Test Specific Guidelines

Peutz-Jeghers Syndrome Genetic Testing

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Introduction

Peutz-Jeghers syndrome genetic 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
STK11 Deletion/Duplication Analysis	81404
STK11 Known Familial Mutation Analysis	81403
STK11 Sequencing	81405

What Is Peutz-Jeghers Syndrome?

Definition

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 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]

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] In addition to 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%
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 in the GI tract. 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 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 and 17-40% of individuals represented isolated cases within their families" [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

The identification of a pathogenic mutation in the STK11 gene confirms the diagnosis of PJS. The 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."

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 testing.

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.

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

Introduction

This section includes relevant guidelines and evidence pertaining to PJS testing.

American Society of Clinical Oncologists

The American Society of Clinical Oncologists (ASCO, 2003) position statement on genetic testing outlined general recommendations for genetic testing for hereditary cancer syndromes:[8]

"Indications for Genetic Testing: ASCO recommends that genetic testing be offered when 1) the individual has personal or family history features suggestive

of a genetic cancer susceptibility condition, 2) the test can be adequately interpreted, and 3) the results will aid in diagnosis or influence the medical or surgical management of the patient or family members at hereditary risk of cancer."

The American Society of Clinical Oncologists (ASCO, 2003) position statement on genetic testing specifically addressed issues around genetic testing in at-risk children:[9]

"Special Issues in Testing Children for Cancer Susceptibility: ASCO recommends that the decision to offer testing to potentially affected children should take into account the availability of evidence-based risk-reduction strategies and the probability of developing a malignancy during childhood. Where risk-reduction strategies are available or cancer predominantly develops in childhood, ASCO believes that the scope of parental authority encompasses the right to decide for or against testing."

The American Society of Clinical Oncologists (ASCO, 2010) position statement on genetic testing stated the following:[10]

"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:[11]

"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."

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2022) 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.

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 that stated:[12]

"We recommend patients patients with any of the following undergo a genetic evaluation: 2 or more lifetime hamartomatous polyps, a family history of hamartomatous polyps, or a cancer associated with a hamartomatous polyposis syndrome in first or second-degree relatives. Genetic testing (if indicated) should be performed using a multigene panel test. (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.[13] 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.

Criteria

Introduction

Requests for STK11 testing are reviewed using these 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 have detected the familial mutation, AND

Diagnostic and Predisposition Testing:

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.

References

Introduction

These references are cited in this guideline.

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