Topic Overview

- Evolution of diagnostic testing
- Pre-competitive collaboration
Evolution of Companion Diagnostics
Multi-plex technologies enable a “patient-centric” approach to CDx development

PAST

First CDx
- 1997
- IHC based
- Single target
- CDx for Herceptin

Multi-plex CDx
- 2017
- NGS based
- Multi-target
- CDx for multiple drug partners

The FUTURE is now!
Companion Diagnostic Testing Paradigm Changing

1 drug, 1 indication
HER2 and Herceptin – Breast Cancer Dako IHC

1 drug, 1 disease indication, 1 test, 1 allele
Abbott VYSIS ALK Break Apart FISH Probe for Xalkori®

1 test, 1 indication, >1 drug same alleles
QIAGEN therascreen KRAS RGQ PCR Kit for CRC for 2 therapeutics Eribitux® and Vectibix®

One indication, >1 drug, 2 different tests for the same gene but different allele representation
BRAF V600 mutation
1) Roche Cobas - Zelboraf®
2) BioMerieux THxID BRAF for Tafinlar® & Mekinist®

EGFR Activating Mutations
1) Roche cobas EGFR Mutation for Tarceva®
2) Qiagen therascreen EGFR RGQ PCR Kit for Gilotrif®

Risk for prescribing drugs to wrong patients!


Celgene
Complexity Requires New Solutions

From Dec 2016 through June 22, 2017 – 3 complex NGS assays approved!

Complexity of Testing

Increase in Approved Drugs with Diagnostics

Increase in Biomarker Driven Trials

Oncology

>16 markers
Tissue & ctDNA

Oncology

1997: 1
Therapeutics
2018: >30

Oncology

1990 ~ 5%
2013 ~45%

I&I (SLE example)
2018: ~6%


Celgene
Increase in Complexity Can Cause Confusion for Physicians

<table>
<thead>
<tr>
<th>Approved PD-L1 Assays</th>
<th>Associated Drugs and Associated Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-L1 IHC 22C3 PHARMDX</td>
<td>• KEYTRUDA® / Pembrolizumab by Merck for</td>
</tr>
<tr>
<td>• Dako Agilent Technologies</td>
<td>1) NSCLC 2) Gastric adenocarcinoma</td>
</tr>
<tr>
<td>• Companion Diagnostic</td>
<td>3) Cervical 4) Urothelial carcinoma.</td>
</tr>
<tr>
<td>PD-L1 (SP142) CDX assay</td>
<td>• TECENTRIQ® / Atezolizumab by Genentech</td>
</tr>
<tr>
<td>• Ventana Medical Systems</td>
<td>1) urothelial cancer</td>
</tr>
<tr>
<td>PD-L1 IHC 28-8 PHARMDX</td>
<td>• OPDIVO® / Nivolumab by BMS</td>
</tr>
<tr>
<td>• Dako /Agilent Technologies</td>
<td>1) Non-squamous NSCLC 2) Head and Neck</td>
</tr>
<tr>
<td></td>
<td>3) squamous cell carcinoma 4) Urothelial cancer, 5) Melanoma</td>
</tr>
<tr>
<td>PD-L1 (SP 263) Assay</td>
<td>• IMFINZI® /Durvalumab by Astra Zeneca</td>
</tr>
<tr>
<td>• Ventana Medical Systems</td>
<td>1) Urothelial cancer</td>
</tr>
<tr>
<td></td>
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<td>• OPDIVO/ Nivolumab by BMS</td>
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<td>1) NSCLC</td>
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Increase in Complexity Can Cause Confusion for Physicians

One indication, >1 drug, 2 different tests for the same gene but different allele representation

<table>
<thead>
<tr>
<th>Test</th>
<th>Drug</th>
<th>Biomarkers</th>
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</thead>
<tbody>
<tr>
<td>Roche Cobas EGFR Mutation Test</td>
<td>TARCEVA®</td>
<td>Exon 19 deletions &amp; L858R</td>
</tr>
<tr>
<td></td>
<td>TARGRESSO®</td>
<td>T790M</td>
</tr>
<tr>
<td>Therascreen EGFR RGQ PCR Kit</td>
<td>GILOTRIF®</td>
<td>Exon 19 deletions, L858R</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Safety &amp; efficacy not established in patients whose tumors have L861Q, G719X, S768I, Exon 20 insertions and T790M</td>
</tr>
</tbody>
</table>

Just one example:

- Physician orders EGFR test
- Cobas EGFR mutation may be “test of choice” by the central lab
- Physician may have a preference to prescribe Gilotrif
  - Physician sees positive results from EGFR test and prescribes Gilotrif
- Patient had T790M mutation and prescribing of Gilotrif was “off-label”
Consolidation into a single Multi-plex Assay
Broad-Based Utility – Single Test

Broad Based Panel

Analytical & Clinical Claims

Lung Cancer

Analytical Claims

Clinical
ROS-1, BRAF, EGFR, ALK, etc.

Broad-based Utility

Deployment onto trials for Lung

Stratification, selection or exploratory analysis

Complementary or Companion Dx

Develop panels with multiple potential utilities
MSK-IMPACT What it Is.....

1st example of streamlining the approval process

- MSK-IMPACT is a targeted Next Generation Sequencing (NGS) assay developed by MSKCC
  - Detects select gene mutations and other critical genetic aberrations in both rare and common cancers; targets 468 genes
- The IMPACT assay is a Class II de novo 510K cleared assay for use in single site
  - de novo pathway meant demonstration of substantial equivalence was not required
  - NYSDOH is accredited as a third party reviewer of in vitro diagnostics by FDA
    - MSK-IMPACT – first submission to use third party review process
- The test is intended to provide information on somatic mutations (point mutations and small insertions and deletions) and microsatellite instability

Approved November 2017
**Indications for Use:**
The MSK-IMPACT assay is a qualitative in vitro diagnostic test that uses targeted next generation sequencing of formalin-fixed paraffin-embedded tumor tissue matched with normal specimens from patients with solid malignant neoplasms to detect tumor gene alterations in a broad multi gene panel. The test is intended to provide information on somatic mutations (point mutations and small insertions and deletions) and microsatellite instability for use by qualified health care professionals in accordance with professional guidelines, and is **not conclusive or prescriptive** for labeled use of any specific therapeutic product. MSK-IMPACT is a single-site assay performed at Memorial Sloan Kettering Cancer Center.

- It is **not** a Companion Diagnostic
- Should *not* be used for making treatment decisions for targeted therapies
• First breakthrough designated device taken through the process
  • 324 gene panel for solid tumors
    • Panel includes microsatellite instability, tumor mutational burden
  • CDx claims
    • 5 solid tumors
    • 15 approved therapies
    • Single site PMA

**CDx Claims:**
• Can identify patients with select cancers (NSCLC, melanoma, breast cancer, colorectal cancer, or ovarian cancer) who may benefit from 15 different FDA-approved targeted treatment options
  • Clinical performance established by comparing the F1CDx to previously FDA-approved companion diagnostic tests
  • Can be used to develop other companion diagnostic tests – assay validation required

Approved November 2017
**Question:** Can Celgene use this assay as an Investigational Use Only (IUO) for any of our trials utilizing selection or stratification without having to do any work?

**Celgene’s CDx/PM Evaluation:**
- Additional analytical validation may be needed before deployment onto the trial
  - Each gene may have been validated to varying levels, FDA during recent meeting indicated that for each application the validation work to date should be assessed and determined if sufficient and/or appropriate
- Significant risk determination should still be submitted to the agency
- If SR, will need to submit the IDE package and/or reference the existing validation
- The product would still need to supported by Foundation Medicine and labeled as an “IUO”

**Question:** Can the FoundationOne CDx (F1CDx) be run at multiple facilities?

**Celgene’s CDx/PM Evaluation:** Not with current approval. The product has been approved for a “single site”

**Question:** Can we add a CDx (additional clinical claim to the panel)?

**Celgene’s CDx/PM Evaluation:** Yes, with appropriate analytical & clinical validation can be added as a sPMA

Disclaimer: These are Celgene's CDx/PM evaluations only, does not necessarily reflect view of Health Authorities (HAs); please consult with your representative HAs as appropriate
Talk overview

- Evolution of diagnostic testing
- Pre-competitive collaboration
Opportunity to Simplify:
Pre-Competitive Collaborations – Winning for our Patients!

• Partnering with “like-minded” Pharma Companies is key for success
  • Enables harmonization & prevents fragmentation of testing
  • Shared model can reduce development & commercialization costs
  • Potential to accelerate clinical trial starts for therapies

• Initial diagnostic panel could have analytical as well as add clinical claims from multiple pharmaceutical partners over time
  • Drive adoption
  • Minimizes confusion and streamlines testing
  • Reduces Healthcare Costs - Single test yields multiple clinical outcomes
  • Advantageous for selecting, stratifying or monitoring patients in clinical trials (already “IDE” ready)
  • Increases commercial penetration through increased commercial value
  • Better informed physicians
Opportunity exists for high content assays: Expand diagnostic utility over time

**Future state**
- **Maximized utility**: This single panel could be used by multiple pharmaceutical companies
- **Expedited development**: New clinical claims would be added via supplemental PMAs (or other) when therapies require CDx

**Broad-based panel**
Start with clinical trial assay (Verification sufficient to support IDE submission for “X” biomarkers)

**Claims**
Analytical and clinical validation to support submission

**Broad-based utility**
Deployment onto trials
Stratification, selection analysis
Exploratory, Complementary, and/or Companion Dx

Celgene
• Approved June 22, 2017
  – Simultaneously report 23 genes clinically associated with NSCLC
  – Three clinical claims relating to multiple drugs and targets (TAFLINAR® in combo with MEKANIST®, XALKORI® and IRESSA®)
  – Analytical claims as well

• First of its kind collaboration between Novartis, Pfizer & Thermo-Fisher Scientific
  – Pharmaceutical companies that are fierce competitors in same space aligning pre-competitively for the good of patients/healthcare system, etc.

• First approved distributable NGS kit for multiple targets/drugs

• Key challenge was “Being first”
  – Unprecedented/unchartered territory
  – Close collaboration with CDER and CDRH was key to the success of the program
  – Numerous pre-submission conversations were had

• Assay was designed to be expandable by incorporating the 46 genes to target most of the known driver mutations for multiple cancers

• Multiple additional pharma partners have been announced to add to the clinical utility
  – Agios
  – Spectrum Pharmaceuticals
  – Blueprint Medicines
  – Etc….

Reference:  www.thermofisher.com
Advantages:

- Ability to rapidly progress to deployment onto registrational trials
- Enables low-cost exploration of all candidate genes simultaneously at a reasonable cost
- Harmonizes data being reported from multiple clinical trials
- Potential for new disease understanding
- Technology only utilizes a finger-prick
- Could result in new complementary or companion diagnostics for patients

Pharma and KOL Adoption

- Designed and developed with leading KOLs
- Evaluated in more than 2,000 lupus, multiple sclerosis, and RA patients
- Used by top pharma companies
- 2019 FDA submission planned
Potential AIP Use Cases

- **Patient Subtyping**: Identify patient sub-groups and prognostic indications
- **Disease Prognosis**: Predict future course of disease, including risk of flare-ups
- **Disease Monitoring**: Monitoring disease status and therapy response
- **Therapy Guidance**: Inform clinical therapy selection by predicting which patients will respond

If you have an interest in learning more, please contact Bob Terbrueggen: bob@dxterity.com
1. Align on Design Requirements for the product

<table>
<thead>
<tr>
<th>Design Requirement Category</th>
<th>Commercial Proposed Minimum Based on VOC</th>
<th>Optimal/Desired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample/Specimen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specimen types</td>
<td>DLBCL</td>
<td>DLBCL</td>
</tr>
<tr>
<td>Allowable Specimens</td>
<td>• FFPE (Fresh &amp; Archived)</td>
<td>• FFPE (Fresh &amp; Archived)</td>
</tr>
<tr>
<td></td>
<td>• Core Biopsies</td>
<td>• Core Biopsies</td>
</tr>
<tr>
<td></td>
<td>• Excisional or Incisional (includes punch, etc.)</td>
<td>• Excisional or Incisional (includes punch, etc.)</td>
</tr>
<tr>
<td>Specimen stability/storage</td>
<td>• Sectioned samples (undipped) must be stable for at least 90 days when stored (15-30°C)</td>
<td>• Sectioned samples (undipped) must be stable for at least 90 days when stored (15-30°C)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ease of Use Characteristics</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Turn-around time (TAT) (From slides through result)</td>
<td>No more than 4 business days for first pass testing.</td>
<td>No more than 3 business days for first pass testing.</td>
</tr>
<tr>
<td>Hands-on Time (from slides through result)</td>
<td>No more than 8 hours hands on time</td>
<td>No more than 6 hours hands on time</td>
</tr>
<tr>
<td>% Un-reportable results Upon initial testing full run</td>
<td>Including failures due to insufficient gDNA and/or RNA (quality and/or input), there should be less than 10% of results unreportable. Once gDNA and/or RNA quality or input has been met, there should be less than 7% of results unreportable.</td>
<td>Including failures due to insufficient gDNA and/or RNA (quality and/or input), there should be less than 7% of results unreportable. Once gDNA and/or RNA quality or input has been met, there should be less than 5% of results unreportable.</td>
</tr>
</tbody>
</table>
Each pharma partner generally has preference on vendors, how does the team make unbiased decision on best vendor?

2. Use a Prioritization Matrix for Vendor Selection

<table>
<thead>
<tr>
<th>Total for Commercial Requirements</th>
<th>Quality Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>94</td>
</tr>
<tr>
<td>Does the company have a GMP manufacturing facility registered with the FDA that could be used to manufacture and sell both instrument &amp; assay reagents?</td>
<td>No = 1, Assay, not instrument = 3, Yes = 5</td>
</tr>
<tr>
<td>Does the company have a well-established Quality System that meets QSR, ISO13485, requirements?</td>
<td>No = 1, Anticipated 2018-19 = 3, Yes = 5</td>
</tr>
<tr>
<td>Has been audited by the FDA &amp;/or other regulatory bodies (5), has been audited by customers (3), has not been audited by external company (1)?</td>
<td>FDA = 5, Customers = 3, No audits = 1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regulatory Requirements</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Must have in country regulatory representation in key countries in EU, US, AU, China, JP and LATAM</td>
<td>Only in US = 1, Only in 2-4 = 3, Only in 5-6 = 5</td>
</tr>
<tr>
<td>1 = no, 3 = planned in '18-20, 5 = already have MAH</td>
<td>5</td>
</tr>
<tr>
<td>Does the vendor have an MAH in Japan?</td>
<td>1 = minimal experience, 3 = lots of exp. w 510k/min, PMA, 5 = PMA experience</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Technical/Design Requirements</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA input</td>
<td>&gt;50 ng = 1, &gt;20 but &lt;50 ng = 3, Less than 20 ng = 5</td>
</tr>
<tr>
<td>1 = 3, 3 = Company A indicates 20 ng for 13 gene panel *(planning to go to 60-240 ng for 2nd release)</td>
<td></td>
</tr>
<tr>
<td>Turn-Around Time (extraction to results)</td>
<td>&gt;5 days = 1, 4-5 days = 3, 3 days or less = 5</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Hands on time (extraction to results) - 8 samples</td>
<td>More than 24 hrs total = 1, 12-24 hours = 3, &lt;12 hours = 5</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Panel contains critical targets anticipated to be needed for trials next 3 years</td>
<td>&lt;80% of targets = 1, 81-90% of targets = 3, &gt;90% of targets</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

Key areas assessed:
- Commercial
- Technical
- Regulatory
- Quality
- Business Relationship
Methodology used for alignment across multiple partners
Some Key Considerations (3)

3. Align on potential vendors then….

- 18 RFI’s Sent to Vendors
- 7 Responses received by Vendors
  - 5 Declined to Participate
  - 6 Did not respond
- 5 Vendors selected for Technical Pilot
- Prioritization Matrix
- 1-2 Vendors Selected
Vision for the future:
Partnership & harmonization

- Partner with other pharmaceutical companies
- Development of standards & protocols
  - Agreed on analytical performance standards
  - Standardized reference materials
  - Collection of real world evidence
  - Consistent, interpretable lab reports
- Development platform considerations
  - Selection of platform(s) for development and deployment of “Investigational Device Exception (IDE) ready” assay(s) in registrational trials
  - Platform(s) selected should be both technically and commercially viable, along with meeting regulatory requirements
We have seen an evolution of diagnostics over 20 years!

Marked increase in biomarker-driven trials Oncology & I&I

Complexity of Diagnostic Landscape is increasing

FDA unveiled a streamlined path for clearance of tumor profiling tests based on recent 510K clearance of MSK-IMPACT

FoundationOne CDx (F1CDx) and Oncomine Dx Target tests are examples of a single assay with broad utility

Pre-Competitive Partnerships can work and have a lot of advantages
Thank you for your time any attention!

Any Questions?