Comprehensive Genomics in Bone Marrow Failure: from Diagnosis to Therapy Stratification

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Accurate genetic diagnosis is essential for inherited bone marrow failure (BMF) syndromes because the treatment approach is very dependent on the underlying genetic cause. The genetic diagnosis must be reached quickly, for example in patients with severe aplastic anemia and suspicion of inherited BMF, while it can wait in patients who can be stabilized with transfusions (example: Diamond Blackfan anemia). The management is tailored to individual patients based on the genetic information, which includes both germline and somatic events, since there is a fine balance between overtreating versus missing the right time point for treatment leading to optimal outcomes. Finally, the surveillance is dictated by the underlying genetic findings.

This presentation will first outline the genetic classification of inherited BMF syndromes and review several studies with large cohorts of BMF patients in which the diagnositc utility of multi-gene NGS panel or whole exome sequencing has been demonstrated. We also show the advantages and disadvantages of whole genome sequencing - based diagnostics in BMF. The second part of the presentation will focus on the newly identified SAMD9/SAMD9L syndromes, which predispose to BMF with high propensity to develop rescue clonal hematopoiesis (somatic genetic rescue) and risk for MDS development. With an estimated prevalence of 8-20% among pediatric BMF/MDS cases, they are among the most common predisposition syndromes in this age group. Thus far, over 250 cases have been reported and summarized in the St. Jude SAMD9/9L registry (www.stjude.org/samd9).