Next-Generation Companion Diagnostics; Adoption, Drivers, and Moderators of NGS-based CDx

Companion Diagnostics Forum
Holmdel, NJ
September 13, 2018

Disclaimer –
Some of the companies listed in this document may be DeciBio Consulting clients or customers
With advances in cancer therapies, analytical technologies, and regulatory policies, the CDx landscape is evolving at a disruptive pace.

The objective of this presentation is to share data and insights from oncology stakeholders about the adoption, drivers, and moderators of new and emerging biomarkers and technologies tests in routine care.
To evaluate emerging oncology biomarkers and assess trends, drivers, and moderators of adoption of future CDx, we assessed biomarker activity in clinical trials and conducted a pulse survey of oncology stakeholders.

**Immuno-Oncology BioMAP**

- Internally-curated database of biomarkers of all types and for all purposes identified in ongoing I/O clinical trials
- Currently contains data from ~1,350 trials

**Oncology Stakeholder Pulse Survey**

- N = 147
- Role: Oncologist, Pathologist, Lab Manager/Director, Other
- Institution Type: AMC, Community Hospital, Other
- Lab Type: MDx Lab, Core Lab, Other Labs
- Cancer Focus: Breast Cancer, Lung Cancer, Brain Cancer, Leukemia/Lymphoma, Other Cancers

- N = 147
- Role: Other
- Institution Type: Community Hospital
- Lab Type: Other Labs

- N = 75
- Role: Oncologist, Pathologist, Lab Manager/Manager/Other
- Institution Type: AMC, Community Hospital
- Lab Type: MDx Lab, Other Labs

- N = 72
- Role: Other
- Institution Type: Other
- Lab Type: Lung Cancer, Breast Cancer, Other Cancers

- Two web-based surveys; one for oncologists, and one for lab directors/pathologists conducting CDx testing
- U.S.-focused due to relatively limited N
Analysis of ongoing clinical trials indicates that next-generation oncology biomarkers will be increasingly sophisticated, driven by multiplex- and signature-type read-outs, tissue-independent, and liquid-based biomarkers.

### Top Biomarkers Explored in Immuno-Oncology Clinical Trials

<table>
<thead>
<tr>
<th>Biomarker / Trial</th>
<th>2018-2019</th>
<th>2020-2021</th>
<th>2022+</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-L1 364 97,332</td>
<td>TILs 148 26,904</td>
<td>Immune cell population and phenotype 79 5,878</td>
<td>Cytokine profile 52 5,894</td>
</tr>
<tr>
<td>Gene expression signature 100 19,153</td>
<td>HER2 71 11,561</td>
<td>Genomic mutation profile 49 17,087</td>
<td>CD19 31 2,432</td>
</tr>
<tr>
<td>PD-L1 58 4,504</td>
<td>Estrogen receptor (ER) 42 7,590</td>
<td>CD20 30 3,975</td>
<td>NY-ESO-1 23</td>
</tr>
</tbody>
</table>

#### 2018-2019:
- **TAPUR (1,440 pts)**
  - ASCO-sponsored trial exploring the use of **genomic profiling** for molecularly-driven (**tissue-independent**) treatment

- **BFAST (580 pts)**
  - Roche-sponsored trial using a **blood-based** TMB assay to stratify patients for various targeted and immunotherapies

- **Impower150 (1,202 pts)**
  - Roche-sponsored trial exploring atezo+chemo combo in 1L mNSCLC pts, including a **Teff gene signature** cohort

- **CheckMate-227 (2,200 pts)**
  - BMS-sponsored trial for the use of nivolumab + ipilimumab in combo in **TMB-high** in 1L mNSCLC patients

- **Javelin Parp Medley (316 pts)**
  - Pfizer-sponsored trial exploring TMB and **genomic profiling** to select for patient response (**tissue-independent**)

- **My Pathway (600 pts)**
  - Roche-sponsored trials using **tissue and/or blood-based molecular profiling** to select patients for response (**tissue-independent**)

- **My Pathway (600 pts)**
  - Roche-sponsored trials using **tissue and/or blood-based molecular profiling** to select patients for response (**tissue-independent**)

- **NAVIGATE / SCOUT (288 pts)**
  - Loxo Oncology-sponsored trials using it’s larotrectinib in patients that are **NTRK-fusion+** (**tissue-independent**)

- **NCT02912559 (700 pts)**
  - NCI-sponsored trial exploring the predictive value of numerous biomarkers (e.g., microbiome, GEP, MMR, TMB)

- **NCT03639714 (214 pts)**
  - BMS and Gritstone-sponsored trial exploring **neoantigens** for personalized vaccine therapy

#### 2020-2021:
- **KEYNOTE-161 (60 pts)**
  - Merck-sponsored trial using **single-cell RNA-seq** to assess predictive value of gene expression and neoepitope profiles

#### 2022+:
- **CUPISCO (790 pts)**
  - Roche-sponsored trials using **tissue and/or blood-based molecular profiling** to select patients for response (**tissue-independent**)

- **KEYNOTE-495 (192 pts)**
  - Merck-sponsored trial using a **composite TMB / GEP** score to predict response
Commercial and regulatory developments signify that pharma and diagnostic stakeholders are preparing for the realization of these next-generation biomarkers into routine clinical care in the near-mid term.

<table>
<thead>
<tr>
<th>Regulatory and Reimbursement Developments</th>
<th>Commercial Developments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Loxo Oncology</strong> has submitted for FDA approval its Larotrectinib for use in NTRK+ patients, independent of cancer type; est. decision date 11/2018</td>
<td><strong>Foundation Medicine</strong> has announced plans to develop a gene expression profiling assay and has discussed offering a kitted version of its FoundationOne test</td>
</tr>
<tr>
<td><strong>BMS</strong> has submitted for FDA approval of Nivo + Ipi in TMB high patients; est. decision date: 02/2019</td>
<td><strong>Guardant Health</strong> is currently collaborating with numerous pharma companies on a 500+ gene liquid biopsy assay</td>
</tr>
<tr>
<td><strong>Guardant Health</strong>, <strong>Foundation Medicine</strong>, and <strong>PGDx</strong> have all submitted for FDA approval their liquid biopsy assays for comprehensive genomic profiling; all have received breakthrough device designation</td>
<td><strong>Illumina and HTG</strong> have partnered to develop IVDs based on HTG’s RNA-seq oriented EdgeSeq technology</td>
</tr>
<tr>
<td>Final <strong>CMS NCD</strong> sets reimbursement for 50+ gene panels at ~$2,900 for FDA-approved panels</td>
<td><strong>Qiagen</strong> and <strong>Freenome</strong> have partnered to use Freenome’s AI to support the development of Qiagen’s liquid TMB CDx</td>
</tr>
<tr>
<td></td>
<td><strong>Multiple companies, such as Tempus, Roche, and Cota</strong> are developing ecosystems enabling the integration of real-world clinical data with -omics data</td>
</tr>
</tbody>
</table>
Oncologists and labs have already begun incorporating new and emerging biomarkers and technologies into their treatment workflows; adoption of some biomarkers, such as tissue-independent markers, remains limited.

Current and Expected Near Term Adoption of Emerging Biomarkers by Oncologists

Current and Expected Near Term In-House Adoption of Emerging Biomarkers by Laboratories**

Adoption of CGP varies widely by lab type; ~75% of molecular pathology labs are conducting CGP compared to ~30% of anatomic pathology labs.

Nearly all labs that offer genomic profiling have developed some kind of LDT, while ~35% of these labs also offer a 3rd-party kit (e.g., Oncomine, TruSight).

Note: * CGP = comprehensive genomic profiling; ** AMC and community hospital labs only; ^ GEP = gene expression profiling; ^^ LBx = liquid biopsy – defined as measurement of soluble nucleic acid material in blood; future adoption data not available.
NGS will be a key driver of oncology biomarkers in the future; various market forces are driving NGS (de)centralization; stakeholders expect NGS volumes to remain centralized to AMCs and reference labs in the U.S.

NGS testing will be distributed across all hospitals/sites that evaluate cancer patients. The vast majority of NGS testing will be distributed across all AMCs. Major cancer centers and reference labs will conduct the vast majority of NGS testing. A handful of large reference labs will conduct the vast majority of NGS testing.

Decentralization Drivers:
- NGS IVD kits (e.g., TMO Oncomine, ILMN TruSight, FMI?)
- CMS NCD for NGS, potential LCD
- Affordable, benchtop sequencers (e.g., Illumina MiniSeq/iSeq)
- Simplified workflow solutions (e.g., Qiagen GeneReader)

Centralization Drivers:
- Centralized, proprietary clinico-genomic databases
- Ultra-high throughput sequencers (e.g., NovaSeq) and economies of scale
- Varying assays, complex analyses, bioinformatics requirements (e.g., TMB)

Note: * U.S.-centric view of centralization/decentralization; ex-U.S. markets, particularly in the EU, are considerably more decentralized.
While comprehensive genomic profiling is gaining traction, there remain multiple barriers to broader adoption, primarily cost and data interpretation, the latter of which is a significant barrier for stakeholders in the community setting.

### Barriers to Adoption of Comprehensive Genomic Profiling (relative significance; normalized to 100 = largest barrier)*

<table>
<thead>
<tr>
<th>Adoption Barriers</th>
<th>Oncologists</th>
<th>Pathologists / Lab Dir.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AMC</td>
<td>CH</td>
</tr>
<tr>
<td>Cost / reimbursement</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Too much info w/o implications</td>
<td>61</td>
<td>90</td>
</tr>
<tr>
<td>Turnaround time</td>
<td>68</td>
<td>56</td>
</tr>
<tr>
<td>Difficult interpretation</td>
<td>30</td>
<td>59</td>
</tr>
<tr>
<td>Sufficiency of status quo</td>
<td>31</td>
<td>32</td>
</tr>
<tr>
<td>Not recommended in guidelines</td>
<td>46</td>
<td>47</td>
</tr>
<tr>
<td>Accessibility</td>
<td>24</td>
<td>39</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limited tissue availability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lack of actionability for many markers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limited tissue availability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Competition from reference labs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lack of knowledgeable lab personnel</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Cost / reimbursement was unanimously considered the most significant barrier to widespread adoption of genomic profiling.
  - The next barriers, excessive data and difficult data interpretation, are particularly impactful on community hospitals.
    - These barriers can be more easily remedied by manufacturers (e.g., vs. guidelines, reimbursement).
- Surprisingly, lack of guideline recommendations for CGP was not identified as a major barrier to adoption, indicating a willingness for users to proactively adopt genomic profiling.
- Limited tissue availability, and lack of knowledgeable lab personnel to run increasingly complex genomics assays were cited as additional barriers to adoption.

**Key differences by Institution Type**

* Score represents the weight assigned to each adoption barrier, in terms of significance of that barrier; the scores have been normalized to 100.
While current and expected future adoption of NGS is high, many stakeholders do not feel equipped to conduct many emerging NGS-based biomarkers; stakeholders anticipate limited in-house adoption of other emerging biomarker modalities.

<table>
<thead>
<tr>
<th>Current Ability to Adopt* (% of Labs)</th>
<th>Potential Future Adoption** (% of Labs)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Current Adoption</strong></td>
<td><strong>Would adopt if IVD were available</strong></td>
</tr>
<tr>
<td>Genomic Assay</td>
<td>Would adopt regardless of IVD availability</td>
</tr>
<tr>
<td>Cellomic Assay</td>
<td>Not expected to adopt in house</td>
</tr>
<tr>
<td>Tissue TMB</td>
<td>36%</td>
</tr>
<tr>
<td>CGP; 10 - 50 genes</td>
<td>41%</td>
</tr>
<tr>
<td>LBx; 1-10 genes</td>
<td>37%</td>
</tr>
<tr>
<td>CGP; 51 - 300 genes</td>
<td>22%</td>
</tr>
<tr>
<td>CTC Analysis</td>
<td>20%</td>
</tr>
<tr>
<td>Multiplex Flow Cytometry</td>
<td>18%</td>
</tr>
<tr>
<td>GEP 3 - 10 genes</td>
<td>15%</td>
</tr>
<tr>
<td>Blood TMB</td>
<td>11%</td>
</tr>
<tr>
<td>GEP 10 - 50 genes</td>
<td>7%</td>
</tr>
<tr>
<td>LBx; 10+ genes</td>
<td>5%</td>
</tr>
<tr>
<td>Immune Cell Population Profiling</td>
<td>3%</td>
</tr>
<tr>
<td>TCR Repertoire Analysis</td>
<td>6%</td>
</tr>
<tr>
<td>IGRA / ELISPOT</td>
<td>4%</td>
</tr>
<tr>
<td>Cytokine Profiling</td>
<td>2%</td>
</tr>
<tr>
<td>WES</td>
<td>1%</td>
</tr>
<tr>
<td>WTS</td>
<td>1%</td>
</tr>
<tr>
<td>Multiplex IHC; 4+ markers</td>
<td>1%</td>
</tr>
<tr>
<td>Neoepitope Burden</td>
<td>1%</td>
</tr>
<tr>
<td>None</td>
<td>3%</td>
</tr>
</tbody>
</table>

- ~2/3 of labs surveyed have adopted NGS, however, relatively few labs feel equipped / capable of conducting NGS-based assays
  - This perception may be driven by the workflow and bioinformatics challenges presented by these markers
- Genomic profiling and TMB in both tissue and blood are the markers labs are most able and willing to adopt
- Except for multiplex IHC, anticipated adoption of emerging proteomic and cellomic biomarkers is low
- IVD status and panel size impact expected adoption
  - IVD availability has the highest impact on GEP, LBx, and multiplex IHC adoption

Note: * The share of labs who feel capable (i.e., have the equipment and expertise) of implementing biomarker testing in-house, today, if there was sufficient demand; ** Among those that have not already adopted the platform.
Adoption of these next-generation diagnostics will be driven primarily by demand from oncologists and testing profitability; oncologists weigh various factors when considering whether to adopt a test.

**Factors Influencing Lab Adoption of Biomarker Testing In-House**

- Oncologist Demand
  - Test Profitability
  - Need to Remain Competitive
  - Personnel / Expertise
  - Instrument Requirements
  - Workflow
  - Bioinformatics
  - IVD Availability
  - Reporting Req.

**Drivers of Oncologist Demand**

- Guideline Recommendations
- Conference Findings
- Availability of Validated Assay
- Adoption by Peers
- Drug Label Guidance
- Internal Policies
- Other

- Oncologist-demand is, by far, the most significant driver of adoption for labs
  - Test profitability and competitiveness with other labs are also top drivers of adoption

- For oncologists, conference findings and the assay availability are almost equally as important as guideline recommendations
  - Current adoption of TMB, NTRK, and GEP are examples of how conferences can drive early adoption

- Adoption by peers was identified as considerably more important to oncologists in the community setting than in AMCs
  - Similarly, for laboratories, new instrumentation requirements are considered more important for community hospital labs than AMCs

**Source:** * Laboratory director / pathologist survey; ** Oncologist survey
Based on this data and other research done in this space, we have developed a few takeaway hypotheses on how we expect the CDx market to evolve:

1. There will be moderate decentralization of testing, as targeted panels shift to the community setting, and comprehensive panels and TMB shift to AMCs

2. NGS will begin to capture share from legacy genetic CDx technologies (e.g., FISH, PCR, Sanger) and will bifurcate to small and large panels

3. Biomarkers in the pipeline will provide opportunities for new CDx development beyond NGS
Hypothesis 1: In the U.S., there will be moderate decentralization of NGS CDx, with targeted panels shifting to the community setting and comprehensive panels (and eventually WES) and TMB shifting from reference labs to AMCs

Expectation for increasing in-sourcing of CDx tests?:*

Rationale

- Do not expect to significantly increase adoption of new CDx tests, however, labs indicated highest willingness to adopt IVD targeted panels and TMB
  - Targeted, disease-specific panels are accessible from a workflow, informatics, and economic perspective
    - Additionally, these panels allow labs to maintain a competitive “personalized medicine” edge
    - The emergence of liquid biopsies kits will further drive decentralization due to simplified sampling
  - Adoption of TMB in the community is likely to be hampered by complexity caused by numerous versions of the test with varying cutoffs (similar to PD-L1)

- Academic medical centers expect to increasingly bring testing in house, particularly comprehensive genomic profiling, TMB, and gene expression profiling
  - TMB is expected to become a routine biomarker in the near-mid term; oncologist demand and rising volumes will prompt labs to in-house TMB and comprehensive panels
  - With the help of clinical data analytics companies (e.g., Tempus, Cota), AMCs will increasingly seek to keep samples and information in-house to build valuable data sets

Note: * Survey question asked the degree of agreement / disagreement with the statement: “I expect to decrease the amount of testing I send out to reference labs due to insourcing” with 1 = Strongly Disagree and 7 = Strongly Agree
Hypothesis 2: Labs will transition traditional biomarker tests (e.g., PCR, FISH) to NGS panels, which will bifurcate to small (<30 genes) or large (>300 genes) panels.

Survey feedback suggests that, while PCR, FISH, and CE-sequencing comprise the majority of CDx volumes today, much of that testing will shift to NGS.

- Laboratory stakeholders have indicated that a single NGS assay offers a compelling workflow efficiency compared to multiple, different single-gene assays, and that the net costs are approaching parity.
- Increasing numbers of tissue-independent markers (e.g., NTRK, MSI, RET?, TMB?) will continue to favor panel-based testing.

NGS panel sizes are expected to bifurcate to small (<30 genes) and large (>300 genes), leaving little utility for medium-sized panels.

- Many labs want panels that contain only clearly actionable information (i.e., only those markers with direct and clear implications on treatment), which, today, is only a few-dozen markers.
- Alternatively, TMB generally requires at least ~300 genes-worth of genetic material to yield a reliable mutation count estimate, necessitating the need for panels this size.
- Labs in decentralized settings typically don’t have the know-how to analyze complex data from large panels.

Current and Expected Future Genetic Testing Volume Share by Test Type*

Source: * Laboratory director / pathologist survey
Hypothesis 3: NGS is expected to capture much of the new CDx share in the near-mid term, however, personalized medicines, particularly personalized immunotherapies, will open the door to other CDx assay technologies in the future.

### Increasing Directness of Measure of Tumor Immunogenicity

<table>
<thead>
<tr>
<th>Biomarker Function</th>
<th>TMB</th>
<th>PD-L1 / GEP</th>
<th>Tumor-Infiltrating Immune Cells</th>
<th>Predicted Neoepitopes</th>
<th>True Neoepitopes</th>
<th>Immune Status / Antigen-Specific Immunity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biomarker Function</strong></td>
<td><strong>TMB</strong></td>
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<td><strong>Predicted Neoepitopes</strong></td>
<td><strong>True Neoepitopes</strong></td>
<td><strong>Immune Status / Antigen-Specific Immunity</strong></td>
</tr>
<tr>
<td><strong>Number of Ongoing Trials</strong></td>
<td>~40</td>
<td>~415 (PD-L1) ~130 (GEP)</td>
<td>~220</td>
<td>~25</td>
<td>~80</td>
<td></td>
</tr>
<tr>
<td><strong>Assay Technologies</strong></td>
<td>NGS</td>
<td>IHC</td>
<td>IHC</td>
<td>NGS (WES + WTS)</td>
<td>NGS</td>
<td>IGRA / ELISPOT, ELISA, Flow cytometry, PCR, NGS</td>
</tr>
<tr>
<td><strong>NGS (RNA-seq)</strong></td>
<td>Digital Pathology</td>
<td>Computational Informatics</td>
<td>Mass Spec or other Proteomics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hyb. Arrays (e.g., Nanostring)</strong></td>
<td>PCR</td>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Potential CDx Implications / Impact</strong></td>
<td>Will drive the adoption of next-generation sequencing and, potentially, the consolidation of genetic testing onto NGS</td>
<td>IHC likely to remain a staple CDx technology as histology is rich in information</td>
<td>Spatial context important; may require advanced image analysis algorithms / digital pathology</td>
<td>Diagnostic value lies in the analytics and predictive algorithm</td>
<td>Would likely require proteomics to confirm the presence / sequence of epitopes</td>
<td>May drive new applications for common analytical platforms (e.g., ELISA / ELISPOT, flow cytometry)</td>
</tr>
<tr>
<td><strong>CDx Time Horizon</strong></td>
<td>Today</td>
<td>Near Term</td>
<td>Mid Term</td>
<td>Long Term</td>
<td>Mid Term</td>
<td></td>
</tr>
</tbody>
</table>
Thank you for your time and attention – I am happy to answer any questions

Special Thanks To:

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  o Seth Schachter – Analyst
  o Anne Marie Collins – Summer Analyst

• All stakeholders who participated in primary research

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