Understanding the impact of cancer and cancer therapies on susceptibility to severe COVID-19 is critical to optimize treatments for these patients. This study documents real-world experience of clinical care for multiple myeloma patients with SARS-CoV-2, with clinical and demographic factors associated with severity of the infection outcomes. Anti-myeloma therapies did not show a detectable influence on COVID-19 outcomes. These findings provide groundwork to understanding vulnerabilities of patients with blood malignancies to COVID-19.

See article, p. 234.

COVID-19 Clinical Outcomes in Patients with Multiple Myeloma in New York City

- COVID-19–caused mortality is 29% among multiple myeloma patients hospitalized with the infection (n = 75).
- Mortality risk is higher among Black and Hispanic/Latino as compared to White patients.
- Inflammatory markers are higher in patients with combined adverse endpoint.

High-Accuracy Gene Expression–Based Cancer Subtyping across Platforms

- The PRPS-ST algorithm classifies lymphoma subtypes by gene expression after self-training on a dataset from any platform.
- The accuracy and consistency of DLBCL classification by PRPS-ST is on par with or exceeding the current alternatives.
- Cases unclassifiable by previous methods can be correctly categorized by PRPS-ST.

Diagnostic classification of cancer subtypes based on gene expression signatures has improved outcome prediction and optimal treatment selection. It is increasingly used to evaluate aggressive lymphoma subtypes. However, training and testing datasets require normalization across batches, technological platforms, and processing pipelines, reducing the accuracy. To overcome this limitation, Ryan Morin and colleagues developed an algorithm PRPS-ST (probability ratio-based classification prediction score), which self-trains on a dataset regardless of how it was generated, thus enabling classification across platforms without compromising accuracy. With accuracy equal to or exceeding that of the commonly used algorithms, PRPS-ST classifies B-ALL and DLBCL cases across different subtyping models, acquisition and processing methods, gene sets, and cohort sizes. With further validation, the algorithm holds the potential to refine and consolidate gene-based binary diagnostic classification of cancer and other complex pathologies.

See article, p. 244.
Revealing the Impact of Structural Variants in Multiple Myeloma

- Integrated analysis reconstructs a landscape of structural aberrations and gene expression in multiple myeloma.
- Several identified novel hotspots and candidate driver mutations include therapeutic target genes.
- Complex rearrangements such as chromothripsis are common and contribute to oncogenesis and clinical outcomes.

Francesco Maura and colleagues present a comprehensive genomic landscape of structural rearrangements in a large, well-annotated, treatment-naive cohort of multiple myeloma (MM) patients from the CoMMpass trial. The analysis, integrated with gene expression data, identifies dozens of new hotspots and candidate driver genes, including BCMA, SLAMF7, and MCL1. It reveals that complex structural aberrations are widespread in MM and often contribute to oncogenic event acquisition—including multiple driver mutations generated by a single structural event in every third case. Among the complex rearrangements, chromothripsis occurred in a quarter of patients at diagnosis and was associated with subsequent poor clinical outcomes. These findings add a new layer to the MM genomic landscape and reveal a major contribution of complex structural rearrangements to genetic mechanisms of myelomagenesis.

See article, p. 258.

CpG Island Hypermethylation Reveals T-ALL Developmental Age

- A landscape of DNA methylation, gene expression, and ChIP-seq in human T-ALL.
- COSMe classification built on this integrative analysis identifies T-ALL subsets with distinct developmental trajectories.
- Developmental age–related methylation pattern is recapitulated in mouse models of T-ALL and is suggestive of self-renewing thymocyte as its cell of origin.

Aberrant DNA methylation in T-ALL has been linked to clinical course of the disease, but its biological origins remain unclear. Pieter Van Vlierberghe and colleagues characterize genome-wide DNA methylation landscape in T-ALL in comparison with normal T cells sorted by developmental stage. Integrated with gene expression data, this analysis identifies two T-ALL subsets suggestive of distinct developmental trajectories. The COSMe-I subset is epigenetically young at diagnosis and accumulates CpG methylation at relapse, whereas the COSMe-II subset appears epigenetically old at diagnosis. This leads the authors to hypothesize that COSMe-II cases may arise from preleukemic thymocytes. In support of this concept, they show that this methylation pattern is mirrored in a genetic mouse model of T-ALL with a long preneoplastic window, but not in a model with rapid T-ALL development. The observations suggest that CpG island methylation is mostly reflective of T-ALL proliferative age rather than its oncogenic state or responsiveness to decitabine, and lay the grounds for a hypothesis that a subset of human T-ALL may originate from thymocytes with long-term self-renewing potential.

See article, p. 274.

In This Issue is written by Blood Cancer Discovery editorial staff. Readers are encouraged to consult the original articles for full details.