

## Introduction to a Review Series on Precision Hematology

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Precision medicine is the aspiration to optimize therapy to individual patients, maximizing benefit while limiting toxicity. This objective is nothing new in the practice of medicine, but the genomics revolution offers the potential for deeper and more individualized insight into the drivers of disease pathology and the likelihood of response to particular treatments in a patient.

Recognizing the opportunity of genomics in clinical practice, President Barack Obama launched the Precision Medicine Initiative during his 2015 State of the Union Address, "to bring us closer to curing diseases like cancer and diabetes – and to give all of us access to the personalized information we need to keep ourselves and our families healthier."<sup>1</sup> Cancer features prominently in the initial goals of this initiative, with the goal of illuminating the genetic complexity of somatic mutations, germline predisposition, drug sensitivity and resistance, and the use of drug combinations.<sup>1</sup>

Hematology has long been at the vanguard of precision medicine. Typing of blood group antigens and the HLA locus have guided the use of transfusions and transplantation for individual patients. Targeted therapies for patients with *BCR-ABL* translocations, *PML-RAR $\alpha$*  translocations, and other genetic lesions have revolutionized the care of subtypes of hematologic malignancies and provide a paradigm for precision medicine more broadly.

The use of clinical genomics for the routine care of hematology patients has accelerated dramatically in recent years, due both to technological advances in DNA sequencing and to the rapidly increasing annotation of hematologic disorders with germline and somatic genetic variants. This issue of *Blood* contains six review articles on precision medicine that highlight the clinical and research opportunities of clinical genomics:

Diagnosis and classification of hematologic malignancies on the basis of genetics  
(Justin Taylor, Wenbin Xiao, and Omar Abdel-Wahab)

Genetic predisposition to hematologic malignancies: management and surveillance  
(Lucy Godley and Akiko Shimamura)

The relative utilities of genome-wide, gene panel, and individual gene sequencing in clinical practice (Frank Kuo, Brenton Mar, R. Coleman Lindsley, Neal Lindeman)

High-throughput sequencing for noninvasive disease detection in hematologic malignancies (Florian Scherer, David Kurtz, Maximilian Diehn, Ash Alizadeh)

The NCI genomic data commons as an engine for precision medicine (Mark Jensen, Vincent Ferretti, Robert Grossman, and Louis Staudt)

Ethical considerations in genomic testing for hematologic disorders (Jonathan Marron and Steven Joffe)

Each hematologic malignancy is associated with a distinct spectrum of somatic mutations, though mutations in any particular gene may span many cancer subtypes. As described by Taylor et al., hematologic malignancies can increasingly be classified and diagnosed on the basis of somatic mutations.<sup>2</sup> In some cases, a specific genetic lesion largely defines a disease subtype. In other cases, combinations of mutations may be indicative of a disease state. For many hematologic malignancies, somatic mutations predict clinical phenotype and response to therapy.

The full potential of precision medicine for hematologic malignancies requires integration of both germline and somatic genetic information. Specific germline alleles powerfully predispose individuals to hematologic malignancies. Godley and Shimamura describe these predisposition syndromes and provide expert consensus recommendations for the care of individuals with germline predisposition to hematologic malignancies.<sup>3</sup>

With dramatic advances in DNA sequencing technology, it is feasible to analyze not only single genes, but also panels of genes, or entire genomes or exomes in clinical practice. Kuo et al. address the relative merits of each of these approaches as they are applied to routine clinical diagnostics.<sup>4</sup> In particular, the authors describe the application of gene panel assays as a component of the pathological work-up for patients with myeloid and lymphoid malignancies.

Beyond the diagnosis and characterization active hematologic malignancies, genetic analyses have the potential to probe and monitor minimal residual disease. Scherer et al. discuss how deep sequencing of blood samples can be used to detect mutations in DNA derived from a hematologic malignancy that is in clinical remission.<sup>5</sup> Increased sensitivity of these genetic assays is improving our understanding of the depth of remissions for lymphomas and other hematologic malignancies and predicting relapse. Mutations derived from a malignancy must be distinguished from mutations arising from a pre-malignant state such as clonal hematopoiesis on indeterminate potential (CHIP). While many of these genetic studies of minimal residual disease are not yet part of routine clinical practice, they hold great promise for improving patient care in the near future.

Achievement of the promise of precision medicine will require the creation of massive databases of genetic and clinical data, given the complexity of genomic data in hematologic malignancies and other disease states, and the extraordinary variability between patients with the same diagnosis. The National Cancer Institute therefore launched the Genomic Data Commons (GDC) in June of 2016. GDC stores both clinical and genomic data, and will actively harmonize data across platforms, providing tools to analyze and visualize the aggregated data. Jensen et al. discuss the operation of GDC to enable researchers to access and analyze large-scale genomic data for hematologic malignancies, and the utility of this database for precision medicine and research into the genetics of hematologic disorders.<sup>6</sup>

Genetic studies, performed either for research or in clinical practice, raise important ethical considerations that must be understood by the investigator or physician. Marron and Joffe describe clinical case studies and discuss ethical issues related to genetic testing in clinical practice.<sup>7</sup> An understanding of the nature and implication of genetic studies is important for informed consent. Both patients and clinicians must realize that results may be ambiguous, even if genetic studies seem more definitive than other types of clinical assays. Incidental genetic findings with clinical implications are an increasing challenge for the practicing clinician. Finally, the introduction of genomic studies into clinical practice has the potential for unequal access and benefit across different patient populations.

The practical implementation of precision medicine for hematology will rely on practical concerns, including how the data will be produced, analyzed, and reimbursed. These challenges are being surmounted rapidly, while ongoing research continues to identify opportunities for individual subgroups of patients to receive precision-guided therapy with improved clinical outcomes.

- 1 Collins, F. S. & Varmus, H. A new initiative on precision medicine. *N Engl J Med* **372**, 793-795, doi:10.1056/NEJMp1500523 (2015).
- 2 Taylor, J., Xiao, W. & Abdel-Wahab, O. Diagnosis and classification of hematologic malignancies on the basis of genetics. *Blood* (In press).
- 3 Godley, L. A. & Shimamura, A. Genetic predisposition to hematologic malignancies: management and surveillance. *Blood* (In press).
- 4 Kuo, F. C., Mar, B. G., Lindsley, R. C. & Lindeman, N. The relative utilities of genome-wide, gene panel, and individual gene sequencing in clinical practice. *Blood* (In press).
- 5 Scherer, F., Kurtz, D. M., Diehn, M. & Alizadeh, A. A. High-throughput sequencing for noninvasive disease detection in hematologic malignancies. *Blood* (In press).
- 6 Jensen, M. A., Ferretti, V., Grossman, R. L. & Staudt, L. M. The NCI Genomic Data Commons as an Engine for Precision Medicine. *Blood* (In press).
- 7 Marron, J. M. & Joffe, S. Ethical considerations in genomic testing for hematologic disorders. *Blood* (In press).



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