Case Presentation
(Fast Forward to 2016)

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Director, Regenerative Liver and Neoplasia
Texas Liver Institute
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Izzy (2016)

• Izzy is now 61 y/o. In the past year, she has become a fan of having 2-3 alcoholic drinks with dinner.
• It has been 9 years since her lap band and she has gained back the weight, in fact she gained 20 more pounds.
• She began to complain of a dull RUQ pain.
• She had labs done and an U/S.
• ALT 145, AST 67, TB 0.9, Alk phos 177, albumin 3.6, Cr 1.1, WBC 4.6, Hb 13.5, Platelet count 145.
• RUQ U/S- increased liver echogenicity c/w fatty infiltration. Normal GB.
NAFLD/NASH: Workup and Diagnosis

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University of Texas Health Science Center, San Antonio
Chief, Hepatology
Vice President, Academic and Clinical Affairs
The Texas Liver Institute
San Antonio, Texas
Is Food or Alcohol Worse for the Liver?

*The Verona Study*

- **Obese Heavy Drinkers** *
  - 94.5%

- **Obese Teetotalers**
  - 76%

- **Normal BMI‡ Heavy Drinkers** *
  - 46%

- **Normal BMI‡ Teetotalers (Controls)**
  - 16%

* >60 g of alcohol/d
†BMI <24 in females and 25 in males.

Percent of Obese Adults (Body Mass Index of 30+)

- 20 - 24.9%
- 25 - 29.9%
- 30 - 34.9%
- 35%+

Adult Obesity in America 2011-12

- Obese: 34.9%
- Overweight or Obese: 68.5%

Childhood Obesity in America 2011-12

- Obese: 16.9%
- Overweight or Obese: 31.8%

TX ranks #11

http://stateofobesity.org/adult-obesity/
The Spectrum of NAFLD and AFLD

- Exclusion of liver diseases (HCV)
- Requires specific pathologic criteria for NASH
- Important for prognosis
- Some reversibility

Clinical Outcome of NASH Variable

- NASH: ~20 million
- Cirrhosis: ~3 million
- HCC: ~3 million

Overall 10-15% incidence, Annual Incidence 2-3%.

Epidemiologic Impact of NAFLD

Worldwide Prevalence of NAFLD

AASLD Guideline:
• Prevalence of NAFLD: 6-33% (Median 20%)
• Prevalence of NASH 3-5%

• Obese: 75% NAFLD and 19% NASH
• Morbidly Obese: 93% NAFLD and 26-49% NASH
• Diabetes: 49.5-87% NAFLD


- In comparison to the prevalence of other etiologies, NAFLD is the most common cause of chronic liver disease.
- Because of the increasing wave of obesity in children, the disease burden from NAFLD will continue to increase.

Natural History of NAFLD

- **NAFLD**
  - Isolated Fatty Liver: ~70-75%
  - Fatty Liver with Mild Inflammation: ~20-25%
  - Possible sampling variability with some risk of progression

- **NASH**
  - ~11% over 15 years, but significant variability

- **NASH Cirrhosis**
  - 1. None to very minimal progression to fibrosis
  - 2. No ↑ risk of death compared with the general population

- **HCC**
  - ~7.2% over 6.5 years

- **Decompensation**
  - 19-45% over 7-10 years

1. ↑ risk of death compared with general population
   1. Cardiovascular
   2. Malignancy
   3. Liver-related
2. NASH with fibrosis portends worse prognosis
   1. Fibrosis progression a/w DM, severe IR, weight gain >5kg, rising ALT, AST

Metabolic Alterations That Lead to NAFLD

Gut - Liver Axis Microbial Translocation

- **TLR4**
- **Kupffer Cell**
- **LPS**
- **TNFα, pro-inflammatory cytokines**
- **Systemic circulation**
- **Portal circulation**
- **Detoxification**
- **Barrier dysfunction**
- **Hepatocyte function**
- **Permeability**
- **Kupffer cell activation**
- **Bacterial overgrowth**
- **LPS sensitization**
- **Microbial translocation**

Gut - Liver Axis Microbial Translocation

**LIVER**

**GUT**

**Gut**

**Liver**

**Detoxification**

**Hepatocyte function**

**Kupffer cell activation**

**LPS sensitization**

**Barrier dysfunction**

**Permeability**

**Bacterial overgrowth**

**Microbial translocation**
Genetically Obese Mice Have Increased Gut Permeability and Endotoxemia

Antibiotics Protect Against High Fructose Diet-induced NAFLD

Genetic Predispositions to NAFLD

• Patatin like phospholipase containing domain 3 gene encodes (PNPLA3) for adiponutrin

• Adiponutrin is a lipogenic enzyme in the liver

• PNPLA3 rs738409 single nucleotide polymorphism (SNP) is a non-synonymous variant, represented by a cytosine to guanosine substitution which encodes an isoleucine to methionine substitution at the amino acid position 148 (I148M)
Proposed Mechanism of Action of Each Genetic Variant Associated With Fatty Liver Disease

- **PNPLA3** - The *PNPLA3* encodes for the adiponutrin, an enzyme expressed in the liver and adipose tissue showing both a lipogenic and lipolytic activity. This variant could cause both a gain of function of the enzyme (which could have a lipogenic activity in the liver) and a loss of function (that could predispose to steatosis by decreasing triglyceride hydrolysis in hepatocytes).

- **GCKR** - The gene product is a regulatory protein that inhibits glucokinase in liver and pancreatic islet cells. The polymorphism could lead to increased hepatic glucokinase activity. This enhance the glycolytic flux and then promotes hepatic glucose metabolism and elevates the concentrations of malonyl coenzyme A, a substrate for de novo lipogenesis.

- **APOC3** - *APOC3* variants could increase the plasma concentrations of apolipoprotein C3. The apolipoprotein C3 could then inhibit the lipoprotein lipase reducing the clearance of triglycerides. Consequence of reduced clearance of triglycerides is the increase of chylomicron-remnant particles that confer a predisposition to both fasting and postprandial hypertriglyceridemia. Higher circulating levels of chylomicron-remnant particles are then especially cleared by the liver through a receptor-mediated process, resulting in NAFLD and hepatic insulin resistance.

- **NCAN** - *NCAN* encodes for a chondroitin sulfate proteoglycan thought to be involved in the modulation of cell adhesion and migration. *NCAN* is a risk factor for liver inflammation and fibrosis, suggesting that this locus is responsible for progression from steatosis to steatohepatitis.

- **LYPLAL1** - *LYPLAL1* encodes for a lysophospholipase and it is associated with increased hepatic steatosis probably preventing breakdown of triglycerides.

- **PPP1R3B** - This gene encodes the catalytic subunit of the serine/theonine phosphatase, protein phosphatase-1. The encoded protein is expressed in liver. It is associated with computer tomography–assessed liver attenuation but not histology-proven NAFLD.

- **GC** - *GC* gene is expressed predominately in the hepatocytes where it encodes for VDBP. VDBP is the main vitamin D carrier, which has been implicated in the development of obesity and diabetes. In fact, low vitamin D concentrations could increase adipocyte intracellular calcium, stimulating lipogenesis, whereas vitamin D supplementation improves insulin resistance and down-regulates inflammatory cytokines such as tumor necrosis factor-a and interleukin-6 in cell models. Vitamin D levels are influenced by *GC* genetic polymorphisms.
PNPLA3:I148M – Ethnic-specific Allele Frequencies in Dallas Heart Study

**PNPLA3: I148M Allele Frequency**
- African Americans: 17%
- European Americans: 23%
- Hispanics: 49%

**Prevalence of Hepatic Steatosis**
- African Americans: 24%
- European Americans: 33%
- Hispanics: 45%
PNPLA3 and Disease Progression

**Hispanics**

- **Serum Alanine Transaminase**
  - II
  - IM
  - MM
  - $P=1.3 \times 10^{-5}$

- **Pathology**
  - ↑LFTs

**PNPLA3**

- NAFLD
- Alcohol

**MM:** 3.8 X risk cirrhosis

Muller, et al. *J. Hepatol.* 2011;

What Are the Clinical Predictors of Advanced Fibrosis in NAFLD?

- NAFLD with liver biopsy (N=432)
- In multivariate analysis, elevated AST and ALT, presence of diabetes mellitus, male gender and Caucasian ethnicity were associated with moderate to severe fibrosis (p<0.0001)

<table>
<thead>
<tr>
<th>Factors</th>
<th>Advanced Fibrosis OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>1.61 (1.21-2.01)</td>
<td>0.0374</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.64 (1.13-2.17)</td>
<td>0.0258</td>
</tr>
<tr>
<td>HTN and DM</td>
<td>1.69 (1.11-2.28)</td>
<td>0.0246</td>
</tr>
<tr>
<td>HTN+DM+Visceral Obesity</td>
<td>1.72 (1.13-2.31)</td>
<td>0.0205</td>
</tr>
</tbody>
</table>

Diagnosis of NAFLD
Despite Being Very Common, NAFLD is Not Well Recognized in Clinical Practice

- Houston VA patients (2001–2011) with chronic elevation of ALT and no liver diseases (n = 19,692)
- Random sample (n = 450)
- Structured chart review to confirm the criteria for NAFLD and metabolic syndrome
- Data from the primary care providers’ notes were abstracted for
  - Recognition of abnormal ALT levels
  - Mention of NAFLD as a possible diagnosis
  - Recommendations for diet or exercise
  - Referral to a specialist for NAFLD evaluation

Liver Stiffness: Ultrasound elastography or MR elastography (problems with reproducibility and inability to discriminate lower stages of fibrosis and no validity for longitudinal studies)

– US elastography can fail in visceral obesity

Liver Fat Content: MRI/MRS proton density fat fraction

<table>
<thead>
<tr>
<th>Image Modality</th>
<th>N</th>
<th>Year</th>
<th>Author</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>165</td>
<td>2002</td>
<td>Mathiesen</td>
<td>• Echogenicity could not detect fibrosis</td>
</tr>
<tr>
<td>US, CT, MRI</td>
<td>25</td>
<td>2002</td>
<td>Saadeh</td>
<td>• Excellent to predict &gt;30% steatosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Unable to diagnose NASH and stage fibrosis</td>
</tr>
<tr>
<td>CT</td>
<td>30</td>
<td>2004</td>
<td>Brunt</td>
<td>• Hepatic fat content (L/S) not associated with steatohepatitis and fibrosis</td>
</tr>
</tbody>
</table>
NAFLD Fibrosis Score

Impaired Fasting Glucose/Diabetes: No

Age:

AST:

ALT:

Platelet Count:

BMI:

Albumin:
NAFLD Fibrosis Score

Formula

• $1.675 + 0.037 \times \text{age (years)} + 0.094 \times \text{BMI (kg/m}^2\text{)} + 1.13 \times \text{IFG/diabetes (yes = 1, no = 0)} + 0.99 \times \text{AST/ALT ratio} - 0.013 \times \text{platelet (} \times 109/l\text{)} - 0.66 \times \text{albumin (g/dl)}$

Explanation of Result

• NAFLD Score < -1.455 = F0-F2
• NAFLD Score -1.455 – 0.675 = indeterminate score
• NAFLD Score > 0.675 = F3-F4

### Pathology Scoring Systems Used in NASH

<table>
<thead>
<tr>
<th>Pathologist</th>
<th>Year</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ludwig, 1980</strong>&lt;br&gt;(Original)</td>
<td></td>
<td>• Steatosis, lobular inflammation, necrosis and Mallory bodies in zone 3, mild portal and periportal inflammation</td>
</tr>
<tr>
<td><strong>Younossi, 1999</strong>&lt;br&gt;(NAFLD Subtypes)</td>
<td></td>
<td>• Steatosis, ballooning degeneration • Steatosis, ballooning with either Mallory’s hyaline or fibrosis</td>
</tr>
<tr>
<td><strong>Brunt, 1999</strong>&lt;br&gt;(Brunt Criteria)</td>
<td></td>
<td>• Steatosis with mixed inflammation, occasional ballooned hepatocytes • Steatosis, ballooning and disarray in zone 3 • Panacinar steatosis + ballooning + disarray + portal inflammation</td>
</tr>
<tr>
<td><strong>Kleiner, 2005</strong>&lt;br&gt;(NAS Criteria)</td>
<td></td>
<td>• Steatosis (0-3), lobular inflammation (0-3), ballooning (0-3) • 0-2 not NASH $\rightarrow \geq 5$ usually NASH</td>
</tr>
</tbody>
</table>
Transient Elastography

- Allows painless and simultaneous measurement of two quantitative parameters:
  - Liver stiffness expressed in kPa
    - Correlated to liver fibrosis\(^1\)
  - Controlled Attenuation Parameter (CAP™) expressed in dB/meter
    - Correlated to liver steatosis\(^2\)
- Both quantitative parameters are assessed on the same volume of liver tissue
- 100 times bigger than liver biopsy

Transient Elastography

- Measures velocity of a low-frequency (50 Hz) elastic shear wave propagating through the liver
  - Normal liver: ~5.5 kPa
- Good performance for excluding advanced stage disease (stage 3-4)
- User-friendly, short procedure time
- Problems still with severe obesity, ascites, operator experience
- False positives: acute hepatitis, extrahepatic cholestasis and congestion
- XL probe has ~25% unreliable results; cut-off concerns
- **Not very good in our hands at predicting fibrosis in NAFLD patients**

Liver Biopsy

• Identify NASH (ballooning, inflammation, etc)
  – Establish diagnosis
  – Clinical trials

• Stage fibrosis

• Rule out concomitant liver disease (iron loading, etc)

• Prognosis
Liver Biopsy Results

• Microscopic description
  – Sections obtained after processing show a 2.7 mm long liver biopsy containing more than 18 portal tracts.
  – The biopsy shows steatosis with scattered lobular and portal inflammation and prominent hepatocellular ballooning with a number of Mallory bodies, indicating an active steatohepatitis.
  – The trichrome stain shows extensive centrilobular pericellular fibrosis as well as several areas of bridging fibrosis.
How Do We Diagnose NAFLD Patients in 2016?

Elevated aminotransferases
Fatty Liver by imaging

• Exclude other causes of CLD
• Confirm lack of excessive ETOH
• Assess risk factors
• Consider assessment for IR

• No evidence of other CLD
• Young age
• No evidence of advanced LD

• Self directed life style modifications
• Professionally directed life style modification
• Repeat lab in 6 months

• Goals achieved
• Monitor q 6-12 m

• Unsuccessful
• Risks (DM, IR)
• Liver enzymes elevated
• High NAFLD Fibrosis score

• Suspicion for other CLD
• Dx of NAFLD uncertain

Liver biopsy
NAFLD and NASH

• NAFLD is a complex disease tied closely to obesity and diabetes

• NASH patients with fibrosis most likely to progress
  – NAFLD/NASH in the setting of DM/MS has adverse outcomes

• Diagnosis needs to be individualized based on suspected risk of NASH and progression

• Non-invasive modalities are best approach with biopsy reserved for those with suspected aggressive disease
Back to Dr. Wells
Izzy

• A liver biopsy is performed 6 months after she quit drinking. She is diagnosed with NASH and fibrosis stage 3-4.

• What is Izzy’s prognosis and how will we manage her?
Prognosis and Management of NASH

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Assistant Professor of Medicine
University of Texas Health Science Center,
San Antonio
Director, Metabolic Liver Disease Program
The Texas Liver Institute
Austin, Texas
NASH is the Subtype of NAFLD that Primarily Progresses

- NAFL
- NAFLD
- NASH
- Stable
- Cirrhosis 10-15% → Stable 65-75%
- NASH 10-15%
- Liver Failure 40-60%
- Death 20-30%
- HCC (Annual incidence 2%)
What Are the Clinical Predictors of Mortality in NAFLD?

- Histologic NAFLD (N=289)
- Clinico-demographic data from biopsy date
- NASH (59.2%), non-NASH (40.8%)
  - **NASH patients were predominantly female, higher AST, ALT and serum glucose**
- Mortality: Median follow-up of 150 months
  - NASH had higher risk of liver-related mortality than non-NASH NAFLD (p= 0.002)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Overall mortality aHR (95% CI)</th>
<th>Liver-related mortality aHR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NASH</td>
<td>1.13 (0.74 - 1.71)</td>
<td>9.16 (2.10 - 9.88)</td>
</tr>
<tr>
<td>Age</td>
<td>1.07 (1.05 - 1.10)</td>
<td>1.06 (1.02 - 1.10)</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.95 (0.62 - 1.47)</td>
<td>1.44 (0.62 - 3.34)</td>
</tr>
<tr>
<td>Caucasian race</td>
<td>1.67 (0.92 - 3.06)</td>
<td>1.85 (0.62 - 5.47)</td>
</tr>
<tr>
<td>Obesity</td>
<td>0.91 (0.60 - 1.40)</td>
<td>0.88 (0.38 - 2.04)</td>
</tr>
<tr>
<td>DM</td>
<td><strong>2.09 (1.39 - 3.14)</strong></td>
<td><strong>2.19 (1.00 - 4.81)</strong></td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1.01 (0.68 - 1.52)</td>
<td>0.48 (0.19 - 1.23)</td>
</tr>
</tbody>
</table>

What Are the Histologic Predictors of Mortality in NAFLD?

- NAFLD liver biopsy and mortality data (N=209)
- Biopsies were read centrally
- During follow-up (146 months), 31% of patients died with 9% dying of LRM

Univariate Survival Analyses

<table>
<thead>
<tr>
<th>Histologic Parameter</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Portal inflam (grade≥2)</td>
<td>[6.68 (2.20-20.3), p&lt;0.001]</td>
<td></td>
</tr>
<tr>
<td>Ballooning (grade≥2)</td>
<td>[5.32 (1.89-14.9), p=0.001]</td>
<td></td>
</tr>
<tr>
<td>MD bodies (grade≥2)</td>
<td>[4.21 (1.66-10.7), p=0.002]</td>
<td></td>
</tr>
<tr>
<td>Portal fib (grade&gt;2)</td>
<td>[14.1 (5.47-36.5), p&lt;0.001]</td>
<td></td>
</tr>
<tr>
<td>Pericellular fib (grade&gt;2)</td>
<td>[4.86 (1.73-13.7), p=0.003]</td>
<td></td>
</tr>
</tbody>
</table>

On multivariate analysis, only significant fibrosis (grade > 2) was an independent predictor of LRM

Multivariate Analysis

<table>
<thead>
<tr>
<th>Fibrosis Stage</th>
<th>Hazard Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1 (ref)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2.4 (0.63, 8.91)</td>
<td>0.2</td>
</tr>
<tr>
<td>2</td>
<td>7.5 (2.26, 24.94)</td>
<td>0.01</td>
</tr>
<tr>
<td>3</td>
<td>13.8 (4.35, 43.65)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>4</td>
<td>47.5 (11.94, 188.61)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>


Non-Pharmacologic Management of NASH
# Treatment of NAFLD: Weight Loss

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Intervention</th>
<th>Duration (months)</th>
<th>Design</th>
<th>ALT*</th>
<th>Histology*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hickman</td>
<td>31</td>
<td>Diet</td>
<td>15</td>
<td>Open label</td>
<td>+</td>
<td>N/A</td>
</tr>
<tr>
<td>Huang</td>
<td>16</td>
<td>Diet</td>
<td>12</td>
<td>Open label</td>
<td>-</td>
<td>+</td>
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<tr>
<td>Palmer</td>
<td>39</td>
<td>Diet</td>
<td>2-111</td>
<td>Case series</td>
<td>+</td>
<td>N/A</td>
</tr>
<tr>
<td>Andersen</td>
<td>41</td>
<td>Diet</td>
<td>4-23</td>
<td>Open label</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Kugelmas</td>
<td>8</td>
<td>Diet/Ex</td>
<td>3</td>
<td>Open- label</td>
<td>+</td>
<td>N/A</td>
</tr>
<tr>
<td>Ueno</td>
<td>15</td>
<td>Diet/Ex</td>
<td>3</td>
<td>Open label</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Zhu</td>
<td>34</td>
<td>Diet/Ex</td>
<td>12</td>
<td>Open label</td>
<td>+</td>
<td>N/A</td>
</tr>
<tr>
<td>Harrison</td>
<td>10</td>
<td>Orlistat</td>
<td></td>
<td>Open label</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Sabuncu</td>
<td>13/12</td>
<td>Sibutramine/Orlistat</td>
<td>6</td>
<td>Open label</td>
<td>+</td>
<td>N/A</td>
</tr>
<tr>
<td>Luyckx</td>
<td>69</td>
<td>Surgery</td>
<td>27</td>
<td>Case series</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Silverman</td>
<td>91</td>
<td>Surgery</td>
<td>2-61</td>
<td>Case series</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Dixon</td>
<td>36</td>
<td>Surgery</td>
<td>26</td>
<td>Case series</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Mummadi</td>
<td>766</td>
<td>Surgery</td>
<td>12</td>
<td>Meta-analysis</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

*Improvement denoted by +; No change denoted by -
NAFLD Guideline Recommendations

• Weight loss generally reduces hepatic steatosis, achieved either by hypocaloric diet alone or in conjunction with increased physical activity  
  
  (Strength - 1, Evidence – A)

• Loss of at least 3-5% of body weight appears necessary to improve steatosis, but a greater loss (up to 10%) may be needed to improve necroinflammation  
  
  (Strength - 1, Evidence – B)

• Exercise alone in adults with NAFLD may reduce hepatic steatosis but its ability to improve other aspects of liver histology remains unknown  
  
  (Strength - 1, Evidence - B)
Bariatric Surgery and NAFLD

<table>
<thead>
<tr>
<th>Study First Author</th>
<th>Year of publication</th>
<th>Sample size</th>
<th>Surgery type</th>
<th>Mean follow-up time</th>
<th>Change in Steatosis</th>
<th>Change in Inflammation</th>
<th>Change in Fibrosis</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranlov</td>
<td>1990</td>
<td>15</td>
<td>RYGB or gastroplasty</td>
<td>12 months</td>
<td>↓</td>
<td>NR</td>
<td>NR</td>
<td>Improved liver enzymes</td>
</tr>
<tr>
<td>Silverman</td>
<td>1995</td>
<td>91</td>
<td>RYGB</td>
<td>18.4 months</td>
<td>↓</td>
<td>↓ / O</td>
<td>↓</td>
<td>Improved lobular but no change in portal fibrosis</td>
</tr>
<tr>
<td>Luyckx</td>
<td>1998</td>
<td>69</td>
<td>Gastroplasty or LAGB</td>
<td>Not declared</td>
<td>↓</td>
<td>↓</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Dixon</td>
<td>2004</td>
<td>36</td>
<td>LAGB</td>
<td>25.6 ± 10 months</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>Significant improvement in all liver panel enzymes.</td>
</tr>
<tr>
<td>Kral</td>
<td>2004</td>
<td>104</td>
<td>Biliopancreatic diversion (BPD)</td>
<td>74 ± 27 months</td>
<td>↓</td>
<td>NR</td>
<td>↑</td>
<td>Increase in fibrosis overall was small)</td>
</tr>
<tr>
<td>Clark</td>
<td>2005</td>
<td>16</td>
<td>RYGB</td>
<td>10 ± 4 months</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>Improvement in lobular and portal fibrosis, ALT and AST</td>
</tr>
<tr>
<td>Keshishian</td>
<td>2005</td>
<td>78</td>
<td>BPD-duodenal switch (BPD-DS)</td>
<td>36 months</td>
<td>↓</td>
<td>↓</td>
<td>NR</td>
<td>NASH grade improved. No significant reduction in ALT</td>
</tr>
</tbody>
</table>

- No RCTs
- Most show decrease in steatosis, inflammation and liver enzymes. Results highly variable.
Pharmacologic Management of NASH
Vitamin E

**Authors** | **N** | **Dose** | **Comparators** | **Outcomes**
---|---|---|---|---
Arendt | 80 | 1000 IU/d | Placebo | Improved steatosis (assessed by CT scan) vs placebo
Sanyal | 247 | 800 IU/d | Pioglitazone, placebo | Improved steatosis, inflammation, and ballooning vs placebo
Lavine | 173 | 800 IU/d | Metformin, placebo | Improved steatohepatitis and ballooning vs placebo
Harrison | 45 | 1000 IU/d | Placebo | Improved fibrosis vs baseline
Sanyal | 20 | 400 IU/d | Vitamin E + pioglitazone | Improved steatosis vs baseline
Dufour | 48 | 800 IU/d | UDCA + placebo, placebo | Improved steatosis, inflammation, and ballooning vs baseline

- **Vitamin E** (α-tocopherol) administered at daily dose of 800 IU/day improves liver histology in non-diabetic adults with biopsy-proven NASH and therefore it should be considered as a first-line pharmacotherapy for this patient population. (Strength - 1, Quality - B)

- Until further data supporting its effectiveness become available, vitamin E is not recommended to treat NASH in diabetic patients, NAFLD without liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis (US Guidelines: Strength - 1, Quality - C)
Lipid Lowering Agents

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Meds</th>
<th>N</th>
<th>ALT</th>
<th>Hist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laurin</td>
<td>Open label</td>
<td>Clofibrate</td>
<td>16</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fernández-Miranda C</td>
<td>Open label</td>
<td>Fenofibrate</td>
<td>16</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Basaranoglu</td>
<td>RCT</td>
<td>Gemfibrozil</td>
<td>46</td>
<td>+</td>
<td>NA</td>
</tr>
</tbody>
</table>

• Given the lack of evidence to show that patients with NAFLD and NASH are at increased risk for serious drug-induced liver injury from statins, **statins can be used to treat dyslipidemia in patients with NAFLD and NASH** (US Guideline: Strength – 1, Quality – B)

• Until RCTs with histological endpoints prove their efficacy, **statins should not be used to specifically treat NASH** (US Guidelines: Strength – 1, Quality B)
### PPAR-γ Agonist

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Drug</th>
<th>Time</th>
<th>DM?</th>
<th>Cirrhosis</th>
<th>ALT</th>
<th>Fat</th>
<th>Bal</th>
<th>Infl</th>
<th>Fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caldwell 2001</td>
<td>10</td>
<td>Troglit 400 mg</td>
<td>3-6 months</td>
<td>1/10</td>
<td>Yes</td>
<td>Yes</td>
<td>?</td>
<td>No</td>
<td>?Yes</td>
<td>No</td>
</tr>
<tr>
<td>Promrat 2004</td>
<td>18</td>
<td>Pio</td>
<td>12</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

- **Pioglitazone** can be (?) used to treat steatohepatitis in patients with biopsy-proven NASH. However, it should be noted that majority of the patients who participated in clinical trials that investigated pioglitazone for NASH were non-diabetic and that **long term safety and efficacy** of pioglitazone in patients with NASH is not established. *(US Guidelines: Strength – 1, Evidence- B)*
## Newer Agents

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Effect on NAFLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucagon-like peptide-1 (GLP-1) analogs</td>
<td></td>
</tr>
<tr>
<td>• Suppress postprandial glucagon production</td>
<td></td>
</tr>
<tr>
<td>• Enhance satiety</td>
<td></td>
</tr>
<tr>
<td>• Improved steatosis and NASH histology in pre-diabetics</td>
<td></td>
</tr>
<tr>
<td>Dipeptidyl peptidase-4 (DPP-4) inhibitors</td>
<td></td>
</tr>
<tr>
<td>• Increase insulin synthesis/release</td>
<td></td>
</tr>
<tr>
<td>• Decreased liver enzymes</td>
<td></td>
</tr>
<tr>
<td>• Improved liver histology</td>
<td></td>
</tr>
</tbody>
</table>

## Treatment of NAFLD—New Regimens

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farnesoid X Receptor (FXR) Agonist</td>
<td>Obeticholic Acid (OCA)</td>
</tr>
<tr>
<td>Anti-lysyl oxidase-like 2 monoclonal antibody</td>
<td>Simtuzumab</td>
</tr>
<tr>
<td>Fatty acid/bile acid conjugate</td>
<td>Aramchol</td>
</tr>
<tr>
<td>Dual inhibitor of CCR2 and CCR5</td>
<td>Cenicriviroc</td>
</tr>
<tr>
<td>Dual peroxisome proliferator-activated receptor alpha/delta agonist</td>
<td>GFT505</td>
</tr>
<tr>
<td>Probiotics</td>
<td>VSL#3</td>
</tr>
</tbody>
</table>
Obeticholic Acid (OCA): A Modified Bile Acid and FXR Agonist

FXR binding site

OCA

FXR

RXR

FIBROSIS

- ↓ Stellate cell activation (PDGF)
- ↓ Fibrogenesis (TGF-β1)
- ↑ Matrix degradation (MMP-2)

INFLAMMATION

- ↓ NF-κB
- ↓ TNFα, IL-1β, IL-17, IFN-γ, etc.
- ↓ IgM
- ↓ CRP

BILE ACID HOMEOSTASIS

- ↓ Bile acid synthesis (CYP7A1)
- ↓ Bile acid uptake (OATP)
- ↑ Bile acid secretion (BSEP)
- ↓ Bile acid absorption (ASBT)
Phase 3 Trial Design- Obeticholic Acid (OCA) (FLINT Study)

**Primary endpoint:** liver histological improvement defined as decrease in NAFLD Activity Score (NAS) of ≥2 points with no worsening in fibrosis

![Diagram showing trial design with OCA 25 mg QD and Placebo QD treatments over a 72-week treatment period and 24 week off treatment.]

*N=283 Patients w/ Histological Evidence of NASH*

*Entry was based upon histologic diagnosis of nonalcoholic steatohepatitis (NASH) based on local CRN site pathologist’s read (end-of-study blinded central read of baseline biopsies revealed 80% of patients enrolled had definite NASH); interim analysis was conducted when ≥50% of patients completed treatment and had repeat liver biopsy; NAFLD: nonalcoholic fatty liver disease*

FLINT Primary Endpoint

• Improvement in NAFLD activity score* (NAS) ≥ 2 pts
  – *NAS = steatosis grade (0-3) + inflammation grade (0-3) + ballooning grade (0-2)

• No worsening of fibrosis

Improvement in Fibrosis and NASH Resolution (FLINT Study)

**Fibrosis**

- Placebo: 19%
- OCA: 35%
- p = 0.004

**NASH Resolution**

- Placebo: 13%
- OCA: 22%
- p = 0.08 (NS)

Adverse Events (FLINT Study)

- 6 severe adverse events in OCA group
  - 4 severe pruritus (1 stopped treatment)
  - 1 hypoglycemia
  - 1 possible cerebral ischemia (dysarthria and dizziness)

- Moderate or severe pruritus
  - 23% in obeticholic acid
  - 6% in placebo

\[ P < 0.0001 \]

```
```
Patients at High Risk for Disease Progression

• Established fibrosis is the best predictor of liver-related mortality$^{1,2}$
  – Hazard ratio (HR) = 20.4 for histologic documentation of fibrosis stage $\geq 2$
• Various factors have been shown to be associated with higher rates of fibrosis progression$^{3-5}$:
  – Diabetes
  – Elevated body mass index (BMI)
  – Elevated ALT
• Based on the literature, high-risk FLINT subgroup was defined:
  – Fibrosis stage 2 (perisinusoidal and portal/periportal) or stage 3 (bridging); or
  – Fibrosis stage 1 (perisinusoidal or periportal) if accompanied by one or more of:
    • Diabetes
    • Obesity (BMI $\geq 30$ kg/m$^2$)
    • Elevated ALT (ALT $\geq 60$ U/L)

**NASH Resolution in High-Risk Subgroup** ☞

**Overall Subgroup**

- **Obeticholic Acid**
  - n = 84
  - 18% of patients

- **Placebo**
  - n = 76
  - 5% of patients

**Subgroup by Baseline Fibrosis Stage**

- **Stage 1**
  - **Obeticholic Acid**
    - OCA n = 26
    - Placebo n = 18
    - 27% resolution
  - **Placebo**
    - 11% resolution

- **Stage 2**
  - **Obeticholic Acid**
    - OCA n = 25
    - Placebo n = 29
    - 16% resolution
  - **Placebo**
    - 3% resolution

- **Stage 3**
  - **Obeticholic Acid**
    - OCA n = 33
    - Placebo n = 29
    - 12% resolution
  - **Placebo**
    - 3% resolution

*p = 0.014; †NASH resolution as defined by NASH CRN pathologists; High-risk subgroup: patients with NAS ≥4 and fibrosis stage 2 or stage 3 or stage 1 with diabetes, BMI ≥30 kg/m2 or ALT ≥60 U/L; Intercept post hoc analyses.

**Fibrosis Improvement in High-Risk Subgroup**

Overall Subgroup

<table>
<thead>
<tr>
<th></th>
<th>Obeticholic Acid</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of Patients</td>
<td>n = 84</td>
<td>n = 76</td>
</tr>
<tr>
<td><strong>39%</strong></td>
<td><strong>21%</strong></td>
<td></td>
</tr>
</tbody>
</table>

Subgroup by Baseline Fibrosis Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Obeticholic Acid</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>OCA n=26, Placebo n=18</td>
<td>31%, 11%</td>
</tr>
<tr>
<td>Stage 2</td>
<td>OCA n=25, Placebo n=29</td>
<td>44%, 21%</td>
</tr>
<tr>
<td>Stage 3</td>
<td>OCA n=33, Placebo n=29</td>
<td>42%, 28%</td>
</tr>
</tbody>
</table>

*p=0.014; †NASH resolution as defined by NASH CRN pathologists; High-risk subgroup: patients with NAS ≥4 and fibrosis stage 2 or stage 3 or stage 1 with diabetes, BMI ≥30 kg/m2 or ALT ≥60 U/L; Intercept post hoc analyses. Neuschwander-Tetri B, et al. Lancet. 2015, 385 (9972), 956-965.
Peroxisome Proliferator-Activated Receptor (PPAR) Agonist

- PPAR-α
  - ↑ β-oxidation
  - ↓ Steatosis

- PPAR-γ
  - ↓ Steatosis
  - ↑ Insulin Sensitivity
  - ↓ Inflammation

- PPAR-α/δ
  - ↓ Hepatic Steatosis
  - ↑ Insulin Sensitivity
  - ↓ Inflammation
  - ↓ Fibrosis
  - ↓ Dyslipidemia

While no significant effect of elafibranor was observed on resolution of NASH without worsening of fibrosis as predefined in the protocol, in the global population, significant effect of elafibranor 120 mg was obtained with the new recommended definition.

---

**Resolution of NASH without Worsening of Fibrosis (N=274)**

- Protocol defined primary endpoint:
  - OR (95% CI) 1.53 (0.70–2.34), p=0.28
  - PBO (n=92): 17/23/21
  - Elafibranor 80 mg (n=93): 12/13/19
  - Elafibranor 120 mg (n=89)

- Updated definition:
  - OR (95% CI) 2.31 (1.02–5.24), p=0.045

---

*Complete resolution of ballooning and either 0 or 1 for lobular inflammation
Simtuzumab-Mechanism of Action

- Phase 2 trials ongoing
- Humanised monoclonal antibody
- Inhibits cross-linking of collagen in pathologic stroma
- Lysyl oxidase-like 2 (LOXL2) levels may correlate with extent of fibrosis and clinically relevant endpoints for idiopathic pulmonary fibrosis

How Do We Manage Our NAFLD Patients in 2016?

Histologic NASH or evidence of fibrosis
- Continue life style modifications
- If non-diabetic: Vitamin E
- If diabetic: Pioglitazone?

Liver biopsy

Steatosis no evidence of significant fibrosis
- Refer to primary for management of MS and risk of CVD

Medical treatment unsuccessful
- Consider RCT of new agents
- Consider bariatric surgery for those who meet criteria
Concluding Thoughts

- NAFLD has tremendous clinical, economic and QoL burden to the patients and to the society and this burden is growing globally
- NASH is the progressive form of NAFLD
- Histologic fibrosis (stage 2 or more) predicts LRM
- Pathogenesis of NASH is complex (multiple hits)
- Current treatment for patients with NASH:
  - Life style modifications for all
  - Vitamin E for non-DM NASH
  - ??Pio for DM with NASH but be aware of safety concerns
  - Consider bariatric surgery for morbidly obese+/-DM with NASH
- Future treatment considerations:
  - Clinical trials of new agents are underway
Back to Dr. Wells
Izzy

• She was counseled on lifestyles modifications. She started to lose weight but could only lose 3% of her initial weight despite only eating 1 meal/day.
• She has become frustrated, she does know what else to do. She is always hungry and all the things she likes to eat, she can’t eat.
• Her hepatologist recommended she start probiotics as there is emerging data on the benefits of probiotics in patients with NASH.
• She is also referred to a dietitian.
• Can diet and gut microbiome have any impact?
Metabolic Effects of Endotoxin Signaling

Nicolas Musi, MD
Director
Geriatric Research, Education and Clinical Center (GRECC)
Audie L Murphy VA Medical Center
Barshop Institute
University of Texas Health Science Center
San Antonio, TX
Inflammation and Metabolic Disease

Type 2 DM
Obesity
NAFLD

Sarcopenia
Muscle Mass
Strength
Elevated TLR4 Expression in Sk. Muscle from IR Subjects

Reyna et al. Diabetes 2008
A Low-dose Lipid Infusion Increases Muscle TLR Expression and Signaling

- Lean Healthy Volunteers (n=12, age = 40, BMI = 23)

- 48 hour Intralipid infusion

Hussey SE, Diabetologia. 2014
A Low-dose Lipid Infusion Does Not Increase Muscle Ceramides and DAGs

Hussey SE, Diabetologia. 2014
A Low-dose Lipid Infusion Increases TLR4 Expression/Signaling in Monocytes

Liang, Musi, unpublished
The gut epithelium is an efficient barrier that prevents absorption of LPS derived from Gram-negative gut microbiota.
Elevated LPS Levels in Plasma of Obese and T2DM Subjects

LPS inhibits insulin action in muscle

- Glucose transport assay
- Rat *epitrochlearis* muscle
- 4 h pre-incubation with LPS

Zhang, Musi, unpublished
Pharmacological inhibition of TLR4 with TAK242
Effect of TAK242 on insulin-stimulated glucose transport

TAK242 protects against high fat diet-induced IR

Zhang N, PLoS one. 2015
Inflammation and metabolic disease

Type 2 DM
Obesity

Sarcopenia
Muscle Mass
Strength
## Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Younger</th>
<th>Older</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>25.5 ± 1.0</td>
<td>73.8 ± 2.1*</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.5 ± 0.7</td>
<td>24.1 ± 1.0</td>
</tr>
<tr>
<td>Fasting Glucose (mg/dl)</td>
<td>77.6 ± 3.6</td>
<td>88.4 ± 2.0*</td>
</tr>
<tr>
<td>Fasting Insulin (mU/ml)</td>
<td>4.4 ± 0.7</td>
<td>6.9 ± 1.1</td>
</tr>
<tr>
<td>VO₂max (ml/kg.min)</td>
<td>27.6 ± 2.4</td>
<td>16.5 ± 0.7*</td>
</tr>
<tr>
<td>IL6 (pg/ml)</td>
<td>1.24 ± 0.26</td>
<td>2.1 ± 0.2*</td>
</tr>
<tr>
<td>TNF α (pg/ml)</td>
<td>1.14 ± 0.25</td>
<td>1.7 ± 0.3</td>
</tr>
</tbody>
</table>

*P<0.05 vs Younger group

Ghosh S, J Geront Biom Sci A. 2015
Metabolic endotoxemia in aging

Ghosh S, J Geront Biom Sci A. 2015
Intestinal Barrier Dysfunction and Aging

Intestinal Barrier Dysfunction
Predicts Death

Rera M, PNAS. 2012
Effect of LPS on Myotube Diameter

Arun Bhattacharya, unpublished
Human Interventions
Pharmacologic Inhibition of TLR4

Effect on:
1) Intralipid-induced IR (lean subjects)
2) Obese Subjects
3) T2DM Subjects
Reduction of plasma endotoxin concentration

Sevelamer

Bifidobacterium longum

Effect on:
1) HFD-induced IR (lean subjects)
2) Obese Subjects
3) T2DM Subjects
Summary

- Increased plasma endotoxin concentration is associated with metabolic disease (obesity, T2DM, NAFLD) and aging.
- Endotoxin induces insulin resistance in muscle and liver.
- Genetic and pharmacological blockade of endotoxin (TLR4) action improves insulin sensitivity in cell culture and animal models.
- Human studies to elucidate the role of metabolic endotoxemia on metabolic disease (IR, diabetes, NAFLD etc) are ongoing.
Acknowledgments

Maggie Liang
Joe Valentine
Sophie Hussey
Tam Sathavarodom
Sangeeta Ghosh
Sarah Reyna
Sophie Hussey
Terry Romo
Beverly Orsak
Helen Lum
Andrea Alvarez
Sara Espinoza
Becky Powers
Ji Li
You Zhou

NIDDK
NIA
ADA
VA
AFAR
Back to Dr. Wells
Izzy

• With the new dietary recommendations, she has lost 10% of her initial weight.
• She is ecstatic. She is now a volunteer Zumba instructor and has been reading up on what she can do to improve her prognosis.
• She goes back to see her hepatologist.
• She is concerned about her risk of liver cancer and wants to know how to be screened for this condition.
Obesity and the Link to Cancer

Jennifer T Wells, MD
Director
Regenerative Liver and Neoplasia
Texas Liver Institute
Assistant Professor, UTHSCSA
Austin, Texas
Cancer Related Deaths

• Prospective study of 900,000 individuals followed for 16 years

• BMI > 40  % increase cancer related death
  – Men:  (578/841) 52%  RR 1.52
  – Women: (329/522) 62%  RR 1.62

Calle, NEJM 2003
Position statement 2014:
"Obesity is quickly overtaking tobacco as the leading preventable cause of cancer in the United States"

The AICR 2015 Cancer Risk Awareness Survey Report

www.AICR.org
Public Awareness: Obesity and Cancer
How Does Obesity Cause Cancer?
State of Hormone Imbalance

Mauro et al, Front. Oncol., 2015
The American Institute for Cancer Research lists these cancers as linked to excess body fat.

### Obesity-Linked Cancers

**100,500 CASES PER YEAR**

- **49%** of endometrial cancers = 20,700 cases/year
- **35%** of esophageal cancers = 5,800 cases/year
- **28%** of pancreatic cancers = 11,900 cases/year
- **24%** of kidney cancers = 13,900 cases/year
- **21%** of gallbladder cancers = 2,000 cases/year
- **17%** of breast cancers = 33,000 cases/year
- **9%** of colorectal cancers = 13,200 cases/year
Possible Links

• Non-Hodgkin lymphoma
• Multiple myeloma
• Cervical
Obesity Worsens Cancer Outcomes

• Research has shown that a variety of cancers grow at faster rates in obese individuals versus in lean individuals.

• Furthermore, obesity appears to increase the chances that a patient’s cancer will metastasize.
Obesity Affects Cancer Treatment

- Decreased effective delivery of systemic cancer therapy
- Increased risk of growth/metastatic disease
- Morbidity from cancer treatment
- Poor wound healing, postoperative infections, and lymphedema
- Comorbid illnesses (eg, heart disease, cerebrovascular disease, and diabetes) in cancer survivors
- Increased risk of a 2nd primary
Hepatocellular Carcinoma

- Primary liver cancer: 90%
- 5\textsuperscript{th} most common cancer worldwide
- 3\textsuperscript{rd} cause of cancer death
- 5 year survival: 15%
HCC Incidence

HCC incidence during the past two decades has more than tripled in the United States, where it is the fastest increasing cause of cancer-related deaths.
Hepatocellular Carcinoma Trends in Texas and the US (SEER)

Hepatocellular Carcinoma Diagnoses, SEER & Texas, 1995-2010

- **Texas**
  - 16 Year PC = 120.8%
  - APC = 5.4%*

- **SEER**
  - 16 Year PC = 86.2%
  - APC = 4.3%*

*The APC is significantly different from zero (p<0.05)

Rates are per 100,000 and age-adjusted to the 2000 US Standard Population (19 age groups - Census P25-1130) standard. Percent changes were calculated using 1 year for each end point; APCs were calculated using weighted least squares method.

Data Sources: Texas Department of State Health Services, Cancer Epidemiology and Surveillance Branch, Texas Cancer Registry, Incidence – Texas, 1995-2010, Cut-off 11/30/12, SEER*Prep 2.5.2 and Incidence – SEER 13 Regs Research Data, Nov 2011 Sub.
Surveillance

• Important to follow and stage NAFLD so patients can be enrolled in surveillance
• Cirrhosis or advanced stage 3
  – US q 6 months
  – AFP not necessary
  – **Often cross-sectional imaging + AFP is used
• Fatty liver without advanced fibrosis: some risk however no official surveillance is recommended

HCC Treatments

• Surgical resection: Rare
• Liver transplantation
  – Milan
  – Region 4 Criteria
Milan Criteria

1 lesion ≤5 cm

3 or less lesions, none >3 cm

+ Absence of Macroscopic Vascular Invasion

Absence of Extra-hepatic Spread

Mazzeferro, *NEJM* 1996
Region 4

1 lesion $< 6$ cm

3 or less lesions, Each $\leq 5$

Absence of Macroscopic Vascular Invasion
Absence of Extra-hepatic Spread

Total tumor volume $< 9$ cm
HCC Treatments

• Surgical resection: Rare
• Liver Transplantation
  – Milan
  – Region 4 Criteria
• Radiofrequency Ablation
• Transarterial Chemo-embolization
• Radio-embolization
• Sorafenib
Summary

- Mass education
- Changing perceptions in large populations
- Appropriate evaluation with opportunity to improve risk factors
- Staging and enrollment in surveillance programs in those with advanced liver disease
Izzy

• She is diagnosed with HCC 2 years later. Treated with LRT.
• About a year later, she underwent liver transplantation.
• 3 years later, she is happy to be able to attend and dance at her son’s wedding.
Panel Discussion/Q&A