genetic testing panels in patients with cancer stated the following:[10]

- "When germline genetic testing is indicated for a patient with cancer, multigene panel testing should be offered if more than one gene is relevant."
- "When considering what to order for multigene panel testing, clinicians should apply the following principles: The minimal panel should include at least the more strongly recommended genes for that patient based on the patient's personal and family history of cancer from **Table 1** of this guideline and may include the less strongly recommended genes. A broader panel may be ordered when the potential benefits of such a panel can be clearly identified. When ordering a panel (especially a broader panel), the clinician should ensure that potential harms are mitigated."
- "Patients who meet criteria for germline genetic testing should be offered that testing regardless of results from tumor testing (ie, genomic profiling from tumor biopsy or circulating tumor DNA testing)."
- "Regardless of germline genetic testing criteria, when a pathogenic variant is identified with tumor testing in a gene listed in **Table 2** germline genetic testing should be offered according to the criteria in **Tables 2** and **3**.

The American Society of Clinical Oncologists (ASCO, 2024) guidelines on genetic testing in patients with breast cancer recommended that testing of high penetrance breast cancer genes beyond BRCA1/2, including STK11, be offered to appropriate breast cancer patients and stated the following:[11]

- "Testing for high penetrance genes beyond BRCA1/2, including PALB2, TP53, PTEN, STK11, and CDH1, could inform medical therapy, influence surgical decision making, refine estimates of risks of second primary cancer, and inform family risk assessment, and thus should be offered to appropriate patients (Type: Formal Consensus; Agreement: 92.31%)."

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2024) guidelines outlined clinical diagnostic criteria and provided some guidance on surveillance.[3]

- "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 pathogenic variants in the STK11 (LKB1) gene."
- Screening procedures and intervals are outlined for breast (women only), colon, stomach, pancreatic, small intestine, cervical, ovarian, uterine, and testicular cancers.[3,12] Additionally, there are pediatric surveillance guidelines. Thus, testing

of minors for STK11 is appropriate as the presence of a pathogenic mutation would impact decisions regarding clinical management.

US Multi-Society Task Force on Colorectal Cancer

The US Multi-Society Task Force on Colorectal Cancer (2022) issued a consensus statement on the diagnosis and management of hamartomatous polyposis syndromes. They stated the following regarding genetic evaluation for Peutz-Jeghers syndrome:[13]

- "We recommend genetic evaluation for any individual with the following: 1) 2 or more histologically confirmed Peutz-Jeghers polyps, 2) any number of Peutz-Jeghers polyps in an individual who has a family history of Peutz-Jeghers syndrome in a first-degree relative, 3) characteristic mucocutaneous pigmentation in a person with a family history of Peutz-Jeghers syndrome, and 4) any number of Peutz-Jeghers polyps in a person with the characteristic mucocutaneous pigmentation of Peutz-Jeghers syndrome. (Strong recommendation, low quality of evidence)"

Selected Relevant Publications

A 2021 expert-authored review stated:[1]

- "Predictive testing for at-risk asymptomatic family members requires prior identification of the germline STK11 pathogenic variant in the family. Because early detection of at-risk individuals who have an STK11 pathogenic variant affects medical management – particularly surveillance (see Table 4) – testing of at-risk individuals (with informed parental assent) during childhood is considered beneficial."
- "Parents often want to know the genetic status of their children prior to initiating screening in order to avoid unnecessary procedures in a child who has not inherited the pathogenic variant. Special consideration should be given to education of the children and their parents prior to genetic testing. A plan should be established for the manner in which results are to be given to the parents and their children."

Evidence-based guidelines for the diagnosis and management of PJS were published in 2010.[2] These guidelines outlined clinical diagnostic criteria for PJS and surveillance recommendations, but do not specifically address the utility of genetic testing. They stated that "no clear genotype-phenotype correlation has been demonstrated in PJS, and no clear differences found between cases with STK11 mutation and in those in whom no mutation has been detected". These guidelines stated that a clinical diagnosis of PJS may be made in an affected person when any ONE of the following is present:

- "Two or more histologically confirmed PJS polyps.
- Any number of PJS polyps detected in one individual who has a family history of PJS in close relative(s).
- Characteristic mucocutaneous pigmentation in an individual who has a family history of PJS in close relative(s).

- Any number of PJS polyps in an individual who also has characteristic mucocutaneous pigmentation."

Clinical diagnostic criteria have been validated by genetic testing in one series of 71 affected individuals.[14] Of 56 individuals who met clinical criteria for PJS, 94% had an STK11 mutation found by a combination of sequencing and deletion/duplication analysis. Twelve individuals had only a "presumptive diagnosis" of PJS based on the presence of hyperpigmentation or isolated PJS polyps, with no known family history. No STK11 mutations were found in those 12 individuals.

Note: This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for Peutz-Jeghers syndrome testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

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