Deletion/Duplication Testing of mtDNA

Clinical Features:
Mitochondrial DNA (mtDNA) deletion syndromes predominately consist of three overlapping phenotypes that usually occur in a single individual in a family. The three phenotypes are Kearns-Sayre syndrome (KSS), progressive external ophthalmoplegia (PEO), and Pearson syndrome (Table 1).

<table>
<thead>
<tr>
<th>mtDNA Deletion Syndromes</th>
<th>Disease Characteristics</th>
<th>Characteristics of mtDNA Deletions¹</th>
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<tr>
<td>KSS</td>
<td>A triad of (1) onset &lt; 20 y/o, (2) pigmentary retinopathy, and (3) PEO, plus at least one of the following: cardiac conduction block, cerebrospinal fluid protein concentration greater than 100 mg/dL, or cerebellar ataxia</td>
<td>~90% have a large-scale 1.3-10 kb deletion usually present in all tissues, but most abundant in muscle, and often undetectable in blood cells. A deletion of 4977 bp is the most common. Over 150 deletions have been associated with KSS. Large-scale duplications have also been reported.</td>
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<td>CPEO</td>
<td>Ptosis, ophthalmoplegia, and variably severe proximal limb weakness may be the early sign of KSS.</td>
<td>Deletion/duplication analysis is estimated to identify a deletion in approximately 50% of patients. Deletions are confined to skeletal muscle.</td>
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<td>Pearson Syndrome</td>
<td>Sideroblastic anemia, exocrine pancreas dysfunction, usually fatal in infancy: children who survive the disease usually go on to develop KSS.</td>
<td>Deletions are usually more abundant in blood than other tissue types. Deletion load gradually decreases in blood and increases in muscle as the disease evolves to PEO and KSS over time.</td>
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Genetics:
Variants in mtDNA arise de novo or are maternally inherited. In most cases, mtDNA point variants are inherited, whereas gross deletions arise de novo. Each mitochondrion has multiple copies of mtDNA and there are hundreds to thousands of mitochondria per cell, dependent on the cell type. Usually, mtDNA variants affect only a fraction of the mtDNA; the coexistence of normal and mutant mtDNA is called heteroplasm. When the percentage of mutant mtDNA (variant load) reaches a certain threshold that varies by tissue type, age, and specific variant the function of that tissue may become impaired. As the variant load varies within and between tissues, the manifestation of mitochondrial disease may reflect tissue-specific variant load. Many factors can affect the percent heteroplasm these include physiologic processes that are affected by the mtDNA variant, the function of the tissue, and the rate of cell division in that tissue. Variants in mtDNA may only be identified in specific tissues, particularly those with a lower rate of cell division such as skeletal muscle, heart and brain. Large deletions of mtDNA associated with Pearson syndrome are detectable in blood, while large deletions associated with KSS and CPEO are detectable in skeletal muscle.

Test Methods:
This test uses a custom-designed microarray with more than 1,600 60-mer probes per mtDNA molecule with probes spaced approximately every 10 bp. Based on this design, any single deletion/duplication larger than 2 Kb can be reliably detected; in addition, heteroplasm can be estimated. Due to the large number of probes, deletion/duplication analysis, as performed by GeneDx, is expected to be highly sensitive and able to detect all large mtDNA deletions/duplications associated with mitochondrial disease including those associated with KSS, CPEO, and Pearson syndrome. Heteroplasm less than 15% may not be detected by this method.

Test Sensitivity:
Approximately 90% of individuals with Pearson syndrome or KSS, and 50% of patients with CPEO have a large-scale (2-10 kb) mtDNA deletion. MtDNA deletions larger than 2 kb account for >95% of the reported disease causing mtDNA deletions and are responsible for >99% cases of mtDNA deletion-associated mitochondrial disease (www.mitomap.org).

References: