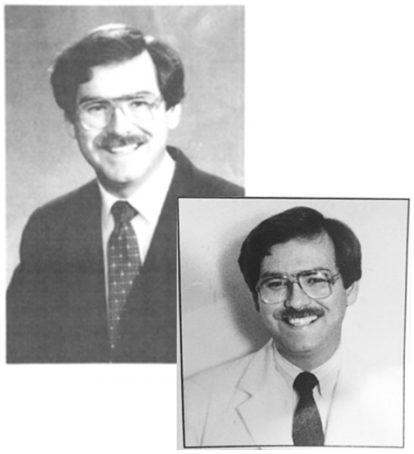
# The Changing Landscape of Liver Care

**James Hanje, MD**
**Director of Hepatology**
**Program Director, Transplant Hepatology Fellowship Program**
**Associate Professor - Clinical**
**The Ohio State University Wexner Medical Center**

# The Evolution of the OSU Liver Program…

# From Then…



# To Now… Hepatology MDs

**James Hanje, MD**
Director of Hepatology
Program Director, Transplant Hepatology Fellowship

**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**

4 |

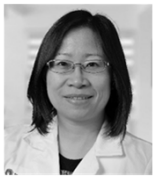
# To Now… Hepatology CNPs

Pamela Kibbe, CNP

Nicole O'Bleness Gray, CNP

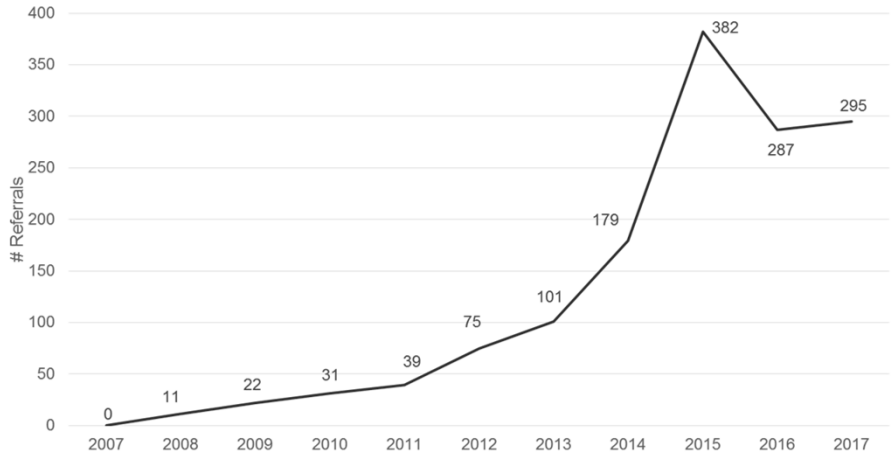
Gail Davidson, CNP

Erica Campbell-Brown, CNP

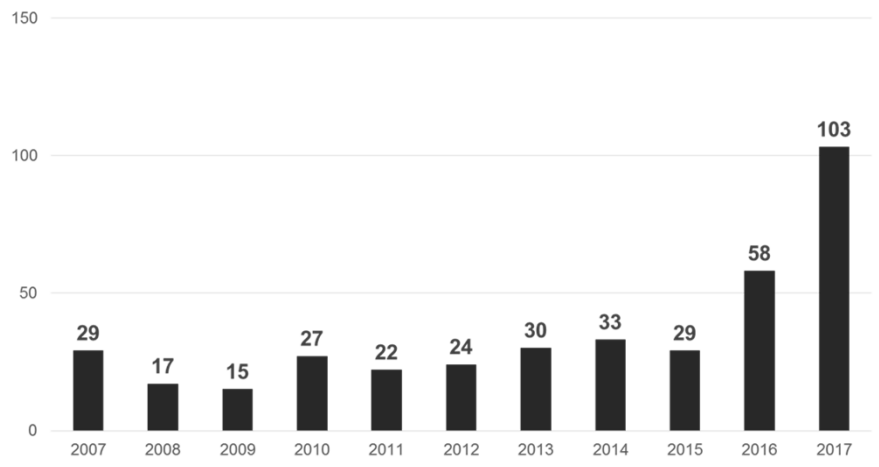


Sherry Ma, CNP

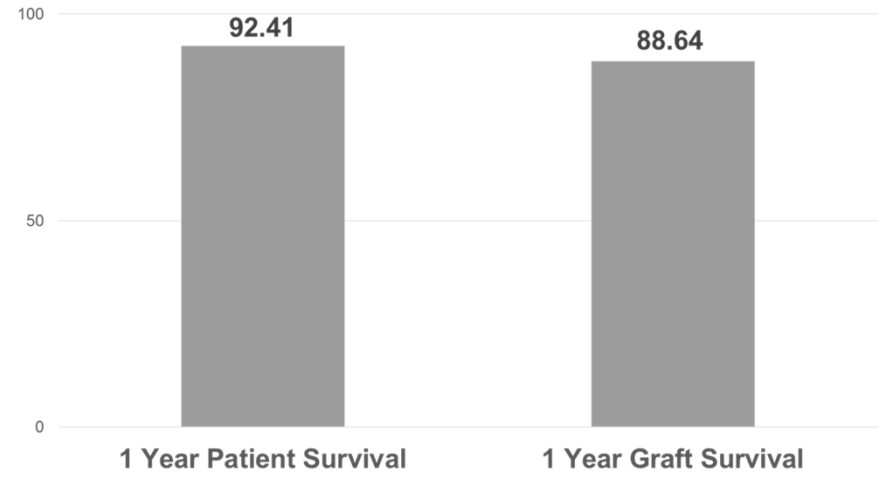
# Hepatology Referrals

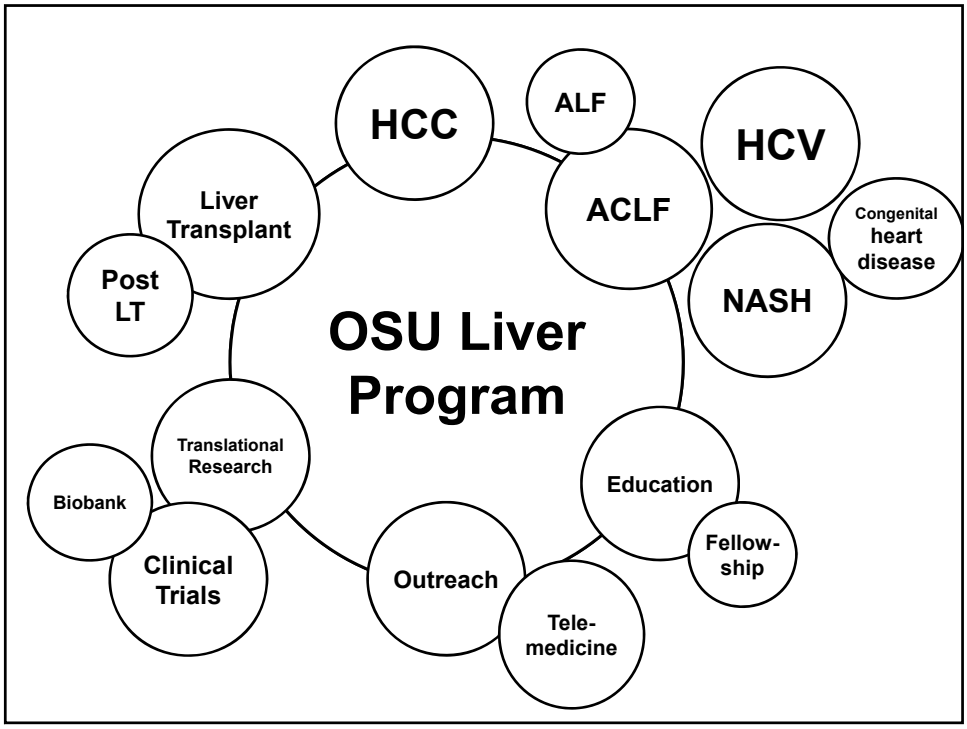


## Ohio State Liver Transplant Volume




## Ohio State Liver Transplant Survival






# Collaborative Clinical Efforts

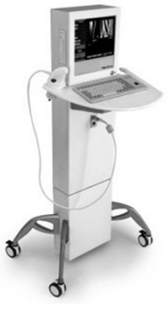
- Multi-disciplinary and sub-specialized clinics
  - Liver tumor clinic
  - HCV treatment
  - NASH and metabolic liver disease
  - Post-transplant care

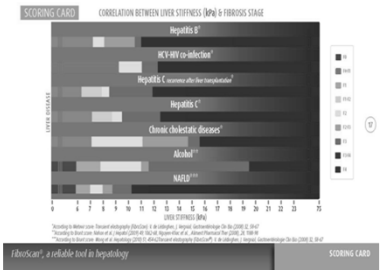
# New Tools and Treatment Options

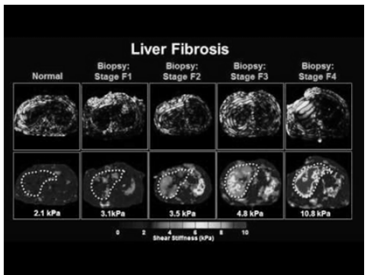
- Hepatocellular Carcinoma (HCC):
  - TACE
  - RFA
  - Y-90
  - SBRT
- Portal hypertensive bleeding:
  - Cyanoacrylate injection of gastric varices
  - Balloon-Occluded Retrograde Transvenous Obliteration (BRTO)
- EUS-guided liver biopsies

# 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.

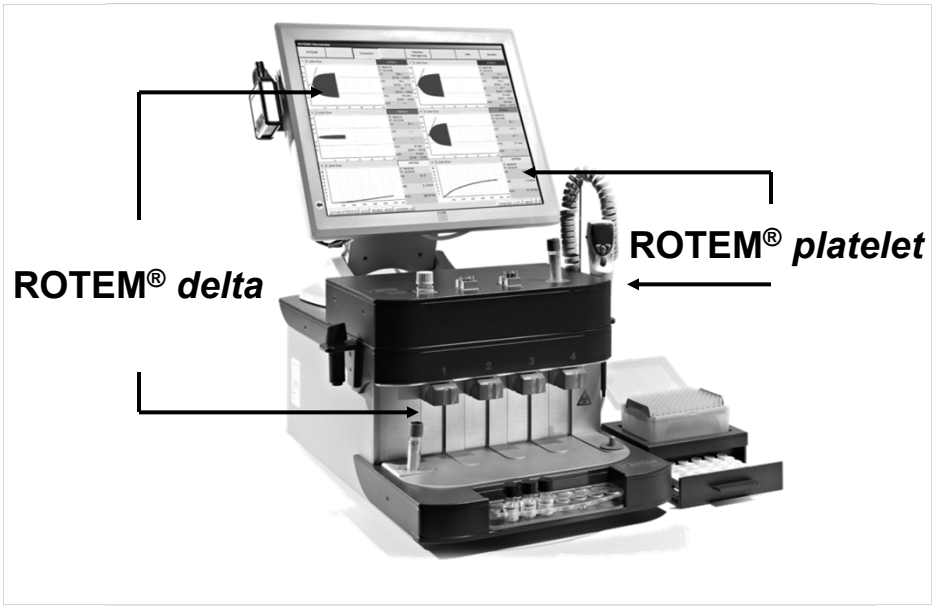





AASLD-IDSA. www.hcvguidelines.org/full-report-view.

## Rotational Thromboelastometry (ROTEM)




## NIH Research Trials


14 |

# Evolution of Care

HEPATOLOGY

*Explore this journal >*

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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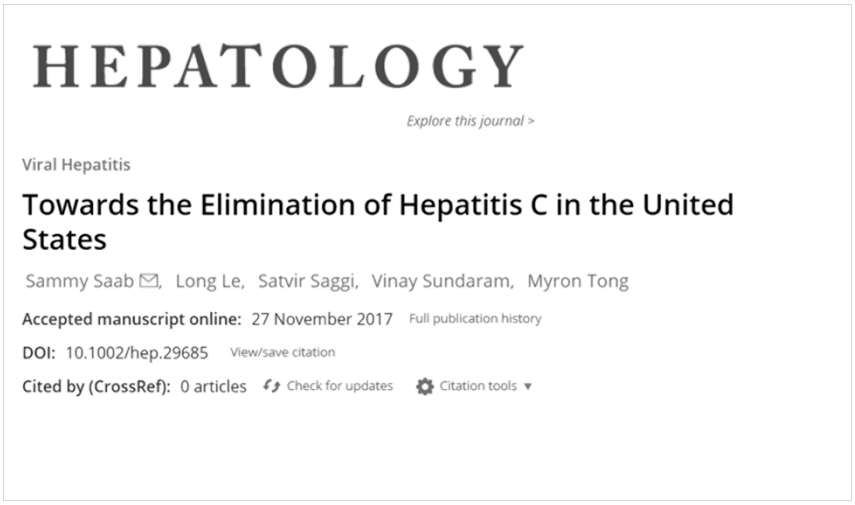
# The Future is Now



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

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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***

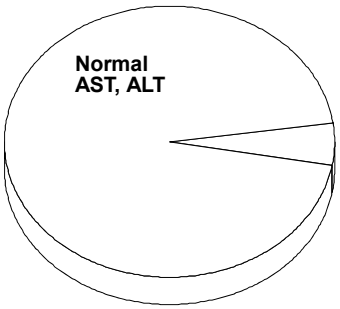
**NHANES III (15, 700 adults)**

- **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%

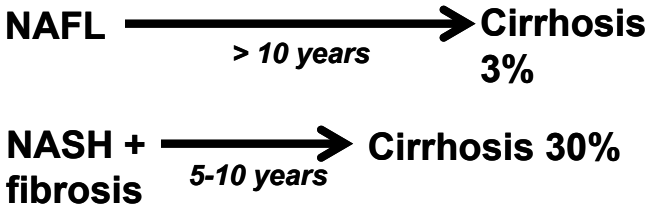
Fibrosis or cirrhosis documented in 20%

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

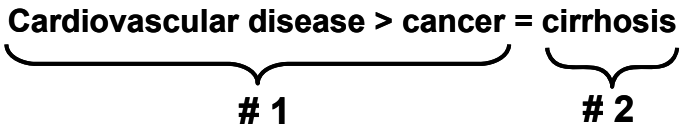
More consistent and rapid progression to cirrhosis than NAFL




Matteoni et al. Gastroenterology 1999; 116:1413

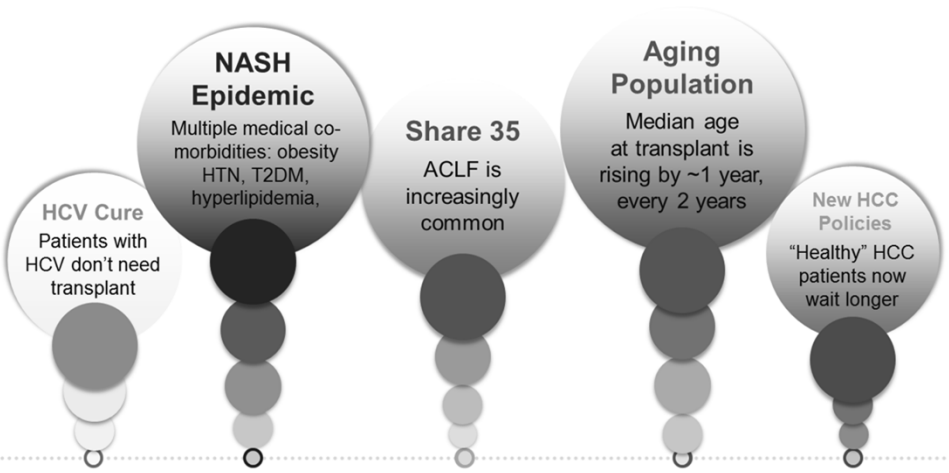
## Prognostic Implications of NASH + Fibrosis

- 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

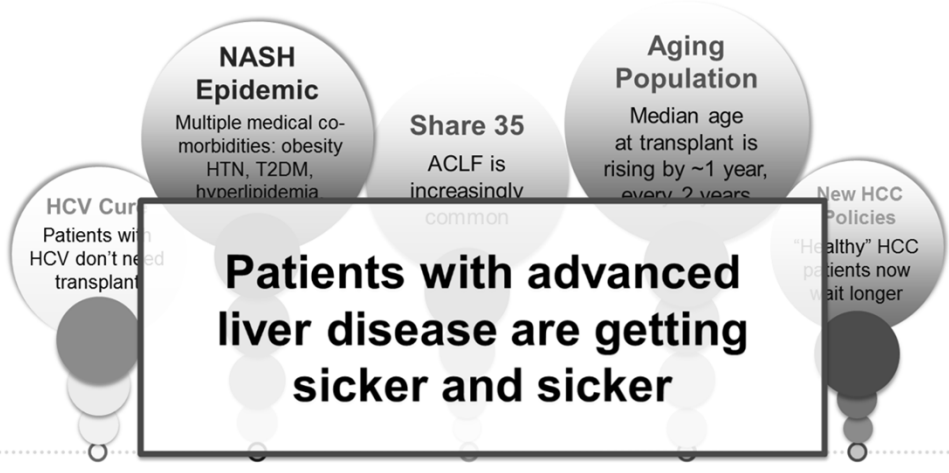



Matteoni et al. Gastroenterology 1999; 116:1413

# Major Changes in Liver Transplant




# Major Changes in Liver Transplant

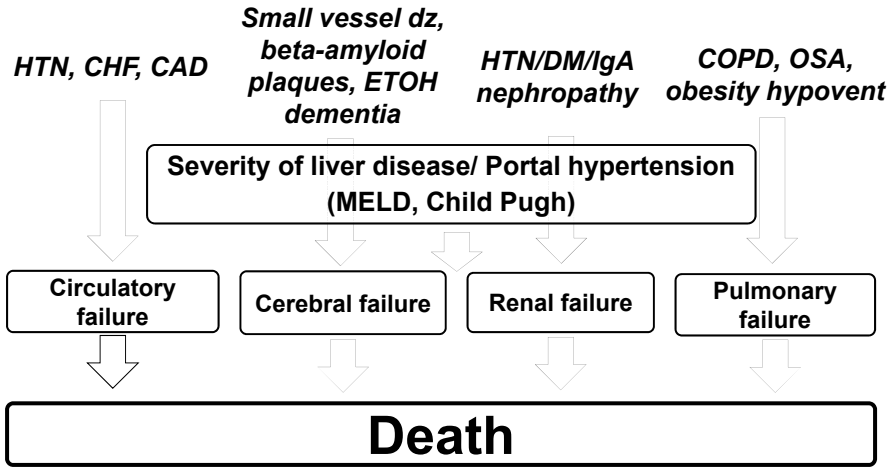


# Acute on Chronic Liver Failure (ACLF)

- 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

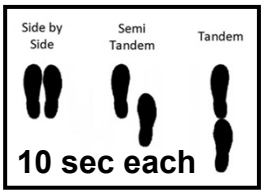
Jennifer C. Lai,[1] Kenneth E. Covinsky,[2] Jennifer L. Dodge,[3] W. John Boscardin,[2,4] Dorry L. Segev,[5] John P. Roberts,[3] and Sandy Feng[3]

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

FrAILT

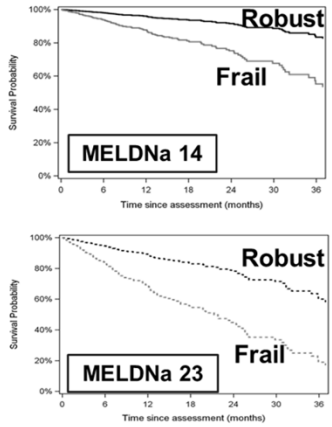
90 s

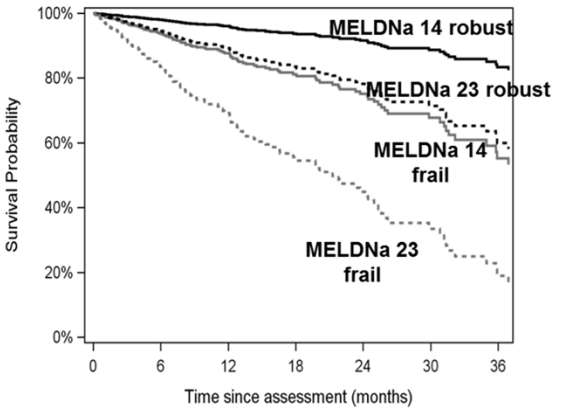
Grip + Chair stands + Balance




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

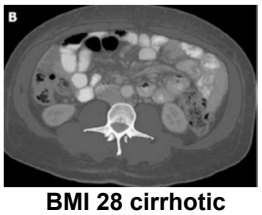
ORIGINAL ARTICLE

CAREY ET AL.

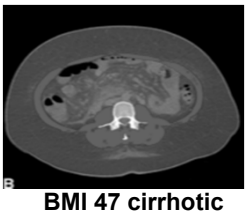
A Multicenter Study to Define Sarcopenia in Patients With End-Stage Liver Disease

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

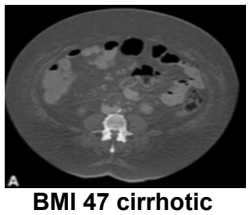
# Sarcopenia by Skeletal Muscle Index



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.

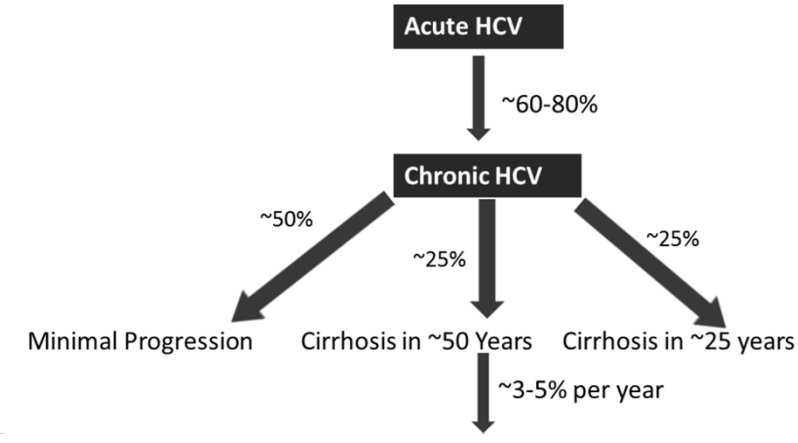
# Disclosures Last 12 Months

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

# Background

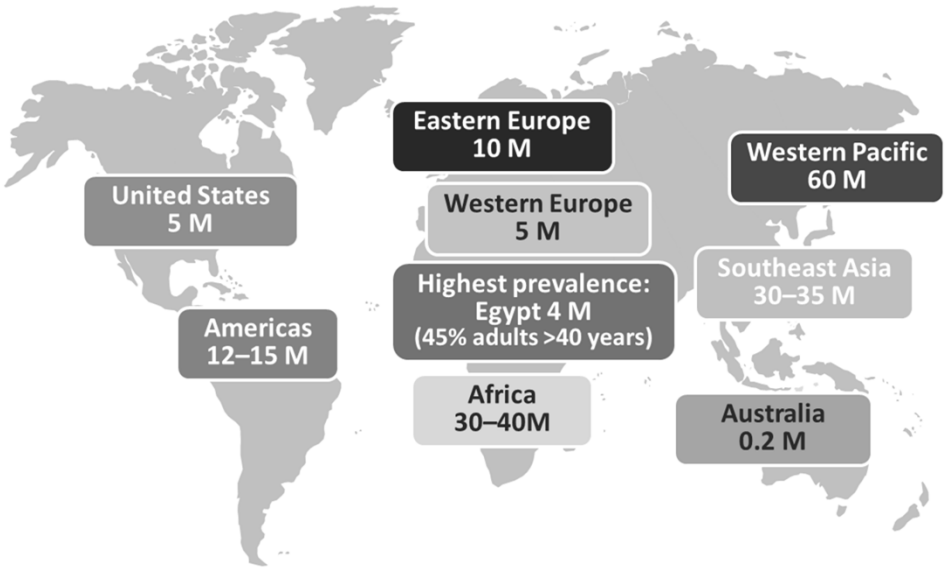
- RNA virus with different subtypes
  - (i.e, genotypes 1-6 (G1 most common in the US))
- Blood exposure (IVD in the US)
- Can cause an acute and/or chronic infection
- Can cause extrahepatic manifestations
  - Hematologic: Mixed cryoglobulinemia
  - Renal: Glomerulonephritis
  - Dermatologic:
    -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

# Natural History



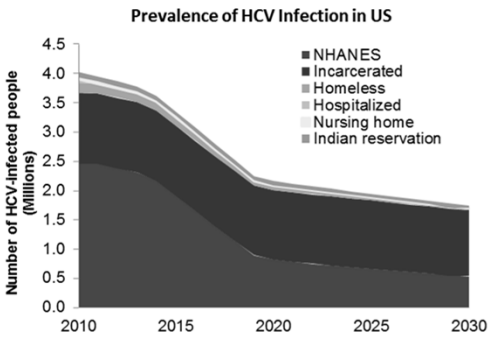

Poynard T et al. Lancet. 1997;349:825-832. Feld JJ, Liang TJ. Hepatology. 2006;43(suppl 1):S194-S206.

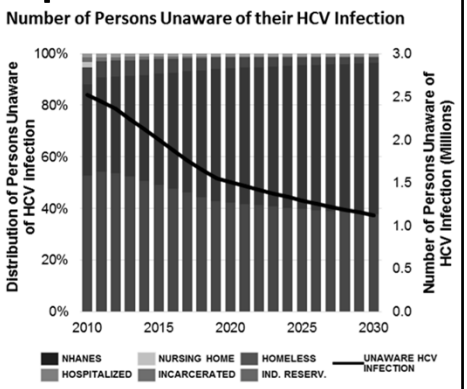
# Worldwide Seroprevalence of Hepatitis C: ~200 million




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



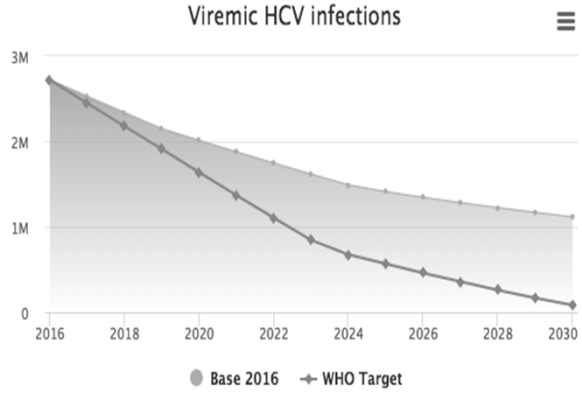




- **In 2010, 4.0 million people were infected with HCV when accounting for non-NHANES groups**
- **In 2017, 2.8 million people have chronic HCV (1.4 million in NHANES and 1.4 million in non-NHANES population)**
- **By 2030, 1.7 million people could remain viremic under current screening and treatment 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**

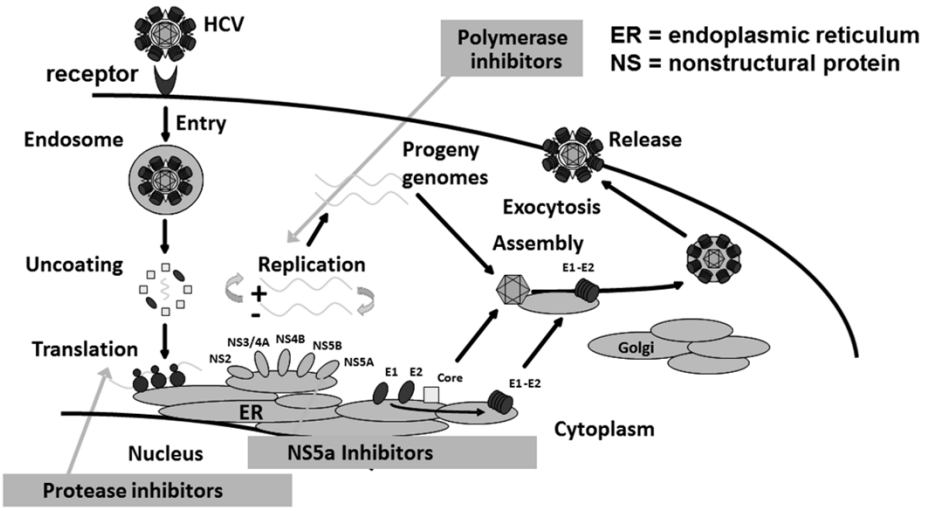
| Descriptive Characteristics | Data |
|---|---|
| # of cases/geography | • 29 cases (5 in US, 19 Japan, 5 in other) |
| Timing | • Temporally related to HCV therapy and occurred within 4-8 weeks (mean time to HBV-R was 53 days) |
| Baseline HBV viral parameters | • HBsAg+ (n=13) (n=12 not reported); 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)

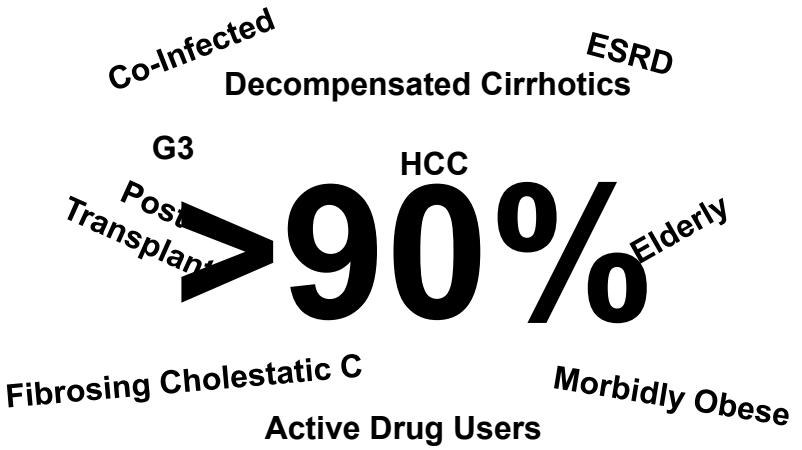



Racanelli V, Rehermann B. *Trends Immunol.* 2003;24(8):456-464.

# 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**

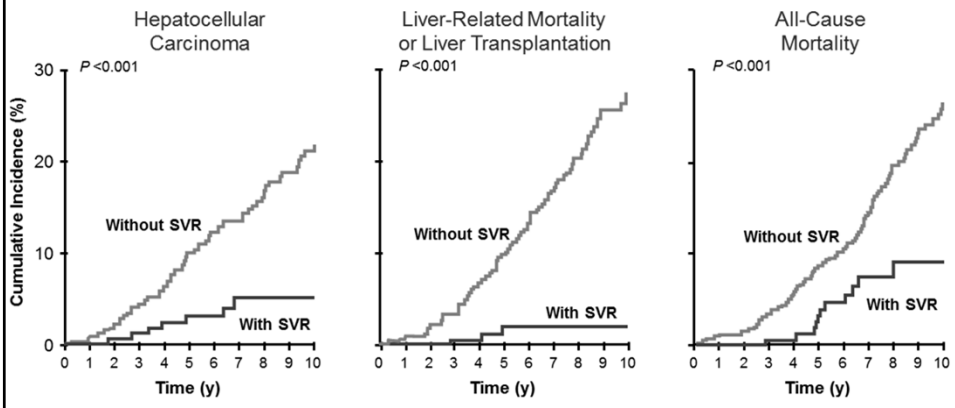
# Sustained Virologic Response




# 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

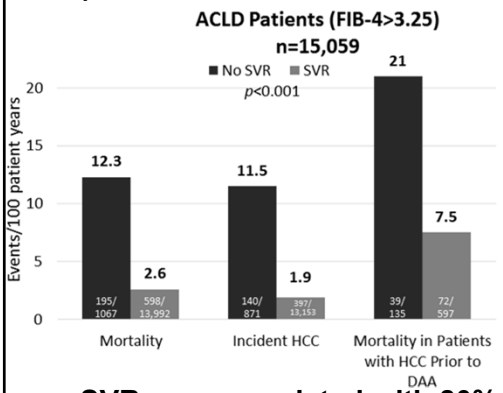


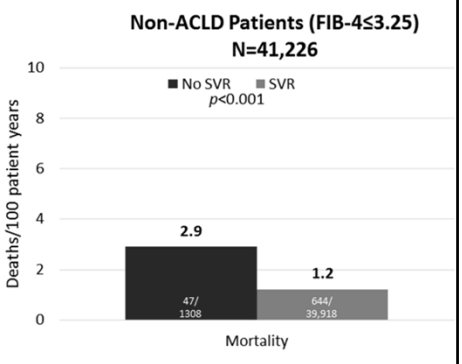

Van der Meer AJ, et al. *JAMA*. 2012;308:2584-2593

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**



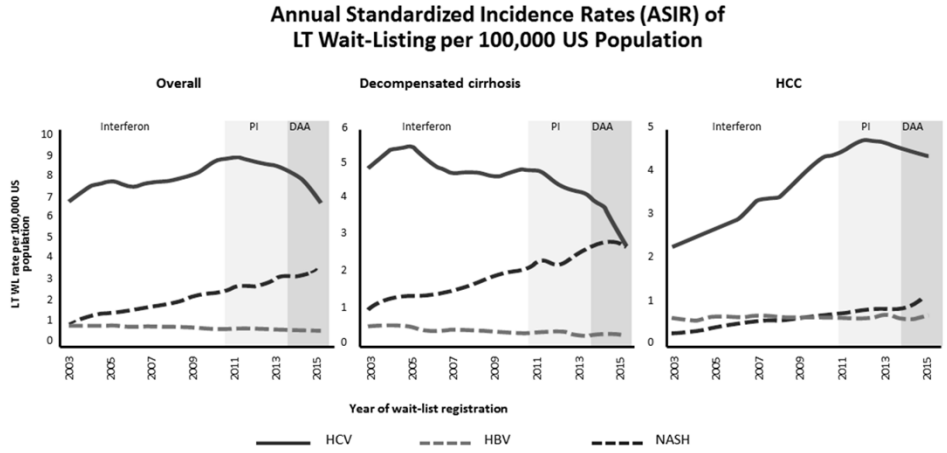

- **SVR was associated with 80% reduction in mortality and 84% reduced incidence in HCC**

**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**



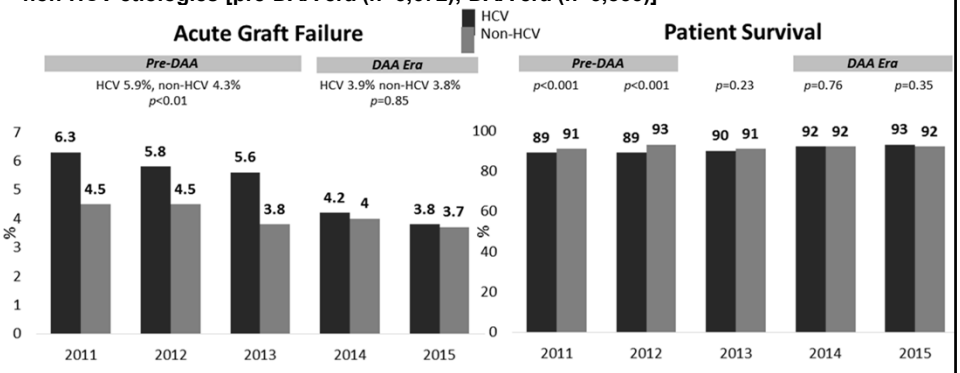

**The rate of liver transplant wait-listing for HCV secondary to decompensated cirrhosis has decreased by 32% in the era of DAA therapy as compared to the IFN era and is now equal to that of NASH**

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**