Comprehensive characterization of multiple myeloma genomes from bone marrow or peripheral blood with a novel clinical assay enables identification of resistance mechanisms

Bruno Paiva[1,*], Patricia T. Greipp[2,*], Danielle Sookiasian[3,*], Julian Hess[3,*], Svetlana Podsvirova[3], Marisa DeMeo[3], Reid Meyer[2], Linda Baughn[2], Ana Sahagun[4], Alejandra Guitron Arredondo[4], Laura Priscila Ochoa Loza[4], Jorge Arturo Hurtado Martinez[4], Ana Echenique Alcázar[4], Jay Hydren[4], Jennifer Ahlstrom[4], Christine-Ivy Liacos[5], Kostantina Taouxi[5], Alexandra Papadimou[5], Meletios Dimopoulos[5], Efstathios Kastritis[5], Jesús Berdeja[6], Timothy Brennan[3], Valentina Nardi[3], Thomas Mullen[3], Doron Lipson[3], François Aguet[3,**] Shaji K. Kumar[2,**]

[1]Cancer Center Clínica Universidad de Navarra, CIMA, IDISNA, CIBERONC, Pamplona, Spain; [2]Division of Laboratory Genetics, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA; [3]Predicta Biosciences, Cambridge, MA, USA; [4]HealthTree Foundation, South Jordan, UT, USA; [5]National and Kapodistrian University of Athens, Department of Clinical Therapeutics, Athens, Greece; [6]Greco-Hainsworth Centers for Research at Tennessee Oncology, Nashville, TN, USA; *Co-first authors; **Co-senior authors

Introduction

Detecting genetic abnormalities is mandatory during diagnostic workup and for potential individualization of therapy selection in multiple myeloma (MM) and its precursor conditions. At present, this requires invasive bone marrow (BM) biopsies, severely limiting early detection, patient monitoring, and precise therapy selection. The current standard for detecting genetic alterations in MM is fluorescence in situ hybridization (FISH), which cannot detect point mutations and other clinically relevant alterations. Consequently, the IMS-IMWG guidelines were recently updated to require next-generation sequencing for the classification of high-risk MM. Moreover, the importance of identifying alterations in therapeutic targets (e.g., BCMA, GPRC5D) for guiding immunotherapies is becoming increasingly recognized.

To address this need, we recently launched GenoPredicta, a CLIA-approved LDT that enables routine monitoring, informing diagnosis, and treatment selection by comprehensively and robustly characterizing MM genomes with whole genome sequencing (WGS) from as few as ~50 circulating tumor cells (CTCs) isolated from peripheral blood (PB) or tumor cells from BM. Here, we describe the characterization of clinical and research samples with GenoPredicta, highlighting resistance-conferring genetic alterations that can only be detected by sequencing and that are consistent with patients' clinical histories, while further demonstrating the complete concordance of GenoPredicta with prior FISH results.

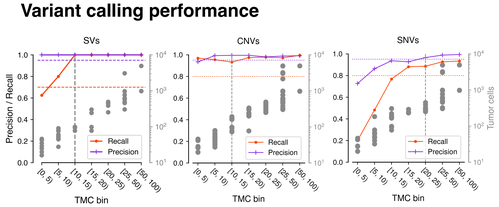
Study design and methods

- 68 viably frozen, paired BM and PB samples from a retrospective cohort of 34 patients were used for validation.
- Tumor cells were isolated from BM or PB samples using fluorescence-activated cell sorting (FACS) (after CD138+ enrichment for PB) and subjected to WGS.
- Copy number alterations, structural variants, and single nucleotide variants and indels were called from WGS using a combination of open-source and proprietary bioinformatics methods.
- For a subset of samples, the BM was also characterized by FISH at Mayo Clinic Laboratories, using a standard clinical panel for characterizing MM.

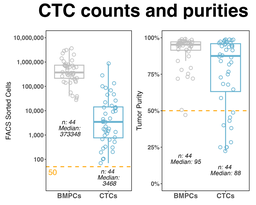
Results

Analytical validation of GenoPredicta shows exceptional sensitivity and specificity

Variant calling performance



CTC counts and purities



Performance summary

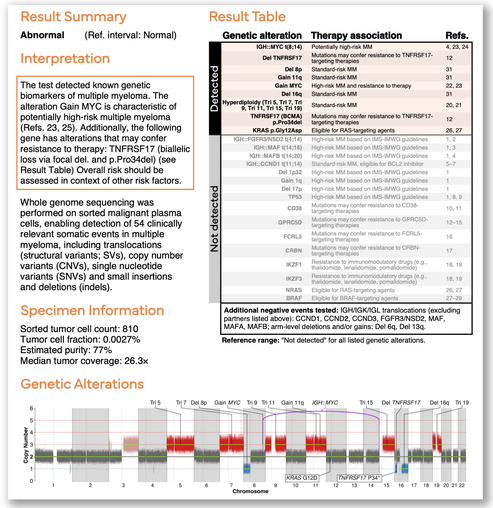
Tumor median coverage	CNV	SV	SNV/indel
10-15x	100% / 100%	100% / 100%	76% / 94%
15-20x	100% / 100%	100% / 100%	88% / 93%
≥20x	100% / 100%	100% / 100%	91% / 98%
Overall	100% / 100%	100% / 100%	87% / 96%

Sensitivity: Recall; Specificity: PPV. CNVs and SVs were evaluated for reportable events, SNVs/indels genome-wide.

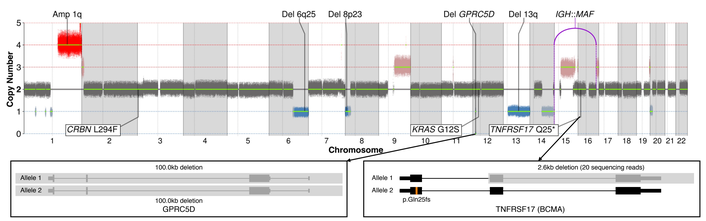
- The ability of GenoPredicta to recover highly pure populations of CTCs enables highly accurate variant detection.
- GenoPredicta can recover clinically actionable results at extremely low CTC counts and purities.

Clinical test enables identification of therapy resistance mechanisms from blood

- GenoPredicta from CTCs enables detection of deletions or mutations of immunotherapy targets.
- In a clinical blood sample from a patient with prior BCMA-targeting therapy (teclistamab), a biallelic alteration of BCMA was observed by WGS (p.Pro34del and focal deletion).
- Patient clinical report shown at right; physician-ready reports are automatically generated end-to-end from raw sequencing data in ~6h.

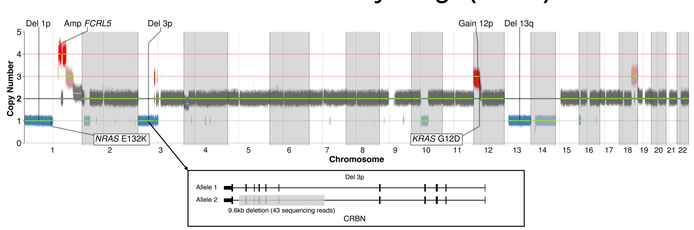


Biallelic loss of BCMA and GPRC5D



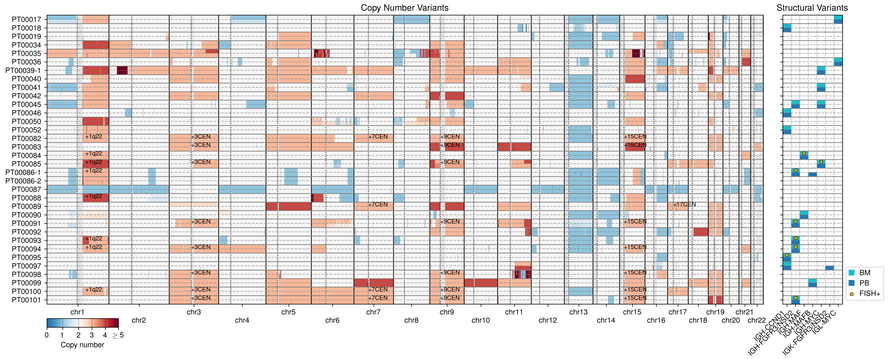
Alterations are consistent with progressive disease after therapy with talquetamab (anti-GPRC5D bispecific), and previous nonresponse to teclistamab (anti-BCMA bispecific) after prior therapy with Cilta-cel (BCMA-directed CAR T).

Resistance to immunomodulatory drugs (IMiDs)



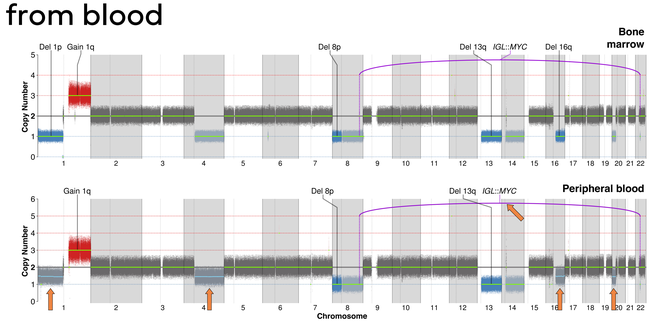
Biallelic loss of CRBN (Del 3p & focal deletion) underlies relapse after therapies that included IMiDs (lenalidomide and pomalidomide).

GenoPredicta on blood recalls 100% of events observed with GenoPredicta on bone marrow, and is concordant with FISH



100% recall of 9 SVs and 30 CNVs observed by FISH, and **100% precision** across 50 SVs and 30 CNVs not detected by FISH.

GenoPredicta identifies and characterizes subclonal events from blood



- GenoPredicta enables accurate detection of subclonal events.
- Subclonal characterization can elucidate tumor evolutionary history and thus predict evolution in response to treatment.
- Subset of copy number changes that are clonal in sampled marrow lesion are subclonal in blood.

Subclonal alterations detected in blood

Blood can capture signal from multiple lesions, including (subclonal) events originating from unbiopsied bone marrow lesions or extramedullary disease, thus providing more complete information about the tumor.

Conclusions

- WGS-based characterization of MM from BM or CTCs is a viable replacement for FISH for clinical diagnosis, with blood-based measurements enabling more dynamic and minimally invasive monitoring of the myeloma cancer genome.
- GenoPredicta enables in-depth characterization of therapy resistance mechanisms.

For more information: tinyurl.com/genoprd
Contact: genopredicta@predictabiosciences.com

Website

Poster