**LMNA-Related Disorders**

**Indications for Ordering**

To confirm a clinical diagnosis of a LMNA-related disorder:
- Hutchinson-Gilford progeria syndrome (HGPS)
- Emery-Dreifuss muscular dystrophy type 2 (EDMD2)
- Limb-Girdle muscular dystrophy 1B (LGMD1B)
- Charcot-Marie-Tooth 2B1 (CMT2B1)
- Familial partial lipodystrophy, Dunnigan type (FPLD)
- LMNA-related dilated cardiomyopathy (DCM)
- Mandibulo-acral dysplasia (MAD)
- Atypical Werner syndrome (WS)
- Restrictive dermopathy (RD)
- Other, intermediate phenotypes

**Test Description**

- Polymerase chain reaction (PCR) followed by bidirectional sequencing of all coding regions and intron/exon boundaries of the LMNA gene
- Multiplex ligation-dependent probe amplification (MLPA) to detect large LMNA deletions/duplications

**Tests to Consider**

**Primary Tests**

- LMNA-Related Disorders (LMNA) Sequencing 2004543
  - Confirm suspected laminopathy caused by LMNA variants, including HGPS, EDMD2, LGMD1B, CMT2B1, FPLD, DCM, MAD, WS, or RD

- LMNA-Related Disorders (LMNA) Deletion/Duplication 2004539
  - Confirm suspected laminopathy caused by LMNA variants, including EDMD2, LGMD1B, or DCM

**Related Test**

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

**Disease Overview**

**Prevalence and/or incidence**

- HGPS: 1/8 million births
- DCM: ~1/2,500 births
  - Familial: 30-60%
    - LMNA gene variants cause ~8% of familial cases
  - Incidence of other LMNA-associated disorders: unknown

**Symptoms**

- Variants in the LMNA gene cause a broad range of clinical diseases collectively termed laminopathies
- Clinical findings are highly variable
- See table

**Genetics**

**Genes:** LMNA

**Inheritance:** see table

**Penetrance:** varies by syndrome

**Structure/Function**

- Composed of 12 exons
- LMNA encodes isoforms A and C of the lamin protein
  - Structural component of the nuclear membrane
  - Anchors heterochromatin to the inner nuclear membrane

**Variants**

- Alternative splicing of the LMNA gene produces two proteins (lamin A and C)
- Variants occur throughout the gene
  - Predominantly missense
  - p.G608G variant in exon 11
    - Present in all individuals with HGPS

**Test Interpretation**

**Sensitivity/Specificity**

- Clinical sensitivity: dependent on the specific LMNA-related disorder
- Analytic sensitivity
  - Sequencing: 99%
  - MLPA: 90%
- Analytical specificity
  - Sequencing: 99%
  - MLPA: 98%
Results
- Positive: single pathogenic LMNA variant detected
  - Consistent with diagnosis of an autosomal dominant laminopathy
  - May indicate carrier status for an autosomal recessive LMNA-related disorder
- Negative: LMNA variant not detected
  - Lack of detection decreases the probability of, but does not exclude, the possibility of a laminopathy
  - Gene variants of uncertain significance may be detected by LMNA sequencing

Limitations
- Diagnostic errors can occur due to rare sequence variations
- Not determined or evaluated:
  - Some regulatory region variants
  - Deep intronic variants
  - Breakpoints of large deletions/duplications
  - Variants in genes other than LMNA
- Large deletions/duplications in exon 8 may not be detected

LMNA-Related Disorders: Clinical Features and Inheritance Patterns

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<th>Disease</th>
<th>Clinical Features</th>
<th>Inheritance</th>
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| HGPS     | • Symptoms that resemble accelerated aging, profound failure to thrive, characteristic facies, alopecia, joint degeneration, growth retardation  
  • Age of onset – ~1 year with average life expectancy of 13 years | All affected individuals carry a de novo, dominant p.Gly608Gly variant in LMNA exon 11 |
| EDMD2    | • Joint contractures, progressive muscle weakness and wasting, cardiac disease with conduction defects and arrhythmias  
  • Age of onset – variable | Autosomal dominant most common; autosomal recessive cases are very rare |
| LGMD1B   | • Progressive proximal lower limb weakness and atroventricular cardiac conduction complications  
  • Age of onset – birth to adulthood, with 50% in childhood | Autosomal dominant |
| CMT2B1   | • Symmetrical distal muscle weakness and atrophy, depressed or absent tendon reflexes  
  • Age of onset – ~14 years | Autosomal recessive; very rare |
| FPLD     | • Progressive loss of subcutaneous fat from the extremities and excess fat accumulation on the face and neck  
  • Age of onset – postpubescent | Autosomal dominant |
| DCM      | • Progressive ventricular dilation and impaired systolic function leading to congestive heart failure  
  • Age of onset – usually adults between 4th and 6th decade | Autosomal dominant |
| MAD      | • Postnatal growth retardation, craniofacial and skeletal anomalies, mottled cutaneous pigmentation  
  • Age of onset – ~4 years | Autosomal recessive |
| Atypical WS | • Progeroid syndrome with features of partial alopecia, premature aging, short stature, hypogonadism, osteoporosis, premature atherosclerosis, weak voice, cataracts  
  • Age of onset – ~13 years | Autosomal dominant |
| RD       | • Skin tightness causes fetal akinesia or hypokinesia deformation sequence – lethal  
  • Age of onset – fetal with live born children usually dying in 1st week | Rarely due to variant of LMNA; reported cases have a de novo, autosomal dominant variant |