A personalized approach to cancer management using circulating tumor DNA

December 2, 2022

What is Signatera?

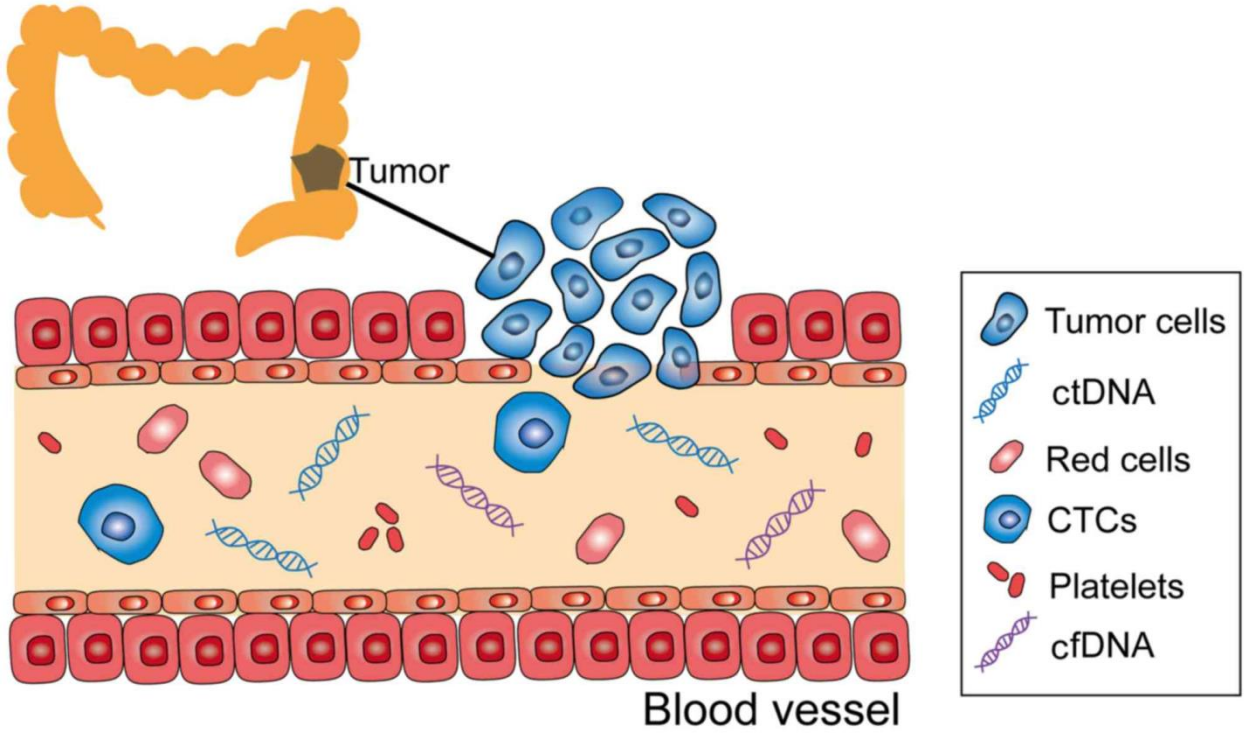
natera™

Each person's cancer is as unique as their fingerprint.

- Signatera is a personalized test that detects ctDNA in the blood
- Custom-designed based on each patient's unique set of tumor mutations

Early detection is key in cancer management

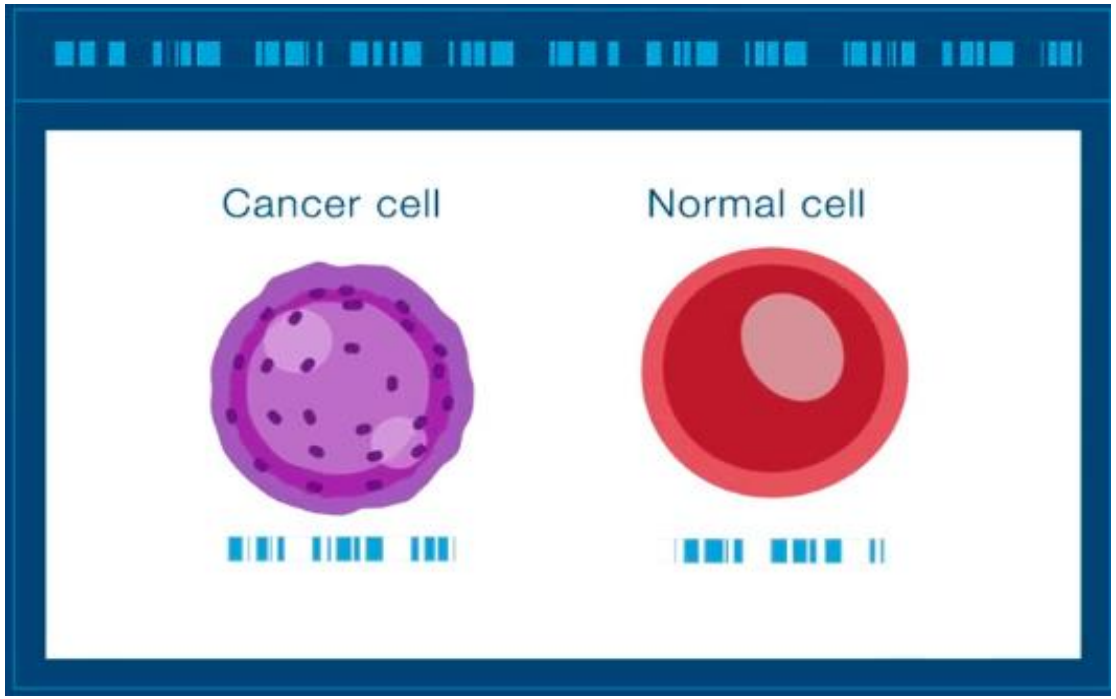
- Following treatment, microscopic fragments of cancer go undetected
- If left untreated, these residual cancer cells are likely to cause a recurrence [1]
- ctDNA testing can accurately measure molecular residual disease or MRD in and identify relapse much earlier
- ctDNA “disintegrates” in <1 hour



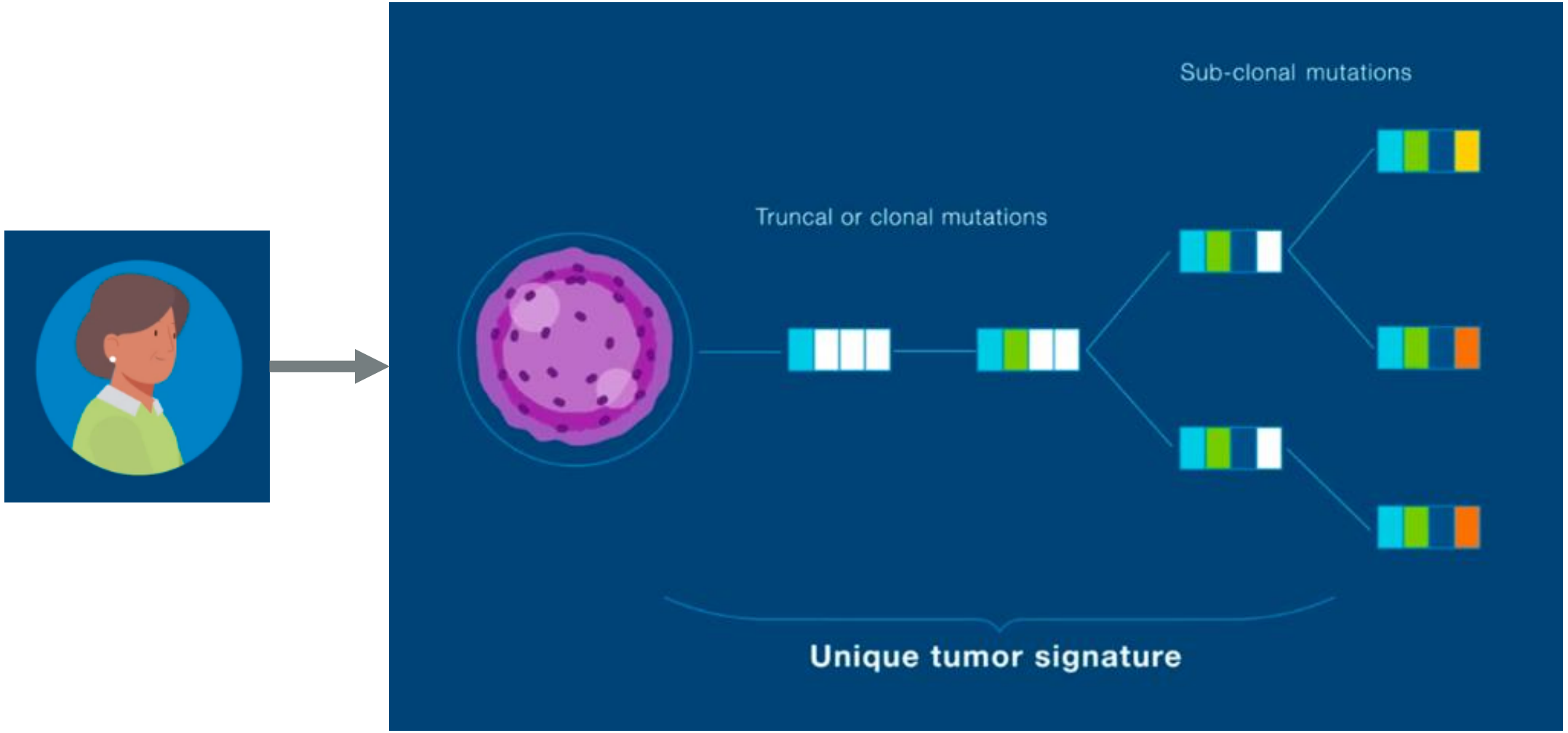
cfDNA (cell-free DNA): pieces of DNA produced by a cell that are circulating in the blood
ctDNA (circulating tumor DNA): pieces of DNA from tumor cells that are in the blood

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

Identifying MRD is like a finding a needle in a haystack

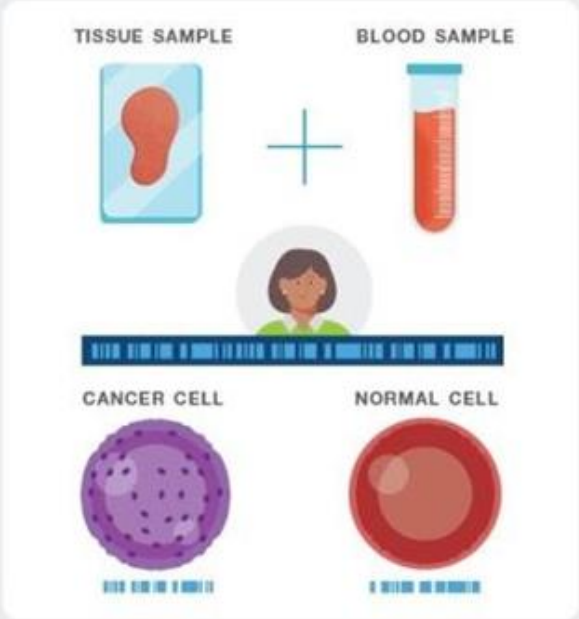


Highly accurate and specific for each patient



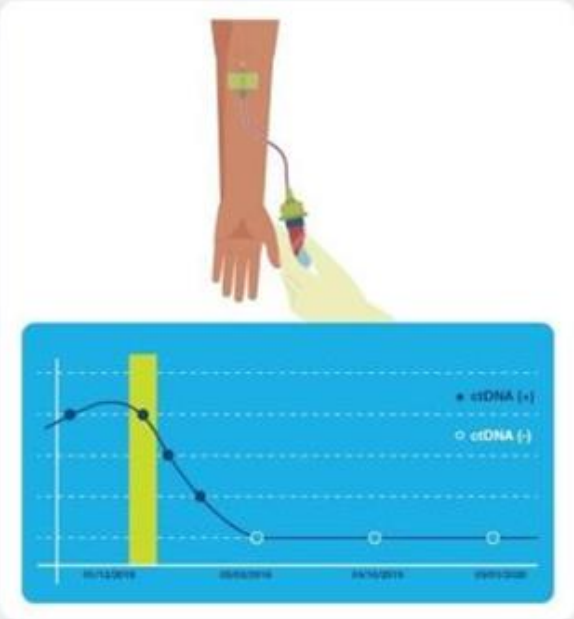
How Signatera works

1 A one-time analysis of both blood and tissue is performed to determine your unique set of tumor mutations



2 The test is custom-built and personalized for you

3 Signatera detects the presence or absence of tumor DNA each time it is ordered as part of your routine follow-up blood tests



Where is Signatera used?

Who benefits from treatment

Do I need chemotherapy?

Detect relapse earlier

Is my cancer coming back?

Monitor treatment response

Is the treatment working?

Understanding your Signatera test results

Negative Result
ctDNA not detected

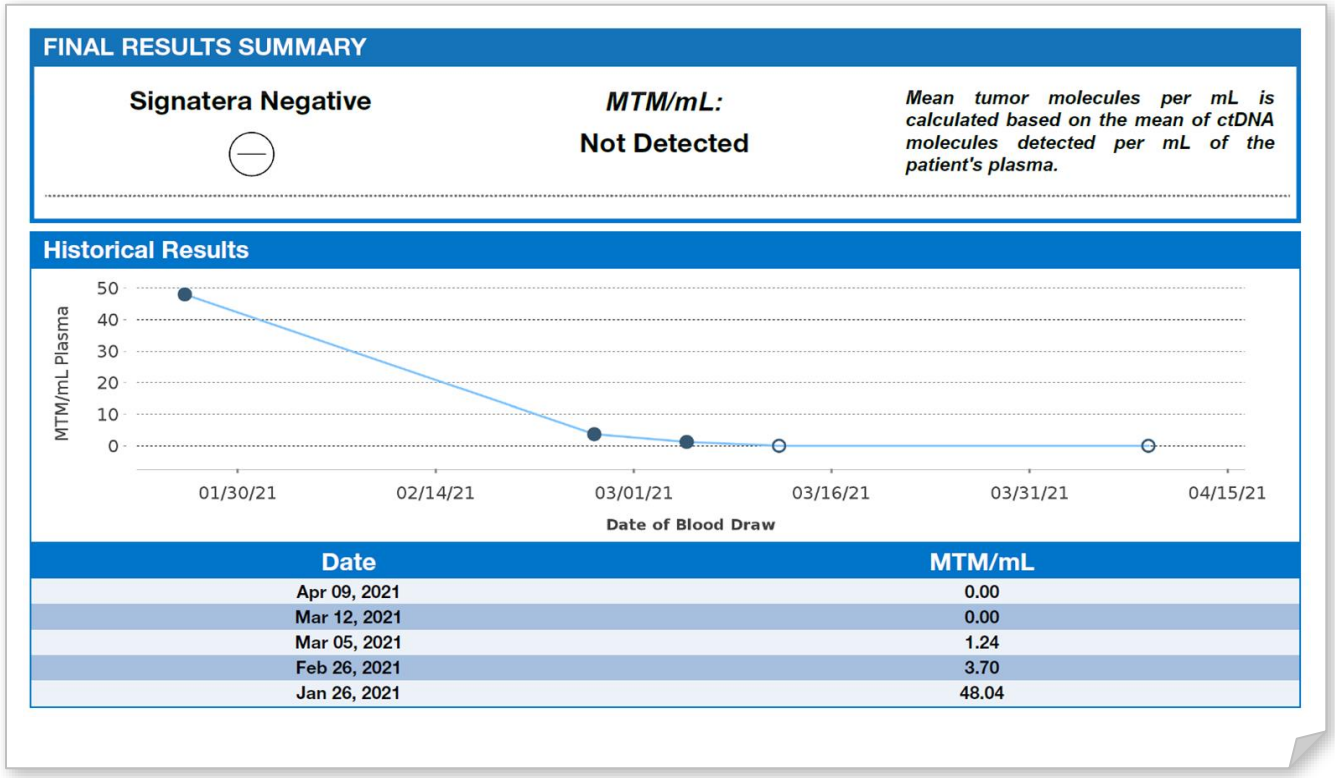
- If you were diagnosed with early-stage cancer, you are more likely to remain cancer-free.
- If you have metastatic cancer, this may mean that your cancer treatment has been effective.

Positive Result
ctDNA detected

- If you were diagnosed with early-stage cancer, there is higher risk for your cancer returning.
- Your doctor may continue to monitor your ctDNA levels to assess your tumor's response to treatment.

IMPORTANT: Negative results may change over time, and ongoing monitoring is recommended.

Signatera tells the story of your cancer over time



FINAL RESULTS SUMMARY

Signatera Negative

MTM/mL:

Not Detected

Mean tumor molecules per mL is calculated based on the mean of ctDNA molecules detected per mL of the patient's plasma.

Historical Results

Date	MTM/mL
Apr 09, 2021	0.00
Mar 12, 2021	0.00
Mar 05, 2021	1.24
Feb 26, 2021	3.70
Jan 26, 2021	48.04

- Tracking your ctDNA levels over time can indicate how your cancer is responding to treatment.
- Signatera is meant for serial use in combination with other biomarkers and imaging as part of your overall cancer care regimen and to closely monitor your treatment journey

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How long until my results arrive?

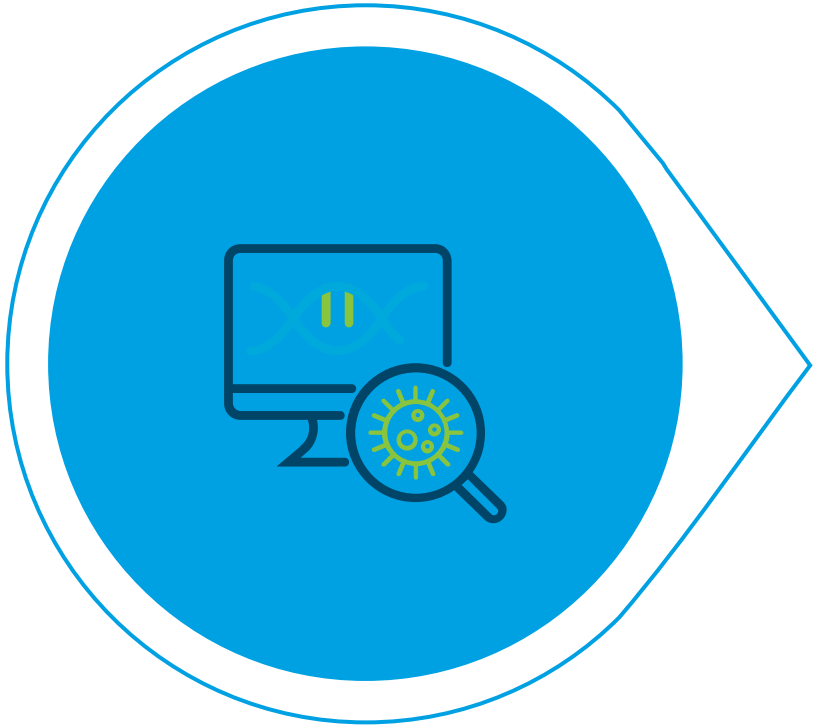
Designing your first Signatera test

The first time the Signatera test is ordered, it will take 2 to 3 weeks from the date the tumor tissue and required blood samples are received to design your personalized test.

After your test has been designed

It will take ~1 week after your blood sample is received in the lab for your test results to become available to your physician.

The significance of ctDNA testing with Signatera™



- Noninvasive tool for close disease monitoring
- Identify cancer cells remaining in your body, even after treatment
- Detect cancer recurrence earlier than before
- Improve confidence in your scans
- Know if your treatment is working

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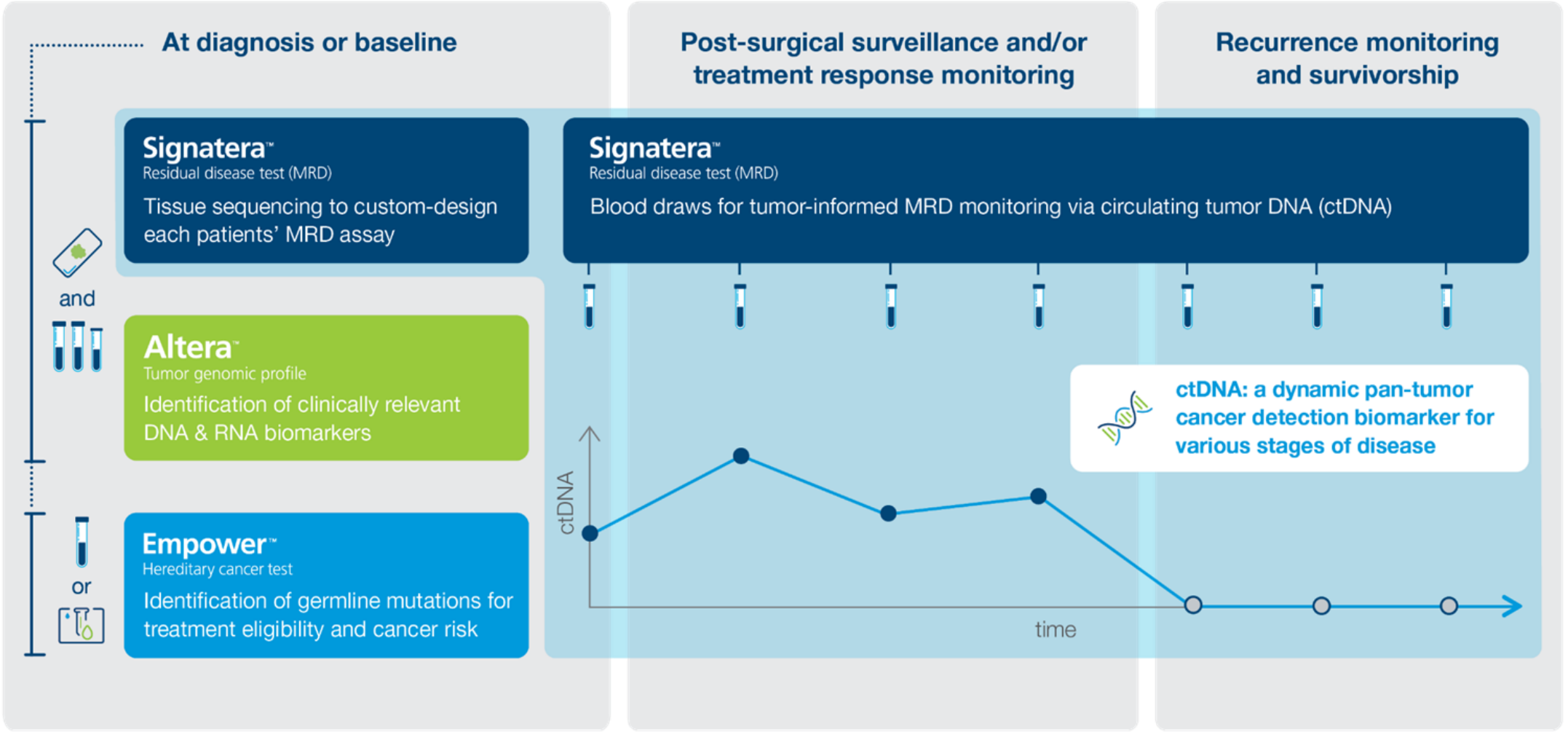
Oncology suite of products

Natera's trio of genetic and genomic assays inform treatment decisions, from diagnosis to survivorship



What is Altera?

- Altera is a test that is used to identify therapy selections and available clinical trials based on your tumor's genetics
- This is known as Comprehensive Genomic Profiling or CGP
- Altera tests for genes that are relevant to your cancer that can impact your cancer treatment.

Altera™
Tumor gene panel

Why does Altera CGP matter?

Historically

- **Target the tumor:** treat all cancers of the same type the same way
- **More = Better:** toxic chemotherapy that damaged healthy and cancer cells

Biomarker-driven Therapy Selection

- **Target the pathway:** all cancers of the same type do not receive the same treatment
- **Treatment to target specific cells:** predict benefit *and* resistance to specific therapy

Altera™
Tumor gene panel

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What does this mean for patients?

Access to Precision Medicine

- Impacts treatment decisions:
  - More informed decision making specific to your cancer
  - Directs selection of available therapies, both new and old
  - Rules out therapies likely to be ineffective
  - Identifies available clinical trials

Altera™
Tumor gene panel

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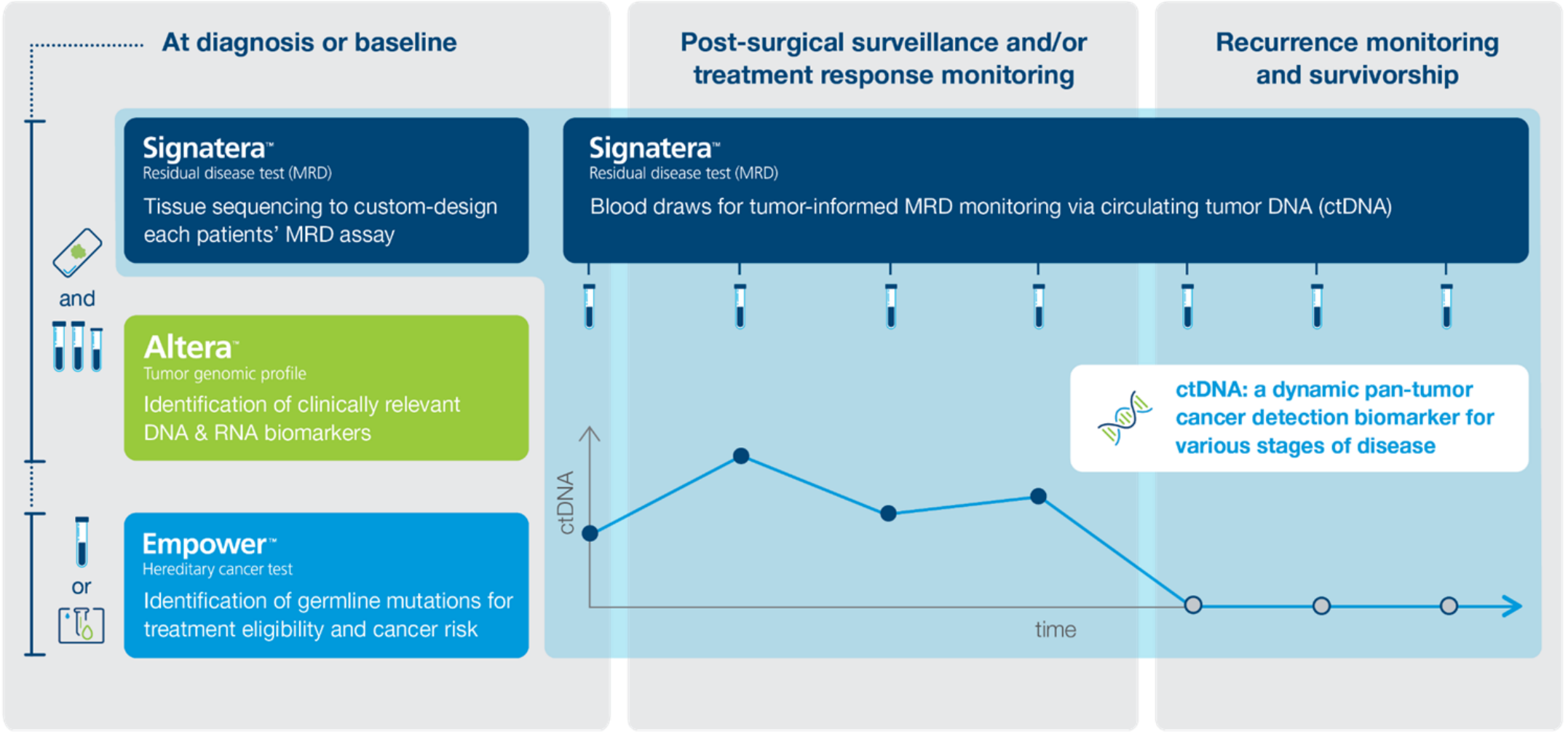
Personalized medicine person image. https://www.needpix.com/photo/938035/

Oncology suite of products

Natera's trio of genetic and genomic assays inform treatment decisions, from diagnosis to survivorship



Choices to Meet the Screening Needs of Each Patient

Lynch syndrome

Hereditary nonpolyposis colorectal cancer (HNPCC)

5 genes

MLH1, MSH2, MSH6, PMS2, EPCAM

GYN guidelines-based

Breast, ovarian, endometrial cancers and Lynch syndrome genes

19 genes

ATM, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, MLH1, MSH2, MSH6, NBN, NF1, PALB2, PMS2, PTEN, RAD51C, RAD51D, STK11, TP53

Multi-cancer

Most commonly screened-for hereditary cancer genes across eight cancer types

40 genes

APC, ATM, AXIN2, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, GALNT12, GREM1, HOXB13, MEN1, MITF, MLH1, MSH2, MSH3, MSH6, MUTYH, NBN, NF1, NTHL1, PALB2, PMS2, POLD1, POLE, PTEN, RAD51C, RAD51D, RNF43, RPS20, SMAD4, STK11, TP53, VHL

Comprehensive

Commonly screened-for hereditary cancer genes plus genes with emerging evidence of elevated cancer risks

81 genes

AIP, ALK, APC, ATM, AXIN2, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDC73, CDH1, CDK4, CDKN1B, CDKN1C, CDKN2A, CEBPA, CHEK2, CYLD, DDX41, DICER1, EGFR, EPCAM, EXT1, EXT2, FH, FLCN, GATA2, GREM1, HOXB13, KIT, LZTR1, MAX, MEN1, MET, MITF, MLH1, MSH2, MSH3, MSH6, MUTYH, NBN, NF1, NF2, NTHL1, PALB2, PDGFRA, PHOX2B, PMS2, POLD1, POLE, POT1, PRKAR1A, PTCH1, PTEN, RAD51C, RAD51D, RB1, RET, RHBDF2, RUNX1, SDHA, SDHAF2, SDHB, SDHC, SDHD, SMAD4, SMARCA4, SMARCB1, SMARCE1, STK11, SUFU, TERC, TERT, TMEM127, TP53, TSC1, TSC2, VHL, WT1

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Serial ctDNA detection using a personalized, tumor-informed assay in esophageal adenocarcinoma patients following resection

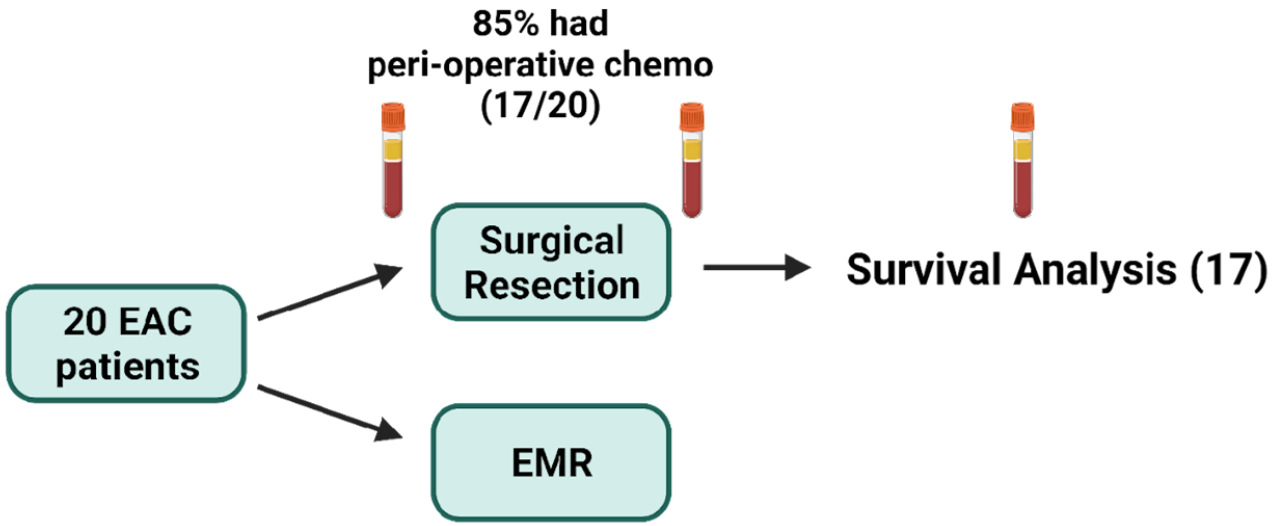
Emma Ococks[1], Shruti Sharma[2], Alvin Wei Tian NG[1], Alexey Aleshin[2], Occams Consortium[1], Rebecca Fitzgerald[1], and Elizabeth Smyth[3]

[1]University of Cambridge, Cambridge, UK
[2]Natera, Inc. San Carlos, CA, USA
[3]Cambridge University Hospitals, Addenbrooke's Hospital, Cambridge, UK

Gastroenterology aga American Gastroenterological Association

Esophageal Adenocarcinoma Retrospective Study Schema

Patient Demographics	n=20	
Female	3	15%
Male	17	85%
Median Age at Diagnosis	62 (48-80)	
Stage		
T1a	2	10%
T1	1	5%
T2	5	25%
T3	12	60%
N0	9	45%

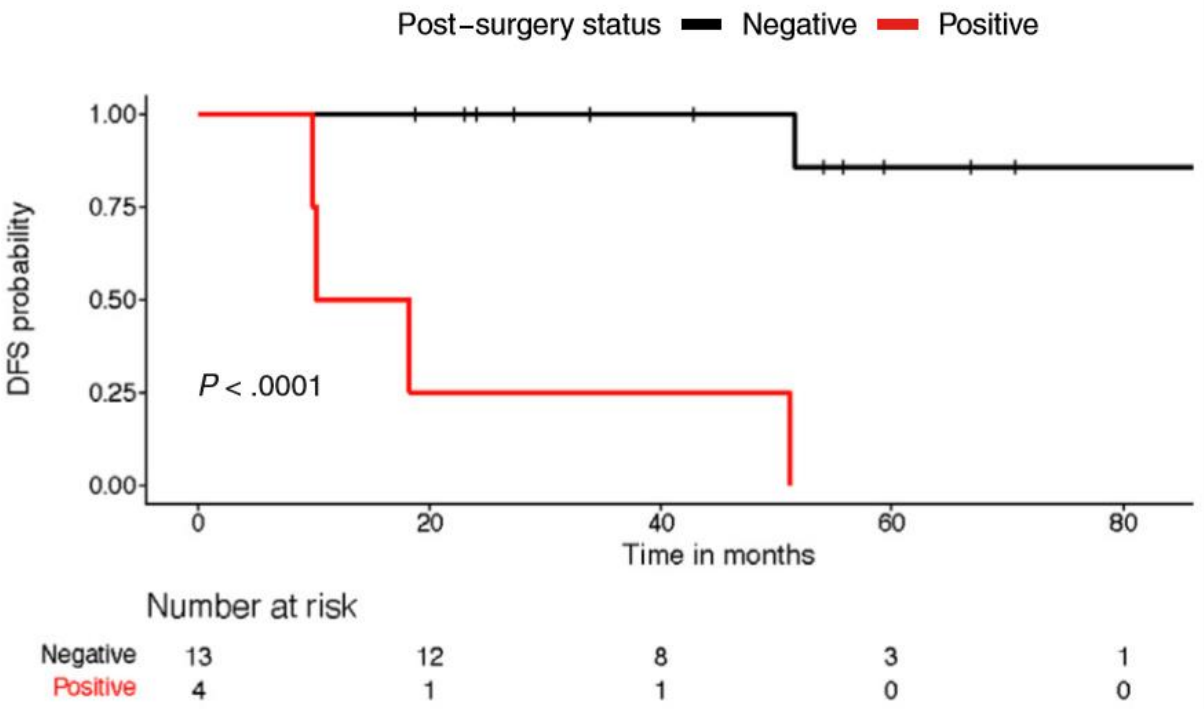


EAC, esophageal adenocarcinoma; EMR, endoscopic mucosal resection

E. Ococks, S. Sharma, Wei Tian, Occams Consortium, A. Aleshin, R. Fitzgerald, and E. Smyth. Serial ctDNA detection using a personalized, tumor informed assay in esophageal adenocarcinoma patients following resection. *Gastroenterology,* 14 July 2021.

Ococks et al
Gastroenterology 2021

Patients with detectable ctDNA post-surgery had significantly worse outcomes



- **Positive ctDNA → 14 months disease-free**
- **Negative ctDNA → 51 months disease-free**

Signatera had 80 % sensitivity and 100 % specificity in post-surgical samples

E. Ococks, S. Sharma, Wei Tian, Occams Consortium, A. Aleshin, R. Fitzgerald, and E. Smyth. Serial ctDNA detection using a personalized, tumor informed assay in esophageal adenocarcinoma patients following resection. *Gastroenterology,* 14 July 2021.

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Clinical utility of ctDNA to evaluate treatment response

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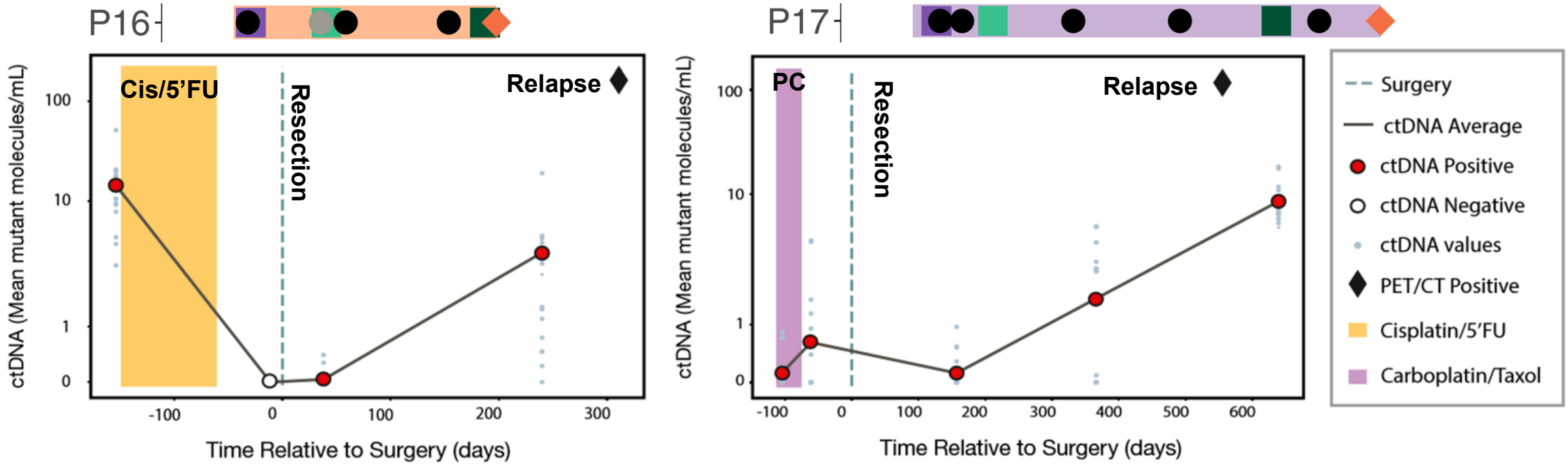

Stage IVA EAC patient
who responded to Cisplatin/5'FU

Stage III EAC patient who was resistant to Paclitaxel/Carboplatin

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E. Ococks, S. Sharma, Wei Tian, Occams Consortium, A. Aleshin, R. Fitzgerald, and E. Smyth. Serial ctDNA detection using a personalized, tumor informed assay in esophageal adenocarcinoma patients following resection. *Gastroenterology*, 14 July 2021.

Performance of a tumor-informed circulating tumor DNA assay from over 260 patients with over 800 plasma time points in esophageal and gastric cancer

Brandon M. Huffman[1], Griffin L. Budde[2], Joseph Chao[3], Farshid Dayyani[4], Diana Hanna[5], Gregory Botta[6], Shifra Krinshpun[2], Shruti Sharma[2], Vasily Aushev[2], Tiffany Farmer[2], Holly Pela[2], Mehrad Tavallai[2], Michael Goodman[2], Katie Baker[2], Bridgette Drummond[2], Alexey Aleshin[2], Pashtoon Kasi[7], Samuel J. Klempner[1]

[1] MGH Cancer Center, Boston, MA; [2]Natera, Inc. San Carlos, CA; [3]City of Hope Comprehensive Cancer Center, Duarte, CA; [4]University of California Irvine, Orange, CA; [5]Keck Hospital of USC, Los Angeles, CA; [6]UCSD Moores Cancer Center, La Jolla, CA; [7]University of Iowa - Holden Cancer Center Iowa City, IA.

Study design and patient characteristics

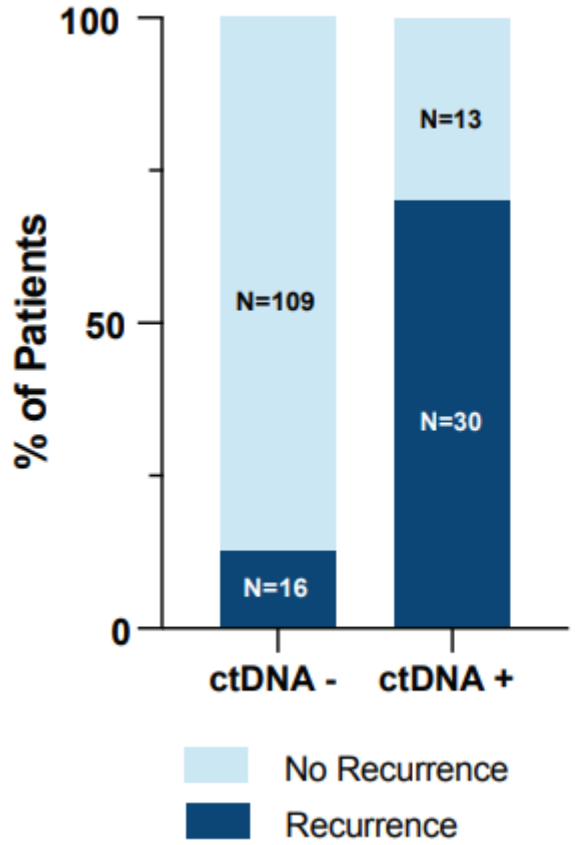
Huffman et al
ESMO 2021

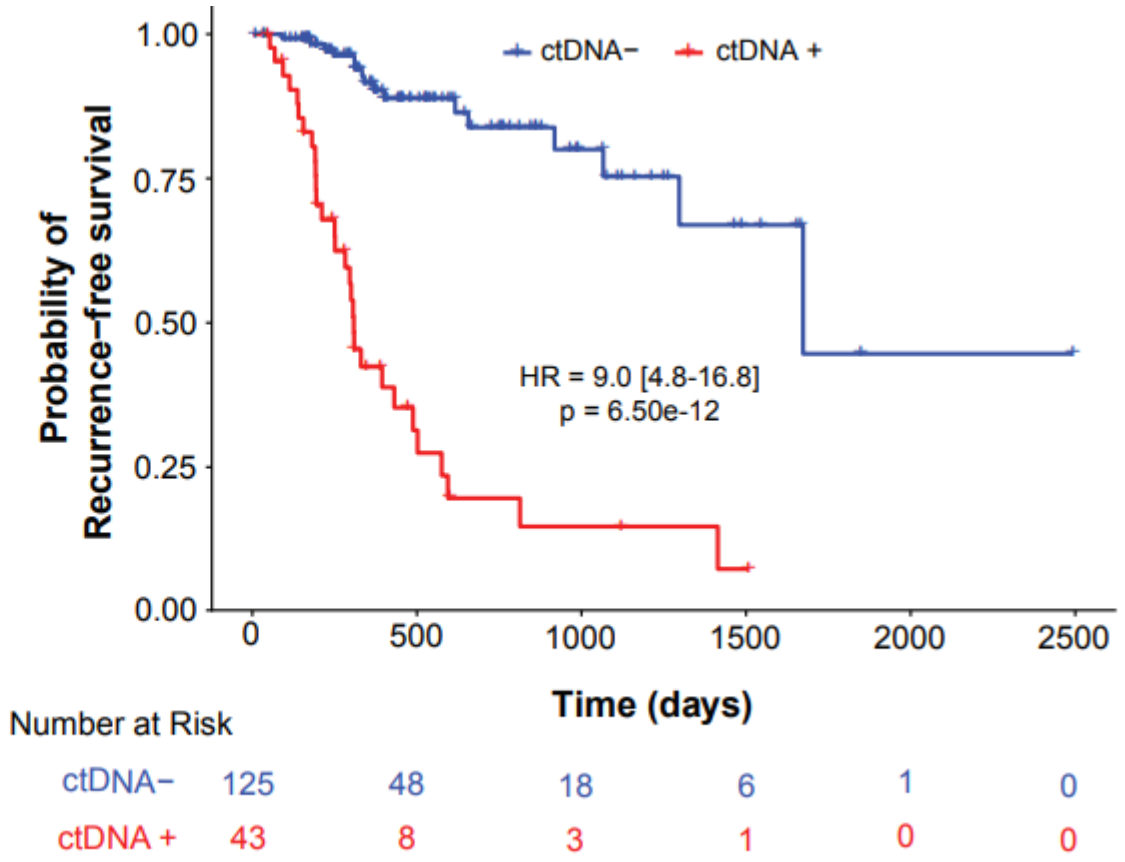
- 886 plasma timepoints on 269 patients were prospectively analyzed for circulating tumor DNA (ctDNA) utilizing the commercially available Signatera assay to monitor MRD levels after curative intent therapy
- This is a real-world cohort of patients undergoing adjuvant therapy and/or surveillance with upper GI malignancies

Age		
Median (range) yr	63.4 (20.4-88.2)	
Follow-Up Time		
Median (range) days	427 (12-2491)	
Gender	**N**	**%**
Female	93	34.6%
Male	176	65.4%
Cancer Location		
Esophageal	79	29.4%
Gastroesophageal Junction	71	26.4%
Gastric	119	44.2%
Histological Subtype		
Adenocarcinoma	249	92.6%
Squamous	19	7.10%
Small Cell	1	0.40%
Overall Pathological Stage		
I	32	11.9%
II	69	25.7%
III	91	33.8%
IV	77	28.6%

Huffman, et al. Performance of a tumor-informed circulating tumor DNA assay from over 260 patients with over 800 plasma time points in esophageal and gastric cancer ESCO, Poster #1415P. Sept 21, 2021.

Outcomes for stage I-III esophageal and gastric cancer patients





Number at Risk

ctDNA−	125	48	18	6	1	0
ctDNA +	43	8	3	1	0	0

Anytime ctDNA-positivity is predictive of relapse and correlates with inferior RFS

Huffman, et al. Performance of a tumor-informed circulating tumor DNA assay from over 260 patients with over 800 plasma time points in esophageal and gastric cancer ESCO, Poster #1415P. Sept 21, 2021.

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Residual disease test (MRD)

This test 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 US Food and Drug Administration (FDA). Although FDA does not currently clear or approve laboratory-developed tests in the US, certification of the laboratory is required under CLIA to ensure the quality and validity of the tests. ©2019 Natera, Inc.