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Editorial

The limitless potential of molecular diagnostics in hematology

Ankit Jitani[1]

[1]Department of Hematology, Blood and Marrow Transplant, Marengo CIMS Hospital, Ahmedabad, Gujarat, India.

***Corresponding author:**
Dr. Ankit Jitani,
Consultant, Department of Hematology, Blood and Marrow Transplant, Marengo CIMS Hospital, Ahmedabad, Gujarat, India.

ankitjitani@gmail.com

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Deoxyribonucleic acid (DNA) has been an integral part of human existence. With the advent of molecular diagnostics, we have gained the remarkable ability to delve into the intricacies of DNA, ribonucleic acid (RNA), and proteins. The utilization of molecular diagnostics in clinical medicine began in the early 1980s with the use of restriction enzymes for prenatal diagnosis of thalassemia. From its humble beginnings in hematology, the field of molecular diagnostics has grown exponentially and, now, encompasses various specialties of medicine.

The field of molecular diagnostics has revolutionized the way we approach clinical hematology. These cutting-edge techniques have become indispensable tools in diagnosing, prognosticating, stratifying risks, and assessing treatment responses in various diseases. From malignant hematological conditions to non-malignant disorders, molecular techniques have empowered clinicians to make informed decisions and provide personalized care. In this short editorial, we will explore the remarkable impact of molecular diagnostics in different aspects of hematology.

In the realm of diagnosing malignant hematological diseases, the significance of molecular diagnostics cannot be overstated. Chronic myeloid leukemia and acute promyelocytic leukemia stand as prime examples of diseases where molecular markers, such as BCR::ABL1 and PML::RARA, play a pivotal role. Not only are these markers used for diagnosis, but they also guide the selection of targeted therapies and enable the monitoring of treatment responses. Furthermore, the specific transcript type of PML::RARA plays a crucial role in prognostication. Molecular diagnostics are pivotal in other myeloid disorders like myeloproliferative neoplasms and chronic neutrophilic leukemia, as well as lymphoid disorders such as hairy cell leukemia. Techniques like end point polymerase chain reactions (PCRs), real-time PCRs, and fragment analysis are commonly employed in these diagnostic processes.

The use of molecular techniques in non-malignant hematology diagnosis is even more widespread. Conditions like thalassemia, hemophilia, and inherited bone marrow failure syndrome rely on a diverse array of testing modalities such as Sanger sequencing, multiplex ligation-dependent probe amplification, and various PCR techniques like Amplification Refractory Mutation System (ARMS) or GAP-PCR. Next-generation sequencing (NGS) is also emerging as a validated method in this field. The choice of technique depends on whether a known or unknown mutation is being explored. Molecular diagnosis, particularly in thalassemia, finds its widest application in prenatal and pre-implantation genetic diagnosis. Molecular diagnosis of hemophilia poses challenges due to the large size of the factor VIII gene and the involvement of large deletions, but it is now widely available for clinical use. NGS has also become instrumental in diagnosing inherited platelet disorders, primary immunodeficiency diseases, and inherited bone marrow failure syndromes,

where the use of clinical exome, whole exome, and whole genome sequencing has significantly enhanced diagnostic capabilities. Collaboration among molecular pathologists, bioinformaticians and clinicians is crucial to interpreting the big data generated through these techniques and reaching meaningful conclusions.

Molecular techniques have firmly established themselves in risk stratification for various hematological malignancies, including acute myeloid leukemia (AML), acute lymphoblastic leukemia, chronic lymphocytic leukemia, multiple myeloma, myelofibrosis, and lymphomas. NGS, with its routine incorporation into clinical practice, has redefined the risk stratification system. It seamlessly integrates RNA-based testing (translocations and rearrangements) and DNA-based testing (point mutations, indels, etc.) into a cost-effective common platform.

Among the arsenal of tests used to assess treatment response, BCR::ABL1 real-time PCR stands as one of the most widely employed. However, cases with rare transcripts pose technical challenges, making a gel-based test for transcript identification at baseline crucial. PML::RARA, another translocation, utilizes both qualitative and quantitative PCRs. Clonality assays have gained prominence in monitoring minimal residual disease (MRD) in lymphoid neoplasms and multiple myeloma. In AML, molecular techniques find widespread application in MRD detection, particularly in core binding factor CBF-AML.

The field of molecular diagnostics is evolving at lightning speed, pushing the boundaries of what we once thought possible, revolutionizing the way we analyze and understand various tests in clinical hematology. Imagine a world where we can delve deeper into tests like BCR::ABL1, thanks to the groundbreaking technology of droplet digital or digital PCRs (ddPCR). By enabling highly precise quantification of nucleic acid targets, ddPCR offers unprecedented sensitivity and accuracy, allowing for more precise and reliable results. These cutting-edge technologies are reshaping the landscape of molecular diagnostics and paving the way for exciting developments in these fields.

This rapidly evolving field is also awaiting the validation of multiple cutting edge technology for clinical use. Single Cell Sequencing, is shedding light on the intricacies of cellular function. This approach provides invaluable information about the individual cells within a sample. Optical Genome Mapping (OGM) represents a breakthrough in visualizing the intricate structure of DNA. By mapping ultralong DNA molecules, this technique efficiently identifies large structural and copy number changes within the genome. Third-generation or long-read sequencing will revolutionize genomic analysis. Long-read sequencing technologies can generate sustainable long reads that surpass the limitations of second-generation sequencing (NGS). Companies like pacific biosciences and Oxford Nanopore are at the forefront, employing diverse approaches to develop error-free and sustainable platforms. This progress opens up new possibilities for exploring our genetic blueprint with unparalleled resolution and depth.

In conclusion, the era of molecular diagnostics is unfolding new frontiers, not only in clinical hematology, but it's also transforming the landscape of oncology as a whole. As these technologies continue to evolve, we can anticipate a future where molecular diagnostics plays an increasingly critical role in personalized medicine and improving patient outcomes. The journey has just begun, and the possibilities are limitless.

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