Caris Assure Executive Summary

Comprehensive genomic profiling (CGP) is a powerful tool for improving treatment outcomes for patients with advanced cancer. With over a million new diagnoses each year, and a significant portion of those patients having actionable genetic mutations,[1-3] it's crucial to identify the most effective therapies quickly. CGP analyzes hundreds of genes at once, identifying a greater number of mutations and biomarkers, including those for targeted therapies and immunotherapy.[4]

By using CGP, oncologists can reduce the time it takes to match a patient to the best possible treatment and avoiding ineffective and toxic therapies. This comprehensive approach, which is supported by major cancer organizations like ASCO and NCCN, also reduces the need for sequential testing and can help delay disease progression, ultimately improving patient survival.[5]

Differentiators for Profiling with Liquid Biopsy

Liquid biopsy offers some advantages over tissue-based CGP testing. Tissue biopsy is invasive, may not provide sufficient yield for all needed testing, and carries risk of harm to the patient. In addition, liquid biopsy can capture tumor heterogeneity, which refers to the molecular diversity within and between tumor sites. Analyzing circulating tumor DNA (ctDNA) in blood offers a whole-body snapshot of tumor material that has been shed from various parts of the primary tumor and any metastatic sites throughout the body, providing a more comprehensive picture of the patient's cancer than tissue biopsy of a single site. Turn-around time (TAT) is generally faster for liquid than tissue biopsy, on the order of 5-7 days compared to 10-14 days, which can expedite the start of targeted therapies and prevent the use of ineffective treatments and their associated toxicities.

The abundance of normal cells in blood makes designing a sensitive liquid biopsy assay challenging. Additionally, mutations in blood cells from clonal hematopoiesis (CH) can mimic cancer signals, reducing specificity and potentially leading to off-target treatment.[6] Caris Assure® addresses these limitations by sequencing DNA/RNA from both the plasma and white blood cells to determine which mutations are derived from CH cells and which are tumor-derived.

White blood cell sequencing allows for the identification of incidental germline variants present in all cells of the body, as well as prediction of HLA genotype, an indicator of immune system compatibility important for enrollment in some clinical trials. It also enables genotyping of pharmacogenomic biomarkers. Caris Assure currently reports germline variants in over 60 genes including ATM, BRCA1/2, CHEK2, MLH1, MSH2, MSH6, PMS2 and TP53. Caris Assure currently reports DPYD genotype, a pharmacogenomic biomarker for mitigating the toxicity of fluoropyrimidine chemotherapy in patients who metabolize fluoropyrimidine drugs poorly. With the increasing number of both somatic and germline-directed treatments, the ability to distinguish tumor-derived, germline, and CH-derived variants is crucial to ensure appropriate, on-label prescribing of biomarker-directed treatments.

Caris Assure is a blood-based liquid biopsy intended for use by qualified healthcare professionals for biomarker-associated therapy selection in patients with recurrent, relapsed, refractory, metastatic, or advanced solid tumor malignancies where tissue-based cancer genomic profiling is not feasible.

It is a laboratory-developed test that uses a novel circulating Total Nucleic Acids (cTNA) sequencing platform to analyze DNA (whole exome sequencing) and RNA (whole transcriptome sequencing) from both plasma and white blood cells in the buffy coat, enabling the detection of tumor-derived and incidental germline* variants while filtering out variants derived from clonal hematopoiesis (CH).[7] Caris Assure detects single nucleotide variants (SNV) and insertions/deletions (indels) across a broad number of genes in cancer pathways. Clinical reporting focuses on ~300 cancer genes with known clinical associations, as well as select copy number alterations (CNA) and gene fusions. The test identifies a comprehensive list of actionable biomarkers recommended by the NCCN for guiding therapy selection and associated with FDA-approved therapies and clinical trials, including *DPYD*, a pharmacogenomic

biomarker for mitigating treatment toxicity. The test also reports complex genomic signatures including microsatellite instability (MSI), blood tumor mutational burden (bTMB) and predicted HLA genotype.*

Caris Assure offers a non-invasive, comprehensive, and timely solution for therapy selection and provides a dynamic and in-depth molecular understanding of a patient's cancer via a simple blood draw. This advanced approach delivers earlier detection of resistance mechanisms, comprehensive and accurate identification of actionable biomarkers, the correction of clinical false positives for more precise therapy selection, and clinically significant incidental germline reporting of cancer-related genotypes. This leads to more informed clinical decisions about drugs with potential benefit or lack thereof, potentially improved patient outcomes, more efficient utilization of healthcare resources, and reduced burden associated with invasive procedures.

*Not a replacement for comprehensive germline testing. Incidental pathogenic alterations are reported, including genes recommended by ACMG to be reported as a secondary finding when clinical exome sequencing is performed.[8] Negative results do not imply the patient does not harbor a germline mutation. The assay is also not a substitute for histocompatibility testing.

Assay Validation and Performance

Caris Assure's performance for detection of SNVs, indels, gene fusions, CNAs, bTMB, and MSI was validated using 166 de-identified matched plasma/tissue specimens (78 metastatic) and showed high sensitivity and high PPV relative to tissue as the gold standard. Detection of SNV and indel driver mutations in blood from metastatic patients compared to matched tumor tissue collected within 30 days demonstrated high concordance (93.8% PPA, 96.8% PPV, and >99.99% NPV).[9] CH correction proved to be essential for avoiding improper therapy selection.[7,10] For example, 22% of mutations in DNA repair genes in the study were from CH and not tumor tissue, and were filtered out.

Plasma Analytical Validation: Contrived reference standards with 415 variants across 72 genes at known variant frequencies (0.1%, 0.25%, 0.5%, 1%, 2%, and 5%) were used to evaluate analytical sensitivity. The assay reached PPA values of 76.3%, 79.26%, 87.71%, 94.08%, 96.45% and 97.15%, respectively. Samples were tested in 12 replicates across three lots of library preparation reagents, using an input of 30ng. Analytical sensitivity was assessed across studies including mass input minimum, limit of detection, limit of blank, and precision. Analytical specificity, including interfering substances, cross contamination, and carry-over, was also characterized.[9]

Incidental Germline Validation: Whole blood from 184 clinical samples was split into two aliquots and profiled by Caris Assure and a clinically validated germline comparator test. Input levels ranged from 110ng (optimal) down to 5ng. For the 47 genes in the orthogonal assay, the results were highly concordant for SNVs and indels: PPA, NPA, and PPV were all 100%.

Validation of Other Features: Caris Assure demonstrated 75% (3/4) PPA, 100% (3/3) PPV, and 99.4% (165/166) OPA to matched tissue for copy number amplification of the *ERBB2* gene. Comparing amplification calls across the 323 genes reported by the tissue assay, Caris Assure demonstrated 76.7% PPA, 94.3% PPV and 99.9% NPA. The sensitivity for fusion detection in *ALK, RET, FGFR2* and *FGFR3* was 100% for samples with tumor fraction > 7% and 46.7% for samples with tumor fraction > 0%, suggesting that false negatives may be attributable to a lack of tumor shedding. All predicted HLA genotypes were identical between Caris Assure and tissue in all samples (100% PPA).[9]

Incidental Germline and Incidental CH Variants

Tissue-based profiling may involve "tumor-versus-normal" matching to distinguish somatic variants (tumor only) from germline variants (inherited in all healthy cells), directly affecting therapy selection or genetic counseling for the patient. Blood-based profiling inherently contains "normal" cells in the form of white blood cells found in the buffy coat. Plasma-only cfDNA biopsies overlook crucial genomic insights, potentially leading to suboptimal treatment decisions. Comparing sequencing results between plasma and buffy coat enables clinicians to distinguish not only CH variants but also germline variants.

While bioinformatic algorithms can attempt to predict the source of variants from plasma-only assays, these methods have proven to be less effective compared to more comprehensive sequencing approaches that also interrogate white blood cells. Tumor-derived mutations can be found in plasma but not in the white blood cell fraction. CH and germline mutations can be found in both, so profiling both compartments provides critical information about the source of each variant. Attempts to identify variant source by applying a bioinformatic algorithm to plasma-only data leads to misclassifications, such as tumor variants being dismissed as germline, or germline/clonal hematopoiesis variants being falsely flagged as actionable tumor mutations. The consequence is a higher rate of clinical false positives or negatives, hindering effective therapy selection.

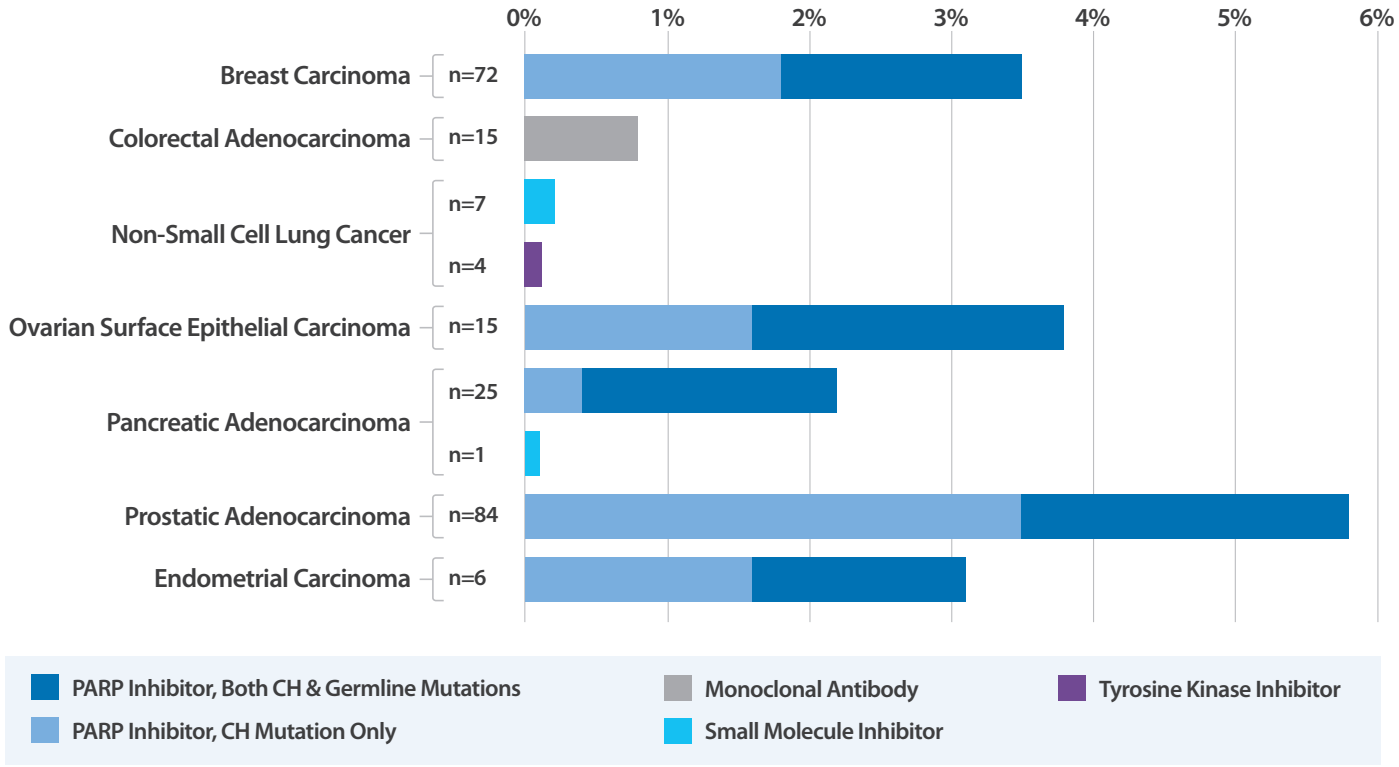
To avoid these errors, the College of American Pathologists (CAP) and Association for Molecular Pathology (AMP) recommend that cfDNA assays should incorporate whole blood controls to differentiate CH from tumor-derived variants.[11]

> **"Laboratories should... consider matched white blood cell sequencing with ctDNA testing to avoid falsely identifying CHIP variants as somatic mutations derived from the tumor."**
>
> *Recommendations for cell-free DNA assay validations: a joint consensus recommendation of the Association for Molecular Pathology and the College of American Pathologists*[11]

Caris Assure's Measurement of Clonal Hematopoiesis is Vital for Accurate Therapy Selection

Caris performed a study to characterize CH variants in 16,812 patients with advanced cancer across 49 tumor types. The highest prevalence of CH mutations in the study occurred in DNA repair genes such as *BRCA1, BRCA2, ATM* and *CHEK2*. Tumor derived mutations in these genes are prescriptive for PARPi therapy, with CH in these genes leading to clinical false positive therapy association with PARPi in a significant proportion of breast, ovarian, pancreatic and prostate cancer patients (Figure 1).[12] While Caris Assure makes therapy associations only based on P/LP variants, it and other assays also report variants of uncertain significance (VUS) in clinically relevant genes. In Caris' database of nearly 500,000 tissue molecular profiles, more than 20% of patients who were given PARP inhibitor therapy had only benign or VUS variants in PARPi biomarker genes and so were treated off-label. In the CH study, two thirds of *BRCA2* somatic variants, for example, were CH-derived. Correctly labeling them as such avoids such off-label prescription of PARPi.

Figure 1. Proportion of Patients with a CH Mutation In Genes Driving Therapy Recommendations



Caris Assure Includes Analysis of *DPYD* Gene Mutations for Personalized Drug Dosing

Inherited variations in the *DPYD* gene can cause severe, even life-threatening, toxicity from common chemotherapy drugs like 5-FU and its oral prodrugs, capecitabine and tegafur. Proactive *DPYD* genotyping identifies at-risk patients before treatment, allowing for personalized dosing or the use of alternative therapies. Clinical data shows a personalized treatment approach accounting for *DPYD* genotype significantly reduces severe *DPYD*-related toxicity, from 73% to 28%,[13] and lowers associated hospitalizations from 64% to 25%.[14] Accounting for *DPYD* genotype in patient care not only improves patient safety and outcomes but also reduces the significant healthcare costs associated with managing severe drug toxicity. For these reasons, NCCN clinical guidelines recommend considering *DPYD* genotyping prior to fluoropyrimidine therapy.[15] Because Caris Assure profiles the germline of white blood cells, it can reliably identify *DPYD* variants, supporting better patient care and more efficient resource utilization.

Guidelines and Coverage

NCCN,[16] ASCO,[17] ESMO,[18] CAP,[11] AMP[11] and IASLC[19] support the use of liquid biopsy when tissue biopsy is not feasible, which is in line with the intended use of Caris Assure. NCCN,[16] ASCO,[17] ESMO[18] and IASLC[19] all acknowledge that tissue and liquid biopsy both have known strengths and limitations and support their use either sequentially or concurrently.

The NCCN Guidelines for cancers including non-small cell lung cancer (NSCLC), breast cancer, and colon cancer strongly recommend comprehensive molecular profiling to identify actionable and rare driver mutations. For metastatic NSCLC, minimally invasive plasma ctDNA testing is recognized as a useful method to identify oncogenic biomarkers like *ALK, BRAF, EGFR,* and others that might otherwise be missed. In breast cancer, if the result of one test is negative, it is recommended that testing with the other modality be considered. Furthermore, liquid biopsy is the preferred method for assessing *ESR1* mutations at the time of disease progression after endocrine therapy because *ESR1* mutations arise in resistance to endocrine therapy and so are not typically detectable in the primary tumor. Similarly, in colon cancer, the NCCN states that NGS panels on either tissue or blood-based biopsies are able to detect rare, actionable genetic alterations such as *NTRK* and *RET* fusions.[16]

The ASCO Expert Panel recommends routine molecular testing for *ESR1* via liquid biopsy for the same reason as the NCCN. To guide treatment selection in patients with ER-positive, HER2-negative metastatic breast cancer, ASCO recommends routine testing for *PIK3CA* mutations as a prerequisite for patients to be eligible for regimens containing a PI3K inhibitor like alpelisib plus fulvestrant. Testing for *PIK3CA* should be performed using next-generation sequencing on either plasma ctDNA or tumor tissue, with a follow-up tissue test if the ctDNA result is negative. This approach ensures that patients are matched with the most effective therapy based on their specific tumor profile, aligning with current evidence-based clinical standards.[20]

ESMO recommends using liquid biopsies as an alternative to traditional tissue genotyping in certain situations, for example in aggressive or time-sensitive tumors in NSCLC, where getting results quickly is crucial.[18] ESMO also recommends liquid biopsy for genotyping in advanced cancer patients in the setting of cancer progression, either treatment-naïve or after prior lines of therapy.[18] ESMO has outlined recommendations for liquid biopsy in this setting for many tumor types including breast cancer, cholangiocarcinoma, colorectal cancer, endometrial cancer, gastric cancer, hepatocellular cancer, NSCLC, ovarian cancer, pancreatic cancer, prostate cancer, soft tissue sarcoma, thyroid cancer, and urothelial cancers.[18]

Health Economics

Liquid biopsy in patients where tissue-based profiling is not feasible impacts therapy selection and subsequently, treatment and healthcare costs. Patients that would have otherwise not received biomarker-informed therapy are able to do so with liquid biopsy. Modelling studies show life-years gained and potential for cost effectiveness depending on the costs of chemo-immunotherapies and targeted therapies, and time spent on therapy, even when used in conjunction with tissue-based profiling.[21-24] One budget impact study indicates a modest incremental per-member-per-year cost compared to single-gene tests in a subset of NSCLC patients receiving liquid biopsy due to insufficient tissue availability.[25] Identifying *DPYD* prior to treatment, results in further cost savings due to a reduction in adverse event-related hospitalizations.[26,27]

Studies are needed to assess the unique economic impact of Caris' liquid biopsy, which includes sequencing in both the plasma and white blood cells and identification of *DPYD* genotype.

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 in the past 6 months 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

Caris Assure delivers actionable results in a single, easy-to-interpret 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) and are continuously updated. With a turnaround time of <7 days, the report provides a comprehensive, evidence-based molecular profile specific to each patient's tumor type. The report helps 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. Clinicians can access a patient's full molecular data through a secure online portal, which can be useful in the context of molecular tumor boards for challenging cases.

Conclusion

In summary, while tissue biopsy remains the gold standard for identifying molecular biomarkers to guide cancer therapy selection, Caris Assure, a next-generation liquid biopsy assay, significantly narrows the gap between tissue and blood. Unlike other profiling companies that must continually update testing platforms based on new science or CDx indications, Caris Assure utilizes comprehensive whole exome (DNA) and whole transcriptome (RNA) sequencing. This approach identifies a broader range of clinically actionable alterations, providing a more complete understanding of therapies expected to be of benefit or lack thereof. By accurately distinguishing the source of each variant—for example, differentiating clonal hematopoiesis (CH) from tumor-derived mutations and separating germline from somatic variants—Caris Assure addresses a major liquid biopsy challenge, achieving high sensitivity balanced with high specificity. Utilizing Caris Assure reduces patient harm by avoiding ineffective or wrong therapies, minimizes the need for repeat or additional testing and provides proactive updates on new treatment options via the look back program. Caris Assure provides comprehensive, accurate, and timely insight leading to optimized treatment spend and improved patient outcomes.

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