INTEGRATED APPROACH TO DIAGNOSTIC ASSESSMENTS IN DIABETES AND NAFLD

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Conflicts of Interest

- President, Sanyal Biotechnologies
- **Stock options**: Genfit, Akarna, Tiziana, Indalo, Durect, Exhalenz, Hemoshear
- **Advisor with compensation**: Lilly, Pfizer, Novartis, Ardelyx, Salix, Hemoshear
- **Advisor without compensation**: Galectin, Intercept, Merck, Bristol Myers, Immuron, Gilead, Chemomab, Affimmune, Protalix, Nitto Denko, Novo Nordisk, Cirius, Boehringer Ingelhiem
- **Grants to institution**: Gilead, Tobira, Allergan, Merck, Bristol Myers, Astra Zeneca, Immuron, Intercept, Novo Nordisk, Shire, Boehringer Ingelhiem, Cirius
Threat Grows From Liver Illness Tied to Obesity

By Anahad O'Connor
Key concepts underlying diagnostic and therapeutic approach

Disease Onset

**Disease Activity**
- Steatohepatitis Activity scores NAS, SAF
- Metabolic, inflammatory, injury markers

**Stage**
- Fibrosis
- Fibrosis markers

**In the short term:** improve histology
**A surrogate outcome**
**In the long term:** reduce clinical Outcomes

**cirrhosis**

**Liver-related outcomes**
- Death
Self-assessment of NAFLD expertise and practice

Varying degree of knowledge and comfort in diagnosing/treating NAFLD patients

Amanda C. Wieland et al., Dig Dis Sci (2013) 58:2809-2816

Use of diagnostics for NASH is variable across health care provider spectrum

<table>
<thead>
<tr>
<th></th>
<th>PCPs N=152</th>
<th>GI/Hep Specialists N=150</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Does the physician diagnose NASH?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YES – with liver biopsy</td>
<td>25%</td>
<td>61%</td>
</tr>
<tr>
<td>YES – without liver biopsy</td>
<td>75%</td>
<td>39%</td>
</tr>
<tr>
<td>NO – patient had biopsy</td>
<td>44%</td>
<td>43%</td>
</tr>
<tr>
<td>NO – patient did not have biopsy</td>
<td>42%</td>
<td>48%</td>
</tr>
<tr>
<td>Unknown biopsy status</td>
<td>14%</td>
<td>8%</td>
</tr>
<tr>
<td><strong>What percentage used non-invasive tools to confirm NASH?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultrasound</td>
<td>74%</td>
<td>66%</td>
</tr>
<tr>
<td>CT scan</td>
<td>27%</td>
<td>20%</td>
</tr>
<tr>
<td>MRI</td>
<td>3%</td>
<td>13%</td>
</tr>
<tr>
<td>Proton magnetic resonance spectroscopy</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Other</td>
<td>2%</td>
<td>19%</td>
</tr>
<tr>
<td><strong>What was the main reason for lack of liver biopsy?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient refusal</td>
<td>51%</td>
<td>33%</td>
</tr>
<tr>
<td>Alternate reason</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Not recommended for biopsy</td>
<td>44%</td>
<td>63%</td>
</tr>
</tbody>
</table>

- Polanco-Briceno et al., BMC Res Notes (2016) 9:157
What does a typical patient with NAFLD look like?

NASH Is Associated With a High Burden of Metabolic Comorbidities

- Obesity: 82%
- Type 2 Diabetes: 44%
- Hyperlipidemia/Dyslipidemia: 72%
- Hypertension: 68%
- Metabolic Syndrome: 71%
Clinically meaningful end-organ outcomes and surrogates in the average patient with NAFLD

<table>
<thead>
<tr>
<th>Cardiac</th>
<th>Diabetes</th>
<th>Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensive heart disease</td>
<td>Glycemic control</td>
<td>cirrhosis</td>
</tr>
<tr>
<td>Atherosclerotic heart disease</td>
<td>Beta cell loss</td>
<td>Liver related outcomes</td>
</tr>
<tr>
<td>HFPEF</td>
<td>Peripheral vascular disease</td>
<td>HCC</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>retinopathy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>neuropathy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>nephropathy</td>
<td></td>
</tr>
</tbody>
</table>
## Diagnostic testing burden for the average patient with NAFLD

<table>
<thead>
<tr>
<th>Cardiac</th>
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<th>liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>EKG</td>
<td>HBA1C</td>
<td>Hepatic panel</td>
</tr>
<tr>
<td>Lipid profile</td>
<td>Eye exam</td>
<td>INR</td>
</tr>
<tr>
<td>CRP</td>
<td>Microalbuminuria</td>
<td>MELD*</td>
</tr>
<tr>
<td>Coronary calcium</td>
<td>eGFR</td>
<td>Measures of disease activity</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td>Autonomic dysfunction</td>
<td>Measures of disease stage</td>
</tr>
<tr>
<td>Stress tests</td>
<td>Vascular studies</td>
<td></td>
</tr>
</tbody>
</table>

* For those with cirrhosis

*Once advanced end-organ disease develops, additional testing is needed*
How the burden of diagnostics and therapeutics affect the patient and society

• Anxiety for patient
• Time away from work to get testing done
• Low compliance with practice guidelines
  - Empirical decision making leading to over- and under-treatment
• Suboptimal outcomes – effectiveness is usually lower than efficacy
  - Cost of testing
  - Cost of managing suboptimal outcomes due to suboptimal clinical practices

The burden of diagnostic testing and its associated cost along with poor adherence with practice guidelines and empirical management approaches provide a strong Rationale to simplify diagnostic and therapeutic approaches to enhance compliance. Reduce costs and improve outcomes.
NASH, Diabetes and cardiovascular disease share common biology

- Common histological elements
- Common pathophysiological mechanisms
- Colinearity between severity of NASH and nonhepatic end organ disease
NASH is characterized by ectopic fat, cell injury (ballooning), inflammation and fibrosis.
Pancreatic fat quantification by MRI

Increased number of islet macrophages in type 2 diabetic islets.

Marc Y. Donath et al. Dia Care 2008;31:S161-S164
Atherosclerosis involves ectopic lipid deposition along with inflammation and fibrosis.

Fat (cholesterol), macrophage infiltration, inflammation, fibrosis, calcification
Colinearity of hepatic and myocardial fat content

Marit Granér et al. Circ Cardiovasc Imaging. 2015;8:e001979
Colinearity of ectopic fat across different regions

From: Cardiac Steatosis Associates With Visceral Obesity in Nondiabetic Obese Men
J Clin Endocrinol Metab | Copyright © 2013 by The Endocrine Society
Fibrosis Stage is Linked To Diastolic Dysfunction and Exercise Capacity

Siddiqui et al. AASLD 2017, ms under review
Adipose tissue inflammation in metabolic syndrome
Increasing hepatic and visceral triglycerides is associated with diastolic dysfunction

Marit Granér et al. Circ Cardiovasc Imaging. 2015;8:e001979
Pathogenesis of beta cell failure in type 2 diabetes

Janikiewicz, et al; Biochemical and Biophysical Research Communications, Volume 460, Issue 3, 2015, 491–496

http://dx.doi.org/10.1016/j.bbrc.2015.03.153
NASH, T2DM, ATHEROSCLEROSIS, HFPEF SHARE COMMON ELEMENTS IN THEIR BIOLOGY

CIRRHOSIS

β CELL LOSS

HFPEF

Metabolic overload

Cell stress apoptosis

Inflammation

Fibrogenic remodeling

Insulin resistance
Lipid load
Lipid droplet proteins

Ox stress
UPR
ATP depletion
Caspase activation

Inflammasome
Cytokines
TLRs
microbiome

Fibrogenesis
Fibrolysis
Fibrosis load
How to leverage knowledge of pathophysiology for biomarker development
Leveraging pathophysiologiosiocal insights for biomarker development

![Diagram showing the progression from Disease Onset to cirrhosis and death. Key stages include:
- Disease Onset
  - Steatohepatitis
  - NAFLD activity score
- Disease Activity
  - Metabolic perturbation
  - Microbiome products
  - Systemic inflammation
  - Cell stress
  - Hepatic inflammation
- Stage
- Cirrhosis
- Generally accepted surrogate
- Clinically meaningful outcome
- Death]
A suggested approach

• In a given context of use, when it makes sense, validate biomarkers of activity and stage against established measures of disease for key additional end organs such as heart, pancreatic islet, coronary artery and kidney.

• Following intervention, validate similar measures for non-hepatic organs.
IMAGINE A WORLD WHERE A SIMPLE BLOOD TEST AND AN IMAGING TEST GIVES US A COMPOSITE READ OUT OF OVERALL MORTALITY RISK, CARDIAC, LIVER, RENAL AND DIABETES RISK AND A COMMON INTERVENTION FIXES ALL OF THE ABOVE!!!