Clinical Features, Molecular Genetics, and Inheritance:

- **Dilated cardiomyopathy (DCM)** is a severe disease of heart muscle characterized by progressive ventricular dilation and impaired systolic function and is a major cause of congestive heart failure. The prevalence of DCM is estimated at 1 in 2,500 individuals, with inherited forms accounting for 30-50%. Inherited forms of DCM show clinical variability and are a genetically heterogeneous group. Mutations of the Lamin A/C gene (LMNA) have been identified in ~8% of all DCM patients (1). Of the subset of inherited DCM patients with accompanying conduction disease, LMNA mutations are present in 40-50% of cases (2). LMNA-associated DCM is inherited in an autosomal dominant fashion.

- **Emery-Dreifuss Muscular Dystrophy (EDMD)** is characterized by early contractures of the elbows and Achilles tendons, slowly progressive muscle wasting and weakness, and late onset cardiomyopathy and arrhythmia. EDMD can be either X-linked or autosomal dominant in inheritance, and the vast majority of autosomal dominant cases are due to mutations in the LMNA gene (3).

- **The Limb Girdle Muscular Dystrophies (LGMD)** are a genetically heterogenous group of disorders. One form, LGMD1B, is autosomal dominant with slowly progressive limb girdle muscular dystrophy, age-related atrioventricular cardiac conduction disturbances, and the absence of early contractures. Mutations of the LMNA gene are the basis of LGMD1B (4).

- **Hutchinson-Gilford progeria syndrome (HGPS)** is a rare autosomal dominant genetic disorder, estimated to affect 1 in 4 million individuals, that causes clinical features in childhood that are associated with premature aging. Such features may include hair loss, growth retardation, joint degeneration, and atherosclerosis. Children with HGPS tend to appear normal at birth and usually have normal motor and mental development, but severe growth retardation is observed by 2 years of age. A vast majority of patients with HGPS have a LMNA G608G mutation, but other mutations in LMNA have been reported (5).

- **Mandibuloacral dysplasia (MAD)** is a rare autosomal recessive disorder caused by LMNA mutations, which results in post-natal growth retardation, craniofacial and skeletal anomalies, and mottled cutaneous pigmentation. Symptoms become evident after 4 years of life and first present with growth retardation (6).

- **Charcot-Marie-Tooth type 2B1** is an axonal autosomal recessive laminopathy and neuropathy, characterized predominantly by symmetrical distal muscle weakness and atrophy. Individuals initially present with depressed or absent tendon reflexes with weakness of foot dorsiflexion at the ankle. The average age of onset is 14 years (7).

- **Familial partial lipodystrophy (FLPD), Dunnigan type**, is an autosomal dominant disease characterized by the progressive loss of subcutaneous fat from the extremities. A muscular appearance with prominent superficial veins results, and excess fat accumulates on the face and neck. Prior to puberty, patients have a normal fat distribution (8).

**Additional Resources:**

**The Progeria Research Foundation**
Phone: 978-535-2594
Fax: 978-535-5849
Email: info@progeriaresearch.org
[www.progeriaresearch.org](http://www.progeriaresearch.org)

**The American Heart Association**
Phone: 1-800-242-8721
[www.americanheart.org](http://www.americanheart.org)
Test methods:
For Hutchinson-Gilford progeria, we offer targeted mutation analysis for the common mutation (G608G). If this testing is positive, we will issue a report and bill only for the targeted analysis. If this testing is negative, we will perform full gene sequencing. We will issue a report at the end of testing and bill only for the full gene sequencing.

For all other indications, we offer comprehensive sequence coverage of the coding regions and splice junctions of the LMNA gene. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20 bp. We also offer oligonucleotide array-CGH analysis to identify deletions/duplications involving the coding region of the LMNA gene. Deletions/duplications of less than 2 kb may not be detected by this methodology. Array-CGH will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of this assay may be reduced when DNA is extracted by an outside laboratory.

Please be clear about the suspected diagnosis or indication on the requisition form.

Targeted mutation analysis (for Hutchinson-Gilford progeria only)
Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
Cost: $500
CPT codes: 81403
Turn-around time: 3 weeks

LMNA sequencing
Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
Cost: $1000
CPT codes: 81406
Turn-around time: 4 weeks

LMNA deletion/duplication analysis
Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
Cost: $1000
CPT codes: 81405
Turn-around time: 4 weeks

Results:
Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

References: