Qualification of NITs for NASH
separating reality from fantasy

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Disclosures

Arun J. Sanyal

• I disclose the following financial relationship(s) with a commercial interest:
• Dr. Sanyal is President of Sanyal Biotechnologies
• Stock options for Genfit, Tiziana, Indalo, Durect, Exhalenz, Galmed
• Consultant- Gilead, Intercept, Allergan, Lilly, Novo Nordisk, Astra Zeneca-Medimmune, Novartis, Pfizer, Genentech, Merck, Bristol Myers, Boehringer Ingelhiem, Immuron, Siemens, Echosense, GE, Birdrock, Tern, Sundise, IFMO, Lipocine, Innovate, Zydus, AMRA, Hemoshear,
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DEFINITION OF A BIOMARKER

An objective patient characteristic that is measured as an indicator of:
• Normal biologic processes
• Pathogenic processes (abnormal biologic processes)
• Biological responses to a therapeutic intervention

FUNCTIONAL DEFINITION OF A DIAGNOSTIC TEST

TRANSLATION OF THE COMPLEX SPECTRUM OF DISEASE BIOLOGY IN TO PRACTICAL ACTIONABLE STEPS FOR CLINICIANS TO IMPROVE PATIENT OUTCOMES

Diagnostics make up 4% of health care costs but informs how 50% of spend is directed
THERE ARE DIFFERENT KINDS OF NIT USES

• Diagnostic- identifies presence of a biological condition
• Prognostic- predicts a future outcome and has element of time
• Predictive- predicts response to treatment before it is initiated
• Disease Monitoring- identifies those whose disease course is progressing or improving whether naturally or following treatment
• Clinical endpoint- a characteristic that reflects how a patient feels, functions or survives
• Surrogate endpoint- may substitute for clinical endpoint based on biological rationale, prediction of clinical endpoint and effect of treatment on clinical endpoint
### Key elements in NIT development

<table>
<thead>
<tr>
<th>Biological plausibility</th>
<th>Analytical performance</th>
<th>Clinical Validity</th>
<th>Clinical utility</th>
<th>Benefit vs Harm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the biomarker relevant to disease biology?</td>
<td>- How well does test detect the biomarker - What conditions are needed for accurate detection - Repeatability - Reproducibility</td>
<td>How does the biomarker relate to its intended use?</td>
<td>How does the biomarker inform patient care or guide disease management?</td>
<td>Value to patient versus harms from misclassification</td>
</tr>
</tbody>
</table>

Grskovich et al, J Mol Diagn (2016)
Biomarker development process

- Drug Approval Process
- Scientific Community Consensus
- Biomarker Qualification Program

- Data Driven
- Subject to regulatory scrutiny
- More than one process can go on
The Specific Context of Use for a Biomarker Drives the Extent of Evidence Needed for Qualification

Analytical Validation
(establish performance and acceptance characteristics of the biomarker assay)

- Reference Ranges/Decision Points
- Pre-Analytical and Assay Performance Characteristics
- Analytical Rigor/Reproducibility
- Sample Handling/Stability

Clinical Validation
(establish that the biomarker acceptably identifies, measures, or predicts the concept of interest)

- Study Design Acceptability
- Clinical Meaningfulness/Decision Points
- Benefit/Risk Assessment

Courtesy Lara Dimick, FDA 2020
Drug and Diagnostic test co-development

Multiple perspectives by multiple stakeholders require strategic approach to meet everyone's needs

<table>
<thead>
<tr>
<th>Clinician</th>
<th>Regulator</th>
<th>Payor</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Able to rule in or rule out</td>
<td>- Analytical robustness</td>
<td>Value proposition</td>
</tr>
<tr>
<td>- Guide next steps</td>
<td>- Accuracy of measurement</td>
<td>- Avoid Rx in low-risk population</td>
</tr>
<tr>
<td></td>
<td>- Predictive value</td>
<td>- Avoid drug exposure if nonresponder</td>
</tr>
<tr>
<td></td>
<td>- Risks of misclassification</td>
<td>- Identify subpopulation most likely to respond</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Identify subpopulation most likely to benefit by improving health and reducing health care resource utilization</td>
</tr>
</tbody>
</table>
Two paths for regulatory oversight

- **Non-Invasive Test**
  - Lab Developed Test
    - CLIA Regulation
  - Traditional FDA Regulated Tests
    - Moderate Risk
      - Performance related to reference standard
        - 510(K)
    - High Risk
      - Demonstrate safety/utility
        - PMA

CLIA= Clinical Lab Improvement Amendments of 1988
Multi-path regulated system for NIT regulation

<table>
<thead>
<tr>
<th></th>
<th>CLIA</th>
<th>CLIA-CAP</th>
<th>CLIA-CAP-NYDOH</th>
<th>Diagnostic Prognostic</th>
<th>Predictive</th>
<th>Payor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analytic 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>Not required</td>
<td>Not required</td>
<td>Not required</td>
<td>Not required</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Lab is approved</td>
<td>Lab is approved</td>
<td>Lab is approved</td>
<td>Lab and test approved</td>
<td>Test approved</td>
<td>Test and Drug approved</td>
<td></td>
</tr>
<tr>
<td>Comparative effectiveness</td>
<td>Not required</td>
<td>Not required</td>
<td>Not required</td>
<td>Not required</td>
<td>Not required</td>
<td>Required</td>
</tr>
</tbody>
</table>

Reimbursement is the key determinant of what diagnostic tests are used
High quality peer-reviewed publications are key to reimbursement
NIMBLE and LITMUS are Collaborative Activities that Build Synergy and are Working in Concert with Regulators to Accelerate Biomarker Development.

- High value contexts of use
- Address specific clinical questions
- Addresses:
  - Analytics
  - Sens/spec without bias
  - Clinical utility
- Will meet regulatory standards
- Will meet many payor perspectives
Translation of biomarker needs in to high priority contexts of use in NIMBLE

Biomarkers that permit decision-making for the following:

• In a patient with clinical risk factors for NASH ➔ To diagnose NASH and determine stage of disease (F2 fibrosis or higher i.e. high-risk NASH)

• In a patient diagnosed with NASH ➔ for detect and quantify change in NASH status (NASH present vs absent, change in disease activity) and stage (fibrosis stage)
Stage 1 will provide specific clinically useful information using *analytically robust set of tests*

- In adults with NAFLD to identify
  - those with steatohepatitis,
  - high NAS (≥ 4),
  - clinically significant fibrosis stage (≥ 2)
  - “at risk’ NASH i.e. NASH + NAS ≥ 4 + fibrosis stage ≥ 2 (NIS4)
  - cirrhosis

*to inform:*

- Enrichment of population with at risk NASH or NASH with advanced fibrosis or cirrhosis for clinical trials
- Guide triage decisions for specific management
Stage 2 will test the performance of selected biomarkers in appropriate intended use populations.

PPV only 16% if prevalence is 1% (typical diabetes clinic) for a test with 95% sens/spec.

- When pretest probability is low, a positive test is more likely to be a false positive.
- Most non-invasive tests have good NPV but poor PPV.
- Enrichment of target population will improve PPV.

\[
PPV = \frac{TP}{TP + FP} \quad \text{NPV} = \frac{TN}{TN + FN}
\]
There are many specific clinical questions that need to be addressed in the care of NASH patient

1. Is NAFLD/NASH likely to develop?
   - Genetics
     - Polygenic risk scores

2. Is NAFLD Present?
   - MRI-PDFF
     - CAP

3. Is the patient likely to die from NASH?
   - Lab aids: FIB4 etc.
     - Circulating panels
     - Imaging
       - Combo: Agile, FAST etc.

4. What intervention is needed?
   - Major Unmet need

5. Is the disease trajectory changing?
   - MRI
     - LSM
     - Circulating panels
MR elastography can predict future decompensation and mortality risk

Liver Stiffness by Magnetic Resonance Elastography Predicts Future Cirrhosis, Decompensation and Death in NAFLD

For each 1 kPa increase in liver stiffness by MRE, non-cirrhotic NAFLD subjects are 3 times more likely to develop cirrhosis in the future.

Adjusted HR=2.93 (95% CI, 1.86-4.62, p<0.0001) per 1 kPa

For each 1 kPa increase in liver stiffness by MRE, subjects with NASH cirrhosis are 32% more likely to develop decompensation and/or die in 5 years.

Adjusted HR for age, sex and MELD-Na =1.32 (95%CI 1.13-1.56, p=0.0007)

A prospective validation of FIB4 to predict death in NAFLD

Incidence rate (per 100 person years) by risk classification at baseline

<table>
<thead>
<tr>
<th>Included Using FIB4 and/or LSM Criteria</th>
<th>Class A (n=554)</th>
<th>Class B (n=536)</th>
<th>Class C (n=846)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate per 100 person yrs</td>
<td>0.07</td>
<td>0.42</td>
<td>3.08</td>
</tr>
<tr>
<td>Deaths *</td>
<td>0.21</td>
<td>1.32</td>
<td>9.33</td>
</tr>
<tr>
<td>Liver events *</td>
<td>0.83</td>
<td>1.60</td>
<td>2.54</td>
</tr>
<tr>
<td>MACE *</td>
<td>0</td>
<td>0.07</td>
<td>1.08</td>
</tr>
<tr>
<td>HCC *</td>
<td></td>
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</tr>
</tbody>
</table>

N= 2523 (median follow up 3 years)

Class A: FIB4 < 1.3, LSM < 8kp
Class B: FIB4 1.3-2.6, LSM 8-12.5 or class A FIB4/LSM but with AST:ALT > 1, platelet < 150k
Class C: FIB 4 > 2.6, LSM > 12.5 kp

Sanyal et al, AASLD 2020
Metabolic vulnerability index predicts all-cause and liver-related outcomes

Sanyal et al. to be fully presented at AASLD 2021

6 NMR of serum- GlycA, small HDL (1P-2P-3P), BCAA and citrate
Diabetes risk index to predict future development of T2DM

Atherosclerosis, CVD, MI
Microvascular and macrovascular disease progression
Retinopathy, nephropathy, neuropathy

Normal glucose tolerance
FPG <100 mg/dL

Impaired fasting glucose/
impaired glucose tolerance
FPG 100-125 mg/dL

T2DM
FPG ≥125 mg/dL

Normal insulin levels
Insulin production
Lipoproteins
1-3 Early marker
GlycA
6-9 Late marker
Valine
4,5
Pre-T2DM
β-cell dysfunction

DRI predicts risk of progressing to T2DM in 5 years and stratifies risk for patients most in need of aggressive treatment and lifestyle modification

T2DM, type 2 diabetes mellitus.

DRI Stratifies Risk in Intermediate Glucose Range
Predicted Probabilities of Diabetes Conversion in ~5 years

Independent of glucose level, DRI identifies patients who need more aggressive interventions

MESA, Multi-Ethnic Study of Atherosclerosis
DRI predicts development of T2DM in non-diabetic patients with NAFLD

N= 700 patients with NAFLD without T2DM or prior CAD event or hepatic decomp event

<table>
<thead>
<tr>
<th></th>
<th>HR/10 point increase</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2DM incidence</td>
<td>1.22</td>
<td>1.11-1.33</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CAD incidence</td>
<td>1.18</td>
<td>1-1.4</td>
<td>0.05</td>
</tr>
<tr>
<td>Hepatic decompensation</td>
<td>1.06</td>
<td>0.87-1.29</td>
<td>0.56</td>
</tr>
</tbody>
</table>

Sanyal et al- unpublished data
Summary: NIT-picking our way through NASH

• NIT development remains a very active field and the area likely to most impact the future of care delivery and translation of therapeutic data into clinical practice.

• The path to routine care requires multi-stakeholder perspectives to be taken into account and high-quality publications to support.

• LITMUS and NIMBLE have a major responsibility to deliver.

• The evidence to be generated will support development for routine use via multi-path regulated system. Reimbursement likely to determine the usage of NITs after regulatory approval.
Thank You

Courtesy - Dr. David Kleiner