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Hematological Malignancies

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Preface

The increasing knowledge on the pathogenesis of hematologic diseases has over the years been translated into diagnostic and prognostic applications. Hematopathology and laboratory hematology were among the first disciplines to embrace molecular diagnostics. As a consequence, the contemporary state-of-the-art hematopathology diagnosis relies on the integration of clinical, laboratory, morphologic, immunophenotypic, and genetic features. Increasingly however, the World Health Organization classification of hematopoietic and lymphoid neoplasms uses genetic/molecular features to separate clinically and prognostically distinct entities with similar morphologic or immunophenotypic characteristics. Hence, the majority of diagnostic entities require karyotyping and/or molecular testing to either confirm a diagnosis or to exclude a potential morphologically overlapping mimicker. This work presents the molecular-based assays frequently used in the routine diagnostic hematopathology and laboratory hematology. Many of these protocols were initially developed as research applications and were further refined as they transitioned to the diagnostic laboratory. Over the years, the field of molecular hematopathology has grown to represent a significant proportion of the routine diagnostic work. The assays, which originally existed only as research tools, were developed into commercially available tests, often packaged into ready-to-use kits. However, even the latter tests benefit from the comprehensive discussion by experts who use them in their everyday practice. The diagnostic testing is highly regulated and, optimally, is standardized among the laboratories. Towards this aim, the national and international collaborative studies led to the development of expert guidelines and international standards for the select of the presented molecular assays.

This work includes the discussion of the tests which have diagnostic, prognostic, and therapeutic implications. In the group of myeloproliferative and myelodysplastic/myeloproliferative neoplasms, detection or exclusion of *BCR-ABL1* rearrangement is critical for a precise diagnosis. Only after this step is completed, can one proceed with further subclassification. Additionally, BCR-ABL1 fusion transcript levels are used in patient follow-up and to monitor the efficacy of tyrosine kinase treatment. Patients demonstrating an increase in BCR-ABL1 transcript levels are considered for alternative therapies and tested for BCR-ABL1 kinase domain mutations. Additional mutations seen in myeloproliferative neoplasms, *JAK2*V617F and *KIT*D816V mutations, have been associated with Philadelphia chromosome-negative myeloproliferative neoplasms and mast cell disease. Both are critical for the diagnosis and are increasingly used as a therapeutic target. The molecular methods for a diagnosis and follow-up of chronic myeloid neoplasms are presented in the opening chapters. Similarly, current classification of acute myeloid and lymphoblastic leukemias relies heavily on genetic features. To bypass the delay in diagnosis typically associated with conventional karyotyping, various molecular techniques have been used to demonstrate the genetic abnormalities in acute leukemias. These tests, and immune and molecular assays, which established a niche in the posttreatment follow-up of patients with acute leukemias are presented next.

The following chapters focus on the molecular applications in lymphoid neoplasms. Initially, lymphomas lagged behind the disorders of blood and bone marrow in terms of classification based on their genetic features. However, in recent years this gap is closing and a molecular work-up is becoming increasingly important in lymphoid malignancies. Molecular tests are used for the confirmation of diagnosis, classification, and detection of residual disease. A proportion of lymphoid malignancies are associated with viral infections. Viruses are also a significant cause of morbidity and mortality in patients with hematologic malignancies who are frequently immunosuppressed. Both in situ demonstration of these pathogenic viruses and the monitoring of infection kinetics are the subjects of molecular testing.

The cornerstones of individualized therapies include the precise, clinically significant disease classification and the knowledge of individual variations in the response to different therapies. Testing of the polymorphisms in drug metabolizing genes is already an integral part of clinical management in select hematologic entities, and the field of molecular pharmacogenetics is rapidly growing due to the application of high-throughput technologies. The latter assays cannot be comprehensively discussed in a single text, and have been presented in separate publications of this series. We have elected to include the microRNA profiling due to its emerging role in hematologic malignancies.

I am indebted to all the authors who contributed to this work for sharing their expertise and for providing excellent yet practical and concise descriptions of the tests essential for contemporary laboratory diagnostics of hematological neoplasms.

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