Linking “intended use” to evidence needed for bringing a diagnostic test to market

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CareDx stock holder and consultant
Sea Changes in Healthcare

- Lack of stakeholder agreement (healthcare provider, regulator, public and private payors, patient)
- Increased cost pressures; more transparent coding; more stringent reimbursement decisions
- High quality evidence needs to be provided by test service (LDT) and test kit providers
- Clinical utility now required for reimbursement instead of only clinical validity as in past
- Narrower subsets of patients eligible for precision targeted management
- Increased role of emr evidence that lacks quality of randomized controlled trials but sufficient for initial narrowly targeted patient management (fit-for-purpose)
- Evolving regulatory science
Pivotal Stages of a Diagnostic Test

**Analytical Validity** refers to how well the test predicts the presence or absence of a particular biomarker.

Does the test accurately and robustly measure analyte/biomarker?

**Clinical Validity** refers to how well the biomarker test being analyzed is related to the presence, absence or risk of a specific disease.

Are there differences in levels of analyte/biomarker measured by the test between different stages of disease?

**Locked assay** (platform, analytes (content), coefficients (weighting), thresholds, informatics, outcomes, etc.)

**Clinical Utility** refers to whether the test can provide information about diagnosis, treatment, management, or prevention of a disease that will be helpful to a patient, healthcare provider, or family member.

Are the differences in the test in different stages of disease clinically actionable?

Will clinicians use the test?
In Vitro Diagnostic Test Regulation

<table>
<thead>
<tr>
<th>Category</th>
<th>CLIA</th>
<th>CLIA-CAP</th>
<th>CLIA-CAP-NYDOH</th>
<th>FDA 1</th>
<th>Parallel CMS and FDA</th>
<th>Payor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tr>
<tr>
<td>Analytical Validation</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Clinical Validation</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Clinical Utility</td>
<td>NR³</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Oversight</td>
<td>Laboratory approved</td>
<td>Laboratory approved</td>
<td>Laboratory and test approved</td>
<td>Test approved</td>
<td>Test and drug approved</td>
<td></td>
</tr>
<tr>
<td>Comparative-effectiveness</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Considered</td>
</tr>
</tbody>
</table>

Even though a multi-path regulated system has developed, reimbursement alone determines what diagnostic tests are used

1 FDA clears and approves IVD kits and single laboratory LDTs if submitted
2 Complementary and Companion
3 Not required
In Other Words

- Intended Use
- Clinical Utility
- Actionability
- Context of Use
A Question Driven Framework for Clinical Utility

- Who should be tested and under what circumstance?
- What does the test tell us that we did not know?
- Against what comparator is the test measured?
- Can we act on the information provided by the test?
- Will we act on the information provided by the test?
- What is the effectiveness of the action?
- Does the outcome of action change in a way in which we find value?

A test may have clinical utility
- In the absence of an effective clinical treatment
- Without actually improving the overall health outcomes of patient management (avoidance of unnecessary additional diagnostic testing or ineffective treatment)

Actionability is an evolving concept and varies with patient, clinician, guideline committee, and payor

- Contextual for stage of disease (primary vs metastatic) and tumor type
- Guidelines and FDA approved drug labels formally define accepted criteria (though clinical validity)
- Inclusion in a clinical trial may be actionable, although may not be reimbursed
- Actionability is not binary but is best thought of as a continuum of evidence
Biomarkers can be used in clinical development to:

- Better balance subjects in arms of trial
- Identify subjects at differential risk of disease
- Identify subjects at differential risk of adverse events (safety)
- Identify patients with sub-clinical disease
- Predict treatment efficacy
- Encourage increased adherence to medication
- Monitor response to treatment
Statistical Metrics for Test Performance

- Prioritize individual classification over group averages
- No single statistical measure provides sufficient insight
- **Predictive values (NPV and PPV) are more important than sensitivity, specificity and ROC curves**
- ROC curves have qualified value and can be insensitive to important changes in absolute risk
- Multivariate analysis with standard measures are critical
- Methods based on risk stratification have recently been proposed to compare models
  - reclassification calibration statistic
- Bayesian models for diagnostic test performance provide key insights (conditional probabilities; likelihood ratios)
- Explore integration of conventional factors and molecular biomarkers

Intended Use and Evidence: refining the tradeoffs

- Acknowledge evidence development is a continuum
- Recognize that different study designs provide various levels of evidence
- Address progressive increase in level of evidence in licensing
- Increase in diversity and number of patients approved over time dependent on benefit/risk of patients

## Phased and Timely Commercialization Based on Patient Benefit/Risk

<table>
<thead>
<tr>
<th>Conventional</th>
<th>‘Adaptive’ (e.g. progressive, contextual)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single gating licensing decision</td>
<td>Phased licensing decisions</td>
</tr>
<tr>
<td>Risk of expanded use</td>
<td>Risk addressed by surveillance and monitoring</td>
</tr>
<tr>
<td>RCT only</td>
<td>Adopt new evidence (EMR)</td>
</tr>
<tr>
<td>Broad population</td>
<td>Targeted subset of population</td>
</tr>
<tr>
<td>Focus on licensing</td>
<td>Focus on patient access</td>
</tr>
<tr>
<td>Open utilization</td>
<td>Specified utilization</td>
</tr>
</tbody>
</table>

Though proposed for drug approvals, equally applicable to diagnostics and reimbursement

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European Medicines Agency, MIT Center for Biomedical Innovation with some FDA co-authors
**Endpoint for clinical trials in NASH**

- **Histological Endpoints**
  - Resolution of NASH (complete resolution of ballooning and inflammation reduced to scores 0 or 1) with no worsening of fibrosis;
  - Improvement of liver fibrosis by >1 stage with no worsening of NASH

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# NASH Pharmacological Agents in Development

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Mechanism of action</th>
<th>Objective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aramchol</td>
<td>Synthetic fatty acid/bile acid conjugate</td>
<td>Impacts lipogenesis by upregulates the ABCA1 reverse cholesterol transporter and functions</td>
<td>liver fat and NAFLD activity score without ↑ of fibrosis</td>
</tr>
<tr>
<td>Emricasan</td>
<td>Pan-caspase inhibitor</td>
<td>Blockage of apoptotic and inflammatory caspase activation involved in hepatocyte cell death</td>
<td>↓ fibrosis and portal hypertension</td>
</tr>
<tr>
<td>GR-MD-02</td>
<td>Galectin-3 protein inhibitor</td>
<td>Anti-fibrogenesis</td>
<td>↓ fibrosis and portal hypertension</td>
</tr>
<tr>
<td>Obeticholic acid</td>
<td>Semi-synthetic derivative of acid chenodeoxycholic acid</td>
<td>Agonist of the farnesoid X receptor: downregulates hepatic glucose and lipid metabolism. May also ↓ portal pressure and have anti-inflammatory and antifibrotic activity</td>
<td>↑ fibrosis without ↑ NASH ; NASH resolution without ↑ of fibrosis</td>
</tr>
<tr>
<td>Elafibranor</td>
<td>Dual PPAR-α/δ agonist</td>
<td>Regulation of metabolic homeostasis, inflammation, cellular growth, and differentiation</td>
<td>NASH resolution without ↑ of fibrosis ; Clinical outcomes</td>
</tr>
<tr>
<td>Cenicriviroc</td>
<td>dual CCR2/CCR5 antagonist</td>
<td>Reduction of hepatic inflammation and fibrosis</td>
<td>↓ NAFLD activity score without ↑ of fibrosis ; fibrosis without ↑ NASH</td>
</tr>
<tr>
<td>Selonsertib (GS-4997)</td>
<td>Apoptosis signal regulating kinase 1 (ASK1) inhibitor</td>
<td>Reduction in oxidative stress-related cell death, fibrosis and inflammation</td>
<td>↓ fibrosis without ↑ NASH</td>
</tr>
</tbody>
</table>

Adapted from Konerman MA. J Hepatol 2018 (Epub ahead of print)
Hierarchy of Evidence

- **Meta-analysis of randomized control trials**
  - Highest level of evidence

- **Randomized control trial**
  - Prospective in design
  - High level of evidence
  - *Post hoc* analysis possible (e.g. pre-specified, avoid subgroups, use primary endpoint)
  - Adaptive designs show promise for precision medicine

- **Observational cohort**
  - Prospective in design
  - Less likely to have masked bias

- **Case control**
  - Retrospective in design
  - Susceptible to masked bias (e.g. survivorship, selection, ascertainment, drug treatment)
  - Most GWAS studies use this design

- **Anecdotal study**
  - Replication rarely reported

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Where are ‘adaptive’ trials, registries, real world and EMR data positioned in this hierarchy?

Sherman et al. NEJM 375, 2293 (2016).
Califf et al. NEJM 375, 2395 (2016).
What is an adaptive designed trial?

- A decision-oriented, sequential learning design that permits pre-specified adaptation or modification of a trial during its progress based on interim results
- ‘Adaptations’ can be based on internal or external information to the trial
- Pre-specification of modifications developed with a Bayesian methodology and computer simulation
- Includes interim statistical analyses for dynamic decisions
- Validated by a final confirmatory phase

Carey & Winer NEJM 375, 83 (2016)
Rugo et al. NEJM 375, 23 (2016)
Park et al. NEJM 375, 11 (2016).
Randomized controlled trials have compromised value
  – Include only narrowly defined, less ill and diverse patients
  – Difficult to find time and funding for all trials desired
  – External validity issue; not real world studies

Registries
  – Permits collection of real world data to complement and extend RCT data
  – Facilitates collection of comprehensive and unbiased data on diagnostic tests to enhance the available body of evidence for informed patient management decisions
  – Provides insights into short and long-term outcomes
  – Allows health systems, clinicians, and patients to work together to create a setting for generating evidence in practice
# Reengineered Evidence Paradigm

<table>
<thead>
<tr>
<th>Clinical trial design</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Registry studies and observational studies</td>
<td>Ideal for description of standards</td>
<td>Data quality is variable and questionable</td>
</tr>
<tr>
<td></td>
<td>Unselected patient populations (generalizable cohorts)</td>
<td>Cannot be used for comparative outcomes research</td>
</tr>
<tr>
<td></td>
<td>Large number of events allows for the identification of rare events</td>
<td>Confounding factors cannot be adjusted for, despite advanced statistical models</td>
</tr>
<tr>
<td></td>
<td>Inexpensive</td>
<td></td>
</tr>
<tr>
<td>Randomized clinical trials</td>
<td>Well-designed studies with adequate power (gold-standard clinical design)</td>
<td>Highly selected populations owing to specific inclusion and exclusion criteria</td>
</tr>
<tr>
<td></td>
<td>Removes confounding factors</td>
<td>Often performed at specialized study centres</td>
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<tr>
<td></td>
<td></td>
<td>Often include surrogate end points</td>
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<tr>
<td></td>
<td></td>
<td>Requires long time to plan and complete</td>
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<tr>
<td></td>
<td></td>
<td>Expensive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Often sponsored by industry (only studies with economic interest will be performed)</td>
</tr>
<tr>
<td>Registry-based randomized clinical trials</td>
<td>Randomization removes potential confounding</td>
<td>Data quality might be variable and questionable</td>
</tr>
<tr>
<td></td>
<td>Less-selected patient populations</td>
<td>Variables might not be well-defined</td>
</tr>
<tr>
<td></td>
<td>Large number of events allows for the identification of rare events</td>
<td>Limited possibility for collection of detailed safety reporting, biospecimens, and pharmacokinetics or</td>
</tr>
<tr>
<td></td>
<td>Simple design</td>
<td>pharmacodynamic indices</td>
</tr>
<tr>
<td></td>
<td>Inexpensive</td>
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</tr>
</tbody>
</table>

Evidence Required for CMS Diagnostic Test Reimbursement

MoLDX Clinical Trial Designations (mCTD)

- **mCTD 3A** - Randomized, Prospectively Controlled Trials
- **mCTD 3B** - Prospective-Retrospective Trials
- **mCTD 2A** - Prospective Observational Studies
- **mCTD 2B** – Retrospective Data Modeling
- **mCTD 1** - Retrospective Observational Studies
- **mCTD 0** - Preclinical Studies
On September 19–20, 2017, the National Academies of Sciences, Engineering, and Medicine held the first workshop of a three-part series titled **Examining the Impact of Real-World Evidence on Medical Product Development**. The workshops are convened under the auspices of the Forum on Drug Discovery, Development, and Translation and sponsored by the U.S. Food and Drug Administration (FDA). The workshops are intended to advance real-world evidence (RWE).

The Health and Medicine Division (HMD) is a division of the National Academies of Sciences, Engineering, and Medicine (the National Academies). HMD previously was the Institute of Medicine (IOM) program unit of the National Academies. On March 15, 2016, the division was renamed HMD.

Robert Califf opened the session suggesting the community build a reusable system embedded in clinical practice and learn from every encounter.

Janet Woodcock said that FDA is committed to exploring the use of RWE in regulatory decisions and cited the recently issued guidance for devices.

Marcus Wilson argued that the solution is to defragment the patient view by sharing data responsibly and creating value by linking data from disparate parts of the health system as well as patient-provided information. He said that institutions that collect and share these data should adhere to core principles, including protecting patient privacy and security. 'Deep' data more relevant than 'Big' data.
Final Remarks
Richard Simon listed potential next steps which could help address challenges and encourage the wider use of RWE:

First, he said that asking fit-for-purpose questions will be critical in determining context-specific value in the health care systems.

Second, he stressed the importance of using appropriate methods, including making choices about when randomization is needed to answer a particular question. Regarding observational studies, he said that elevating the rigor of trial designs through transparency and sharing of methods and data will become more important.

Finally, he suggested accommodating diverse evidence needs across stakeholders, defining smaller studies based on simple questions and sound research design, and reconsidering the delineation between the pre-approval and post-approval processes.
Conclusions

• Specific definition of clinical utility (Intended use) and evidence varies with stakeholder (clinician, public and private payor, patient, regulator)

• Imperative that intended use be reengineered to balance patient access and efficacy

• Evidence is undergoing sea change in our understanding of quality and needs to be fit-for-purpose

• Recognition of need and value of data science and improved statistical tools to measure diagnostic test performance

• Even though a clear multi-path regulated system has developed, reimbursement alone determines what diagnostic tests are used

• Failure to reimburse appropriately will stifle precision medicine and translational science

What does the future hold for clinical diagnostics?

• Diagnostics determines how most of health care dollar spent and is the keystone of precision medicine

• Diagnostic test development is much more rigorous than in past and provider investment is substantially increased

• Payors will increasingly look to professional organizations due to complexity and dynamic nature of evidence (need increased frequency of professional guidelines)

• Patient advocacy is a critical element of encouraged test development, demonstrated value and adoption

• Clinical judgment will remain critical, superimposed on guideline-directed care
Thanks to all the patients who participated in randomized controlled trials and subjects who participated in observational studies in past and those in future who provide evidence for healthcare decisions.

Every number is a life™
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