

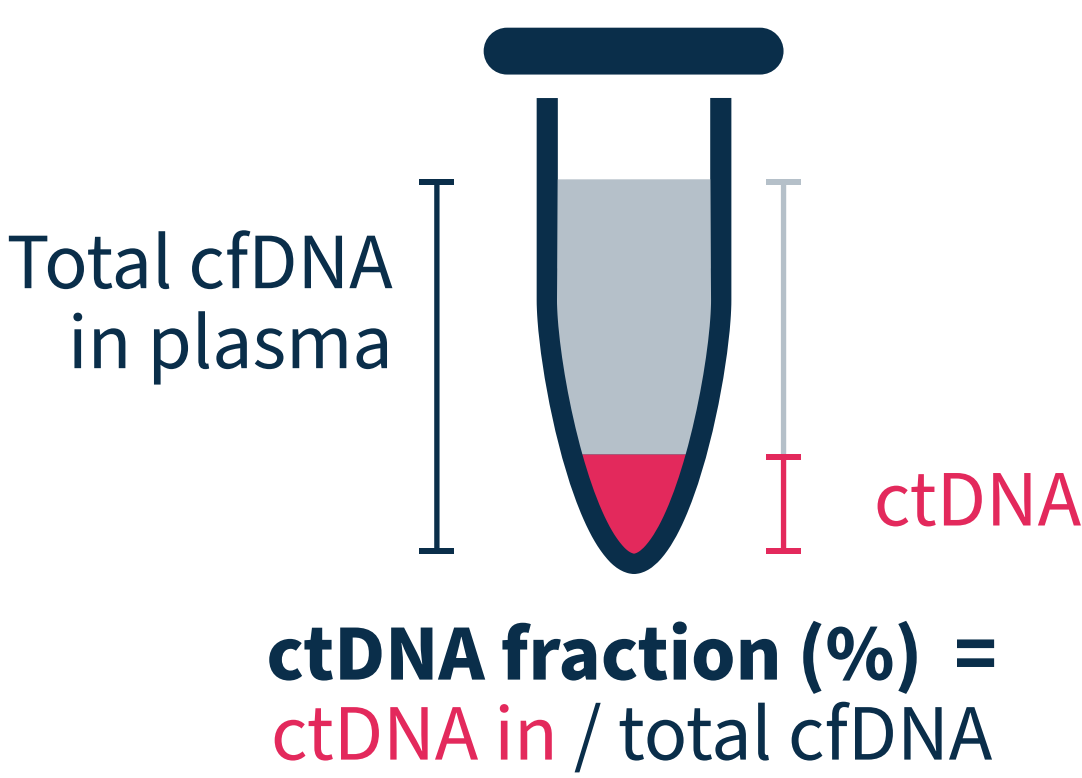
Liquid biopsy results in context: measuring circulating tumor DNA fraction with SOPHiA DDM™

Liquid biopsy is increasingly used for genomic testing when tissue biopsy is not feasible; however, interpreting negative results remains challenging. SOPHiA DDM™ measures circulating tumor DNA fraction to provide contextual information that supports confident decision-making.

What is ctDNA?

Liquid biopsy provides molecular insights from peripheral blood plasma cell-free DNA (cfDNA) to guide precision oncology approaches.

CfDNA is released in the bloodstream through the breakdown of cells from various sources, including healthy tissues, immune cells, and tumors. **CtDNA refers exclusively to tumor-derived fragments**, typically comprising a small percentage of total cfDNA in a blood sample.

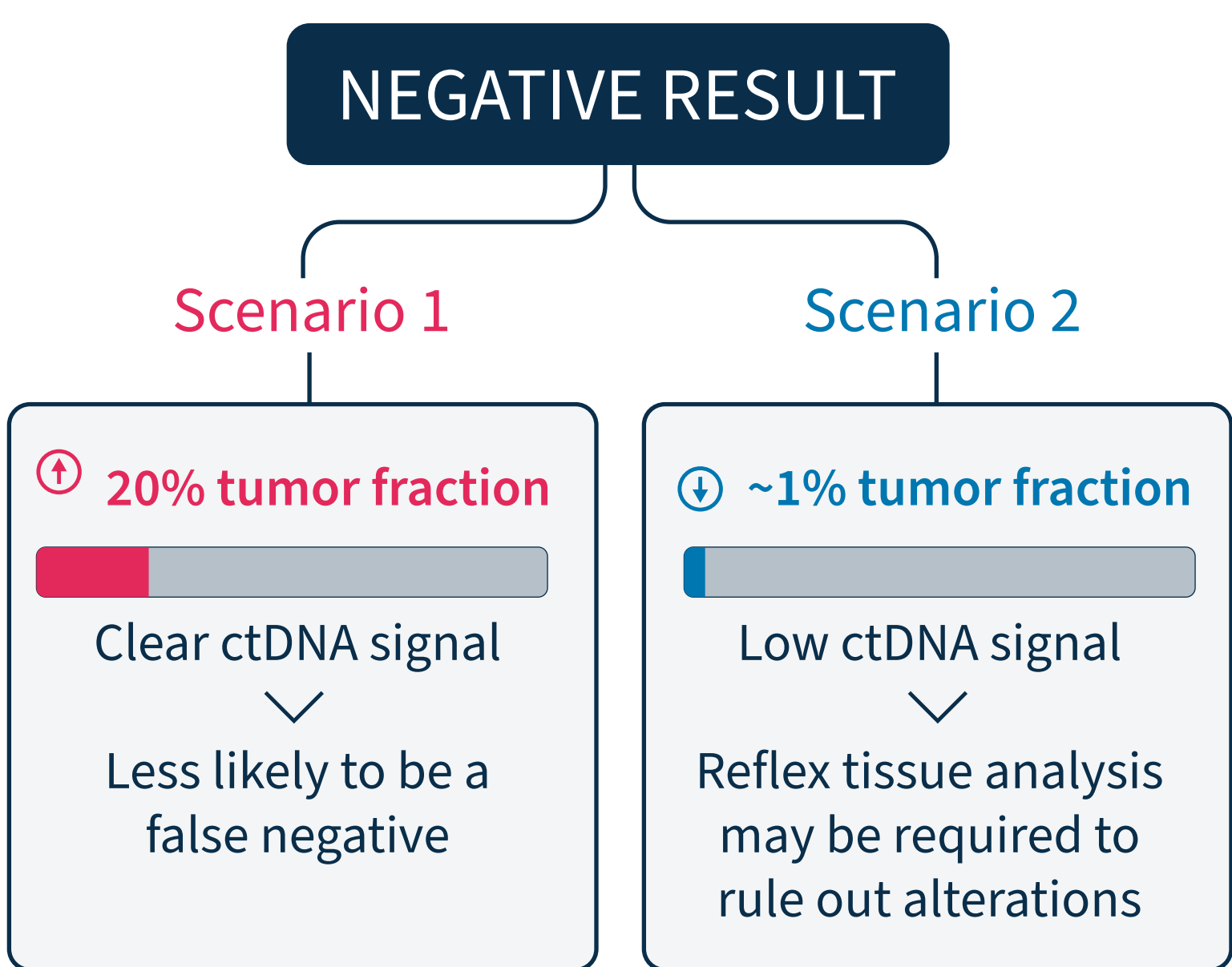


Why measure ctDNA fraction?

The fraction of ctDNA in a sample directly affects variant interpretation. When a variant or biomarker such as microsatellite instability (MSI) is detected, ctDNA fraction establishes the **reliability** of the finding by indicating what proportion of the sample consists of tumor signal.

For a negative result, ctDNA fraction helps distinguish between **true alteration absence** or **insufficient ctDNA** to reliably detect low-frequency variants. In cases of low ctDNA fraction, **confirmatory tissue biopsy** may be required¹.

Beyond results interpretation, ctDNA fraction estimates support assessment of **treatment response** over time and characterization of **resistance evolution** during cancer progression by distinguishing clonal driver mutations from sub-clonal variants that emerge in resistant cell populations^{2,3}.

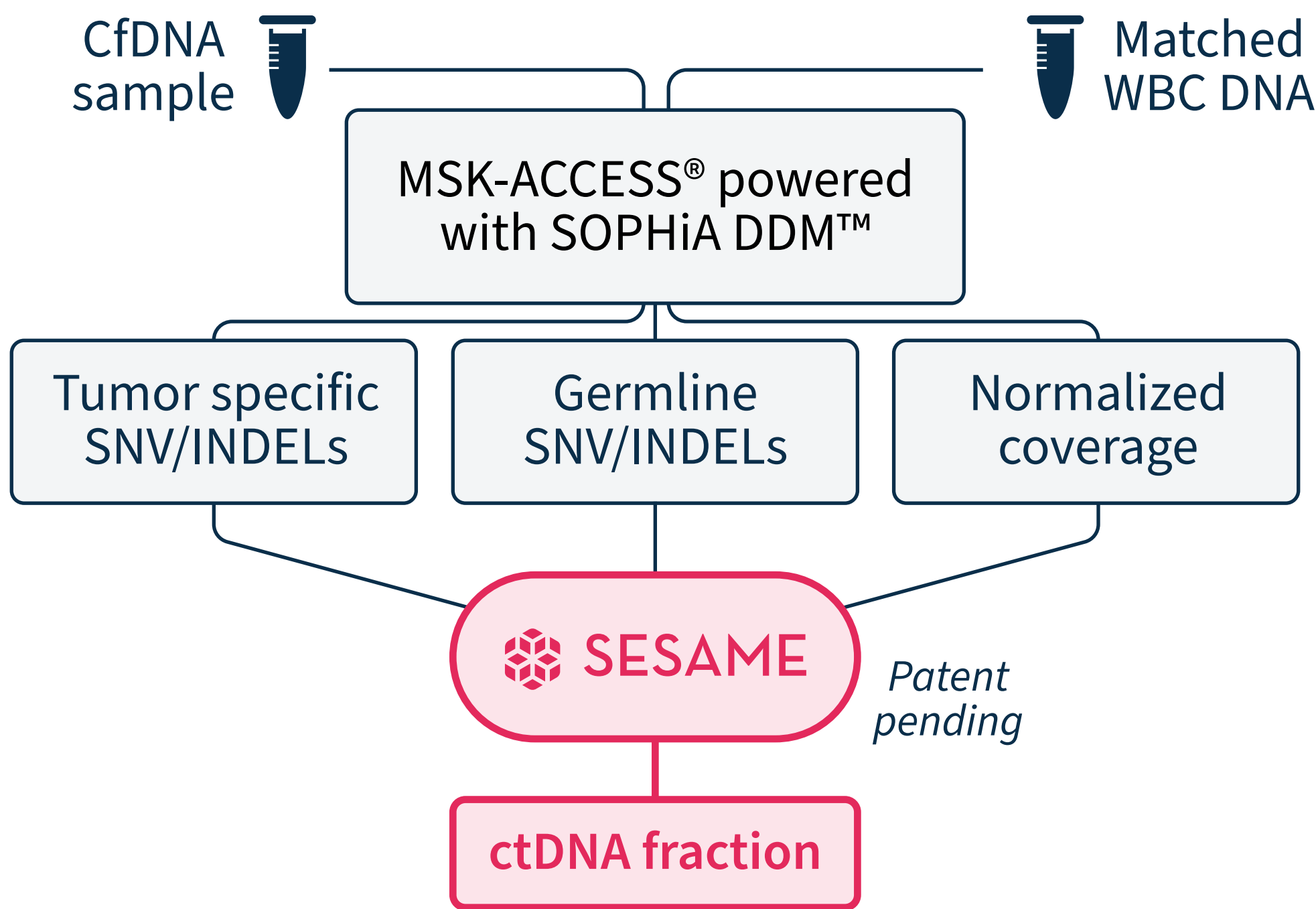


LEVEL OF CLINICAL MATURITY			
ESTABLISHED		EVOLVING	EMERGING
Interpret negative results	Signal context	Treatment response monitoring	Clonal & resistance evolution
KEY QUESTION Was the tumor DNA present at a sufficient level to be detected? ESTABLISHED	KEY QUESTION How reliable are the variant calls? ESTABLISHED	KEY QUESTION How are patients responding to treatment over time? EVOLVING	KEY QUESTION Is the resistance alteration clonal or sub-clonal? EMERGING

Open SESAME: Uncovering ctDNA fraction with SOPHiA DDM™

MSK-ACCESS® powered with SOPHiA DDM™ measures ctDNA fraction through the proprietary SESAME AI agent (patent pending). SESAME leverages the solution’s matched tumor-normal approach to integrate multiple, complementary genomic signals for a robust ctDNA estimation.

An analysis of 46 samples showed **high analytical concordance** (r=0.91) between SOPHiA DDM™ reported ctDNA fraction and an orthogonal send-out cfDNA assay.



ctDNA fraction in context: Interpreting MSI results

CtDNA fraction estimates can be a **key interpretive parameter** when evaluating liquid biopsy results.

Seven cfDNA samples classified as MSI-high (MSI-H) by an external laboratory were analyzed with MSK-ACCESS® powered with SOPHiA DDM™, now **enhanced with MSI detection**.

In two samples showing discordant statuses, the ctDNA fraction estimate revealed no detectable tumor-derived signal, suggesting the SOPHiA DDM™ MSS (microsatellite stable) status should be interpreted with caution due to lack of ctDNA for reliable assessment.

Sample	External MSI status	SOPHiA DDM™ MSI status	SOPHiA DDM™ ctDNA content	Time passed between external & SOPHiA DDM™ testing (weeks)
MSI-H 1	MSI-H – cfDNA NGS	MSI-H	12.1%	18
MSI-H 2	MSI-H – tissue PCR	MSS	0.0%	116
MSI-H 3	MSI-H – cfDNA NGS	MSI-H	1.6%	174
MSI-H 4	MSI-H	MSI-H	16.6%	N/A
MSI-H 5	MSI-H – tissue IHC & PCR	MSI-H	12.0%	55
MSI-H 6	MSI-H – tissue IHC	MSI-H	6.0%	78
MSI-H 7	MSI-H – tissue + cfDNA	MSS	0.0%	13

From data to decisions with SOPHiA DDM™

MSK-ACCESS® powered with SOPHiA DDM™ streamlines the liquid biopsy workflow with **fully integrated** analytics, interpretation, and reporting in one intuitive interface.

ctDNA fraction estimates, as well as quality assurance metrics and visualized input data, are easily accessible in the top-level ribbon and Biomarker tab for in-depth insights to complement variant detection results.



About MSK-ACCESS® powered with SOPHiA DDM™

A decentralized version of the validated liquid biopsy solution used at Memorial Sloan Kettering Cancer Center. It combines an expertly-curated 147-gene panel with the advanced analytics of SOPHiA DDM™, detecting SNVs, Indels, CNVs, MSI and fusions, and measuring ctDNA fraction in an end-to-end workflow. The matched tumor-normal approach helps distinguish somatic variants from clonal hematopoietic and germline variants, enabling accurate variant classification.

Contact your local Sales representative to schedule a demo