Whole genome sequencing of circulating multiple myeloma cells with a novel clinical assay enables identification of genetic alterations underlying immunotherapy resistance

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Introduction

Detecting genetic abnormalities is required during diagnostic workup and for potential individualization of therapy selection in multiple myeloma (MM) and its precursor conditions. Presently, this requires invasive bone marrow (BM) biopsies, hindering early detection, frequent longitudinal monitoring, and precise therapy selection. The standard for detecting genetic alterations in MM remains 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.

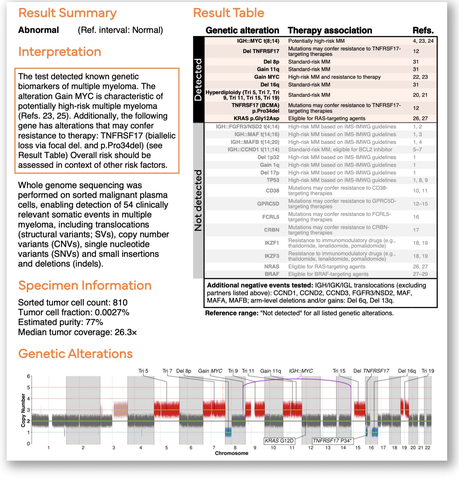
To address these needs, we recently launched GenoPredicta, a CLIA-approved LDT that comprehensively characterizes MM genomes with whole genome sequencing (WGS) from as few as 50 circulating tumor cells (CTCs) isolated from peripheral blood (PB) or tumor cells from BM and enables risk classification according to the new IMS-IMWG guidelines, as well as identification of genetic alterations underlying resistance to therapy.

Study design and methods

- Clinical cohort: 100 samples processed with GenoPredicta, spanning disease stages and risk categories, and annotated with information from medical records where available.
- Tumor cells were isolated from BM or PB samples using fluorescence-activated cell sorting (FACS) 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.

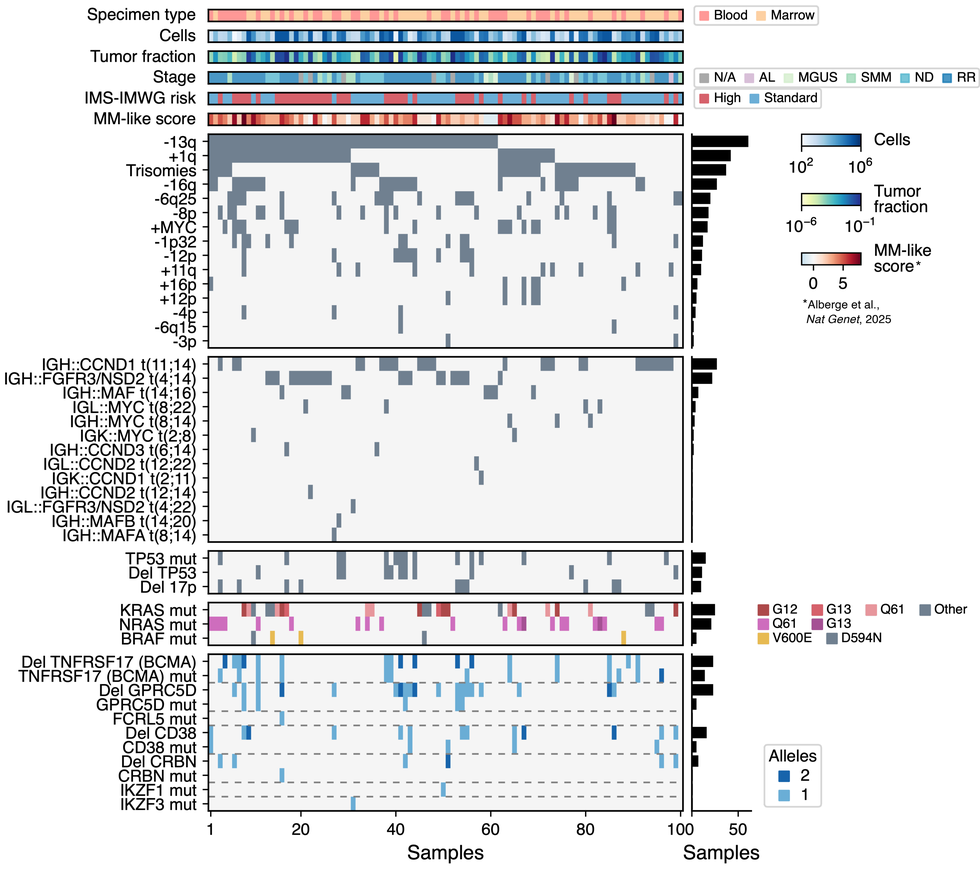
Clinical test enables identification of therapy resistance mechanisms from blood

- 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).



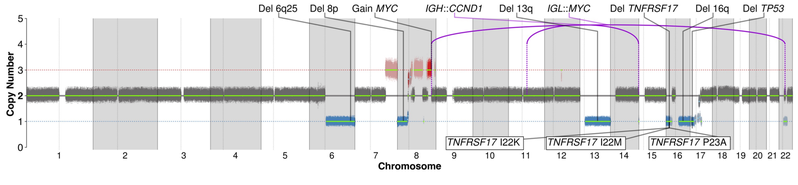
- Patient clinical report shown; physician-ready reports are automatically generated end-to-end from raw sequencing data in ~6h.

Results



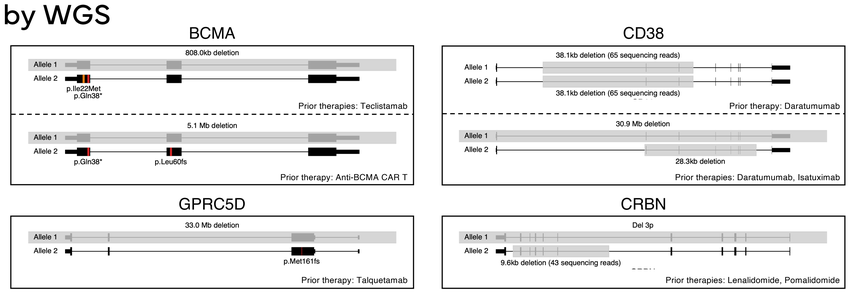
Summary of key alterations identified in the cohort

- >50% of identified alterations not detectable via FISH
  - ~85% of samples had ≥1 event not detectable by FISH (median: 2 events)
- 26 samples had *TP53* deletions and/or mutations
- 42 high-risk cases; 5/42 cases (12%) classified as high risk from *TP53* mutations only
- 10 samples with non-IGH translocations, including 4 *IGL::MYC*
- 29/56 (52%) of relapsed/refractory samples had alterations in BCMA and/or GPRC5D
  - 19 samples (34%) had biallelic alterations of BCMA and/or GPRC5D



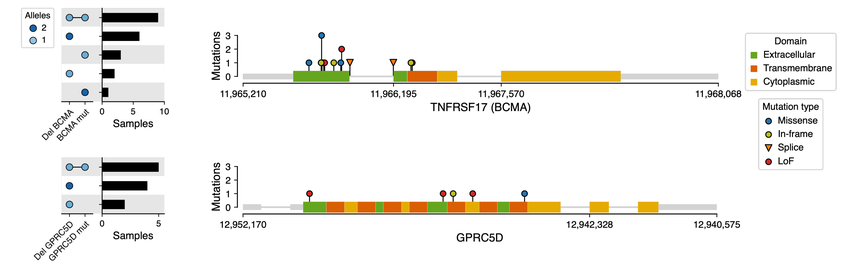
GenoPredicta enables deep characterization of myeloma genomes and reveals genetic resistance mechanisms to therapy.

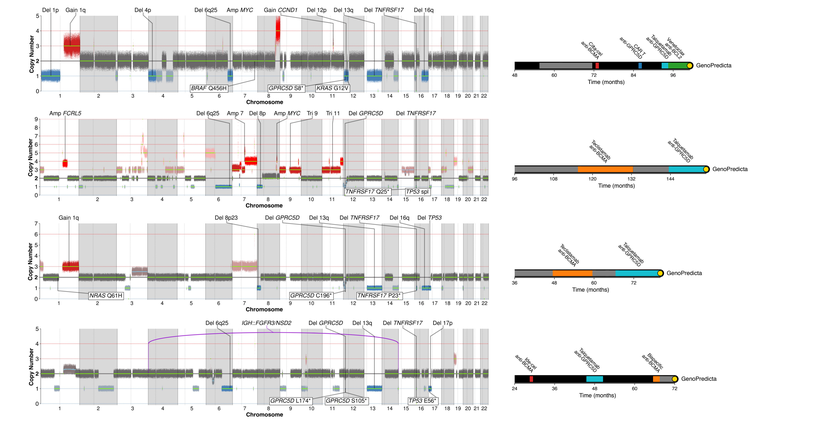
Broad spectrum of resistance mechanisms only measurable by WGS



Resistance mechanisms identified in clinical production samples range from point mutations and small focal deletions to large arm-level deletions, many of which are undetectable via WES/targeted sequencing or FISH.

Biallelic loss of BCMA and GPRC5D





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.
- WGS catches complex resistance mechanisms targeted sequencing misses.
- GenoPredicta enables in-depth characterization of therapy resistance mechanisms.

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Website