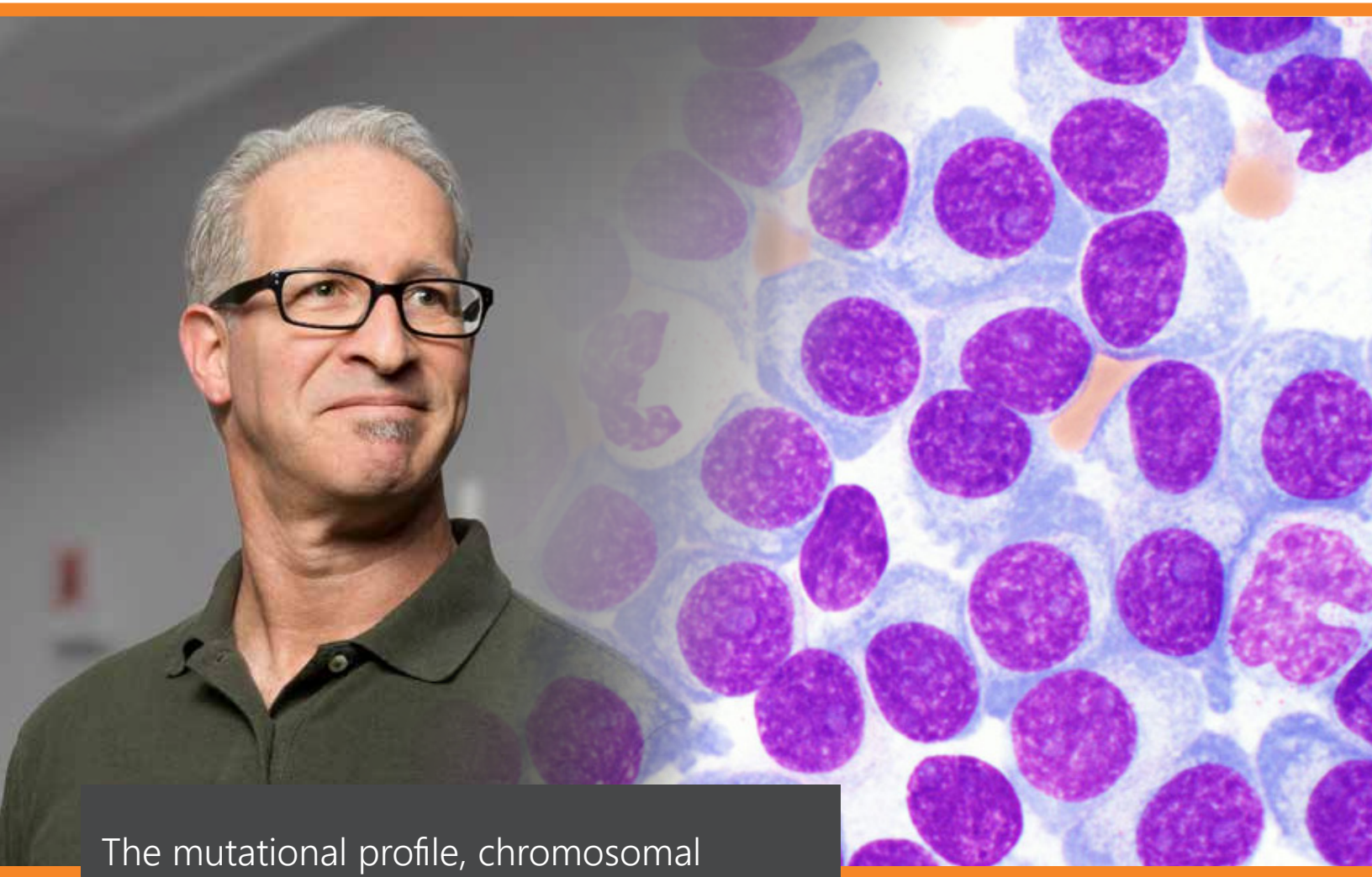
# Case Study
# Multiple Myeloma

## as Detected by GTC's Liquid Trace™ Hematology



The mutational profile, chromosomal translocations/abnormalities and b-cell clonality in a patient with multiple myeloma

GENOMIC TESTING COOPERATIVE®


Cancer Hope
אונקולוגיה מותאמת אישית
לתיאום בדיקה: 03-919-57-57
וצאפ: 054-468-7377
מייל: info@CancerHope.co.il

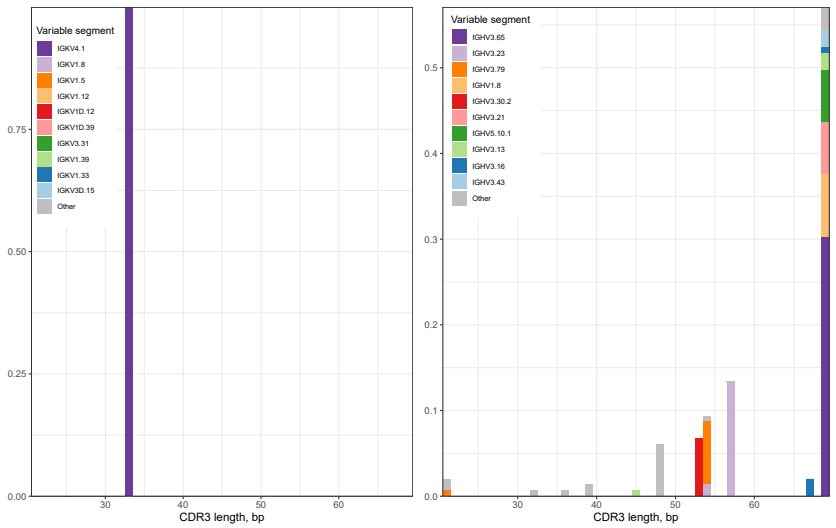
## Background

Multiple myeloma is a malignancy originating in plasma cells. It is characterized by bone marrow infiltration, excessive production of monoclonal proteins, bone destruction, plasma cell aggregates, renal involvement, and associated anemia and immunodeficiency.

Multiple myeloma is heterogeneous in its genetic abnormalities and shows molecular evolution during disease progression and treatment. In addition, there is molecular diversity between subclones in the same or different bone marrow (BM) sites, between BM and the extramedullary sites, and between individuals. These features may explain why despite improving and longer overall median survival over the past few years, some patients survive for decades, whereas others succumb to the disease rapidly. As a result of these characteristics, optimal management of this malignancy requires testing modalities capable of capturing a comprehensive profile of the mutational and chromosomal landscape of the disease, enabling new risk stratification systems and individual therapy options previously unavailable.

Liquid biopsy has emerged as a promising non-invasive diagnostic tool frequently used in solid tumors but rarely used in multiple myeloma. While bone marrow biopsy, supplemented by flow cytometry, immunohistochemistry, cytogenetics and Fluorescent In Situ Hybridization (FISH) has traditionally been the gold standard for diagnosis and follow-up of multiple myeloma patients, liquid biopsy is emerging as a one-stop source, capable of not only supplementing, but increasingly replacing and surpassing many facets of traditional bone marrow biopsy. It offers several advantages over traditional bone marrow biopsy for evaluation of multiple myeloma, including but not limited to ease of sampling, real-time monitoring, identification of potential molecular targets, drug resistance and enhanced detection of chromosomal abnormalities, translocations, gene amplifications and assessment of B-cell as well as T-cell clonality.

Liquid biopsy also has the potential to be used as an ultimate tool for measuring minimal residual disease because it provides information on b-cell clonality as well as mutations.




## Clinical History

- 61 year old male with hypercalcemia, anemia, and new lytic bone lesions involving the left iliac bone and the right 9th rib.
- The patient has a free kappa light chain of 1195 mg/L and a free lambda light chain of 3.2 mg/L with a kappa to lambda ratio of 373. Immunofixation shows an IgG monoclonal protein with kappa light chain specificity.

## Molecular Profiling Findings

- Mutations in KMT2C (2 mutations), PTPN11 (2 mutations), WHSC1, PRKAR1A, TP53 (low level), CCNE1, TSHR, POLD1, EGFR, and DNMT3A genes.
- No detectable autosomal chromosomal structural gain or loss by Copy Number Variation (CNV analysis)
- Increased plasma cell mRNA markers CD138 and BCMA.
- Marked increase in CCND1 mRNA, reflecting promoter hijacking, characteristic of t(11;14) CCND1-IgH.
- No evidence of high risk chromosomal abnormalities consisting of t(4;14)(FGFR3/NSD2), t(14;16)(MAF), t(14;20)(MAFB), 1q21 + , del(1p), and del(17p) by RNA fusion or CNV analysis.
- No evidence of mutations in KRAS, NRAS, ATM, ATR, MYC and DIS3.
- Positive B-cell clonality detection (IgHV3.65/IgKV8.61), see figure 1.

## Discussion

The mutational profile, elevated mRNA marker levels for plasma cells, and a positive B-cell clonality test are diagnostic of multiple myeloma.

The detection of t (11;14) CCND1-IgH by fusion mRNA is considered an intermediate risk category in multiple myeloma and confers a worse outcome compared to standard-risk myeloma. In addition, t(11;14) myeloma cases have been shown to be particularly sensitive to Bcl-2 inhibitors, making Bcl-2 a potential target in this subtype of myeloma.

This case also showed absence of poor prognostic chromosomal abnormalities consisting of t(4;14), t(14;16), t(14;20), 1q21+, del(1p), and del(17p), as well as high risk mutations consisting of KRAS, NRAS, ATM, ATR, MYC and DIS3, all of which are typically associated with poor risk multiple myeloma.

The aggregate findings in this case provide comprehensive genomic profiling that is superior to single-site tissue biopsy for diagnosis, prognostic profiling, treatment and longitudinal management due to its less invasiveness and better representation of up-to-date tumor genome abnormalities and tumor genomic diversity.

### References

1. Davies FE, Walker BA. What Is Genomic High-Risk Myeloma? Hemato. 2022; 3(2):287-297. https://doi.org/10.3390/hemato3020021
2. Ferreira, B., Caetano, J., Barahona, F. et al. Liquid biopsies for multiple myeloma in a time of precision medicine. J Mol Med 98, 513–525 (2020). https://doi.org/10.1007/s00109-020-01897-9
3. Liu Y, Guo J, Yi Y, Gao X, Wen L, Duan W, Wen Z, Liu Y, Guan Y, Xia X, Ma L, Fu R, Liu L, Huang X, Ge Q, Lu J. Circulating Tumor DNA: Less Invasive, More Representative Method to Unveil the Genomic Landscape of Newly Diagnosed Multiple Myeloma Than Bone Marrow Aspirates. Cancers (Basel). 2022 Oct 7;14(19):4914. doi: 10.3390/cancers14194914. PMID: 36230837; PMCID: PMC9563595.
4. Li S, Zhang E, Cai Z. Liquid biopsy by analysis of circulating myeloma cells and cell-free nucleic acids: a novel noninvasive approach of disease evaluation in multiple myeloma. Biomark Res. 2023 Mar 8;11(1):27. doi: 10.1186/s40364-023-00469-6. PMID: 36890597; PMCID: PMC9997021.


GENOMIC® TESTING COOPERATIVE


Cancer Hope
אונקולוגיה מותאמת אישית
לתיאום בדיקה: 03-919-57-57
וצאפ: 054-468-7377
מייל: info@CancerHope.co.il