XIX CONGRESSO NAZIONALE SIES2026
Firenze | 4-6 marzo 2026 Palazzo degli Affari

XIX Congress of the Italian Society of Experimental Hematology ABSTRACT N. A08

Institutional Session E

CLONAL HEMATOPOIESIS, MYELOID NEOPLASMS AND BONE MARROW FAILURE SYNDROMES

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Genetic characterization of bone marrow failure and leukemia predisposition syndromes (BMF/LPS) has become increasingly important for the precise diagnosis of entities that require personalized treatment and follow-up strategies. The widespread availability of genomic sequencing has improved the detection of germline variants; however, it also poses challenges in identifying appropriate candidates for testing and in interpreting variants of uncertain significance. In this setting, the role of routine testing aimed at defining somatic genetic alterations (both molecular and cytogenetic) is enhanced through integration with germline-specific diagnostic tools. Somatic findings provide critical information for diagnostic orientation, support the interpretation and pathogenicity assessment of germline variants, and inform personalized surveillance strategies. Here, I summarize the experience developed within the hematologist–geneticist outpatient clinic (GEMMA project) at Policlinico Tor Vergata, Rome, in collaboration with the St. Jude Children's Research Hospital BMF referral center. This integrated clinical model focuses on conditions at risk for germline predisposition, emphasizing the dynamic interplay between germline background and somatic clonal evolution. Specific somatic alterations can act as diagnostic red flags for underlying germline conditions, such as monosomy 7 in young patients with myelodysplastic syndromes (MDS), suggestive of GATA2 deficiency, or the absence of canonical MDS-defining somatic mutations and cytogenetic abnormalities in elderly patients with hypocellular MDS, raising suspicion for DDX41-related disorder. Moreover, somatic characterization can refine the interpretation of germline variants. A paradigmatic example is represented by SAMD9 and SAMD9L syndromes, in which somatic rescue mechanisms, namely UPD7q or secondary somatic *SAMD9/9L* mutations, support the reclassification of germline variants of uncertain significance as pathogenic. Finally, the integration of germline and somatic data has direct implications for surveillance strategies. While some expert panels recommend annual bone marrow (BM) evaluations, robust evidence is often lacking, as most studies are retrospective. We explored the role of peripheral blood–based genetic surveillance as monitoring strategy, with the aim of reducing BM investigations in lower-risk settings while optimizing their timing in higher-risk conditions. Our data indicates that the emergence of new high-risk clones or a significant increase in the clonal size of known high-risk clones, such as in Shwachman-Diamond syndrome, ERCC6L2 disease, and GATA2 deficiency, warrants timely BM assessment due to the imminent risk of leukemic transformation.[1]

Overall, detecting and monitoring clonal hematopoiesis in genetically predisposed individuals is of growing clinical relevance and provides a foundation for the development of standardized, risk-adapted clinical guidelines for BMF/LPS.

References

1. **Attardi E, Gray N, Lewis S, et al.** - Utility of Peripheral Blood Testing for Detection and Surveillance of Clonal Hematopoiesis in Predisposed Individuals (CH-IPI). Blood. 2025 Nov 10:blood.2024028042. doi: 10.1182/blood.2024028042.