Gaucher Disease Biomarker: Lyso-GL1

Disease Overview

Gaucher disease type 1 is one of the most common lysosomal storage disorders (LSDs).
• Gaucher disease is caused by a deficiency of the enzyme acid β-glucosidase (glucocerebrosidase), encoded by the GBA gene. Deficiency of this enzyme leads to a buildup of glucosylceramide (GL1) and glucosylsphingosine (also called lyso-GL1, lyso-GB1, or glucopsychosine) in cells of the macrophage monocyte lineage.\(^1\)
• Accumulation of these lipids throughout the body leads to progressive anemia, thrombocytopenia, and hepatosplenomegaly. Skeletal disease is caused by displacement of normal marrow cells with disease-affected cells, resulting in bone pain, osteopenia, osteonecrosis, and fractures.\(^1,2\)
• Macrophage proliferation leads to elevated levels of numerous inflammatory and proinflammatory proteins, such as angiotensin-converting enzyme, tartrate-resistant acid phosphatase, and chitotriosidase, as well as chemokines and cytokines.\(^3,4,5\)

Biomarker: Glucosylsphingosine (Lyso-GL1, Lyso-GB1)

Metabolic Pathway:

Glucosylsphingosine (lyso-GL1) is the deacylated form of glucosylceramide (GL1). Both lyso-GL1 and GL1 accumulate in Gaucher disease as a direct result of acid β-glucosidase deficiency, making lyso-GL1 a highly specific biomarker.

A biologically active molecule implicated in the pathophysiology of Gaucher disease, lyso-GL1 is known to:
• Mediate osteoblastic dysfunction and alter intracellular calcium homeostasis.\(^6\)
• Be a potent antigen for type II natural killer T cells,\(^7\) which
  • Trigger proliferation of B cells that differentiate into anti-lyso-GL1- and anti-GL1-autoantibody-secreting plasma cells,\(^8\) which
  • Activate the complement pathway leading to chronic inflammation,\(^7,8\) triggering a feedback loop that increases expression of glucosylceramide synthase (GCS), leading to increased production of GL1 and lyso-GL1.\(^9\)

In patients with Gaucher type I, lyso-GL1 correlates with chitotriosidase, CCL18, spleen volume, liver volume,\(^10\) platelets, and hemoglobin.\(^11\) Splenectomized patients have been shown to have higher lyso-GL1 levels than non-splenectomized patients.\(^10\)
Utility of Lyso-GL1 in the Diagnostic Setting

- There is clear differentiation between Gaucher patients and healthy controls.\(^{13}\) There also appears to be differentiation by genotype with N370S/L444P patients having higher average levels than N370S homozygotes, suggesting lyso-GL1 levels correlate with disease severity.\(^{13}\)
- Carriers of either mutation have levels similar to normal controls.\(^{13}\)

### Lyso-GL1 testing options:

<table>
<thead>
<tr>
<th>Lab</th>
<th>Test Name &amp; Code</th>
<th>Sample Requirements</th>
<th>Kits</th>
<th>Mobile Blood Draw</th>
<th>Billing</th>
<th>Contact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genzyme Clinical Specialty Lab</td>
<td>Plasma Lyso-GL1</td>
<td>Plasma: 3 x 2 ml; WB: 1 x 6 ml sodium heparin (green) tube</td>
<td>Blood</td>
<td>30 d</td>
<td>No charge*</td>
<td>P: 800-745-4447, Option 1</td>
</tr>
<tr>
<td></td>
<td>β-glucosidase enzyme</td>
<td>WB: 3-5 ml sodium heparin (green) tube; DBS card: 2-5 circles</td>
<td>Blood, DBS, Saliva</td>
<td>3 d</td>
<td>Yes</td>
<td>P: 866-354-2910; E: <a href="mailto:genomics@perkinelmer.com">genomics@perkinelmer.com</a>; W: <a href="http://www.LanternProjectDx.com">www.LanternProjectDx.com</a></td>
</tr>
<tr>
<td></td>
<td>GBA Sequencing</td>
<td>WB: 3-5 ml EDTA (lavender) tube; DBS card: 2-5 circles; Saliva</td>
<td>3 wks</td>
<td></td>
<td>No charge*</td>
<td>E: <a href="mailto:genomics@perkinelmer.com">genomics@perkinelmer.com</a></td>
</tr>
<tr>
<td></td>
<td>Lyso-GL1(^{17})</td>
<td>DBS: 2 spots</td>
<td>3 d</td>
<td></td>
<td></td>
<td>P: 866-354-2910; E: <a href="mailto:genomics@perkinelmer.com">genomics@perkinelmer.com</a>; W: <a href="http://www.LanternProjectDx.com">www.LanternProjectDx.com</a></td>
</tr>
<tr>
<td>The Lantern Project (performed at PerkinElmer Genomics)</td>
<td>β-glucosidase enzyme</td>
<td>WB: 6 ml ACD (yellow) tube</td>
<td>Blood</td>
<td>8-15 d</td>
<td></td>
<td>E: <a href="mailto:clientservices@sema4.com">clientservices@sema4.com</a>; W: <a href="http://www.sema4.com">www.sema4.com</a></td>
</tr>
<tr>
<td></td>
<td>GBA Sequencing</td>
<td>WB: 3 ml EDTA (lavender) or ACD (yellow) tube; DBS card: 2-5 circles</td>
<td>Yes</td>
<td>Inst, Ins (account required)</td>
<td>P: 800-533-1710; E: <a href="mailto:mcl@mayo.edu">mcl@mayo.edu</a>; W: <a href="http://www.mayocliniclabs.com">www.mayocliniclabs.com</a></td>
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<tr>
<td></td>
<td>Glucopsychosine (GPSY/GPSYP or GPSYW)</td>
<td>WB: 1 ml EDTA (lavender) tube; DBS card: 2 spots; Plasma: 0.3 ml</td>
<td>14-20 d</td>
<td></td>
<td></td>
<td>P: 866-354-2910; E: <a href="mailto:genomics@perkinelmer.com">genomics@perkinelmer.com</a>; W: <a href="http://www.LanternProjectDx.com">www.LanternProjectDx.com</a></td>
</tr>
<tr>
<td>Mayo Clinic Laboratories</td>
<td>Glucosylsphingosine (Lyso-GB1) Monitoring, B0030</td>
<td>DBS: 2 spots</td>
<td>DBS</td>
<td>3 d</td>
<td>No charge*</td>
<td>P: 866-354-2910; E: <a href="mailto:genomics@perkinelmer.com">genomics@perkinelmer.com</a>; W: <a href="http://www.LanternProjectDx.com">www.LanternProjectDx.com</a></td>
</tr>
<tr>
<td>PerkinElmer Genomics</td>
<td>β-glucosidase enzyme</td>
<td>WB: 5-10 ml EDTA (lavender), ACD (yellow), or sodium heparin (green) tube</td>
<td>Blood, Saliva</td>
<td>7 d</td>
<td>Yes</td>
<td>P: 800-298-6470; E: <a href="mailto:clientservices@sema4.com">clientservices@sema4.com</a>; W: <a href="http://www.sema4.com">www.sema4.com</a></td>
</tr>
<tr>
<td></td>
<td>GBA Sequencing</td>
<td>WB: 2 x 5-10 ml EDTA (lavender) tube; Saliva</td>
<td>14 d</td>
<td></td>
<td></td>
<td>P: 800-298-6470; E: <a href="mailto:clientservices@sema4.com">clientservices@sema4.com</a>; W: <a href="http://www.sema4.com">www.sema4.com</a></td>
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<tr>
<td></td>
<td>Lyso-GL1</td>
<td>WB: 1-2 ml EDTA (liver message) or heparin (green) tube</td>
<td>5 d</td>
<td></td>
<td></td>
<td>P: 800-298-6470; E: <a href="mailto:clientservices@sema4.com">clientservices@sema4.com</a>; W: <a href="http://www.sema4.com">www.sema4.com</a></td>
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\(\text{d=days, DBS=dried blood spots, Ins=Insurance, Inst=Institutional, WB=whole blood, w=weeks.}\)

\(^{*}\)Testing is performed at no charge; local charges may apply for sample collection, processing or shipping. Lyso-GL1 as part of The Lantern Project is for diagnostic assistance only, not monitoring of existing patients.


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