Important considerations in exploring the value of bringing molecular testing in your lab

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Learning objectives

1. Describe the current environment of molecular diagnostics in the clinical laboratory

2. Discuss the key considerations to evaluate whether molecular diagnostic testing is appropriate for your laboratory
Genomics is driving personalized medicine

Mardis ER. Nature. 2011;470:198-203
“Precision” therapeutics can be directed by molecular diagnostics

Cancer patients
• Metastatic/recurrent
• Incident

Patients without identified genomic markers: pursue alternative treatments

Patients with identified genomic markers: match to targeted therapy
MDx can be categorized by testing type

- Genetics
- Infectious diseases
- Oncology
- Pharmacogenetics
MDx tests are rapidly growing

- Academic laboratories report 14-18% annual increase in molecular tests
  - Non-MDx tests at same institutions 2-5% annual increase

- Market analysts predict 11% US annual growth in MDx

Billable MDx are similarly increasing

![Bar chart showing billable MDx, billions from 2010 to 2020, with projected growth.](chart.png)

Potential rationales for offering MDx:

- Respond to clinical needs
- Establish institutional leadership
- Reduce send-out expenses
- Differentiate lab from competitors
- Increase lab revenues
Key considerations for MDx lab

- Strategic planning
- Regulations and guidelines
- Clinical utility
- Facility requirements
- Lab operations (TAT, reflex testing)
- Instrument platform(s)
- Personnel
- Quality, proficiency testing, and accreditation
- Pro forma, business case financials
- Coding and billing
- Sales and marketing
Professional societies and regulatory agencies provide practice guidance
Molecular expertise required for novel tests

**Established test**
- Demonstrated clinical utility
- Reimbursement clear
- Test likely offered at large reference laboratories
- IVD assays may be available

**Novel, Lab-developed test (LDT)**
- Does literature support clinical utility?
- Assess reimbursement
- Design novel assay
- Requires extensive validation
- Complex assay set-up
Is my test available as an FDA IVD?

CLIA requires significant validation documentation for all LDTs

<table>
<thead>
<tr>
<th>CLIA performance characteristic</th>
<th>Molecular-adapted definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accuracy</td>
<td>Degree of agreement b/t assay and reference sequence; concordance</td>
</tr>
<tr>
<td>Precision</td>
<td>Repeatability (within-run precision); reproducibility (between-run precision)</td>
</tr>
<tr>
<td>Analytical sensitivity</td>
<td>Probability true positives will be detected</td>
</tr>
<tr>
<td>Analytical specificity</td>
<td>Probability assay will not identify a variant when none are present (false positive rate is helpful)</td>
</tr>
<tr>
<td>Reportable range</td>
<td>Region of gene/genome test accurately detects variants</td>
</tr>
<tr>
<td>Reference range</td>
<td>Variants detectable by assay expected to occur in an unaffected population</td>
</tr>
</tbody>
</table>

Respond to clinical needs: 3 vignettes

1. A prestigious clinician sends a specimen to the lab requesting Test X

2. A clinician returns from a professional meeting full of news about Test X, which she claims will be ordered on many patients

3. A vendor contacts you about Test X and claims that it will help patients, physicians, and the laboratory
Establishing clinical utility

• Tier 1: The 3-step evidence check (est <30 min)
  • Access the vendor’s materials
  • Browse PubMed
  • Check articles’ abstracts

• Tier 2: Exploring in more depth, if necessary (est 30-60 min)
  • Reading the full text of study or studies from Tier 1
  • Only necessary if red flags raised during Tier 1

• Tier 3: Consider test-specific and patient-specific recommendations and prerequisites
  • Germline testing requires genetic counseling
  • Somatic testing must start with tumor tissue
Facilities: unidirectional workflow essential

- Nucleic acid isolation
- Amplification
- Detection post-amplification
Differential pressure facilitates containment

- Nucleic acid isolation
  - Negative pressure

- Amplification
  - Negative pressure

- Detection post-amplification
  - Negative pressure

Maintain airflow inward to contain nucleic acids, especially when amplified.
Assess turnaround time requirements

- Is batch testing acceptable?
  - Typically yes for inherited diseases
  - Shorter TAT may be required for infectious disease testing
  - Variable for pharmacogenetics and oncology

- If immediate testing is necessary…
  - Will MDx be offered in a central lab or satellite labs?
  - Trained personnel must be available

- Communication with clinicians is key!!
Prevention and control of MRSA infection

- Methicillin-resistant *Staphylococcus aureus* (MRSA)
  - Causes healthcare-associated bloodstream and catheter-related infections
- Rapid tests in select patient populations advocated to limit spread of infections
- Multiple methods available
  - Lab-developed tests (real-time PCR based)
  - Closed systems
Lab-developed tests vs closed platforms

- Extract DNA
- Real-time PCR set-up
- Amplify
- Analyze

BD MAX MRSA assay
Clinical need will dictate assay design

Korf BR and Rehm HL. JAMA 2013; 309: 1511-1521
Hereditary thrombophilia

• Risk of hereditary thrombophilia from factor V Leiden (c.1601 G>A) and prothrombin G20210A (c.*97G>A) variants

• People with these variants have an increased risk of abnormal blood clotting, specifically
  • Deep venous thrombosis
  • Slightly increased risk of miscarriage

• FVL variant present in ~5% of Caucasians
• Prothrombin variant ~2% of Caucasians

• However, many people with these variants do NOT develop abnormal blood clots
Methodology depends on multiple factors

- Risk of hereditary thrombophilia from factor V Leiden (c.1601 G>A) and prothrombin G20210A (c.*97G>A) variants
- Platforms range from lab-developed test to FDA IVD
Clinical need will dictate assay design or need for reflex testing.

Specific mutation in a specific gene in all affected individuals.

Multiple potential mutation sites in a specific gene in affected individuals.

Multiple potential mutation sites in several genes in affected individuals.

Non small-cell lung cancer (adenocarcinoma).

Korf BR and Rehm HL. *JAMA* 2013; 309: 1511-1521.
Multiplexing may offer advantages over single gene testing: NSCLC

**Single gene testing**
- Single gene (KRAS)
- Limited region
  - Narrowly targeted
  - Result may trigger additional gene testing

**Multiple gene testing**
- All relevant genes (KRAS, EGFR, ALK translocations)
- Simultaneously determine mutation status
  - Cost effective
  - Specimen/tissue-sparing
  - Efficient/time-saving
  - Yields unexpected findings
Personnel expertise requirements vary by test complexity

1. **Low** complexity
   - Clinical laboratory associate or entry-level clerk can perform

2. **Moderate** complexity
   - Clinical laboratory scientist OR
   - Trained medical technologist with experience

3. **High** complexity
   - Clinical molecular biologist OR
   - Technologist with experience using platform on regular basis
Personnel expertise requirements vary by test complexity

- Cepheid GeneXpert: Moderate complexity
- Lab-developed PCR assay: High complexity

- National regulations apply (CLIA, CAP)
- State guidelines may also exist
Reference materials and proficiency testing

• Reference materials
  • Commercial vendors
  • For rare genetic diseases, previous patient samples
  • Laboratory-synthesized (plasmids)

• Proficiency testing may not be available for all assays
  • Alternative assessment is necessary
  • Sample exchange with another laboratory
  • Sample splitting
  • Commercially available assayed materials
Getting started: cystic fibrosis

• Clinical population
  • Diagnostic testing
  • Carrier screening

• Desired sequence – reflex testing is an option
  1. Common mutations (ACOG/ACMG recommended 23 mutations)
  2. Expanded mutations (<200)
  3. Full gene sequencing

• Platform selection
  • IVD assays available for common mutations
  • Turnaround time increases with increasing complexity
Cost accounting: calculate *all* costs

<table>
<thead>
<tr>
<th>Category</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>New equipment costs</td>
<td>Acquisition cost for new test equipment</td>
</tr>
<tr>
<td></td>
<td>Interest and depreciation</td>
</tr>
<tr>
<td></td>
<td>Service and maintenance contracts</td>
</tr>
<tr>
<td></td>
<td>Setup, validation, and training costs</td>
</tr>
<tr>
<td>Direct laboratory costs</td>
<td>Reagents and supplies</td>
</tr>
<tr>
<td></td>
<td>Labor to process test</td>
</tr>
<tr>
<td>Indirect laboratory costs</td>
<td>Management and supervision costs</td>
</tr>
<tr>
<td></td>
<td>Quality assurance personnel and programs</td>
</tr>
<tr>
<td></td>
<td>Employee benefits</td>
</tr>
<tr>
<td></td>
<td>Other laboratory equipment costs</td>
</tr>
<tr>
<td>Overhead costs</td>
<td>Business office expenses</td>
</tr>
<tr>
<td></td>
<td>Client services</td>
</tr>
<tr>
<td></td>
<td>Administration and general</td>
</tr>
<tr>
<td></td>
<td>Courier and transport expenses</td>
</tr>
<tr>
<td></td>
<td>Utilities and building costs (rent)</td>
</tr>
<tr>
<td></td>
<td>Sales and marketing</td>
</tr>
<tr>
<td></td>
<td>Benefits</td>
</tr>
<tr>
<td></td>
<td>Information systems</td>
</tr>
<tr>
<td></td>
<td>Other (telephone and miscellaneous)</td>
</tr>
</tbody>
</table>

Bolick DR. *Arch Pathol Lab Med.* 2003; 127: 984-990
Calculating cost savings: reference lab testing

<table>
<thead>
<tr>
<th>Category</th>
<th>Unit cost</th>
<th>General formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual volume 5000 tests/year</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pre-analytical costs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supplies</td>
<td>$.50</td>
<td>1 tube, phlebotomy supplies</td>
</tr>
<tr>
<td>Labor</td>
<td>$3.00</td>
<td>10 min ($0.30/min)</td>
</tr>
<tr>
<td>Transport</td>
<td>$2.50</td>
<td>10 min ($0.25/min)</td>
</tr>
<tr>
<td>Accessioning</td>
<td>$.90</td>
<td>3 min ($0.30/min)</td>
</tr>
<tr>
<td>Specimen preparation</td>
<td>$1.50</td>
<td>5 min ($0.30/min)</td>
</tr>
<tr>
<td>Total preanalytic cost</td>
<td></td>
<td>$8.40 per sample</td>
</tr>
<tr>
<td><strong>Analytical costs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference lab charge</td>
<td>$50</td>
<td></td>
</tr>
<tr>
<td>Total analytic cost (per test)</td>
<td></td>
<td>$257,500</td>
</tr>
</tbody>
</table>

MacMillon D. *Clin Chim Acta* 2014; 427: 123-126
Cost accounting: fictitious example

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unit cost</th>
<th>General formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analytical costs — each analyte</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reagent</td>
<td>$.75</td>
<td>$75/100 tests kit</td>
</tr>
<tr>
<td>Quality control</td>
<td>$1.40</td>
<td>3 levels/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$70,000/year</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50,000 tests/year</td>
</tr>
<tr>
<td>Semivariable (labor)</td>
<td>$.42</td>
<td>5 min ($.42/min) per specimen</td>
</tr>
<tr>
<td>Fixed</td>
<td>Unit cost</td>
<td></td>
</tr>
<tr>
<td>Service</td>
<td>$.05</td>
<td>$2500/year</td>
</tr>
<tr>
<td>Analyzer</td>
<td>$1.00</td>
<td>$50,000/year</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50,000 tests/year</td>
</tr>
<tr>
<td>Laboratory indirect (overhead)</td>
<td>$1.00</td>
<td>Total costs/total laboratory volume</td>
</tr>
<tr>
<td>note 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organization indirect (overhead)</td>
<td>$1.00</td>
<td>Total cost/sq ft</td>
</tr>
<tr>
<td>note 2</td>
<td></td>
<td>Total cost/ft</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total cost/invoice</td>
</tr>
</tbody>
</table>

Total pre-analytical cost $6.90 per sample

Total analytical cost $5.62 (each analyte) and total analytical cost $28.10 (each panel).

5-test set
Annual volume
10,000 sets
50,000 tests
## Cost accounting framework: HPV break-even analysis on the Qiagen Hybrid Capture 2

<table>
<thead>
<tr>
<th>Component</th>
<th>Unit cost</th>
<th>General formula</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Analytical costs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reagent</td>
<td>$30/test</td>
<td></td>
</tr>
<tr>
<td>Non-kit disposables</td>
<td>$1.71/test</td>
<td>$18.69/run</td>
</tr>
<tr>
<td>Labor (MT)</td>
<td>$1.77/test</td>
<td>5.3 min/test</td>
</tr>
<tr>
<td>Labor (Assistant)</td>
<td>$0.67/test</td>
<td>4 min/test</td>
</tr>
<tr>
<td><strong>Fixed costs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HC2-specific equipment</td>
<td>$1.62/test</td>
<td>4632 test/y</td>
</tr>
<tr>
<td>Service</td>
<td>Not included</td>
<td></td>
</tr>
<tr>
<td>Laboratory indirect</td>
<td>$6.25/test</td>
<td></td>
</tr>
</tbody>
</table>

- Intended as an illustrative example
- Break-even with numerous assumptions is 4,632 tests/year

Bolick DR. *Arch Pathol Lab Med.* 2003; 127: 984-990
Additional financial considerations

• Cost of molecular assays must be considered in light of the patient’s care

• MRSA
  • MRSA screening costs are high
  • Payers may not reimburse healthcare-acquired infections
  • Decreasing the number of ICU hospital days has a significant financial impact that may outweigh screening costs

• AML
  • Poor prognosis from molecular tests expedites bone marrow transplant
  • Overall reimbursement for BMT may support molecular testing
Reimbursement is challenging

- 2013 CPT codes are being refined
- CMS Medicare Administrative Contractors (MACs) have different practices
- Each organization has a unique relationship with payers

- Available benchmarks
  - Current reimbursement from send-out testing
  - For established tests, CMS is becoming more transparent and has published reimbursement values
Potential rationales for offering MDx

- Respond to clinical needs
- Reduce send-out expenses
- Increase lab revenues
- Differentiate lab from competitors
- Establish institutional leadership
Infrastructure for large commercial labs

- Insurance relationships: one-stop shopping
- Service centers and/or phlebotomists
- Courier/transport services
- Interfacing
- Sales force
- Marketing
- Billing system
What will distinguish your laboratory?

- Clinical information
- Relationships with patients, clinicians, practices
- Early access to new inventions/technologies
- Flexibility
- Education and training
Conclusions

• Human genome sequence and plummeting costs of genomic analyses are driving molecular testing

• Clinical utility and validity are essential

• Extensive strategic planning is required prior to implementation

• Laboratories must leverage their unique expertise and clinical relationships
Additional resources

- Regulatory and accreditation agencies
  - FDA IVD database, CAP checklists, CDC quality guidance and reference materials
- Clinical Laboratory Standards Institute (CLSI)
  - Molecular-specific guidelines (MM-19 “Establishing molecular testing in clinical laboratory environments”, others)
  - Quality guidelines (QM)
  - General laboratory guidelines (GP)
- Professional society resources
  - AACC, ACMG, ASM, AMP, CAP
Questions?