MI Cancer Seek Executive Summary

Over the last two decades, rapid and accessible genomic tumor sequencing has revolutionized cancer treatment by allowing oncologists to personalize care. This approach, known as precision oncology, involves using comprehensive genomic profiling to identify specific tumor biomarkers. By understanding a tumor's genetic makeup, doctors can select therapies that are more likely to be effective, avoid treatments that won't work, and connect patients with relevant clinical trials. The increasing number of new precision oncology drugs has made comprehensive testing panels, which assess multiple biomarkers at once, a more practical and effective method than limited testing, ensuring patients receive the most optimal therapy.

MI Cancer Seek® is the first and only simultaneous NGS-based assay that analyzes both DNA and RNA. It carries FDA-approved Companion Diagnostic (CDx) indications for the molecular profiling of solid tumors.

MI Cancer Seek is a next-generation sequencing (NGS)-based in vitro diagnostic device using total nucleic acid (TNA) isolated from FFPE tumor tissue specimens for the detection of single nucleotide variants (SNVs), insertions/deletions (InDels), microsatellite instability (MSI), tumor mutational burden (TMB), in patients with previously diagnosed solid tumors, and copy number amplification (CNA) in one gene in patients with breast cancer. The assay is intended as a companion diagnostic to identify patients who may benefit from treatment with the targeted therapies listed in the Companion Diagnostic Indications table (Table 1), in accordance with the approved therapeutic product labeling. MI Cancer Seek is intended for patients with either a recurrent, relapsed, refractory, metastatic, or advanced stage III or IV solid tumor malignancy, that have not been previously tested with the same test using NGS for the same cancer genetic content and have decided to seek further cancer treatment. MI Cancer Seek is available for adult and pediatric (ages 1-22) patients.

Additionally, MI Cancer Seek is intended to provide tumor mutational profiling to be used by qualified healthcare professionals in accordance with professional oncology guidelines for cancer patients with previously diagnosed solid tumors.

Additional DNA and RNA sequencing-based analyses are reported as professional services and provide a more in-depth look at a tumor's molecular characteristics. The DNA-based analyses include: genomic loss of heterozygosity (gLOH), homologous recombination deficiency (HRD), human leukocyte antigen (HLA) genotype, chromosomal alterations, and viruses. RNA-based analyses include gene expression, fusions, and variant transcripts (including *MET* exon 14 skipping, *EGFR*vIII, and AR-V7).

This comprehensive approach enables the assay to identify all major classes of genomic alterations—including SNVs, InDels, fusions, copy number variants, and splice variants—as well as other clinically relevant genomic signatures like MSI, TMB, and HRD. While some of these analyses, such as those for identifying HRD, gene fusions, and variant transcripts, have associated FDA-approved therapies, other features are considered to have emerging clinical relevance.

Caris also leverages artificial intelligence with Caris FOLFIRSTai® for predicting chemotherapy efficacy in metastatic colorectal cancer (mCRC) cases and Caris GPSai™ for identifying tumor origin in cancers of unknown primary (CUP) cases, aiding in more precise treatment recommendations.

Genomic findings other than those listed in Table 1 are not prescriptive or conclusive for labeled use of any specific therapeutic product. This comprehensive profiling aims to provide actionable insights for cancer treatment, covering a comprehensive list of guideline-recommended actionable biomarkers associated with 80+ FDA-approved and emerging therapies.

MI Cancer Seek Technical Specifications and Test Components

Indication	Biomarker	Performance	Therapy	FDA-approved Comparator Method	Sample Size, N[a]
Breast Cancer	*PIK3CA* (C420R; E542K; E545A, E545D [1635G>T only], E545G, E545K, Q546E, Q546R; and H1047L, H1047R, H1047Y)	PPA: 99.4% NPA: 100%	PIQRAY® (alpelisib)	therascreen *PIK3CA* RGQ PCR Kit	343
Colorectal Cancer (CRC)	*KRAS* wild-type (absence of mutations in exons 2, 3, and 4) and *NRAS* wild-type (absence of mutations in exons 2, 3, and 4)	PPA: 100% NPA: 97.2%	VECTIBIX® (panitumumab)	therascreen *BRAF* V600E RGQ PCR Kit	352
	BRAF V600E	PPA: 99.4% NPA: 100%	BRAFTOVI® (encorafenib) in combination with ERBITUX® (cetuximab)		
Melanoma	*BRAF* V600E	PPA: 98.7% NPA: 99.4%	*BRAF* inhibitors approved by FDA*	bioMérieux THxID *BRAF* Kit	330
	BRAF V600E or V600K	PPA: 98.9% PA: 99.3%	MEKINIST® (trametinib) or *BRAF/MEK* inhibitor combinations approved by FDA*		
Non-small cell lung cancer (NSCLC)	*EGFR* exon 19 deletions and exon 21 L858R alterations	PPA: 98.1% NPA: 99.4%	*EGFR* Tyrosine Kinase Inhibitors approved by FDA*	Roche cobas *EGFR* Mutation Test V2	315
Solid Tumors	MSI-H	PPA: 97.54% NPA: 98.5%	KEYTRUDA® (pembrolizumab), JEMPERLI® (dostarlimab-gxly)	Ventana MMR RxDx Panel	401
Endometrial Carcinoma	Not MSI-H	PPA: 98.4% NPA: 97.6%	KEYTRUDA® (pembrolizumab) in combination with LENVIMA® (lenvatinib)	KEYTRUDA® (pembrolizumab) in combination with LENVIMA® (lenvatinib)	251

Table 1. MI Cancer Seek Companion Diagnostic Indications and Test Performance

TNA extraction with ≥50 ng of DNA is the minimum assay input requirement to perform MI Cancer Seek

*For the most current information about the device indications for the therapeutic products in this group, go to: https://www.fda.gov/medical-devices/in-vitro diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools

Genomic Alterations: MI Cancer Seek identifies tumor biomarkers representing all major genomic variant classes including SNVs, InDels, CNAs, Fusions, and Variant Transcripts across a broad number of genes in cancer pathways, maximizing the ability to identify clinically actionable alterations.[1,2]

Genomic Signatures: MI Cancer Seek also assesses important genomic signatures including MSI and TMB, both of which have significant implications for immunotherapy response, and HRD, which predicts response to PARP inhibitor therapies. MI Cancer Seek demonstrates high analytical performance for detecting key biomarkers across different cancer types, as indicated by high Positive Percent Agreement (PPA) and Negative Percent Agreement (NPA).[1,2]

TMB: MI Cancer Seek calculates TMB using whole exome sequencing (WES), which is the gold standard assessment method according to the American Society of Clinical Oncology (ASCO).[3] The test analyzes nonsynonymous, somatic mutations in the tumor's coding regions and reports the result as mutations per megabase (mut/Mb). TMB-High cutoff of 10 or greater is aligned with both the FDA's recommendations and those from the Friends of Cancer Research,[4,5] which helps identify patients who may benefit from specific immunotherapies.

MSI: MI Cancer Seek determines MSI status using an NGS method that adheres to the College of American Pathologists (CAP) guidelines. By analyzing microsatellite sequences across more than 3,200 genes, this approach is more comprehensive than older methods like PCR-based testing, which use a smaller, standardized panel of markers. This NGS-based method

detects instability and assigns an MSI status to the tumor, a crucial biomarker for various solid tumors. A positive MSI result can help identify patients who are likely to respond to certain immunotherapies.[6]

Biomarkers with Emerging Clinical Relevance

HRD: For advanced ovarian cancer patients, HRD is a crucial biomarker that helps predict the effectiveness of FDA-approved PARP inhibitor therapies. The MI Cancer Seek test provides a more comprehensive assessment of HRD by analyzing not only BRCA1/2 mutations but also a Genomic Scar Score, which includes gLOH and Large-scale State Transitions. This is important because relying solely on BRCA1/2 mutations, as is often done, only identifies about half of all HRD-positive cases.[7] Caris has performed concordance studies that demonstrate our results align with those of an FDA-approved HRD assay, ensuring a complete and accurate picture of a patient's HRD status.[8]

gLOH: Genomic loss of heterozygosity is a biomarker of genomic instability in a tumor. High levels of genomic instability can identify a tumor that may be susceptible to drugs that impact the DNA-damage/repair pathway, such as PARP inhibitors and platinum agents. MI Cancer Seek measures gLOH to identify cases of potential HRD that are not identified with standard NGS testing.

HLA Genotyping: is an emerging biomarker with significant clinical relevance. It provides insight for patient enrollment in clinical trials and can influence drug response and prognosis. Ongoing research shows a correlation between a patient's HLA genotype and their response to checkpoint blockade immunotherapy. This information can also be used in the development of personalized cancer vaccines and for discovering new immunotherapy biomarkers.[9]

Chromosomal Alterations: MI Cancer Seek uses WES in combination with analysis of single nucleotide polymorphisms throughout the genome to identify clinically actionable structural variants like whole or partial chromosome duplications or deletions, which can play a role in cancer development and progression.

Viruses: Several viruses play a significant role in cancer development and can impact a patient's prognosis and treatment. Caris reports on the following strains of Human Papillomavirus (HPV): 16, 18, 31, 33, and 45. These are the most common HPV genotypes linked to oral and anogenital cancers. Tumors with an HPV-associated cause are often linked to better prognosis and may benefit from less intensive treatment.

Additionally, Caris tests for Epstein-Barr Virus (EBV), which is frequently found in gastroesophageal junction, and nasopharyngeal carcinomas. EBV-positive tumors often show signs of being sensitive to immunotherapy. Lastly, we analyze for Merkel Cell Polyomavirus (MCPyV), which is associated with Merkel Cell Carcinoma (MCC). MCPyV-positive MCC tumors typically have more stable genomes and a lower mutational burden compared to MCPyV-negative cases.

Gene expression: MI Cancer Seek uses RNA sequencing to provide information on gene expression levels. This information can help guide treatment decisions by highlighting which biological pathway can be targeted with an approved drug or within a clinical trial.

While the primary focus of the MI Cancer Seek assay is on clinically actionable targets it also incorporates these biomarkers with emerging clinical relevance that have significant value for clinical trials and research. This approach clearly distinguishes these features from the assay's primary intended use, while highlighting their potential to help match patients to clinical trials and advance precision medicine research.

Biomarker Testing Improves Outcomes for Cancer Patients

One of the first large-scale studies to demonstrate the benefit of genomic profiling for biomarker-linked therapies was the Initiative for Molecular Profiling in Advanced Cancer Therapy (IMPACT) study, which was started in 2007. The exploratory IMPACT study tested the hypothesis that therapy selection based on molecular profiling would improve clinical outcomes compared to standard therapy. Patients recruited to the Phase I study had exhausted all standard care options or had uncurable rare cancers.

Results from the IMPACT study showed that around 40% of enrolled patients had at least one targetable alteration.[10] Patients who went on to receive a molecularly matched therapy had significantly better overall response rates (ORRs), longer time to treatment failure, and longer survival. The subsequent IMPACT2 randomized trial found that matched targeted therapies are also associated with longer progression-free survival (PFS) than standard, non-matched treatments.[11]

Since IMPACT, numerous studies have demonstrated that biomarker testing and matched targeted therapies improve patient outcomes (Figure 1). An evaluation of the effect of Caris' tumor molecular profiling on survival showed that outcomes are better when patients receive biomarker-matched therapies across a range of cancer types.[12] Patients whose treatments aligned with comprehensive genomic profiling predictions lived longer than those whose treatments were unmatched. At the end of the study, two-thirds of the molecularly matched patients were still alive compared to only half of those in the unmatched group.[12] In addition to reduced mortality, molecularly matched patients also received fewer treatments than unmatched patients. In roughly nine out of ten Caris tested patients, their pre-testing treatment plan was changed in response to profiling results.[13]

Adding RNA sequencing to DNA analysis can increase treatment options for patients.[14,15] In a recent study, 16% (36/232) of NSCLC cases that were negative for oncogenic drivers by standard DNA analysis were found to be positive by RNA sequencing, with the majority (33/36) clinically actionable.[16] Furthermore, the addition of transcriptomic profiling to DNA analysis led to 35% of patients receiving a matched targeted therapy in the WINTHER trial. Without RNA analysis, only 23% of patients would have received matched treatment.[17]

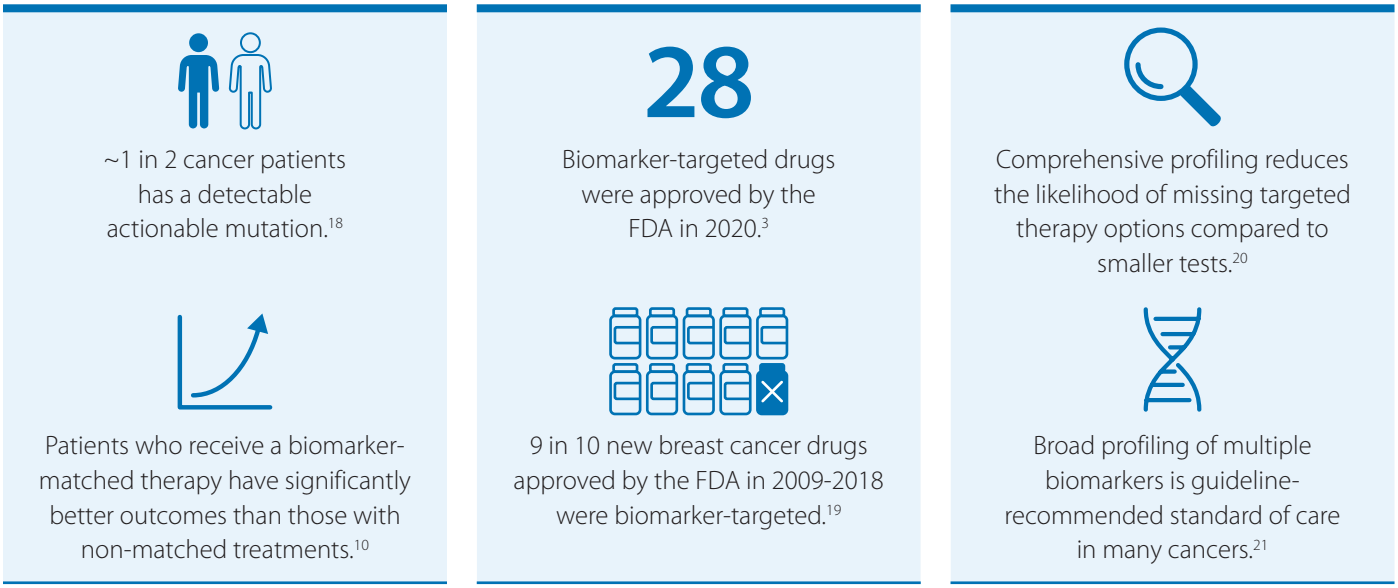

Figure 1. Biomarker testing and matched targeted therapies improve patient outcomes. Studies support and clinical guidelines recommend broad molecular profiling for solid tumors.

Guidelines and Coverage

Adherence to National Comprehensive Cancer Network (NCCN) cancer diagnosis guidelines require testing for multiple biomarkers using multiple technologies.[22] Current ASCO guidelines recommend that patients with advanced and metastatic solid tumors undergo molecular profiling when there are approved biomarker-linked therapies and support the rationale for testing all solid tumors based on site-agnostic drug approvals.[3] Broad DNA profiling of multiple biomarkers is the guideline-recommended standard of care in many cancers, including aNSCLC. More than 15 FDA-approved targeted therapies are available for biomarker-positive patients with aNSCLC. These therapies have objective response rates (ORRs) in the 60-80% range and PFS of 9-34 months, compared with 20-45% ORR and 5-6 months PFS in patients receiving standard chemotherapy.[21]

ASCO guidelines recommend RNA-based fusion testing for patients when no oncogenic drivers have been identified through multigene panel-based DNA sequencing and in those without standard care options.[3] Fusion testing is also strongly recommended if approved fusion-targeted, disease-specific therapies are available for a patient's metastatic or advanced cancer.[3] Additionally, outside of disease-specific approvals, patients with metastatic or advanced solid tumors who may be candidates for TRK-inhibitor therapy should undergo *NTRK* fusion testing.[3]

MI Cancer Seek is listed as a covered service under the CMS National Coverage Determination (NCD) 90.2 for advanced stage patients with any solid tumor cancer. In addition, MI Cancer Seek was reviewed by the MolDX program and received a positive coverage determination.

Health Economics

By identifying all known actionable biomarkers at initial diagnosis, CGP has unrivaled power to guide therapy selection and subsequently impact treatment and healthcare costs. CGP enables clinicians to match patients with the right treatment the first time.[12,13,23-25] A retrospective analysis of treatment data from multiple clinical studies showed results from Caris' profiling changed the treatment plan in 88% of cases.[13] When treatment decisions aligned with recommendations from profiling, patients spent more time on treatments expected to be of benefit, avoided ineffective therapy cost, and on average, received fewer treatments.[12,23,24]

With CGP-informed cancer management, patients also see improvements in downstream clinical outcomes. Multiple studies show improved median overall survival and median progression free survival for patients on matched targeted therapies.[10-12,24,26,27] While some select studies show varying impacts to treatment costs as patients are more likely to receive targeted therapy and spend a longer time on treatment compared to those not receiving comprehensive tumor biomarker testing, a retrospective cohort study of over 25,000 patients with advanced cancer showed CGP testing, including the panel from Caris, does not significantly increase total all-cause healthcare costs compared to non-CGP testing (defined as individual biomarker testing or small panel testing).[13,25] Coupled with improved clinical outcomes, CGP can have a modest budget impact and be a cost-effective approach.[28,29]

Look Back Program – "Future Proofing"

The Look Back program offered by Caris builds on the promise of personalized medicine by alerting physicians when a new drug or indication is approved that may provide previously profiled patients with a new treatment option. As the FDA approves new treatment options associated with a biomarker drug indication, Caris' Look Back Program will proactively review results of patients previously tested to determine if there are biomarkers with new therapeutic relevance. If so, Caris will notify the provider of the new therapeutic opportunity. This program future proofs the initial testing investment by leveraging Caris' simultaneous DNA and RNA analysis data and the original test results. This approach reduces the need for repeat biopsies and subsequent retesting for new indications. By empowering physicians with timely actionable information for evolving therapies, Caris can help ensure patients are being considered for the most effective, current treatments based on their unique profile to drive optimized outcomes. The Look Back program provides a continuous justification for the original simultaneous DNA/RNA analysis. The data generated from that single test remains clinically relevant and valuable over time. This justifies the comprehensive nature of the test from the outset, demonstrating that it's a strategic investment in long-term patient care rather than a one-time transaction.

Actionable Test Report

MI Cancer Seek delivers actionable results in a single, easy-to-read report, with potentially beneficial therapies highlighted in green and those with a likely lack of benefit in red. The therapeutic associations are ranked by evidence level, from FDA-approved biomarkers (Level 1) to those with supporting literature (Level 3). With a turnaround time of 10-14 days, the report provides a comprehensive, evidence-based molecular profile specific to each patient's tumor type. These molecular insights help oncologists navigate treatment options, identify therapies they may not have considered, and match patients to relevant clinical trials. The underlying technology also allows for the assessment of additional genes and pathways as they become clinically relevant, with clinicians able to access a patient's results through a secure online portal.

Conclusion

MI Cancer Seek is a powerful, FDA-approved diagnostic tool that offers a comprehensive molecular profile of solid tumors using a unique, simultaneous analysis of both DNA and RNA. By detecting a wide range of genomic alterations and signatures including TMB, MSI, along with professional services such as HRD, this test provides oncologists with critical, evidence-based insights to guide personalized treatment decisions. This detailed analysis helps identify patients who may benefit from FDA-approved therapies and clinical trials, ensuring a more precise and effective approach to cancer care for both adult and pediatric patients.

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