AFTER DEFINITIVE THERAPY IN COLORECTAL CANCER

Signatera looks deeper

Is there residual disease?
Is the treatment working?
Is the cancer recurring?

Signatera™ is a personalized, tumor-informed assay for ultrasensitive detection of molecular residual disease (MRD), an early predictive marker of relapse.
In the adjuvant setting

Is there residual disease? Is the treatment working?

Use Signatera after surgery to evaluate the need for adjuvant chemotherapy and potentially avoid unnecessary treatment.

Signatera MRD status after surgery can help you and your patient more confidently decide on a treatment plan or monitor adjuvant treatment response.

Decisive intelligence to inform treatment decisions

Better tools to determine risk of recurrence could identify colorectal cancer (CRC) patients who may need additional treatment

- Most patients with stage II CRC are not treated with adjuvant chemotherapy, despite 10% to 15% of patients relapsing after surgery.¹
- Although most patients with stage III CRC receive adjuvant therapy, more than 50% of patients are cured by surgery alone.²,³ Approximately 30% of patients who are treated with adjuvant therapy experience recurrence.¹,⁴

Signatera accurately identifies patients at high risk of recurrence

Signatera MRD status outperforms known clinicopathologic risk factors in predicting relapse⁵-⁶

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMR status (MSI-H vs MSI-L)</td>
<td>0.73</td>
</tr>
<tr>
<td>Tumor grade (High vs low)</td>
<td>1.36</td>
</tr>
<tr>
<td>Stage II (T4 vs T1-T3)</td>
<td>1.55</td>
</tr>
<tr>
<td>30 days after surgery, before adjuvant therapy (+) vs (-)*</td>
<td>7.2</td>
</tr>
<tr>
<td>First time point after adjuvant therapy (+) vs (-)*</td>
<td>17.5</td>
</tr>
<tr>
<td>During serial monitoring (+) vs (-)*</td>
<td>43.5</td>
</tr>
</tbody>
</table>

*Negative is defined as ctDNA negative at all time points.
Detect recurrence early to support treatment planning

Identifying recurrence while interventions can still be curative remains a challenge in CRC

- With current surveillance tools and biomarkers, only 10% of metachronous metastases are treated with curative intent.\(^9\)
- At the ASCO recommended threshold of 5 \(\mu\)g/L, more than half of patients who experience recurrence of CRC will not have elevated CEA levels.\(^10\)

Signatera detects relapse with clinically meaningful lead time over CT scan and CEA\(^5\)

<table>
<thead>
<tr>
<th></th>
<th>Signatera</th>
<th>CEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>88%</td>
<td>69%</td>
</tr>
<tr>
<td>Specificity</td>
<td>98%</td>
<td>64%</td>
</tr>
</tbody>
</table>

Average lead time of ctDNA detection before CT scan

8.7 months

Unlike CEA testing, Signatera specificity is not affected by liver dysfunction, alcohol intake, or smoking.\(^{11-13}\)

CT = computed tomography; CEA = carcinoembryonic antigen; ctDNA = circulating-tumor DNA

In the surveillance setting
Is the cancer recurring?

Use Signatera along with CEA testing to detect recurrence earlier, while the tumor may still be resectable, or to reduce false positive CEA results.

Signatera MRD status can help you and your patient more confidently decide on a surveillance or treatment plan.
Decisions informed by the tumor

Signatera optimizes risk stratification after surgery and may inform treatment changes during adjuvant chemotherapy

97% of patients with a positive Signatera result who will relapse without additional treatment

30% of patients who were ctDNA-positive after surgery cleared their ctDNA with adjuvant chemotherapy

Detectable ctDNA either after surgery or completion of adjuvant therapy is strongly associated with a high risk of disease recurrence, suggesting that ctDNA is a robust marker for MRD.

US NCI Colon and Rectal-Anal Task Forces

Clinical utility in the adjuvant setting

<table>
<thead>
<tr>
<th>Stage II colon</th>
<th>ctDNA High risk</th>
<th>ctDNA Reduced risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manage as high risk</td>
<td>Risk similar to stage I, consider repeat testing and observation</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage IIA rectal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manage as high risk</td>
</tr>
<tr>
<td>Consider repeat testing and de-escalation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage III colon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manage as high risk</td>
</tr>
</tbody>
</table>

ADJUVANT SETTING
(Post-surgery observation or adjuvant chemotherapy)

Whole-exome sequencing and initial Signatera test design

Up to 4 time points in the first 6 months of adjuvant window to inform treatment decision making

Medicare draft coverage: Stage II-III colon cancer and stage IIA rectal cancer
**Actionable intelligence sooner**

Signatera determines recurrence with confidence during routine follow-up testing

Serial testing with Signatera improves sensitivity and negative predictive value of test results

![ctDNA](image)

result during surveillance, especially when CT scan or CEA results are indeterminate, enables early detection of recurrence and potential for curative intervention

**Longitudinal RFS after definitive treatment**

Relapse rate of patients with serially negative MRD results

3%

*Signatera ctDNA positive is defined as positive at any time point at or before clinical relapse

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**Clinical utility in the surveillance setting**

**Stage II-III colorectal**

**ctDNA + High risk**

Consider more frequent CT scans or escalating to PET or MRI to locate disease while potentially resectable

**ctDNA - Reduced risk**

Consider monitoring with reassurance

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**SURVEILLANCE SETTING** (≥ 6 months after surgery)

Test with the same frequency as CEA

<table>
<thead>
<tr>
<th>Months</th>
<th>Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>6m</td>
<td>3y</td>
</tr>
<tr>
<td>9m</td>
<td>5y</td>
</tr>
<tr>
<td>12m</td>
<td></td>
</tr>
<tr>
<td>15m</td>
<td></td>
</tr>
<tr>
<td>18m</td>
<td></td>
</tr>
<tr>
<td>21m</td>
<td></td>
</tr>
<tr>
<td>24m</td>
<td></td>
</tr>
</tbody>
</table>

*Medicare draft coverage: Stage II–III colorectal cancer
The personalized, tumor-informed approach behind Signatera

The only commercially available test to detect MRD and assess disease recurrence

Personalized, tumor-informed assay (TAT = 2-3 weeks)
- Primary tissue sample and matched normal tissue are required for whole exome sequencing and personalized test design.

Ultrasensitive ctDNA detection
- Signatera is designed to detect ctDNA of somatic and truncal variants to optimize sensitivity.
- This tumor-informed method enables filtering of germline and CHIP mutations to decrease false positive rates.

Optimized for longitudinal monitoring (TAT = 1 week)
- Only a blood sample is needed each time Signatera is ordered for the adjuvant or surveillance settings.

Easy-to-interpret longitudinal report

Test report indicates the presence or absence of detectable ctDNA

For each time point, disease burden is quantified by mean tumor molecules (MTM) per milliliter.

Unlike ctDNA assays used for liquid biopsies, Signatera detects ctDNA to indicate the presence of MRD.
- Not designed for early cancer screening
- Does not identify actionable mutations for cancer therapy selection

CHIP = clonal hematopoiesis of indeterminate potential; TAT = turnaround time
Meet Natera’s team of clinical experts who will support you and your patients

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**CLINICAL ONCOLOGY SPECIALISTS**
- Fulfills requests for requisition forms and kits
- Answers provider portal inquiries

**CUSTOMER EXPERIENCE**
- Acquires tumor tissue from pathology for whole-exome sequencing
- Answers test status inquiries from providers

**ONCOLOGY CLINICAL INFORMATION**
- Sets blood draw schedule for recurring orders
- Discusses test results and testing programs and enrollment with providers and patients

**PATIENT COORDINATOR**
- Places welcome call to patients
- Schedules mobile phlebotomy for Natera-managed blood draws
- Answers general billing inquiries and questions about compassionate care qualification
- Answers testing-related inquiries from patients

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A provider portal made simple

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**CUSTOMIZABLE FEATURES AVAILABLE TO PROVIDERS INCLUDE:**
- Ability to order tests and upload necessary documents directly to the provider portal
- Easily schedule future draw dates based on our recommended schedules in the adjuvant and surveillance settings
- Receive reminders for upcoming patient blood draws
- Track status of samples and view test results
Look deeper – so you can know sooner

Signatera is validated across multiple tumor types

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>JAMA Oncology</th>
<th>CLINICAL CANCER RESEARCH</th>
<th>NATURE</th>
<th>JOURNAL OF CLINICAL ONCOLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>Colon</td>
<td>Breast</td>
<td>Lung</td>
<td>Bladder</td>
</tr>
<tr>
<td>ctDNA negative</td>
<td>ctDNA positive</td>
<td>ctDNA negative</td>
<td>ctDNA positive</td>
<td>ctDNA negative</td>
</tr>
<tr>
<td>(n=60)</td>
<td>(n=15)</td>
<td>(n=30)</td>
<td>(n=10)</td>
<td>(n=47)</td>
</tr>
<tr>
<td>HR, 43.5</td>
<td>P &lt; 0.001</td>
<td>HR, 35.84</td>
<td>P &lt; 0.005</td>
<td>ctDNA positive</td>
</tr>
<tr>
<td>Days from surgery</td>
<td>Years from surgery</td>
<td>Days from surgery</td>
<td>Days from surgery</td>
<td>Days from surgery</td>
</tr>
<tr>
<td>0 1 2 3 4 5</td>
<td>0 1 2 3 4 5 6</td>
<td>0 1 2 3 4 5 6</td>
<td>0 1 2 3 4 5 6</td>
<td>0 1 2 3 4 5 6</td>
</tr>
<tr>
<td>0.00 0.25 0.50 0.75 1.00</td>
<td>0.00 0.25 0.50 0.75 1.00</td>
<td>0.00 0.25 0.50 0.75 1.00</td>
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<td>0.00 0.25 0.50 0.75 1.00</td>
</tr>
</tbody>
</table>

88% sensitivity to relapse
Average lead time 8.7 mos

89% sensitivity to relapse
Average lead time 9.5 mos

92% sensitivity to relapse
Average lead time 4.0 mos

100% sensitivity to relapse
Average lead time 2.8 mos

NOTES:

REFERENCES


Learn more about Signatera:
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The test has been developed and its performance characteristics determined by the CLIA-certified laboratory performing the test. The test has not been cleared or approved by the US Food and Drug Administration (FDA). Although FDA is exercising enforcement discretion of premarket review and other regulations for laboratory-developed tests in the US, certification of the laboratory is required under CLIA to ensure the quality and validity of the tests. CAP accredited, ISO 13485 certified, and CLIA certified. © 2020 Natera, Inc. All Rights Reserved. 20200821_NAT-802022.