# The Changing Landscape of Liver Care

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Director of Hepatology
Program Director, Transplant Hepatology Fellowship Program
Associate Professor - Clinical
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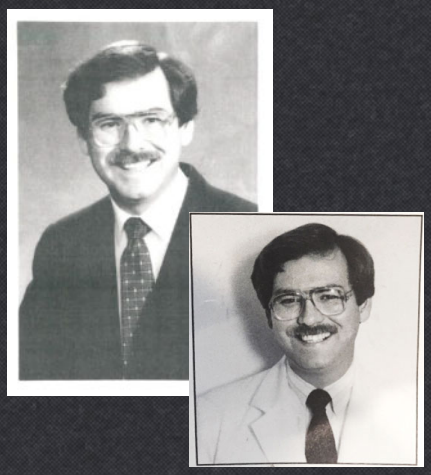
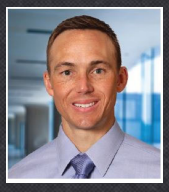
# The Evolution of the OSU Liver Program…

# From Then…



# To Now… Hepatology MDs



**James Hanje, MD**
Director of Hepatology
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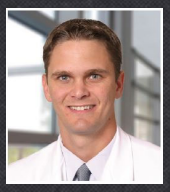
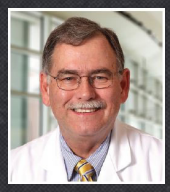
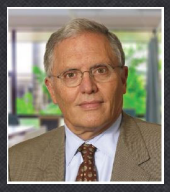


**Anthony Michaels, MD**
Medical Director of Liver Transplantation

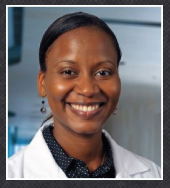


**Robert Kirkpatrick, MD**
Associate Director of GI Fellowship

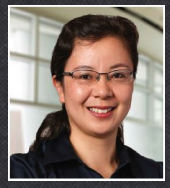


**Douglas Levin, MD**

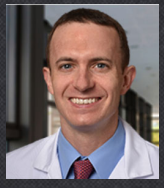
**Khalid Mumtaz, MBBS**
Director of Hepatology Research



**Lanla F. Conteh, MD, MPH**
Director of Hepatobiliary Tumor Program



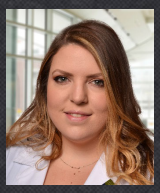
**Na Li, MD, MPH**



**Sean Kelly, MD**

# To Now… Hepatology CNPs

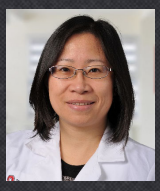
Pamela Kibbe, CNP



Nicole O'Bleness Gray, CNP

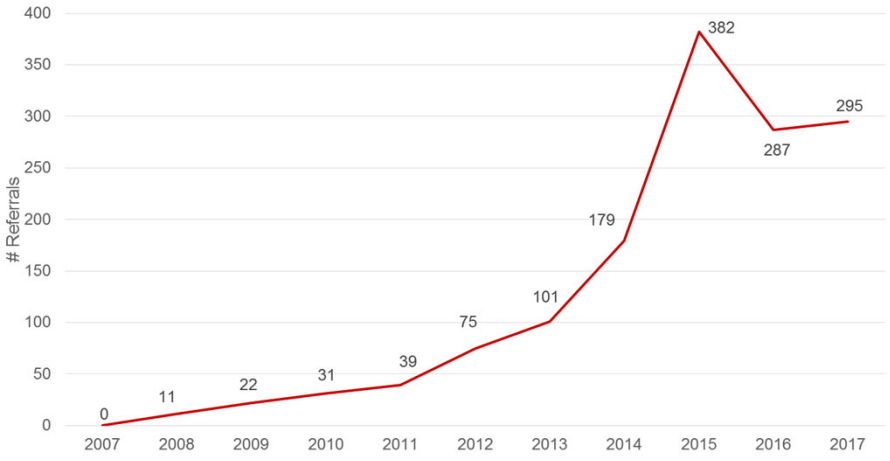
Gail Davidson, CNP

Erica Campbell-Brown, CNP

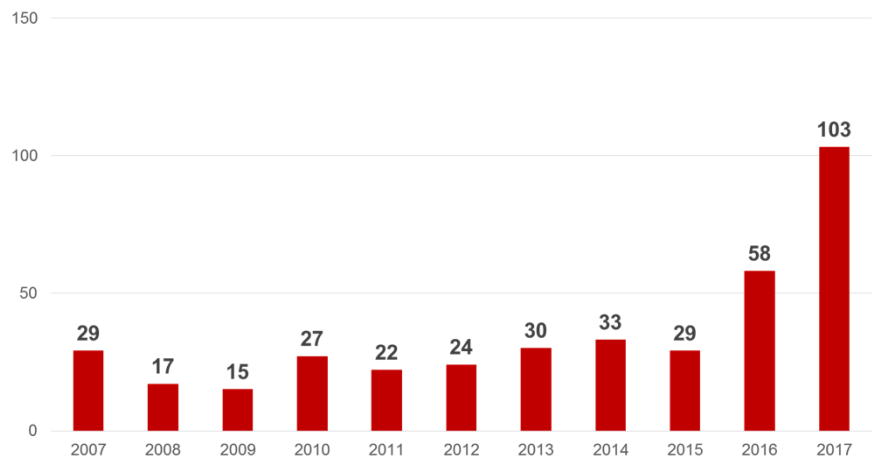


Sherry Ma, CNP

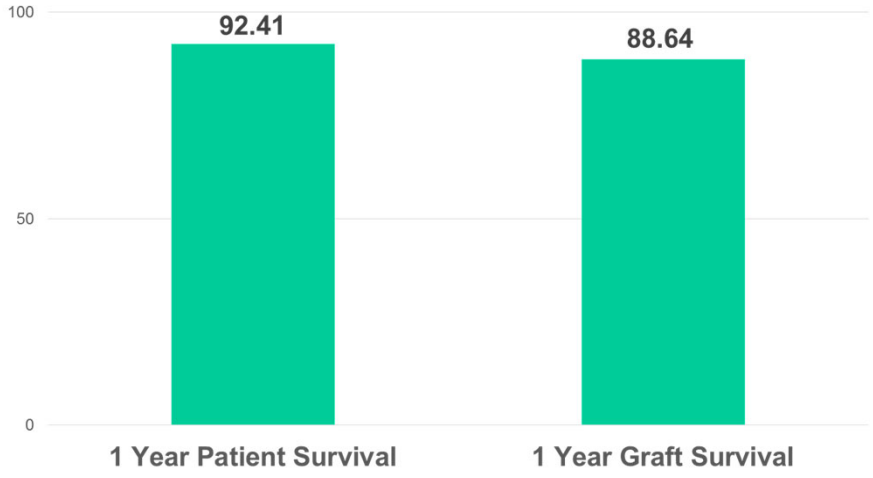
# Hepatology Referrals

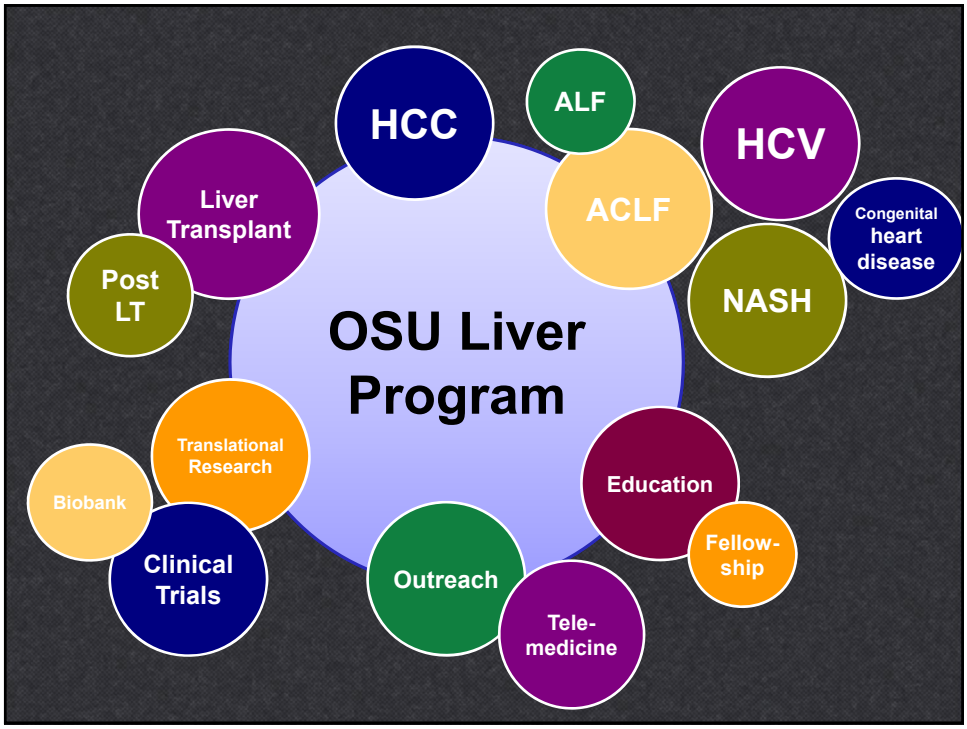


## Ohio State Liver Transplant Volume




## Ohio State Liver Transplant Survival






# Collaborative Clinical Efforts

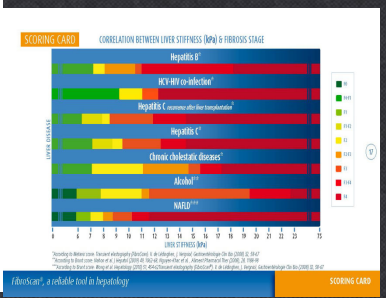
- Multi-disciplinary and sub-specialized clinics
  - Liver tumor clinic
  - HCV treatment
  - NASH and metabolic liver disease
  - Post-transplant care

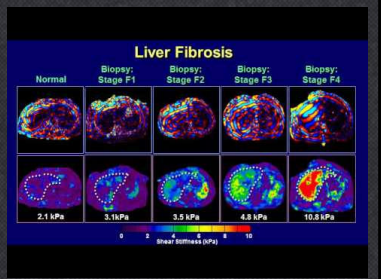
# New Tools and Treatment Options

- Hepatocellular Carcinoma (HCC):
  - TACE
  - RFA
  - Y-90
  - SBRT
- Portal hypertensive bleeding:
  - Cyanoacrylate injection of gastric varices
  - Balloon-Occluded Retrograde Transvenous Obliteration (BRTO)
- EUS-guided liver biopsies

# Transient Liver Elastography (Fibroscan)

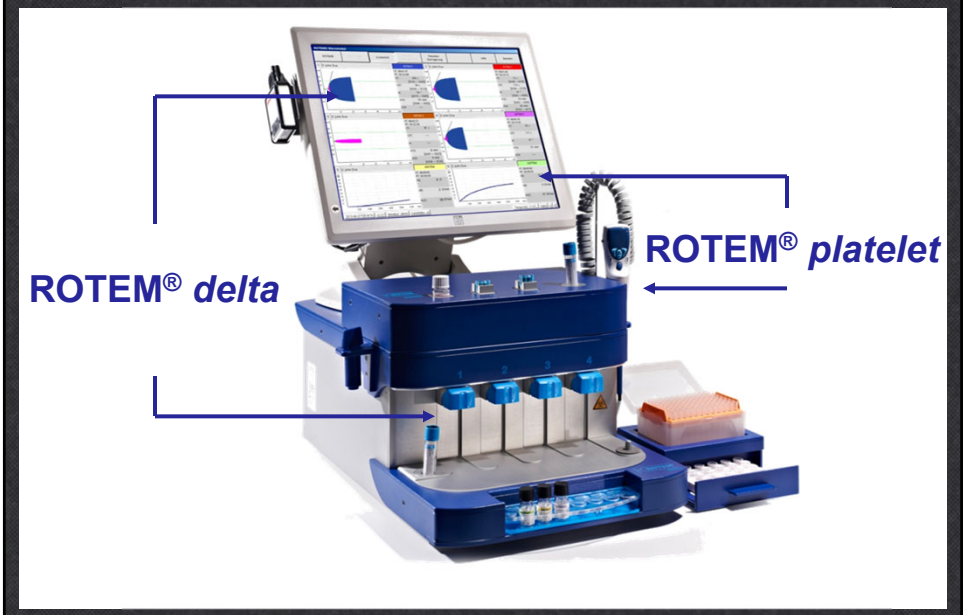
- The most efficient approach to fibrosis assessment is to combine direct biomarkers and vibration-controlled transient liver elastography
  - A biopsy should be considered for any patient who has discordant results between the 2 modalities that would affect clinical decision making.



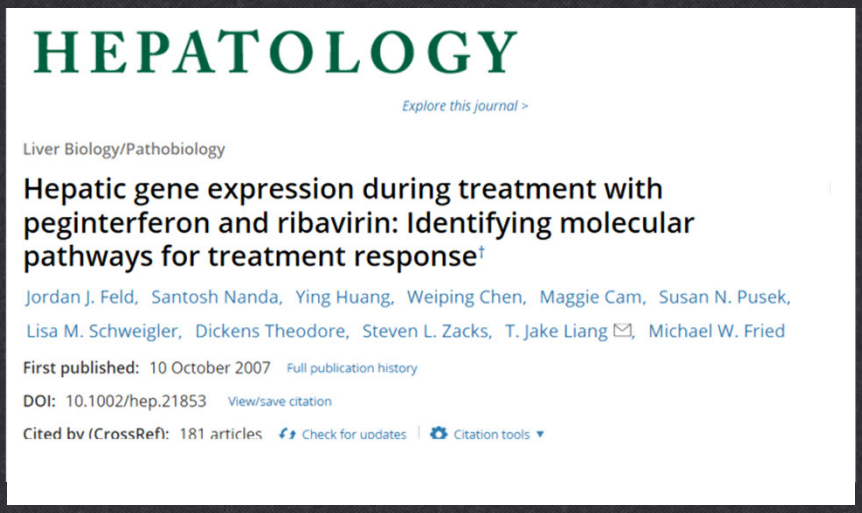

AASLD-IDSA. www.hcvguidelines.org/full-report-view.

## Rotational Thromboelastometry (ROTEM)




## NIH Research Trials

# Evolution of Care



HEPATOLOGY

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Liver Biology/Pathobiology

Hepatic gene expression during treatment with peginterferon and ribavirin: Identifying molecular pathways for treatment response†

Jordan J. Feld, Santosh Nanda, Ying Huang, Weiping Chen, Maggie Cam, Susan N. Pusek, Lisa M. Schweigler, Dickens Theodore, Steven L. Zacks, T. Jake Liang ✉, Michael W. Fried

First published: 10 October 2007 Full publication history

DOI: 10.1002/hep.21853 View/save citation

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# Evolution of Care

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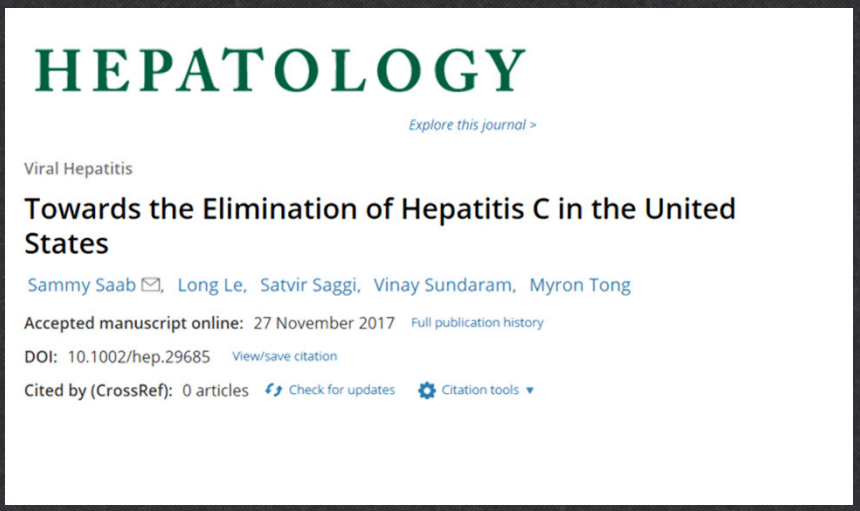
# The Future is Now



HEPATOLOGY

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Viral Hepatitis

**Towards the Elimination of Hepatitis C in the United States**

Sammy Saab, Long Le, Satvir Saggi, Vinay Sundaram, Myron Tong

**Accepted manuscript online:** 27 November 2017 Full publication history

**DOI:** 10.1002/hep.29685 View/save citation

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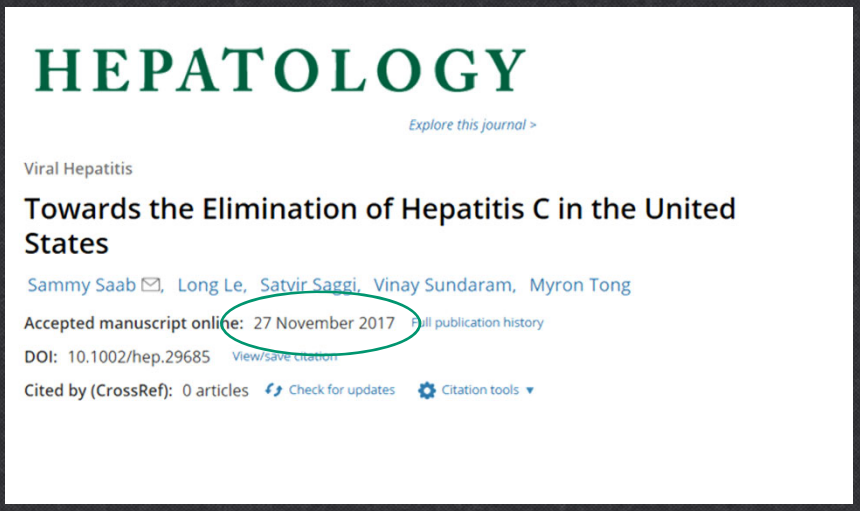
# The Future is Now



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# Current Population: Hepatitis C


- Baby Boomers (Born in 1945–1965) account for 76.5% of HCV in the US
- Almost 35% of undiagnosed baby boomers with HCV are estimated to currently have advanced fibrosis (F3-F4; bridging fibrosis to cirrhosis)

Smith BD et al. *MMWR Recomm Rep.* 2012;61:1-32. 2. Pyenson B et al. Milliman report, 2009. Available at www.milliman.com/expertise/healthcare/publications/rr/consequences-hepatitis-c-virus-RR05-15-09.php . McGarry LJ et al. *Hepatology.* 2012;55:1344-1355.

# Future Population: Non-alcoholic Fatty Liver Disease (NAFLD)

**Dallas Heart Study (2,200 adults)**

- ***Assessed NAFLD with liver imaging***
- General prevalence of fatty liver 31% (range 24% - 45%)
- ***Most individuals (79%) with fatty liver do not exhibit aminotransferase elevations***

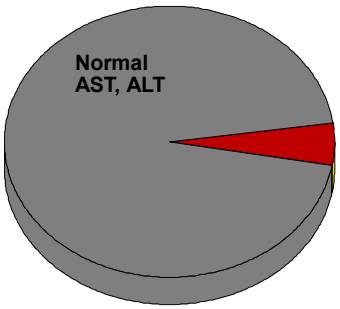
**NHANES III (15, 700 adults)**

- Assessed NAFLD with aminotransferases
- General prevalence of NAFLD 5.5%

**NAFLD prevalence 5.5-31%**

**3-10 x more prevalent than Hepatitis C**

# NAFLD: Risk Factors




5.5%

**Unexplained Hepatitis**

- ↑ BMI
- Waist circumference
- Triglycerides
- Insulin
- ↓ HDL cholesterol

***Metabolic Syndrome***

Clark, Brancati, Diehl. Am J Gastro 2003; 98:960

# NAFLD Natural History

**Liver-related morbidity and mortality**

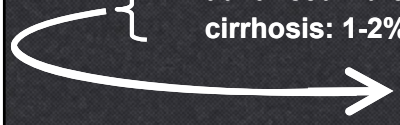
**NAFL NASH Cirrhosis**

## NAFLD in High-Risk Populations: Morbidly Obese Gastric Bypass Patients

Liver disease often unsuspected pre-operatively

Intraoperative liver biopsy typically shows NAFLD

- Steatosis: 30-90%
- Steatohepatitis: 33-42%
- Fibrosis:
  - idiopathic portal fibrosis: 33%
  - advanced fibrosis: 12%
  - cirrhosis: 1-2%



*Advanced fibrosis 13-14%*

## NAFLD in High-Risk Populations: Type 2 Diabetes Mellitus

Prevalence of NAFLD is high

- -ultrasound detects fatty liver in 50%

NASH unusually common

- -NAFL: 12%
- -NASH: 87%

Fibrosis or cirrhosis documented in 20%

Standardized mortality rate for death from liver disease > than that for coronary disease

Gupter et al. J Gastro Hepatol 2004;19:854-859
Tolman et al. Ann Intern Med 2004; 141:946-956

## Prognostic Implications of NASH + Fibrosis

More consistent and rapid progression to cirrhosis than NAFL


Matteoni et al. Gastroenterology 1999; 116:1413

## Prognostic Implications of NASH + Fibrosis

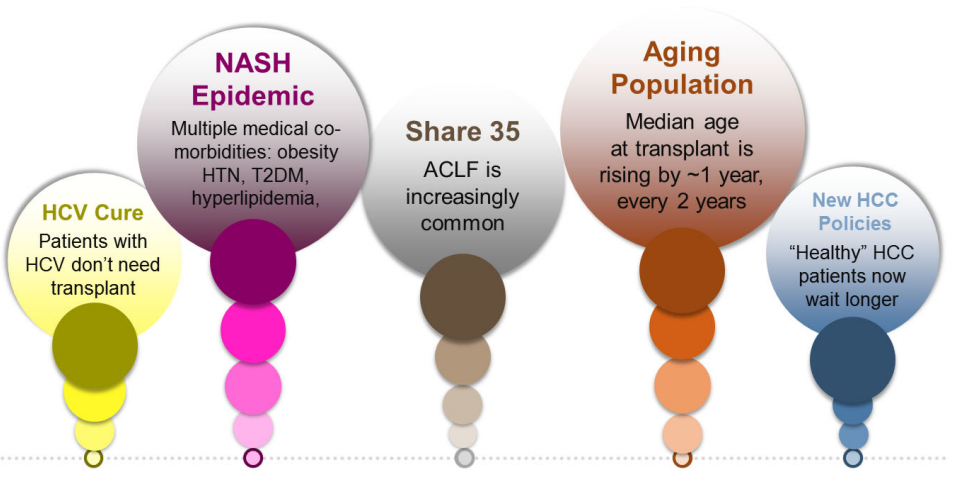
- More consistent and rapid progression to cirrhosis than NAFL
- Rate of liver related mortality about 10% within 10 years
- Liver disease is a major cause of mortality

Cardiovascular disease > cancer = cirrhosis

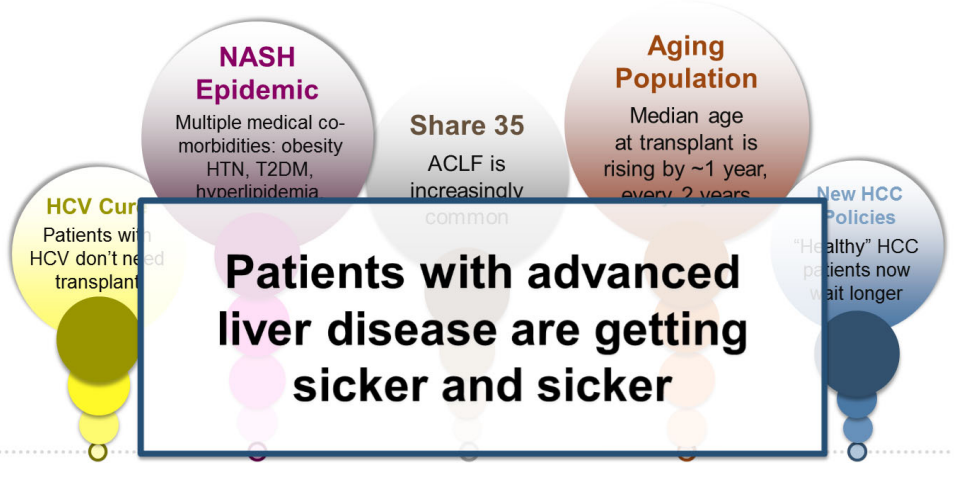
# 1 # 2

Matteoni et al. Gastroenterology 1999; 116:1413

# Major Changes in Liver Transplant




# Major Changes in Liver Transplant

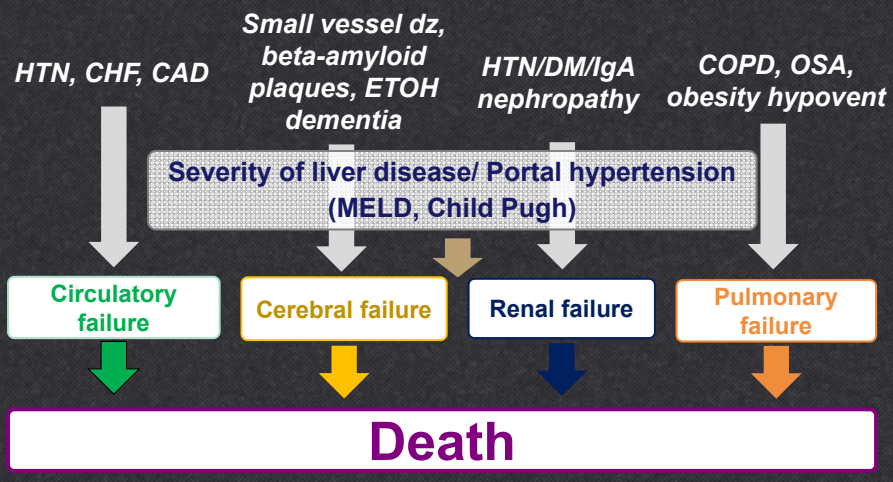


# Acute on Chronic Liver Failure (ACLF)

- Acute decompensation (defined as worsening coagulopathy and jaundice) in a patient with chronic liver disease
- Often precipitated by infection
- Multi-organ system dysfunction
- Associated with poor prognosis

WGO consensus statement Jalan et al. Gastroenterology 2014;147(1):4-10

# Severity and Prognosis of ACLF



## Co-morbidities Matter in Cirrhosis

- Diabetes increases risk of death in patients with ESLD
- Older age is associated with increased waitlist mortality
- Older age is associated with increased risk of post-transplant mortality
- CHF, COPD, and DM are predictive of mortality after liver transplant

## For the Increasingly Complex Patient, We Need…

**Frameworks**
***For dynamic, personalized decision-making for patients with multi-organ dysfunction***

**Tools**
***To provide us with information that incorporates all systems to help us prognosticate and engage in shared decision-making***

# "Frailty"

- From the geriatrician's toolbox
- "A distinct biologic syndrome of decreasing physiologic reserve and increasing vulnerability to health stressors"
- "Aggregate expression of risk resulting from age- and disease-related subthreshold decrements of multiple physiologic systems"

Fried L. J Gerontol A Biol Sci Med Sci 2004.

# Karnofsky Performance Status

Assessed by the clinical provider or patient

| | | |
|---|---|---|
| 100 | Normal; no evidence of disease | High |
| 90 | Able to perform normal activities with only minor symptoms | |
| 80 | Normal activity with effort; some symptoms | |
| 70 | Able to care for self but unable to do normal activities | Inter-mediate |
| 60 | Requires occasional assistance; cares for most needs | |
| 50 | Requires considerable assistance | |
| 40 | Disabled; requires special assistance | Low |
| 30 | Severely disabled | |
| 20 | Very sick; requires active supportive treatment | |
| 10 | Moribund | |

- Predicts 3-month mortality after hospitalization (better than MELD + age alone)
- Predicts 30-day mortality after liver transplantation

Karnofsky, Cancer 1948. Tandon, Hepatology 2016. Dolgin, Clin Transpl 2016.

# Frailty Assessment

HEPATOLOGY
HEPATOLOGY, VOL. 66, NO. 2, 2017

## Development of a Novel Frailty Index to Predict Mortality in Patients With End-Stage Liver Disease

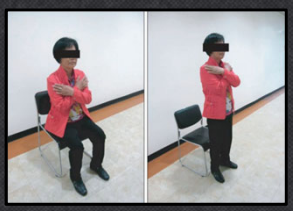
Jennifer C. Lai,[1] Kenneth E. Covinsky,[2] Jennifer L. Dodge,[3] W. John Boscardin,[2,4] Dorry L. Segev,[5] John P. Roberts,[3] and Sandy Feng[3]

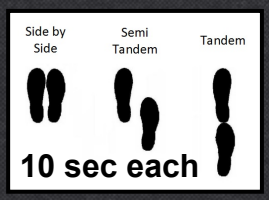
# The Liver Frailty Index
*liverfrailtyindex.ucsf.edu*

FrAILT

90 s

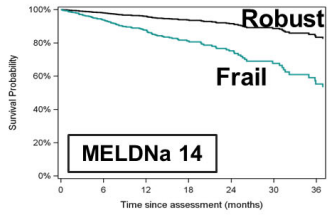
**Grip** + **Chair stands** + **Balance**

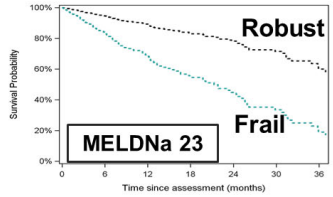


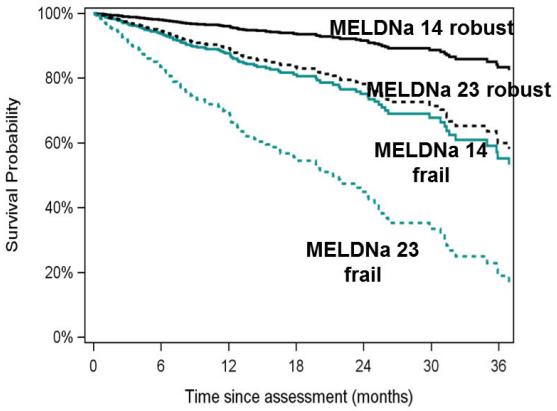



Lai JC, Hepatology 2017.

# LFI Predicts Mortality Better Than MELD-Na Alone




* Robust / Frailty defined as the 20% / 80%ile Liver Frailty Index values.

# Sarcopenia

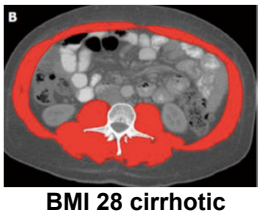
ORIGINAL ARTICLE

CAREY ET AL.

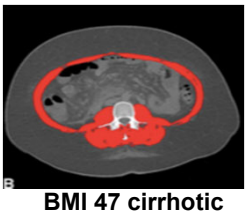
A Multicenter Study to Define Sarcopenia in Patients With End-Stage Liver Disease

Elizabeth J. Carey,[1*] Jennifer C. Lai,[2*] Connie W. Wang,[3] Srinivasan Dasarathy,[5] Iryna Lobach,[4] Aldo J. Montano-Loza,[6] and Michael A. Dunn[7] for the Fitness, Life Enhancement, and Exercise in Liver Transplantation Consortium

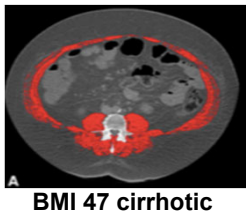
# Sarcopenia by Skeletal Muscle Index



BMI 28 cirrhotic
Non-sarcopenic



BMI 47 cirrhotic
Non-sarcopenic



BMI 47 cirrhotic
Sarcopenic

Montano-Loza, WJG 2014

**SMI cut-offs to define sarcopenia that predict mortality: 47 $cm^2/m^2$ for men; 42 $cm^2/m^2$ for women**

Carey/Lai, Liver Transpl 2017

# Final Thoughts

- A framework for medical decision-making that accounts for frailty can facilitate more individualized decisions
- Tools for medical decision-making need to move beyond organ-specific assessments and incorporate the aggregate effects of multi-morbidity and aging
- "Frailty" tools such as the KPS, ADL, Liver Frailty Index, and skeletal muscle index should be incorporated into routine assessments

## Acknowledgements

- Jennifer C. Lai, MD, MBA, Division of Gastroenterology & Hepatology, University of California, San Francisco
- Anthony Michaels, MD, Division of Gastroenterology, Hepatology and Nutrition, The Ohio State University
- Nicole O'Bleness Gray, CNP, Division of Gastroenterology, Hepatology and Nutrition, The Ohio State University


# Update on Hepatitis C


**Anthony Michaels, MD**
Associate Professor of Clinical Medicine
Medical Director of Liver Transplantation
The Ohio State University Wexner Medical Center

# Objectives

1. Review methods of diagnosis.
2. Describe modalities of staging fibrosis.
3. Review current therapeutic options.
4. Discuss how to choose appropriate candidates for therapy.

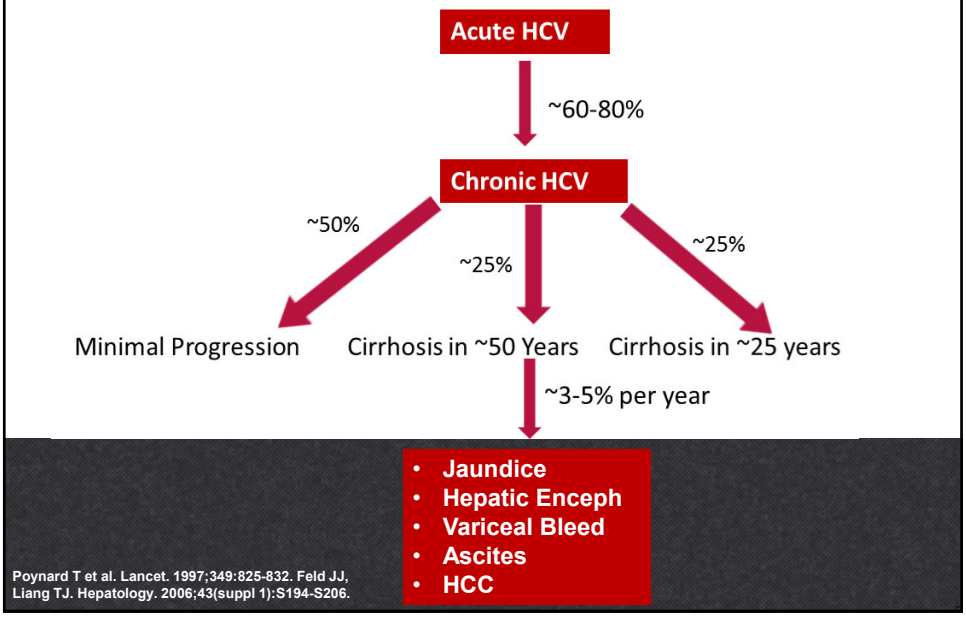
# Disclosures Last 12 Months

- Speaker Contract: Gilead, Abbvie, DOVA
- Advisory Board: Gilead, Abbvie

# Background

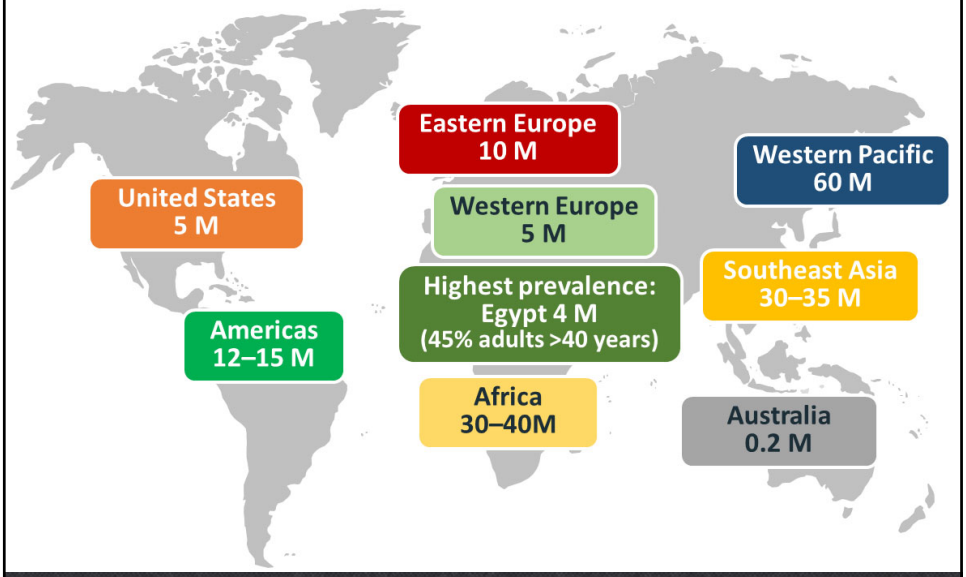
- RNA virus with different subtypes
  - (i.e, genotypes 1-6 (G1 most common in the US))
- Blood exposure (IVD in the US)
- Can cause an acute and/or chronic infection
- Can cause extrahepatic manifestations
  - **Hematologic:** Mixed cryoglobulinemia
  - **Renal:** Glomerulonephritis
  - **Dermatologic:**
    - Porphyria cutanea tarda
    - Leukocytoclastic vasculitis
    - Lichen planus

# Natural History



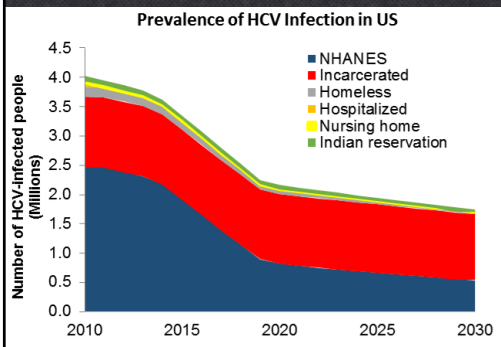

Poynard T et al. Lancet. 1997;349:825-832. Feld JJ, Liang TJ. Hepatology. 2006;43(suppl 1):S194-S206.

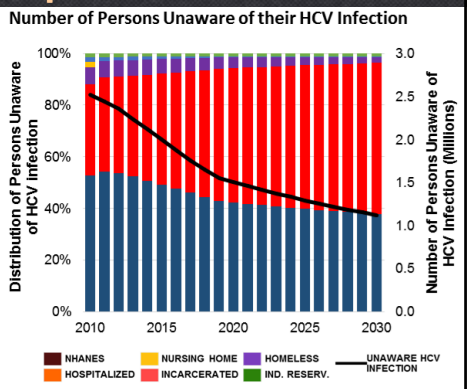
# Worldwide Seroprevalence of Hepatitis C: ~200 million




World Health Organization. *Wkly Epidemiol Rec.* 2000;75:18-19.
Edlin B et al. *Hepatology.* 2005;42(4 suppl 1): 213A (abstract 44).

# Updated Prevalence of Hepatitis C in the U.S. Results from a Simulation Model Including the Non-NHANES Population



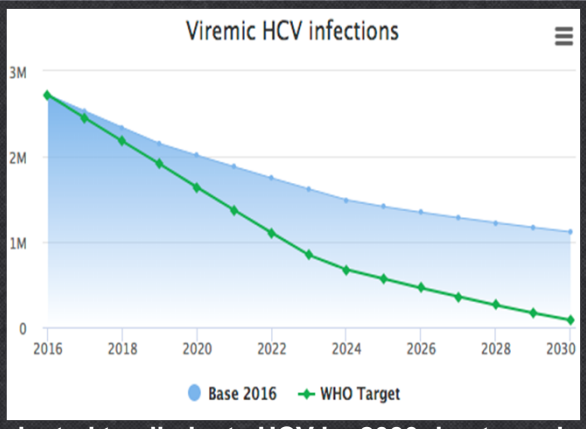

- In 2010, 4.0 million people were infected with HCV when accounting for non-NHANES groups
- In 2017, 2.8 million people have chronic HCV (1.4 million in NHANES and 1.4 million in non-NHANES population)
- By 2030, 1.7 million people could remain viremic under current screening and treatment practices
- From 2017 to 2030, the burden of HCV will shift from the NHANES to non-NHANES populations, implying a needed shift in resources in addressing these HCV populations, especially those who are incarcerated.

- In 2017, 1.8 million viremic people were unaware of their HCV status.
- By 2030, 1.1 million people would still remain unaware of their HCV.

Chhatwal et. al. The Liver Meeting, 2017, #989

## POLARIS Observatory Database

### The Road to Elimination of HCV: Projections for USA Treatment and New Infections from 2016 – 2030




"© CDA Foundation"

http://polarisobservatory.org/

**USA not projected to eliminate HCV by 2030 due to projected increase in new HCV infections and projected decrease in treatment rates**

**In 2016, WHO called for a 90% reduction in new HCV infection by 2030**

**Far higher rates of treatment are required worldwide for elimination of HCV**

## Need to Improve Our Screening and Linkage to Care

- **Only approximately 50% of chronic HCV pts in the US have been diagnosed**
  - **Approximately 9% of these patients have been successfully treated.**

## Need to Improve Our Screening and Linkage to Care

- Baby Boomers (Born in 1945–1965) Account for 76.5% of HCV in the US
- Almost 35% of undiagnosed baby boomers with HCV are estimated to currently have advanced fibrosis (F3-F4; bridging fibrosis to cirrhosis).

Smith BD et al. *MMWR Recomm Rep.* 2012;61:1-32. 2. Pyenson B et al. Milliman report, 2009. Available at www.milliman.com/expertise/healthcare/publications/rr/consequences-hepatitis-c-virus-RR05-15-09.php . McGarry LJ et al. *Hepatology.* 2012;55:1344-1355.

## How to Screen and Diagnose?

- Hepatitis C Antibody
  - If positive, then can check for Hepatitis C RNA levels to actually DIAGNOSE.
- Hep C RNA
  - If POSITIVE, this indicates a current infection. Won't know chronicity until have a repeat RNA level in 6 months.
    - Can obtain a genotype to help further differentiate
  - If NEGATIVE, then the patient doesn't have an active infection (previous exposure with subsequent clearance vs a false positive)

# Pretreatment Assessment

- **The most efficient approach to fibrosis assessment is to combine direct biomarkers and vibration-controlled transient liver elastography.**
  - **A biopsy should be considered for any patient who has discordant results between the 2 modalities that would affect clinical decision making.**

AASLD-IDSA. www.hcvguidelines.org/full-report-view.

## FDA HBV Reactivation Cases ‡
## HBV Reactivation Associated with HCV DAA Therapy

**Query of the FDA Adverse Event Reporting System (FAERS) for cases of HBV-R associated with HCV DAAs from 11/22/2013–10/15/2016**

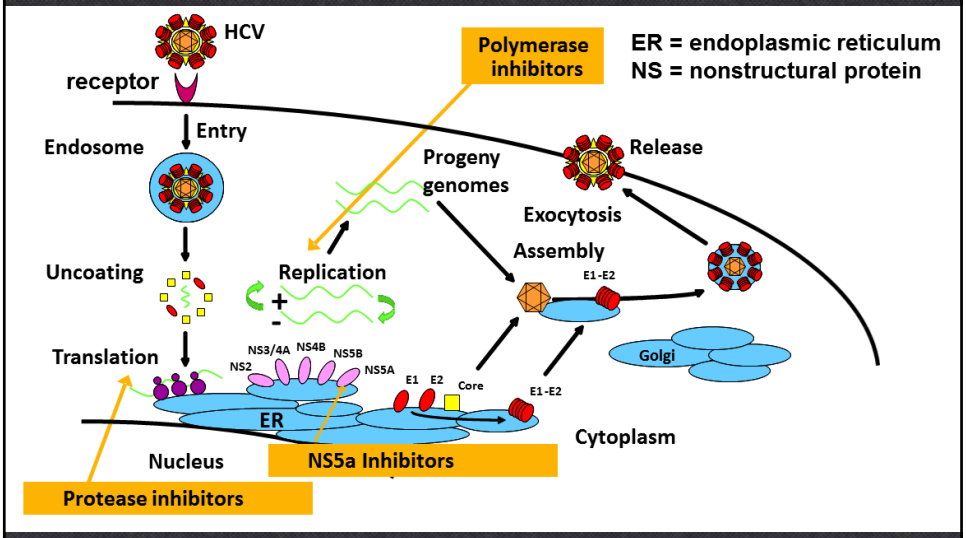
| Descriptive Characteristics | Data |
|---|---|
| # of cases/geography | • 29 cases (5 in US, 19 Japan, 5 in other) |
| Timing | • Temporally related to HCV therapy and occurred within 4-8 weeks (mean time to HBV-R was 53 days) |
| Baseline HBV viral parameters | • HBsAg+ (n=13) (n=12 not reported); HBcAb+ (n=6) (n=23 not reported); HBV DNA undetectable/detectable (n=16/9) |
| Outcome | • Death (n=2) (due to decompensated liver failure); transplant (n=1); hospitalization (n=6); other (n=20) |
| Specific DAAs used | • SOF-based (n=16); DCV+ASV (n=11); PI-based (n=2) |
| HBV treatment | • In 16 patients who received HBV treatment, treatment was delayed in at least 7 of the cases (44%); one of these 7 patients died; possible delay in at least 7 other cases (one had a liver transplant) |

- **"Our data show that HBV-R is a safety concern in pts previously infected with HBV who take DAAs"**
- **"The benefit of high HCV cure rate with DAAs continues to outweigh the risks, even in those patients who may be at risk of HBV-R"**
- **"Patients with a history of HBV require careful clinical monitoring while on DAA therapy"**

***HBV-R is defined as the abrupt increase in HBV replication in a patient with inactive or resolved HBV (HBsAg positive or negative, respectively), and hepatitis B core antibody (HBcAb) positive**

Bersoff-Matcha , AASLD 2016, Poster LB-17

# Targeting the Viral Life Cycle: Direct Acting Antivirals (DAAs)

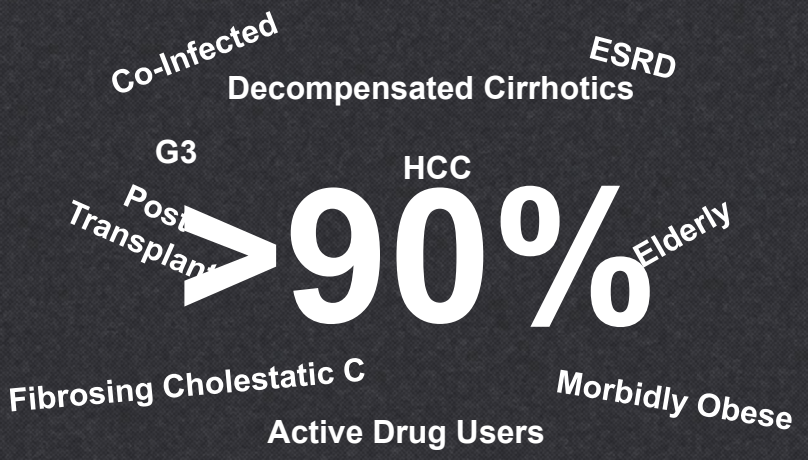



Racanelli V, Rehermann B. *Trends Immunol.* 2003;24(8):456-464.

# Current Treatment Options Simplified

- Treatment Naïve and IFN Experienced Patients
  - Glecaprevir+Pibrentasvir 8-16 wks
  - Sofosbuvir+Velpatasvir 12 wks
    - Sofosbuvir+Ledispavir for 8-24 wks +/- RBV (insurance driven)
    - Elbasvir+Grazoprevir 12-16 wks +/- RBV (insurance driven)
- DAA Experienced Patients
  - Sofosbuvir+Velpatasvir+Voxilaprevir 12 wks
    - (96% overall SVR12 in Polaris-1 (99% in noncirrhotics and 93% in cirrhotics))
  - Glecaprevir+Pibrentasvir
    - (i.e, Sofosbuvir+Ledispavir relapsers would get 16 wks)
- All HCV patients prior to starting therapy need HBV screening

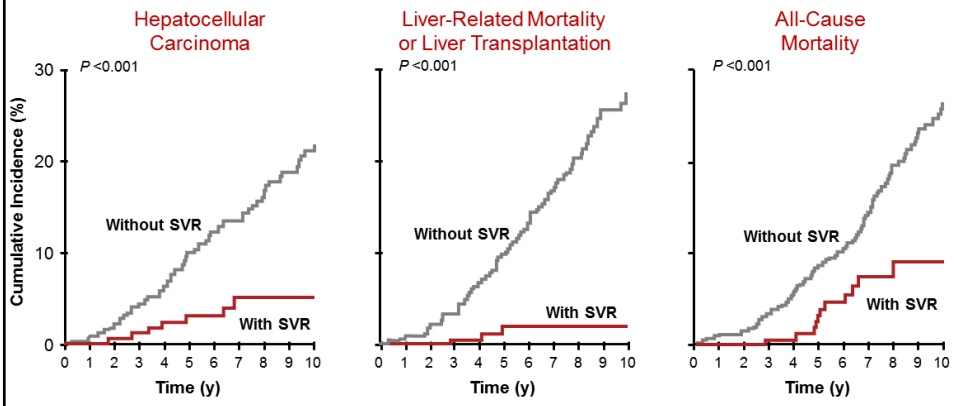
## Sustained Virologic Response




## Hepatitis C Treatment

- More Common Side Effects of the Current DAAs
  - Headache
  - Fatigue
  - Nausea
  - Insomnia
- Overall very well tolerated
  - Discontinuation rates <1%

# SVR Associated With a Reduction in HCC, Liver-Related Mortality, Transplantation, and All-Cause Mortality

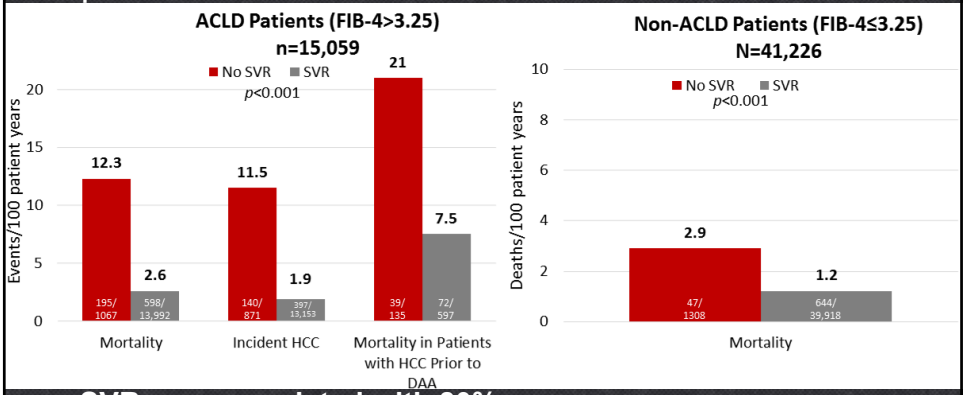



Van der Meer AJ, et al. *JAMA*. 2012;308:2584-2593

## Veterans Affairs HCV Clinical Case Registry

# Impact of SVR with DAAs on Mortality and HCC

**All-cause mortality rates and incident HCC rates in Veterans ± advanced chronic liver disease (ACLD) in the HCV registry treated with DAAs through Sept 2016**



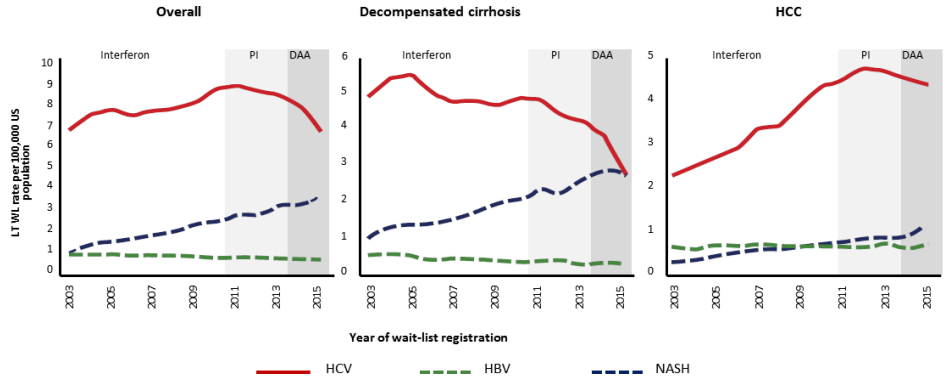

- **SVR was associated with 80% reduction in mortality and 84% reduced incidence in HCC**
- **SVR was associated with 59% reduction in mortality**

ACLD, FIB-4>3.25 at DAA start
Backus, AASLD 2017, Oral 78

# Reduction in Liver Transplant Waitlist in the Era of HCV DAAs

**Cohort study of 47,591 adults wait-listed for liver transplant (LT WL) using the Scientific Registry of Transplant Recipients database from 2003–2015**

**Annual Standardized Incidence Rates (ASIR) of LT Wait-Listing per 100,000 US Population**



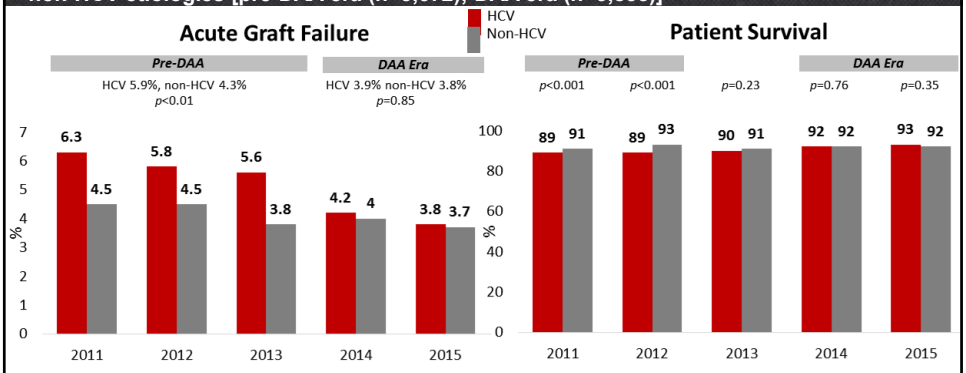

**The rate of liver transplant wait-listing for HCV secondary to decompensated cirrhosis has decreased by 32% in the era of DAA therapy as compared to the IFN era and is now equal to that of NASH**

Flemming JA, et al. Hepatology, Vol.65, NO.3, 2017.

UNOS Database

# Short-Term Survival in HCV Patients Following Liver Transplantation in the Era of DAAs

**Impact of the DAA era on short-term post-LT outcomes among HCV patients compared to non-HCV etiologies [pre-DAA era (n=3,672); DAA era (n=3,855)]**




**DAA era was associated with a 34% reduction in one-year post-LT patient mortality (*adjusted HR 0.66, *P* <.001) among HCV LT recipients**

**DAA era was associated with a 34% reduction in one-year post-LT patient mortality (*adjusted HR 0.66, *P* <.001) among HCV LT recipients**

**Patient and graft survival rates have improved during the DAA era and they are no longer different from non-HCV transplant patients**

Pre-DAA era (2010-2012), DAA era (2014-2015)
Cholankeril. AASLD 2017. Oral 4

# Current Treatment Options

- Issues still with treatment
  - Not everyone can be treated
    - Insurance/Cost
    - Fibrosis stage
  - Should we be treating active drug users or alcoholics?
  - Pediatrics/Adolescents
  - Should we be treating everyone?
    - Significant comorbidities
    - Older patients with early stage disease
  - What to do with DAA relapsers? Any options left?
  - Need more treaters