Integrate molecular diagnostics: Create a strategic menu

By Ronald C. McGlennen, MD

Certainly in concept, if not in one's own experience, the use of nucleic-acid-based testing is viewed by the whole of the lab industry as having come a long way toward being technically feasible, financially rewarding, and clinically utilitarian. Despite the value that offering molecular testing imbues to the lab that can do it, many lab directors struggle to envision a strategic plan for the molecular lab: Who are the customers we serve? Where does the molecular lab fit within the larger lab organization? How does one deal with the series of apparent "one-off technologies and tests" that are typical of this discipline? By what set of molecular tests can we facilitate mainstreaming this type of information for patient care?

We all know molecular diagnostics is the place where the lab does DNA testing. The word “diagnostics” implies that these DNA tests are no longer a research project but, rather, are dedicated for use in patient care. Despite these simple descriptors, the molecular-diagnostics lab has been and is increasingly in the throes of an identity crisis. In terms of mission, the molecular team has most often been followers rather than leaders in establishing policies as to how and where these tests should be employed. The common effect is that clinicians read about a new test that sounds interesting: and they, in turn, make a request to the molecular lab to make that test available. This well-meaning behavior occurs regardless of whether that test has been demonstrated to be analytically or clinically valid or clinically useful — illustrating the point that one clinician’s request does not establish a market for that test.

Failure to have a plan to develop a strategic menu is of concern to any lab new to the molecular arena as well as established labs now looking for the means to expand their impact. We present one perspective as to how the molecular-diagnostics lab might change its image and, through the invention of a strategic menu, better define its mission, operation, and philosophy. At the core of creating a strategic menu is the advancement of information technology (IT) to integrate the elements of a strategic plan.

The hub-and-spoke model

One approach as to how the molecular-diagnostics lab might find its identity as an integrator of lab information is that of a hub-and-spoke model, the elements of which are first, the customer layer, where combinations of clinical tests serve particular clinical/patient care needs; second, the layer consisting of the technologies required to answer those particular clinical questions; a third layer consists of the laboratory facility, infrastructure, expertise, and commitment to quality that makes the use of the specific technologies possible. Finally, there is the hub consisting of the IT systems and capabilities that bring the whole model together. Although contrived, this model is a response to the actual state of piecemeal systems and bench-top operations that are typical of many molecular-diagnostics labs. It acknowledges that stand-alone and commercial IT systems are not ready to plug-and-play in the molecular lab, and also recognizes that such “integrating” systems do exist and can readily be built.

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Layer 1: Where the rubber hits the road

The rubber hits the road where the customer says it does. Customers have understandable, intelligent needs for which they seek information from their labs. For any person in charge of test offerings for a molecular-diagnostics lab, it is important to remember that the types of customers who now rely on molecular-test results are few. The days of the “shotgun strategy,” where today’s test of interest becomes the low-volume and high-complexity challenge of tomorrow, are over. The integrated lab focuses on those medical specialties that can provide volumes of samples and for whom those results are useful. These include the obstetrician/gynecologist (Ob/Gyn) interested in tests for “women’s health;” the hospital administrator charged with reducing costs of patient care, whose concerns relate to hospitalization issues, including nosocomial sepsis, pneumonia with unknown organisms, and wounds with their specter of drug-resistant pathogens; the oncologist concerned with finding the key molecular diagnostic marker for a certain cancer and then monitoring its ebb and tide in response to treatment (see Table 1); and to a lesser extent, the internist with questions on a spectrum of common diseases but who generally wants answers to concerns about coagulation, infections, and markers of cardiovascular health. That is it.

There are not that many more customers to serve (e.g., clinicians who order molecular tests, or patients who are the recipients of those test results) or, for that matter, many more ready-for-prime-time tests to be offered. In testing for rare genetic diseases — which expertise resides principally within academia — the molecular arena remains well defined. Similarly, one can see that the drive for molecular-test volumes can be specific for the sample type. In the case of tests offered to the Ob/Gyn, it is in fact the liquid-Pap collection sample that makes possible the host of tests for infectious disease, tests for prenatal screening, and, most recently, genetic markers (such as those for inherited thrombophilia) that are predictive of several critical clinical conditions.

Layer 2: The circle of technology

Responding to customer requests involves a strategy we will call the “circle of technology.” The various technologies needed to offer molecular-diagnostic-test selections and to produce analytic results are considerably more complex than the correlates in other

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areas of the clinical lab. Adding to the challenge is the rate of change of technologies in vogue.

We have thus far inherited two aspects of the molecular-diagnostics legacy. Many of us have developed with a series of the “one-box, one-test” approach. Innovative companies in this discipline, eager to introduce their technical solutions to tests currently in the rage, often fail to expand the menu of assays within a diagnostic theme or for an area of clinical specialization. This has led to several technical platforms that offer products capable of only a single task (so-called “one-off” products). One example is the development of a more complete menu of assays for inherited thrombophilia; interest in FDA clearance of the Factor V Leiden assay has not been followed with similar clearance for other markers such as the prothrombin mutation, tests for MTHFR, and a panel for arteriothrombotic-risk indicators. As a consequence, the lab serving an ambitious group of hematologists and/or gynecologists would be forced to incorporate several disparate platforms into their operations to provide a reasonably complete test menu.

The alternative strategy is to work with an “open platform” such as conventional PCR. This approach, however, may tax the nascent abilities of the lab personnel to develop analyte-specific-reagent- or ASR-based tests and to find the necessary support for those assays (i.e., source of control material, quality metrics, reference methods), particularly for small molecular operations. Moreover, expectations for lab operations should be different than those held for the more conventional lab disciplines such as chemistry, coagulation, hematology, and microbiology. Test volumes and revenues are smaller, efficiencies are less, and the technology is, at best, a piecemeal collection of “one-box, one-test” products. The operations of the molecular-diagnostic lab lack integration of methods and technologies for cost-effectiveness as well as clinical relevance needed to be the “go-to” strategy for key diagnostic situations.

In conventional sections of the clinical lab, the methods for performing a test imply that the platform can inclusively move the sample to result. In contrast, the molecular lab is tasked with piecing together several disparate methods to achieve the same — its second aspect. In fact, few manufacturers of assays have considered the equally important issue of sample procurement, nucleic-acid extraction, and applied to each of the representative sample types. The success of any integration plan would be to design the combinations of technology for the anticipated advancement of sample through these “front-end requirements,” thereby gaining the throughput of those samples delivered to the assay “set-up” bench.

One exercise that will aid in the development of a strategic menu — and with that, the likelihood of integration of the molecular lab — is to categorize each of the proposed tests into groups defined by the basic genetics of the disease for which those tests are designed. In general, only a few types of testing methodologies exist to consider: detection of a nucleic-acid sequences, detection of a particular mutation or SNP, and quantitative analysis of a specific sequence. The goal here is to establish whether the strategic menu can “fit” onto one or two technical platforms. To achieve this goal consider several ancillary questions to see if it is possible to use fewer technologies:

1. Do the selected platforms accommodate the full spectrum of sample types used for the tests on the lab’s strategic menu?
2. Is the lab’s challenge to address the volume of tests (throughput) or to deal with the complexity of the analytic results?
3. Are the platforms flexible enough to handle added test offering to the lab’s strategic menu?
4. Does the lab really need quantitative or real-time technologies, or would endpoint detection assays suffice?

The discussion surrounding your review of the catalog of genetic methods and the corresponding analytic technologies should lead to the reduction, not expansion, of boxes needed for your lab. Having fewer platforms will facilitate using IT to extract more value from those systems — and make life easier on your personnel.

The circle of design, validation, compliance, and competency
Every molecular test, regardless of the simplicity of its result or the basis of the analytic method used to get the answer, requires interpretation. While few in number, the FDA-approved molecular tests, when performed according to their precise protocols, are understood to have significant problems with false-positives and false-negatives. If personnel assigned to the clinical performance of such tests are not versed in the art of interpretation, liabilities may ensue. The circle of design, validation, compliance, and

Table 1.
<table>
<thead>
<tr>
<th>Test Panel</th>
<th>Molecular Tests Examples</th>
<th>Sample Type</th>
<th>Ordering Physician</th>
<th>How Test Results Are Used</th>
<th>Favord Technical Platform</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women’s Health</strong></td>
<td>HPV, Cytomegolavirus &amp; Herpesvirus</td>
<td>Liquid Pap sample</td>
<td>OB/Gyn</td>
<td>Screening Prenatal</td>
<td>Marker Detection Sensitive Specific</td>
</tr>
<tr>
<td><strong>Molecular Oncology Hematology</strong></td>
<td>Bcl-2 Gene Rearrangements, Leukemia transcript markers, Drug resistance markers</td>
<td>Blood, bone marrow, lymph node</td>
<td>Medical oncologist/hematologist</td>
<td>Disease detection, quantitation and Rx monitoring</td>
<td>End point and real time PCR detection with quantitation</td>
</tr>
<tr>
<td><strong>Molecular Oncology Solid tumors</strong></td>
<td>Colon cancer, MSI, Oncogene/Suppressor gene mutational analysis, Cancer marker transcripts</td>
<td>Paraffin embedded tissues</td>
<td>Surgical and medical oncology Pathology</td>
<td>Disease prognosis and treatment planning</td>
<td>Satellite marker detection, sequencing and real time detection with quantitation</td>
</tr>
<tr>
<td><strong>Infectious Disease</strong></td>
<td>Fungal organisms: TB, fungi, Drug resistance markers, Viral load genotypes</td>
<td>Tissue specific Small biopsies, Swabs and culture material</td>
<td>Pediatrics Internal medicine</td>
<td>Disease detection</td>
<td>End point detection Real time detection with quantitation</td>
</tr>
<tr>
<td><strong>Respiratory Panel</strong></td>
<td>Influenza viruses, CMV, HSV, TB and fungi common in Immunosuppression</td>
<td>Bronchial lavage, sputum and small bi</td>
<td>Pulmonary medicine Transplant surgery</td>
<td>Cystic fibrosis from small or rare diseases</td>
<td>Marker detection Sensitive Nonquantitative</td>
</tr>
<tr>
<td><strong>Inherited Diseases</strong></td>
<td>Cystic fibrosis, Fragile X syndrome, Muscle dystrophy, Neurodegeneration</td>
<td>Blood</td>
<td>Medical genetics Pediatrics Neurology</td>
<td>Diagnosis confirmation</td>
<td>Mutational Analysis-multiple methods</td>
</tr>
</tbody>
</table>

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Competency must be part of a lab’s strategic plan to develop the tools and the metrics to evaluate performance for every test on the menu — regardless of its FDA status — as well as to train personnel.

The prepared molecular-diagnostics lab assumes nothing and prepares for every contingency. The expansion of the molecular inspection checklist is a testament to that fact. This means that every test on the strategic menu undergoes the “in-house” evaluation of its likely everyday performance for each of the proposed sample types with each of the available extraction methods and with all available sets of hands. The integrated molecular lab works to invest in the infrastructure that readily checks these measures against current and historical benchmarks. The centerpiece of this effort is IT.

Prospective planning as to what should be measured before a test is offered is key to supporting a strategic menu. Consider the construction of one measurable output integrated into the IT system for every standard operating procedure in the laboratory manual. Some examples of this include reagents-utilization monitors, swab test for surveillance of PCR contamination, and random sampling of DNA for purity and integrity. Sadly, few off-the-shelf IT systems have even moderately sophisticated features such as these to support molecular-lab bench work. Just as there is the common practice of piecemeal integration of bench operations, IT systems are non-uniform and piecemeal as well.

**The hub: IT infrastructure**

At the heart of an integrated molecular lab is a robust IT system. There is little choice of a comprehensive IT solution among the producers of the large LIS. Home-grown solutions, often based on “spreadsheet” technology (to enter and compare one test to another) are too cumbersome and inefficient to be sustained by a lab executing its strategic plan and likely to grow fast as molecular labs tend to do. Contemporary IT systems have the capability to “pull” data from essentially any analytic instrument. Once captured, these data can be collated into a variety of reports including concurrent batch-type reviews (historical data that tallies comparable assays) and to produce patient-specific interpretative reports. Combining these features with transmission and connectivity via the Internet means that experts, wherever they reside, can see and interpret molecular tests in real-time.

Capturing the output of data from a host of lab instruments, including those that produce fluorescent signals, analog and numerical values, and digital pixels from image-capture technologies and their respective analyses, can be reconstructed into displays that lend to interpretation of those results. This information — along with the complementary patient-specific identifiers and demographics — make possible the creation of combinations of integrated patient reports that bring together complementary diagnostics panels of molecular and non-molecular results. Examples include combining Pap-smear morphology with HPV tests with/without findings from other STD molecular tests (i.e., chlamydia, *Neisseria*, and herpes simplex).

Such reports are what clinicians want and — along with those patient-specific results — additional factors that measure a lab’s performance over time and across intervals with the same patients. These can be part of quality control, quality assurance, and quality improvement. Only when the lab IT system can pull data from all of the assay platforms can such quality programs be constructed.

Finally, it is important to accept the fact that most clinicians view the results of the molecular test as ancillary or adjunctive information, often to support the more conventional diagnostics modalities. Attempts to routinely “correlate” such combinations of information are prerequisite for the integrating IT system. Offering such data as part of periodic quality reports to requesting physicians leads to more appropriate utilization of those services and highlights the greater value of the molecular information. In this sense, the molecular result will most often be the “integrating” piece in the diagnostic puzzle.

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