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pharmacogenomics (which uses an individual's genome to provide a more informed and tailored drug prescription).[xi]

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Molecular Informatics: Shaping Change in the Lab

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Molecular diagnostics is revolutionizing healthcare by paving the way for personalized medicine. Yet, while remarkable advances are being made in molecular testing, information systems and reimbursement models struggle to keep up. In molecular testing, the future role of the laboratorian shifts away from specimen handling to data processing and interpretive guidance. By providing molecular and genetic data analysis and result interpretation, laboratory professionals help providers and patients gain the full benefit of molecular testing, and promote maximum lab value.

Less Complexity Makes Molecular Tests More Available

In the past, molecular testing was too complex and expensive to be performed in many laboratory scenarios. However, advances in molecular testing continue to happen at a rapid pace, changing the status and availability of molecular tests. Not only is testing becoming more affordable, but there are also a multitude of different platforms and footprints, and testing has become less complex with faster turnaround time (TAT). The availability of more multi-analyte assays, load-and-walk-away analyzers, point-of-care testing, and automation enables a wide range of laboratories to offer molecular assays and genetic tests. There are molecular systems currently available that automate all steps of testing, including nucleic acid extraction, amplification, and detection. Advances have been made in large, high-throughput automated systems for high-volume testing that require very little training, and progress has occurred in polymerase chain reaction (PCR) testing that allows molecular testing at the point of care.

Applications of Molecular Testing

In response to demand, molecular menus are growing rapidly. In fact, CLIA certificates were issued to more than 40 new genetic testing labs in 2016.[1] Southern blot and Sanger sequencing, widely used 20 years ago, are considered much too complex and uneconomical for today's laboratory. Currently, the majority of clinical applications for molecular testing fall within six general areas: infectious disease, oncology, pharmacogenomics, genetic disease screening, human leukocyte antigen typing, and coagulation (see Figure 1).[2]

Molecular testing can be beneficial for diagnostics, newborn screening, pre-symptomatic and carrier screening, prenatal diagnosis, prognosis, and personalized or precision medicine. Molecular test results can help a cancer patient understand the likelihood of reoccurrence, aid a provider in selecting the best drug for a specific tumor, or inform a pregnant couple how likely they are of passing on an inheritable gene mutation. Molecular tests can

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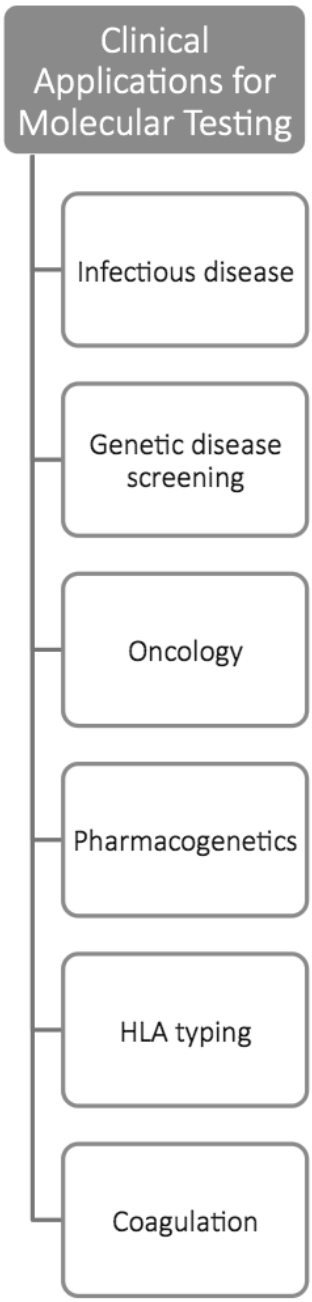
be used to monitor virus level to determine treatment efficacy, screen donated blood for infectious diseases, identify infectious pathogens, and more.

- ***Infectious Disease Advances***

Microbiology has gained enormously from advances in molecular testing in the diagnosis and treatment of infectious diseases. For example, molecular identification of Methicillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridium difficile* has been instrumental in the reduction of hospital-acquired infections (HAIs). With payments being tied to performance, reducing HAIs has become a priority, and molecular tests are becoming the solution.



To address the prevalence of sepsis, which is frequently encountered in the ICU and historically difficult to diagnose, there are FDA-approved molecular tests for blood culture panels that correlate well with culture and sensitivity testing and provide results in just a few hours; a vast improvement over the traditional TAT associated with culture growth in the microbiology lab.

- ***Successful Molecular Genetic Tests & Cancer Biomarkers***

Molecular genetic testing is available for several applications (e.g., prenatal diagnosis, risk for hereditary cancer, diagnosis of neurological disorders, diagnosis/staging of malignancies, etc.). For cancer patients, molecular prognostic (e.g., HER2/neu) or predictive (e.g., EGFR, KRAS) biomarkers provide the clinician with information about the patient's overall prognosis or about the efficacy of a treatment plan, respectively.[3]

- ***Molecular Testing at the POC***

The rapid TAT offered by point-of-care testing (POCT) has greatly increased the demand for molecular testing at the patient location. In a healthcare environment that is looking to decrease unnecessary hospital admissions and reduce length of stay, the new methodologies offered in molecular POCT can provide rapid, accurate results to meet these specific needs and make significant financial and patient outcome improvements.

Furthermore, molecular testing technology has made big strides in POCT. The introduction of single-use closed systems has created an opportunity for almost any lab to perform molecular testing. There are molecular POCT devices that require minimal training and incorporate built-in QC. For many of these devices, the specimen is added to a cartridge and results are available within a few hours.

Challenges in Molecular Testing

In spite of molecular testing being more widely available and affordable, with high sensitivity and specificity, there remain myriad challenges to molecular implementation. The biggest challenges currently faced in molecular testing are sorting out the reimbursement process and handling the tremendous amount of data generated by molecular and genetic testing. Finding information systems that can handle the data deluge has become difficult.

- ***Reimbursement Challenges***

Reimbursements for molecular diagnostic tests are a detriment to more widespread adoption because of the conflicting and confusing reimbursement landscape. The historical and inadequate approach for molecular reimbursement involved using CPT "stacking codes" that coded for the steps of the process (e.g., isolation, amplification, enzymatic digestion, separation). This method often resulted in denials or low reimbursements because it did not accurately identify the tests. Having codes based on the method or step being performed rather than on the analyte made it nearly impossible for payers to properly identify and reimburse for molecular

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testing. CPT codes are evolving and improving, but the pace of change is slow.

In 2012, the American Medical Association (AMA) introduced an analyte-specific tiered coding system for molecular pathology—MoPath codes—to replace stacking codes. MoPath codes allow for more accurate labeling and identification of molecular diagnostic tests, which in turn helps payers properly identify and bill for testing. Palmetto GBA, a CMS contractor, introduced the MolDX Program in 2011 to begin registration of molecular tests in order to identify available testing and determine clinical utility of molecular tests. This information was to be used to improve claims processing and reimbursement.[5] Meanwhile, McKesson Corporation created the McKesson Diagnostics Exchange™ (DEX) to allow manufacturers to submit and catalog information about their specific molecular tests. Providers and payers use this index to evaluate the tests, tracking outcomes and analyzing the clinical utility of each test.[6] The DEX assigns unique Z-Code Identifiers to each test and catalogs it for reference. In 2014, McKesson and the AMA began collaborating to group and index the Z-Codes with corresponding CPT codes to improve and simplify the reimbursement process.[6]

Yet, coverage determinations still remain difficult. Payers are looking for clear evidence to support coverage of tests, including analytical validity, clinical validity, and clinical utility. Clinical utility, which refers to how much a test influences clinical decision making or improves patient outcomes, has become the most difficult to measure and prove, and, consequently, the most important to payers in determining coverage.

- ***PAMA will Impact Molecular Reimbursements***

The Protecting Access to Medicare Act (PAMA) of 2014 will further muddy the waters of molecular reimbursement as many molecular tests will fall under PAMA's definition of advanced diagnostic laboratory tests (ADLTs). An ADLT is a test offered by a single lab that also meets one of the following criteria: includes DNA, RNA, or protein analysis and uses an algorithm to yield a single-patient specific result; meets other similar criteria established by the CMS; or is FDA approved. In any case, PAMA will only add to the confusion surrounding molecular test reimbursements and likely result in further reductions.

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- ***Data Handling Challenge***

In addition to reimbursement complexity, the amount of data produced by molecular and genetic testing creates a further challenge. With sequencers producing up to 0.5 terabases per device per day, there is a need to store, manage, and share a large quantity of data. The difficulty is no longer in test performance, but in interpretation of large, complex data sets. Mountains of genomic data are accumulating that are of little use because they are not tied to clinical information, such as family medical history. Often, genomic data are in documents that cannot easily be searched, shared, or understood by physicians.[7] In fact, the cost of genome sequencing is now decreasing several times faster than the cost of storage, promising that at some time in the not-too-distant future, it will cost less to sequence a base of DNA than to store the resulting data.[8]

Advances in Molecular Testing Change the Role of the Laboratorian

Lab testing, along with many medical specialties, has steadily moved from being a very hands-on process to becoming more automated. The majority of large laboratories now include automation lines that handle the routing of samples, and automation is expanding its reach into microbiology, anatomic pathology, and molecular testing. As a result, the laboratorian's role is expected to become more consultative, specifically aiding providers in the interpretation of genetic test results.[9] We are looking at a future where IT systems can analyze databases with genome analyses from hundreds of thousands of patients for trends or connections that aid in determining the best treatment plan for a particular patient.[4,7] The lab will be involved in using software solutions to sort through and analyze the large amounts of data generated by genetic testing.

With IT advances and molecular and genetic testing advances combined with the changing healthcare environment, the lab is transitioning further away from hands-on processes to a reality where the specimen is rarely touched. What the laboratorian will "touch" is the data—being involved in valuable interpretations, test consultations, algorithms, and lab informatics. Future generations of laboratorians will be expected to be involved in molecular informatics, take a bigger role on the healthcare team, have advanced lab IT skills, and be involved in projects outside the laboratory.

Let's look at the facts: Sanger sequencing was developed in 1975, the entire genome was sequenced in 2003, the first moderately complex molecular test was developed in 2006, and the first CLIA-waived molecular test approval was in 2015.[10] It is clear that the molecular industry pace is exponentially accelerating. We are looking into uncharted territory, where genetic sequencing is routinely performed and we use molecular lab data to quickly and accurately assess a patient's health. These advances in research and treatment are transforming the practice of medicine, and the laboratory plays an exciting role in that transformation.

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