At the time that the majority of this issue was being prepared, our country and the world were facing a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic beyond what many of us have ever experienced before. Although there was a lot of criticism about the laboratory community’s slow response, the shining beacon that helped turn the tide on this pandemic was the ability of molecular diagnostic testing laboratories to implement laboratory-developed tests (LDTs). The practice of molecular pathology has been and continues to be dependent upon new and robust molecular diagnostic technologies to interrogate DNA and/or RNA sequences for detection of sequence variants associated with a particular diagnosis, prognosis, or therapeutic response. Many molecular diagnostic tests require nucleic acid extraction, an analytical procedure such as polymerase chain reaction (PCR) or sequencing, and then data analysis and reporting. This 3-step process is combined into the workflow of a single test. Upon completion of the Human Genome Project, the field of molecular diagnostics began to evolve rapidly, and it became clear that the need for more molecular-based tests far outweighed the commercial and financial interests of most vendors to seek Food and Drug Administration (FDA) approval. Many academic and hospital laboratories were left to develop primers/probes targeting genes of clinical interest for their patient population even though test volumes were relatively low compared with other clinical laboratory tests. Southern blot-based testing for linkage analysis and Duchenne muscular dystrophy as well as PCR-based test for cystic fibrosis, parvovirus B19, and cytomegalovirus were only a few examples of tests with clinical utility but no commercial vendor.

Hence, the LDT was born! Initially these tests were called “homebrew” assays, but with regulatory oversight by federal agencies looming, a brand name discouraging a negative perception of the hard work being performed by laboratories to develop and validate these assays as mad scientists huddled around a cauldron of reaction mixture was needed. Laboratory Developed Test or LDT became accepted by those in the field. LDTs represented the “freedom to operate” that laboratories needed to keep up with the pace of new molecular discoveries and to rapidly deliver those to clinical practice. After all, the promises of the Human Genome Project included better diagnostic testing, more accurate
prognostication, and better therapeutics that would target disease in individuals with specific genetic variants. Under the Clinical Laboratory Improvement Amendment of 1988 and with developing guidelines from various professional organizations, including the College of American Pathologists and the Association for Molecular Pathology, laboratories began validating new tests using a variety of specimen types and technologies that would change the way we assessed patients for genetic diseases, hematologic disorders, infectious diseases, identity, and oncology. As an example, our laboratory performs some 60 different molecular tests of which only 11 are FDA approved or cleared. The majority of these assays are for higher-volume infectious disease tests that were selected by commercial industries based on the number of tests being performed globally in order to help recoup development and regulatory costs.

The LDT played a pivotal role in combating the SARS-CoV-2 pandemic. While some delays were experienced in the United States due to regulatory hurdles, globally many countries were able to mobilize efforts quickly to sequence and identify the virus, establish real-time PCR assays, and implement universal screening strategies. In the United States, the Centers for Disease Control and Prevention and the FDA established a plan for Public Health Laboratories and then hospital-based and private laboratories to begin testing using a variety of different commercially available tests under the Emergency Use Authorization (EUA) ruling. Obtaining EUA status for a particular test was somewhat involved from a validation standpoint due to lack of appropriate positive samples and control materials, but for laboratories using these EUA-marked assays, the “verification” steps involved were very lax compared with traditional LDT validations. In retrospect, there are many lessons to be learned from this experience for the laboratory community. No other scenario could better speak to the importance of LDTs than the crisis we all faced.

In this third issue of Advances in Molecular Pathology, we include a special section on COVID-19 experiences and review some of the newest developments in the field of molecular pathology as the need for genetic disease, hematologic disease, infectious disease, pharmacogenomic, solid tumor, and identity testing continues to increase. The articles included in this third issue provide further support for the importance of molecular testing in routine patient care and management, for the continued development of new tests and technologies, and for the appropriate reimbursement and regulation of such testing. As technologies become more robust, faster, and cheaper, we will far exceed the promises of the Human Genome Project.

I am grateful to those friends and colleagues who during the most pressing of times once again agreed to becoming section editors and authors of the fantastic articles presented here.

Happy reading!

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