ELSEVIER

Blood 142 (2023) 534–536

The 65th ASH Annual Meeting Abstracts

ORAL ABSTRACTS

652.MULTIPLE MYELOMA: CLINICAL AND EPIDEMIOLOGICAL

Confirmed Pathogenic Germline Variants in Cancer Predisposition Genes Incidentally Detected in Somatic Genomic Profiling of Multiple Myeloma Patients

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Introduction: We previously showed that ~10% of patients with multiple myeloma (MM) carry pathogenic or likely-pathogenic (P/LP) germline variants (PGVs) in known cancer predisposition genes, and that moderate/high-penetrance PGVs in DNA repair genes may be associated with MM risk and favorable response to alkylating chemotherapy. Increasingly applied in MM, genomic profiling by next-generation sequencing (NGS) can identify prognostically-relevant and therapeutically-actionable somatic mutations, but it may also incidentally unveil PGVs, which can have significant implications for patients and their families. We here test the diagnostic accuracy of a novel referral tool designed to flag likely PGVs warranting confirmatory germline testing among mutations identified in somatic NGS studies of 1161 MM patients from our institution.
Methods: We retrospectively reviewed 1715 commercial NGS reports of 1161 MM patients treated at the Icahn School of Medicine at Mount Sinai (ISMMS) between 2015 & 2022 (targeted 448-gene somatic profiling panels performed by a single genomic testing company for clinical purposes on bone marrow aspirate samples). In collaboration with certified genetic counselors at our institution, we applied evidence-based criteria to develop a tool to flag P/LP variants of likely germline origin warranting a referral for confirmatory germline testing ("Likely PGVs"). The resulting referral tool flags variants detected in 35 well-established cancer predisposition genes at a variant allele frequency (VAF) of >10%, as well as 24 cancer predisposition founder variants at any VAF. Next, we tested the positive predictive value (PPV), negative predictive value (NPV), sensitivity and specificity of our approach for the detection of true PGVs by analyzing paired germline whole-exome sequencing (WES) in 382/1161 (33%) MM patients in the study cohort. Germline WES data were generated for research purposes using a clinically-validated pipeline for PGV detection and annotation.
Results: 385 P/LP variants were reported in somatic NGS studies of 382 MM patients who had paired somatic/germline sequencing data. Of these, 38/385 (9.9%) were found to be true PGVs in confirmatory germline testing. True PGVs detected in more than one gene included nine *APC*, seven *CHEK2*, five *BRCA1*, three *BRCA2, three ATM* and three *MUTYH* variants. The referral tool flagged 41/385 (10.6%) of the cohort's somatic variants as likely PGVs, identifying 32/38 (84.2%) true PGVs. The six PGVs missed by the referral tool were detected in the following genes: one *APC*, one *CHEK2*, one *MITF*, one *MUTYH*, one *NF1* and one *SHDA* variant. In contrast, the nine variants that were mislabeled as likely PGVs but were in fact somatic were: two *ATM*, two *BRCA2*, two *TSC1*, one *CHEK2*, one *BRIP1*, and one *RET*. With a variant allele threshold of >10%, the tool had a PPV of 78.0% and a NPV of 98.3% for the detection of true PGVs. The sensitivity and specificity were 84.2% and 97.5%, respectively. Among the 692/1161 MM patients who did not have confirmatory germline testing (67%), the proportion of variants flagged as likely PGVs was very similar to that of the paired somatic/germline group (77/696, 11.1%), and variants were detected in similar genes. Assuming a PPV of 78%, 60 of these variants could represent true PGVs.
Conclusion: A novel tool designed to flag likely PGVs among mutations identified in somatic genomic profiling of MM patients had high sensitivity and specificity for the detection of true PGVs. 9.9% of all MM patients with paired somatic/germline testing were found to have a true PGV, validating the results of our prior study and once again highlighting the need to implement

screening strategies in high-risk subgroups of MM patients, such as those with strong family history of cancer or prior personal history of cancer.

Disclosures Chari: *Amgen:* Consultancy, Other: Advisory Board, Research Funding; *BMS:* Consultancy, Other: Advisory Board, Research Funding; *Sanofi:* Other: Advisory Board; *Seattle Genetics:* Other: Advisory Board, Research Funding; *Millenium/Takeda:* Consultancy, Research Funding; *Janssen:* Consultancy, Other: Advisory Board, Research Funding; *Antengene:* Consultancy; *Shattuck Labs:* Other: Advisory Board; *Secura Bio:* Consultancy, Other: Advisory Board; *Glaxo Smith Kline:* Other: Advisory Board; *Karyopharm:* Other: Advisory Board; *Genentech:* Other: Advisory Board; *AbbVie:* Other: Advisory Board. **Rossi:** *JNJ:* Membership on an entity's Board of Directors or advisory committees; *Adaptive:* Membership on an entity's Board of Directors or advisory committees; *Sanofi:* Membership on an entity's Board of Directors or advisory committees; *BMS:* Membership on an entity's Board of Directors or advisory committees. **Rodriguez:** *Janssen, Takeda, Bristol Myers Squibb, Amgen, Karyopharm Therapeutics:* Membership on an entity's Board of Directors or advisory committees. **Sanchez:** *Janssen Pharmaceuticals:* Consultancy, Honoraria. **Richard:** *Bristol Myers Squibb:* Honoraria; *Janssen:* Honoraria; *C4 Therapeutics:* Research Funding; *Heidelberg Pharma:* Research Funding. **Richter:** *Astra Zeneca:* Membership on an entity's Board of Directors or advisory committees; *Celgene:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Bristol-Meyers-Squibb:* Membership on an entity's Board of Directors or advisory committees; *Janssen:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Sanofi:* Membership on an entity's Board of Directors or advisory committees; *Pfizer:* Consultancy; *Genentech:* Consultancy; *Takeda:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Adaptive Biotechnologies:* Membership on an entity's Board of Directors or advisory committees; *Abbvie:* Consultancy; *Karyopharm:* Membership on an entity's Board of Directors or advisory committees. **Jagannath:** *Karyopharm:* Consultancy; *Legend Biotech:* Consultancy; *Janssen:* Consultancy; *Caribou:* Consultancy; *Regeneron:* Consultancy; *Sanofi:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Bristol Myers Squibb:* Consultancy. **Parekh:** *Grail, LLC:* Membership on an entity's Board of Directors or advisory committees; *Amgen:* Research Funding; *Celgene/BMS Corporation:* Research Funding; *Karyopharm Therapeutics:* Research Funding; *Caribou Biosciences:* Research Funding.

https://doi.org/10.1182/blood-2023-190878

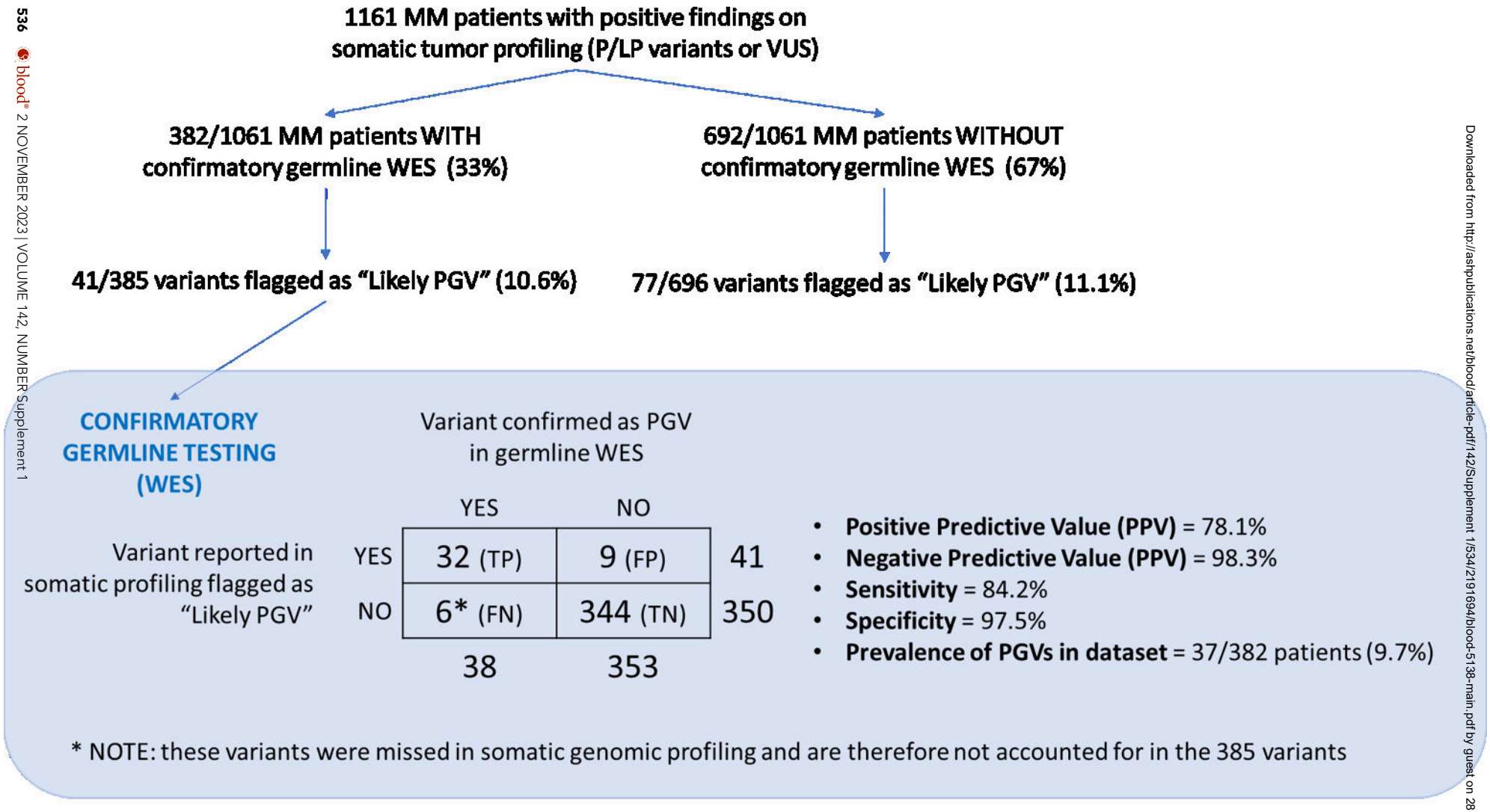

Figure 1: Study Schema and Main Findings; P/LP = pathogenic/likely pathogenic; VUS = variants of unknown significance; PGV = pathogenic germline variant; TP = true positives; FN = false negatives; FP = false positives; TN = true negatives

Figure 1