The Chronic Liver Disease Foundation (CLDF) and the International Coalition of Hepatology Education Providers (IC-HEP) present:

THE LIVER SUMMIT
Learning Objectives

• Identify the risk factors and symptoms of chronic liver disease

• Discuss laboratory tests and invasive/noninvasive methodologies used to ascertain the underlying cause and classify the stage of disease

• Describe screening and treatment for patients with cirrhosis/hepatocellular carcinoma

• Apply the AASLD guidelines on screening, diagnosis, and treatment of patients infected with chronic hepatitis C

• Recognize the safety and efficacy of currently available HCV therapies and those expected in the next 6 months and advise patients regarding treatment options based on their individual characteristics
Cirrhosis: Diagnosis and Management
Outline

• Diagnosis
• Prevalence
• Staging and Prognosis
• Complications of Cirrhosis
• Hepatic Encephalopathy
Cirrhosis

- Accumulation of collagen deposition = fibrosis → cirrhosis
- Final common pathway for most chronic liver diseases
- Histologically often indistinguishable from one another
- Note the loss of central venules, loss of the hepatic acinus, many regenerative nodules
- Former terms “micronodular” or “macronodular” largely abandoned
- “Liver Cirrhosis” is redundant

Cirrhosis: Symptoms and Signs

- Anorexia, weight loss
- Weakness, fatigue
- Muscle loss, cramps
- Nausea
- Vague (RUQ) abdominal pain
- Pruritus
- Easy bruising, epistaxis
- GI bleeding
- Confusion, sleep disturbance
- Amenorrhea or irreg menses
- Spider angiomata
- Palmar erythema
- Gynecomastia, testicular atrophy
- Abdominal distention, edema
- Parotid hypertrophy
- Dupuytren’s contractures
- Clubbing, leukonychia
- Jaundice, icterus
- Caput medusa
- Splenomegaly
- Enlarged left or caudate lobe
- Asterixis, fetor hepaticus
- Cachexia

However.....often asymptomatic
Cirrhosis: Diagnosis

- Gold standard remains liver biopsy
- Biopsy not required for all, “Clinical or radiologic cirrhosis”
- Clues: physical exam, abdominal imaging, low platelet count, AST:ALT ratio >1, cholestasis, low albumin, prolonged INR
- Non-invasive assays (FibroTest, APRI, FIB-4)
- U/S Elastography (FibroScan, Aixplorer), Magnetic Resonance Elastography
- Beware of non-cirrhotic portal hypertension
Transient Elastography

• Works by measuring shear wave velocity
• Non-invasive
• High concordance with biopsy
• Also effective in predicting portal hypertension
• Eliminates the need for biopsy in some patients

Afdhal NH. *Gastroenterol Hepatol (NY)* 2012;8:605-607.
Technical Limitations of Transient Elastography

- Ascites
- Morbid obesity
- Adipose tissue within the chest wall
- Acute hepatitis
- Congestive hepatopathy
- Post-prandial variability

Afdhal NH. Gastroenterol Hepatol (NY) 2012;8:605-607.
Prevalence
Prevalence of Cirrhosis

- Experts estimate that 5.5 million people in the United States have cirrhosis
- Many cirrhotics remain undiagnosed
  - 40% of cases of cirrhosis “latent”
- Twelfth leading cause of death in US

US Hospital Discharges Due to Cirrhosis Are Increasing

Number of Discharges With Cirrhosis*  

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of Discharges</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>403,665</td>
</tr>
<tr>
<td>2005</td>
<td>411,029</td>
</tr>
<tr>
<td>2006</td>
<td>436,901</td>
</tr>
<tr>
<td>2007</td>
<td>444,883</td>
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<td>2008</td>
<td>459,496</td>
</tr>
<tr>
<td>2009</td>
<td>498,181</td>
</tr>
<tr>
<td>2010</td>
<td>526,096</td>
</tr>
<tr>
<td>2011</td>
<td>576,573</td>
</tr>
</tbody>
</table>

*ICD-9-CM diagnosis codes 571.2, 571.5, 571.6; all listed diagnoses.

Progressive Increase in Incidence of HCV-Related Cirrhosis and HCC in US

Annual Prevalence Rates Between 1996 and 2006 Among HCV-Infected Veterans

Disease Severity and Prognosis
## Stages of Cirrhosis

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
<th>1-year mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Compensated <strong>without varices</strong></td>
<td>1%</td>
</tr>
<tr>
<td>2</td>
<td>Compensated <strong>with varices</strong></td>
<td>3%</td>
</tr>
<tr>
<td>3</td>
<td>Decompensated with ascites <strong>without variceal hemorrhage</strong></td>
<td>20%</td>
</tr>
<tr>
<td>4</td>
<td>Decompensated with or w/out ascites <strong>with variceal hemorrhage</strong></td>
<td>57%</td>
</tr>
</tbody>
</table>
Baveno IV International Consensus Workshop Staging System for Cirrhosis: 1-Year Outcome Probabilities

Cumulative Proportion of Patients Transitioning from Compensated to Decompensated Cirrhosis Over Time

Half of patients decompensated over 5 years

# Classification of Cirrhosis: Child-Turcotte-Pugh (CTP)

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Encephalopathy</strong></td>
<td>None</td>
<td>Grade 1 – 2 (or precipitant-induced)</td>
<td>Grade 3 – 4 (or chronic)</td>
</tr>
<tr>
<td><strong>Ascites</strong></td>
<td>None</td>
<td>Mild/Moderate (diuretic-responsive)</td>
<td>Severe (diuretic-refractory)</td>
</tr>
<tr>
<td><strong>Bilirubin (mg/dL)</strong></td>
<td>&lt;2</td>
<td>2-3</td>
<td>&gt;3</td>
</tr>
<tr>
<td><strong>Albumin (g/dL)</strong></td>
<td>&gt;3.5</td>
<td>2.8 - 3.5</td>
<td>&lt;2.8</td>
</tr>
<tr>
<td><strong>INR</strong></td>
<td>&lt;1.7</td>
<td>1.7-2.3</td>
<td>&gt;2.3</td>
</tr>
</tbody>
</table>

**Total Numerical Score**
- 5 - 6: Class A
- 7 - 9: Class B
- 10 - 15: Class C

**Child-Pugh Class**
- Class A considered “compensated”
- Class B/C considered “decompensated”

Classification of Cirrhosis Severity

Model for End Stage Liver Disease Score

- Calculated from 3 variables:
  - INR
  - Bilirubin
  - Serum creatinine
- The MELD score equation:
  - \[9.6 \times \log_e \text{creatinine (mg/dL)} + 3.8 \times \log_e \text{bilirubin (mg/dL)} + 11.2 \times \log_e \text{INR} + 6.4\]
- Eliminates subjectivity of HE and ascites evaluation used in CTP
- Etiology removed without affecting predictive ability

MELD and Survival

Cumulative Percent Surviving

Months from Listing

- < 15
- 15-20
- 20-29
- 30+

p < 0.001

92.3%
90.7%
66.0%
33.8%
MELD Score: 3 Month Mortality**

**Mortality includes death on waitlist and removed for “too sick”
Liver-Related Mortality in the US is Underestimated

- Liver related mortality in the United States is underestimated by the National Center for Health Statistics (NCHS), in part, as a result of incomplete inclusion of liver-related deaths.

- Use of an updated definition of liver mortality increased the estimated death rate by >2 fold from 11.7 to 25.7 deaths/100,000.
Hospital Readmissions Among Patients with Decompensated Cirrhosis are Common

- Retrospective study of 402 patients from an academic transplant center
- Follow-up time censored at death, elective admissions such as transplant or post-procedure observation, or the date of last clinic note; median follow-up was 203 days
- Included cirrhotic patients hospitalized for ascites, SBP, renal failure, hepatic encephalopathy, or variceal hemorrhage
- Median time to readmission was 67 days
- Median number of readmissions was 2 (range 0-40); overall rate was 3 hospitalizations/person-year

Complications of Cirrhosis
Complications of Cirrhosis: Distinguish Portal Hypertension from Liver Insufficiency

- Hepatopulmonary syndrome
- Portopulmonary hypertension
- Variceal hemorrhage
- Ascites, Hydrothorax
- SBP
- Hepatorenal syndrome
- Encephalopathy
- “Coagulopathy”
- Jaundice
- Hypoalbuminemia
General Management Guidelines - Cirrhosis

- Screen for hepatocellular carcinoma
  - Abdominal US (or CT/MRI) every 6 months
  - Alfa-fetoprotein (AFP) no longer recommended by AASLD but many experts still utilize
- Vaccinate for HAV, HBV, influenza (annual), Pneumovax; consider Zoster and HPV
- Avoid non-steroidals; acetaminophen preferred but in limited quantities (consider < 2-3gm/day)
- Cautious use of benzodiazepines and opioids; contraindicated in decompensated cirrhosis w/ HE
- Beware of raw shellfish (Vibrio vulnificus)
- Dietary considerations: adequate protein intake (1-1.2gm/kg/day), careful sodium intake (ideally <2gm/day)
General Management Guidelines - Varices

- **Screening endoscopy:**
  - All cirrhotic patients at diagnosis (*Class IIa, Level C*)
  - Every 2-3 years in Childs A with no or small varices
  - Annually in Childs B/C (or at time of decompensation)

- **Non-selective beta-blocker (NSBB: propranolol, nadolol, carvedilol):**
  - Childs B/C with small varices or Childs A with small varices with red signs (*Class IIa, Level C*)
  - Childs A with medium/large varices without red signs (*Class I, Level A*)
  - Childs A with small varices without red signs (*optional*) (*Class III, Level B*)

- **NSBB or Esophageal Variceal Ligation (EVL, “banding”):**
  - Medium/large varices in Childs B/C or Child A with red signs (*Class I, Level A*)

- **EVL:**
  - Acutely bleeding varices
  - Medium/large EV in Childs A, intolerant or non-compliant with NSBB (*Class I, Level A*)
  - All patients with previously bleeding varices (in combination with NSBB, secondary prophylaxis) (*Class I, Level A*)
Varices Increase in Diameter Progressively

No varices

Small varices
Lower risk of bleeding

Large varices
Higher risk of bleeding

7-8%/year

Merli et al. J Hepatol 2003;38:266
Hepatic Encephalopathy
Hepatic Encephalopathy: Pathophysiology

Astrocyte Swelling

Glutamate & NH₃
Glutamine

Cerebral Blood Flow

Increased brain water, deterioration in neuropsychological function & hepatic encephalopathy

Hepatic Encephalopathy: Pathophysiology

Astrocyte

Proinflammatory Cytokines

Nitric Oxide & Oxidative Stress

NH₃

Inflammation

Characterization of HE Stages

Categorization is often arbitrary and varies between raters.

Worsening cognitive dysfunction

“Overt” HE Stages

Clinical Diagnosis

AASLD PRACTICE GUIDELINE

Hepatic Encephalopathy in Chronic Liver Disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver

Hendrik Vilstrup, Piero Amodio, Jasmohan Bajaj, Juan Cordoba, Peter Ferenci, Kevin D. Mullen, Karin Weissenborn, and Philip Wong

Published online in Hepatology and Journal of Hepatology July 2014
Clinical Classification of HE

Hepatic encephalopathy should be classified according to the type of underlying disease, severity of manifestations, time course, and precipitating factors (GRADE III, A, 1).

<table>
<thead>
<tr>
<th>Type</th>
<th>Grade</th>
<th>Time Course</th>
<th>Spontaneous or Precipitated</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>MHE</td>
<td>Covert</td>
<td>Episodic</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td></td>
<td>Spontaneous</td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
<td>Recurrent</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Overt</td>
<td>Persistent</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td></td>
<td>Precipitated (specify)</td>
</tr>
</tbody>
</table>
Role of Ammonia Testing in HE

• “Increased blood ammonia alone does not add any diagnostic, staging, or prognostic value for HE in patients with CLD. A normal value calls for diagnostic reevaluation (GRADE II-3, A, 1)”
Specific Approach to Overt HE Treatment

• Four-pronged approach to management of HE (GRADE II-2, A, 1):
  – Initiation of care for patients with altered consciousness
  – Alternative causes of AMS should be sought and treated
  – Identification of precipitating factors and their correction
  – Commencement of empirical HE treatment
Management of Overt HE (OHE)

- Identify and treat precipitating factors for HE (GRADE II-2, A, 1)
  - Controlling precipitating factors is critical, because nearly 90% of patients can be treated with correction of the precipitating factor alone.
- Lactulose is the first choice for treatment of episodic OHE (GRADE II-1, B, 1)
- Rifaximin is an effective add-on therapy to lactulose for prevention of OHE recurrence (GRADE I, A, 1)
- Neomycin is an alternative treatment of OHE (GRADE II-1, B, 2)
- Metronidazole is an alternative treatment of OHE (GRADE II-3, B, 2)
- Lactulose is recommended for prevention of recurrent episodes of HE after the initial episode (GRADE II-1, A, 1)
- Rifaximin as an add-on to lactulose is recommended for prevention of recurrent episodes of HE after the second episode (GRADE I, A, 1)
- Routine prophylactic therapy (lactulose or rifaximin) is not recommended for the prevention of post-TIPS HE (GRADE III, B, 1)
- Under circumstances where the precipitating factors have been well controlled (i.e., infections and VB) or liver function or nutritional status improved, prophylactic therapy may be discontinued (GRADE III, C, 2)

Treatment Approach for Episodic OHE: Lactulose + Rifaximin vs. Lactulose

172 Cirrhotic Patients Screened

120 Patients Enrolled

Randomization

Lactulose (30-60 mL TID) + Rifaximin (one 400 mg capsule TID)
n=63 (10 grade 2, 20 grade 3, 33 grade 4)

Lactulose (30-60 mL TID) + Placebo (one sugar capsule TID)
n=57 (12 grade 2, 20 grade 3, 25 grade 4)
Treatment Approach for Episodic OHE: Lactulose + Rifaximin vs. Lactulose

- Given via nasogastric tube until recovery of HE or a maximum of 10 days
- Hospital stay was shorter with Lactulose + Rifaximin than with Lactulose + Pbo (5.8±3.4 vs. 8.2±4.6 days, P=0.001)

Summary

- Cirrhosis is increasing in prevalence in the U.S. and recognition with accurate diagnosis is critical for patient care.
- Histologic or clinical diagnosis.
- Be familiar with the various staging and prognostic tools: MELD, CTP, Baveno.
  - Recognize the clinical importance of transition from compensated to decompensated cirrhosis.
- HE is a frequent complication of cirrhosis.
  - Familiarize yourself with new guidelines for its diagnosis, classification, and treatment.
Global View of HCC

- Primary liver cancer increased from 437,408 cases in 1990 to 714,600 in 2002

- Incidence and mortality rates
  - Decreasing in areas of high and intermediate incidence, including China and Japan
  - Increasing in low-incidence areas, including the United States and Canada
The Incidence and 5-Year Survival of HCC in United States

Liver Fibrosis and HCC

HCC can occur in non-cirrhotic livers, but most HBV patients with HCC have cirrhosis.

HCC in HCV

- Prevalence of HCV+ HCC (20-90%)
- Relative Risk of HCC
  - Compared to HCV- controls (25 fold)
- Absolute Risk of HCC
  - HCC in HCV (1 per 100 at 30 years)
  - HCC in HCV-related cirrhosis (3.5 per 100 [1-7])
Risk Factors for HCC in Chronic HCV: Host Factors

- Older age
- Duration of HCV infection
- Male sex
- Race
- Alcoholism
- Obesity
- Diabetes
- HBV co-infection
- HIV co-infection
HCV Viral Factors and Risk of HCC

• HCV Viremia (HCV RNA)
  – Any level (vs. none)
  – High level (vs. low)
    • Taiwan study show high HCC risk
    • US studies only as predictor of treatment response

• HCV Genotype
  – Possibly GT 1b
    • Meta analysis (1.78 increase in HCC odds)
  – GT 3
HCV Genotype 3 in the VA HCV Clinical Case Registry 2000-2009: Cirrhosis and HCC

- 88,348 patients with genotype 1 (80%)
- 13,077 genotype 2 (12%)
- 8,337 genotype 3 (7.5%)
- Mean followup 5.4 years

After adjustment for demographic, clinical and antiviral treatment factors, comparison between genotypes 3 and 1:

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio</th>
<th>Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis</td>
<td>1.31</td>
<td>1.22-1.39</td>
</tr>
<tr>
<td>HCC</td>
<td>1.80</td>
<td>1.61-2.03</td>
</tr>
</tbody>
</table>

Conclusion: Genotype 3 is associated with a significantly higher risk of cirrhosis and HCC vs genotype 1, independent of age, diabetes, BMI or antiviral treatment

Kanwal F et al, Hepatology 2014;60:98-105
HCV-related Cirrhosis by Cohort

Davis GL, Alter MJ, El-Serag H, Poynard T, Jennings L Gastroenterology 2010
## Determinants of HBV Disease Progression

<table>
<thead>
<tr>
<th>HBeAg-positive</th>
<th>HBeAg-negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged interval before e-seroconversion</td>
<td>Persistent viral replication</td>
</tr>
<tr>
<td>Age &gt; 40</td>
<td>HBV-DNA</td>
</tr>
<tr>
<td>Mildly, persistently abnormal ALT</td>
<td>Abnormal ALT</td>
</tr>
<tr>
<td>Genotype (C &gt; B)</td>
<td>Precore/BCP mutation</td>
</tr>
<tr>
<td>Male</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
</tr>
<tr>
<td>Co-infection with HCV, HDV, HIV</td>
<td></td>
</tr>
</tbody>
</table>

Risk Factors for HCC in HBsAg-Positive Carriers

- Timing of HBV acquisition
- Older age
- Males > Females
- Cirrhosis > no cirrhosis
- Family History of HCC
- Heavy alcohol drinking
- Aflatoxin exposure
- HBeAg-positive carriers
- HBV genotype C
- HBV precore (decrease), core promoter (increase)
- Co-infection with HCV or HIV or HDV
Hepatitis B: Association Between Viral Load and Incidence of HCC

Baseline HBV DNA Level (copies/ml)

- ≥10⁶: 13.50%
- 10⁵–<10⁶: 7.96%
- 10⁴–<10⁵: 3.15%
- 300–<10⁴: 0.89%
- <300: 0.74%

Year of follow-up

HBeAg negative, normal ALT, no liver cirrhosis at entry (n=2,925)

Chen CJ et al. JAMA. 2006;295:65–73
REACH-B Model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Data</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>M/F</td>
<td>0-2</td>
</tr>
<tr>
<td>Age</td>
<td>Q 5 years over 30</td>
<td>0-6</td>
</tr>
<tr>
<td>ALT</td>
<td>&lt;15</td>
<td>0-2</td>
</tr>
<tr>
<td></td>
<td>15-44</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;45</td>
<td></td>
</tr>
<tr>
<td>HBeAg</td>
<td>+/-</td>
<td>0-2</td>
</tr>
<tr>
<td>HBV DNA</td>
<td>Und.</td>
<td>0-4</td>
</tr>
<tr>
<td></td>
<td>$\sim 10^4$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$\sim 10^5$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$\sim 10^6$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;$10^6$</td>
<td></td>
</tr>
</tbody>
</table>

- 60 year-old HBeAg+ male ALT 47, HBV DNA 50,000
- REACH-B score=13
Alcohol and Viral Hepatitis

Graph showing the relationship between alcohol intake (g/day) and log (odds ratio) with and without HCV and HBV infections.
Tobacco Smoking

- **Smoking alone**
  - Positive associations and no associations reported in different studies

- **Smoking PLUS HBV and HCV infection**
  - More than additive interaction between HBV infection and cigarette smoking
  - More than multiplicative interaction between HCV infection and cigarette smoking
HCV is the Dominant Risk Factor for HCC in the United States

- HBV most frequent in Asians
- HCV most frequent in whites and blacks
Mortality from Cancer in Obese US Men (n=900,053)

Calle, NEJM 2003
Obesity and Risk of HCC

- Systematic review of 10 cohort studies
  - Positive association between BMI and risk of HCC in 7 studies (relative risks ranging from 1.4 to 4.1)
  - No association in 2 studies
  - Inverse association in 1 study

- Limited by small number of cases with HCC, possibility of misclassification, and inconsistent adjustment for confounders
Diabetes Is Associated with a Two-fold Increase in Risk of HCC

NAFLD and Risk of HCC

- No evidence from population based data
- Possible increase in HCC risk in clinic based cohorts of NASH
  - ? Magnitude
  - ? Risk factors
- Consistent evidence from clinic based cohorts with NAFLD/NASH cirrhosis
  - Magnitude < HCV cirrhosis
  - Risk factors: obesity and diabetes
HCC in the Absence of Cirrhosis in United States Veterans

• ~13% of 1500 HCC cases developed in absence of cirrhosis

• These cases were more likely than HCC in cirrhosis to have
  – NAFLD or idiopathic compared to HCV or alcohol
  – Co-morbidities associated with metabolic syndrome

• While a small proportion, this poses logistical problems for HCC surveillance
## HCC Risk Factors:
Prevalence, Risk Estimates, Attributable Fraction?

<table>
<thead>
<tr>
<th></th>
<th>Prevalence in general population</th>
<th>Risk estimate of HCC</th>
<th>Current prevalence in HCC cases</th>
<th>Population attributable fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV</td>
<td>0.5-1%</td>
<td>20-25</td>
<td>10-15%</td>
<td>5-10%</td>
</tr>
<tr>
<td>HCV</td>
<td>1-2%</td>
<td>20-25</td>
<td>30-60%</td>
<td>20-25%</td>
</tr>
<tr>
<td>Alcoholic liver disease</td>
<td>10-15%</td>
<td>2-3</td>
<td>20-30%</td>
<td>20-30%</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>30-40%</td>
<td>1.5-2.5</td>
<td>20-50%</td>
<td>30-40%</td>
</tr>
</tbody>
</table>
Prevention of HCC

- HBV vaccination
- Treatment of viral hepatitis
- Coffee
- Statins
- Surveillance for HCC
HBV Vaccination and HCC: Taiwan Experience

Decreased Incidence of Hepatocellular Carcinoma in Hepatitis B Vaccinees: A 20-Year Follow-up Study


- HCC prevention extended from childhood to early adulthood
- Failures: incomplete vaccination, maternal HBsAg or HBeAg
HCC and Hepatitis C Treatment

A

<65 years

Cumulative incidence of HCC (%)

Year

Non-SVR

SVR

0 5 yrs. 10 yrs. 15 yrs.

Patients with HCC

565

Cumulative incidence 0%

of HCC

0 0 6 12 12

376 184 56

1.2% 3.3% 3.3%

B

≥65 years

Non-SVR

SVR

0 5 yrs. 10 yrs. 15 yrs.

Patients with HCC

121

Cumulative incidence 0%

of HCC

0 7 10 10

67 21 5

6.0% 11.0% 11.0%

Patients with HCC

980

Cumulative incidence 0%

of HCC

33 72 85

723 345 141

3.6% 10.9% 15.5%

0 46 61 64

376 179 43 25

14.1% 25.5% 31.1%
Impact of HBV Treatment on HCC

• Randomized controlled trial comparing lamivudine versus placebo
  – Patients with advanced fibrosis or cirrhosis
  – HBV-DNA (>10^5 copies/mL) or HBeAg+
  – Study terminated prematurely by DSMB (median Tx=32.4 mo)

Prevention of HCC (Antiviral Treatment)

Efficacy in Clinical Trials and Research Centers

Effectiveness in Community Practice

Efficacy x Access x Correct Diagnosis x Recommendation x Acceptance x Adherence

Statins and HCC
Systematic Review

- Ten studies
  - 7 observational, 3 clinical trials
- Pooled OR: 0.63 (0.52-0.76)
  - Not in the 3 clinical trials
- Not other lipid lowering medications
- Unclear
  - Dose, duration, type
Metformin and Reduced Risk of HCC in Diabetic Patients: a Meta-analysis

• Seven studies:
  – Three cohort studies
  – Four case-control studies

• Significantly reduced risk of HCC in metformin users versus nonusers in diabetic patients
  – RR: 0.24, 95% CI 0.13–0.46, $p < 0.001$
Epidemiologic studies: coffee consumption is inversely related to
- Serum liver enzyme activity
- Liver cirrhosis
- HCC

For each additional 1 cup of coffee:
- Case-control studies
  - (0.77, 0.72-0.83)
- Cohort studies
  - (0.75, 0.65-0.85)
HCC Surveillance: Randomized Controlled Trials

- Cirrhosis (NONE)
- Hepatitis C infection (NONE)
- Hepatitis B infection carriers
  - China
  - Two trials
  - One showed benefit (Zhang et al. 2004)
  - One did not show benefit (Chen et al. 2003)
Surveillance for HCC Reduces Mortality: A Randomized Controlled Trial of AFP+US q 6 months

## Recommended Groups for HCC Surveillance

<table>
<thead>
<tr>
<th>Population Group</th>
<th>Threshold Incidence for Efficacy of Surveillance (&gt;0.25 LYG)(%/year)</th>
<th>Incidence of HCC (%/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asian male hepatitis B carriers &gt; age 40</td>
<td>0.2</td>
<td>0.4–0.6</td>
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<td>Asian female hepatitis B carriers &gt; age 50</td>
<td>0.2</td>
<td>0.3–0.6</td>
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<td>Hepatitis B carrier with family history of HCC</td>
<td>0.2</td>
<td>Incidence higher than without family history</td>
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<td>African/North American Blacks</td>
<td>0.2</td>
<td>HCC occurs at a younger age</td>
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<td>Cirrhotic hepatitis B carriers</td>
<td>0.2-1.5</td>
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<tr>
<td>Hepatitis C cirrhosis</td>
<td>1.5</td>
<td>3–5</td>
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</table>

### Groups in Whom the Risk of HCC is Increased, but in Whom Efficacy of Surveillance Has Not Been Demonstrated

<table>
<thead>
<tr>
<th>Population Group</th>
<th>Threshold Incidence for Efficacy of Surveillance (&gt;0.25 LYG)(%/year)</th>
<th>Incidence of HCC (%/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B carriers &lt;40 (males) or 50 (females)</td>
<td>0.2</td>
<td>&lt;0.2</td>
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<tr>
<td>Hepatitis C and stage 3 fibrosis</td>
<td>1.5</td>
<td>&lt;1.5</td>
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<tr>
<td>Noncirrhotic NAFLD</td>
<td>1.5</td>
<td>&lt;1.5</td>
</tr>
</tbody>
</table>

AFP and Des-gamma-carboxy Prothrombin (DCP) in the Early Diagnosis of HCC

- 1031 patients randomized in the Hepatitis C Antiviral Long-term Treatment Against Cirrhosis (HALT-C) Trial
  - Nested case-control study of 39 HCC cases and 77 controls
- Testing within one month prior to HCC diagnosis
- DCP: sensitivity (74%) and specificity (86%) at a cutoff of 40 mAU/mL
- AFP: sensitivity (61%) and specificity (81%) at a cutoff of 20 ng/mL
- Combining both markers increased the sensitivity to 91% at month 0 but the specificity decreased to 74%
Ultrasound Surveillance in Early HCC: Systematic Review

Study

Surveillance every 6 months or less
Kobayashi 1985
0.50 (0.15, 0.85)
Oka 1900
0.68 (0.53, 0.82)
Pateron 1904
0.75 (0.33, 0.99)
Cottone 1994
0.91 (0.82, 1.01)
Zoli 1996
0.70 (0.56, 0.85)
Henrion 2000
0.67 (0.29, 1.04)
Bolondi 2001
0.82 (0.72, 0.92)
Subtotal ($I^2 = 83.6\%, P = 0.000$)

Surveillance 6–12 months
Arrigoni 1998
0.69 (0.46, 0.91)
Tradati 1998
0.33 (−0.04, 0.71)
Santagostino 2003
0.25 (−0.05, 0.55)
Sangiovanni 2004
0.50 (0.41, 0.60)
Sangiovanni 2006
0.50 (0.38, 0.62)
Subtotal ($I^2 = 33.8\%, P = 0.196$)
HCC Surveillance Recommendations

- The target population for surveillance are those with liver cirrhosis (and HBV-infected patients without cirrhosis in special circumstances).
- US and AFP are the recommended screening tests for HCC in patients at the highest risk:
  - US is central
  - Not AFP alone
  - Premature to recommend dropping AFP
Diagnostic Criteria for HCC

Mass on surveillance ultrasound (US) in a cirrhotic liver

- **<1 cm**
  - Repeat US every 3-4 mo
  - Stable >18-24 mo
    - Return to surveillance every 6-12 mo
  - Enlarging
    - Proceed according to lesion size

- **1-2 cm**
  - Two dynamic imaging studies
    - Coincidental typical vascular pattern
    - Typical vascular pattern with 1 technique
    - Atypical vascular pattern with both techniques
      - Biopsy
        - Diagnostic of HCC
        - Nondiagnostic of HCC
          - Repeat biopsy or imaging follow-up
            - Change in size/profile
              - Repeat imaging and/or biopsy

- **>2 cm**
  - One dynamic imaging technique
    - Atypical vascular pattern
      - Typical vascular pattern on dynamic imaging or AFP >200 ng/mL
      - Other diagnosis
        - Repeat imaging and/or biopsy

Treat as HCC

Adapted from Bruix J and Sherman M. Hepatology. 2005; 42(5):1208
Hepatocellular Carcinoma: Treatment

Very early stage
1 HCC <2 cm
Carcinoma in situ

1 HCC
Portal pressure / bilirubin
Normal
Resection

Early stage
1 HCC or 3 nodules <3 cm, PS 0

3 nodules <3 cm
Associated diseases

Intermediate stage
No portal vein thrombosis
Multinodular, PS 0

Chemo-embolization

Advanced stage
Portal invasion
Metastases, PS 0-2

Sorafenib

Terminal stage

Potential curative treatments
Resection

Palliative treatments

Symptomatic Therapy

Hepatocellular Carcinoma: Treatment
Very Early Stage HCC

Tumors < 2 cm with normal synthetic function
Hepatocellular Carcinoma: Treatment
Randomized Trial of RFA versus Resection for Very Early HCC

- Study Groups: RFA = 71; Resection = 90

- No difference among groups in terms of liver function, performance status and tumor burden (all < 3 cm)

Hepatocellular Carcinoma: Treatment
Early Stage HCC (Milan)

Single Tumor 2-5 cm or < 3 lesions each < 3 cm
with Child class A or B
Hepatocellular Carcinoma: Treatment Transplantation (LT)

- Curative for HCC and chronic liver disease
- MELD exception points for HCC
- Live donor LT considered for HCC progression outside MILAN criteria
- UCSF criteria not implemented in current MELD exception allocation policy

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<td>1 year</td>
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<td>2 year</td>
<td>75%</td>
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<tr>
<td>5 year Milan</td>
<td>&gt;70%</td>
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<tr>
<td>5 year (extended)</td>
<td>~50%</td>
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Hepatocellular Carcinoma: Treatment
Intermediate Stage

Single Tumor > 5 cm or multifocal tumor WITHOUT vascular Involvement; Child class A or B
## Sensitivity Meta-Analysis of Core RCTs Reporting 1 or 2-year Survival with Chemoembolization / Embolization: Various Treatment Comparisons

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<td>Treatment vs control: 1 year survival</td>
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</table>

Favors Treatment | Favors Control

P = 0.022

P = 0.039

P = 0.021

P = 0.14

P = 0.051

Adapted from Llovet JM, Bruix J. *Hepatology* 2003; 37:429
Phase III SHARP Trial: Overall Survival (Intent-to-Treat Population)

Hazard ratio (Sorafenib/Placebo): 0.69 (95% CI, 0.55-0.87)  
P = 0.00058*

Sorafenib
Median: 10.7 months (95% CI, 40.9-57.9)
Placebo
Median: 7.9 months (95% CI, 29.4-39.4)

*O'Brien-Fleming threshold for statistical significance was P = 0.0077; CI=confidence interval
Llovet JM et al. NEJM. 2008; 359(4):378
Kaplan-Meier Analysis: Overall Survival, Time to Symptomatic Progression, Time to Radiologic Progression With Sorafenib

Management of Hepatocellular Carcinoma Requires a Multidisciplinary Approach

Hepatobiliary Surgery

Hepatology

Pathology

Liver Transplant Program

Oncology

Radiology
Nonalcoholic Fatty Liver Disease (NAFLD) and Nonalcoholic Steatohepatitis (NASH)
Visceral Obesity

NAFLD is Closely Associated with Visceral Obesity and Insulin Resistance

Dyslipidemia
Hypertension
Endothelial Dysfunction
Atherosclerosis
Insulin Resistance
Type 2 Diabetes

Polycystic Ovarian Syndrome (PCOS)
Coronary Artery Disease (CAD)
Non-alcoholic Fatty Liver Disease (NAFLD)
The Spectrum of NAFLD

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

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

Prevalence of NAFLD in Children

• Using surrogate markers, prevalence of NAFLD in children is 2.6-17.3%

• Autopsy study from UCSD (N=742)
  – Prevalence: 9.6%, rates increasing with age
  – More common in boys
  – Highest rate in Hispanics
Prevalence of NAFLD in Large US Cohort

- Cohort: 11,613 NHANES-III participants
- NAFLD was defined as the presence of moderate-severe hepatic steatosis (by ultrasound), absence of excessive alcohol use and other chronic liver diseases
- Prevalence of overall NAFLD: 18.8% (N=2,185)

Younossi Z et al. *Medicine* Vol 91, Number 6, November 2012
Comparison of Lean and Non-Lean Patients with NAFLD

- NAFLD
  - 7% in lean population
  - 28% in overweight-obese population
- Both lean and non-lean NAFLD patients were older, more commonly of Hispanic ethnicity and had components of metabolic syndrome
- Data validates the independent association of NAFLD with components of metabolic syndrome and Hispanic ethnicity in a large population-based study

Younossi Z et al. *Medicine* Vol 91, Number 6, November 2012

- 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.

Younossi Z et al. *Clin Gastro and Hep* 2011
Natural History of the Spectrum of NAFLD
Simple Steatosis or NAFL

Most patients

Simple Steatosis

A few patients

NASH

Natural History of NAFLD
Evidence to Support Progression of NASH

Tertiary Medical Centers Data
Sequential Biopsies Data
Community Based Data
Population Based Data
Cryptogenic Cirrhosis Data
HCC Data
NAFLD and HCC

• Several case reports and case series of well documented HCC in patients with NAFLD/NASH
• Two population-based cohort studies of NAFLD
  – One study suggested 0.3% over 6 years
• Three clinic based cohort studies of NAFLD or NASH (not restricted to cirrhosis)
  – Between 0 and 6% absolute risk of HCC in approximately 20 year follow up
  – Lower relative risk compared to alcohol or HCV

Summary of Outcomes of NASH

Can We Predict the Outcomes of Patients with NAFLD?
Predicting Outcomes of NAFLD
Liver Related Mortality

- 209 NAFLD patients with liver biopsy slides, clinical data and mortality data were included.
- Median follow up = 146 months (max 342 months).
- During follow-up, 31% of patients died with 9% dying of LRM.
- Regardless of the pathologic criteria used, NASH patients had higher LRM than non-NASH NAFLD
  - (13.0% vs. 1.3% for Original NAFLD NASH, p = 0.0047)
Association of Pathologic Features with LRM

Univariate survival analyses [HR (95% CI) , p-value]

- Portal inflammation (grade ≥ 2)  [6.68 (2.20-20.3), p<0.001]
- Ballooning degeneration (grade ≥ 2)  [5.32 (1.89-14.9), p=0.001]
- Mallory-Denk bodies (grade ≥ 2)  [4.21 (1.66-10.7), p=0.002]
- Portal fibrosis (grade > 2)  [14.1 (5.47-36.5), p<0.001]
- Pericellular fibrosis (grade > 2)  [4.86 (1.73-13.7), p=0.003]
Association of Pathologic Features with LRM

- On multivariate analysis, only significant fibrosis (grade > 2) was an independent predictor of LRM
Predicting Advanced Fibrosis
NAFLD Patients With Components of MS are at Highest Risk for Advanced Fibrosis

- 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-value<0.0001)

Predicting Mortality
Long-term Outcomes of Diabetics with NAFLD

• NAFLD & DM (n=44) vs. NAFLD alone (n=88)

• Patients with NAFLD and DM have*:
  – Higher rate of cirrhosis (25% vs. 10.2%, p=0.04)
  – Higher liver-related mortality (RR=22.83, p=0.003)
  – Higher mortality (RR=3.3, p=0.002)

*Average follow up = 10 years

Younossi et al. Clin Gastro and Hepatology 2004
Predicting Outcomes of NAFLD
Liver Related Mortality

• NHANES III-NDI Linked Mortality Files (N=15,866)
  – NAFLD (N=991) and No Liver Disease (13,004)
• Over 160 months, 3,662 deaths (177 NAFLD)
• Independent risks for liver-related mortality in NAFLD:
  – IR: AHR = 53.55 (9.22 - 344.29), p < 0.0001
  – Obesity: AHR = 11.19 (2.43 - 51.56), p = 0.003
  – Metabolic syndrome: AHR = 12.08 (1.10 - 132.22), p = 0.042
  – Older age: AHR = 1.10 (1.08 - 1.12), p = 0.020
  – Male gender: AHR = 9.53 (1.36 - 66.55), p = 0.024
Predictors of Advanced Fibrosis or Liver-related Mortality

<table>
<thead>
<tr>
<th>Variables</th>
<th>Angulo</th>
<th>Marchesini</th>
<th>Ratziu</th>
<th>Dixon</th>
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Clinical Presentation & Routine Laboratory Data

Liver Biopsy & Pathologic Protocols

Routine Radiologic Tests (Ultrasound, CT, MRI)

Diagnostic & Prognostic Tests for NASH

New Biomarkers (NASH or Fibrosis)

Predictive Panels Based on Clinical and Lab Data

New Radiologic Modalities (Fibroscan MRS)
Radiologic Assessment of Non-alcoholic Fatty Liver Disease

- **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>
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<th>Study</th>
<th>Yr</th>
<th>N</th>
<th>Mod</th>
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<tr>
<td>Mathiesen</td>
<td>2002</td>
<td>165</td>
<td>US</td>
<td>• Echogenicity could not detect fibrosis</td>
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<td>Saadeh</td>
<td>2002</td>
<td>25</td>
<td>US, CT, MRI</td>
<td>• Excellent to predict&gt;30% steatosis</td>
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<td></td>
<td></td>
<td></td>
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<td>• Unable to diagnose NASH and stage fibrosis</td>
</tr>
<tr>
<td>Brunt</td>
<td>2004</td>
<td>30</td>
<td>CT</td>
<td>• Hepatic fat content (L/S) not associated with steatohepatitis and fibrosis</td>
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</table>
NAFLD Guideline Recommendations
Non-invasive Assessment

• NAFLD Fibrosis Score is a clinically useful tool for identifying NAFLD patients with higher likelihood of having bridging fibrosis and/or cirrhosis (Strength - 1, Evidence - B)

• Although serum/plasma CK18 is a promising biomarker for identifying steatohepatitis, it is premature to recommend in routine clinical practice (Strength - 1, Evidence - B)
## Pathologic Protocols Used in NASH

| **Ludwig, 1980**  
| (Original) | • Steatosis, lobular inflammation, necrosis and Mallory bodies in zone 3, mild portal and periportal inflammation |
| **Younossi, 1999**  
| (NAFLD Subtypes) | • Steatosis, ballooning degeneration  
| | • Steatosis, ballooning with either Mallory’s hyaline or fibrosis |
| **Brunt, 1999**  
| (Brunt Criteria) | • Steatosis with mixed inflammation, occasional ballooned hepatocytes  
| | • Steatosis, ballooning and disarray in zone 3  
| | • Panacinar steatosis + ballooning + disarray + portal inflammation |
| **Kleiner, 2005**  
| (NAS Criteria) | • Steatosis (0-3), lobular inflammation (0-3), ballooning (0-3)  
| | • 0-2 not NASH  
| | $\geq 5$ usually NASH |
Role of Biopsy

- Liver biopsy should be considered in patients with NAFLD who are at increased risk to have steatohepatitis and advanced fibrosis (Strength - 1, Evidence - B)

- Liver biopsy should be considered in patients with suspected NAFLD in whom competing etiologies for hepatic steatosis and co-existing chronic liver diseases cannot be excluded without a liver biopsy (Strength - 1, Evidence - B)
Targets for Treatment and Intervention
Targets Used for Treatment of Non-alcoholic Fatty Liver Disease

GLP-1 ANALOGS and DPP-4 INHIBITORS

METFORMIN and Tiazolidinediones

LIFESTYLE CHANGES

FXR AGONISTS

ORLISTAT

STATINS and EZETIMIBE

Insulin resistance

Obesity

Dyslipidemia

NAFLD

CANNABINOID CB2 ANTAGONISTS

Adipokines

PENTOXIFYLLINE and ANTI-TNFα

PUFAs

PPAR δ PPAR α/δ

FIBRATES

ANTIOXIDANTS

UDCA and DERIVATIVES

Oxidative stress

MONOClonal ANTIBODY

Fibrosis

NASH

Cirrhosis HCC

RAS BLOCKERS
# Treatment of NAFLD: Weight Loss

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<th>N</th>
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<th>Duration (months)</th>
<th>Design</th>
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<td>+</td>
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</tbody>
</table>

*Improvement denoted by +; No change denoted by -
### 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>
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<td>91</td>
<td>RYGB</td>
<td>18.4 months</td>
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<td>↓ / 0</td>
<td>↓</td>
<td>Improved lobular but no change in portal fibrosis</td>
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<td>Luyckx</td>
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<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>
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<tr>
<td>Kral</td>
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<td>104</td>
<td>Bilopancreatic diversion (BPD)</td>
<td>74 ± 27 months</td>
<td>↓</td>
<td>NR</td>
<td>↑</td>
<td>Increase in fibrosis overall was small)</td>
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<tr>
<td>Clark</td>
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<td>16</td>
<td>RYGB</td>
<td>10 ± 4 months</td>
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<td>↓</td>
<td>↓</td>
<td>Improvement in lobular and portal fibrosis, ALT and AST</td>
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<tr>
<td>Keshishian</td>
<td>2005</td>
<td>78</td>
<td>BPD-duodenal switch (BPD-DS)</td>
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<td>↓</td>
<td>NR</td>
<td>NASH grade improved. No significant reduction in LFTs.</td>
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<tr>
<td>Mattar</td>
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<td>70</td>
<td>RYGB, LAGB or SG</td>
<td>15 ± 9 months</td>
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<td>↓</td>
<td>↓</td>
<td></td>
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<tr>
<td>Mottin</td>
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<td>RYGB</td>
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<td>Stratopoulos</td>
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<td>216</td>
<td>VBG</td>
<td>18 ± 9.6 months</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>Improvement is ALT and AST</td>
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<tr>
<td>Meinhardt</td>
<td>2006</td>
<td>30</td>
<td>End-to-side jejuni-ileal bypass</td>
<td>70 ± 42.8 months</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>No change in histology scores. ALT and AST levels tended higher.</td>
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</tbody>
</table>
Bariatric Surgery and NAFLD

<table>
<thead>
<tr>
<th>Study First Author</th>
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<th>Change in Fibrosis</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>Csendes</td>
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<td>16</td>
<td>RYGB</td>
<td>22 months</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>“normalisation of histology” reported</td>
</tr>
<tr>
<td>de Almeida</td>
<td>2006</td>
<td>16</td>
<td>RYGB</td>
<td>23.5 ± 8.4 months</td>
<td>NR</td>
<td>↓</td>
<td>NR</td>
<td>Reductions in hepatocellular ballooning and lobular inflammation</td>
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<td>60</td>
<td>LAGB</td>
<td>29.5 ± 16 months</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>Improvements in inflammation and fibrosis with lowering in GGT</td>
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<td>7</td>
<td>RYGB</td>
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<td>↓</td>
<td>NR</td>
<td>NR</td>
<td>GGT the only enzyme to fall significantly</td>
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<tr>
<td>Puruya</td>
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<td>18</td>
<td>RYGB</td>
<td>24 months</td>
<td>↓</td>
<td>NR</td>
<td>↓</td>
<td>No improvement in portal fibrosis. ALT improved</td>
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<tr>
<td>Liu</td>
<td>2007</td>
<td>39</td>
<td>RYGB</td>
<td>18 months</td>
<td>↓</td>
<td>NR</td>
<td>↓</td>
<td>No change 1 and 5 year follow-up Reduced ALT and GGT</td>
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<tr>
<td>Mathurin</td>
<td>2006; 2009</td>
<td>185</td>
<td>BPD, LAGB, RYGB</td>
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<td>↓</td>
<td>0</td>
<td>↑</td>
<td>Reduced ALT and GGT</td>
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<tr>
<td>Bell</td>
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<td>20</td>
<td>RYGB, LAGB, SG</td>
<td>15 months</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>Reduced ALT and GGT</td>
</tr>
<tr>
<td>Weiner</td>
<td>2010</td>
<td>116</td>
<td>LAGB, RYGB, BPD-DS</td>
<td>18 months</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>Reduced ALT and GGT</td>
</tr>
<tr>
<td>Tai</td>
<td>2011</td>
<td>21</td>
<td>RYGB</td>
<td>12 months</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>No overall improvement in portal fibrosis.</td>
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<tr>
<td>Moretto</td>
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<td>NR</td>
<td>↓</td>
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<tr>
<td>Vargas</td>
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<td>26</td>
<td>Banded - RYGB</td>
<td>16 months</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td></td>
</tr>
</tbody>
</table>
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 weight 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)
<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Drug</th>
<th>Duration (months)</th>
<th>Design</th>
<th>ALT</th>
<th>Histology</th>
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</thead>
<tbody>
<tr>
<td>Caldwell</td>
<td>10</td>
<td>Troglitazone</td>
<td>3-6</td>
<td>Open label</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Acosta</td>
<td>8</td>
<td>Pioglitazone</td>
<td>2-12</td>
<td>Open label</td>
<td>+</td>
<td>N/A</td>
</tr>
<tr>
<td>Shadid</td>
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<td>Pioglitazone</td>
<td>4.5</td>
<td>Open label</td>
<td>+</td>
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</tr>
<tr>
<td>Sanyal</td>
<td>21</td>
<td>Pioglitazone + Vit E</td>
<td>6</td>
<td>RCT</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Promrat</td>
<td>18</td>
<td>Pioglitazone</td>
<td>12</td>
<td>Open label</td>
<td>+</td>
<td>+</td>
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<tr>
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<td>Rosiglitazone</td>
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<td>+</td>
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<tr>
<td>Belfort</td>
<td>55</td>
<td>Pioglitazone ± Diet</td>
<td>6</td>
<td>RCT</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Torres</td>
<td>49</td>
<td>R vs.R+M vs. R+Losartan</td>
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<td>Open</td>
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<td>Yes (No D)</td>
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<tr>
<td>Marchesini</td>
<td>14</td>
<td>Metformin</td>
<td>4</td>
<td>Open label</td>
<td>+</td>
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<tr>
<td>Nair</td>
<td>15</td>
<td>Metformin</td>
<td>12</td>
<td>Open label</td>
<td>+</td>
<td>N/A</td>
</tr>
<tr>
<td>Bugianesi</td>
<td>55</td>
<td>Metformin</td>
<td>6</td>
<td>RCT</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Uygun</td>
<td>17</td>
<td>Metformin</td>
<td>6</td>
<td>RCT</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Duseja</td>
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<td>Metformin</td>
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<td>Open label</td>
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<td>N/A</td>
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<td>Schwimmer</td>
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<td>Metformin</td>
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<td>Open label</td>
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<tr>
<td>Morita</td>
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<td>Nateglinide</td>
<td>5</td>
<td>Open</td>
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<td>Yes</td>
</tr>
</tbody>
</table>
NAFLD Guideline Recommendations

• Metformin has no significant effect on liver histology and is not recommended as a specific treatment for liver disease in adults with NASH. (Strength - 1, Evidence - A)

• Pioglitazone can be (?) used to treat steatohepatitis in patients with biopsy-proven NASH. (Strength - 1, Evidence - B)
  – However, the majority of patients who participated in clinical trials that investigated pioglitazone for NASH were non-diabetic
  – Long term safety and efficacy of pioglitazone in patients with NASH is not established
<table>
<thead>
<tr>
<th>Therapy</th>
<th>Author</th>
<th>N</th>
<th>Design</th>
<th>Duration (Months)</th>
<th>ALT Improve</th>
<th>Histo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin E</td>
<td>Lavine</td>
<td>11</td>
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<td>4-10</td>
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<tr>
<td>Vitamin E</td>
<td>Kawanaka</td>
<td>10</td>
<td>Open</td>
<td>6</td>
<td>Yes</td>
<td>N/A</td>
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<tr>
<td>Vitamin E</td>
<td>Sanyal</td>
<td>10</td>
<td>RCT</td>
<td>6</td>
<td>Yes</td>
<td>N/A</td>
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<tr>
<td>Vitamin E</td>
<td>Hasegawa</td>
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<tr>
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<td>Vajro</td>
<td>14</td>
<td>RCT</td>
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<tr>
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<tr>
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<td>Open</td>
<td>3</td>
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<td>N/A</td>
</tr>
<tr>
<td>Vitamins E+C</td>
<td>Harrison</td>
<td>23</td>
<td>RCT</td>
<td>6</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
NAFLD Guideline Recommendations

• Vitamin E (a-tocopherol) administered at daily dose of 800 IU/day improves liver histology in non-diabetic adults with biopsy-proven NASH and therefore 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 (Strength - 1, Quality - C)
## Treatment: Lipid Lowering Agents

<table>
<thead>
<tr>
<th>Study</th>
<th>Design (pts)</th>
<th>Meds</th>
<th>N</th>
<th>ALT</th>
<th>Hist</th>
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<tbody>
<tr>
<td>Laurin</td>
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<td>Clofibrate</td>
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<tr>
<td>Fernández-Miranda C</td>
<td>Open label (12)</td>
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<td>+</td>
<td>+/-</td>
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<tr>
<td>Basaranoglu</td>
<td>RCT (1)</td>
<td>Gemfibrozil</td>
<td>46</td>
<td>+</td>
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<tr>
<td>Horlander</td>
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<td>Atorvastatin</td>
<td>7</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Kiyici</td>
<td>Open label (6)</td>
<td>Atorvastatin</td>
<td>27</td>
<td>+</td>
<td>N/A</td>
</tr>
<tr>
<td>Hatzitolios</td>
<td>Open label (6)</td>
<td>Atorvastatin</td>
<td></td>
<td>+</td>
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</tr>
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<td>Gomez-Dominguez</td>
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<td>Pravastatin</td>
<td>5</td>
<td>+</td>
<td>+/-</td>
</tr>
</tbody>
</table>
NAFLD Guideline Recommendations

• 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 (Strength - 1, Quality - B)

• Until RCTs with histological endpoints prove their efficacy, statins should not be used to specifically treat NASH (Strength - 1, Quality - B)
Non-alcoholic Fatty Liver Disease
Other Treatment Regimens

- **Antioxidants**
  - Betaine
  - N-Acetyl-cysteine
  - Lecithin
  - Silymarin
  - Beta-carotene

- **Anti-TNF agents (Pentoxifylline)**

- **Probiotics (VSL#3)**

- **ACE inhibitors/ARBs**

- **Caspase inhibitors**

- **Cytoprotective agents/Bile Acids**
  - Ursodeoxycholic acid (UDCA)
  - Obeticholic Acid (OCA)-FLINT Study (NASH CRN)
# Treatment: Ursodeoxycholic Acid

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Author</th>
<th>N</th>
<th>ALT</th>
<th>Histology</th>
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<td>Holoman</td>
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<td>UDCA &amp; Diet</td>
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<tr>
<td>UDCA &amp; Diet</td>
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<td>UDCA</td>
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</tr>
</tbody>
</table>
How Do We Manage Our NAFLD Patients in 2014?

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

Liver biopsy

- Suspection for other CLD
- Dx of NAFLD uncertain
How Do We Manage Our NAFLD Patients in 2014?

Histologic NASH

- Continue life style and modifications
- If non-diabetic: Vitamin E
- If diabetic: Pioglitazone?

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

Liver biopsy

Simple Steatosis

Refer to primary care for management of MS and risk of CVD
NAFLD and NASH

- NAFLD is a complex disease tied closely to obesity
- Prevalence of NAFLD parallels the epidemic of obesity
- Only NASH patients can progress
- NAFLD/NASH in the setting of DM/MS has adverse outcomes
- Lack of effective treatment from dozens of clinical trials of NAFLD suggests the heterogeneity of the NAFLD phenotype
- Personalized targeted treatment may be the best future option to treat NASH
- Some considerations for current 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
  - Clinical trials (OCA and others)
  - Consider bariatric surgery for morbidly obese+/-DM with NASH
HCV
Chronic Hepatitis C Infection is a Major Concern in the US
HCV is Nearly 4 Times as Prevalent as HIV and HBV

- A 2011 study estimated that as many as 5.2 million persons are living with HCV in the United States\(^2\)

HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus.
By 2007, Deaths From HCV Surpassed Those From HIV

Change in Mortality Rates From 1999 to 2007

HCV Can Now Be Cured in Most Patients

• Unlike HIV and HBV infection, HCV infection is a curable disease

• What does cure mean?
  – Sustained Viral Response
  – Undetectable HCV RNA 12 weeks after completion of antiviral therapy for chronic HCV infection
  – Long term morbidity and mortality benefits

SVR Was Associated With Reduced Long-Term Risk of All-Cause Mortality in an International, Multicenter Study

International, multicenter, long-term follow-up study from 5 large tertiary care hospitals in Europe and Canada. Patients with chronic HCV infection started an interferon-based treatment regimen between 1990 and 2003 (n=530).

Which Patients Should We Screen?
Estimated Prevalence by Age Group


Majority of Persons Infected With HCV Are Baby Boomers (Those Born Between 1945–1965)
Hepatitis C Virus Testing of Persons Born During 1945 to 1965: Recommendations From the Centers for Disease Control and Prevention


Who Should Be Screened for HCV?

CDC Recommendations
- Everyone born from 1945 through 1965 (one-time)
- Persons who ever injected illegal drugs
- Persons who received clotting factor concentrates produced before 1987
- Chronic (long-term) hemodialysis
- Persons with persistently abnormal ALT levels
- Recipients of transfusions or organ transplants prior to 1992
- Persons with recognized occupational exposures
- Children born to HCV-positive women
- HIV positive persons

USPSTF Grade B Recs*
- Everyone born from 1945 through 1965 (one-time)
- Past or present injection drug use
- Sex with an IDU; other high-risk sex
- Blood transfusion prior to 1992
- Persons with hemophilia
- Long-term hemodialysis
- Born to an HCV-infected mother
- Incarceration
- Intranasal drug use
- Receiving an unregulated tattoo
- Occupational percutaneous exposure
- Surgery before implementation of universal precautions

*Only pertains to persons with normal liver enzymes; if elevated liver enzymes, need HBV and HCV testing
CDC and USPSTF Recommendations for HCV Screening

• Regardless of risk factors, one-time testing for HCV of adults born between 1945–1965\textsuperscript{1,2}
  – Testing of persons of all ages \textit{at risk} for HCV infection

• CDC also recommends for those identified with HCV infection\textsuperscript{1}
  – Brief alcohol screening and intervention as clinically indicated
  – Referral to appropriate care and treatment services for HCV infection and related conditions

Why Screen, Diagnose and Cure?
Chronic HCV Infection May Lead to Chronic Liver Disease and Liver Cancer

• ~75% of patients infected with HCV will develop a chronic infection and approximately 65% of those are expected to develop chronic liver disease
Projected Burden of Advanced Fibrosis Over the Next Decade

- 1990 → 77.6% F0/1; cirrhosis = 5%
- 2010 → 41.8% F0/1; cirrhosis = 25%
- 2020 → cirrhosis = 37.2%

Complications Due to HCV-Related Cirrhosis Expected to Rise Over the Next 10 Years

Projected Number of Cases of Hepatocellular Carcinoma and Decompensated Cirrhosis Due to HCV

Year

Cases, N


0 20,000 40,000 60,000 80,000 100,000 120,000 140,000 160,000

Hepatocellular carcinoma

 Decompensated cirrhosis

Screening and Linkage to Care
Current Status of HCV in the US: Screening and Linkage to Care Rates Remain Low

US population with chronic HCV infection
3.2 million

HCV detected
1.6 million (50%)

Referred to care
1.0 – 1.2 million (32%–38%)

HCV RNA test
630,000 – 750,000 (20-23%)

Liver biopsy
380,000 – 560,000 (12%-18%)

Treated
220,000 – 360,000 (7-11%)

Successfully treated
170,000 – 200,000 (5-6%)

Highly Efficacious Treatments Are Not Enough

- All HCV patients:
  - PEG-IFN/RBV: 100%
  - 95% SVR: 100%
  - 95% SVR and higher rates of diagnosis/treatment: 100%

- Diagnosis and treatment:
  - 20%
  - 20%
  - 90%

- Cure:
  - 10%
  - 19%
  - 85%

Slide courtesy of Prof. Michael Manns
Can We Predict Who Is At Higher Risk for Disease Progression?
Rate of Liver Progression is Affected by Several Patient Factors

- Male gender\(^1\)
- Age at infection\(^1\)
- Comorbidities such as HIV and HBV status\(^1\)
- High levels of alcohol consumption\(^1\)
- Immune status\(^1\)
- Visceral obesity with steatosis\(^2,3\)
- Diabetes\(^4\)
- Insulin resistance\(^5-7\)
- Synergy between risk factors\(^8\)

\(\text{Metabolic Syndrome Affects 37–54}\%\text{ of adults over 40 years old}\(^9\)\)

What Treatments Are Available and How Effective Are They?
Rapid Improvement in Treatment Options

Sustained Virological Response

<table>
<thead>
<tr>
<th>Year</th>
<th>Treatment</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991</td>
<td>IFN</td>
<td>6%</td>
</tr>
<tr>
<td>1995</td>
<td>IFN</td>
<td>16%</td>
</tr>
<tr>
<td>1998</td>
<td>IFN/R</td>
<td>34%</td>
</tr>
<tr>
<td>2001</td>
<td>PegIFN</td>
<td>42%</td>
</tr>
<tr>
<td>2002</td>
<td>PegIFN/R</td>
<td>55%</td>
</tr>
<tr>
<td>2011</td>
<td>PR + PI</td>
<td>75%</td>
</tr>
<tr>
<td>2013</td>
<td>PR + NI</td>
<td>90%</td>
</tr>
</tbody>
</table>

First Direct Acting Antivirals (DAAs) for the Treatment of GT 1 Chronic Hepatitis C

• Boceprevir and telaprevir were approved in 2011
• Both compounds act by inhibiting HCV nonstructural NS3/4A protease
• Major advancement over PEG/RBV
• In 2014, use of boceprevir and telaprevir not recommended in AASLD/IDSA guidance document
Simeprevir (SMV) (TMC 435)

- FDA approval: November 22, 2013
- NS3/4A protease inhibitor
- One capsule taken once daily with food
- Approved for GT 1 infected subjects with compensated liver disease (including cirrhosis)
- Alternative therapy according to AASLD/IDSA guidance document
**QUEST 1, QUEST 2 and PROMISE Study Designs**

**Response Guided Treatment**

- **SMV 150mg/PEG/RBV**
- **Placebo/PEG/RBV**

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Response Guided Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-24</td>
<td>PEG/RBV</td>
</tr>
<tr>
<td>24-48</td>
<td>PEG/RBV</td>
</tr>
<tr>
<td>48-72</td>
<td>Post-Therapy Follow-Up</td>
</tr>
</tbody>
</table>

- **Post-Therapy Follow-Up**

- **Response Guided Therapy**: if HCV RNA <25 International Units/mL at Week 4 and undetectable at Week 12, complete treatment at Week 24
- **QUEST 1 and QUEST 2**: GT 1, Treatment Naïve
- **PROMISE**: GT 1, Prior Relapsers

*PEG/RBV=Peginterferon/Ribavirin*
SVR12 Rates in Treatment Naive Patients (QUEST 1 and QUEST 2 Combined)

*Observed prevalence of Q80K variants at baseline in US population in the Phase 2b/3 trials: 48% of GT 1a and 0% of GT 1b patients

Simeprevir is Well Tolerated

- Mild unconjugated hyperbilirubinemia → transporter
- No anemia signal beyond P/R
- Rash up to 25% (mild)

Summary of Simeprevir

Pros

• Once daily PI
• Well tolerated with less rash and no anemia
• >85% only require 6 months of treatment and most achieve SVR

Cons

• Q80K an issue with SMV – pre-treatment testing required in all GT 1a
• DDIs still an issue – less than TVR/BOC
• Resistance profile similar to TVR/BOC when used with PEG/RBV
Sofosbuvir (SOF) (GS-7977)

- FDA approval: December 6, 2013
- Nucleotide analog NS5B polymerase inhibitor
- One oral 400 mg tablet once daily with or without food
- Approved for GT 1, 2, 3 and 4
Sofosbuvir + PEG/RBV
GT 1, 4, 5 and 6 Naïve (NEUTRINO)

SOF + PEG/RBV x 12 wks

<table>
<thead>
<tr>
<th></th>
<th>SVR12 (%)</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>90</td>
<td>295/327</td>
</tr>
<tr>
<td>GT 1a</td>
<td>92</td>
<td>206/225</td>
</tr>
<tr>
<td>GT 1b</td>
<td>82</td>
<td>54/66</td>
</tr>
<tr>
<td>GT 4</td>
<td>96</td>
<td>27/28</td>
</tr>
<tr>
<td>GT 5*</td>
<td>100</td>
<td>1/1</td>
</tr>
<tr>
<td>GT 6*</td>
<td>100</td>
<td>6/6</td>
</tr>
</tbody>
</table>

AEs similar to PEG/RBV → no control arm

*not in label
Lawitz E, et al. NEJM 2013
SVR Rates in Selected Subgroups (NEUTRINO)

*Patients with GT 1, METAVIR F3/F4, IL28B non-CC, HCV RNA >800,000 IU/mL (factors traditionally associated with a lower response to interferon-based treatment).

Summary on Sofosbuvir

Pros
• Once daily nucleotide polymerase inhibitor
• Very well tolerated
• 12 week total treatment duration
• High SVR even in cirrhosis (80%)
• Some data in GT 4, 5 and 6
• High barrier to resistance - no breakthrough → only few relapses

Cons
• No control group
• No clinical trial data in treatment experienced – naïve only
SOF+SMV: All Oral 12 Week Treatment Option? (COSMOS)

- **Arm 1**: SMV + SOF + RBV
- **Arm 2**: SMV + SOF
- **Arm 3**: SMV + SOF + RBV
- **Arm 4**: SMV + SOF

Enrollment ratio 2:1:2:1

- **Cohort 1**: Prior null responders (METAVIR F0-F2)
- **Cohort 2**: Treatment-naïve and prior null responders (METAVIR F3-F4)

All Oral Regimen in Null Responders (F0-F2) Treated For 12 Weeks

Treatment Naïve and Null Responders (F3-F4) With All Oral Regimen For 12 Weeks

Lawitz, E. et al. EASL 2014, Abstract #O165
## COSMOS: Safety and Tolerability in Treatment Naïve and Null Responders (F3-F4)

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>24 weeks</th>
<th>12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SMV/SOF + RBV (N=30)</td>
<td>SMV/SOF (N=16)</td>
</tr>
<tr>
<td>Grade 3 or 4 AEs</td>
<td>5 (16.7)</td>
<td>2 (12.5)</td>
</tr>
<tr>
<td>Any serious AE (SAE)</td>
<td>3 (10.0)</td>
<td>1 (6.3)</td>
</tr>
<tr>
<td>AE leading to discontinuation of all study drugs</td>
<td>0</td>
<td>1 (6.3)</td>
</tr>
<tr>
<td>Death during treatment</td>
<td>1 (3.3)*</td>
<td>0</td>
</tr>
</tbody>
</table>

*Fatal accident (not related to study medication)

AE, adverse event; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir
SOF+SMV Combination Therapy

• Not in FDA prescribing information for either drug
• However, treatment guidance document recommends the regimen for IFN-intolerant patients with GT 1 infection
Sofosbuvir/Ledipasvir Fixed Dose Combo

- Sofosbuvir (SOF) is a potent nucleotide polymerase inhibitor
- Ledipasvir (LDV) is a potent NS5A inhibitor
- Co-formulated SOF/LDV was used in Phase 3 studies
- Approved by FDA October 10, 2014
<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Recommended Treatment Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-naïve with or without cirrhosis</td>
<td>12 weeks*</td>
</tr>
<tr>
<td>Treatment-experienced** without cirrhosis</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Treatment-experienced** with cirrhosis</td>
<td>24 weeks</td>
</tr>
</tbody>
</table>

* Treatment-naïve patients without cirrhosis who have pre-treatment HCV RNA <6 million IU/mL can be treated with **8 weeks** of therapy

** Treatment-experienced patients who previously failed treatment with either PEG/RBV or a PI/PEG/RBV

Sofosbuvir + Ledipasvir + RBV

ION-1

S/L 211/214 99
S/L/R 211/217 97
S/L 215/217 99

ION-2

S/L 102/109 94
S/L/R 107/111 96
S/L 108/110 99
S/L/R 110/111 99

ION-3

S/L 202/215 94
S/L/R 201/216 93
S/L 206/216 95

SVR12 (%)

12 wks 24 wks 12 wks 24 wks 8 wks 12 wks

Naïve

Prior Trt (incl PI) Failures

S/L=sofosbuvir/ledipasvir; S/L/R=sofosbuvir/ledipasvir/ribavirin

SOF/LDV ± RBV in Treatment-Experienced Patients With Cirrhosis (ION-2)

<table>
<thead>
<tr>
<th></th>
<th>12 Weeks</th>
<th>24 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SVR12 (%)</td>
<td>SVR12 (%)</td>
</tr>
<tr>
<td>LDV/SOF</td>
<td>95/83/87</td>
<td>99/86/86</td>
</tr>
<tr>
<td></td>
<td>86/19/22</td>
<td>100/22/22</td>
</tr>
<tr>
<td>LDV/SOF + RBV</td>
<td>100/89/89</td>
<td>100/88/88</td>
</tr>
<tr>
<td></td>
<td>82/18/22</td>
<td>22/22/22</td>
</tr>
</tbody>
</table>

Afdhal EASL Abst O109
SOF/LDV ± RBV for Prior PI Failures (ION-2)

- No cross resistance with PI and either SOF/LDV

Afdhal EASL Abst O109
SOF/LDV Summary

- Very effective single pill regimen
- RBV does not appear necessary
- No difference GT 1a vs GT 1b
- Very well tolerated
- No issue with resistance
Near Term Options For GT 1
(Not Currently Approved)
3D Regimen

• ABT-450 is a potent NS3/4A protease inhibitor
  – Co-dosing of ABT-450 with ritonavir (ABT-450/r) increases the peak, trough, and overall drug exposures of ABT-450, and also enables once daily dosing

• Ombitasvir (formerly ABT-267) is a potent NS5A inhibitor

• Dasabuvir (formerly ABT-333) is a non-nucleoside NS5B polymerase inhibitor

• Co-formulated ABT-450/r/ombitasvir was used in Phase 3 studies

• Known as the “3D Regimen”
12 week treatment duration

**SVR12 (%)**

- **Naive**
  - All: 96%
  - GT 1a: 95%
  - GT 1b: 98%

- **Treatment Failures (49% nulls)**
  - All: 96%
  - GT 1a: 96%
  - GT 1b: 97%

Feld J EASL 2014 Abst 060, NEJM 2014
Zeuzem S EASL 2014 Abst 01, NEJM 2014
3D Regimen + RBV for Prior Nonresponders (SAPPHIRE II)

12 week treatment duration

<table>
<thead>
<tr>
<th></th>
<th>SVR12 (%)</th>
<th>Relapsers</th>
<th>Partial</th>
<th>Nulls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>95</td>
<td>100</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>82/86</td>
<td>65/65</td>
<td>139/146</td>
<td></td>
</tr>
</tbody>
</table>

Zeuzem S EASL 2014 Abst 01, NEJM 2014
### 3D Regimen + RBV: Safety/Tolerability

<table>
<thead>
<tr>
<th>Adverse Events (AEs)</th>
<th>SAPPHIRE I</th>
<th>Placebo</th>
<th>SAPPHIRE II</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3D + RBV (n = 473)</td>
<td>Placebo (n = 158)</td>
<td>3D + RBV (n = 297)</td>
<td>Placebo (n = 97)</td>
</tr>
<tr>
<td>Any AE, n (%)</td>
<td>414 (87.5)</td>
<td>116 (73.4)</td>
<td>271 (91.2)</td>
<td>80 (82.5)</td>
</tr>
<tr>
<td>AE leading to D/C, n (%)</td>
<td>3 (0.6)</td>
<td>1 (0.6)</td>
<td>3 (1.0)</td>
<td>0</td>
</tr>
<tr>
<td>Any serious AE, n (%)</td>
<td>10 (2.1)</td>
<td>0</td>
<td>6 (2.0)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Grade 3/4 lab events, n/N (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ ALT&gt;5x ULN</td>
<td>4/469 (0.9)</td>
<td>7/158 (4.4)</td>
<td>5/296 (1.7)</td>
<td>3/96 (3.1)</td>
</tr>
<tr>
<td>▪ Creatinine</td>
<td>--</td>
<td>--</td>
<td>2/297 (0.7)</td>
<td>0</td>
</tr>
<tr>
<td>▪ <strong>Total bilirubin</strong></td>
<td>13/469 (2.8)</td>
<td>0</td>
<td>7/296 (2.4)</td>
<td>0</td>
</tr>
<tr>
<td>▪ Hemoglobin 8-10 g/dL*</td>
<td>27 (5.8)</td>
<td>0</td>
<td>14/296 (4.7)</td>
<td>0</td>
</tr>
</tbody>
</table>

- ALT improved with continued dosing
- Bilirubin – total, related to transporter inhibition
- No one met Hy’s law → not hepatotoxicity
- Anemia – RBV dose reduction 5.5-6.4%, no effect on SVR

Feld J EASL 2014 Abst 060, NEJM 2014; Zeuzem S EASL 2014 Abst 01, NEJM 2014
3D Regimen +/- RBV in GT 1b Patients (PEARL III)

12 week treatment duration

Naïve non-cirrhotic

- 3D: 99%
- 3D + RBV: 99%

Experienced non-cirrhotic

- 3D: 100%
- 3D + RBV: 97%
3D + RBV in Cirrhosis by GT 1 Subtype

Poordad EASL 2014, LB, NEJM 2014
GT 1a Null Cirrhotics Likely Need 24 Weeks

<table>
<thead>
<tr>
<th></th>
<th>12 weeks</th>
<th>24 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naive</td>
<td>93/64</td>
<td>93/56</td>
</tr>
<tr>
<td>Relapsers</td>
<td>14/15</td>
<td>13/13</td>
</tr>
<tr>
<td>Partialys</td>
<td>11/11</td>
<td>10/10</td>
</tr>
<tr>
<td>Nulls</td>
<td>40/50</td>
<td>39/42</td>
</tr>
</tbody>
</table>

- Suggests that 24 weeks optimal for GT 1a null cirrhotics
- 12 weeks adequate for all others

Poordad EASL 2014, LB, NEJM 2014
Summary of 3D Regimen + RBV

• Highly effective 12 week regimen
  – SVR 96% naïve/experienced
  – Similar GT 1a (95%) and GT 1b (98%)

• Large cirrhotic trial
  – Similar efficacy & safety
  – 12 weeks adequate for all but GT 1a nulls → 24 weeks

• Safety
  – Placebo controlled – minimal toxicity
  – Mostly to do with RBV – not needed for GT 1b
Treatment Options for GT 4 Infected Patients
Options for GT 4

- **3D +/- RBV – under study**

Lawitz *NEJM* 2013, Ruane EASL 2014, Moreno EASL 2014
Treatment Options for GT 2 and GT 3 Patients
**SOF+RBV: IFN Free Regimen Available for GT 2 and GT 3 Infected Patients**

<table>
<thead>
<tr>
<th></th>
<th>Genotype 2 SOF + RBV</th>
<th>Genotype 3 SOF + RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>12 weeks</strong></td>
<td><strong>12 weeks</strong></td>
<td><strong>24 weeks</strong></td>
</tr>
<tr>
<td><strong>N=73</strong></td>
<td><strong>N=250</strong></td>
<td><strong>N=250</strong></td>
</tr>
<tr>
<td>Overall SVR</td>
<td>93% (68/73)</td>
<td>84% (210/250)</td>
</tr>
<tr>
<td>Outcome for subjects without SVR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>On-treatment virologic failure</td>
<td>0% (0/73)</td>
<td>&lt;1% (1/250)</td>
</tr>
<tr>
<td>Relapse</td>
<td>7% (5/73)</td>
<td>14% (34/249)</td>
</tr>
<tr>
<td>Treatment-naïve</td>
<td>3% (1/32)</td>
<td>5% (5/105)</td>
</tr>
<tr>
<td>Treatment-experienced</td>
<td>10% (4/41)</td>
<td>20% (29/144)</td>
</tr>
<tr>
<td>Other</td>
<td>0% (0/73)</td>
<td>2% (5/250)</td>
</tr>
</tbody>
</table>

Overall Summary
Summary

• One time testing of all baby boomers is essential
• Linkage to experts that can assess disease progression and treatment options
• Highly efficacious, short duration regimens with favorable safety profiles are now available
• Additional treatment options expected in the next 6 months
• Rapidly evolving field…
Recommendations for Testing, Managing, and Treating Hepatitis C

Background of the Hepatitis C Guidance
New direct-acting oral agents capable of curing hepatitis C virus (HCV) infection have been approved for use in the United States. The initial direct-acting agents were approved in 2011, and many more oral drugs are expected to be approved in the next few years. As new information is presented at scientific conferences and published in peer-reviewed journals, health care practitioners have expressed a need for a credible source of unbiased guidance on how best to treat their patients with HCV infection. To provide healthcare professionals with timely guidance, the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) in collaboration with the International Antiviral Society-USA (IAS-USA) have developed a web-based process for the rapid formulation and dissemination of evidence-based, expert-developed recommendations for hepatitis C management.

New sections will be added, and the recommendations will be updated on a regular basis as new information becomes available. An ongoing summary of “recent changes” will also be available for readers who want to be directed to the latest version of the recommendations.
What is Quality?

- Quality care is **safe, effective, patient centered, timely, efficient, and equitable**

National Quality Agenda

• Better care
• Better health
• Lower costs through improvement
  – Looking at quality through an economic lens will lead to results when it is measured appropriately and accurately
Quality Priorities

• Making care safer by reducing harm caused in the delivery of care
• Engaging patients in their care
• Promoting effective communication and coordination of care
• Effective prevention and treatment practices
• Enable healthy living
• Making quality care more affordable through new health care delivery models
Why Quality Reporting?

• Healthcare is moving from a performance- to outcomes-based environment

• Reimbursement will be driven by measurement of value and quality
Value and Quality

• Focus on Patient Value
  – Value = Quality per unit cost over time
  – Improve quality, safety, efficiency, value of care
  – Control cost of care
  – Improve care coordination

• The future lies in cooperation, interaction and transparency around organized, personalized care
Value-Based Purchasers Seeking Lower-Cost Health Care

Overall Health Care Costs vs. Time

Status Quo

1. Government Payers
   - Aims: Reduce Pricing

2. Commercial Payers
   - Aims: Lower Utilization

3. Employers
   - Driving a New Model of Care

Purchaser Aims
- Reduce Pricing
- Lower Utilization
Defined Benefit Health Insurance Plan

Employers cost shift premiums to employees and adopt higher deductible plans.

<table>
<thead>
<tr>
<th></th>
<th>2012 (Pre-exchanges)</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPO</td>
<td>70%</td>
<td>47%</td>
</tr>
<tr>
<td>HMO</td>
<td>18%</td>
<td>14%</td>
</tr>
<tr>
<td>CDHP*</td>
<td>12%</td>
<td>39%</td>
</tr>
</tbody>
</table>

*Consumer Directed Health Plan
Defined Contribution Health Insurance Plan

- Employers provide all their employees with monetary support to buy coverage on private exchanges
- Accenture study predicts 40 million employees covered by 2018 with a defined contribution plan
Sculpted Networks

- Insurances and large employers will contract directly with providers at transparent reference prices to pay a set amount for procedures or episodes of care.
Payment Issues

- Narrow networks
- Bundled payments
- Episodes of care (Providers paid to treat a specific condition over a set period of time)
- High deductible health plans (Require collection at time of service)
Texas Care Alliance (TCA)

Nine regional health systems throughout the state to form the Texas Care Alliance (TCA), which seeks to pool patient and administrative data for large scale analysis that is expected to result in lower health care costs for the large companies the TCA targets. Those companies typically fund their own insurance plans.
The Move to Integrated Health Care Systems

- Healthcare is being directed toward Integrated Health Care Systems.
- Healthcare providers are going to have to interpret what this push means to their individual practices and how they will continue to fit into the equation.
“There is no evidence that one organizational structure delivers better care than others. What matters are an organization’s internal capabilities and market environment, including the presence of strong leadership and organizational culture; clear purpose and shared goals; the sharing of data to help providers reach these goals; performance feedback and accountability for individual providers; participation in external quality improvement incentive programs; advanced care coordination capabilities and the use of coordinated chronic care teams; the use of recommended care management processes for the treatment of chronic illnesses; robust health information technology infrastructure; provider acceptance and use of evidence-based guidelines; and strong market incentives to improve value.”
A range of relationships exist between physician organizations and hospitals. Alignment of incentives between physician organizations and hospitals offer important opportunities for performance improvements across the entire continuum of care.

Compensation methodologies have played a key role in shaping hospital-physician organization relationships in California; in the absence of joint financial incentives, it is difficult to create alignment between hospitals and the physician organizations that use their services. Closer alignment between physician organizations and hospitals is critical, as a physician organization-centric model cannot bring about the institutional operational changes that will be needed to control overall costs. Hospitals are the highest-cost element of the delivery system, thus including them in initiatives to control costs and increase value is essential.
ACOs are not a panacea for health care spending control. Higher-cost and inefficient providers have not faced enrollment penalties because the current market does not incentivize purchasers or consumers to choose lower-cost or more cost-efficient providers. As ACOs are rolled out across the country, health insurance benefit designs should reward patients for choosing higher-value ACOs, which will necessitate that cost and quality data are available and that consumer cost sharing is higher for less efficient providers.
Example of Successful Outcomes Based Reimbursement

- On July 3rd, 2014 the American Society of Clinical Oncology published a study showing that an experimental physician-payment method was found to have lowered costs by more than a third for caring for patients with three types of cancers

- The pilot (launched in 2009), involved five medical oncology groups collaborating with United Healthcare, and, “used an episode payment model, which reimbursed physicians on a fixed-price, based on episodes of best-practices and patient outcomes”

- By December of 2012, “use of this model for treatment of breast, lung, and colon cancers in 810 patients led to savings of more than $33 million when compared to anticipated costs”
Here Comes the VM

- The value-based modifier (VM) assesses both quality of care furnished and the cost of that care under the Medicare Physician Fee Schedule
- Begin phase-in of VM in 2015, phase-in complete by 2017
- For 2015, apply VM to physician payment in groups of 100+ eligible professionals (EPs)
- Performance period for 2015 VM is calendar year 2013, so the VM 2013 penalty will hit in 2015 like the 2013 PQRS penalty
VM Requirements

- Groups with 100+ EPs MUST select one of the following PQRS quality reporting mechanisms to avoid the -1.0% VM adjustment

<table>
<thead>
<tr>
<th>PQRS Reporting Mechanism</th>
<th>Type of Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. GPRO Web Interface</td>
<td>Measures focus on preventive care and care for chronic diseases (aligns with the Shared Savings Program)</td>
</tr>
<tr>
<td>2. GPRO using CMS-qualified registries</td>
<td>Groups select the quality measures that they will report through a PQRS-qualified registry</td>
</tr>
<tr>
<td>3. Administrative Claims Option</td>
<td>Measures focus on preventive care and care for chronic diseases (calculated by CMS from administrative claims data)</td>
</tr>
</tbody>
</table>
Physician Quality Reporting System (PQRS)

- Started in 2007
- CMS program to report quality
- “By reporting PQRS quality measures, providers can quantify how often they are meeting a particular quality metric. Using the feedback report provided by CMS, eligible health care professionals (EPs) can compare their performance on a given measure with their peers” - www.cms.gov
- PQRS has been using incentive payments, and will begin to use payment adjustments in 2015 to encourage EPs to report on specific quality measures
- Quality reporting for these measures span 6 National Quality Standard (NQS) Domains
NQS Domains (All PQRS Quality Measures Fall Under These 6 Domains)

1. **Person and Caregiver-Centered Experience Outcomes**
   Measures that reflect the potential to improve patient-centered care and the quality of care delivered to patients.

2. **Patient Safety**
   Measures that reflect the safe delivery of clinical services in both hospital and ambulatory settings and include processes that would reduce harm to patients and reduce burden of illness.

3. **Communication and Care Coordination**
   Measures that demonstrate appropriate and timely sharing of information and coordination of clinical and preventive services among health professionals in the care team and with patients, caregivers, and families to improve appropriate and timely patient and care team communication.
4. **Community, Population and Public Health**
   Measures that reflect the use of clinical and preventive services and achieve improvements in the health of the population served.

5. **Efficiency and Cost Reduction Use of Healthcare Resources**
   Measures that reflect efforts to significantly improve outcomes and reduce errors.

6. **Effective Clinical Care**
   Measures that reflect clinical care processes closely linked to outcomes based on evidence and practice guidelines.
   - Examples of quality measures from effective clinical care on following slide.
Where to Start

• Go to cms.gov and download:
  – 2014 Physician Quality Reporting System (PQRS) Measures List

• Choose 9 measures from the PQRS Measures List across 3 different NQS domains and report each measure for at least 50% of Medicare Part B patients seen during the reporting period

• Report these measures using 1 of 4 Reporting Options
Other Reporting Options for PQRS

- **Medicare Part B Claims**
  - Report QDCs listed in the individual measures you have selected on applicable Medicare Part B Claims. Measures are calculated by CMS after they are received via claims.

- **Qualified PQRS Registry**
  - Choose a qualified registry (CMS has a list of these registries at their website) Group practices must also register under the Group Practice Reporting Option (GPRO). GPRO aligns with the Shared Savings Program.

- **Electronic Health Record (EHR) Reporting**
  - Your EHR must be Certified EHR Technology (CEHRT) OR you may use a CEHRT Data Submission Vendor (DSV). Lists of CEHRT DSVs can be obtained at cms.gov.

- **Qualified Clinical Data Registry (our example was the AGA DHRP)**
  - New to 2014 - Differs from the PQRS Registry in that it is not limited to the measures listed under the PQRS option. Data submitted to CMS via a QDCR covers quality measures across multiple payers and is not limited to Medicare beneficiaries.
CMS announced the entities that self-nominated to participate as a 2014 qualified registry. The 2014 qualified registry will be able to report quality measure data to CMS, on behalf of individual eligible professionals and Group Practice Reporting Organization (GPRO) group practices, for the 2014 PQRS program year.
CMS provides a table with all Qualified Registries with the information below listed for each.

<table>
<thead>
<tr>
<th>Registry Name</th>
<th>Contact Information</th>
<th>Accepting New Clients</th>
<th>Individual Measures Supported</th>
<th>Measures Groups Supported</th>
<th>GPRO Supported</th>
<th>Participated in Prior Year Registry Program</th>
<th>Services Offered and Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entity</td>
<td>• Contact Person</td>
<td>Yes</td>
<td>Measure Number</td>
<td>• IBD</td>
<td>Yes</td>
<td>Yes</td>
<td>• Comprehensive PQRS solutions</td>
</tr>
<tr>
<td></td>
<td>• Website</td>
<td></td>
<td></td>
<td>• Hepatitis C</td>
<td></td>
<td></td>
<td>• All practices (solo, group, large academic)</td>
</tr>
<tr>
<td></td>
<td>• Phone Number</td>
<td></td>
<td></td>
<td>• Preventative Care</td>
<td></td>
<td></td>
<td>• Pricing – Average $300</td>
</tr>
</tbody>
</table>

The Hepatitis C (chronic) Measures Group is comprised of the following:

- **Measure 84**: RNA testing before initiating treatment
- **Measure 85**: HCV genotype prior to treatment
- **Measure 86**: Antiviral treatment prescribed
- **Measure 87**: HCV RNA testing at week 12 of treatment
- **Measure 89**: Counseling regarding risk of alcohol consumption
- **Measure 90**: Counseling regarding use of contraception prior to anti-viral therapy
- **Measure 183**: Hepatitis A vaccination in patients with HCV
- **Measure 184**: Hepatitis B vaccination in patients with HCV

The Hepatitis C Measures Group may be reported via claims or registry.
PQRS: The Inflammatory Bowel Disease (IBD) Measures

Group is comprised of the following measures:

- **Measure 269**: IBD: Type, Anatomic Location and Activity All Documented
- **Measure 270**: IBD: Preventive Care: Corticosteroid Sparing Therapy
- **Measure 271**: IBD: Preventive Care: Corticosteroid Related Iatrogenic Injury – Bone Loss Assessment
- **Measure 272**: IBD: Preventive Care: Influenza Immunization
- **Measure 273**: IBD: Preventive Care: Pneumococcal Immunization
- **Measure 274**: IBD: Testing for Latent Tuberculosis (TB) Before Initiating Anti-TNF (Tumor Necrosis Factor) Therapy
- **Measure 275**: IBD: Assessment of Hepatitis B Virus (HBV) Status Before Initiating Anti-TNF (Tumor Necrosis Factor) Therapy
- **Measure 226**: Preventive Care and Screening: Tobacco Use: Screening and Cessation Intervention

The IBD measures can only be reported as a group via the registry reporting mechanism.
PQRS: The Preventive Care Measures Group is comprised of the following measures:

- **Measure 39**: Screening or Therapy for Osteoporosis for Women Aged 65 Years and Older
- **Measure 48**: Urinary Incontinence: Assessment of Presence or Absence of Urinary Incontinence in Women Aged 65 Years and Older
- **Measure 110**: Preventive Care and Screening: Influenza Immunization
- **Measure 111**: Preventive Care and Screening: Pneumonia Vaccination for Patients 65 years and Older
- **Measure 112**: Preventive Care and Screening: Breast Cancer Screening
- **Measure 113**: Preventive Care and Screening: Colorectal Cancer Screening
- **Measure 128**: Preventive Care and Screening: Body Mass Index (BMI) Screening and Follow-Up
- **Measure 173**: Preventive Care and Screening: Unhealthy Alcohol Use – Screening
- **Measure 226**: Preventive Care and Screening: Tobacco Use: Screening and Cessation Intervention

The preventive care measures group may be reported via claims or registry.
## Why You Should Care = CMS ‘Penalty Box’

<table>
<thead>
<tr>
<th>Year</th>
<th>eRx</th>
<th>EMR</th>
<th>PQRS</th>
<th>Total Penalty</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>-1.0%</td>
<td>No penalty</td>
<td>No penalty</td>
<td>-1.0%</td>
</tr>
<tr>
<td>2013</td>
<td>-1.5%</td>
<td>No penalty</td>
<td>No penalty</td>
<td>-1.5%</td>
</tr>
<tr>
<td>2014</td>
<td>-2.0%</td>
<td>No penalty</td>
<td>No penalty</td>
<td>-2.0%</td>
</tr>
<tr>
<td>2015</td>
<td>No penalty</td>
<td>-1.0%</td>
<td>-1.5%</td>
<td>-2.5%</td>
</tr>
<tr>
<td>2016</td>
<td>No penalty</td>
<td>-2.0%</td>
<td>-2.0%</td>
<td>-4.0%</td>
</tr>
</tbody>
</table>
ASC Quality Reporting (ASCQR) Measures
### ASC Quality Codes 1-5: G Codes Reported on Claims

<table>
<thead>
<tr>
<th>Key Notes:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>G8907 is used when no untoward events occur, and is subsequently used on the majority of claims.</td>
<td></td>
</tr>
<tr>
<td>Patient falls in the parking lot DO NOT COUNT in regards to code G8910.</td>
<td></td>
</tr>
<tr>
<td>Patients who are admitted to a hospital AFTER discharge DO NOT COUNT in regards to code G8914.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No adverse event</th>
<th>G8907</th>
<th>No burn, no fall, no hospital, no wrong site/side/patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Burn</td>
<td>G8908</td>
<td>Patient experienced a burn prior to discharge</td>
</tr>
<tr>
<td>Patient Burn</td>
<td>G8909</td>
<td>No burn</td>
</tr>
<tr>
<td>Patient Fall in ASC facility</td>
<td>G8910</td>
<td>Fell within center (Parking Lot NOT included)</td>
</tr>
<tr>
<td>Patient Fall in ASC facility</td>
<td>G8911</td>
<td>No fall</td>
</tr>
<tr>
<td>Wrong site, wrong side, wrong patient, wrong procedure, wrong implant</td>
<td>G8912</td>
<td>Patient documented to have experienced a wrong site, wrong side, wrong patient, wrong procedure or wrong implant event</td>
</tr>
<tr>
<td>Wrong site, wrong side, wrong patient, wrong procedure, wrong implant</td>
<td>G8913</td>
<td>Patient documented <strong>not</strong> to have experienced a wrong site, wrong side, wrong patient, wrong procedure or wrong implant event</td>
</tr>
<tr>
<td>Hospital Transfer/Admission</td>
<td>G8914</td>
<td>Patient documented to have experienced a hospital transfer or hospital admission upon discharge from ASC</td>
</tr>
<tr>
<td>Hospital Transfer/Admission</td>
<td>G8915</td>
<td>Patient documented <strong>not</strong> to have experienced a hospital transfer or hospital admission upon discharge from ASC</td>
</tr>
<tr>
<td>Timing of Prophylactic Antibiotic Administration</td>
<td>G8916</td>
<td>Patient with preoperative order for IV antibiotic surgical site infection (SSI)</td>
</tr>
</tbody>
</table>
### ASCQR Measures 6-11 (Reported via Quality Net Secure Portal)

<table>
<thead>
<tr>
<th>Number</th>
<th>Measures for CY 2016 Payment Year</th>
<th>Data Collection Period</th>
<th>Submission Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASC-8</td>
<td>Influenza Vaccination Coverage among Healthcare Personnel</td>
<td>October 1, 2014 – March 31, 2015</td>
<td>To Be Determined†</td>
</tr>
<tr>
<td>ASC-11</td>
<td>Cataracts: Improvement in Patient’s Visual Function within 90 Days Following Cataract Surgery††</td>
<td>January 1, 2015 - December 31, 2015</td>
<td>To be Determined</td>
</tr>
</tbody>
</table>

ASC – 6 : Safe Surgery Checklist

• The use of a checklist creates an expectation that organizations assess effective communication and safe practices during three perioperative periods:
  – Before induction of anesthesia
  – Before scope entry
  – Before patient leaves the endoscopy suite

• Impact on Patient Safety:
  – In pilot study, WHO Checklist was found to reduce the rate of postoperative complications and death by more than one-third

New ASC Measures for 2014

• ASC-9: Appropriate Follow-up interval for normal colonoscopy in average risk patients

• ASC-10: Colonoscopy interval for patients with a history of adenomatous polyps – avoidance of inappropriate use
Proposed Measure ASC 12

- ASC–12: Facility Seven-Day Risk-Standardized Hospital Visit Rate after Outpatient Colonoscopy
  - The outcome measured will be all-cause, unplanned hospital visits (admissions, observation stays, and emergency department visits) within 7 days of an outpatient colonoscopy procedure
Conclusion: Adapt and Adopt or Face Monetary Loss

• Despite limited evidence, reporting of hospital quality data and performance based reimbursement have emerged as two of the most widely advocated strategies for accelerating quality improvement

• Subsequent reform has produced hundreds of quality measures subject to penalties or incentives (PQRS alone has 281 quality measures). This is the beginning of the new norm in healthcare