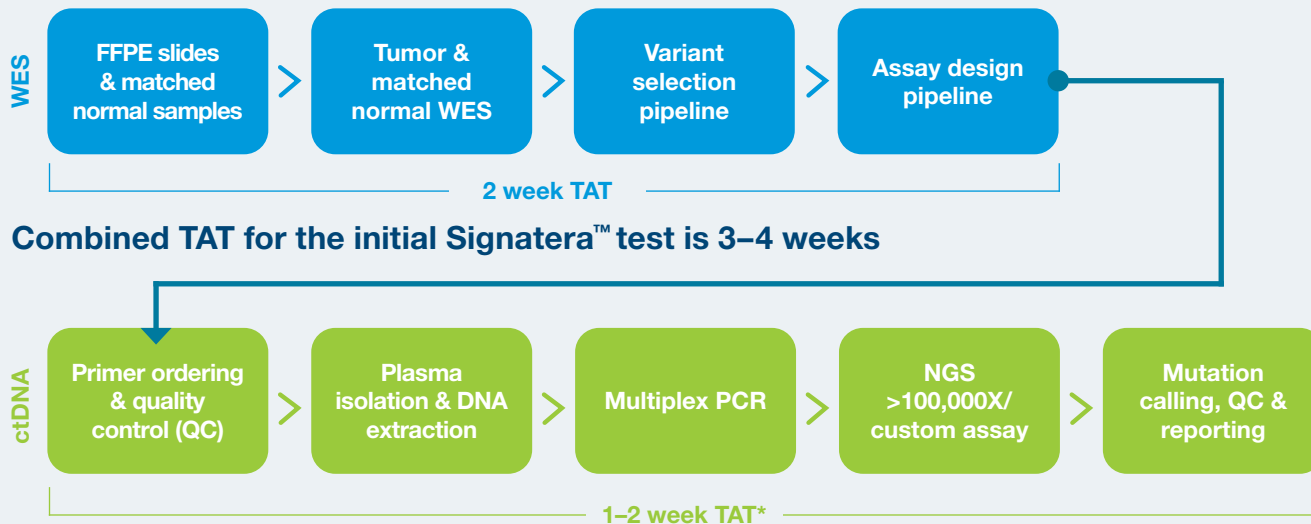


# The Signatera™ Process

**Signatera™ is a highly sensitive and tumor-informed molecular residual disease assay (MRD) using circulating tumor DNA (ctDNA), custom designed for each patient to help identify recurrence treatment response earlier than standard of care tools**

## Signatera™ initial timepoint workflow and turnaround times (TAT)



WES = tissue based whole exome sequencing ctDNA = plasma based ctDNA analysis

## 1. Specimen Preparation for Signatera™

A. Tissue specimen (only one of the below is required)

### Option 1 (Preferred)



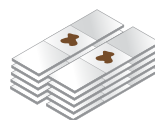
FFPE Tissue block

1 H&E slide

**FFPE Tissue block (> 25 mm<sup>2</sup> minimum)  
+ 1 H&E slide (if available)**

The original H&E slide and FFPE Tissue block will be shipped back to the customer upon test completion.

### Option 2



+



**10 unstained slides (10 µm each) 1 H&E slide**

**Unstained slides + 1 H&E slide (required)**

Unstained slides must be accompanied by 1 H&E slide for tumor content evaluation.

**Acceptable options for unstained slides:**

- (Preferred) 10 unstained slides; 10 µm thickness each
- (Comparable) 20 unstained slides; 5 µm thickness each

B. Blood Specimen: tissue is sent separate from blood

Plasma samples can be collected in clinic or via Natera's complimentary mobile phlebotomy service. Only plasma is needed for subsequent samples q3 mos or as directed by the ordering physician.



One 6 mL EDTA tube for initial matched normal (germline) sequencing



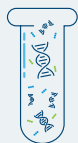
Two 10 mL Streck tubes of peripheral blood

## 2. Signatera™ is personalized and tumor informed



### Whole exome sequencing (WES) of tumor tissue and matched normal

- Both tumor and blood samples will be accessioned at Natera
- Natera's WES lab partner will perform WES studies for germline (blood sample in EDTA tube) and tumor tissue
- WES data will be sent back to Natera for bioinformatics processing (any remaining FFPE blocks will be returned to the pathology department, but utilized slides will not be returned; any remaining extracted DNA/blood specimen will be discarded)



### Custom-design of Signatera™ assay for each patient

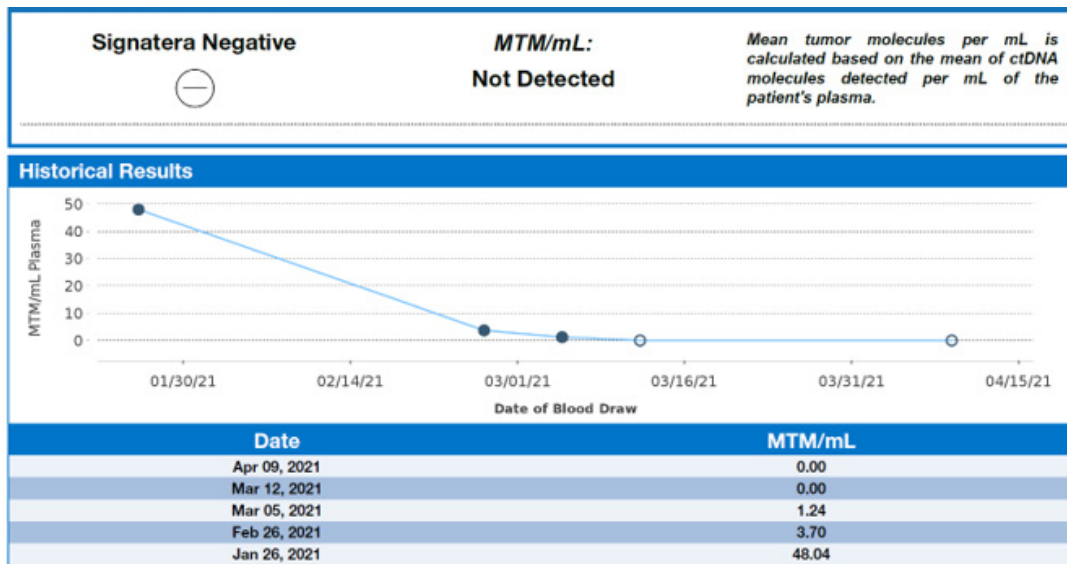
- WES data will be sent back to Natera for bioinformatics processing
- Natera's proprietary bioinformatics algorithm will select 16 clonal, somatic variants present only in the tumor tissue, and compatible for multiplex PCR



### Signatera™ results are delivered in a clear format

- Test report indicates the presence or absence of detectable ctDNA
- ctDNA is quantified by mean tumor molecules (MTM) per milliliter

## 3. Analysis of data to determine presence of ctDNA



MTM = mean tumor molecules

[Learn more at natera.com/oncology](https://www.natera.com/oncology)