Idiopathic and Hereditary Pancreatitis

Indications for Ordering
Confirm diagnosis and/or genetic cause for pancreatitis in symptomatic individuals

Test Description
Polymerase chain reaction followed by bidirectional sequencing of coding regions and intron/exon borders

Tests to Consider

Primary tests
Pancreatitis, Panel (CFTR, CTRC, PRSS1, SPINK1) Sequencing 2010876
• Preferred test for individuals with history of idiopathic pancreatitis

Pancreatitis (CTRC) Sequencing 2010703
• For adults with idiopathic pancreatitis if other components of panel (CFTR, PRSS1, SPINK1) have been sequenced without providing a complete explanation for the pancreatitis

Pancreatitis (PRSS1) Sequencing 2002016
• Preferred test for individuals with idiopathic pancreatitis who
  o Are <20 years of age OR
  o Have 2 affected first-degree relatives

Pancreatitis (SPINK1) Sequencing 2002012
• For adults with idiopathic pancreatitis if other components of panel (CFTR, CTRC, PRSS1) have been sequenced without providing a complete explanation for the pancreatitis

Related tests
Cystic Fibrosis (CFTR) Sequencing 0051110
• May be used to test for variants causative for mild cystic fibrosis for individuals with idiopathic pancreatitis

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

Disease Overview

Incidence/prevalence
• Chronic pancreatitis
  o Incidence – 5-12/100,000 per year (Yadav, 2013)
  o Prevalence – ~50/100,000 (Yadav, 2013)
• Idiopathic chronic pancreatitis
  o ~20% of all cases of pancreatitis (Masson, 2013)

Symptoms
• Acute pancreatitis
  o Can be life-threatening
  o Symptoms
    ▪ Sudden onset of pain in the upper abdomen, fever, nausea and vomiting, rapid pulse
    ▪ Pancreatic enzymes (amylase, lipase) – increased levels
  o Etiologies
    ▪ Common – gallstone passage or obstruction; chronic, heavy alcohol use
    ▪ Other – abdominal trauma, medications, infections, tumors, genetic abnormalities
• Chronic pancreatitis
  o Chronic inflammation and progressive disease
  o May lead to permanent tissue damage
  o Up to a 40% lifetime risk for pancreatic cancer
  o Symptoms
    ▪ Abdominal pain, nausea, vomiting, weight loss, diarrhea, oily stools
    ▪ Advanced stages – pain often decreases, malabsorption and diabetes may occur
  o Etiologies
    ▪ Chronic, heavy alcohol use (70% of cases)
    ▪ Other factors (10% of cases)
      • Autoimmune
      • Hereditary disorders of the pancreas
        ▪ Cystic fibrosis
      • Hypercalcemia
      • Hyperlipidemia
      • Hyperparathyroidism
      • Medications
      • Idiopathic (20% of cases)
Genetics

Genes – CFTR, CTRC, PRSS1, SPINK1

Inheritance
• PRSS1 – autosomal dominant with gain-of-function variants
• CFTR, CTRC, SPINK1 – autosomal recessive/digenic

Penetrance – 80% for PRSS1 variants R122H and N29I (Sossenheimer, 1997)

Test Interpretation

Sensitivity/specificity in idiopathic pancreatitis
• Clinical sensitivity for contributory or causative variants
  o Pancreatitis panel (CFTR, CTRC, PRSS1, SPINK1) sequencing – ~48% (Masson, 2013)
  o Pancreatitis (CFTR) sequencing – ~28%
  o Pancreatitis (SPINK1) sequencing – ~16%
  o Pancreatitis (PRSS1) sequencing – ~9%
  o Pancreatitis (CTRC) sequencing – ~4%
• Analytical sensitivity/specificity – 99%

Results
• Positive
  o Single gain-of-function PRSS1 gene variant detected, OR
  o Two pathogenic CFTR, SPINK1, or CTRC gene variants detected, OR one pathogenic variant detected in two different genes (digenic inheritance)
    ▪ Causative for pancreatitis
  o Single pathogenic CFTR, SPINK1, or CTRC gene variant detected
    ▪ Increased risk for pancreatitis, but not causative
• Negative
  o No pathogenic variants detected in CFTR, CTRC, PRSS1, or SPINK1 genes
    ▪ No genetic etiology for pancreatitis determined
      ▪ Does not exclude genetic etiology
• Inconclusive
  o Gene variant detected, but whether variant is pathogenic or benign is unknown

Limitations
• Not detected
  o Regulatory region and deep intronic mutations
  o Large deletions/duplications
• Diagnostic errors can occur due to rare sequence variations
• Variants in currently unknown genes may be associated with pancreatitis

References