Sema4 Elements™
Expanded Carrier Screen
With Personalized Residual Risk
The advantages of expanded carrier screening

Informed by ancestry, delivered with confidence

Sem4, Elements Expanded Carrier Screen (ECS) is one of the most comprehensive and accurate carrier screens available, with personalized residual risk reporting based on a patient’s molecular ancestry.

- Uses proprietary technology to identify a patient’s molecular ancestry on a genome-wide level for tailored personalized residual risk
- Integrates patient-specific genealogical information to help providers precisely understand a patient’s residual risk for passing on inherited disease
- Provides patients with personalized residual risk education and the option to view their ancestry report in Sem4’s Patient Portal

| Detects more high-risk pregnancies than traditional carrier screening by identifying up to 30 times as many carrier couples
<table>
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<tbody>
<tr>
<td>Traditional Carrier Screening</td>
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<td>1 in 800 CF and SMA</td>
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The American College of Obstetricians and Gynecologists (ACOG) recommends discussing carrier screening options—including expanded carrier screening—with all women who are pregnant or considering pregnancy.

- Preconception screening allows patients to consider more reproductive options, including preimplantation genetic diagnosis or donor gametes
- Screening while pregnant allows patients to consider options such as prenatal diagnosis and may help to inform care during pregnancy and after delivery

A negative test result for any given disease does not exclude an individual from being a carrier for that disease, but only reduces the risk of being a carrier. The patient may still have a pathogenic variant that was not identified by this testing.


Specimen requirements

- **Blood**: Two 5-10 mL EDTA tubes (lavender top), and either a third 5-10 mL EDTA tube or one 5-10 mL ACD tube (yellow top).
- **Saliva**: Saliva specimens are accepted in Oragene DNA (OG-500) kits by DNA Genotek. Please note that Tay Sachs enzyme analysis cannot be performed on saliva.
- If carrier screening was previously performed through Sem4, reanalysis and/or test enhancements may be ordered without providing an additional specimen. Please contact the laboratory to determine if an additional specimen is required.

Shipping requirements

- Ship at room temperature

Turnaround time

- Approximately 2 weeks from receipt of specimen

To request specimen kits or for more information about our carrier screening panels, please contact 800-298-6470.
More than 500 insights to guide family planning

Sema4 Elements™ ECS is one of the most comprehensive carrier screens available

Our ECS solution provides highly accurate insight into carrier status for more than 500 diseases to help patients make informed family planning choices.

Conditions covered by this panel

- **Cardiovascular conditions**
  - Duchenne muscular dystrophy
  - Becker muscular dystrophy
  - Glycogen storage disease, type II
  - Limb-girdle muscular dystrophy, type 2i

- **Endocrine conditions**
  - Alstrom syndrome
  - Combined pituitary hormone deficiency 2
  - Lipoid adrenal hyperplasia

- **Hematologic disorders**
  - Alpha-thalassemia
  - Beta-globin-related hemoglobinopathies
  - Factor XI deficiency

- **Hepatic conditions**
  - Acute infantile liver failure
  - Citrin deficiency
  - Progressive familial intrahepatic cholestasis, type 2

- **Immunodeficiencies**
  - Adenosine deaminase deficiency
  - Omenn syndrome (RAG2-related)
  - X-linked severe combined immunodeficiency

- **Metabolic disorders**
  - Glutaric acidemia, type I
  - Isovaleric acidemia
  - Tyrosinemia, type I

- **Neurological disorders**
  - Leukoencephalopathy with vanishing white matter
  - Spinal muscular atrophy
  - X-linked adrenoleukodystrophy

- **Pulmonary disorders**
  - Cystic fibrosis

- **Renal conditions**
  - Alport syndrome
  - Nephrogenic diabetes insipidus, type II
  - Polycystic kidney disease, autosomal recessive

- **Skeletal disorders**
  - Hypophosphatasia
  - Spondylothoracic dysostosis
  - Steel syndrome

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- **Early-onset and severe**

- **Onset in childhood or early adulthood and progressive severity**

- **Amenable to early detection, where treatment or intervention can improve lifetime management of the disease**

To view a full list of conditions that this test screens for, please visit sema4.com/carrierscreening.
Comprehensive coverage for patients with Jewish ancestry

Semaq Elements™ ECS includes 101 genes associated with conditions that are more common in people of Jewish ancestry

There are many known pathogenic variants found at increased frequencies in the Ashkenazi Jewish (Central and Eastern European), Sephardi Jewish (Southern European and Northern African), and Mizrahi Jewish (Middle Eastern and Arab) populations.

Comprehensive Jewish carrier screen
- 101 genes

Ashkenazi Jewish carrier screen
- 64 genes

Sephardi-Mizrahi carrier screen
- 54 genes

Diseases common to all Jewish groups
- 17 genes

Ashkenazi Jewish diseases
- 47 genes

Sephardi-Mizrahi diseases
- 37 genes

- Alpha-thalassemia (HBA1 and HBA2)
- Beta-globin-related hemoglobinopathies (HBB)
- Congenital adrenal hyperplasia due to 21-hydroxylase deficiency (CYP21A2)
- Congenital disorder of glycosylation, type Ia (PMM2)
- Cystic fibrosis (CFTR)
- Duchenne muscular dystrophy or Becker muscular dystrophy (DMD)
- Familial Mediterranean fever (MEFV)
- Fragile X syndrome (FMR1)
- Glycogen storage disease, type II (GAA)
- Medium chain acyl-CoA dehydrogenase deficiency (ACADM)
- Phenylketonuria (PAH)
- Retinitis pigmentosa 28 (FAM161A)
- Smith-Lemli-Opitz syndrome (DHCR7)
- Spinal muscular atrophy (SMN1)
- Tay-Sachs disease (HEXA)
- Wilson disease (ATP7B)
- 3-phosphoglycerate dehydrogenase deficiency (PHGDH)
- Abetalipoproteinemia (MTP)
- Alport syndrome (COL4A3-related)
- Cerebrotendinous xanthomatosis (CYP27A1)
- Ehlers-Danlos syndrome, type VIIa (ADAMTS2)
- Enhanced S-cone syndrome (NR2E3)
- Factor XI deficiency (FII)
- Familial dysautonomia (IKBKAP)
- 3-methylglutaconic aciduria, type III/3/4 Optic atrophy 3 with cataract (OPA3)
- Acute infantile liver failure (TRMU)
- Adrenoleukodystrophy, X-linked (ABCD1)
- Asparagine synthetase deficiency (ASNS)
- Ataxia-telangiectasia (ATM)
- Cerebrotendinous xanthomatosis (CYP27A1)
- Chronic granulomatous disease (CYBA-related)
- Congenital insensitivity to pain with anhidrosis (NFTRX)
- Congenital myasthenic syndrome (RAPS1-related)
- Carnitine palmitoyltransferase II deficiency (CPT2)
- Choreoacanthocytosis (VPS13A)
- Congenital amegakaryocytic thrombocytopenia (MPL)
- Deafness, autosomal recessive 77 (LOR77D2)
- Dyserthropoietic congenita (RTEL1-related)
- Factor XI deficiency (FII)
- Familial dysautonomia (IKBKAP)
- 32 additional genes

While expanded carrier screening can be beneficial for all patients, we also offer panels designed to test specifically for conditions that are more common in people of Jewish ancestry.
## Flexible panel options for your patients

<table>
<thead>
<tr>
<th>Expanded Carrier Screen panel</th>
<th>502 genes</th>
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<tbody>
<tr>
<td>- Includes all genes in the 283 panel, plus 200+ additional genes that provide clinically relevant and actionable information</td>
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<tr>
<th>Expanded Carrier Screen panel</th>
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<td>- Pan-ethnic panel of genes associated with a wide-array of clinically relevant conditions, including cardiovascular, endocrine, neurological, hematologic, and pulmonary disorders</td>
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<tr>
<th>Expanded Carrier Screen panel</th>
<th>152 genes</th>
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<td>- Includes 84 genes recommended for expanded carrier screening panels by Stevens, et al.* based on a 2013 position statement from American College of Medical Genetics and Genomics (ACMG) and ACOG Committee Opinion 690</td>
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<tr>
<td>- Also includes an additional 53 genes from our comprehensive Jewish carrier screening panel and 15 other genes with a carrier frequency of &gt;1 in 100 in an ethnic subgroup</td>
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<th>Expanded Carrier Screen panel</th>
<th>39 genes</th>
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<td>- Includes 23 genes highlighted in ACOG Committee Opinion 690: Carrier Screening in the Age of Genomic Medicine</td>
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<tr>
<td>- Also includes 16 additional higher-frequency genes associated with conditions such as Duchenne muscular dystrophy, autosomal recessive polycystic kidney disease, and congenital disorder of glycosylation, type 1A</td>
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<th>East Asian carrier screen</th>
<th>95 genes</th>
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<td>- Includes 95 genes reported to have an increased carrier frequency in the East Asian population, such as USH2A (Usher syndrome, type 2A), SLC12A3 (Gitelman syndrome), and SLC26A4 (Pendred syndrome)</td>
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<td>- Genes with known founder mutations in the East Asian population, like SLC25A13 (citrin deficiency), ATP7B (Wilson disease), and GJB2 (non-syndromic hearing loss), are also covered by this panel</td>
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<tr>
<th>High-frequency pan-ethnic panel</th>
<th>11 genes</th>
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<tr>
<td>- Alpha-thalassemia (HBA1 and HBA2)</td>
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<td>- Beta-thalassemia (HBB)</td>
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<td>- Beta-globin-related hemoglobinopathies, HbC variant (HBB)</td>
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<td>- Congenital disorder of glycosylation, type Ia (PMM2)</td>
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<td>- Spinal muscular atrophy (SMN1)</td>
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<th>Standard pan-ethnic panel</th>
<th>4 genes</th>
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<tr>
<td>- Cystic fibrosis (CFTR)</td>
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<td>- Spinal muscular atrophy (SMN1)</td>
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<td>- Smith-Lemli-Opitz syndrome (DHCR7)</td>
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<th>Optional Add-on genes</th>
<th>19 genes</th>
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<td>- Detects carrier status for conditions including thrombophilia with Factor II and Factor V deficiency. One or more of these genes may be added to any carrier screening panel</td>
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<th>Custom carrier screening</th>
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<tr>
<td>- If a customized panel is desired, any subset of the 502 genes included on the Expanded Carrier Screen panel may be selected for testing</td>
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To learn more about our different carrier screening panels, please visit [sema4.com/testcatalog](http://sema4.com/testcatalog).
Support for your practice and patients

Our CLIA-certified lab offers comprehensive prenatal testing

- In the case of a positive carrier screen for autosomal recessive disease(s), custom testing for partner follow-up is available
- Prenatal diagnostic testing is also available directly from Sema4, including chromosome analysis, aneuploidy FISH, or chromosomal microarray. Diagnostic testing is available through chorionic villus sampling (CVS) at 10-12 weeks of pregnancy and amniocentesis after 15 weeks of pregnancy

Genetics can be complicated for your patients. Our counselors can help.

Before testing

Genetic counselors can help educate patients about carrier screening and answer questions about testing.

If your patient has a family history of genetic disease, our genetic counselors can help determine which carrier screening panel may be appropriate.

After results are received

Genetic counselors are available to disclose carrier screening results and can offer guidance and support for patients with positive results.

Full-scale support for seamless workflow integration

- Wrap-around genetic counseling and customer service support, including explanation of results, patient video education, and multiple reporting options (EMR, portal, paper)

Multiplatform testing technologies for highly accurate results

Multiple methods of analysis are used in parallel to ensure the highest detection rate for each gene based on gene-specific mutation mechanisms.

- **High-throughput, next-generation sequencing (NGS)** is performed to examine multiple genes at once. Additionally, a custom bioinformatic algorithm is used to analyze this data in order to identify copy number variants (CNVs). Pathogenic or likely pathogenic deletions and duplications of 2 or more exons in length will be reported. Additionally, single-exon pathogenic or likely pathogenic CNVs will also be reported when detected.

- **Long-range polymerase chain reaction (PCR)** is used to capture the functional gene for accurate analysis of genes with known pseudogenes, including CYP21A2, GBA, HBA1 and HBA2. Long-range PCR followed by Sanger sequencing is used to confirm SMN1 variants detected via NGS.

- **Multiplex ligation-dependent probe amplification (MLPA)** is used to detect copy number changes for congenital adrenal hyperplasia (CYP21A2), spinal muscular atrophy (SMN1 and SMN2), alpha-thalassemia (HBA1 and HBA2), and Duchenne and Becker muscular dystrophy (DMD). MLPA may also be employed for Gaucher disease (GBA), cystic fibrosis (CFTR), and non-syndromic hearing loss (GJB2/GJB6) when indicated.

- **Fragile X CGG repeat analysis** is performed by PCR amplification followed by capillary electrophoresis for allele sizing. Samples positive for FMR1 CGG repeats in the premutation or full mutation size ranges are further evaluated by Southern blot analysis. Reflexing to AGG interruption testing for premutation carriers via our partnership with Asuragen is also now available.

- **Genotyping analysis** is used to identify or confirm variants that are complex in nature or are present in low copy repeats.

- **Tay-Sachs enzyme testing** is a biochemical assay used to detect carriers of Tay-Sachs disease that may be missed by molecular testing.

- **Sanger sequencing** may be used for select genes on the panel due to inadequate next-generation sequence coverage or for confirmation of variants identified by NGS.

- **Exon array and/or qPCR** may be performed to confirm CNVs identified by bioinformatic analysis of the NGS data.

Our carrier screening technologies are >99% accurate.
At Sema4, we are dedicated to helping every patient access advanced genetic testing

Sema4 is contracted with all major national payors.

Carrier screening is covered by most insurance plans, however, copays, co-insurance, and/or deductibles may vary by health plan.

We appeal coverage determinations on behalf of patients if precertification or pre-authorization requests are denied.

We are committed to ensuring that all patients can access testing. Affordable payment plans, self-pay pricing, and other financial assistance options are available for patients who are uninsured or underinsured. More than 90% of patients pay $0 out of pocket.

If patients have any questions about the explanation of benefits from their insurance provider or their Sema4 bill, our billing specialists are here to help.

800-298-6470    billing@sema4.com

Sema4 Elements™ offers a portfolio of information-driven genomic solutions, digital tools for patients and providers, and services that enable providers to treat patients holistically during their reproductive and generational health journey.

Learn more at sema4.com/Elements