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By *Helen Fernandes*

Preface: Molecular Pathology: Life Beyond the Pandemic, *xvii*

By *Gregory J. Tsongalis*

Genetics

Polygenic Risk Scores in Clinical Care, *1*

By *Emily R. Soper and Noura S. Abul-Husn*

Polygenic risk scores (PRS) combine the effect of common variants obtained from genome-wide association studies to estimate the risk for common diseases. PRS have the potential to identify large proportions of the population at high risk for disease, and there is growing interest in using this information to guide clinical decision-making. However, the clinical utility of PRS remains unknown. Here, we discuss how PRS are generated and validated, how they can be interpreted and used to guide clinical care, and ongoing challenges and considerations for widespread implementation.

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Hereditary Cancer and Cancer Predisposition Syndromes, *9*

By *Erfan Aref-Eshghi and Marylin M. Li*

Germline genetics influences cancer incidence in various ways. Traditional cancer predisposition syndromes are caused by inherited pathogenic variants in tumor suppressor genes in an autosomal dominant fashion and predispose individuals to cancer as the main phenotype. Many other genetic syndromes can also present with cancer as part of the phenotype, the underlying causes of which are broad and include cytogenetic abnormalities, imprinting defects, and single-gene disorders. More recently, non-syndromic germline contribution to malignancies has expanded the scope of hereditary cancer, and many sporadic tumors are being recognized to have an inherited basis. For most cancer occurrences, however, a multifactorial or polygenic contribution is still the predominantly accepted model. Advances in sequencing technology have enabled the discovery of novel contributors to hereditary cancer. With the increasing use of genomic testing in the diagnostic setting, demands for testing guidelines for hereditary cancer are on the rise.

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Hematopathology

Expanding the Molecular Landscape of Cutaneous T-Cell Lymphoma, 29

By Mark G. Evans and Carlos A. Torres-Cabala

Cutaneous T-cell lymphoma represents a genetically heterogeneous group of diseases thought to be derived from skin-homing lymphocytes. The genomic landscape of these conditions has been recently redefined to incorporate findings from cutting-edge molecular and cytogenetic testing. Recurrent genetic alterations that have been detected include those associated with chromatin modification, DNA repair, cell cycle control, JAK/STAT pathway activation, TCR/NF κ B signaling, and MAPK pathway regulation. Many of these changes can be targeted by current/upcoming personalized therapies.

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High-Grade B-cell Lymphomas, 41

By Anna Shestakova and Kristin H. Karner

Accurate diagnosis of mature B-cell lymphomas is essential for adequate treatment. There is a morphologic and immunophenotypic overlap between high-grade B-cell lymphoma (HGBL) with *MYC* and *BCL2* and/or *BCL6* rearrangements, HGBL, not otherwise specified (NOS), and Burkitt-like lymphoma with 11q aberration. Therefore, cytogenetic and molecular testing are essential for an accurate diagnosis. HGBL with *MYC* and *BCL2* and/or *BCL6* rearrangements is defined by rearranged *MYC* and *BCL2* and/or *BCL6* genes, also known as double-hit and triple-hit lymphomas. Burkitt-like lymphoma with 11q is characterized by the absence of the rearrangement of the *MYC* gene and a peculiar aberration of 11q with proximal gain and terminal loss.

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Molecular Advances in Nodal Peripheral T-Cell Lymphoma, 51

By Safina Hafeez and Allison M. Cushman-Vokoun

Peripheral T-cell lymphoma (PTCL) is a rare and heterogeneous group of mature T-cell malignancies. It is an aggressive form of the disease, which is frequently associated with a

poor prognosis. It can be subdivided into four major categories based on the clinical presentation and location of the disease: nodal, extranodal, cutaneous, and leukemic. The diagnostic approach in PTCL requires multiple factors such as clinical presentation, morphology, immunophenotype, cytogenetics, and molecular genetic findings. The recent advances in gene expression profiling and next-generation sequencing technologies have opened up new insights into the pathogenesis and molecular genetic changes of different subtypes of PTCL. In this review article, we will focus on nodal PTCL.

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Multiple Myeloma, 59

By Loren J. Joseph

Multiple myeloma is a malignant clonal proliferation of plasma cells; it evolves through several stages of progressive pathology, marked by one or more of several specific cytogenetic abnormalities and subsequent accumulation of mutations in one or more of 80 driver genes, possibly in conjunction with alterations in stromal cells. Multiple lines of therapy have been developed, directed at different pathways. Each case bears a unique rearrangement of the IGH/L genes that permits sensitive detection of residual disease by next-generation sequencing. Overall survival has improved so dramatically that some experts have started using the “C(ure)” word.

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Infectious Disease

Prevalence and Clinical Disease Severity of Respiratory Coinfections During the Coronavirus Disease 2019 Pandemic, 73

By Maxwell D. Weidmann, Gregory J. Berry, Daniel A. Green, and Fann Wu

Respiratory tract infections represent a global health concern. More than 1 pathogenic organism in the respiratory tract has been widely recognized owing to the availability of molecular detection technologies. However, the association between the occurrence of multiple-pathogen infections and clinical disease severity remains unclear. Multiple infections fall into two broad categories: Coinfection occurs when a person is found to be infected by two or more micro-organisms, but which infection was established first cannot be clearly determined, while superinfection is an infection arising when one or more infections is already present. This review presents an overview of the prevalence and clinical disease severity of respiratory coinfections and superinfections and discusses possible mechanisms of the interactions between viral infections.

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Applications of Long-Read Sequencing Technology in Clinical Genomics, 85

By Shivaprasad H. Sathyanarayana, Sophie J. Deharvengt, Guohong Huang, Rachael E. Barney, Parth S. Shah, and Joel A. Lefferts

Next-generation sequencing (NGS) using traditional short-read sequencing (SRS) has transformed the field of clinical genetics and genomics research. Newer long-read sequencing (LRS) technologies have emerged more recently that are able to reveal specific types of genetic information that traditional SRS technologies may not be able to detect. Detection of structural variants and highly repetitive sequences, differentiating homologous genomic sequences, and establishing allele phasing are some benefits of LRS. This review article highlights the power of LRS technology in different clinical testing areas and addresses some of its current limitations and challenges.

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Pharmacogenomics

SLCO1B1 Pharmacogenetics in Pediatrics, 109

By Laura B. Ramsey, Jason A. Sprowl, J. Steven Leeder, and Jonathan B. Wagner

Organic polypeptide transporting polypeptide 1B1 (OATP1B1), encoded by the *SLCO1B1* gene, is a major transporter involved in the hepatic uptake of several endogenous molecules and medications relevant to pediatrics. In children, the magnitude of effect of *SLCO1B1* allelic variation on systemic exposure of statins is similar to that observed in adults, but is associated within genotype variability (>10-fold) that exceeds reported variability in adults; sources of the intra-genotype variability appear to be drug-specific. For methotrexate, the influence of rare variants appears to be comparable to common variants. Taken together, existing pharmacogenetic-driven dosing guidelines based on adult experience may not be directly applicable to pediatric age groups and should be used with caution. Integration of *SLCO1B1* pharmacogenetics into clinical care will benefit from improved knowledge of non-genetic factors that contribute to inter-individual variability in drug disposition.

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Implementation of a Clinical Pharmacogenomics Service in a Large Freestanding Pediatric Health System, 119

By Courtney Paetznick, David Gregornik, Lane Miller, Damon Olson, and Jacob Brown

As a large, freestanding pediatric health system, Children's Minnesota is faced with unique challenges and opportunities with pharmacogenomics (PGx) implementation as compared with adult health systems. The PGx program was initially developed to meet a growing desire to incorporate PGx information into clinical decision-making, particularly in hematology/oncology and behavioral health, and to lead the clinical PGx implementation. Since the launch of the PGx program, new possibilities have emerged with contributions to PGx research and on going development of an in-house genotyping assay as ways to better serve our diverse pediatric population.

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Artificial Intelligence/Machine Learning and Mechanistic Modeling Approaches as Translational Tools to Advance Personalized Medicine Decisions, 131

By George A. Mystridis, Fani Chatzopoulou, George P. Patrinos, and Ioannis S. Vizirianakis

Nowadays, advancements in omics-based methodologies, data analysis, informatics, and bioinformatics, as well as nanotechnology have continuously led to a more digitized, robust, as well as information-based environment in biomedicine and health care. Precision in therapy will be ensured through the application of computerized platforms, as well as interdisciplinary integrated analysis and decision-making. In this review, artificial intelligence/machine learning approaches and mechanistic modeling methodologies will be discussed as translational tools aiming to advance personalized medicine decisions and patient care.

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Solid tumors

Advances in Cell-Free DNA, 141

By Elizabeth S. Barrie and Andrea Ferreira-Gonzalez

This chapter will focus on a subtype of liquid biopsy that uses cell-free DNA as a blood-based biomarker to detect and monitor solid tumors. While this assay has clear advantages in terms of patient safety, improved turnaround time, and the ability to sample more frequently over time, the complexity lies in its application and interpretation.

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