Understanding Cancer Screening Performance Metrics

As multi-cancer early detection (MCED) testing becomes more widely adopted, understanding how to interpret test performance across different studies and technologies is crucial. However, assessing the accuracy of these tests is complex. Learn the basics and details behind MCED performance metrics below.

MCED Goals at a Glance

Cancer screening saves lives, but **70% of cancer deaths** are caused by cancers without recommended screening tests.*[1,2]

Performance metrics help us understand how confident we can be in a cancer screening test in different populations. In other words, how confident can we be in the test's ability to detect cancer in the population it's intended for without creating other problems that offset its value?

Performance Metrics 101

There are two fundamental questions related to MCED test results:

1. Will the test correctly provide a cancer signal detected (positive) result if the person has cancer?
2. Will the test correctly provide a no cancer signal detected (negative) result if the person doesn't have cancer?

True Positive, True Negative, False Positive, False Negative

These fundamental questions are impossible to answer without knowing if someone has cancer or not. So, to see how well MCED tests perform, we initially evaluate them in what's known as case-control studies. In these studies, we know who has cancer and who doesn't, but the blood samples are blindly tested with the MCED test.

Each use of an MCED test gives us one of four possible outcomes, shown in the table.[3]

		Clinical Outcome	
		Patient has cancer	**Patient does not have cancer**
MCED Test Result	**Cancer signal detected**	**True Positive (TP)** Test detects a cancer signal, and cancer is present	**False Positive (FP)** Test detects a cancer signal, but cancer is absent
	No cancer signal detected	**False Negative (FN)** Test detects no cancer signal, but cancer is present	**True Negative (TN)** Test detects no cancer signal, and cancer is absent

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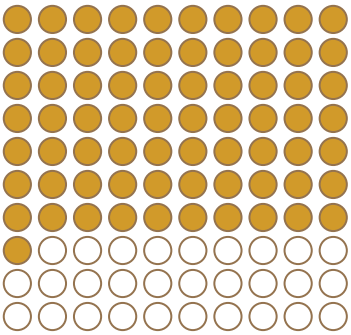
Some metrics help us understand whether the test does what it's supposed to: accurately detect a cancer signal.

Sensitivity and Specificity

Sensitivity measures how likely the test is to return a positive result in individuals with cancer. We determine the sensitivity of a test — **or true positive rate** — by measuring how many people with confirmed cancer got a positive result.

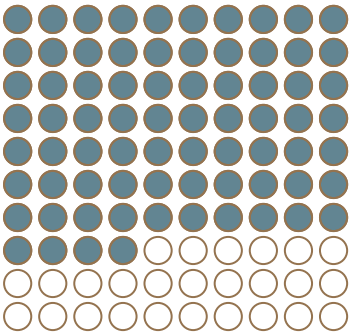
Of 100 people known to **have cancer,** 71 receive a **positive MCED** result



Sensitivity is 71%

Specificity measures how likely the test is to return a negative result in individuals without cancer. We determine the specificity of the test — **or true negative rate** — by measuring how many people without cancer got a negative result.

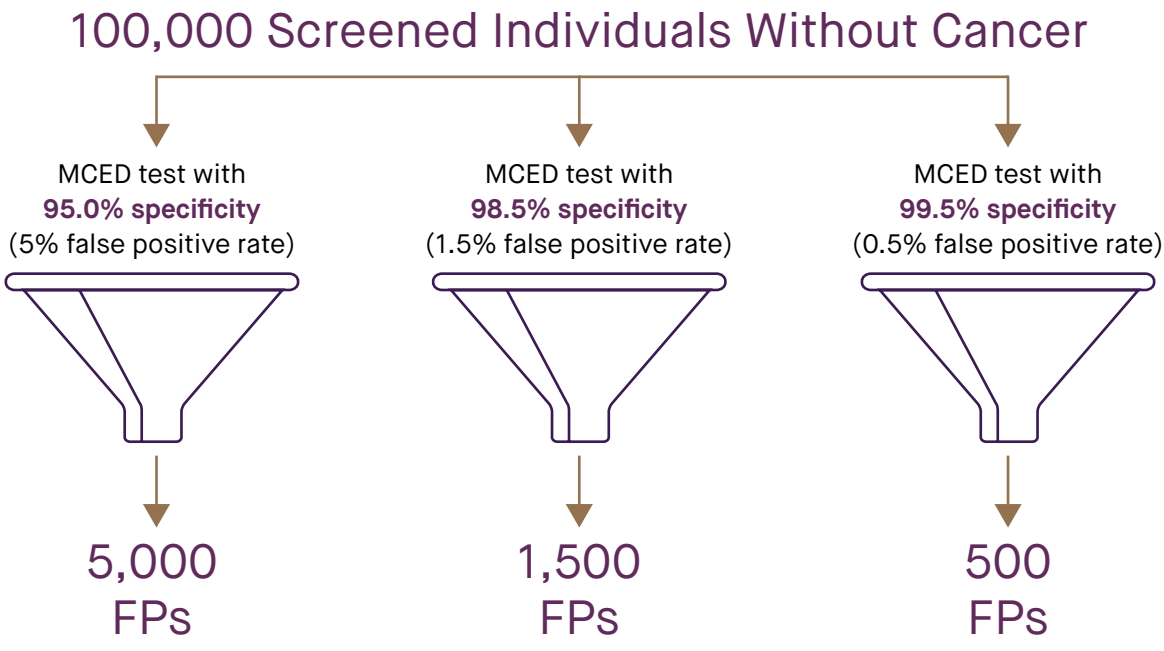
Of 100 people known **not to have cancer,** 74 get a **negative MCED** result



Specificity is 74%

Seemingly small changes in specificity have major implications at the population level.

For example, an MCED with a specificity of 98.5% will lead to three times as many false positives (FPs) as a test with a specificity of 99.5%. This could increase the number of people who receive FP results by thousands when the test becomes widely used in the intended population.



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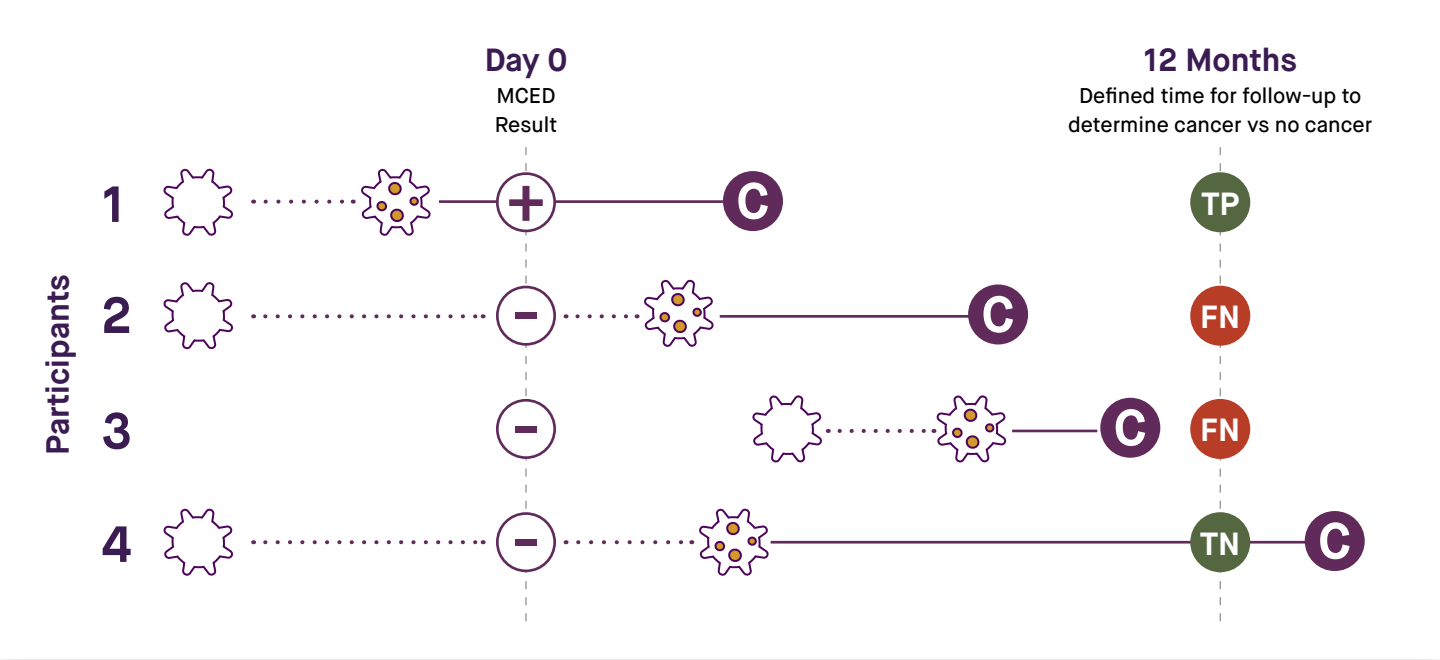
Episode Sensitivity

Sensitivity and specificity are important metrics to define during test development. However, in real-world practice, we don't know if someone has cancer when they take the test.

Instead, we must follow the patient for a certain period of time (often a year[4,5,6]) to determine if they receive a cancer diagnosis or not. **Episode sensitivity** is the proportion of cancers detected at the time of the initial screening test, out of all cancers diagnosed in individuals during a predefined follow-up period.



These are representative of different possible outcomes, but not all are equally likely.

Cancer is present

Cancer shedding cfDNA and detectable by MCED

C
Clinical cancer diagnosis

Following 4 participants above in a clinical trial:

Before the test is given, **participants 1, 2, and 4 have cancer.** But only **participant 1** has a cancer that is shedding enough cell-free DNA to be detected by MCED.

In **participant 2**, cancer began shedding cell-free DNA at a level detectable by MCED after the test was taken, leading to a false negative result.

Participant 3 developed cancer after the MCED test was done, but is still considered a false negative as it is within the predefined time frame.

In **participant 4**, cancer was diagnosed after the predefined time frame, which results in a true negative.

The outcomes (cancer or no cancer) at the **predefined time point of 12 months** are used to calculate episode sensitivity. Episode sensitivity is defined by **length of follow-up**.

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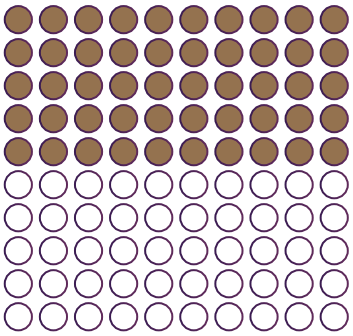
Other metrics indicate how confident we can be in a positive and negative result. In other words, if we get a positive or negative result, how likely is that result to be true? Positive predictive value (PPV) and negative predictive value (NPV) are calculated based on prospective, real-world studies with a defined length of follow-up (similar to episode sensitivity), not from case control studies.

Positive Predictive Value (PPV)

PPV indicates how likely it is that a person with a positive test result actually has cancer. Higher PPV equates to fewer false positives. This is one of the most important individual-level MCED test metrics since it describes the confidence in a positive test result.



Out of 100 people who receive a **positive MCED test result**, 50 people go on to receive a cancer diagnosis

PPV = 50%

Negative Predictive Value (NPV)

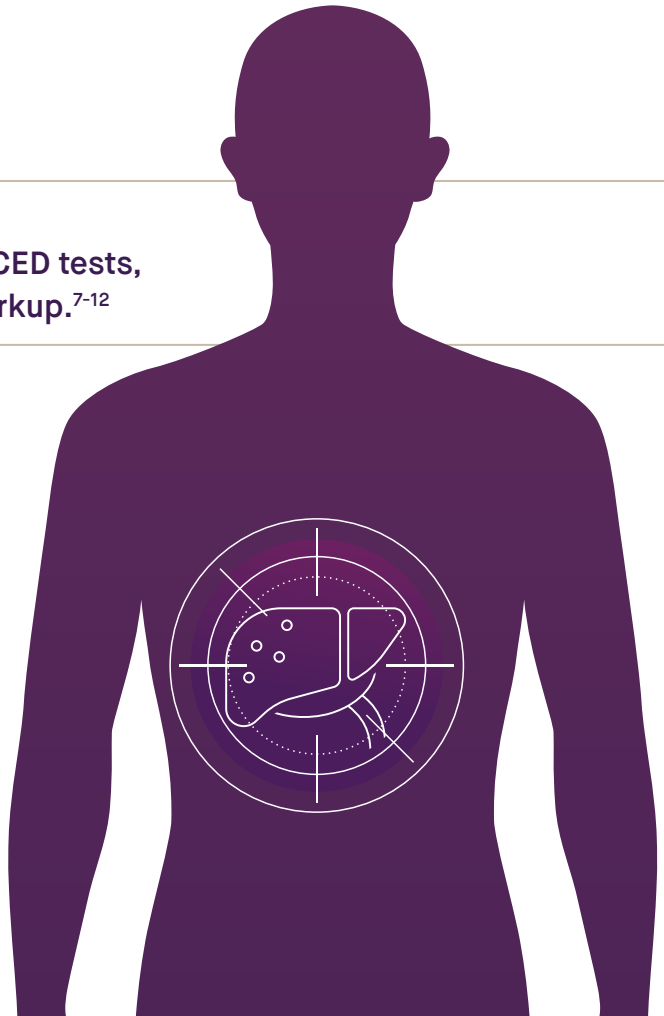
NPV indicates how likely it is that a person with a negative test result does not have cancer.

High NPV indicates a low likelihood that a person with a negative result has cancer.

The ability to predict the Cancer Signal Origin is increasingly recognized as a critical feature of MCED tests, to enable an efficient and targeted diagnostic workup.[7-12]

Cancer Signal Origin (CSO) Accuracy

CSO predicts where the cancer signal originated in the body so clinicians can focus their diagnostic workup.



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It is important to also understand the total number of cancer diagnoses made in people who have been screened.

Cancer Detection Rate (CDR)

The CDR represents the number of cancers identified in the screened population, typically expressed as a percentage.

An MCED test designed to detect as many cancer types as possible will maximize the CDR.

Similarly, the **cancer signal detection rate (CSDR)** is the number of cancer *signals* identified as a proportion of the total screened population.

10,000 people receive an **MCED test** → 120 **cancers** are detected

CDR = 1.2%

MCEDs are ushering in a transformative era in cancer screening. As the field evolves, it becomes increasingly important to understand the diverse metrics – both those measuring individual- and population-level performance.

Performance Metrics 101: Definitions

Term	Definition	Calculation
Sensitivity (True Positive rate)	How likely the test is to find cancer in individuals who actually have cancer (i.e., their cancer status is known)	$\frac{TP}{(TP+FN)}$
False Positive rate	Proportion of individuals without cancer that have a positive test	$\frac{FP}{(FP+TN)}$
Specificity (True Negative rate)	How likely the test is to return a negative result in individuals without cancer	$\frac{TN}{(FP+TN)}$
False Negative rate	Proportion of individuals with cancer that have a negative test	$\frac{FN}{(TP+FN)}$
Episode Sensitivity	The proportion of cancers detected at the time of the initial screening test, out of all cancers diagnosed in individuals during a predefined follow-up period	$\frac{TP}{(TP+FN)^*}$ * During a predefined follow-up period

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Performance Metrics 101: Definitions (continued)

Positive Predictive Value	How likely it is that a person with a positive test result actually has cancer	$\frac{TP}{(TP+FP)}$
Negative Predictive Value	The proportion of negative test results that are not cancer	$\frac{TN}{(TN+FN)}$
Cancer Signal Origin Accuracy	Accuracy of test's prediction of where the cancer signal originated in the body	$\frac{\text{Confirmed diagnoses based on prediction}}{\text{Total number of predictions}}$
Cancer Detection Rate	The number of cancers identified in the screened population	$\frac{\#\text{ of cancers identified}}{\#\text{ of people screened}}$
Cancer Signal Detection Rate	The number of cancer signals identified in the screened population	$\frac{\#\text{ of cancer signals identified}}{\#\text{ of people screened}}$

To learn more, click here to read "Making Sense of the Numbers: Interpreting Multi-Cancer Early Detection Test Performance"

* Assumes screening is available for all prostate, breast, cervical, and colorectal cancer cases and 43% of lung cancer cases (based on the estimated proportion of lung cancers that occur in screen-eligible individuals older than 40 years)

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