Peutz-Jeghers Syndrome

Indications for Ordering

• Confirm diagnosis of Peutz-Jeghers syndrome (PJS) in symptomatic individual
• Disease prediction in presymptomatic individual with family history of PJS

Test Description

• Polymerase chain reaction followed by bidirectional sequencing of STK11 coding regions and intron/exon boundaries
• Multiplex ligation-dependent probe amplification to detect large STK11 deletions/duplications

Tests to Consider

Primary tests

Peutz-Jeghers Syndrome (STK11) Sequencing and Deletion/Duplication 2008398
• Preferred test to confirm diagnosis of PJS in symptomatic individual

Peutz-Jeghers Syndrome (STK11) Sequencing 2008394
• Acceptable test to confirm diagnosis of PJS in symptomatic individual
• Detects most pathogenic variants

Related test

Familial Mutation, Targeted Sequencing 2001961
• Useful when a pathogenic familial variant identifiable by sequencing is known

Disease Overview

Prevalence – 1/25,000-280,000

Age of onset

• Hyperpigmented macules most pronounced by age 4 – not usually present at birth
• Median age for gastrointestinal (GI) symptoms is 10-12 years

Symptoms

• GI polyposis
• Hamartomatous polyps resulting in
  o Chronic bleeding
  o Anemia
  o Recurrent obstruction
  o Intussusception
  o Adenomatous polyps in
    ▪ Colon
    ▪ Small intestine
    ▪ Stomach
    ▪ Large bowel
    ▪ Nasal passages
• Lifetime risk for any cancer varies between 37-90%
• Hyperpigmentation presenting as dark-blue to brown macules around
  o Mouth
  o Eyes
  o Nostrils
  o Perianal area
  o Buccal mucosa
  o Fingers
• Increased risk for epithelial malignancies
  o Colorectal
  o Gastric
  o Pancreatic
  o Breast
  o Ovarian
  o Sex cord tumors with annular tubules
  o Adenoma malignum of cervix

Diagnostic consensus criteria

• Any one of the following
  o At least two histologically confirmed Peutz-Jeghers (PJ)-type polyps
  o At least one PJ polyp and family history of PJS
  o Characteristic hyperpigmented macules and family history of PJS
  o At least one PJ polyp and characteristic hyperpigmented macules
Recommended follow-up testing

- Surveillance by video capsule endoscopy starting at age 10 years
- Gastroduodenoscopy at 20 years
- Breast exam and MRI at 25 years
- Pelvic exam, cervical smear, transvaginal ultrasound, and CA-125 at 25-30 years
- Colonoscopy at 25-30 years
- MRI and endoscopic ultrasound of pancreas at 30 years
- Mammography and MRI at 30 years

Genetics

Gene – STK11

Inheritance – autosomal dominant

Penetrance – 100%

De novo variant(s) – 50%

Variants – >290 STK11 variants reported

Test Interpretation

Sensitivity/specificity

- Clinical sensitivity
  - PJS (STK11) sequencing and deletion/duplication
    - 100% sensitivity in individuals with family history of PJS
    - ~91% in individuals without a family history
  - PJS (STK11) sequencing
    - ~55% sensitivity in individuals with a family history of PJS
    - ~70% in individuals without a family history
  - PJS (STK11) deletion/duplication
    - ~45% sensitivity in individuals with a family history of PJS
    - ~21% in individuals without a family history
- Analytical sensitivity/specificity – 99%

Results

- Positive – diagnosis confirmed
- Negative – diagnosis of PJS is less likely but not excluded
- Uncertain – gene variant detected, but whether the variant is benign or pathogenic is unclear

Limitations

- Regulatory region and deep intronic variants will not be detected
- Large deletion/duplication breakpoints will not be determined
- Diagnostic errors can occur due to rare sequence variations