Inherited Insulin Resistance Syndromes (INSR) Genetic Testing

**Indications for Ordering**
- Confirm diagnosis of inherited insulin resistance syndromes in individuals with clinical and/or biochemical evidence
- Not intended for evaluation of individuals with nonsyndromic forms of insulin resistance, such as isolated diabetes mellitus with no other physical features

**Test Description**
Polymerase chain reaction, followed by bidirectional sequencing of the entire coding region and intron/exon boundaries of the INSR gene

**Tests to Consider**
**Primary test**
*Inherited Insulin Resistance Syndromes (INSR) Sequencing 2006274*

**Related tests**
Initial biochemical tests for suspicion of inherited insulin resistance syndrome
- Insulin, Fasting 0070063
- Glucose, Plasma or Serum 0020024

**Disease Overview**
**Incidence** – unknown, but estimated to be rare

**Clinical presentation**
Variants in the INSR gene cause three main syndromes
- Donohue syndrome (most severe)
  - Intrauterine growth restriction
  - Failure to thrive
  - Loss of glucose homeostasis
  - Hyperinsulinemia
  - Enlarged heart and kidneys
  - Dysmorphic features
    - Prominent eyes
    - Thick lips
    - Upturned nostrils
    - Low-set, posteriorly rotated ears
    - Thick skin with lack of subcutaneous fat
    - Distended abdomen
    - Enlarged genitalia
    - Polycystic ovaries in females
    - Death often occurs prior to age 1
- Rabson-Mendenhall syndrome (intermediate phenotype)
  - Growth retardation
  - Hyperinsulinemia
  - Acanthosis nigricans
  - Diabetes mellitus
  - Dysmorphic features
    - Premature or dysplastic teeth
    - Gingival hyperplasia
    - Pineal hyperplasia
  - Survival ranges from early childhood to adolescence
- Type A insulin resistance syndrome (least severe)
  - Hirsutism
  - Reduced subcutaneous fat
  - Diabetes mellitus
  - Acanthosis nigricans
  - Hyperinsulinemia
  - Amenorrhea and polycystic ovaries in females
  - Survival often beyond middle age
Pathophysiology
Insulin resistance occurs when insulin receptors are unable to bind insulin
• Results in decreased insulin action on target organs
  o Decreased insulin is compensated for by the pancreas with increased insulin release
  ▪ Pancreatic beta cells become unable to compensate
• Leads to increased glucose production by the liver and lipolysis of adipose tissue, resulting in ketoacidosis

Diagnosis
Inherited insulin resistance syndrome is often diagnosed based on
• Clinical features
• Glucose and insulin levels
• Fibroblast studies for insulin binding
• Genetic testing

Genetics
Gene – INSR
Inheritance
• Donohue syndrome – autosomal recessive
• Rabson-Mendenhall syndrome – autosomal recessive
• Type A insulin resistance syndrome – autosomal recessive or autosomal dominant
  o Recessive forms are more severe
  o Dominant forms may require contribution of other genetic or environmental factors to produce phenotype
Penetrance – unknown, but expected to be reduced for individuals with a dominant variant

Test Interpretation
Sensitivity/specificity
• Clinical sensitivity – predicted to be >90% in individuals with a clinical diagnosis
• Analytical sensitivity/specificity – 99%

Results
• Positive
  o One copy of pathogenic INSR gene variant detected
    ▪ Predicts carrier status for an inherited insulin resistance syndrome
    ▪ In some cases, one copy of a variant may indicate an increased likelihood for developing type A insulin resistance
    ▪ Depends on other genetic and environmental factors
  o Two pathogenic INSR gene variants detected
    ▪ Predicts a diagnosis of an inherited insulin resistance syndrome
• Negative
  o No pathogenic variants detected
    ▪ Likelihood is reduced that the individual is a carrier of or is affected with an inherited insulin resistance syndrome
• Inconclusive
  o INSR gene variants of unknown clinical significance may be detected by this test

Limitations
• Diagnostic errors can occur due to rare sequence variations
• Not detected
  o Regulatory region and deep intronic variants
  o Large deletions and duplications
• Genes other than INSR will not be evaluated
• Medical management of patient should rely on clinical and/or biochemical findings