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
  - Chronic bleeding
  - Anemia
  - Recurrent obstruction
  - Intussusception
  - 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
  - Mouth
  - Eyes
  - Nostrils
  - Perianal area
  - Buccal mucosa
  - Fingers
- Increased risk for epithelial malignancies
  - Colorectal
  - Gastric
  - Pancreatic
  - Breast
  - Ovarian
  - Sex cord tumors with annular tubules
  - Adenoma malignum of cervix

Diagnostic consensus criteria

- Any one of the following
  - At least two histologically confirmed Peutz-Jeghers (PJ)-type polyps
  - At least one PJ polyp and family history of PJS
  - Characteristic hyperpigmented macules and family history of PJS
  - 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