Characterization of plasma cell-free DNA variants as of tumor- or clonal hematopoiesis-origin in 11,914 advanced cancer patients

Daniel Magee[1], Valeriy Domenyuk[1], Jim Abraham[1], Maria Perdigones Borderias[1], Jeff Swensen[1], Praveena Solipuram[2], Adanma Ayanambakkam[3], Raja Mehdi[4], Jagathi Challagalla[5], Elisabeth Heath[6], Megan Landsverk[7], Magdalena Jurkiewicz[8], Brian Shimkus[9], Ian Pino[10], Daniel Patterson[11], David Hsiehchen[12], Supriya Koya[3], Bradley Somer[13], Michel Velez[14], Anthony F. Shields[6], Jennifer Cultrera[15], Jennifer R Ribeiro[1], Robert Hahn-Lowry[1], George W. Sledge[1], Matthew Oberley[1], Milan Radovich[1], David Spetzler[1]

[1] Caris Life Sciences, Irving, TX [2] Rocky Mountain Cancer Centers, Thornton, CO [3] OU Health University of Oklahoma Medical Center, Oklahoma City, OK [4] Hope Cancer Center of Nevada, Las Vegas, NV [5] Texas Oncology, Wichita Falls, [6] Karmanos Cancer Institute, Wayne State University, Detroit, MI [7] University of South Dakota Sanford School of Medicine, Sioux Falls, SD [8] Palmetto GBA, Columbia, SC [9] Lone Star Oncology, Georgetown, TX [10] Baptist Health, Jacksonville, FL [11] Advent Health, Ocala, FL [12] University of Texas Southwestern Medical Center, Dallas, TX [13] West Cancer Center and Research Institute, Germantown, TN [14] Holy Cross Health, Fort Lauderdale, FL [15] Florida Cancer Specialists and Research Institute, Leesburg, FL

dmagee@carisls.com | Abstract ID: 187

Abstract

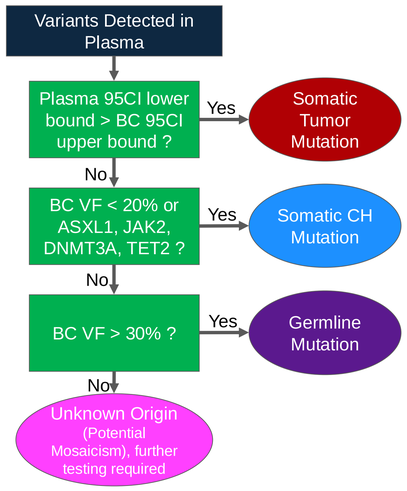
Background
Plasma-based liquid biopsy tests can detect tumor-specific genetic alterations and offer many advantages that complement tissue-based Comprehensive Genomic Profiling (CGP). However, age-related clonal hematopoiesis (CH) mutations can confound liquid biopsy results and potentially lead to incorrect therapy choice.

Methods
We assessed the landscape of 11,914 liquid profiles across 48 cancer types using the Caris Assure assay, a whole exome and whole transcriptome NGS workflow that independently sequences both plasma-derived cell-free total nucleic acids (cfTNA) as well as the white blood cell DNA and RNA from the buffy coat. The variant source was identified algorithmically by comparing plasma and buffy coat variant frequency and read quality metrics.

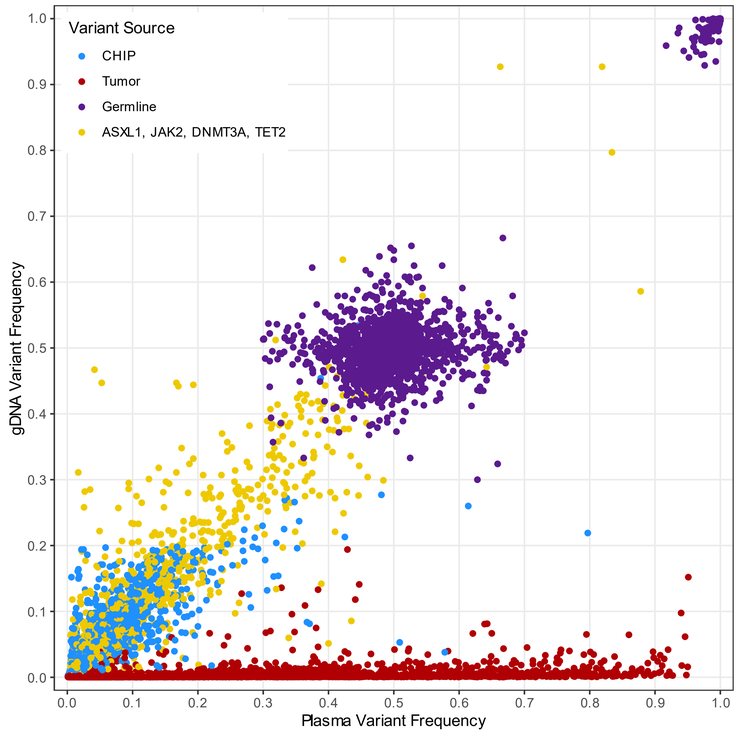
Results
39.5% of 11,914 patients presented at least one pathogenic or likely pathogenic CH variant among reportable clinical genes. We found 79.9% of all BRCA2 variants to be of CH origin, as well as 79.4% of CHEK2, 68.5% of BRCA1, 41.9% of ATM, 6.3% NRAS, 6.2% BRAF, 2.4% KIT, 2.3% KRAS, and 1.8% EGFR. For patients aged 65-69, the median rate of CH variant classification was 17%, whereas it was 29% for patients aged 70-74, 33% for ages 75-79, and 50% for ages 80+. We found high rates of CH detected in what would be otherwise druggable targets in many cancer types typically treated with PARP inhibitors, including breast, female genital tract, ovarian, pancreatic, prostate, and endometrial cancers.

Variant Classification Algorithm

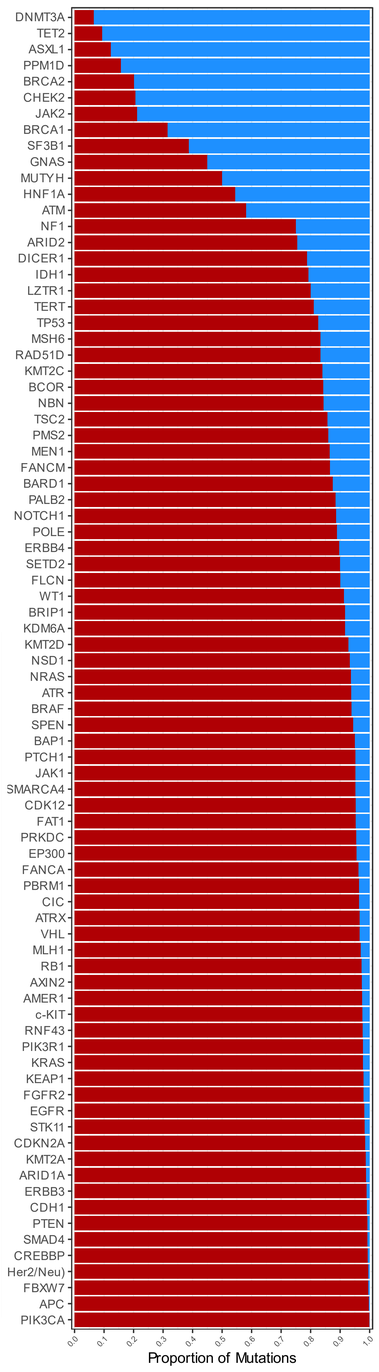
Variant Classification Methodology. VF = variant frequency; BC = buffy coat; CH = clonal hematopoiesis of indeterminate potential.



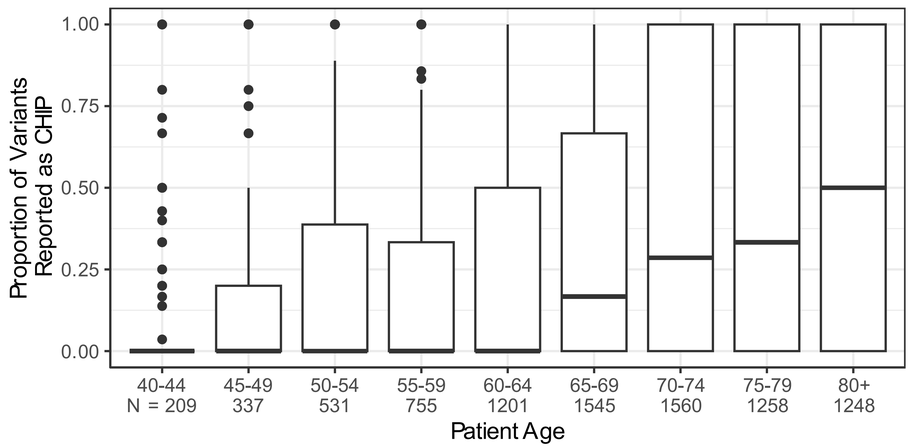
Variants Detected by Variant Frequency



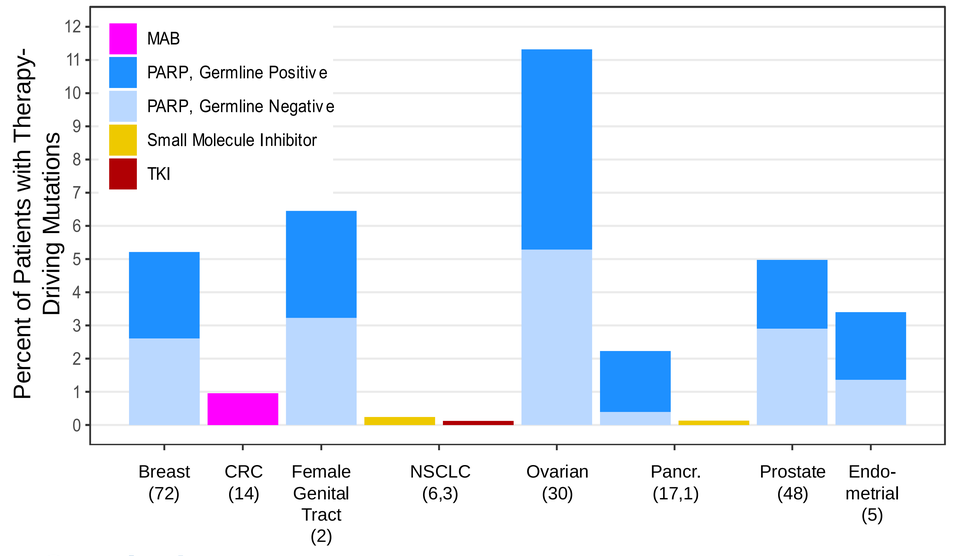
CH- vs Tumor-derived Variants by Gene



CH Variants by Age Group



Patients with CH Results Driving Therapy Recommendations



Conclusions

Studies show that liquid biopsy is complementary to tumor-based CGP, ultimately leading to more patients being treated with targeted therapies [1-3]. However, our findings strongly suggest that treating clinicians should carefully consider the results of any liquid biopsy test used to determine PARP inhibitor treatment, and avoid reliance on liquid biopsy results unless the assay specifically identifies and excludes false positive findings due to confounding CH variants.

References

1. Ezeife et al., Ther Adv Med Oncol, 2022
2. Schwartzberg, et al., JTO Clin Res Rep, 2022
3. Hiemenz et al., Oncologist, 2022