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
  o 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
  o Structural component of the nuclear membrane
  o 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
  o Predominantly missense
  o 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
  o Sequencing – 99%
  o MLPA – 90%
• Analytical specificity
  o Sequencing – 99%
  o MLPA – 98%

Results
• Positive – single pathogenic LMNA variant detected
  o Consistent with diagnosis of an autosomal dominant laminopathy
  o May indicate carrier status for an autosomal recessive LMNA-related disorder
• Negative – LMNA variant not detected
  o 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

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<tr>
<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 atrioventricular 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 |