**MEDICARE COVERAGE**
for use in stage II-III colorectal cancer

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)**

natera™ | Signatera™
Residual disease test (MRD)

# 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.

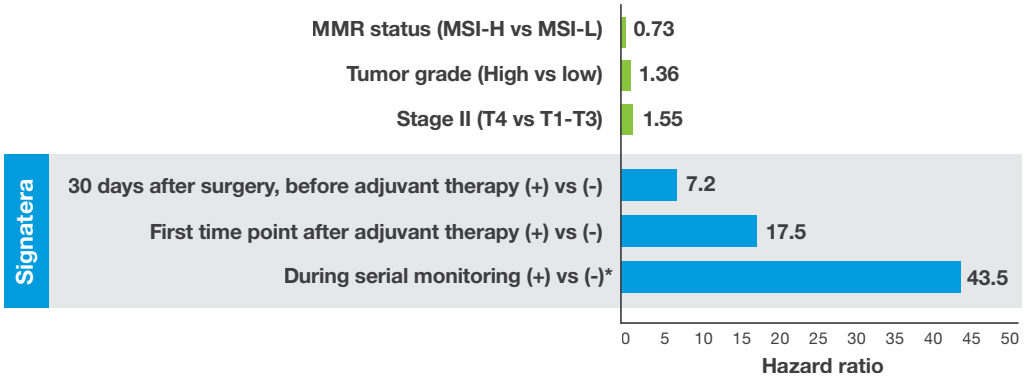
## Decisive intelligence to inform treatment decisions

**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 relapse[5-8]**




*Negative is defined as ctDNA negative at all time points.

## 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.

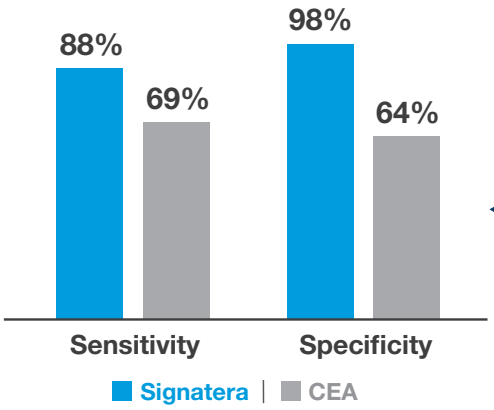
## Detect recurrence early to support treatment planning

**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 ug/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]

**Accuracy in detecting relapse**




**Unlike CEA testing, Signatera specificity is not affected by liver dysfunction, alcohol intake, or smoking.[11-13]**

**Average lead time of ctDNA detection before CT scan**

**8.7 months**

Maximum lead of 16.5 months

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

# Decisions informed by the tumor

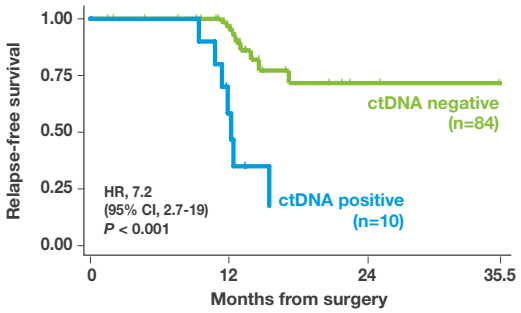
**Signatera optimizes risk stratification after surgery and may inform treatment changes during adjuvant chemotherapy**

**97%** of patients with a positive Signatera result will relapse without additional treatment[5]

**30%**

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

RFS stratified by postoperative day 30 MRD status[5]




Relapse rate of patients with a single negative Signatera result after surgery

**12%**

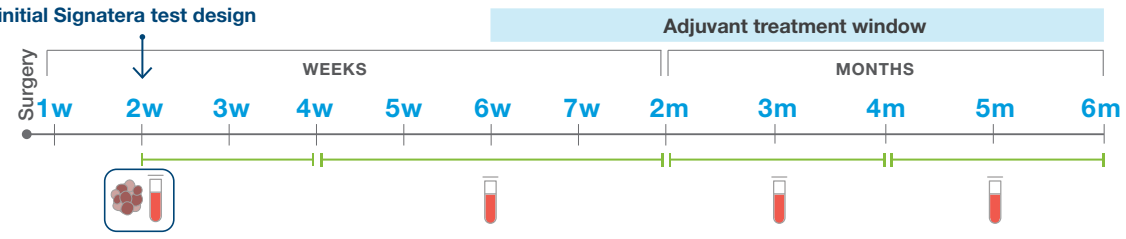
> **Detectable ctDNA either after surgery or completion of adjuvant therapy is strongly associated with a high risk of disease recurrence, suggesting that ctDNA is a robust marker for MRD.**
>
> *— US NCI Colon and Rectal-Anal Task Forces[14]*

## Clinical utility in the adjuvant setting

| | ctDNA ⊕ High risk | ctDNA ⊖ Reduced risk |
|---|---|---|
| **Stage II colon Stage IIA rectal** | Manage as high risk | Risk similar to stage I, consider repeat testing and observation |
| **Stage III colon** | Manage as high risk | Consider repeat testing and de-escalation |

## 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**

# Actionable intelligence sooner

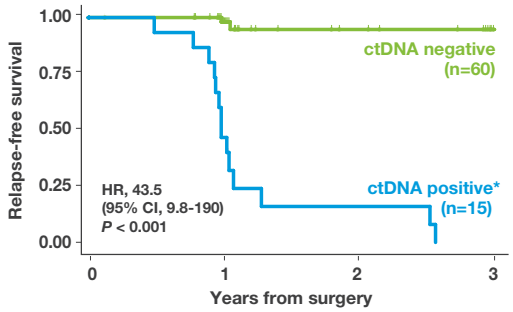
**Signatera determines recurrence with confidence during routine follow-up testing**

## Serial testing with Signatera improves sensitivity and negative predictive value of test results[5]

**ctDNA +**

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[5]**




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

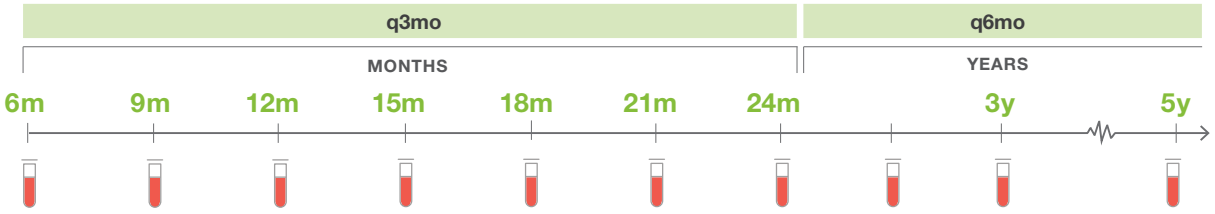
## Clinical utility in the surveillance setting

| | ctDNA ⊕ High risk | ctDNA ⊖ Reduced risk |
|---|---|---|
| **Stage II-III colorectal** | Consider more frequent CT scans or escalating to PET or MRI to locate disease while potentially resectable | Consider monitoring with reassurance |

> **I'm excited that [Signatera] can continue to monitor me, so if there is a recurrence we can catch it quickly.**
>
> — *Patient living with CRC*

## SURVEILLANCE SETTING (≥ 6 months after surgery)

**Test with the same frequency as CEA**




**Primary tumor tissue sample required if first Signatera test is ≥ 6 months after surgery**

# The personalized, tumor-informed approach behind Signatera

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

### Personalized, tumor-informed assay (TAT = 2-3 weeks)

- Primary tissue sample and a blood sample are required for whole exome sequencing and personalized test design.

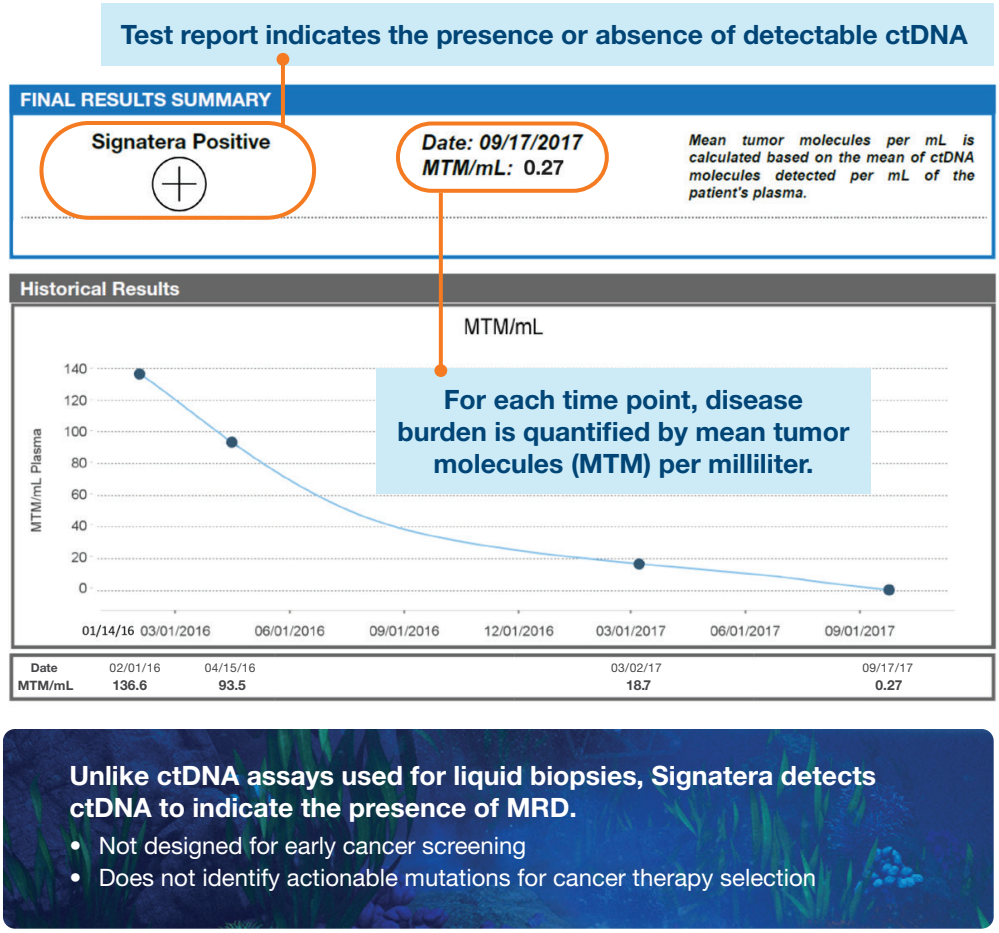
### Ultrasensitive ctDNA detection

- 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




**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 hematopoeisis of indeterminate potential; **TAT** = turnaround time

# Meet Natera's team of clinical experts who will support you and your patients

### 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 COORDINATORS
- 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

## A provider portal made simple

### CUSTOMIZABLE FEATURES AVAILABLE TO PROVIDERS INCLUDE:

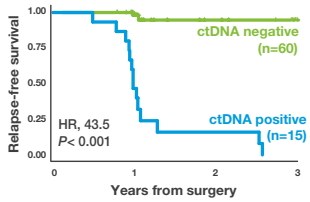
- Ability to order tests and upload necessary documents directly to the provider portal
- Easily schedule future draw dates based on our recommended schedules in the adjuvant and surveillance settings
- Receive reminders for upcoming patient blood draws
- Track status of samples and view test results

# Look deeper – so you can know sooner

## Signatera is validated across multiple tumor types [5,15-17]

**JAMA ONCOLOGY**

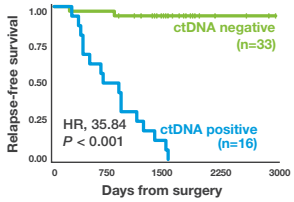
Colon




**88% sensitivity to relapse**
Average lead time 8.7 mos

**CLINICAL CANCER RESEARCH**

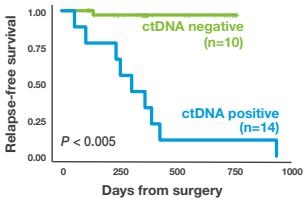
Breast




**89% sensitivity to relapse**
Average lead time 9.5 mos

**NATURE**

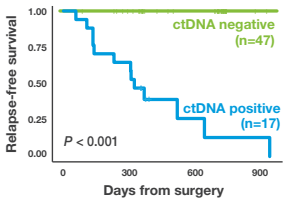
Lung




**92% sensitivity to relapse**
Average lead time 4.0 mos

**JOURNAL OF CLINICAL ONCOLOGY**

Bladder




**100% sensitivity to relapse**
Average lead time 2.8 mos

**NOTES:**


**REFERENCES**

1. Osterman E, Glimelius B. Recurrence risk after up-to-date colon cancer staging, surgery, and pathology. *Dis Colon Rectum.* 2018;61(9):1016-1025. 2. Påhlman LA, Hohenberger WM, Matzel K, Sugihara K, Quirke P, Glimelius B. Should the benefit of adjuvant chemotherapy in colon cancer be re-evaluated? *J Clin Oncol.* 2016;34(12):1297-1299. 3. Böckelman C, Engelmann BE, Kaprio T, Hansen TF, Glimelius B. Risk of recurrence in patients with colon cancer stage II and III. *Acta Oncol.* 2015;54(1): 5-16. 4. Lash TL, Riis AH, Ostenfeld EB, et al. Associations of statin use with colorectal cancer recurrence and mortality in a Danish cohort. *Am J Epidemiol.* 2017;186(6):679-687. 5. Reinert T, Henriksen TV, Christensen E, et al. Analysis of plasma cell-free DNA by ultradeep sequencing in patients with stages I to III colorectal cancer. *JAMA Oncol.* 2019;5(8):1124–1131. 6. Aoyama, Oba K, Honda M, et al. Impact of postoperative complications on the colorectal cancer survival and recurrence: analyses of pooled individual patients' data from three large phase III randomized trials. *Cancer Med.* 2017;6(7):1573–1580. 7. Yothers G, O'Connell MJ, Lopatin M, et al. Validation of the 12-gene colon cancer recurrence score in NSABP C-07 as a predictor of recurrence in patients with stage II and III colon cancer treated with fluorouracil and leucovorin (FU/LV) and FU/LV plus oxaliplatin. *J Clin Oncol.* 2013;31(36):4512-4519. 8. Sinicrope FA, Foster NR, Thibodeau SN, et al. DNA mismatch repair status and colon cancer recurrence and survival in clinical trials of 5-Fluorouracil-based adjuvant therapy. *J Natl Cancer Inst.* 2011;103(11):863–875. 9. Elferink MA, de Jong KP, Klaase JM, et al. Metachronous metastases from colorectal cancer: a population-based study in North-East Netherlands. *Int J Colorectal Dis.* 2015;30(2):205-212. 10. Shinkins B, Nicholson BD, Primrose J et al. The diagnostic accuracy of a single CEA blood test in detecting colorectal cancer recurrence: Results from the FACS trial. *PLoS One*. 2017;12(3):e0171810. doi: 10.1371/journal.pone.0171810. 11. Barton, MK. False elevations of carcinoembryonic antigen levels are common in patients under surveillance for colorectal cancer recurrence. *CA: A Cancer Journal for Clinicians*. 2014:64(6):365-366. 12. Bell H, Orjasaeter H, Lange HF. Carcinoembryonic antigen (CEA) in patients with alcoholic liver diseases. *Scand J Gastroenterol.* 1979;14(3):273-9. 13. Lee SU, Jwa E, Kim DY, et al. Analysis of unexplained carcinoembryonic antigen elevation after curative treatment of locally advanced rectal cancer. *Int J Clin Oncol.* 2018 Oct;23(5):924-929. 14. Dasari, A., Morris, V.K., Allegra, C.J. et al. ctDNA applications and integration in colorectal cancer: an NCI Colon and Rectal–Anal Task Forces whitepaper. *Nat Rev Clin Oncol* (2020). https://doi.org/10.1038/s41571-020-0392-0. 15. Coombes RC, Page K, Salari R, et al. Personalized detection of circulating tumor DNA antedates breast cancer metastatic recurrence. *Clin Cancer Res*. 2019;25(14):4255-4263. 16. Abbosh C, Birkbak NJ, Wilson GA, et al. Phylogenetic ctDNA analysis depicts early-stage lung cancer evolution. *Nature.* 2017;545:446-451. 17. Christensen E, Birkenskamp-Demtroder K, Sethi H, et al. Early detection of metastatic relapse and monitoring of therapeutic efficacy by ultra-deep sequencing of plasma cell-free DNA in patients with urothelial bladder carcinoma. *J Clin Oncol.* 2019;37(18):1547-1557.


## Learn more about Signatera:

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