Sema4 Expanded Carrier Screen

Comprehensive and accurate insight to help guide family planning

sema4

Specimen requirements

- **Blood:** Two 5-10 mL EDTA tubes (lavender top) and 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 Sema4, 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

- 10 to 14 days from receipt of specimen

To request specimen kits or for more information about our carrier screening panels, please contact **800-298-6470**.

The advantages of expanded carrier screening

As families and societies grow more diverse, ethnicity-based screening becomes more challenging

- Clinical guidelines often recommend carrier screening based on a patient's ethnicity
- However, self-reported ethnicity may not accurately reflect a patient's unique ancestry[1]

In one study (n=1752), self-reported ethnicity did not match geographic ancestry in

nearly 1 in 5 people[2]

Expanded screening can help ensure comprehensive coverage for diverse patient populations

- Expanded carrier screening may better identify risk for genetic conditions in diverse populations than smaller or ethnicity-based panels

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

[1]Shraga R, et al. Evaluating genetic ancestry and self-reported ethnicity in the context of carrier screening. *BMC Genetics*. 18(1):99. doi: 10.1186/s12863-017-0570-y.

[2]Hollenback JA, et al. Race, ethnicity and ancestry in unrelated transplant matching for the national marrow donor program: A comparison of multiple forms of self-identification with genetics. *PloS ONE*. 2015;10(8): e0135960

sema4

One test. 283 insights to guide family planning.

Sema4 Expanded Carrier Screen is one of the most comprehensive carrier screens available

Our Expanded Carrier Screen provides highly accurate insight into carrier status for **more than 280 diseases** to help patients make informed family planning choices

Conditions covered by this panel

Cardiovascular conditions

- Duchenne muscular dystrophy and 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

→ To view a full list of conditions that this test screens for, please visit **sema4.com/carrierscreening**.

Designed to maximize clinical utility

All conditions included on the Expanded Carrier Screen panel met strict criteria for inclusion.

- Early-onset and severe

or

- Onset in childhood or early adulthood and progressive severity

or

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

Conditions that matter

Our Expanded Carrier Screen includes conditions that are not found on standard carrier screening panels, such as Leber congenital amaurosis 10 and other *CEP290*-related ciliopathies.

Leber congenital amaurosis 10 and other *CEP290*-related ciliopathies are a spectrum of severe genetic conditions that may cause symptoms such as congenital blindness, intellectual disability, and death in infancy.

While *CEP290*-related ciliopathies are considered to be rare diseases,

1 in 120

people worldwide are carriers.

This number is even higher for certain ethnicities.

1 in 32

people with East Asian ancestry are carriers.

sema4

Comprehensive coverage for patients with Jewish ancestry

Our Expanded Carrier Screen 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.

Diseases common to all Jewish groups
17 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*)
- Phenylalanine hydroxylase deficiency (*PAH*)
- Retinitis pigmentosa 28 (*FAM161A*)
- Smith-Lemli-Optiz syndrome (*DHCR7*)
- Spinal muscular atrophy (*SMN1*)
- Tay-Sachs disease (*HEXA*)
- Wilson disease (*ATP7B*)

Ashkenzi Jewish diseases
47 genes

- 3-phosphoglycerate dehydrogenase deficiency (*PHGDH*)
- Abetalipoproteinemia (*MTTP*)
- Alport syndrome (*COL4A3*-related) (*COL4A3*)
- Arthrogryposis, mental retardation, and seizures (*SLC35A3*)
- Bardet-Biedl syndrome (*BBS2*-related) (*BBS2*)
- Bloom syndrome (*BLM*)
- Canavan disease (*ASPA*)
- Carnitine palmitoyltransferase II deficiency (*CPT2*)
- Choreoacanthocytosis (*VPS13A*)
- Congenital amegakaryocytic thrombocytopenia (*MPL*)
- Deafness, autosomal recessive 77 (*LOXHB1*)
- Dyskeratosis congenita (*RTEL1*-related) (*RTEL1*)
- Ehlers-Danlos syndrome, type VIIc (*ADAMTS2*)
- Enhanced S-cone syndrome (*NR2E3*)
- Factor XI deficiency (*FII*)
- Familial dysautonomia (*IKBKAP*)

+31 additional genes

Sephardi-Mizrahi diseases
37 genes

- 3-methylglutaconic aciduria, type III/ 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) (*CYBA*)
- Congenital insensitivity to pain with anhidrosis (*NTRK1*)
- Congenital myasthenic syndrome (*RAPSN*-related) (*RAPSN*)
- Corticosterone methyloxidase deficiency (*CYP11B2*)
- Cystinosis (*CTNS*)
- Fanconi anemia, group A (*FANCA*)
- Glycogen storage disease, type III (*AGL*)
- Glycogen storage disease, type V (*PYGM*)
- Hereditary spastic paraparesis 49 (*TEXPR2*)
- Homocystinuria due to *MTHFR* deficiency (*MTHFR*)
- Inclusion body myopathy 2 (*GNE*)

+20 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.

Comprehensive Jewish carrier screen	Ashkenazi Jewish carrier screen	Sephardi-Mizrahi carrier screen
101 genes	**64 genes**	**54 genes**

Personalized options for your patients

If an expanded panel isn't right for your patient, we also offer flexible carrier screening options

Custom carrier screening

- If a customized panel is desired, any subset of the 283 genes included on the Expanded Carrier Screen panel may be selected for testing

---

Standard pan-ethnic panel

4 genes

- Cystic fibrosis *(CFTR)*
- Spinal muscular atrophy *(SMN1)*
- Smith-Lemli-Opitz syndrome *(DHCR7)*
- Fragile X syndrome *(FMR1)*

High-frequency pan-ethnic panel

11 genes

- Alpha-thalassemia (*HBA1* and *HBA2*)
- Beta-thalassemia *(HBB)*
- Beta-globin-related hemoglobinopathies, HbC variant *(HBB)*
- Congenital disorder of glycosylation, type Ia *(PMM2)*
- Cystic fibrosis *(CFTR)*
- Duchenne muscular dystrophy or Becker muscular dystrophy *(DMD)*
- Fragile X syndrome *(FMR1)*
- Medium chain acyl-CoA dehydrogenase deficiency *(ACADM)*
- Phenylalanine hydroxylase deficiency *(PAH)*
- Sickle cell disease *(HBB)*
- Smith-Lemli-Opitz syndrome *(DHCR7)*
- Spinal muscular atrophy *(SMN1)*

NEW

Expanded Carrier Screen panel

39 genes

- Includes 23 genes highlighted in ACOG Committee Opinion 690: *Carrier Screening in the Age of Genomic Medicine*
- 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

NEW

Expanded Carrier Screen panel

152 genes

- Includes 84 genes recommended for expanded carrier screening panels by Stevens, et al.[3] based on a 2013 position statement from American College of Medical Genetics and Genomics (ACMG) and ACOG Committee Opinion 690
- Also includes an additional 53 genes from our comprehensive Jewish carrier screening panel and 15 other genes with a carrier frequency of >1 in 100 in an ethnic subgroup

---

NEW

East Asian carrier screen

95 genes

- 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)
- 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

→ To learn more about our different carrier screening panels, please visit **sema4.com/testcatalog**.

[3]Stevens B. et al. Finding middle ground in constructing a clinically useful carrier screening panel. *Obstet Gynecol.* 2017;130(2):279-284.

sema4

Nine 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 confirmed and reported. Additionally, single-exon pathogenic or likely pathogenic CNVs will also be reported when detected and confirmed

- **Long-range polymerase chain reaction** is used to capture the functional gene for accurate analysis of genes with known pseudogenes, including *CYP21A2*, *GBA*, *HBA1* and *HBA2*

- **Multiplex ligation-dependent probe amplification (MLPA)** is used to detect copy number changes for congenital adrenal hyperplasia, Gaucher disease (when indicated), spinal muscular atrophy, alpha-thalassemia, and Duchenne and Becker muscular dystrophy

- **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

- **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.**

Support for your practice and patients

Our CLIA-certified lab offers comprehensive prenatal testing

- In the case of a positive carrier screen, custom testing for partner follow-up may be ordered
- Prenatal diagnostic testing may also be ordered 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
- Maternal serum screening and noninvasive prenatal testing are available

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.

sema4

Actionable insights with accessible pricing

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.

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**

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.

sema4

P: 800-298-6470 **F:** 646-859-6870

Branford CT Lic#: CL-0830 I Stamford CT Lic#: CL-1016