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INVITAE

Invitae Personalized Cancer Monitoring (PCM™)

Get ahead of cancer

A pan-cancer,* personalized liquid biopsy test to monitor minimal residual disease (MRD), with high sensitivity in solid tumors to detect residual cancer earlier. Empowering oncologists to risk stratify patients, assess treatment response and act sooner.

*With exceptions – such as CNS malignancies and sarcomas – this test is not intended to be used in hematological malignancies such as leukemias or lymphomas.

Introduction

Determining the best treatment plan for a cancer patient after surgical resection or completion of adjuvant chemotherapy depends on several factors, including the results of monitoring for disease progression.[1] MRD monitoring based on circulating tumor DNA (ctDNA), which is DNA shed from cancer cells into the bloodstream, is a method already proven to help predict recurrence risk of cancer after definitive interventions, such as surgery.

Why Invitae

PCM is brought to you by a trusted leader in advanced medical genetics

Invitae is a leading genetic healthcare company and an early pioneer in personalized medicine. Chosen by more than 2 million patients and their providers, our team is committed to transforming oncology screening, diagnosis and treatment through the power of genomic information.

Molecular residual disease (MRD)

MRD is the cancer that persists in a patient that may not be detected with standard histology, pathology or diagnostic imaging.[2]

Studies have demonstrated a strong correlation between the presence of ctDNA in plasma and cancer recurrence.[3,4] Growing evidence suggests that MRD monitoring can detect recurrence sooner than standard imaging in patients who have undergone treatment with curative intent.

How MRD monitoring may fit into patient care

Studies have shown the utility of ctDNA MRD in risk stratifying to determine which patients have a high risk of relapse following their therapy.

Therapy response assessment and tailoring treatments: Because MRD monitoring can detect post-surgical recurrence earlier than standard imaging, it may allow additional treatment to be started when tumor burden is still relatively low. For patients who are already being treated after surgery, the type and level of ctDNA burden detected could help clinicians and patients decide to continue with a given therapy, switch to an alternative one or cease treatment altogether in the event of a cure.

Surveillance and longitudinal monitoring can refine and complement current imaging protocols and may allow for earlier detection of recurrence than standard imaging. Research has shown that MRD monitoring can reliably predict progression in patients on immunotherapy,[5] and studies are being implemented to see if it can determine how patients are responding to other types of therapy as well.[6]

There is a clinical need for risk stratification across solid tumor types as well as the need for molecular tools to complement and improve upon standard of care methods for recurrence detection. MRD monitoring and methods such as PCM have the potential to identify relapse prior to current monitoring methods, allowing clinicians to to optimize available information for treatment planning."

Robert Nussbaum, MD, Chief Medical Officer, Invitae

Why is MRD so important?

In a clinical setting, PCM has the potential to detect ctDNA following surgical resection or completion of adjuvant chemotherapy. This would allow a clinician to assess therapy response and monitor detectable ctDNA in the months or even years after a patient finishes treatment. If an MRD-positive result were to be obtained at any point in a patient's cancer journey, the clinician and patient could discuss the implications of the result and the most appropriate treatment or clinical trial options.

MRD monitoring by PCM

A pan-cancer,* **personalized** liquid biopsy test that uses next-generation sequencing (NGS) to monitor MRD in solid tumors with high sensitivity at low variant allele fractions.[7]

Personalized: A unique assay is developed using a patient's tumor and blood sample.

Sensitive: Optimized test chemistry demonstrates ctDNA detection with an analytic sensitivity of >99.9%.[7] This allows for monitoring for individuals with low DNA shedding tumor types or very low levels of residual disease.

Flexible: Designed to utilize up to **50 unique tumor variants**, which provides flexibility to capture unique aspects of each patient's tumor

Broad: PCM may be used for MRD measurements in a wide range of cancers, such as colorectal, lung, breast, gastrointestinal, genitourinary and others.

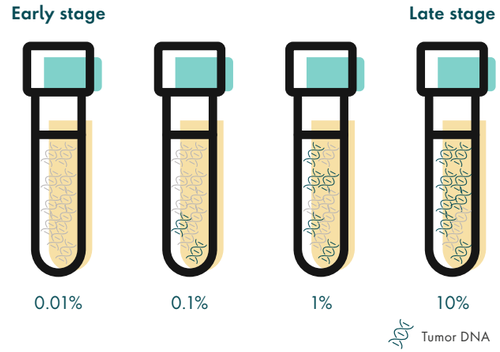


Figure 1. Examples of increasing variant allele fractions as cancer progresses

Clinical data

Numerous studies are building evidence for MRD as an important component of precision medicine.[8]

TRACERx (TRAcking non-small cell lung Cancer Evolution through therapy [Rx])

PCM predicted relapse after resection in 13 (93%) of 14 cases and detected recurrence a median of 70 days earlier than standard computed tomography imaging.[9]

In an additional set of patients, PCM detected ctDNA at or before clinical relapse in 37 (82%) of 45 patients.[10]

The data from this cohort also suggests that PCM may detect recurrence earlier than initially predicted, as the test had a median lead time of **136 days over standard imaging**.[10] The study validated the sensitivity of PCM in a clinical setting, detecting ctDNA at 60 ng input with >99% sensitivity for a variant allele frequency (VAF) of 0.005%.[10]

Ongoing research

PCM is incorporated into ongoing international clinical trials[7] for continued investigation of its utility in detecting MRD earlier than standard methods, and as an indicator for risk stratification, therapy management and longitudinal monitoring to improve patient outcomes.[11-13]

*With exceptions – such as CNS malignancies and sarcomas – this test is not intended to be used in hematological malignancies such as leukemias or lymphomas.

Analytical validation

A complete analytical validation was performed at our laboratory, which is CAP-accredited, and the assay's performance was determined according to current Clinical Laboratory Improvement Amendments (CLIA) guidance.

Sensitivity and limit of detection

108 samples were used to determine the sensitivity of PCM, or the probability that the assay would detect ctDNA at low variant allele fractions. The study showed greater than 99.9% sensitivity with inputs of cell-free DNA ranging from 10 ng to 60 ng and in allele fractions as low as 0.005% **(Figure 2)**, demonstrating the test's potential to detect variant alleles across most solid tumor types.

PCM has shown a limit of detection (LOD) with >99.9% sensitivity for a 60 ng DNA input at 0.008% VAF and for a 10 ng of DNA input and 0.03% variant allele frequency.

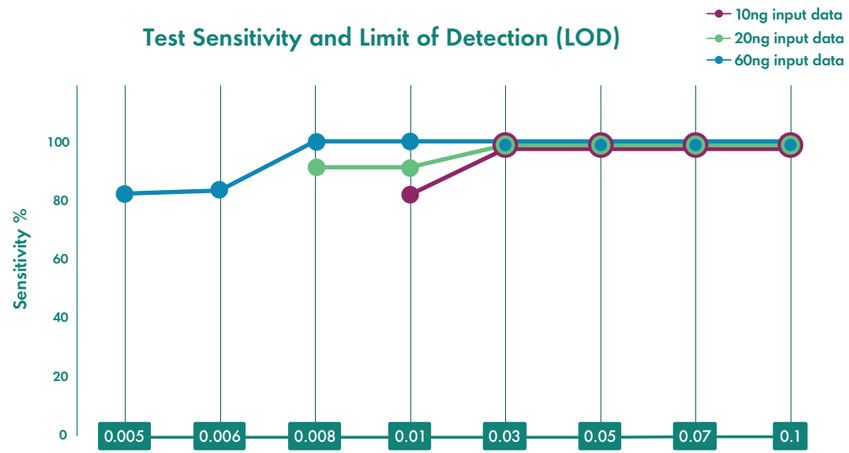


Figure 2. High sensitivity at low allele fractions

How it works

MRD baseline

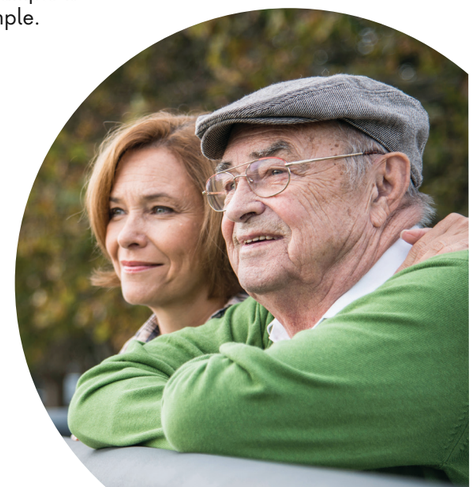
STEP 1: Tumor tissue and blood collection
After initial tumor resection, a tumor sample is sent to the laboratory. A blood sample is also sent to the laboratory to be processed in parallel with the tumor tissue sample.

STEP 2: Whole exome sequencing to identify variants
Whole exome sequencing is performed on both tumor and blood samples to identify unique variants of the somatic genome sequence.

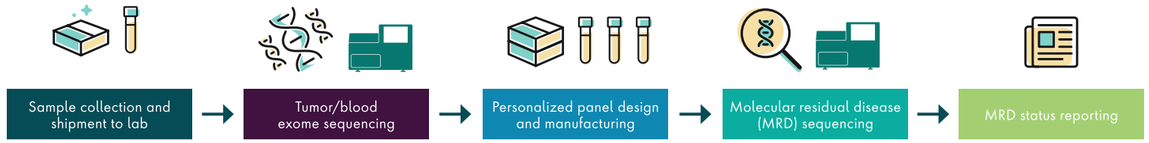
STEP 3: Variant selection and panel design
Based on the results of whole exome sequencing of both tumor and blood samples, our proprietary variant selection software chooses up to 50 tumor-specific variants for inclusion on a personalized ctDNA panel.

STEP 4: Detection of molecular residual disease
After the personalized panel is manufactured, the patient's ctDNA is extracted from plasma and processed through the customized assay to provide an initial MRD result.

STEP 5: Reporting
Initial report showing the presence or absence of MRD.



Personalized MRD panel development + 1st MRD time point



Serial MRD monitoring

Figure 3. A simple PCM workflow

Baseline test - Specimen requirements		
Formalin Fixed Paraffin Embedded (FFPE) Tissue	**Whole blood**	
FFPE block OR	K2 EDTA collection tube	Cell-Free DNA blood collection tube (black and tan top)
10 unstained FFPE slides	Minimum 3 mL	Fill two tubes with whole blood (2x 10mL)

Specimen kits: PCM collection kits come with instructions and all packaging materials needed to send the kits to Invitae. Conveniently request kits online at: www.invitae.com/request-a-kit

Expected turnaround time: 35-42 calendar days on average from the time all samples arrive at the laboratory.

Serial monitoring

Over time, additional MRD results can be obtained for comparison with earlier results. At each time point, a new plasma sample is sent to the laboratory and processed using the patient's same personalized panel. The number of time points for monitoring can be adjusted to fit each patient's needs based on tumor type and stage.

Serial monitoring - Specimen requirements	
Whole blood	
K2 EDTA collection tube	Cell-Free DNA Blood Collection Tube (black and tan top)

Specimen kits: PCM collection kits come with instructions and all packaging materials needed to send the kits to Invitae. Conveniently request kits online at: www.invitae.com/request-a-kit

Expected turnaround time: 7-14 calendar days on average from the time the sample arrives at the laboratory.

Timing options for testing

Current use across studies often begins with a baseline measurement **at diagnosis** and at timepoints starting **4-6 weeks** after definitive interventions, such as surgery. Co-timing PCM ctDNA MRD measurements with start or completion of treatment regimens for risk stratification, or in mid-phase and at completion to assess response, and alongside standard imaging events and other considerations will factor into planning timepoints for test use. Serial monitoring in studies has been performed at intervals of 2 to 6 months. The cadence of serial timepoints will also depend on the proposed use of the test within risk stratification, response assessment or surveillance settings, and will relate to other cardinal events within the patient's treatment and management as illustrated by the adjoining graphic **(Figure 4)**.

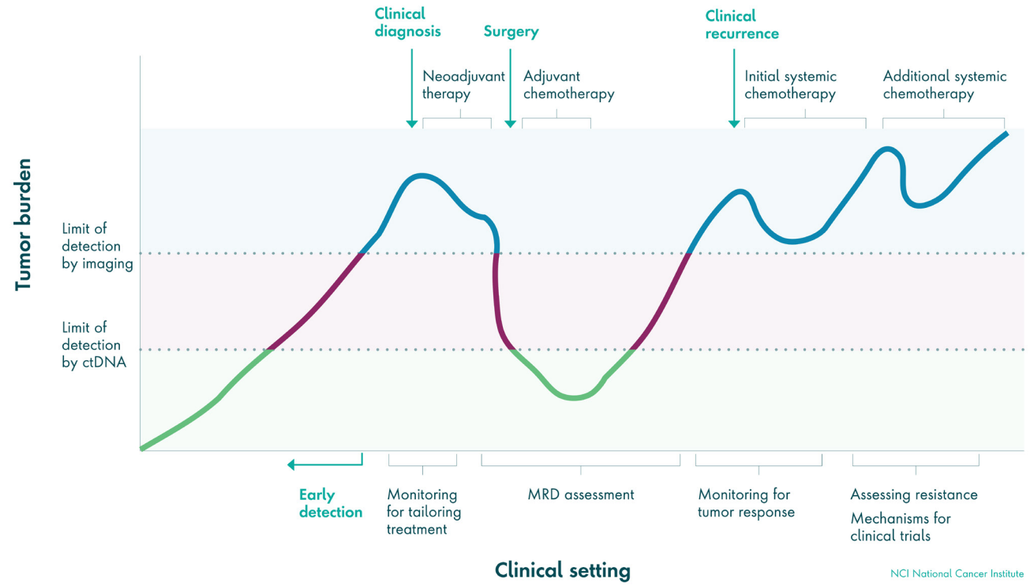


Figure 4. NCI colon cancer task force recommendations on ctDNA-MRD colorectal cancer studies

Possible results

ctDNA+ Patient Specific Signature: **Detected**
PCM test found tumor DNA in the patient's blood. There is a higher chance for cancer coming back.

ctDNA– Patient Specific Signature: **Not Detected**
PCM test did not find tumor DNA in the patient's blood. There is a lower chance for cancer coming back.

What do the results mean?

ctDNA+ Patient Specific Signature: **Detected**
You could use this information along with other tools about your patient's tumor to make treatment decisions.

If ctDNA is detected in someone's blood after they've had surgery or chemotherapy meant to cure, it means that tumor cells are still present. Finding ctDNA in the blood in the months or years after treatment has been related to increased risk of recurrence.

ctDNA– Patient Specific Signature: **Not Detected**
When someone is in remission after their cancer treatment is finished, we would not expect to detect ctDNA in the blood. This patient might have a lower risk of recurrence, although recurrence is still possible.

Support you can count on
Our team of clinical experts can assist with case review and result interpretation.