Caris ChromoSeq Executive Summary

Caris ChromoSeq™

- **Replaces multiple genomic tests with a single assay**
- **~7 day turnaround time**
- **Medicare coverage established**
- **Potential to reduce diagnostic complexity and improve clinical decision making**

Myeloid malignancies, such as acute myeloid leukemia (AML), myelodysplastic neoplasms (MDS), and myeloproliferative neoplasms (MPNs) are genetically complex blood cancers in which genomic alterations drive diagnosis, risk stratification, and treatment selection. Although these diseases may present with overlapping clinical features (e.g., cytopenias, leukocytosis, splenomegaly, increased blasts), they differ substantially in prognosis and management. Current diagnostic workflows rely on multiple assays, including morphology, cytogenetics, FISH, and targeted next-generation sequencing (NGS) which may capture only a subset of clinically relevant alterations and can miss higher-order genomic events.

Whole-genome sequencing (WGS) enables comprehensive, single-assay detection of genomic alterations across variant classes, from single-nucleotide variants to large chromosomal abnormalities. This approach can reproduce many findings obtained through conventional methods while also identifying additional clinically relevant alterations beyond predefined genes, hotspots, or breakpoints. As structural variants and complex genomic alterations are central to disease classification and risk stratification in myeloid malignancies, broader genomic assessment may improve diagnostic yield and provide a more complete genomic profile to inform clinical decision-making.

Accurate diagnosis and risk stratification are central to clinical decision-making because they determine not only whether a patient has AML, MDS, or an MPN, but also whether that patient should receive urgent induction therapy, lower-intensity therapy, supportive care, cytoreduction, targeted therapy, or referral for allogeneic stem cell transplant.[1,2] In AML, contemporary risk assignment incorporates cytogenetic and molecular findings and informs the use of intensive versus non-intensive therapy, incorporation of targeted agents such as FLT3 or IDH inhibitors, measurable residual disease strategies, and consideration of transplant in first remission.[1,2] In MDS, prognosis is driven by cytopenias, marrow blasts, cytogenetics, and increasingly mutational status, with lower-risk disease generally managed with strategies aimed at improving cytopenias and reducing transfusion burden, whereas higher-risk disease is typically approached with hypomethylating agents, clinical trials, and transplant evaluation in appropriate candidates.[3,4,5] In MPNs, diagnosis and genomic classification guide thrombosis prevention, symptom control, and identification of patients with myelofibrosis who may require transplant evaluation rather than purely palliative JAK-inhibitor-based management.[6,7]

Modern clinical guidelines increasingly define myeloid neoplasms by genetic features rather than morphology alone.[8,9] Updates to the WHO classification reduced morphology-only AML diagnoses from 13% to 5%, reflecting the central role of genomics in contemporary practice.[10] Risk stratification frameworks including European Leukemia Net (ELN) 2022 for AML,[1] Molecular International Prognostic Scoring System (IPSS-M) for MDS,[4] and Molecular International Prognostic Scoring Systems (MIPSS) for MPN,[11] depend on genomic data to inform prognosis and treatment decisions. Despite this genomic reliance, the current standard of care for many hematologic malignancies involves ordering multiple parallel assays (cytogenetics, FISH, PCR and targeted NGS) to identify the multiple, variable biomarkers needed for diagnosis, prognosis, and treatment decision-making. Additionally, these disparate reports must be manually integrated to generate a complex molecular profile. This fragmented approach increases complexity, turnaround time, and the risk of incomplete data, underscoring the need for comprehensive genomic profiling with unified reporting.

Product Description

Caris ChromoSeq uses a whole-genome sequencing platform to detect and report genomic alterations considered clinically relevant in AML, MDS and MPN respectively. The assay delivers integrated detection of clinically relevant genomic alterations informing diagnosis, risk stratification, and therapeutic targeting including SNVs, indels, gene fusions, copy number alterations, and large-scale genomic changes traditionally assessed by karyotype, based on the specific diagnosis in a single test, with an expected turnaround time of approximately seven days.

Compared with conventional cytogenetic karyotyping, Caris ChromoSeq detects chromosomal abnormalities at higher resolution (≥5 Mb vs ≥10 Mb) using bone marrow aspirate or whole blood, reducing failure rates and shortening turnaround times.[12] Caris ChromoSeq has been analytically and clinically validated using a sequencing depth of 210x, supporting robust detection and future clinical expansion. Caris ChromoSeq is a laboratory-developed test performed at single CLIA-certified site.[12]

Caris ChromoSeq is intended for molecular profiling of patients with AML, MDS, and MPN. The assay identifies genomic alterations relevant for diagnosis, risk stratification, and therapeutic targeting, including those required for ELN 2022 AML and IPSS-M MDS classifications.

Assay Validation and Performance

Mass Input Range: Minimum and optimal DNA inputs of 250 ng and 500 ng were established, with optimal input yielding an average mapped read depth of 210x, substantially higher than the predicate assay.[13]

Limit of Detection: The assay reliably detects clinically relevant SNVs and indels at ≥10% variant allele frequency and copy number and structural variants at ≥20% tumor fraction, aligning with established thresholds for the predicate assay and ensuring consistent clinical interpretation.[13]

Analytical Sensitivity and Specificity: Validation studies demonstrate high analytical sensitivity, specificity, reproducibility, and robustness, with minimal interference, contamination, or carryover.[13]

Clinical Validation: Clinical equivalence to the WashU ChromoSeq assay was demonstrated across 93 paired samples. Additional concordance was established against standard-of-care methods including targeted NGS panels, FISH, and cytogenetic karyotyping across more than 200 clinical samples. Caris ChromoSeq consistently detected comparator-identified alterations and identified additional clinically relevant copy number and structural abnormalities not detected by traditional methods.[13]

Clinical Utility

National guidelines (NCCN) recommend disease-appropriate cytogenetic and molecular profiling for AML, MDS, and MPN patients prior to treatment initiation.[2,5,7] Genomic findings increasingly guide therapy selection, including use of FDA-approved targeted agents (e.g., FLT3 inhibitors) and decisions regarding allogeneic stem cell transplantation.[14,15]

WGS has demonstrated clinically meaningful impact, including improved identification of high-risk genotypes such as bi-allelic *TP53* inactivation that may be under-detected by conventional testing and are associated with markedly different treatment pathways and outcomes.[16,17] Prior studies of the ChromoSeq approach showed identification of all structural variants, CNAs, and complex cytogenetic alterations identified by comparator assays and additional reportable genomic events in 25% and 29% of AML and MDS patients, respectively, with changes to risk stratification in over half of those patients.[12]

Guidelines and Coverage

Hematologic malignancies including AML, MPN, and MDS are increasingly managed through guideline-driven, biomarker-informed treatment pathways that emphasize diagnostic precision and risk stratification. Current clinical guidelines support comprehensive molecular and cytogenetic testing at diagnosis and relapse to inform prognosis, therapeutic selection, transplant eligibility, and monitoring strategies.[2,5,7]

Consistent with NCCN Guidelines across myeloid malignancies, diagnostic evaluation should include assessment of recurrent cytogenetic abnormalities and clinically relevant molecular alterations to support disease classification, risk stratification (e.g., ELN, IPSS-R/IPSS-M), and treatment selection. Recommended testing includes clinically relevant markers such as FLT3, NPM1, and IDH1/2 in AML; JAK2, CALR, and MPL in MPN; and SF3B1, TET2, and DNMT3A in MDS, along with additional prognostic mutations (e.g., ASXL1, RUNX1, TP53, and spliceosome genes).[2,5,7]

Caris ChromoSeq has received a positive coverage determination from the MolDX program under LCD L38123 – *Next-Generation Sequencing Lab-Developed Tests for Myeloid Malignancies and Suspected Myeloid Malignancies,* supporting Medicare coverage when criteria are met.

Actionable Test Report

Caris ChromoSeq consolidates multiple required genomic assays into a single, integrated report with an approximate 7-day turnaround time. The test results include relevant genomic findings, as well as those that may indicate response or lack of response to FDA-approved therapies or therapies under investigation in clinical trials. The report also denotes the strength of evidence supporting each biomarker-therapy association (e.g., FDA drug label, guideline-supported, curated scientific literature). By integrating these insights and assigning an evidence-based risk category, the test streamlines clinical decision-making, reducing diagnostic fragmentation, and supports appropriate, guideline-aligned therapy selection.

Conclusion

By consolidating multiple guideline-recommended tests into a single assay, Caris ChromoSeq may reduce diagnostic complexity, improve risk stratification, and support appropriate therapy selection. This streamlined approach has the potential to improve clinical decision-making while reducing inefficiencies associated with multi-assay testing workflows.

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