INTEGRATED APPROACH TO DIAGNOSTIC ASSESSMENTS IN DIABETES AND NAFLD

Arun J. Sanyal M.B.B.S., M.D.
Professor of Medicine, Physiology and Molecular Pathology
Virginia Commonwealth University School of Medicine
Causes of death in the United States
Total n= 2.62 million for 2015

National Center for Health Statistics, 2015, Library of Congress Catalog 76-# 641496
Biomarkers used to intended for use for cardiovascular disease and type 2 diabetes

• **Cardiovascular:**
  - Lipid profile
  - Advanced profiles:
    - sdLDL
    - HDL class II
    - ApoB
    - ApoE genotype
    - Inflammatory markers
    - Vitamin D
    - Homocysteine
  - Coronary calcium score
  - Carotid intimal thickness

• **Type 2 diabetes:**
  - Diabetes related:
    - HBA1C
    - Beta cell mass and function
    - Markers of insulin resistance
  - End-organ related:
    - eye exam
    - micro-albuminuria
    - neuropathy
    - peripheral vascular disease
- Monday: PCP + blood work
- Tuesday: Imaging - heart + liver
- Wednesday: Eye exam
- Thursday: peripheral vascular exam
- Friday: Nutritionist
What is needed?

• Integrated approach

• Predict risk or diagnose (based on context of use) -
  • along a continuous scale with dynamic range
  • integrate principal risks to the patient

• Need to define when to do the test, how soon to repeat etc

• Should drive decision to treat
Use of diagnostics in patients at risk

Assessment of risk

Primary Prevention

Diagnosis and Prognosis

Personalized Therapeutic strategy

Personalized Response-guided therapy

- Family History
- Genetics
- Microbiome
- Behavioral analysis

STRATIFY FOR RISK OF OBESITY, DIABETES, HEART DISEASE, NAFLD AND CIRRHOSIS
SNPs associated with the metabolic syndrome

- Over 50 SNPs related to BMI, diabetes
- Key SNPs for glucokinase, PPAR-γ, IRS
- They explain 1-5% of variance in phenotype

Scott et al, Nature Genetics: 2012; 44:991–1005,
The critical role of behavioral factors in the metabolic syndrome and NAFLD

- healthy lifestyle choices
- Compliance
- Motivation
- Ability to change behavior
Average patient in average clinic

- Fasting Blood Sugar: 100 mg/dl
- AST and ALT: 35 and 41 IU/L
- Serum Lipids:
  - LDL cholesterol: 135 mg/dl
  - HDL cholesterol: 40 mg/dl
  - Triglycerides: 180 mg/dl
Reverse engineering to identify biomarkers

• Define context of use
• Define common biological pathways linking NAFLD, diabetes and cardiovascular disease
• Search circulating metabolome, proteome, MiRNA, exosome etc to link back to common biological pathways
• Validate them against clinical surrogates or hard endpoints
Pathogenesis of coronary artery disease

Fat (cholesterol), macrophage infiltration, inflammation, fibrosis, calcification
There is a close concordance of liver fat with atherogenic dyslipidemia

Siddiqui et al, Gastroenterology, 2013
Increased cholesterol synthesis in NASH

Min et al, Cell Metabol, 2012,
Additive Risk for Incident CHD for LDL <130 by Lp-PLA₂ and hs-CRP Tertiles in ARIC Study

Adjusted for demographics, current smoking status, blood pressure, diabetes, and HDL


Risk Ratios

- hs-CRP top tertile: 1.2
- hs-CRP bottom tertile: 1.0
- Lp-PLA₂ top tertile: 4.2
- Lp-PLA₂ bottom tertile: 1.4

95% CI 1.7-10.3, p=0.001
Myocardial fibrosis associated with diet-induced obesity + NASH (Data from DIAMOND mice)
ER stress is activated in NASH/obesity-associated cardiomyopathy

Sanyal lab - based in DIAMOND mice)
CIRRHOSIS

Metabolism (steatosis)

Cell stress apoptosis

inflammation

Fibrogenic remodeling

CIRRHOSIS
Pathways associated with advanced stage in humans with NASH

N=84

<table>
<thead>
<tr>
<th>Pathway</th>
<th>p-value</th>
<th>Activation/ Inhibition</th>
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</thead>
<tbody>
<tr>
<td>EIF2 Signaling</td>
<td>7.15E-45</td>
<td>activation</td>
</tr>
<tr>
<td>FXR/RXR Activation</td>
<td>1.90E-17</td>
<td>n/a</td>
</tr>
<tr>
<td>Oxidative Phosphorylation Signaling</td>
<td>6.28E-16</td>
<td>n/a</td>
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<tr>
<td>Regulation of eIF4 and p70S6K</td>
<td>8.14E-16</td>
<td>inhibition</td>
</tr>
<tr>
<td>Mitochondrial Dysfunction</td>
<td>2.61E-15</td>
<td>n/a</td>
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</tbody>
</table>

Vincent et al, EASL 2017
Adipose tissue inflammation in metabolic syndrome

Sanyal lab (unpublished)
Pancreatic fat quantification by MRI

Diabetes Risk Index is Derived from Components Related to Pathophysiology of T2DM

T2DM, type 2 diabetes mellitus.

DRI Adds Significantly and Independently of BMI to Diabetes Prediction in MESA and IRAS

<table>
<thead>
<tr>
<th>Model</th>
<th>Parameter</th>
<th>MESA (n=234/4031)</th>
<th>IRAS (n=88/844)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>AUC</td>
<td>AUC</td>
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<tr>
<td>Base</td>
<td>age, sex, race, glucose</td>
<td>0.796</td>
<td>0.715</td>
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<tr>
<td></td>
<td></td>
<td>OR (95% CI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>_</td>
<td>_</td>
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<tr>
<td>Base + DRI</td>
<td>DRI</td>
<td>0.829</td>
<td>0.775</td>
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<tr>
<td></td>
<td></td>
<td>2.09 (1.74-2.51)</td>
<td>2.26 (1.68-3.04)</td>
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<tr>
<td>Base + DRI + BM</td>
<td>DRI</td>
<td>0.835</td>
<td>0.780</td>
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<tr>
<td></td>
<td></td>
<td>1.85 (1.53-2.25)</td>
<td>2.13 (1.57-2.90)</td>
</tr>
<tr>
<td></td>
<td>BMI</td>
<td>1.37 (1.18-1.58)</td>
<td>1.21 (0.96-1.53)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;0.0001</td>
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</tbody>
</table>

Relationship of NASH histological scores with diabetes risk score

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<thead>
<tr>
<th></th>
<th>Diabetes Risk Score</th>
<th>P value</th>
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<tbody>
<tr>
<td><strong>Steatosis</strong></td>
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<tr>
<td>gd 1</td>
<td>74</td>
<td>n.s.</td>
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<tr>
<td>gd2</td>
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<tr>
<td>gd3</td>
<td>78</td>
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<tr>
<td><strong>Inflammation</strong></td>
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<td></td>
</tr>
<tr>
<td>1</td>
<td>77</td>
<td>n.s.</td>
</tr>
<tr>
<td>2</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>78</td>
<td></td>
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<tr>
<td><strong>Ballooning:</strong></td>
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<td>0.02</td>
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<tr>
<td>0</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td><strong>Fibrosis:</strong></td>
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<td>0.01</td>
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<tr>
<td>1</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>74</td>
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</tr>
<tr>
<td>3</td>
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<tr>
<td>4</td>
<td>80</td>
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</tbody>
</table>

Sanyal et al (unpublished)
Diastolic dysfunction in NASH

Unpublished data - (Siddiqui/Oliver/Sanyal project)

N= 9 in each group
Key biological elements in end-organ disease in NAFLD subjects

Abnormal Metabolism

Heart disease

Inflammation

Fibrosis

Diabetes

Signature
• Is disease present
• How bad is it
• What is the prognosis

NAFLD
Integrated risk assessment in population

- At Birth: Genetic testing
- Pre-puberty (age 10-12): Metabolic risk profiling
  - cardiovascular
  - Diabetes
  - liver
- Post-puberty (age 25): Metabolic risk profiling
  End-organ assessment
- Age 40: End-organ assessment
  Continued risk profiling
Diagnostic assessment of the average patient with NAFLD

It is thornlike in appearance, but I need to order a battery of tests
Thank you for your attention

Prediction is very difficult.
Especially about the future.

Niels Bohr

Wikipedia.com; nobelprize.org