Changing the Course of Human Health Through Bold Pursuits in Science

CDx Forum
“Clear as Mud”
Where do we go from here!

December 6, 2017
1. Precision Medicine
2. In Vitro Diagnostics including Companion and Complementary Diagnostics
3. Laboratory Developed Tests
4. Next Generation Sequencing tests – how this is streamlining the regulatory process
Companion & Complementary Diagnostic Tests are the Hallmarks of Precision Medicine and are becoming more critical to patient outcomes.

**Evolution of drug development**

**PAST**
- Blockbuster
  - Trial & error based drug design
  - “one drug fits all”

**PRESENT**
- Precision Medicine
  - Target-oriented design
  - “Right drug for right patient group”

**FUTURE**
- Personalized Medicine
  - Network-oriented design
  - “Right drug for right patient at right time & dose”

**Future State:**
Increased complexity with a focus on biological pathways and tumor evolution vs. single targets
Integrated evidence development model
In Vitro diagnostics are a subgroup of Medical Devices and are defined as:

In vitro diagnostic products are those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae.... for use in the collection, preparation, and examination of specimens from the human body”
Companion and Complementary Diagnostics

**Companion Diagnostic**

- Is a medical device, often an in vitro device, which provides information that is **essential for the safe and effective use** of a corresponding drug or biological product.
- >30 Approved Companion Diagnostics
- >18 Approved Cancer Therapeutic Products

**Complementary Diagnostic**

- Is “an IVD that identifies a biomarker defined **subset of patients with a different benefit-risk profile than the broader population** for which a therapeutic product is indicated, but that is not a prerequisite for receiving the therapeutic product.”  
  Adam C. Berger, Office of IVD and Radiological Health
- Multiple PDL-1 IHC examples of complementary diagnostics
## Complementary vs Companion Dx - Labeling

<table>
<thead>
<tr>
<th>Stand-Alone Dx</th>
<th>Complementary Dx</th>
<th>Companion Dx</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Relates to a disease or condition, not a therapy</td>
<td>- Is <strong>NOT</strong> required for the safe and effective use of a therapy</td>
<td>- Is <strong>REQUIRED</strong> for the safe and effective use of a therapy</td>
</tr>
<tr>
<td>- Can be for screening, diagnosis, prognosis, or monitoring</td>
<td>- Dx is in Rx label in “Clinical Studies” section</td>
<td>- Dx is in Rx label in “Indications and Usage” section (FDA Approved Test)</td>
</tr>
<tr>
<td>- Can be referenced in Rx labeling (e.g. “Warnings &amp; Precautions”)</td>
<td>- Rx is in Dx label in the “intended use”</td>
<td>- Rx is in Dx label in the “intended use”</td>
</tr>
<tr>
<td>- Part of the existing lab infrastructure in most cases</td>
<td>- Identifies patients “most likely to benefit” based on either safety or efficacy</td>
<td>- Dxs identifies patients likely or not likely to benefit from Rx</td>
</tr>
</tbody>
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Types of Potential IVD Claims

- **Selective IVD**
  - Selection of a patient population eligible for a specific therapy; *required for the safe and effective use of the therapy*
  - Patients that are appropriate for the treatment
  - Patients at risk for serious adverse events
  - Used to select patients for treatment in a clinical trial

- **Predictive IVD**
  - Identify patients *most likely to benefit* from a specific therapy

- **Prognostic IVD**
  - Provides information about risk of disease progression or other disease-related endpoints; *independent of therapy*
Companion Diagnostics Example: ZELBORAF

- **Indication:** Zelboraf is a kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by and FDA-approved test.

- **Limitation of use:** Zelboraf is not indicated for the treatment of patients with wild type BRAF melanoma.

BRAF V600E status is essential for the safe and effective use of the drug.

Companion Diagnostic
Complementary Diagnostics Example: TECENTRIQ

- **Indication:** Tecentriq is a PD-L1 blocking antibody indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma. *(NOTE: “FDA Approved Test” is not included in the label)*

- **Clinical efficacy described for all patients, as well as based on PD-L1 IHC assay result (SP142)**

No patients excluded from receiving Tecentriq therapy based on SP142 status

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>PD-L1 Expression of &lt; 5% in ICs[^1] (N=210)</th>
<th>PD-L1 Expression of ≥ 5% in ICs[^1] (N=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of IRF-assessed Confirmed Responders</td>
<td>46</td>
<td>20</td>
<td>26</td>
</tr>
<tr>
<td>ORR % (95% CI)</td>
<td>14.8% (11.1, 19.3)</td>
<td>9.5% (5.9, 14.3)</td>
<td>26.0% (17.7, 35.7)</td>
</tr>
<tr>
<td>Complete Response (CR) (%)</td>
<td>5.5%</td>
<td>2.4%</td>
<td>12.0%</td>
</tr>
<tr>
<td>Partial Response (PR) (%)</td>
<td>9.4%</td>
<td>7.1%</td>
<td>14.0%</td>
</tr>
<tr>
<td>Median DoR, months (range)</td>
<td>NR (2.1+, 13.8+)</td>
<td>12.7 (2.1+, 12.7)</td>
<td>NR (4.2, 13.8+)</td>
</tr>
</tbody>
</table>

[^1]: PD-L1 expression in tumor-infiltrating immune cells (ICs)

NR = Not reached
+ Denotes a censored value
Laboratory-Developed Test (LDT): in vitro diagnostic test that is developed, validated and used exclusively for in-house diagnostic purposes.

- Laboratory developed tests (LDTs) serve an important role in health care. However, they have become more complex and higher risk.

- Level of validation of the LDT is at the discretion of the Laboratory Director (highly varied).

- FDA has generally exercised enforcement discretion towards LDTs (i.e., generally not enforced under the FD&C Act and FDA regulations).

- Laboratories that offer LDTs follow the regulatory requirements of CLIA, which are intended to regulate the operations of laboratories, and are not specifically intended to regulate in vitro diagnostic devices.
Draft Guidance on regulation of LDTs issued 2014; not yet final

- FDA has exercised regulatory discretion with regard to laboratory-developed predictive tests (LDTs) and does not oversee their development.
- The laboratories that provide LDTs are subject to oversight by CMS under the Clinical Laboratory Improvement Act (CLIA) to ensure quality of testing.
Increased Complexity of Assays (e.g. NGS) – One Drug, One Test will not be sustainable...

- **Foundation Medicine – FoundationFocus CDxBRCA Assay**
  - 1 marker – 1 drug (Rubraca for Ovarian Cancer) – Single Site PMA
  - Dec 19 ‘16

- **Illumina- Praxis Extended RAS Panel**
  - 56 gene panel – Single drug for CRC – Distributable Kit
  - June 29 ‘17
  - • Vectibix® (Panitumumab)

- **Thermo-Fisher Scientific-Oncomine™ Dx Target Test**
  - 23 Markers – Multiple Drugs – Distributable Kit (PMA)
  - June 22 ‘17
  - • Clinical claims for:  ● Tafinlar® (dabrafenib)  ● Mekinist® (trametinib)  ● Xalkori® (crizotinib)  ● Iressa® (gefitinib)
  - • Analytical: 4 claims

3 Complex NGS assays approved within 12 months
Increased Complexity of Assays (e.g. NGS) - One Drug, One Test will not be sustainable…

MSK-IMPACT
NGS Panel; de novo 510K; Class II device; single site; not a CDx

November 15, '17

FoundationOne CDx – NGS panel, 468 Marker; multidrug; Breakthrough Device Designation; PMA with analytical and CDx claims; single site PMA

November 30, '17

2 Complex NGS assays approved within 2 weeks of each other
MSK – IMPACT: NGS 341 Gene Panel – Class II de novo 510K cleared. FDA is establishing a
Class II regulatory pathway for the review of NGS-based tumor profiling tests for use in cancer
patients. These tests are eligible for the 510(k) clearance process, either by applying to the FDA
directly or through an accredited third-party reviewer like NYSDOH.

• MSK-IMPACT developed by MSKCC is a targeted tumor sequencing test; can detect
  select gene mutations and other critical genetic aberrations in both rare and common
cancers; targets 468 genes
• Can be used for any solid tumor regardless of origin.
• Single site; 510K cleared;
• NYSDOH accredited as a third party reviewer of in vitro diagnostics by
  FDA; MSK IMPACT was the first submission to use the third party review
  process
First breakthrough device-designated, NGS in vitro diagnostic (IVD) test to complete the PMA process

Can detect genetic mutations in 324 genes, microsatellite instability and tumor mutational burden in a number of solid tumor types.

Can also 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 – CDx claim

Clinical performance of the test was established by comparing the F1CDx to previously FDA-approved companion diagnostic tests
Breakthrough Device Program

- Draft Guidance issued October 25, 2017
- Will replace “Expedited Access for Premarket Approval and De Novo Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions” issued April 23, 2015
- Voluntary; request for designation
Summary

- Record year for approval of increasingly complex NGS assays!
- FDA has unveiled a streamlined path for the authorization of tumor profiling tests based on the recent 510K clearance of the MSK-IMPACT and the PMA approval for FoundationOne CDx
- MSK-IMPACT – de novo 510K clearance (not a CDx); third party review (NYSDOH)
  - Expect more accredited third party reviewers and similar approvals using this streamlined path to approval
- FoundationOne CDx used the Breakthrough Device Program for PMA approval (CDx)
- Both tests can be used for additional claims and CDx development with proper analytical and clinical validation
- So, Where do we go from here………..
THANK YOU!
Cancer Treatment in the Future?

"Here's my sequence"

The New Yorker