Enhanced Carrier Testing for Spinal Muscular Atrophy
Detection of SMA (2+0) Silent Carriers and Improved Residual Risk Estimates

Background Information:
Spinal muscular atrophy (SMA) is one of the most common autosomal recessive diseases with an incidence of about 1 in 10,000 livebirths and a carrier frequency of 1 in 35 to 1 in 117, depending on ethnicity. The disease is characterized by the progressive degeneration and loss of anterior horn cells in the spinal cord and brain stem nuclei causing symmetric muscle weakness and atrophy. SMA is caused by mutations in the SMN1 gene generally involving its deletion or gene conversion with the highly homologous, tightly linked SMN2 gene. SMA carrier screening employs dosage sensitive methods that determine SMN1 copy number; however, these methods are limited by their inability to identify silent (2+0) carriers, with two copies (duplication) of SMN1 on one chromosome and deletion on the other. Consequently, carrier detection rates currently range from 71 - 94% depending on ethnicity. Sema4™ has identified an SMN1 specific haplotype that delineates duplication alleles, which significantly improves detection rates and/or residual risk estimates for SMA carrier screening in all populations examined.

Schematic of SMN1 and SMN2 Gene Configuration:

Wild-Type: 2 copies of SMN1
Carrier: 1 copy of SMN1
Duplication: 3 copies of SMN1
Silent Carrier: 2 copies SMN1

Testing Methods, Detection Rates, Turnaround Time, and Residual Risk Estimates:
Enhanced SMA carrier screening developed at Mount Sinai involves testing for a single polymorphism in intron 7 of SMN1, g.27134T>G, which is part of a haplotype specific for SMN1 duplication alleles in the Ashkenazi Jewish and Asian populations and is significantly enriched in individuals with SMN1 duplications in the African American, Hispanic and Caucasian populations. Importantly, the detection rate in the Ashkenazi Jewish population increases from 90 to 94% by testing for the g.27134T>G polymorphism as part of the carrier screen. For African Americans, testing negative for g.27134T>G decreases the residual risk of being a carrier in an individual with two copies of SMN1 from 1 in 121 to 1 in 396. Conversely, African Americans with two copies of SMN1 that test positive for g.27134T>G have a residual risk that is increased to 1 in 34.

Testing is performed in parallel with general carrier screening for SMA by dosage sensitive methods and the results are reported together with final residual risk estimates calculated based on the presence or absence of g.27134T>G (see Residual Risk Estimates table). This testing strategy keeps the overall turnaround time of SMA screening within the usual 7-12 day period.
### Residual Risk Estimates

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Carrier Frequency</th>
<th>Current Detection Rate</th>
<th>Residual Risk After Negative Result*</th>
<th>Enhanced Detection Rate with g.27134T&gt;G Negative</th>
<th>Residual Risk g.27134T&gt;G* Positive</th>
<th>Residual Risk g.27134T&gt;G* Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashkenazi Jewish</td>
<td>1 in 41(^i)</td>
<td>90%(^{1,4})</td>
<td>1 in 345(^i)</td>
<td>94%(^{i})</td>
<td>1 in 580(^i)</td>
<td>^Likely Carrier(^i)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 in 53(^i)</td>
<td>92.6%(^1)</td>
<td>1 in 628(^i)</td>
<td>93.3%(^{4})</td>
<td>1 in 702(^i)</td>
<td>^Likely Carrier(^4)</td>
</tr>
<tr>
<td>African American</td>
<td>1 in 66(^i)</td>
<td>71.1%(^1)</td>
<td>1 in 121(^i)</td>
<td>1 in 396(^4)</td>
<td>1 in 34(^4)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>1 in 117(^i)</td>
<td>90.6%(^1)</td>
<td>1 in 1061(^i)</td>
<td>1 in 1762(^4)</td>
<td>1 in 140(^4)</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>1 in 35(^i)</td>
<td>94.9%(^1)</td>
<td>1 in 632(^i)</td>
<td>1 in 769(^4)</td>
<td>1 in 29(^4)</td>
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</tr>
</tbody>
</table>

* Residual risk with two copies SMN1 detected using dosage sensitive methods
^ Parental follow-up may be requested by the laboratory for confirmation at no additional cost

### Specimen & Shipping Requirements:

Two lavender-top (EDTA) 5-10 ml tubes of blood shipped refrigerated or at room temperature (do NOT freeze).

### References: