Less Invasive, **More Intelligent** Than Ever

Whole Exome and Whole Transcriptome Sequencing

Tumor-Derived, Incidental Germline*, and Incidental CH Variant Detection

All from a Blood Sample

CARIS ASSURE®

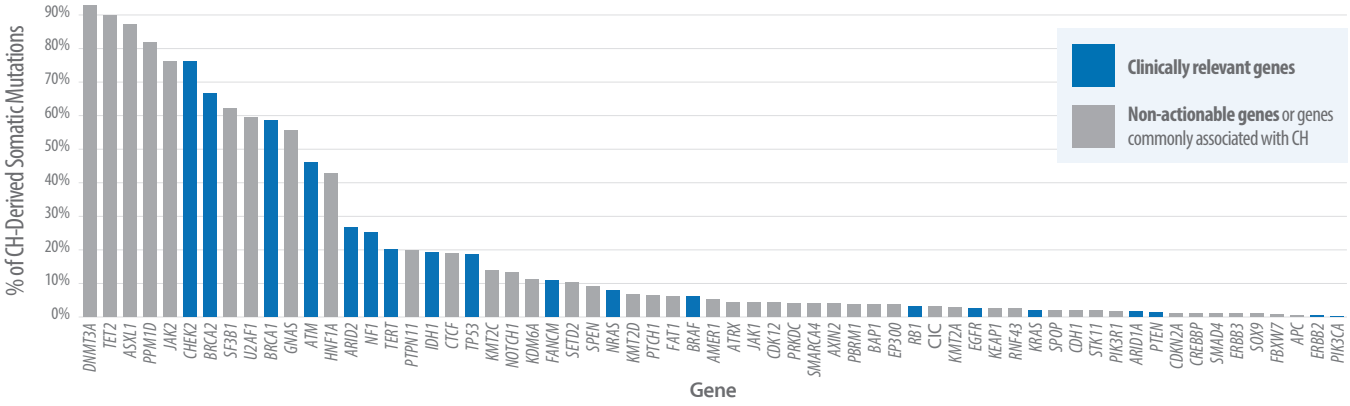
THERAPY SELECTION

False Positives From CH Are a Key Challenge for Plasma-Only Assays

Analyzing plasma-only can lead to mutation misinterpretation

42.3% of 16,812 patients had clonal hematopoiesis (CH) mutations in reportable clinical genes including *BRCA2*, *BRCA1*, *KRAS*, *BRAF*, *ATM*, and *CHEK2* across 49 tumor types.[1]

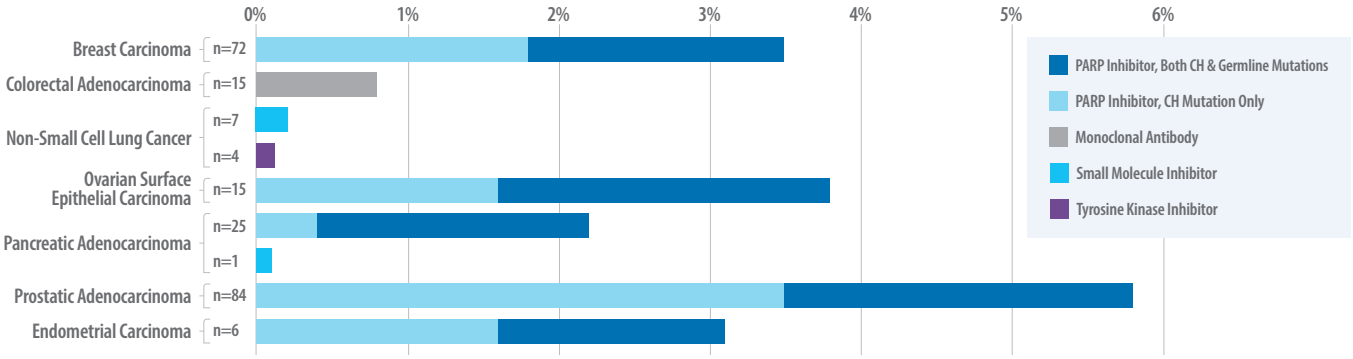
Prevalence of CH by Gene[1]



Patients may be directed toward an inaccurate therapy if white blood cells are not analyzed.[1,2]

High CH rates were detected in druggable targets in many cancers typically treated with PARP inhibitors, including breast, ovarian, pancreatic, prostate, and endometrial cancers.[1]

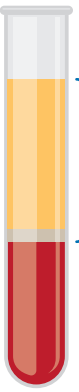
Proportion of Patients with a CH Mutation In Genes Driving Therapy Recommendations[1]



Plasma-only assays may mischaracterize variants[1,2]

To avoid misdiagnosis, the College of American Pathologists (CAP) and Association for Molecular Pathology (AMP) recommend that cfDNA assays should incorporate whole blood controls to differentiate clonal hematopoiesis (CH) from tumor-derived variants.[3]

Real-World Consequences of False Positives



Plasma-Only | **Plasma + White Blood Cells**

PATIENT

Plasma-only may yield false positives

John has advanced prostate cancer. Plasma-only liquid biopsy finds an *ATM* gene mutation, suggesting potential benefit from treatment with the PARP inhibitor olaparib.

RESULTS

Plasma (cfDNA)	Buffy Coat (WBCs)	Tumor-Derived
ATM *FOXA1*	NOT TESTED	*ATM* ? *FOXA1*

OUTCOMES

- Receives **ineffective olaparib treatment at $15,000 per month**.[5]
- Suffers **anemia, nausea,** and **fatigue** during treatment.
- Time is lost while John's **tumor continues to grow**.

PATIENT

Plasma + WBCs minimize false positives

John's *ATM* mutation is found in both plasma and white blood cells (WBCs).

Caris Assure determines that it is CH-derived and not an actionable target[4], providing the clinician and John more accurate information about potential future treatment options.

RESULTS

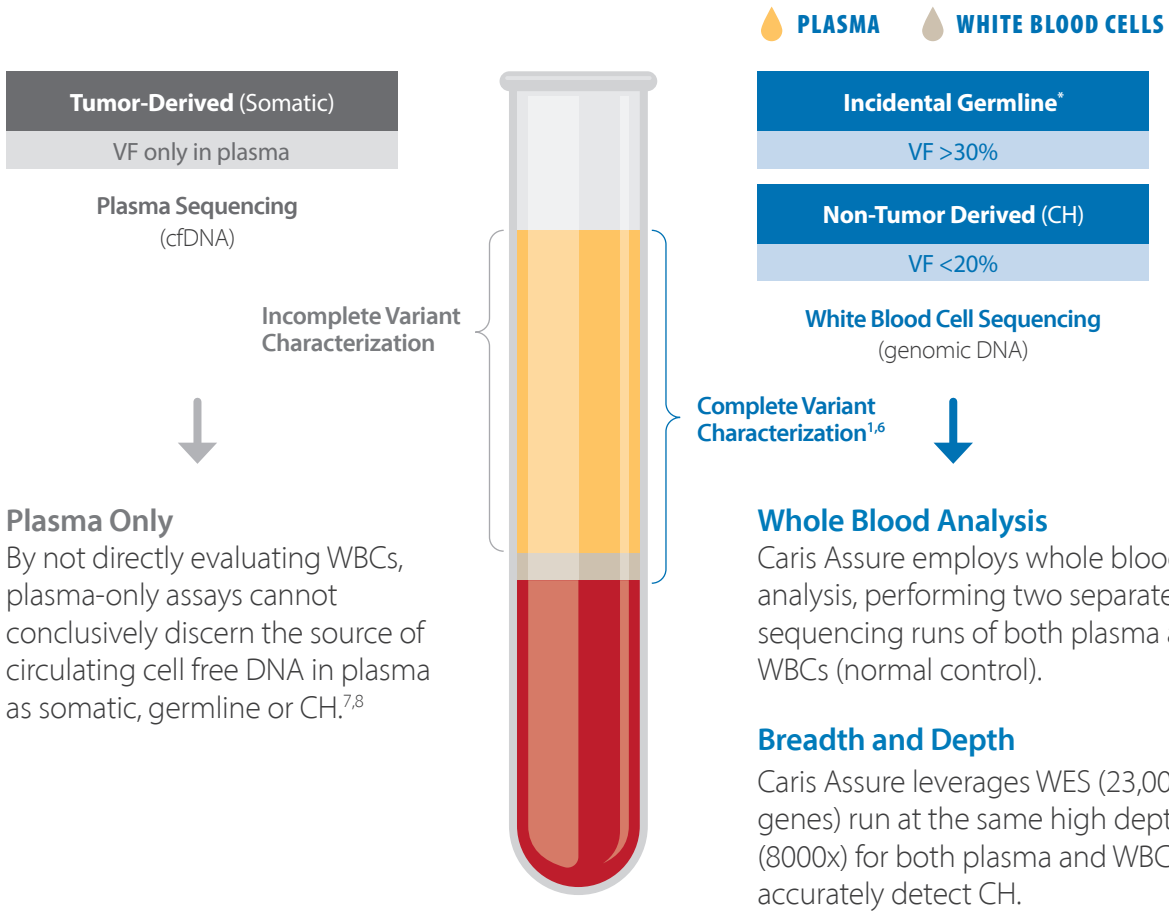
Plasma (cfDNA)	Buffy Coat (WBCs)	Tumor-Derived
ATM *FOXA1*	*ATM* ✕ FALSE POSITIVE (CH)	*FOXA1* ✓

OUTCOMES

- **Spared $15,000 per month**[5] for an ineffective treatment.
- **Avoids side effects** from off-target therapy.
- **Avoids lost time** and can begin next line of therapy.

A New Approach to Overcoming Uncertainty

Caris Assure's advanced testing methods offer a new approach by providing the most complete picture of the patient's tumor.



Plasma Only

By not directly evaluating WBCs, plasma-only assays cannot conclusively discern the source of circulating cell free DNA in plasma as somatic, germline or CH.[7,8]

Whole Blood Analysis

Caris Assure employs whole blood analysis, performing two separate sequencing runs of both plasma and WBCs (normal control).

Breadth and Depth

Caris Assure leverages WES (23,000+ genes) run at the same high depth (8000x) for both plasma and WBCs to accurately detect CH.

Variant Classification

Caris Assure's algorithm distinguishes variants based on their frequency and where they're detected — plasma and/or white blood cells.

VF = Variant Frequency **CH =** Clonal Hematopoiesis

Caris Assure detects what other assays can not to minimize false positives, avoid off-target drugs and improve patient outcomes.

Tumor-Derived, Incidental Germline* and Incidental CH Detection in a Single Assay

Tumor Associated Findings

Have confidence that the finding is real.

- ✓ Detect tumor-specific alterations including rare fusions.
- ✓ Caris Assure leverages clonal hematopoiesis (CH) subtraction resulting in high specificity (>99.9%).

Incidental Germline Findings

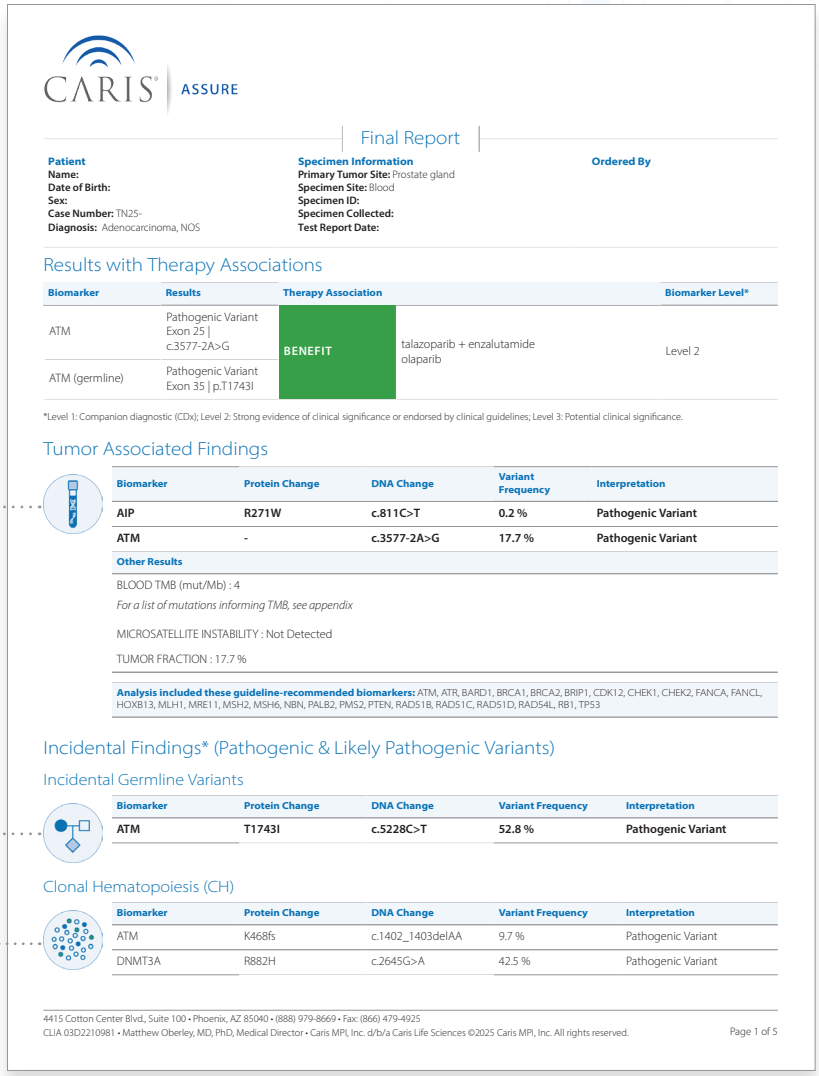
Treat a germline alteration that may have been missed.

- ✓ Not all germline alterations will be detected under current guidelines.
- ✓ Detection & reporting of incidental germline can guide proper therapy selection.

Incidental CH Findings

Guide patients toward accurate treatment decisions.

- ✓ CH confounds results and are a key source of false positives for biomarker-directed therapy.
- ✓ Whole blood analysis of CH can improve accuracy and prevent incorrect therapy choice.



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Final Report

Patient
Name:
Date of Birth:
Sex:
Case Number: TN25-
Diagnosis: Adenocarcinoma, NOS

Specimen Information
Primary Tumor Site: Prostate gland
Specimen Site: Blood
Specimen ID:
Specimen Collected:
Test Report Date:

Ordered By

Results with Therapy Associations

Biomarker	Results	Therapy Association		Biomarker Level*
ATM	Pathogenic Variant Exon 25 | c.3577-2A>G	BENEFIT	talazoparib + enzalutamide olaparib	Level 2
ATM (germline)	Pathogenic Variant Exon 35 | p.T1743I			

*Level 1: Companion diagnostic (CDx); Level 2: Strong evidence of clinical significance or endorsed by clinical guidelines; Level 3: Potential clinical significance.

Tumor Associated Findings

Biomarker	Protein Change	DNA Change	Variant Frequency	Interpretation
AIP	R271W	c.811C>T	0.2 %	Pathogenic Variant
ATM	-	c.3577-2A>G	17.7 %	Pathogenic Variant

Other Results

BLOOD TMB (mut/Mb) : 4

For a list of mutations informing TMB, see appendix

MICROSATELLITE INSTABILITY : Not Detected

TUMOR FRACTION : 17.7 %

Analysis included these guideline-recommended biomarkers: ATM, ATR, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCA, FANCL, HOXB13, MLH1, MRE11, MSH2, MSH6, NBN, PALB2, PMS2, PTEN, RAD51B, RAD51C, RAD51D, RAD54L, RB1, TP53

Incidental Findings* (Pathogenic & Likely Pathogenic Variants)

Incidental Germline Variants

Biomarker	Protein Change	DNA Change	Variant Frequency	Interpretation
ATM	T1743I	c.5228C>T	52.8 %	Pathogenic Variant

Clonal Hematopoiesis (CH)

Biomarker	Protein Change	DNA Change	Variant Frequency	Interpretation
ATM	K468fs	c.1402_1403delAA	9.7 %	Pathogenic Variant
DNMT3A	R882H	c.2645G>A	42.5 %	Pathogenic Variant

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Additional Caris Assure® Report Insights

- ✓ **bTMB:** bTMB is measured across the whole exome and leverages CH and germline subtraction resulting in a high concordance to tissue TMB.
- ✓ **Predicted HLA Genotype:** Genotyping results can help direct patients to clinical trials recruiting based on specific genotypes.
- ✓ **TRACK Table:** Highlights changes in disease at time of progression. Can be used to identify potential resistance mechanisms and new therapeutic options.
- ✓ ***DPYD* Pharmacogenomics:** *DPYD* variants are detected by directly analyzing both plasma and white blood cells to help ensure the right dose of chemotherapy, avoiding dangerous toxic side effects.

CARIS ASSURE®

THERAPY SELECTION

Comprehensive analysis of 23,000+ genes

Biomarker analysis (including resistance mutations)

Less invasive alternative to tissue biopsy

Reports tumor-derived, incidental germline* and incidental CH variants

Reduces false positives from incidental CH mutations

Be Sure with Caris Assure.

To order or learn more, visit www.CarisLifeSciences.com/Assure.

Caris Assure® is intended for patients with previously diagnosed solid malignant neoplasms when tissue is not feasible and is to be used by qualified healthcare professionals. RNA results are intended for investigational purposes only. Not available in all locations.

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LIFE SCIENCES

Where Molecular Science Meets Artificial Intelligence.

*Not a replacement for comprehensive germline testing. Incidental pathogenic alterations are reported, including ACMG recognized cancer genes. Negative results do not imply the patient does not harbor a germline mutation.

1. Magee D, et. al. *Clin Cancer Res*. (2025). **2.** Bernard E, et. al. *Clin Cancer Res*. (2025). **3.** Lockwood CM, et al. *J Mol Diagn*. (2023). **4.** Jensen K, et. al. *JAMA Oncol 7, 107*. (2021). **5.** Based on the method in Roskoski R, Jr. (2024) *Pharmacol Res* 199, 107036, olaparib price per pill from pharmacychecker.com (in zip code 75039, Irving, TX) was combined with dosage from the FDA label to yield drug price per 30-day period.
6. Additional criteria, including the confidence interval, factor into determining the variant source. **7.** Guardant360-CDx-Physician-Insert-US. **8.** FoundationOne Liquid CDx Technical Information (FDA Label)