Sema4 Signal®
Data-driven Precision Oncology
Sema4 Signal enables and advances precision oncology care, from prevention to treatment to remission

Sema4 Signal is a family of data-driven precision oncology solutions incorporating advanced analytics, digital tools, and exome-based genomic testing. Component products and services can be leveraged individually or as part of a holistic solution to meet the specific needs of providers, patients, payors, and health systems. Sema4 Signal is:

- **Comprehensive**: Identify, treat, and monitor cancer with data-driven precision oncology solutions
- **Advanced**: Make better care decisions guided by sophisticated analytics, digital tools, and exome-based testing
- **Tailored**: Partner with us to deliver bespoke care solutions as unique as your patient’s cancer

A holistic approach to personalized cancer care

With its comprehensive suite of offerings, Sema4 Signal enables a holistic approach to deliver precision medicine throughout a patient’s journey, from assessing the risk of cancer to analyzing cancer for treatment options and long-term monitoring.

Comprehensive molecular profiling to guide personalized cancer treatment

The Sema4 Signal portfolio offers multiple cancer profiling solutions to meet providers’ clinical, research, and trial needs. Our **Sema4 Signal Somatic Cancer** tests generate actionable insights that help providers treat patients today while preparing to take advantage of the insights of tomorrow.

**Sema4 Signal Whole Exome/Transcriptome Sequencing (WES/WTS)**
Captures data from ~18,500 genes to provide the most comprehensive molecular picture of a patient’s cancer.

**Sema4 Signal PanCancer**
Reports findings on ~2,200 of the most relevant cancer driver genes, based on comprehensive WES/WTS data.

**Sema4 Signal Solid Tumor (+MSI)**
Targets 161 of the most clinically relevant and actionable cancer genes using as little as 10-20 ng of DNA.

To learn more about the Sema4 Signal Solid Tumor Panel, please call 833-486-6260, email ClientServicesOncology@sema4.com, or visit sema4.com/solid-tumor

1 - As of July 2020
Which test best meets my patient’s needs?

<table>
<thead>
<tr>
<th>Sema4 Signal WES/WTS</th>
<th>Sema4 Signal PanCancer</th>
<th>Sema4 Signal Solid Tumor Panel (+MSI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cancer type</strong></td>
<td>Solid tumors</td>
<td>Solid tumors</td>
</tr>
<tr>
<td>Hematologic malignancies</td>
<td>Hematologic malignancies</td>
<td></td>
</tr>
<tr>
<td><strong>Number of genes reported</strong></td>
<td>~18,500</td>
<td>~2,200&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Most suitable for</strong></td>
<td>Providers seeking the broadest data available</td>
<td>Researchers looking for the most comprehensive somatic panel</td>
</tr>
<tr>
<td>*</td>
<td>Smaller sample sizes*&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><strong>Molecular alterations detected</strong></td>
<td>SNVs/InDels</td>
<td>SNVs/InDels</td>
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<tr>
<td>Certain splice variants</td>
<td>Certain splice variants</td>
<td>Certain splice variants</td>
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<tr>
<td>CNVs</td>
<td>CNVs</td>
<td>CNVs</td>
</tr>
<tr>
<td>Fusions</td>
<td>Fusions</td>
<td>Fusions</td>
</tr>
<tr>
<td><strong>Immuno-oncology biomarkers analyzed</strong></td>
<td>MSI</td>
<td>MSI</td>
</tr>
<tr>
<td>MMR</td>
<td>MMR</td>
<td>MMR</td>
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<tr>
<td>PD-L1</td>
<td>PD-L1</td>
<td>PD-L1</td>
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<tr>
<td><strong>TMB</strong></td>
<td>TMB</td>
<td>TMB</td>
</tr>
<tr>
<td><strong>Germline findings reported (patient can opt out)</strong></td>
<td>Hereditary cancer genes</td>
<td>Hereditary cancer genes</td>
</tr>
<tr>
<td>Non-cancer genes, as per ACMG guidelines&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td></td>
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<tr>
<td><strong>Post-test genetic counseling</strong></td>
<td>For positive germline findings</td>
<td>For positive germline findings</td>
</tr>
<tr>
<td><strong>Turnaround time</strong></td>
<td>14-21 days</td>
<td>14-21 days</td>
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</tbody>
</table>

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Cancer whole exome sequencing

Sema4 Signal WES/WTS and Sema4 Signal PanCancer integrate tumor-normal matched whole exome sequencing (WES) with whole transcriptome sequencing (WTS) to deliver clinically actionable information about somatic and germline alterations in solid tumors and hematologic malignancies.

### WES (DNA)
- Delivers data from ~18,500 genes to provide the most in-depth profile of a patient’s cancer
- WES is the gold standard method for measuring tumor mutational burden (TMB)<sup>4</sup>

### WTS (RNA)
- Provides information on gene fusions and splice variants to help define molecular signatures, stratify risk, and inform the use of targeted therapies

### WES + WTS

By pairing WES with WTS, Sema4 provides information that meets the current and future needs of cancer patients, enabling providers to identify therapies and clinical trials today and leverage the advancements of tomorrow.

### Tumor-normal matched analysis
- Tumor DNA alone does not give the full story of a patient’s cancer. We sequence DNA from both tumor and normal (non-cancerous) samples to provide information on germline (inherited) contributions, which can inform treatment in a significant proportion of advanced cancer patients
- This analysis is of particular importance in specimens with high tumor cellularity in which somatic variants may be present at a similar allele frequency to germline variants, thereby complicating interpretation of variant origin and TMB analysis

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>99% Sema4 Signal WES/WTS & Sema4 Signal PanCancer can detect >99% of mutations associated with FDA-approved therapies, standard-of-care treatments, and investigational therapies in clinical trials<sup>5</sup>

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<sup>1</sup> ~18,500 genes reported on from WES/WTS data (~18,500 genes)

<sup>2</sup> Offered as reflex testing if WES/WTS or PanCancer not possible

<sup>3</sup> ACMG Recommendations for Reporting of Secondary Findings in Clinical Exome and Genome Sequencing (ACMG SF v2.0). PMID: 27854360


<sup>5</sup> Based on an analysis of actionable alterations from OncoKB. For additional information, please see Chakrevarty D, Gao K, Phillips S, et al. OncoKB: A Precision Oncology Knowledge Base. JCO Precision Oncology. 2017
As part of a comprehensive care plan, Sema4 Signal WES/WTS and PanCancer can help clinicians:

- **Determine diagnoses and prognoses for solid tumor and hematologic cancer**
  - Detection of a broad range of genomic alterations
  - Analysis of immuno-oncology biomarkers, including PD-L1, DNA mismatch repair (MMR), TMB, and microsatellite instability (MSI)

- **Identify and select available targeted therapies**
  - Identification of variants not picked up by targeted panels to inform decisions for patients whose previous treatment has failed
  - Clinically actionable findings are presented on the first page of the easy-to-read results report

- **Make decisions regarding the suitability of current clinical trials**
  - Current trials are outlined in the comprehensive results report
  - Report may be tailored to prioritize trials at the provider’s institution
  - By partnering with Sema4 to combine somatic testing with Sema4 Signal data structuring and informatics tools, providers can leverage real-world data to enable advanced trial matching

- **Learn about certain hereditary contributions to various cancer types**
  - Patients can consent to receive secondary findings on clinically-relevant hereditary cancer genes from the tumor-normal matched analysis, as per ACMG guidelines
  - Germline findings may inform treatment and care management, including whether a patient qualifies for PARP inhibitors for BRCA-related breast or ovarian cancer
  - Findings may also have potential clinical relevance for family members
  - Further testing can be done with Sema4 Signal Hereditary Cancer
  - If hereditary cancer is suspected in the patient or their family member(s), Sema4 Signal Hereditary Cancer testing, delivered via the Sema4 Traversa™ genomic platform, can provide more comprehensive germline insights.

For more information please call 833-486-6260, email ClientServicesOncology@sema4.com, or visit sema4.com/hereditary-cancer

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**One exome.**

**Two options for actionable insights**

- **Sema4 Signal WES/WTS**
  - ~18,500 genes sequenced
  - ~18,500 genes reported

- **Sema4 Signal PanCancer**
  - ~2,200 genes reported

**Actionable insights based on clinical guidelines and scientific evidence**:

- **165+ targeted genes mentioned in NCCN guidelines**
  - for cancer treatment, detection, prevention, and risk reduction

- **200+ genes included in active clinical trials in the United States**

- **35+ genes associated with 46+ targeted therapies**
  - that are approved by the FDA and associated with alteration status

- **70+ genes associated with diagnostic relevance**

- **60+ genes associated with prognostic significance**

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1 - Please note that while some inherited genetic changes may be detected, these tests do not replace comprehensive germline testing. If an inherited condition is suspected in the patient or their family members, a different test to examine germline genetic changes based on family and/or personal history, such as Sema4 Signal Hereditary Cancer, may be appropriate.

2 - Patient can choose to opt out

3 - Figures updated August 2020

4 - NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines®): Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Guideline Name v.X.2019. © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed January 10, 2020. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding its content, use or application and disclaims any responsibility for its application or use in any way.
Sema4 Signal WES/WTS

Time and information are our most powerful tools in the fight against cancer. Sema4 Signal WES/WTS maximizes both.

You shouldn’t have to spend time running multiple panels to unlock the answers to your patient’s cancer. Sema4 Signal WES/WTS analyzes the entire coding exome and transcriptome in a single comprehensive test to rapidly deliver the most in-depth molecular insights, and enable clinical care, research, and trial discovery.

Compared with running multiple targeted panels sequentially, Sema4 Signal WES/WTS provides:
- More information
- Faster TAT
- Smaller sample size
- Lower cost
- Reduced administrative burden
- A single comprehensive report

Why choose Sema4 Signal WES/WTS?

While Sema4 Signal WES/WTS and PanCancer are run on the same whole exome and whole transcriptome platform, only Sema4 Signal WES/WTS reports findings on all ~18,500 genes. In addition to the benefits common to both tests, Sema4 Signal WES/WTS also enables clinicians and researchers to:
- Access the broadest holistic view of a patient’s genome
- Gain deep insights into novel fusions, splice variants, and molecular pathways
- Research cancer driver mutational signatures
- Learn about germline findings for cancer and non-cancer genes, as per ACMG guidelines, with relevance to:
  - Comorbidities (e.g., familial hypercholesterolemia)
  - Certain drug interactions

Sema4 Signal PanCancer

The advantage of whole exome/whole transcriptome sequencing, with the focus of a targeted panel.

Sema4 Signal PanCancer integrates tumor-normal matched WES with WTS in one comprehensive test to rapidly deliver insights on over 2,000 of the most clinically relevant and actionable cancer genes.

Compared with running smaller targeted panels sequentially, Sema4 Signal PanCancer provides:
- More information
- Faster TAT
- Smaller sample size
- Lower cost
- Reduced administrative burden
- A single comprehensive report

Why choose Sema4 Signal PanCancer?

By reporting only on genes with a known association with cancer, Sema4 Signal PanCancer delivers the most relevant and actionable information to help guide a patient’s treatment. Sema4 Signal PanCancer harnesses the power of WES/WTS in the form of a panel and, compared to smaller targeted panels, is designed to provide:
- Greater diagnostic yield, based on extensive results from ~2,200 cancer-related genes and immunotherapy biomarkers
- Deeper clinical insights into the cancers of patients who are progressing, relapsing, or not responding to therapy and looking for additional therapeutic options such as immunotherapies and on-/off-label therapies
- Identification of clinical trial matches, prioritizing trials at the provider’s institution

1 - Patient can choose to opt out
2 - ACMG Recommendations for Reporting of Secondary Findings in Clinical Exome and Genome Sequencing (ACMG SF v2.0). PMID: 27854360
3 - Genes selected for inclusion based on large publicly available datasets, current understanding of the genomic landscape of somatic changes in solid tumors and hematologic malignancies, competitors’ platforms, and novel content for predicting prognosis and disease progression.
Comprehensive profiling deserves comprehensive support

Sema4’s mission is to make comprehensive genomic profiling accessible to all, without logistical or financial barriers. We go the extra mile to deliver our advanced solutions with outstanding service and support:

• Streamlined workflow integration (EMR, Sema4 Provider Portal) for simplified ordering and easy access to results
• Post-test genetic counseling for all positive germline findings
• Broad network coverage and supportive billing policies
• Easy-to-read report including therapy and clinical trial recommendations, with prioritization of health system’s own trials
• Support for patients and providers in understanding testing and the implications for clinical care
• Troubleshooting for sample collection and consent
• Sample retrieval and case management services

Helping every patient access advanced genomic testing

• Sema4 is contracted with all major national payors and is in-network for >200 million lives
• Our billing specialists will contact a patient’s insurance company to verify eligibility and obtain pre-certification or pre-authorization to ensure, to the fullest extent possible, insurance coverage for testing
• We appeal coverage determinations on behalf of patients if pre-certification or pre-authorization requests are denied
• We offer patient support to break down barriers to testing. Payment plans, self-pay pricing, and other financial assistance options are available

Questions about billing or insurance coverage?
Call the Sema4 Billing team at 800-298-6470

Digital clinical decision support tools

Comprehensive, easy-to-read report

• Appropriate targeted therapies
• Relevant clinical trials
• MSI and TMB status
• Resistance markers
• Clinically relevant negative result
• Patient prognosis
• Germline findings
• Non-cancer related, secondary germline findings

Interactive lookup tools

Find information on specific cancer genes and indications included in our Sema4 Signal WES/WTS and PanCancer tests:
sema4.com/signal-gene-card
sema4.com/signal-gene-tool
Advanced molecular profiling technologies

Sema4 Signal WES/WTS and PanCancer integrate tumor-normal matched WES with WTS to deliver the most comprehensive molecular insights

- Hybrid capture-based next generation sequencing of ~18,500 genes
- Run on the state-of-the-art Illumina NovaSeq 6000 system in our CLIA-certified, CAP-accredited laboratory
- Tumor-normal sequencing to enable differentiation between somatic and germline alterations

Reporting of genomic variants:

- Single Nucleotide Variants (SNVs)
- Insertions and deletion (InDels)
- Copy Number Variants (CNVs)

Assessment of immunotherapy biomarkers:

- Microsatellite Instability (MSI) - identifies which patients may be candidates for immunotherapy or MSI-indicated trials and may help identify Lynch Syndrome in colon and endometrial cancer
- PD-L1 antibodies 22C3 and SP142 for immunotherapies
- Tumor Mutational Burden (TMB) – a measurement of the number of genetic alterations in a tumor, which may be a predictive biomarker for response to immuno-oncology therapies

Technical specifications

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>SNV/InDels</td>
<td>&gt;99%</td>
<td>&gt;99%</td>
<td>&gt;99%</td>
<td>&gt;99%</td>
<td>Sensitivity 97% at 5% VAF</td>
</tr>
<tr>
<td>CNV</td>
<td>&gt;93%</td>
<td>&gt;99%</td>
<td>&gt;93%</td>
<td>&gt;99%</td>
<td>&gt;=20%</td>
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<tr>
<td>Fusions</td>
<td>&gt;99%</td>
<td>&gt;99%</td>
<td>&gt;99%</td>
<td>&gt;99%</td>
<td>&gt;10% tumor cellularity</td>
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<tr>
<td>Tumor Mutation Burden</td>
<td>&gt;99%</td>
<td>&gt;99%</td>
<td>&gt;99%</td>
<td>&gt;99%</td>
<td>&gt;20% tumor cellularity</td>
</tr>
<tr>
<td>Microsatellite Instability</td>
<td>&gt;99%</td>
<td>&gt;99%</td>
<td>&gt;99%</td>
<td>&gt;99%</td>
<td>Sensitivity 83.3% at 20% tumor cellularity</td>
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</table>

To learn more about our validation, please visit sema4.com/WES-validation

Specimen Requirements

<table>
<thead>
<tr>
<th>Test options</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Sema4 Signal PanCancer: ~2,200 genes</td>
</tr>
<tr>
<td>• Sema4 Signal WES/WTS: ~18,500 genes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Specimen type accepted</th>
</tr>
</thead>
<tbody>
<tr>
<td>• For tumor: FFPE, fresh frozen, bone marrow, and blood are accepted</td>
</tr>
<tr>
<td>• For normal: Saliva, buccal swab, and blood (for non-hematologic cancer)</td>
</tr>
<tr>
<td>• Tumor/normal pair required</td>
</tr>
<tr>
<td>• 10 unstained slides of tumor, 5-10 microns each and H&amp;E-stained paired normal (if solid tumor, use similar tissue; if hematologic, supply one EDTA tube of blood or saliva or buccal swabs)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Specimen requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal samples accepted:</td>
</tr>
<tr>
<td>• FFPE: 9 unstained slides at 5-10 microns and 1 standard H&amp;E slide, or 1 block</td>
</tr>
<tr>
<td>• Fresh frozen: 5-10 mm³</td>
</tr>
<tr>
<td>• Bone marrow: 3-5 ml EDTA</td>
</tr>
<tr>
<td>• Blood: 3-5 ml EDTA</td>
</tr>
<tr>
<td>• Saliva: 2 ml</td>
</tr>
<tr>
<td>• Buccal swab: 1 swab</td>
</tr>
<tr>
<td>• Tumor cellularity: &gt;20%</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Turnaround time</th>
</tr>
</thead>
<tbody>
<tr>
<td>14-21 days</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Target sequencing depth</th>
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</thead>
<tbody>
<tr>
<td>• Tumor: 250X</td>
</tr>
<tr>
<td>• Normal: 100X</td>
</tr>
<tr>
<td>• RNA: 100M read</td>
</tr>
</tbody>
</table>

Additional requirements

- All specimens must be labeled with two unique identifiers. Slides should also be labeled with a block label identity that corresponds with the surgical pathology report
- Must include a surgical pathology report where available
Sema4 Signal Informatics

Partnering to drive data-driven precision oncology

Sema4 partners with providers, health systems, and payors to support precision care by structuring and analyzing large sets of clinical and genomic data. We use machine learning and natural language processing to draw insights from this structured data at the individual and cohort level. These insights, powered by our proprietary health intelligence platform Centrellis™, are then made accessible through our digital tools:

Cohort builder tool
Provides the ability to define groups of patients according to parameters such as stage, histology, and treatments to help health systems instantly understand treatment patterns, identify and prioritize appropriate research, and better comprehend how to meet quality-of-care and financial metrics.

Clinical trial matching tool
Enables patient identification and enrollment into clinical trials and predicts accrual rates for trials using precise clinical and genomic inclusion/exclusion criteria.

Patient Journey tool
Provides an interactive timeline visualization of the patient’s longitudinal health journey, complete with diagnoses, treatments, and molecular profiles to enable data-driven care decisions.

Delivering insight at the point of care
The integration of genomic testing with structured clinical data can help drive better personalized care across the patient journey. Our informatics solutions enable providers to:

• Incorporate cohort-based real-world evidence into treatment decisions
• View clinical, molecular, and therapeutic patient journeys in one integrated timeline
• Continually monitor health trajectories to understand disease progression
• More precisely match patients to clinical trials

Enabling health systems to leverage better insights
Health system access to data is critical to enable research, clinical trial planning, and quality of care. We use advanced natural language processing, powered by Centrellis, to structure clinical data and empower health systems to compare patient cohorts using complex queries. These advanced informatics solutions enable health systems to:

• Standardize protocols to deliver cost-effective, high-quality care systemwide
• Fill clinical trials more rapidly through intelligent, real-time patient matching
• Identify which research and trials to prioritize, based on patient population
• Determine the potential for additional research and trial sites

State-of-the-art profiling, enabled by cutting-edge informatics
Sema4 Signal somatic tests are powered by several proprietary data tools, including:

Sema4’s cancer knowledgebase
Contains comprehensive, structured data and the most current state of knowledge for over 7,000 variants, including clinical trials curated based on biomarker status by PhD oncology experts.

Sema4’s variant interpretation station for oncology
Automates clinical reporting by managing the variant curation process and recommending suitable therapies. This artificial intelligence-driven genomic platform is updated regularly with the latest literature and prioritizes clinically-significant variants, enabling providers to quickly review and leverage actionable insights.
Your partner in precision oncology

- Sema4 is a patient-centered health intelligence company dedicated to improving the diagnosis, treatment, and prevention of disease through data-driven insights.

- Our world-class expertise in data science, machine learning, and network modeling, combined with our best-in-class genomic tests and understanding of how to deploy these tests across a system, give us a critical edge in delivering precision oncology care solutions.

- We partner with health systems, practices, individuals, and payors to enable today’s cancer care while driving the therapeutic advances of tomorrow.

>150 PhDs, MDs, & Certified Genetic Counselors

>500,000 large next generation sequencing panels run

>1,800 peer-reviewed publications

Highly qualified, interdisciplinary team of scientists, clinicians, and data engineers

One of the world’s leading clinical genomics laboratories

World-class experts in artificial intelligence, predictive modeling, and genomics

At the forefront of cancer research

- Sema4’s research focuses on structuring data into validated clinical insights.

- Our researchers have published more than 1,000 peer-reviewed papers in the last five years on subjects including prognostic biomarkers, tumor profiling, and chemoimmunotherapy, and indications including non-small cell lung cancer, glioblastoma, and multiple myeloma.

- We collaborate with major health systems, research consortia, and advocacy groups.

- We have recognized expertise in customized clinical trial development and recruitment, making us a trusted partner to pharma.

As a research partner, Sema4 can support you throughout the therapeutic discovery process, from accelerating clinical trial enrollment to optimizing biomarker discovery and leveraging our biorepository services. To find out more, please call 833-486-6260, email ClientServicesOncology@sema4.com, or visit sema4.com/research.

Want to know more about our innovative biopharma solutions? Visit sema4.com/biopharma