natera™ | Signatera™
Residual disease test (MRD)

Know cancer's next move

Treat with confidence

- Does my patient need adjuvant chemotherapy?
- Is the cancer recurring?
- Is the treatment working?

Signatera™ MRD assay

A personalized, tumor-informed approach for molecular residual disease (MRD) detection and treatment response monitoring

Deeper insights along the continuum of care

Order Signatera™ at any time

- Common initial time points are at the time of diagnosis or before treatment
- Can be run on core biopsy or surgical resection

Add on Altera™ Genomic Profiling test at the same time as Signatera™ Residual Disease testing

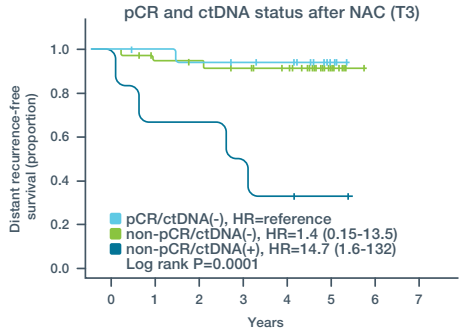
- For stage III/IV patients when you order Signatera™ MRD testing to get clinically relevant biomarkers to guide treatment selection with no additional sample needed
- Altera™ utilizes whole-exome and whole-transcriptome sequencing

Add on Empower™ for hereditary cancer testing to complete the patient profile

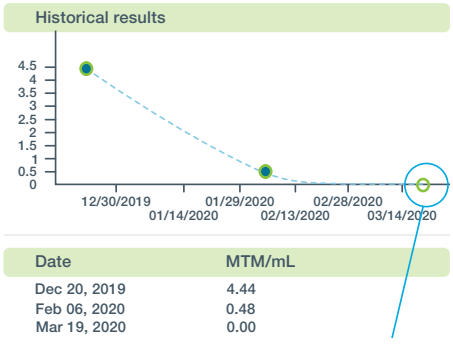
- Analyze up to 81 genes across 12+ common hereditary cancers (panel can also be customizable up to 190 genes)
- Helps guide surgical and therapeutic decisions following a cancer diagnosis

Signatera™ has been widely validated in various clinical settings

1. Neoadjuvant response monitoring Tailor neoadjuvant treatment or surgical strategies based on MRD status (e.g., rectal cancer TNT)



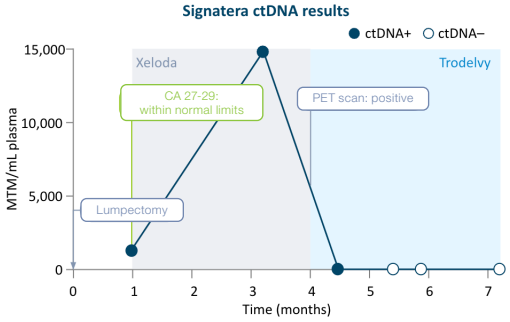
Breast cancer patients achieving ctDNA clearance but not pCR demonstrated similar risk of recurrence as those who achieved pCR.[1]



Date	MTM/mL
Dec 20, 2019	4.44
Feb 06, 2020	0.48
Mar 19, 2020	0.00

Case example: Rectal cancer patient who achieved ctDNA clearance during TNT elected for nonsurgical management[2]

2. Postsurgical MRD assessment
Evaluate the need for adjuvant therapy by identifying risk of postsurgical relapse



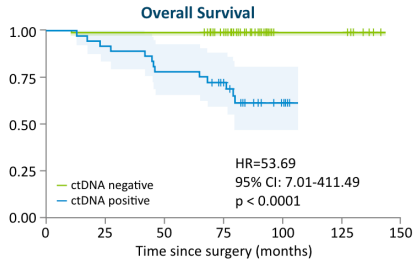
Case example: Stage III triple-negative breast cancer patient with increasing ctDNA during adjuvant therapy, which triggered the identification of metastatic disease and a subsequent change in therapy that led to ctDNA clearance.

Signatera™ MRD assay may provide personalized information when current tools are unable to answer important clinical questions

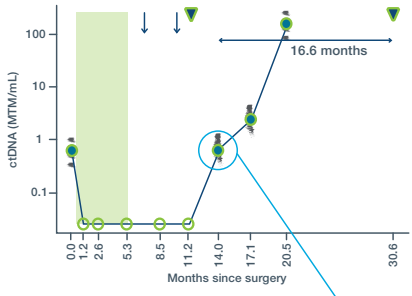
1. Neoadjuvant | 2. Adjuvant | 3. Surveillance | 4. Advanced/ metastatic

	Signatera™ clinical applications	Why tumor-informed MRD?
1	Neoadjuvant response monitoring	Tailor neoadjuvant treatment or surgical strategies to patient's specific needs (e.g., rectal cancer TNT)
2	Postsurgical MRD assessment	Identify patients who may or may not benefit from adjuvant therapy
3	Recurrence monitoring	Triage indeterminate nodules; rule in/rule out disease recurrence
4	Assess treatment effectiveness	Monitor ctDNA dynamics (increase or decrease in ctDNA levels) to quickly identify if there is any response to treatment

3. Recurrence monitoring Triage indeterminate nodules; detect disease recurrence early while the tumor may still be resectable

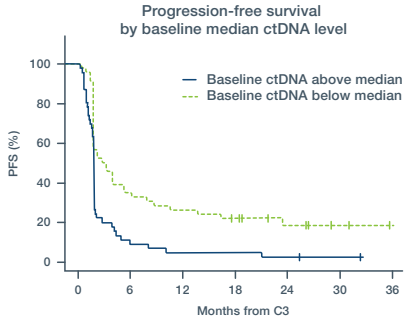


Signatera™ demonstrated 93% relapse sensitivity in a longitudinal analysis of more than 800 patients with colorectal cancer.[3]

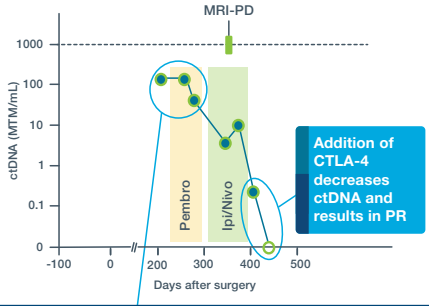


Case example: Colon cancer patient with ctDNA detected 16.6 months ahead of radiographic recurrence[4]

4. Assess treatment effectiveness Identify patients who may not be responding to therapy, as well as exceptional responders who clear ctDNA



Signatera™ assessment of ctDNA dynamics at 6 weeks in conjunction with imaging was 100% predictive of treatment nonresponse to immunotherapy.[5]



Case example: CRC patient with elevated ctDNA, despite pembrolizumab monotherapy, experiences radiographic recurrence[6]

Clinically validated across multiple tumor types with broad coverage for Medicare patients

Reliable results from a single test, deeper insights with serial sampling

	From a single test	With serial sampling
⊕	**Residual disease present** 97% of MRD-positive patients with early-stage CRC relapsed without further treatment[4,7]	**Actionable dynamics** Know if disease burden is increasing or shrinking with trackable MTM values[1–4]
⊖	**No evidence of residual disease** Only 12% of MRD-negative patients with early-stage CRC relapsed after surgery[1–4]	**Reduce recurrence risk** Only 3% of patients with serial ctDNA negative results relapsed[1]

Performance

- Tumor-informed MRD assessment for high sensitivity and specificity
- **>85K Signatera™ MRD tests** conducted in the US
- **>4K + patient cases** published or presented at industry conferences or in peer-reviewed journals
- **40 + peer-reviewed publications**

Established Medicare coverage in multiple tumor types including:

CRC, MIBC, stage IIB and higher breast cancer and patients on immunotherapy, regardless of tumor type

Learn more by scanning the QR code here

CLIA=Clinical Laboratory Improvement Amendments; **CRC**=colorectal cancer; **ctDNA**=circulating tumor DNA; **CTLA-4**=cytotoxic **T**-lymphocyte antigen 4; **DFS**=disease-free survival; **GI**=gastrointestinal; **GU**=genitourinary; **Gyn**=gynecological; **IO**=immuno-oncology; **MIBC**=muscle-invasive bladder cancer; **MTM**=mean number of tumor molecules; **NAC**=neoadjuvant chemotherapy; **NETS**=neuroendocrine tumors; **NSCLC**=non-small cell lung cancer; **OS**=overall survival; **pCR**=pathologic complete response; **PFS**=progression-free survival; **PR**=partial response; **TNT**=total neoadjuvant treatment.

References: 1. Magbanua MJM, Swigart LB, Wu H-T, et al. Circulating tumor DNA in neoadjuvant-treated breast cancer reflects response and survival. *Ann Oncol.* 2021;32(2):229-239. doi:10.1016/j.annonc.2020.11.007 **2.** Natera. Data on file. **3.** Shirasu H, Taniguchi H, Watanabe J, et al. Monitoring molecular residualdisease by circulating tumor DNA in resectable colorectal cancer: molecular subgroup analyses of a prospective observational study GALAXY in CIRCULATE-Japan. Presented at: ESMO World Congress on Gastrointestinal Cancer; June 30-July 3, 2021; Lugano, Switzerland; Virtual **4.** 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. doi:10.1001/jamaoncol.2019.0528 **5.** Powles T, Assaf ZJ, Davarpanah N, et al. ctDNA guiding adjuvant immunotherapy in urothelial carcinoma. Nature. 2021;595(7867):432-437. doi:10.1038/s41586-021-03642-9 6. Chapman JS, Pierson WE, Smith-McCune K, et al. Circulating tumor DNA predicts disease recurrence in ovarian cancer patients. Presented at: American Association of Cancer Research; April 9-14, 2021; Virtual **6.** Kasi P, Krainock M, Budde G, et al. Circulating tumor DNA (ctDNA) serial analysis during progression on PD-1 blockade and later CTLA-4 rescue in patients with mismatch repair-deficient metastatic colorectal cancer. Presented at: Society for Immunotherapy of Cancer 35th Annual Meeting; November 9-14, 2020; Virtual **7.** Natera data on file

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