Patient guide

Signatera™
Molecular monitoring (MRD)

Detect relapse or progression early

A new way to get earlier, more precise information after cancer treatment

Brought to you by Natera, a global leader in genetic testing and cell-free DNA analysis.

natera®
Conceive. Deliver. Thrive.

Why is cancer monitoring important?

When someone has been treated for cancer, there are several monitoring tools doctors use to detect cancer remaining in the body. Knowing if there are traces of cancer present, can help the doctor or oncologist decide:

- How the patient is responding to treatment
- If further cancer treatment needs to be considered
- Whether there are signs that the cancer has returned or progressed

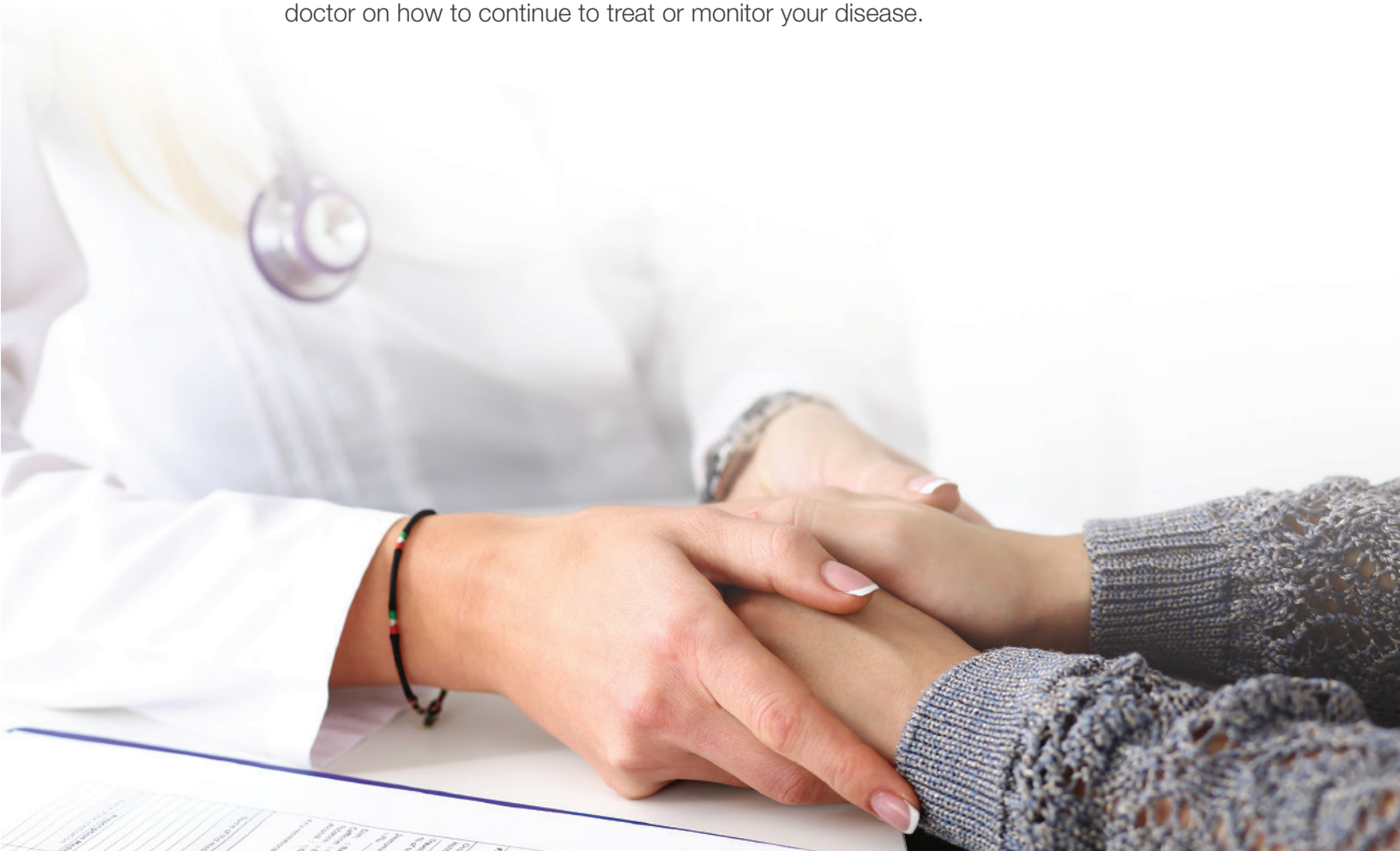
The most common imaging tools used to detect the presence of cancer are computerized tomography (CT) scan, magnetic resonance imaging (MRI), positron emission tomography (PET) scan, mammography, and X-ray. However, these imaging tools are limited in their ability to detect very small traces of cancer in the blood called molecular residual disease (MRD). If left untreated, residual cancer cells are highly likely to multiply and cause a recurrence.[1]

Molecular residual disease is the presence of small traces of cancer in the blood, such as circulating tumor DNA (ctDNA) or microscopic pieces of tumor DNA.

Signatera is a new cancer monitoring test that is personalized for each patient

Signatera is a custom-designed test generated based on each patient's unique set of tumor mutations.

Knowing earlier if your cancer is likely to recur or has progressed after treatment can help you have a more informed discussion with your doctor on how to continue to treat or monitor your disease.



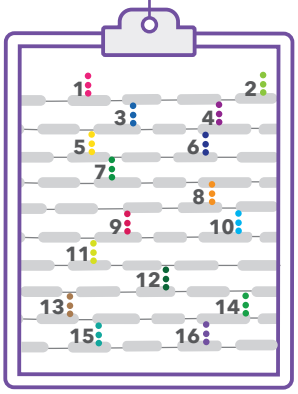
How is the Signatera test performed?

1

Analysis to determine your unique set of tumor mutations

The DNA sequence from your tumor tissue and normal cells from your blood are compared to determine the unique set of mutations specific to your tumor tissue. This process happens only once.

2



Custom-designed and personalized for you

The next step of the Signatera process is to select 16 tumor DNA mutations that occurred early in your cancer's origination. These mutations are called "clonal mutations" and would also be present in all future cancer cells. The clonal mutation selection process happens only once.

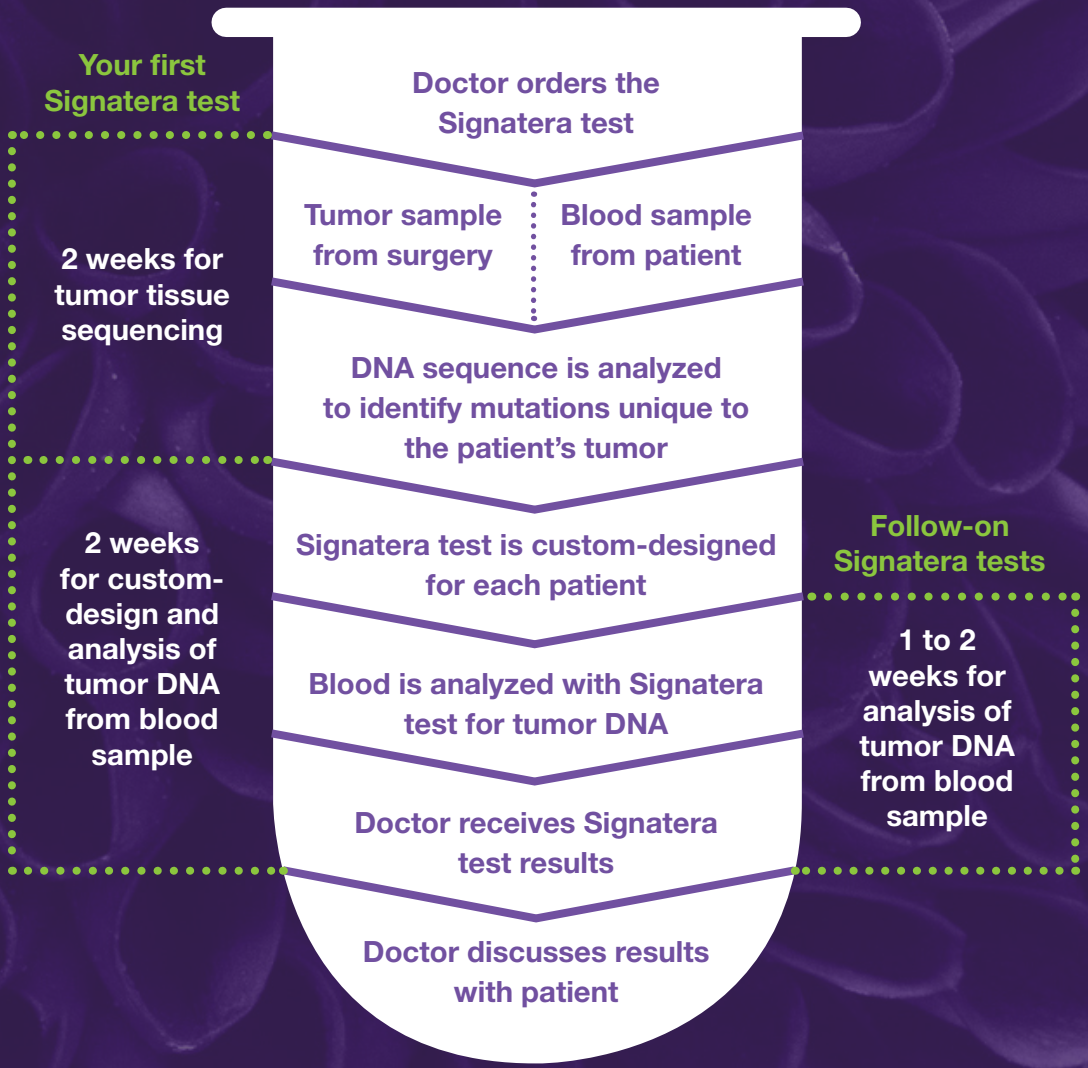
3

Signatera test detects presence or absence of tumor DNA

Once your personalized Signatera test is created, it can be used to detect the presence or absence of tumor DNA from any future blood samples.

How long will it take to receive the Signatera test results?

- The first time the Signatera test is ordered, it will take 2 weeks for tumor tissue sequencing results to become available from the date the tumor tissue is received. Then, it will take another 2 weeks for your personalized test design and for your physician to receive the first Signatera test result
- After the test has been designed, it will take 1 to 2 weeks for your Signatera test results to become available after your blood sample is received by the Natera laboratory



What do the Signatera test results mean?

Your test result will either be positive or negative for the presence of tumor DNA in your blood. Your doctor will receive the test report and then will be able to discuss your results and answer questions.

A positive Signatera test result indicates that tumor DNA has been detected in your blood.

Early stage

A positive result means there is higher risk for your cancer returning. Consult your doctor or oncologist to discuss additional options for cancer monitoring or treatment.

Metastatic

Prior to receiving your treatment, you are likely to have a positive result. Your doctor may monitor for changes in ctDNA levels to monitor your tumor's response to treatment.

A negative Signatera test result indicates that tumor DNA was NOT detected in your blood

Early stage

A negative result means that you are more likely to remain cancer-free.

Metastatic

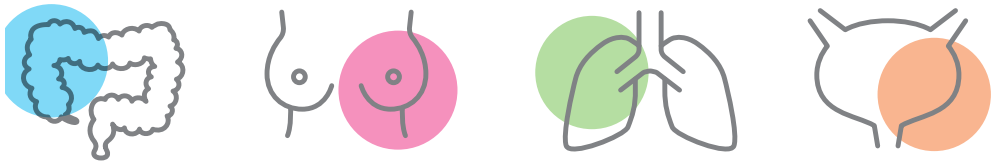
A negative result after your treatment may mean that the therapy was able to decrease the amount of cancer cells to levels undetectable to the Signatera test.

No test is perfect, and negative results may change over time. A negative Signatera result doesn't guarantee that tumor DNA was not in your blood, nor that it will never be detected in the future. That is why the Signatera test is recommended for periodic use over the course of your cancer care as directed by your doctor, to detect changes in the presence or absence of tumor DNA.

Limitations of the test: While the Signatera test is highly sensitive and specific, no screening test is 100% accurate in predicting cancer progression status. A negative Signatera test result does not guarantee your cancer is cured or that you will remain cancer-free forever. A positive Signatera test result also does not indicate that every patient will have a recurrence of cancer. Signatera is not designed to detect ctDNA in patients with more than one primary cancer, provide treatment selection guidance, or test for hereditary cancer syndromes.

How accurate is the Signatera molecular monitoring test?

Signatera has been studied in clinical studies across multiple solid cancer tumor types including colon, breast, lung, and bladder.[2-5]



Signatera can detect extremely small amounts of tumor DNA before cancer recurrence can be seen by traditional imaging tools such as CT scans or MRI.[2-5] The Signatera test is highly sensitive and specific, meaning that if your test result is positive, there is a high likelihood that your cancer may recur without further treatment. The test's ability to correctly identify the presence of molecular residual disease (MRD), is what makes Signatera unique.

Signatera clinical study results

Performance of Signatera in clinical studies of non-metastatic patients across several common cancer types

Cancer type	Risk of cancer recurrence after a postive result*	Average time MRD was detected before clinical recurrence†	Maximum time MRD was detected before clinical recurrence†
 **Colorectal cancer[3]**	93%	8.7 months	16.5 months
 **Breast cancer[5]**	> 99%	9.5 months	2 years
HR+/HER2-	> 99%	10.9 months	2 years
HER2+	> 99%	5.5 months	10.4 months
TNBC	> 99%	8.5 months	1 year 7 months
 **Non-small cell lung cancer[2]**	> 99%	4 months	11.5 months
 **Muscle invasive bladder cancer[4]**	93%	2.8 months	8.2 months

*Without recieving further treatment †Versus imaging tools, without further treatment

When should the Signatera test be considered?

- At initial cancer diagnosis, to establish a baseline before surgery or treatment
- After surgery, before starting chemotherapy
- During treatment, to evaluate treatment response
- After treatment, to monitor for molecular residual disease or tumor response to treatment

This test can only be ordered by a licensed oncologist or doctor treating your cancer. Talk to your doctor to see if you may be a candidate for the Signatera test.

Leading cancer centers around the world are using the Signatera test in their studies

Signatera is used extensively in research studies with leading cancer academic centers, including Aarhus University, Cancer Research UK, Columbia University, Fox Chase Cancer Center, Imperial College of London, Institut Jules Bordet, UC San Francisco, University of Leicester, and Vanderbilt University.

Glossary of terms

Cell-free DNA: DNA fragments circulating freely in the blood that are not associated with cells. Cell free DNA may be released from cells in the body such as tumor cells or cells from the placenta.

Circulating tumor DNA (ctDNA): Fragments of cell-free DNA in the bloodstream that originated from the tumor

Clonal mutations: Mutations in DNA that occurred in the early stages of cancer cell formation

DNA: Deoxyribonucleic acid is a molecule that makes up the genetic material present in all cells of living organisms

Molecular monitoring: Measurement of response to treatment using techniques that can detect molecular levels of disease

Molecular residual disease (MRD): Traces of tumor cell DNA left after treatment of non-metastatic cancer that are only detectable by highly sensitive and specific tests

Mutations: Changes in a cell's genetic material, or DNA, that can lead to the cell transforming into a cancer cell

Tumor DNA: DNA from cancer cells that contain multiple genetic mutations contributing to cancer development

References

1. Corcoran RB, Chabner BA. Application of cell-free DNA analysis to cancer treatment. *N Engl J Med.* 2018;379(18):1754-1765.
2. Abbosh C, Birkbak NJ, Wilson GA, et al. Phylogenetic ctDNA analysis depicts early-stage lung cancer evolution. *Nature*. 2017;545(7655):446-451.
3. 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. doi:10.1001/jamaoncol.2019.05282. [Epub ahead of print]
4. 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. doi: 10.1200/JCO.18.02052. [Epub ahead of print]
5. Coombes RC, Page K, Salari R, et al. Personalized detection of circulating tumor DNA antedates breast cancer metastatic recurrence. *Clin Cancer Res.* 2019. doi: 10.1158/1078-0432.CCR-18-3663. [Epub ahead of print]
6. Sethi H, Salari R, Navarro S, et al. Analytical validation of the Signatera™ RUO assay, a highly sensitive patient-specific multiplex PCR NGS-based noninvasive cancer recurrence detection and therapy monitoring assay. Poster presented at: American Association for Cancer Research (AACR) Annual Meeting; April 17, 2018; Chicago, IL. Abstract 4542.

For more information about Signatera or to review published studies, visit our website www.natera.com/signatera

Contact Natera patient support services at: 650.489.9050

About Natera, the maker of Signatera

Natera was founded with a mission to improve the early detection of genetic conditions in pregnancies through innovative technology. Since then, Natera has helped over a million women and their families learn about the genetic health of their babies through a leading suite of products that help families on their path to parenthood. Using this extensive experience, Natera is applying its expertise in detecting very small amounts of DNA in the blood (or cell-free DNA) to the early and precise detection of molecular residual disease in cancer patients. The company's mission is to change the management of disease worldwide and is focused on improving reproductive health, cancer, and organ transplant care for patients.

Signatera was developed by Natera, Inc. a laboratory certified under the Clinical Laboratory Improvement Amendments (CLIA). This test has not been cleared or approved by the U.S. Food and Drug Administration (FDA). Although FDA does not currently clear or approve laboratory-developed tests in the U.S., certification of the laboratory is required under CLIA to ensure the quality and validity of the tests.

natera | Signatera™ Molecular monitoring (MRD)