NGS Testing in Today’s Precision Medicine Landscape

What Labs are Running and What Your Lab should do now

Chris Callahan,
Chief Operating Officer and Executive Vice President
Today
- Full suite of software and services
- Independent CLIA/CAP “dry lab”
- 40+ medical center, cancer center, health system, and reference lab clients
- 200+ yrs of clinical genomics experience

2014
- PierianDx est. after ~50 labs visit WashU to learn how clinical NGS is operationalized.

2011
- WashU among first to validate and clinically report on somatic cancer NGS panels.

2003
- WashU plays critical role in Human Genome Project.

Pioneers in Precision Medicine
Leaders in Clinical Genomics
Overview

1. Recent Trends
2. ROI to Bringing Testing In House
3. What Your Laboratory Should Do Now
Recent Trends

NGS Testing is Coming of Age

Key Findings

- AMCs and NCI Centers have brought clinical NGS in-house
- Physicians in community still sending out to reference labs
- Some laboratories have implemented reflex testing for certain tumor types
- Despite improved coverage, cost and reimbursement can be challenging

Pathologists anticipate an increase in NGS-based testing moving forward as coverage landscape continues to improve and more targeted therapies get approved

Anticipated Growth of NGS Testing Market

Source: Epstein Health
Recent Trends

CMS’ National Coverage Decision

Two Pathways for Coverage

CMS has created 2 pathways for coverage for next generation sequencing in advanced cancers for FDA-approved or cleared companion diagnostics:

- CMS-identified, Covered Assays
  - FoundationFocus™ CDxBRCA (Foundation Medicine)
  - F1CDx (Foundation Medicine)
  - Oncomine™ Dx Target Test (Thermo Fisher Scientific, Inc.)
  - Praxis™ Extended RAS Panel (Illumina)

On March 16, 2018 CMS released a national coverage determination to cover NGS in patients with cancer.

Source: BHA Analysis

The NCD preserves a Medicare coverage pathway for LDTs through the LCD process

Private payors are covering for their managed Medicare lives, but not uniformly for commercial lives
Recent Trends

Key Reimbursement Updates

Oncology
- Molecular testing in advanced cancers expected to move from single marker to NGS
- NGS testing will expand when coverage is widely established

NGS Coverage
- Payors are moving toward mutation-based coverage policies
- Private payors don’t embrace coverage with evidence development but there is movement to incorporate real-world evidence in coverage decisions
- MolDx program expected to expand

Payer Cost Control
- Outsourcing to laboratory benefit managers is creating additional bureaucracy for laboratories
- Several private payors have a desire to engage in risk-sharing agreements/value based contracting in oncology but may have challenges implementing given cost and complexity

Coding and Payment
- Coding and payment for NGS has evolved considerably with a move toward bundled or test-specific coding as opposed to stacked coding
- There are recent examples of incremental reimbursement for FDA-approved testing from Medicare but similar examples aren’t expected from private payors

Regulatory
- FDA is seeking to oversee and regulate LDTs; this will likely push labs to adopt FDA-approved kits whenever possible
- Class-based CDx labeling will change the pharma-Dx partnering landscape with the potential for more consortia-type agreements

Source: Boston Healthcare Associates Analysis
## What Type of Tests are Labs Running?

<table>
<thead>
<tr>
<th>NGS Testing</th>
<th>Biomarker Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>More laboratories performing NGS for common tumor types with approved therapies</td>
<td>Progressive increase in oncology due to tumor agnostic biomarkers developed to inform targeted and immune therapies</td>
</tr>
<tr>
<td><strong>Tumor agnostic</strong> markers, such as MSI, TMB and NTRK fusions are significant driver of more NGS testing</td>
<td><strong>Standardized testing algorithms</strong> drive biomarker testing for common tumors (NSCLC, CRC, breast) at diagnosis at many healthcare settings</td>
</tr>
<tr>
<td><strong>Improving payor coverage</strong> with recent Medicare coverage for FDA-approved NGS tests</td>
<td></td>
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</table>

*“Explosion of biomarker testing. It’s been huge in the lung field, expanded in breast and colon. I think it's being used more in thyroid. I can't speak to the other rare tumor types. I know we'll do an NGS panel on tumors when we are unclear on primary diagnosis or we are looking for targeted therapy.”*

- Pathologist, Community Hospital

*Growth of NGS testing for TMB, and MMR proficiency with a view towards immunotherapy* and more generally, an increase in testing to qualify patients for therapy.”

- Pathologist, Community Hospital

Source: BHA Analysis

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Oncology Testing is Evolving

Recent Trends

**Single Markers and Hotspot Panels**
Specific patient populations are tested for specific biomarkers using conventional methods (e.g., EGFR PCR for NSCLC)
Limits on tissue availability make this approach less sustainable long-term

**Multi-Modality**
Mix of test methods gives best picture
Possible reflex test patterns with some tests being prioritized because of their ease of use/affordable cost
Some FDA approved; some LDTs

**Broad NGS Testing**
NGS / CGP increasingly dominates conventional methods (e.g., PCR, FISH)
Use of a single test on a single sample to obtain a comprehensive biomarker status of the patient

Informatics deployed to create genotypic and phenotypic profile of patient
What if, instead of multiple tests, you could perform a single test that looked at all relevant biomarkers simultaneously?
CGP Can Identify Actionable Alterations

Recent Trends

<table>
<thead>
<tr>
<th>30%–90%</th>
<th>Of patients who undergo Genomic Profiling may have actionable alterations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2 Studies with pediatric solid tumors</strong></td>
<td><strong>Prospective Clinical Trials—843 patients with advanced cancers</strong></td>
</tr>
<tr>
<td><strong>500 patients with advanced cancer, multiple tumor types</strong></td>
<td><strong>96 patients with multiple tumor types</strong></td>
</tr>
<tr>
<td>31–39%</td>
<td>49%</td>
</tr>
<tr>
<td></td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td>90%</td>
</tr>
</tbody>
</table>

% of patients found to have an ACTIONABLE genetic alteration, after genomic profiling

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Recent Trends

CGP Has Value in Patient Management

- **Increase Clinical Trial Eligibility**
  - Greater than 1000-fold
  - Increase from 4% to 54%

- **Increase Targeted Therapy**
  - Utilization projected to double
  - Increase from 6% to 13%

- **Reduce Adverse Events**
  - Decreased by one-third
  - Reduction of 33%

- **Reduce Costs of Non-targeted Therapy**
  - Cost decreases by $6.6M
  - Decrease of $6.6M

Insourcing NGS Testing

Molecular diagnostic market size is projected to reach $10.12 Billion from $6.54 Billion in 2016, at a CAGR of 9.1%.

As most diagnostic tests are performed in-house, the hospital & academic laboratories segment is expected to dominate the market.

Hospitals billing for comprehensive genomic profiling (CGP)

Today, most of the CGP volume is going to a few independent reference labs.¹

However, academic medical centers and community hospitals are expected to insource more of these tests now that there’s a clear pathway to reimbursement.
Why Bring NGS Testing In-House
Return on Investment
### Gain Control, Reduce Costs, and Expand Leadership

<table>
<thead>
<tr>
<th><strong>Control</strong></th>
<th><strong>Costs</strong></th>
<th><strong>Leadership/ROI</strong></th>
</tr>
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<tbody>
<tr>
<td><strong>Tissue Quality Workflow</strong></td>
<td><strong>Achieve reduction in QNS by performing in-house</strong>&lt;sup&gt;4&lt;/sup&gt;</td>
<td><strong>Limit need for rebiopsy</strong></td>
</tr>
<tr>
<td></td>
<td>■ QNS as high as 27% in NSCLC&lt;sup&gt;2&lt;/sup&gt; send-out tests</td>
<td>■ Reduce costs associated with invasive and risky tissue biopsies&lt;sup&gt;3,6&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>■ University of Vermont has a QNS of 1-2% by bringing testing in-house&lt;sup&gt;1&lt;/sup&gt;</td>
<td>■ Dartmouth has achieved cost savings of 77% in direct variable costs compared with send-outs. When considering labor and other fixed costs, the hospital saved 39%&lt;sup&gt;1&lt;/sup&gt;.</td>
</tr>
<tr>
<td></td>
<td><strong>Decrease TAT</strong></td>
<td><strong>Reduce spend to send-out laboratories</strong></td>
</tr>
<tr>
<td></td>
<td>■ TAT for send-outs is 21+ days</td>
<td>■ Dartmouth has achieved cost savings of 77% in direct variable costs compared with send-outs. When considering labor and other fixed costs, the hospital saved 39%&lt;sup&gt;1&lt;/sup&gt;.</td>
</tr>
<tr>
<td></td>
<td>■ Pull data from qual survey</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Adverse Events Testing</strong></td>
<td><strong>Accumulate Valuable Data</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Market Value Data</strong></td>
<td>■ Attract/retain patients&lt;sup&gt;5,7&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td><strong>Leadership/ROI</strong></td>
<td>■ Improve relationships with payors/providers&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ Recruit top talent&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ Increase clinical trial referrals&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Research</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ ACO/Population health</td>
</tr>
</tbody>
</table>

**Sources:**
4. Comprehensive Validation of Cytology Specimens for NGS and Clinical Practice Expertise. 2018
5. The High Cost of Cancer Treatment. AARP. 2018.
ROI to Bring NGS Testing in House

Survey of Early Adopters

<table>
<thead>
<tr>
<th>Reason for Insourcing NGS</th>
<th># of Institutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demand from clinicians</td>
<td>★ ★★ ★★</td>
</tr>
<tr>
<td>Anticipated efficiencies</td>
<td>★ ★★ ★★</td>
</tr>
<tr>
<td>Gain expertise in tech, informatics</td>
<td>★ ★★ ★★</td>
</tr>
<tr>
<td>Advance personalized medicine</td>
<td>★ ★★ ★★</td>
</tr>
<tr>
<td>Institutional stature</td>
<td>★ ★★ ★★</td>
</tr>
<tr>
<td>Value for research</td>
<td>★ ★★ ★★</td>
</tr>
<tr>
<td>Improved TAT for Molecular DX</td>
<td>★ ★★ ★★</td>
</tr>
<tr>
<td>Develop in-house expertise</td>
<td>★ ★★ ★★</td>
</tr>
<tr>
<td>Desire to provide leadership</td>
<td>★ ★★ ★★</td>
</tr>
<tr>
<td>Competitive market advantage</td>
<td>★ ★★ ★★</td>
</tr>
<tr>
<td>Reduce overall cost in clinical care</td>
<td>★ ★★ ★★</td>
</tr>
</tbody>
</table>

★ Most cited benefits from PierianDx customers
ROI to Bring NGS Testing in House

Financial Data from Dartmouth

<table>
<thead>
<tr>
<th>NGS Panel</th>
<th>Direct Variable</th>
<th>Complete Cost</th>
<th>If Sent Out</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myeloid</td>
<td>~$75,000</td>
<td>~$215,000</td>
<td>~$325,000</td>
</tr>
<tr>
<td>Lung</td>
<td>~$70,000</td>
<td>~$175,000</td>
<td>~$300,000</td>
</tr>
<tr>
<td>Melanoma</td>
<td>~$20,000</td>
<td>~$50,000</td>
<td>~$90,000</td>
</tr>
<tr>
<td></td>
<td>~$165,000</td>
<td>~$440,000</td>
<td>~$715,000</td>
</tr>
</tbody>
</table>

Savings

76.79% to Lab
38.57% to Institution

*Data figures were altered for confidentiality. Savings are accurate.

“It does make financial sense to [insource]...The goal for our lab is to maintain the send-out volume at less than 5% and keep the send out costs at about 7-8% of the total operating costs for the lab.”

Eric Loo
Asst. Professor, Pathology & Lab Medicine

How to Bring NGS Testing In-House

Recommended Strategies
What Your Lab Should Do Now

What We Have Learned

| Initiate Planning | Institutional Approval | Procure Equipment | Training and Optimization | Test Validation | Pre-Launch Preparation | Go-Live |

How We Can Help

- Scarcity of informatics expertise
- Validation of clinical testing protocols
- Amount of data to curate
- Rapidly changing nature of technologies
- Expense of implementation
- Reimbursement Uncertainty

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Align with Your Larger Organization

Identify key stakeholders and clinical areas
Evaluate your organization, identify stakeholders and key strengths, secure funding, and develop a plan. Consider what other internal initiatives are synergistic.

Take a multidisciplinary approach
Collaborate with laboratory personnel, oncologists, bioinformaticians, and other staff to build a test menu that physicians want to order from

Think about how data will be used
- Align with research?
- Biobank?
- Integration with EMR or other phenotypic database?
- Data warehouse?

“We fundamentally believe that genomically-informed clinical care involves strategic integration of the best genomic technology, with people and processes beyond the laboratory to realize the promise of precision medicine for each unique patient.”

Nikoletta Sidiropoulos
MD, Associate Professor and Director of Molecular Pathology

Align with Your Larger Organization

What Your Lab Should Do Now

Identify Clinical Need

Examine Institutional Strengths

Examine Institutional Priorities

Establish Business Plan

Prioritize Initial Clinical Applications

Develop Project Plan

Obtain Institutional Approval

Implement

Monitor

Based on recommendations from the CAP Personalized Health Care Committee

A CLIA/CAP certified lab is allowed to outsource any of the three components to another CLIA/CAP certified lab.

Consider a Distributive Model
Take a Strategic Approach to Test Menu

One Example

<table>
<thead>
<tr>
<th>Solid Tumor</th>
<th>All Solid Tumor</th>
<th>All Solid Tumor</th>
<th>TSO 500</th>
<th>TSO 500</th>
<th>TSO 500</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoid, Myeloid</td>
<td></td>
<td></td>
<td>Liquid Biopsy</td>
<td>Liquid Biopsy</td>
<td></td>
</tr>
<tr>
<td>Lymphoid</td>
<td></td>
<td></td>
<td>ArcherDx Myeloid</td>
<td>ArcherDx Myeloid</td>
<td></td>
</tr>
<tr>
<td>Hereditary Cancer</td>
<td></td>
<td></td>
<td>TruSight Cancer</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Today 3 Months 6 Months 12 Months 2+ Years
Address the Interpretation Bottleneck

Interpretation of the clinical significance of genomic alterations remains the most severe bottleneck preventing the realization of personalized medicine in cancer.

Good, et al. Organizing knowledge to enable personalization of medicine in cancer. Genome Biology 2014
Develop a Reimbursement Strategy

What Your Lab Should Do Now

- High Quality Test
- Actionable Turnaround Time
- Actionable Reporting

Clinical and Economic Evidence

Clinical Validity
- Clinical Utility
- Economic Utility

Coverage and Access

Key to Successful Commercialization

Strategic development of clinical and economic evidence that clearly communicate the test’s value story

Source: BHA Analysis
## What Your Lab Should Do Now

### Develop a Reimbursement Strategy

<table>
<thead>
<tr>
<th>Payor Tool</th>
<th>Description</th>
</tr>
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</table>
| Payor Coverage Presentation | 30-min slide presentation which succinctly makes the case for coverage  
                           | Shown to payor medical directors by payor relations group, medical science liaison, local KOL physician supporters |
| Payor Monograph, Dossier | White paper type document which explains issues with current treatment paradigm and describes the test's impact on treatment |
| Payor Data Binder        | Binder containing the key supportive studies and clinical trial information                                                                |
| Cost/Budget Impact Models | Spreadsheet model which shows savings to payor or benefit to physician in financial terms over 2-3 year timeframe (i.e., avoided treatment costs, etc.) |
| Payor Profiling          | Database of account level information about major relevant payors which can be used to create account-specific tactics for driving positive coverage |

Source: BHA Analysis
Conclusion

1. Recent trends indicate increased NGS testing and in particular, Comprehensive Genomic Profiling.

2. Laboratories can increase quality, reduce costs, and gain expertise by insourcing clinical NGS testing.

3. Align, strategize on test menu and reimbursement, and consider distributing the workload.
Let us Help!

**Technology Enabled Services**

**Clinical Genomics Workspace**
All-in-one informatics and reporting software

**Laboratory Services**
Turnkey, validated assays and informatics

**Validation & Interpretation Services**
Experienced team to fast-track growth

**Medically Powered Knowledgebase**
The largest opt-in content sharing network

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Let Us Help!

Building Your NGS Testing Program?

Resources Available

www.pieriandx.com

Chris Callahan
Chief Operations Officer and Executive Vice President
chris@pieriandx.com
Recent Trends
A Record Number of Personalized Therapies
Recent Trends

Pan-Cancer Biomarkers

- **Approved**
  - Microsatellite Instability
  - NTRK Fusions (Vitrakvi)

- **Emerging**
  - Tumor Mutational Burden

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**Microsatellite Instability**

[Image of a research article]

**NTRK Fusions (Vitrakvi)**

[Image of a research article]

**Tumor Mutational Burden**

[Image of a research article]
Recent Trends

Comprehensive Genomic Profiling (CGP)

Frequency of molecular aberrations in various driver oncogenes in lung adenocarcinomas and current available drugs against these oncogenic proteins.

Recent Trends

Reimbursement Tied to Evidence, Payor Policy

Protecting Access to Medicare Act (PAMA) is ensuring that all codes on the Clinical Lab Fee Schedule are valued according to commercial payor rates.

Coverage and payment for those related to CGP and TMB will be driven by strength of evidence and Payor policy.

Source: CMS CLFS, BHA analysis
Most NGS testing is at the request of the oncologist or treating physician. Reflex testing employed in specific tumor types is a mix of single biomarkers and panels. Many labs indicate NGS testing may be done at initial diagnosis or upon disease progression depending on tumor type/stage.

Source: BHA analysis of qualitative interviews with 30 Pathologists and/or Lab Directors.
### What Your Lab Should Do Now

#### Develop a Reimbursement Strategy

<table>
<thead>
<tr>
<th>Overview</th>
<th>Goal</th>
<th>Tools</th>
</tr>
</thead>
</table>
| **Top Down**  
(Policy level)  
Direct engagement with key decision makers (Medical Director or Tech Assessment Influencer)  
Payor education for access expansion  
Leveraging KOL support  
Driving policy change through evidence and/or guidelines inclusion | Positive coverage policy that can be leveraged by sales force as evidence of assured reimbursement | Payor value dossier/presentation, account profiling, etc. |

| **Bottom Up**  
(Claims level)  
Working at the grassroots level to ensure each test request is bolstered by supporting medical necessity documentation  
Managing/Guiding prior authorization requests with physicians  
Align with payor on preferred coding approach (e.g., code stacks vs. GSP codes)  
Leveraging denied/claims paid to create enough interest in test to encourage Payors to generate a policy and pay for the test | Maximize the number of claims paid, build interest in the test at Payor level | Medical necessity documentation, appeals  
A defined coding strategy: Z-codes should be applied for in advance |

Source: BHA Analysis