Ethical Challenges: Who Should Receive a Liver Transplantation?

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NUTORC
Transplant Outcomes Research Collaborative

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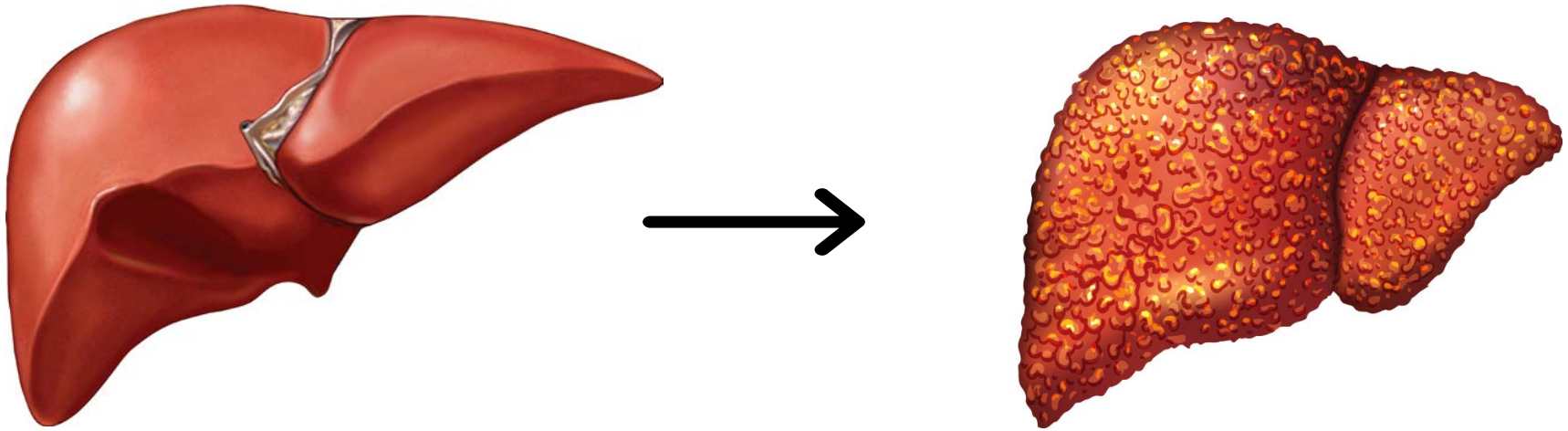
- R21DK108104 (Mehrotra)
- R01DK104876 (Gordon/Caicedo)

Overview

- Cirrhosis
- Liver Transplantation
- Liver Allocation
- Ethical Principles & Final Rule
- Geographic Liver Allocation
- Frailty
- Alcohol use disorder, Liver cancer
- Next Steps

Cirrhosis

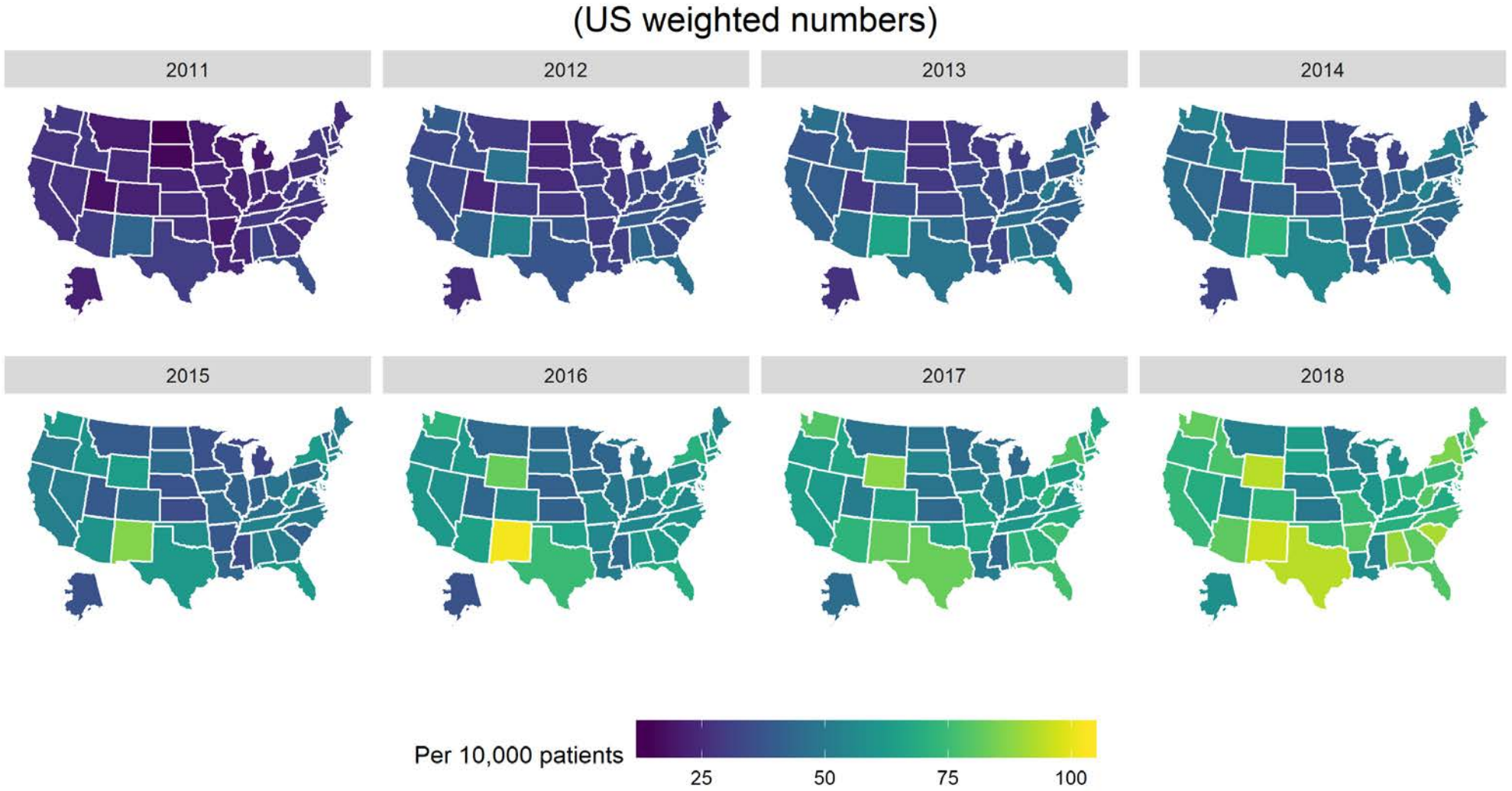
- Cirrhosis is highly prevalent (0.7—4.5%)



- In autopsies 4.5% are found to have cirrhosis
- Administrative data suggests a prevalence of 0.7%

Mazumder, AASLD, 2020; Scaglione, J Clin Gastro, 2015;

Cirrhosis is increasing (2011-2018)



Mazumder, AASLD, 2020

Etiology of cirrhosis

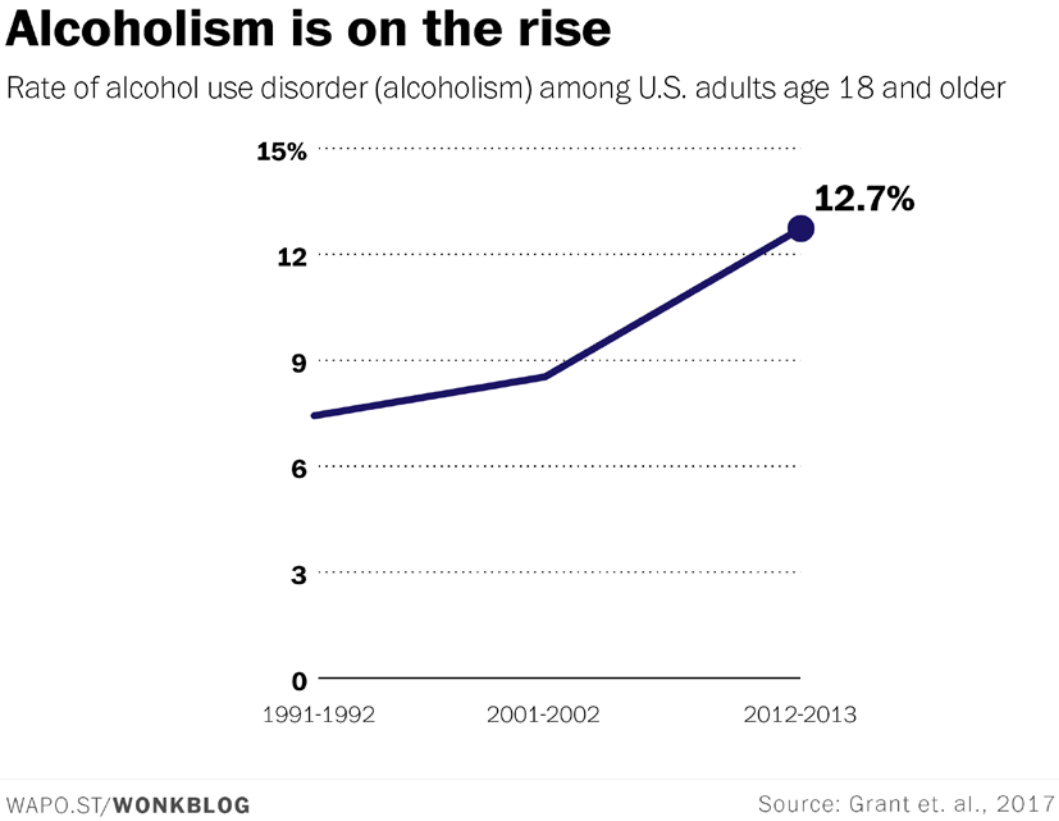
- Hepatitis C
- Alcohol use disorder
- Non-alcoholic steatohepatitis (NASH)
- Biliary – primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC)
- Others

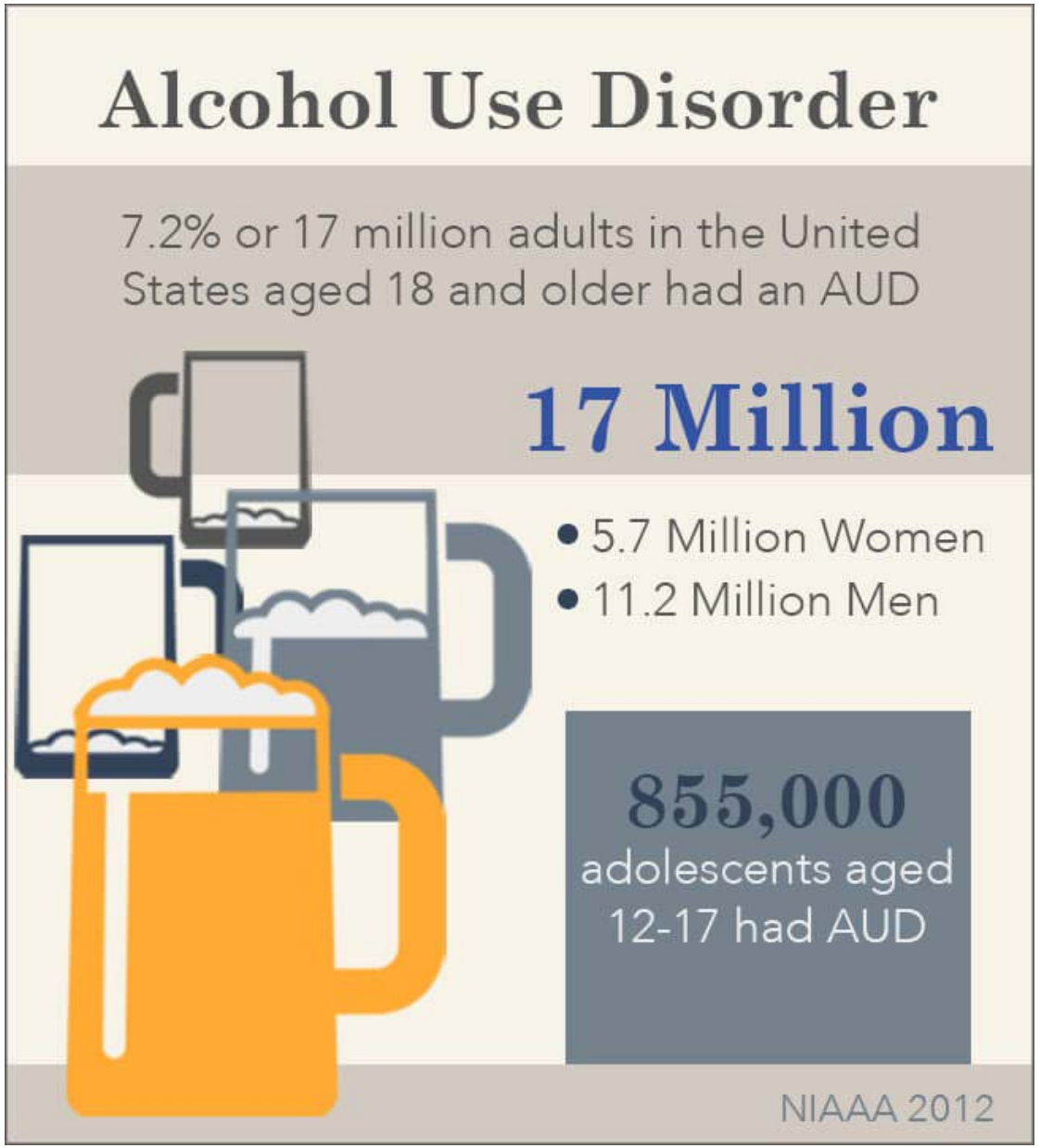
D'Amico et al, Alimentary pharmacology & therapeutics. 2014; Garcia-Tsoa, Hepatology. 2017; Kim WR, et al, NEJM, 2008

Hepatitis C


TREATMENT
1980s
INTERFERON MONOTHERAPY
2001
PEGYLATED INTERFERON
40-80% cure rate
½-1 year treatment duration
Injections
Difficult side effects
2011
DIRECT-ACTING ANTIVIRALS
95% cure rates
12-week treatment duration
Tablets
Fewer side effects

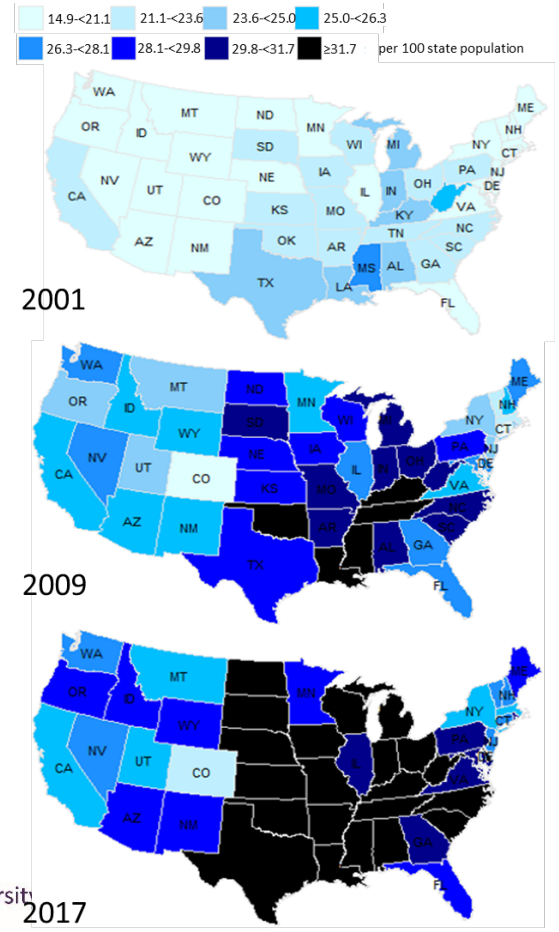
Alcohol


Alcoholism is on the rise
Rate of alcohol use disorder (alcoholism) among U.S. adults age 18 and older
15%
12
9
6
3
0
12.7%
1991-1992
2001-2002
2012-2013
WAPO.ST/WONKBLOG
Source: Grant et. al., 2017

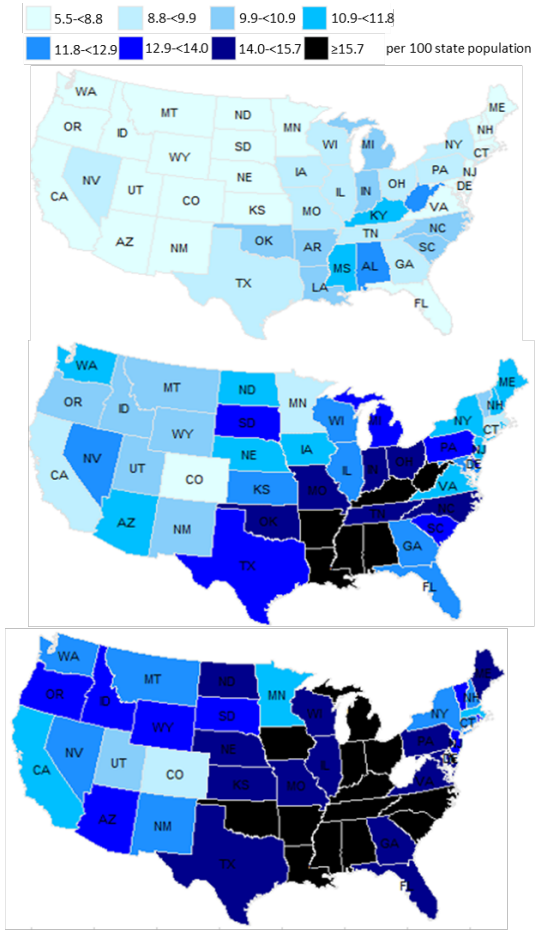

Alcohol Use Disorder
7.2% or 17 million adults in the United States aged 18 and older had an AUD
17 Million
• 5.7 Million Women
• 11.2 Million Men
855,000
adolescents aged 12-17 had AUD
NIAAA 2012

Non-alcoholic steatohepatitis (NASH)

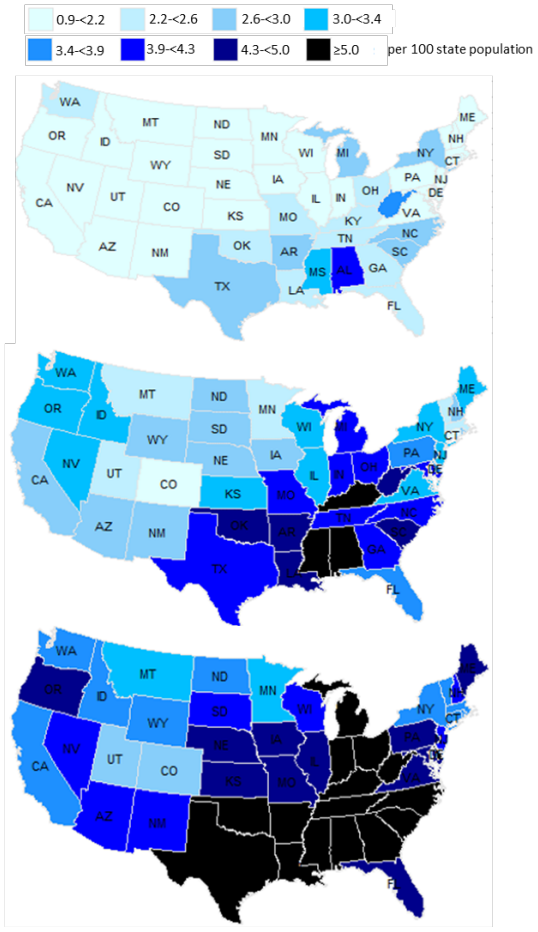
Prevalence of obesity

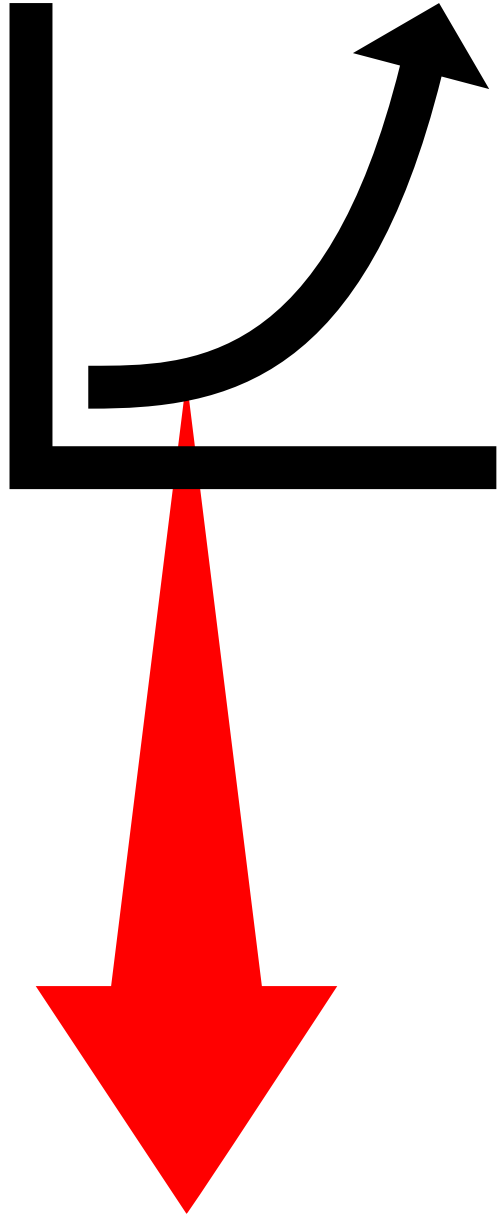


Prevalence of obesity + hypertension



Prevalence of obesity + hypertension + diabetes





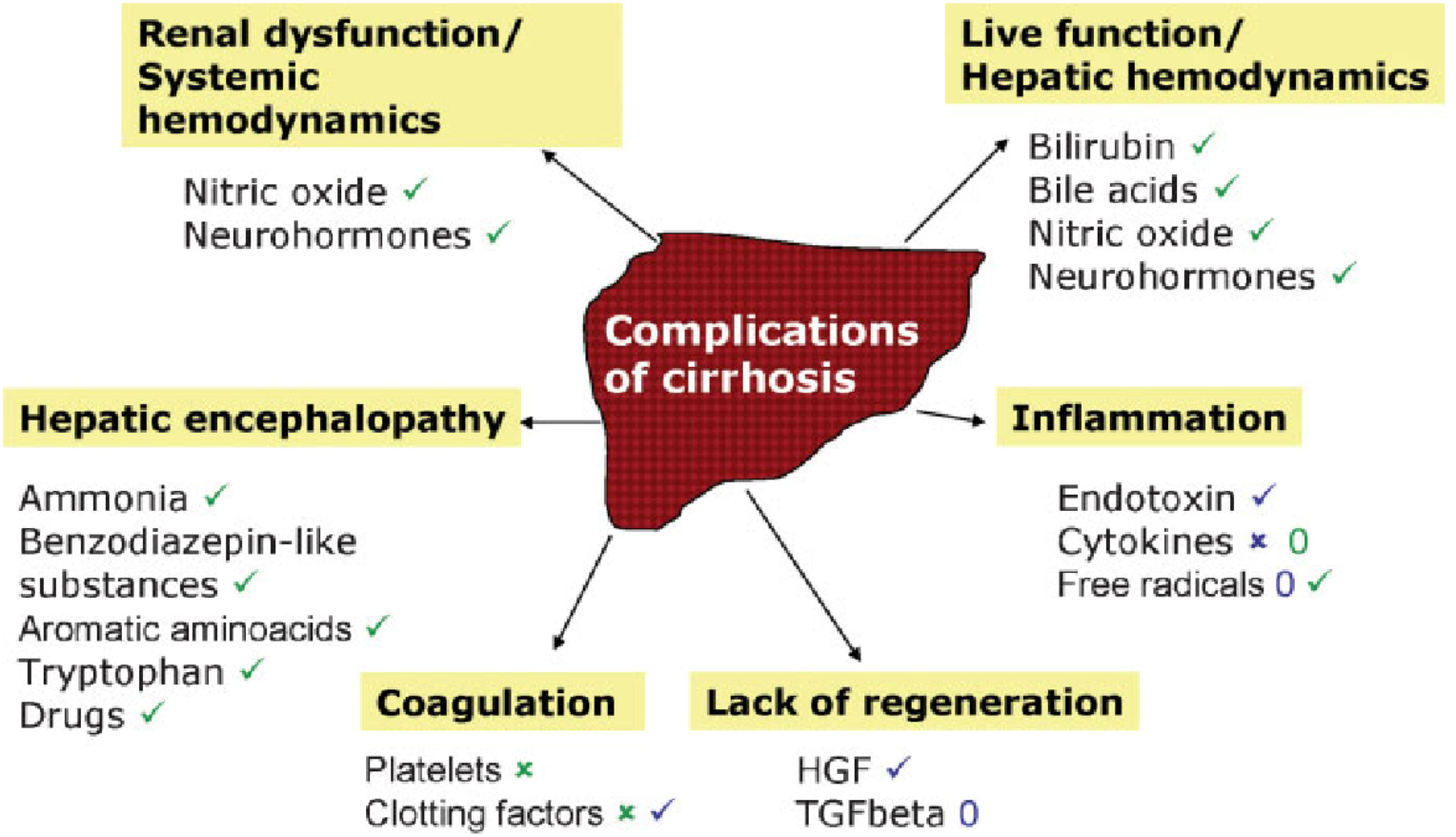
Chang et al. – unpublished data

Ethical Challenges

- Disadvantaged groups are more affected
  - Patients with psychiatric disorders
  - Ethical, clinical, economic and social barriers
    - Prevention
    - Treatment
    - Referral to transplant center

Effects of Cirrhosis

- Estimated survival with cirrhosis is 15 years
- Median survival of those with decompensation is 1.8 years

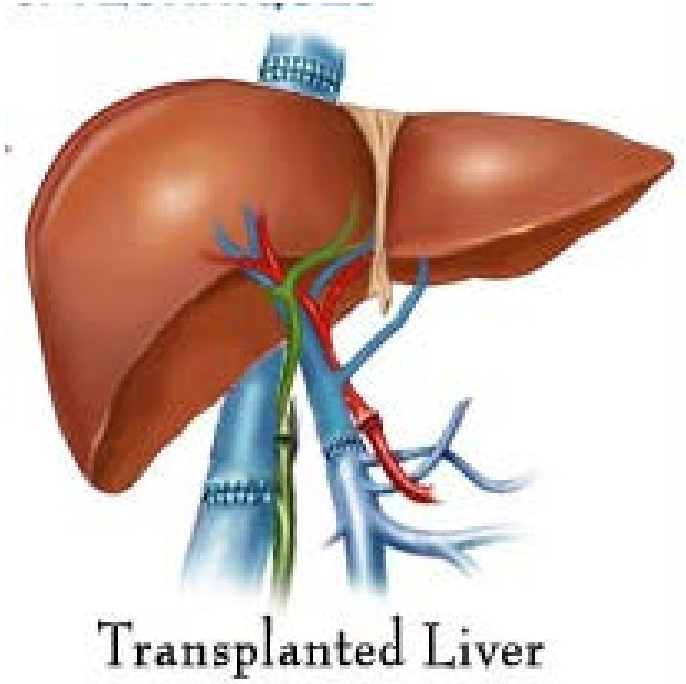


D'Amico et al, Alimentary pharmacology & therapeutics. 2014; Garcia-Tsoa, Hepatology. 2017; Kim WR, et al, NEJM, 2008

Indication for Liver Transplantation

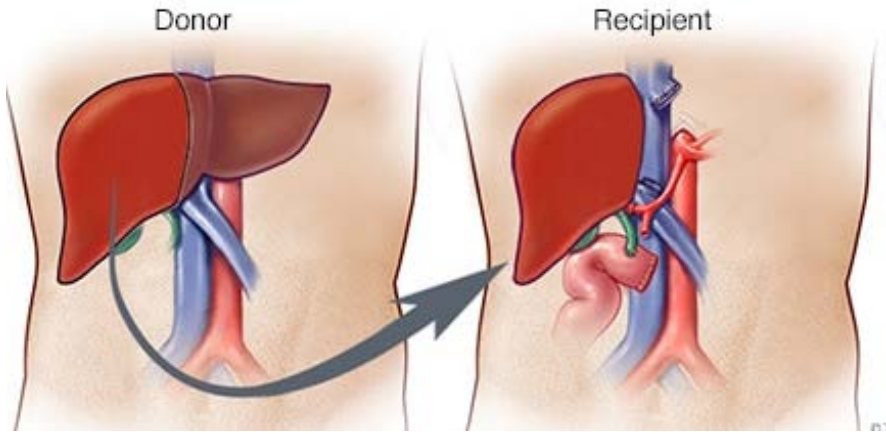
- Curative treatment for cirrhosis

- Also indicated for
  - Acute liver failure (ALF)
  - Liver Cancer (e.g. hepatocellular carcinoma)

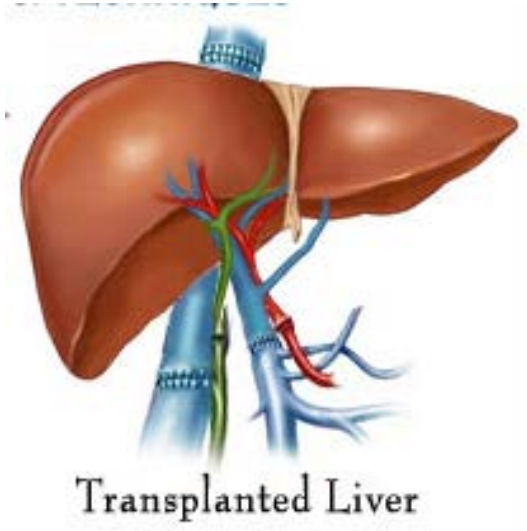


Liver Transplantation – 2019: **8,896**

- Living donor liver transplantation
  - **524** (5.8%)



- Deceased Donor Liver Transplant: **8,372**
  - Waitlisted for liver transplant 11/18/2020: **12,301**
    - ~1,500 removed annually due to sickness
    - ~1,500 die on waitlist



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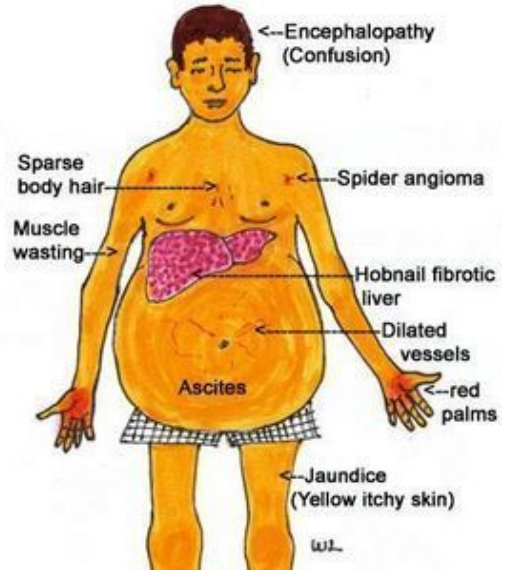
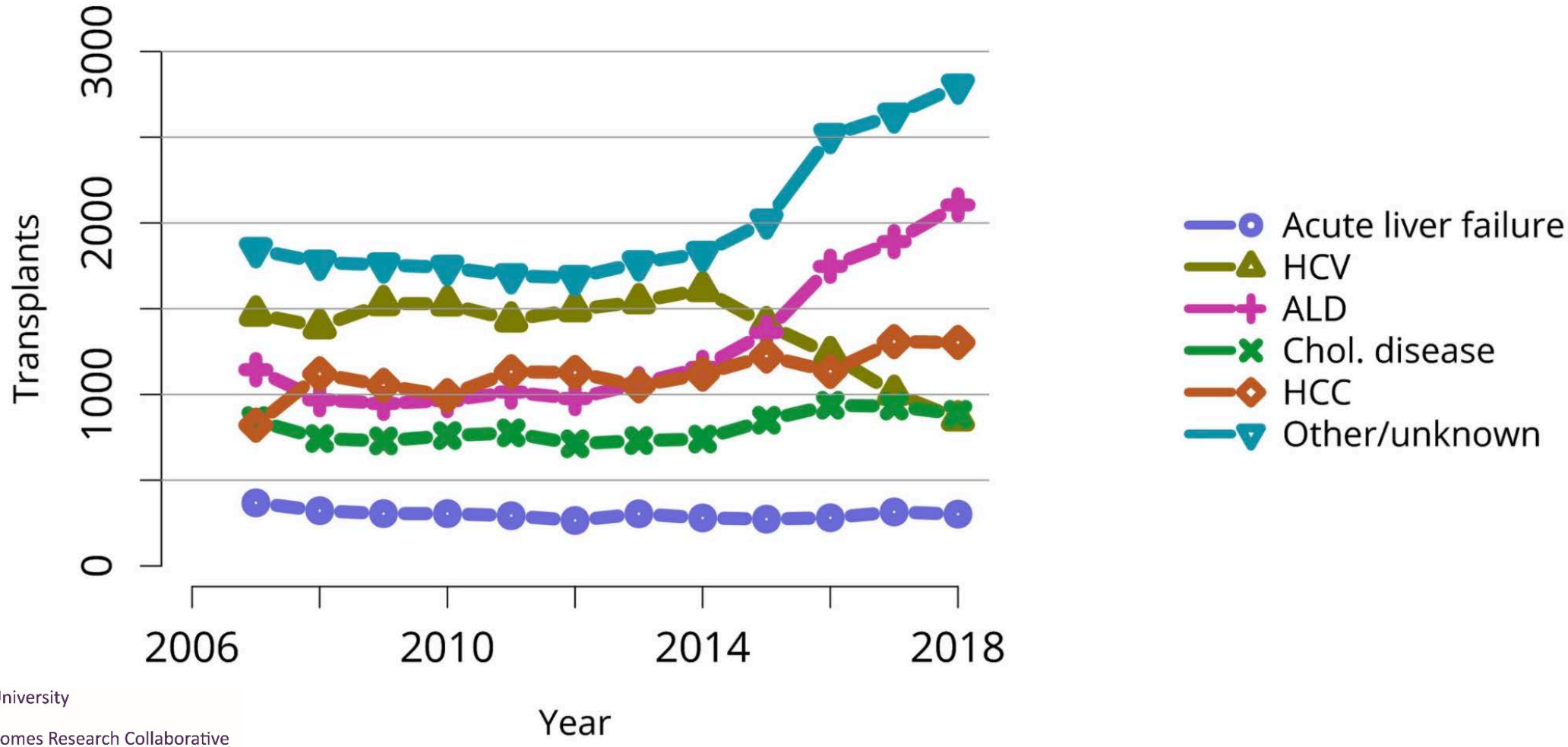
Liver Allocation – Priority for deceased donors

- Allocation rules follow tenant of the "**sickest first**" determined by Model for End-stage Liver Disease (MELD) score
- Disease severity often measured by **Childs-Turcot-Pugh (CTP)** Score or **Sodium-MELD** score
  - CTP: Clinical categories – A, B, C
    - Bilirubin, INR, albumin, ascites, encephalopathy
  - Model for End-stage Liver Disease (MELD) score:
    - INR, bilirubin, creatinine, sodium – scores 6 to 40
      - MELD 6: healthy person
      - MELD 40: ~80% 3-month mortality



HHS, Kim WR, et al, NEJM, 2008

Etiologies of Liver Transplant Recipients



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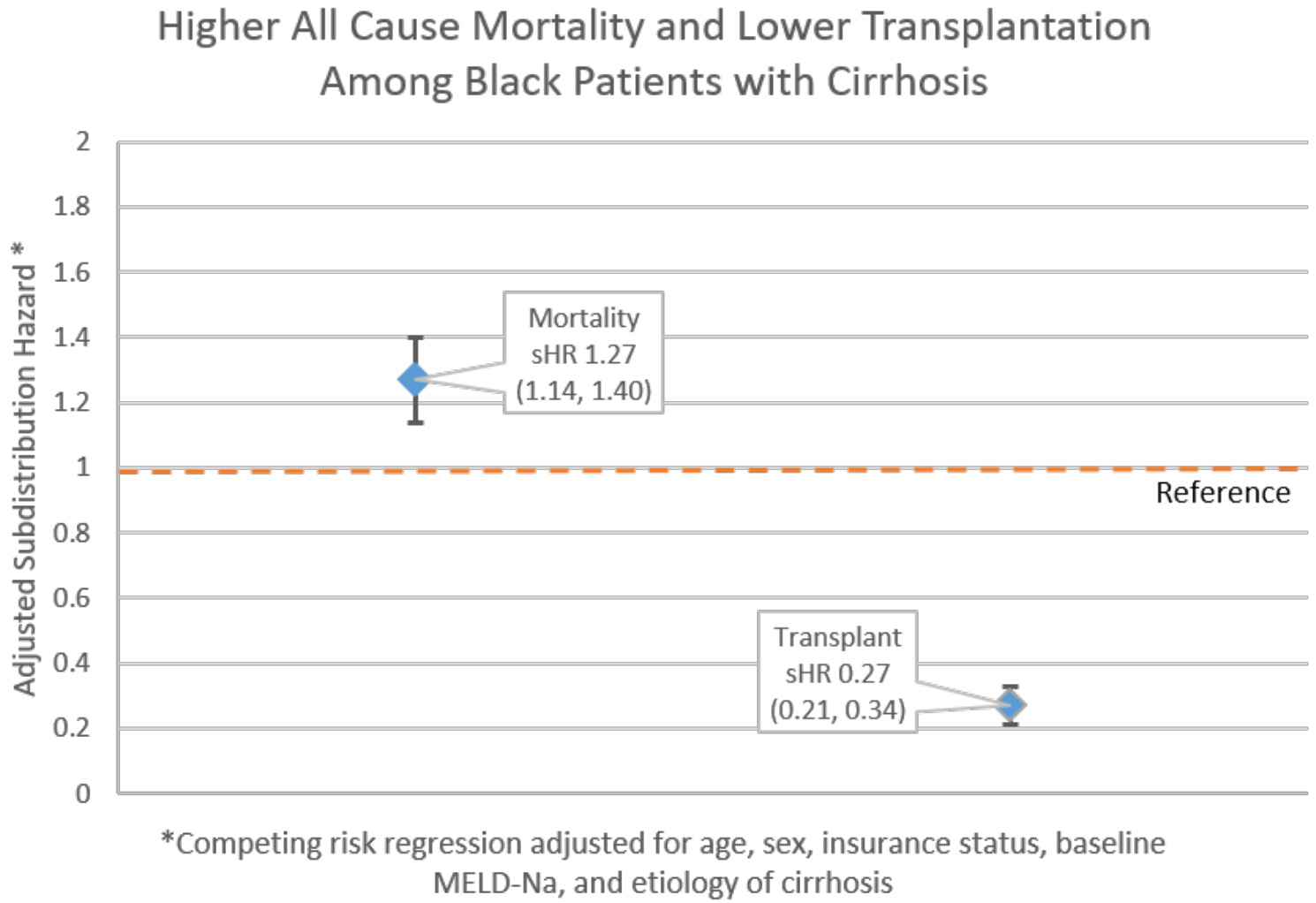
Racial disparity



Mazumder, Hepatology- accepted

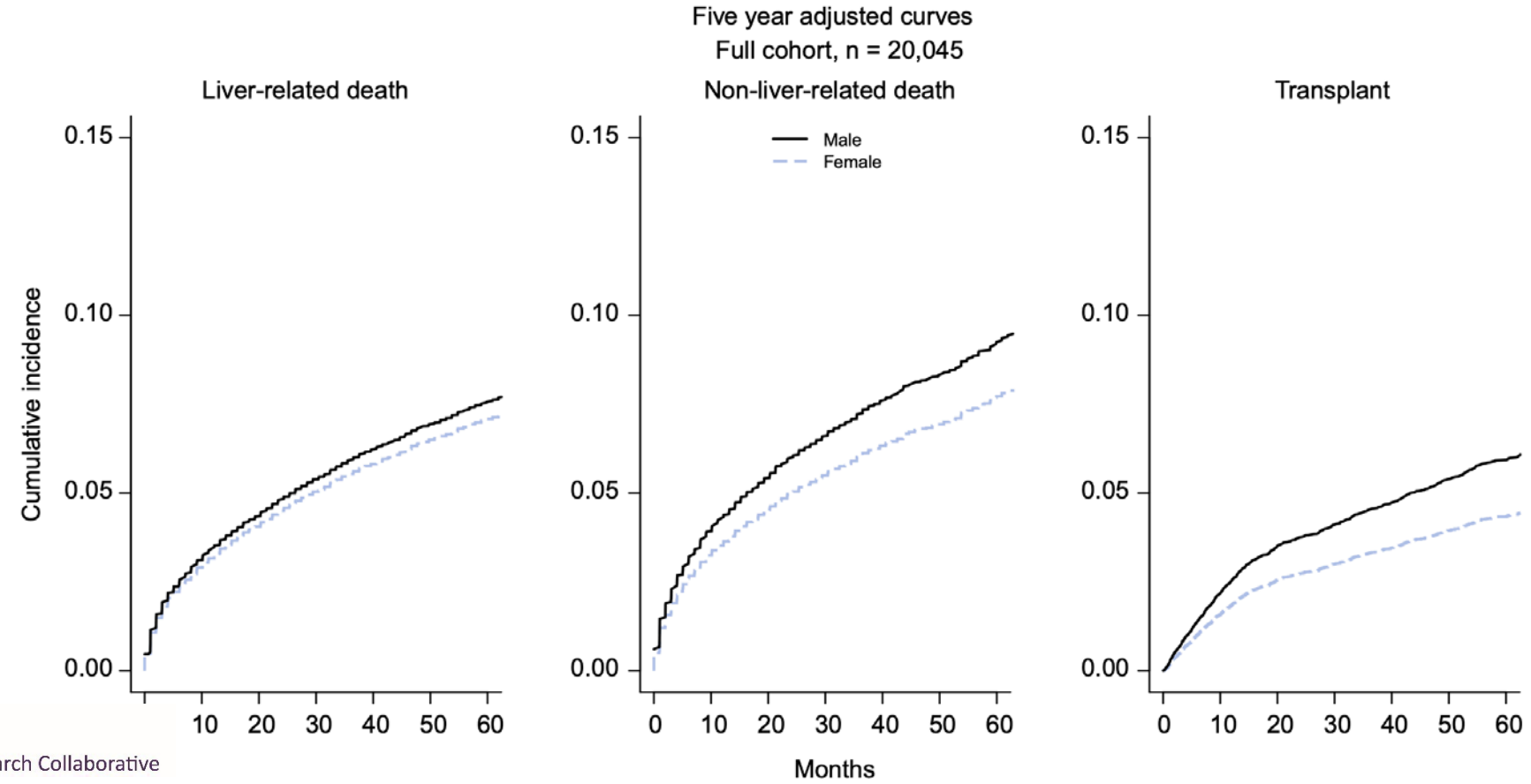
Gender disparity

Research Article
Cirrhosis and Liver Failure

JOURNAL OF HEPATOLOGY

Liver-related mortality is similar among men and women with cirrhosis

Nikhilesh R. Mazumder[1], Stela Celaj[2], Kofi Atiemo[3], Amna Daud[3], Kathryn L. Jackson[4], Abel Kho[4], Josh Levitsky[1,3], Daniela P. Ladner[3,5,*]



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Who gets a transplant?

2M – 10M
cirrhosis

12,300
listed

8,896
liver transplant

7 Ethical Principles of Care

1. Non-Maleficence
2. Beneficence
3. Health Maximization
4. Efficiency
5. Respect for Autonomy
6. Justice
7. Proportionality

The Final Rule

The Final Rule stipulated by the US Department of Health and Human Services (**HHS**) to provide **parity** for waitlisted patients, including socioeconomic and geographic parity

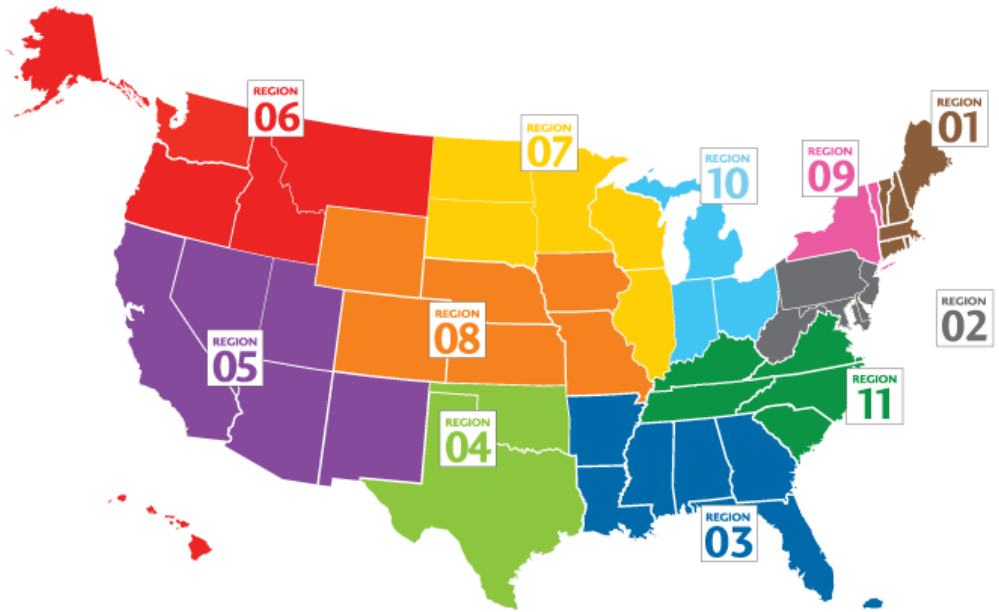
HHS, Kim WR, et al, NEJM, 2008

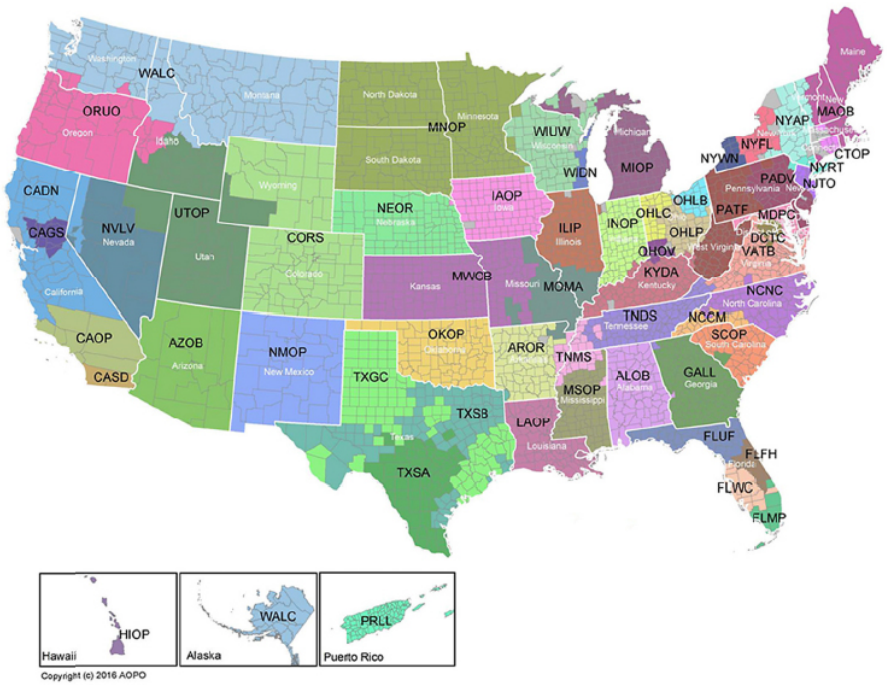
Ethical Challenges related to Access

- Not all patients have equal access to liver transplantation
- Barriers to transplantation
  - Shortage of organs
  - Socioeconomic (e.g., insurance, family support)
  - Structural (eg., race, gender)
  - **Bias**
- One barrier was recently tackled
  - Geographic disparity

Historic Liver Allocation

- 11 UNOS Regions
- 58 Donor Service Areas (DSA)
- “Old” Allocation: DSA → UNOS Region → National





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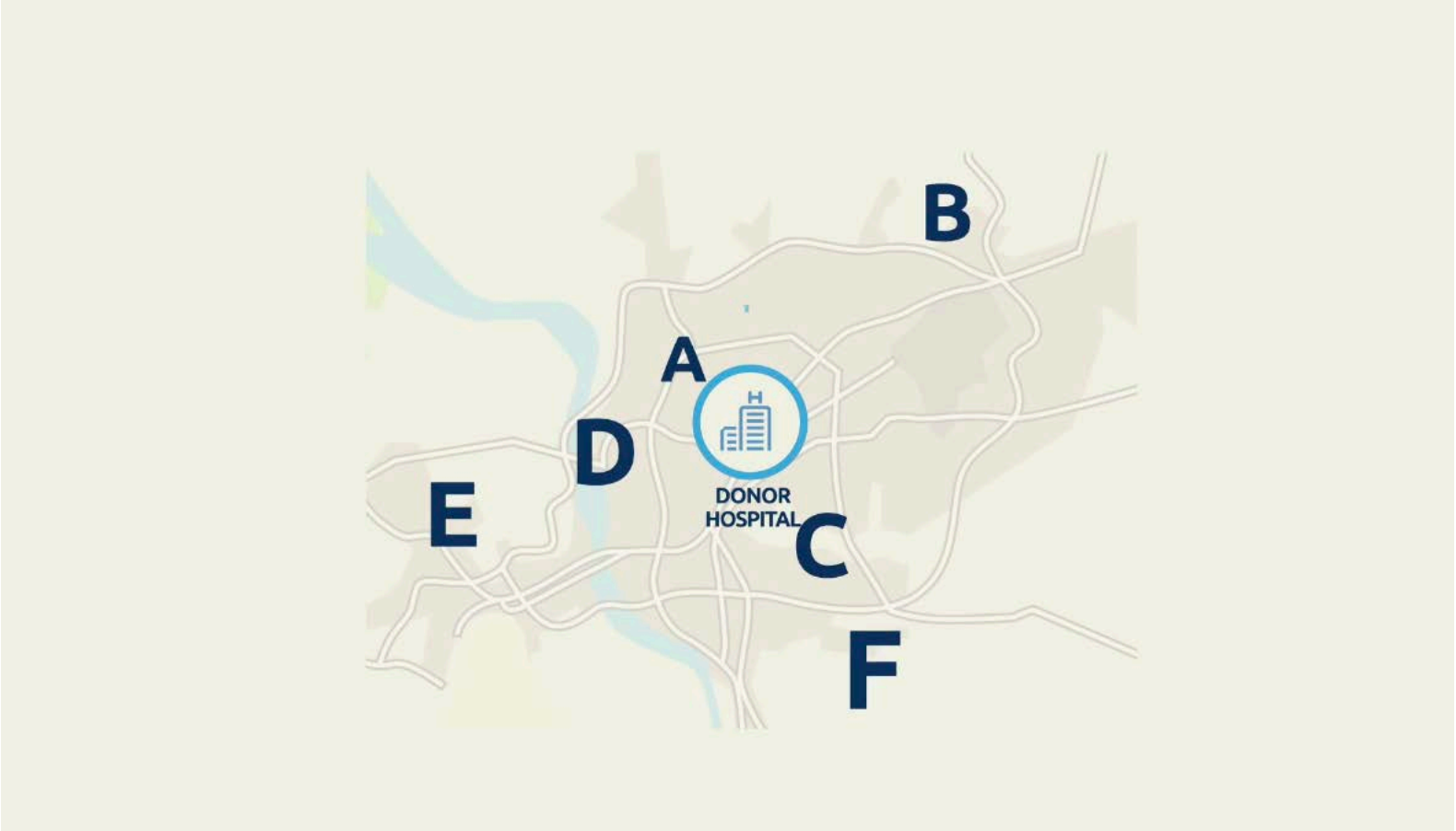
Geographic Challenges with allocation

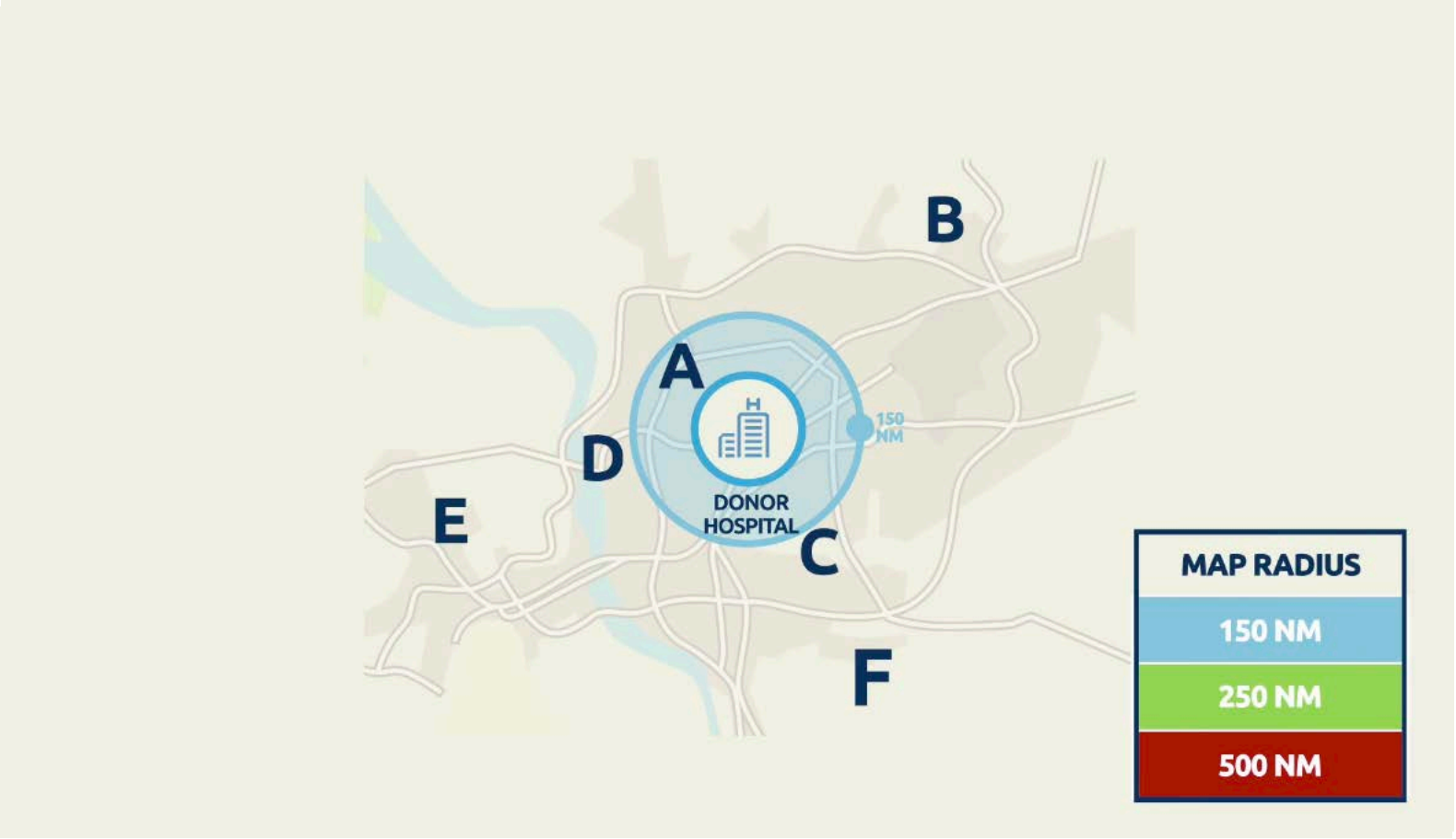
- Depending on geographic location the average MELD score was different
  - Violation of the “HHS Final Rule”
- 2012 OPTN strategic plan to reduce geographic disparity
- Concentric circle system was approved in 2017 and implemented 4/30/2019

Ladner et al. JAMA Surgery 2016; Yeh et al Transplantation, 2011 Adler, AJT 2015;

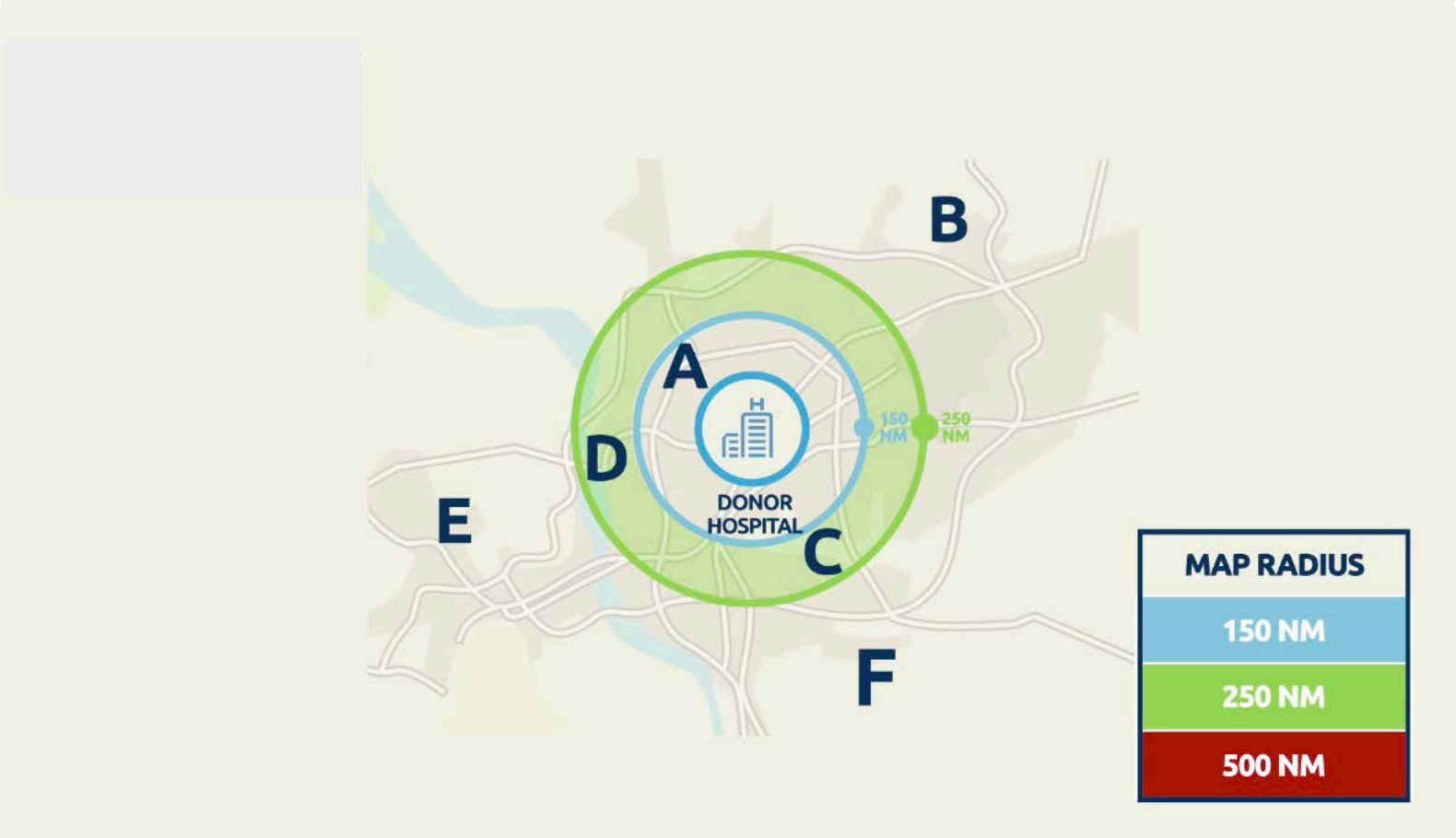
Liver Allocation Today



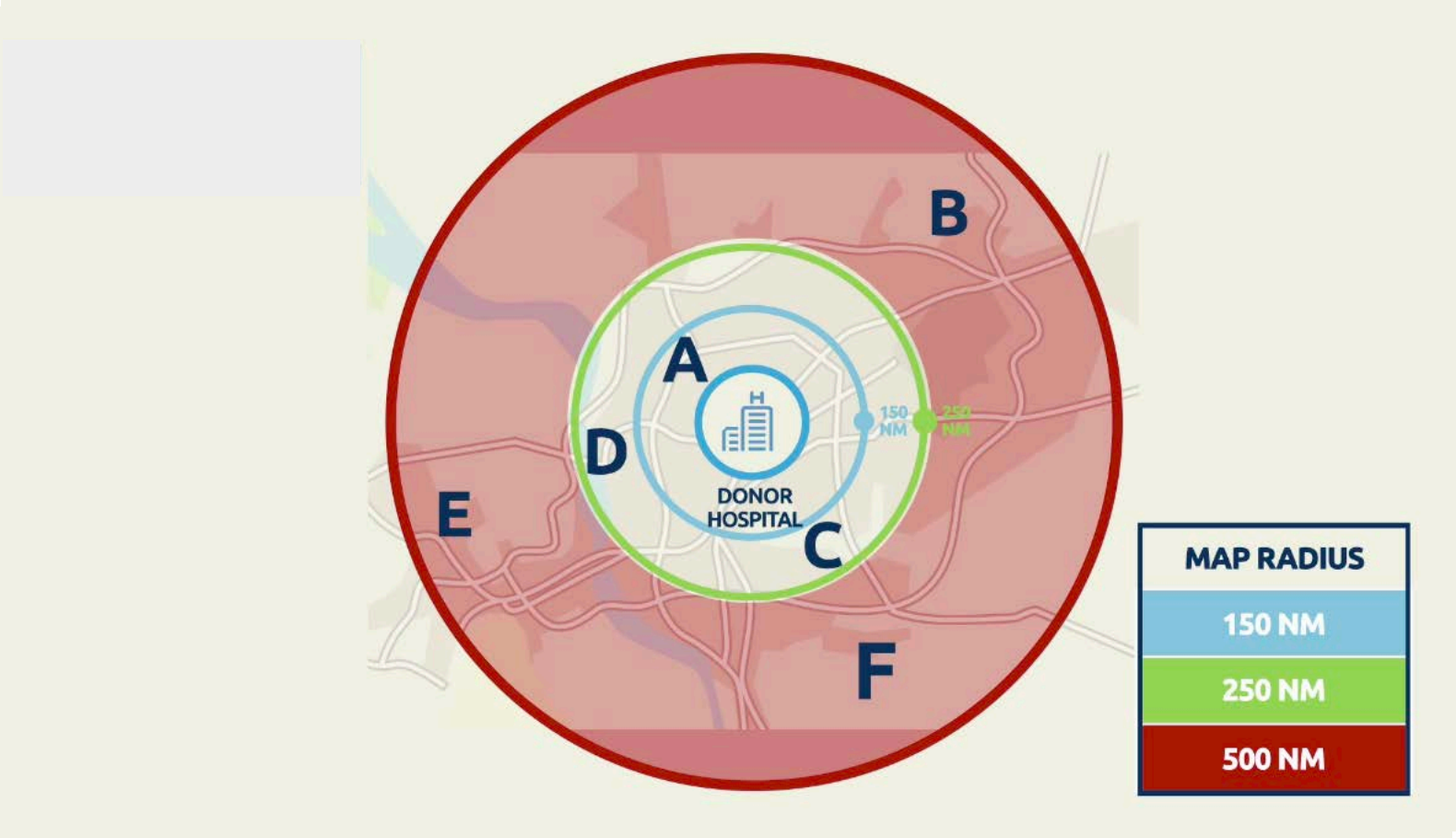
Concentric Circles – 150 miles



Concentric Circles – 250 miles



Concentric Circles – 500 miles



Sequence of Liver Allocation

- Sequence of allocation:
  - **Status 1A, 1B**: 500 miles from donor hospital (<1%)

  - **MELD >36**: 150 miles, 250 miles, 500 miles
  - **MELD 33-36**: 150 miles, 250 miles, 500 miles
  - **MELD 29-33**: 150 miles, 250 miles, 500 miles
  - **MELD 15-28**: 150 miles, 250 miles, 500 miles

Ethical Challenges as Custodians of Organs which are in Short Supply

- Once patients overcome the hurdles
  - Diagnosis
  - Referral
  - Evaluation for transplantation
  - Listed for transplantation

- Now what?
  - Frailty
  - Other considerations: alcohol use dependency, cancer

Frailty

- Clinical state in which there is an increase in a patients' vulnerability to develop a negative health-related event when exposed to a stressor (e.g. transplantation)

Frailty

American Journal of Transplantation | AST American Society of Transplantation | ASTS

Original Article | Free Access

ant Candidates

du/10.1111/ajt.12762 |

World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
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DOI: 10.3748/wjg.v23.i5.899

World J Gastroenterol 2017 February 7; 23(5): 899-905
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

ORIGINAL ARTICLE

Prospective Study

Frailty is independently associated with increased hospitalisation days in patients on the liver transplant waitlist

Frailty

HEPATOLOGY

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

Original Article | Full Access

Published in final edited form as:
Gastroenterology. 2019 May ; 156(6): 1675–1682. doi:10.1053/j.gastro.2019.01.028.

Frailty Associated With Waitlist Mortality Independent of Ascites and Hepatic Encephalopathy in a Multi-Center Study

Jennifer C. Lai, MD, MBA[a], Robert Rahimi, MD[b], Elizabeth C. Verna, MD, MS[c], Matthew R. Kappus, MD[d], Michael A. Dunn, MD[e], Mara McAdams-DeMarco, PhD[f,g], Christine E. Haugen, MD[g], Michael L. Volk, MD, MSc, MD[h], Andres Duarte-Rojo, MD[i], Daniel R. Ganger, MD[j], Jacqueline G. O'leary, MD, MPH[k], Jennifer L. Dodge, MPH[l], Daniela Ladner, MD[m], and Dorry Segev, MD, PhD[g]

Frailty

Liver Transplantation

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Original Article | Full Access

Frailty Is Associated With Increased Rates of Acute Cellular Rejection Within 3 Months After Liver Transplantation

Laila Fozouni, Yara Mohamad, Adrienne Lebsack, Chris Freise, Peter Stock, Jennifer C. Lai

First published: 26 October 2019 |
https://doi-org.ezproxy.galter.northwestern.edu/10.1002/lt.25669 | Citations: 5

Frailty

HEPATOLOGY

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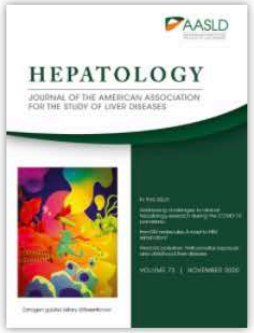


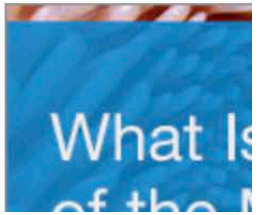
Original Article | Full Access

Identifying an Optimal Liver Frailty Index Cutoff to Predict Waitlist Mortality in Liver Transplant Candidates

Ani Kardashian, Jin Ge, Charles E. McCulloch, Matthew R. Kappus, Michael A. Dunn, Andres Duarte-Rojo , Michael L. Volk, Robert S. Rahimi, Elizabeth C. Verna, Daniel R. Ganger, Daniela Ladner, Jennifer L. Dodge, Brian Boyarsky, Mara McAdams-DeMarco, Dorry L. Segev, Jennifer C. Lai ✉

... See fewer authors

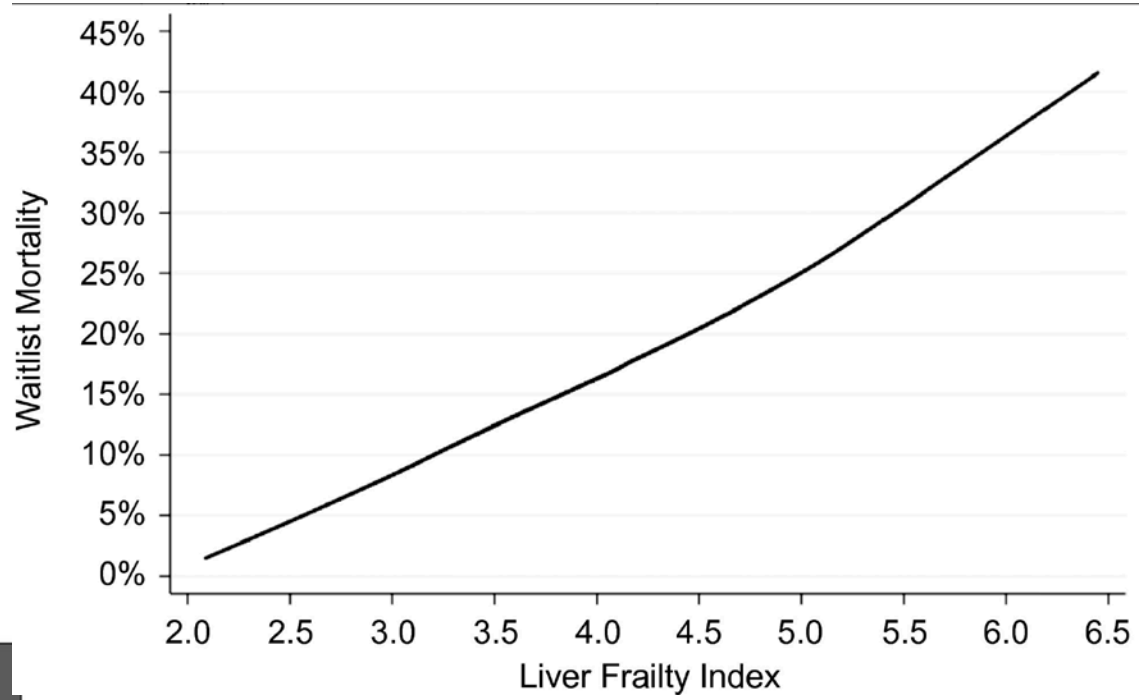
First published: 03 June 2020 | https://doi-org.ezproxy.galter.northwestern.edu/10.1002/hep.31406



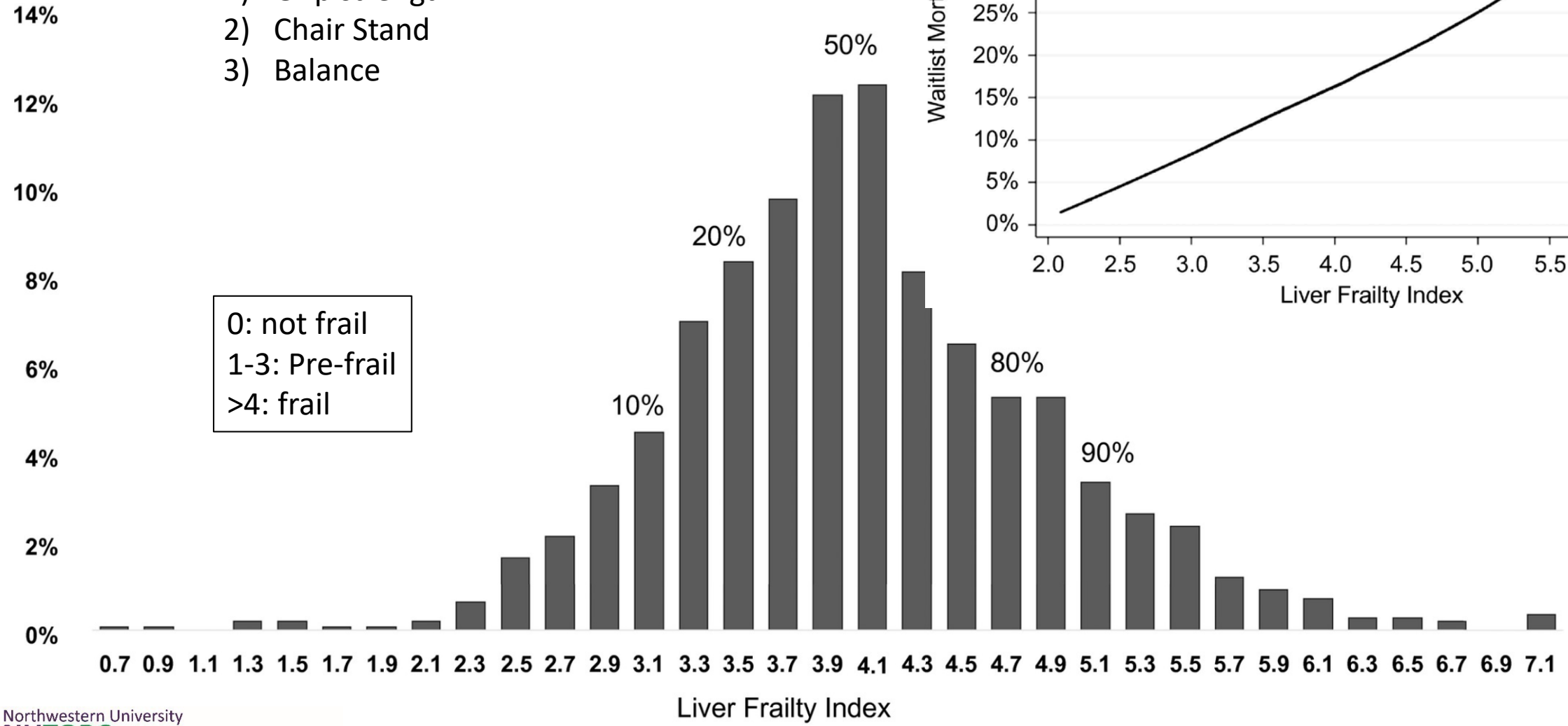
Liver Frailty Index

TESTS:

1) Grip strength
2) Chair Stand
3) Balance



0: not frail
1-3: Pre-frail
>4: frail



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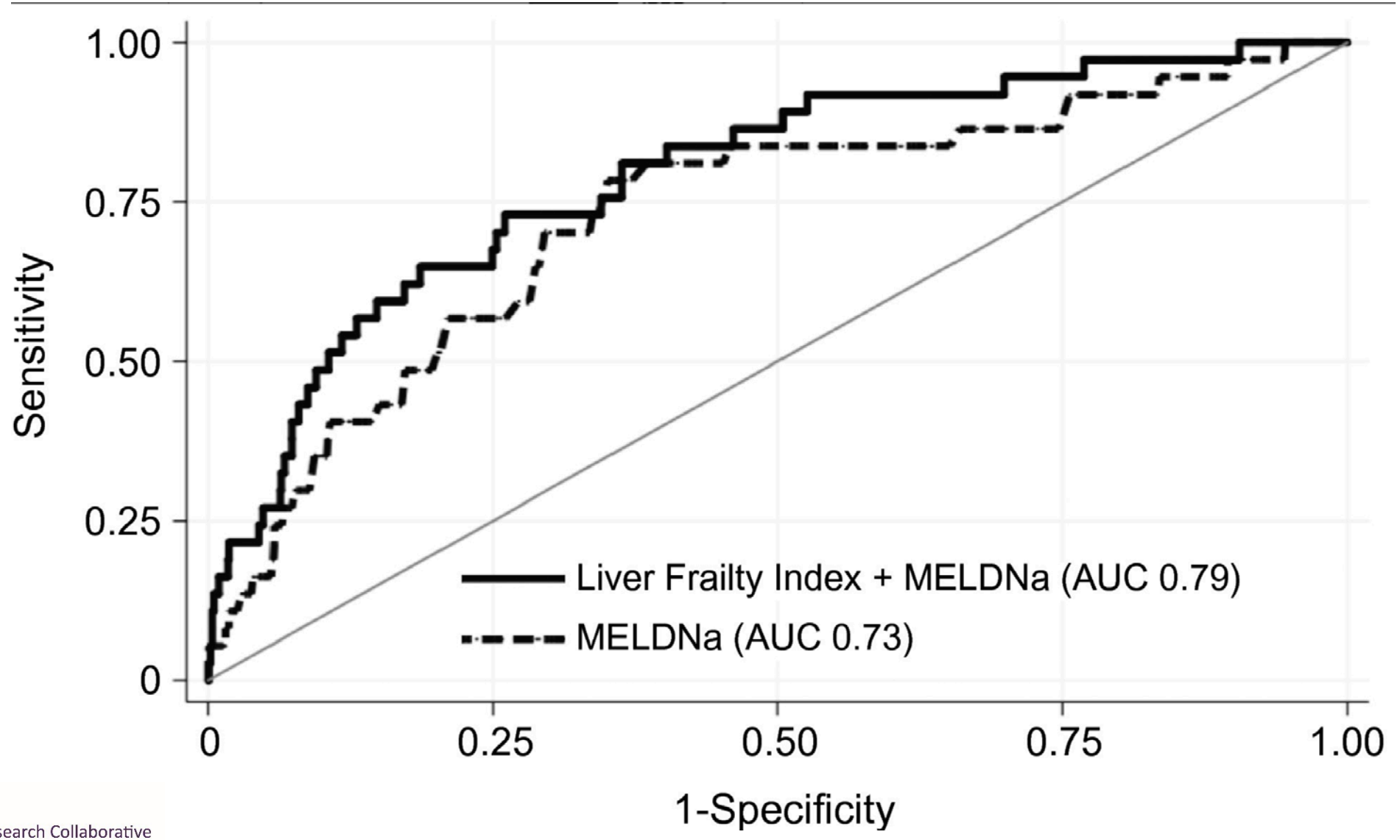
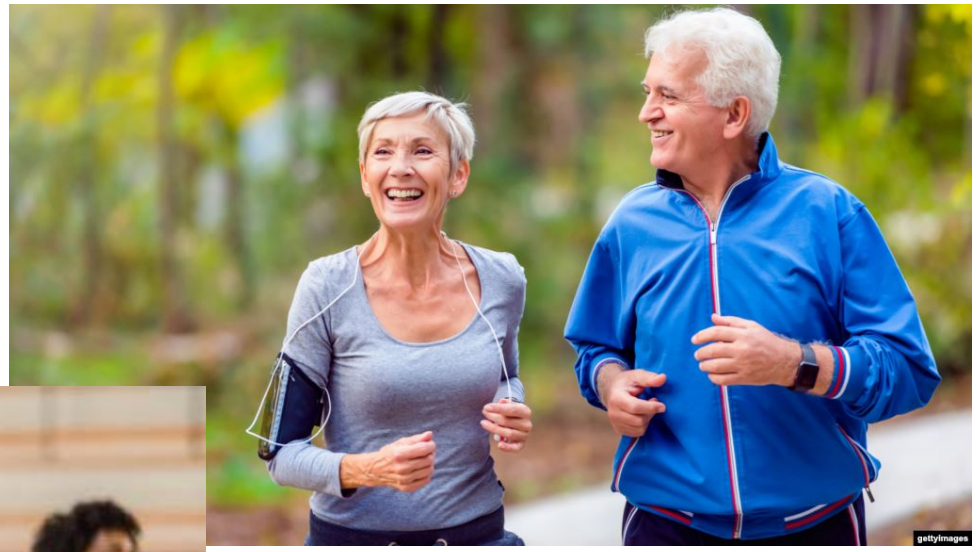
Improved Prediction of Mortality with LFI



Ethical Challenges related to Frailty

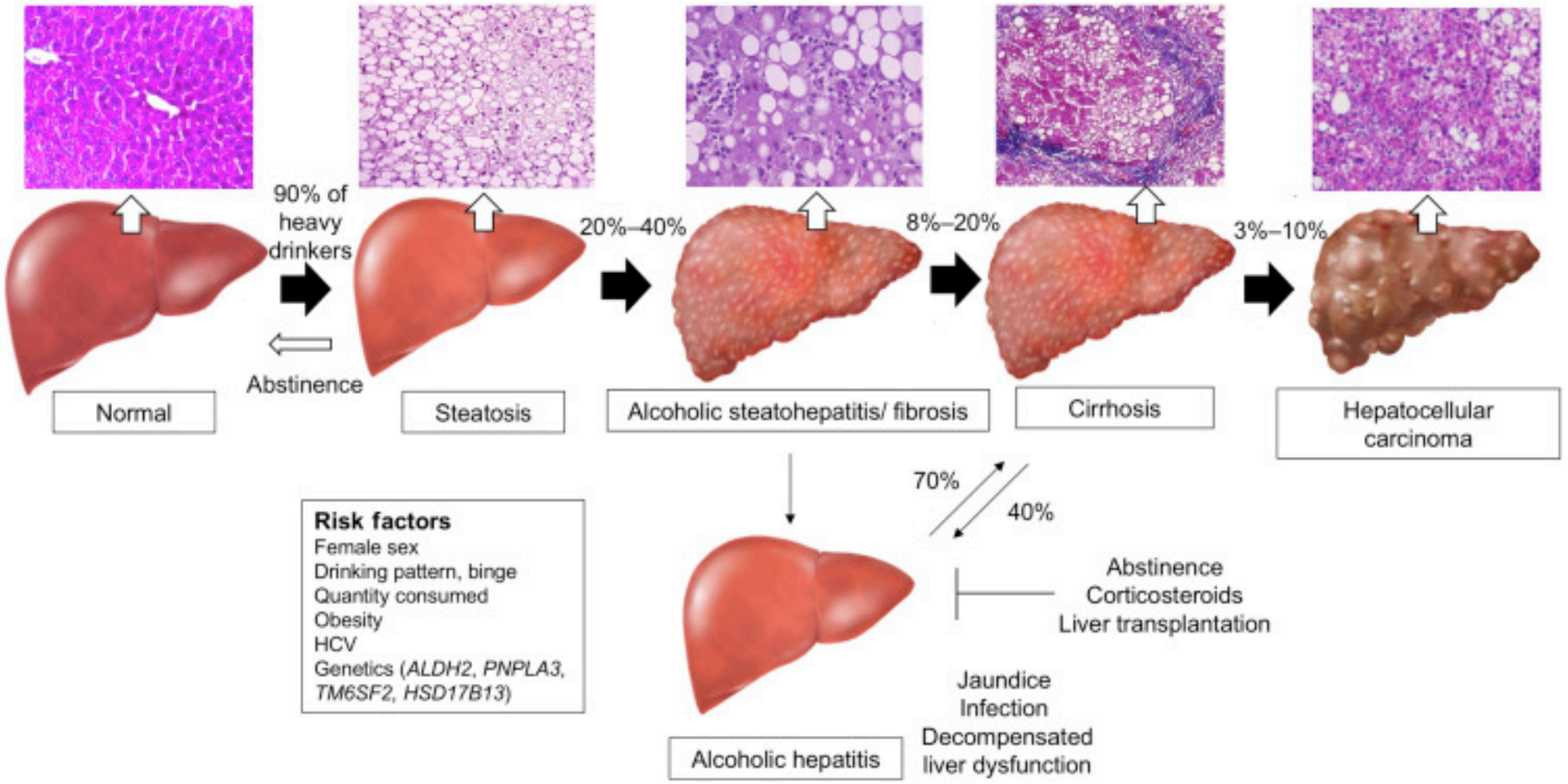
- Should frailty be part of the evaluation process?
  - Systematic assessment
- As patients get sicker their frailty increases
  - Inpatient assessments?
- Point of no return?
  - How to discuss this with patients
- How to manage patients towards optimal physical health?
  - Are patients NOT WILLING or NOT ABLE to exercise?

Exercise



Nutrition

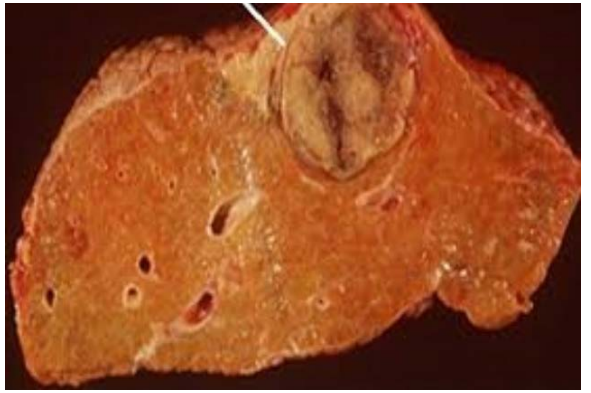
Alcoholic hepatitis



Alcoholic hepatitis – Ethical Challenges

- 1-year transplant outcomes for patients is excellent
  - Superior to transplant for NASH and HCV cirrhosis
- <u>Alcohol use disorder is a DISORDER</u>
  - Tremendous bias among population and clinicians
  - Lack of understanding of the disease
    - **Relapse is part of the disease**
- **Insight and willingness of patient to treat disorder is paramount!**

Liver Cancers



- Cirrhosis is a risk factor for development of cancers
  - Most frequent cancers are hepatocellular carcinoma (HCC)
- Patients with HCC do not have a high MELD
- Patients with aggressive HCC have poor outcomes after liver transplant

  → Patients with HCC receive **MELD POINTS**

  → have to be limited in size
- Old system:
  - 6-month window and then 3-point increase every 3 months
    - Previous system preferentially gave access to HCC
    - Too preferential towards HCC
- New allocation
  - After 6 months
  - Median MELD points within 250 miles/365 days MINUS 3 (MMeld-3)

Ethical challenges – What to do?

- Cirrhosis affects population disproportionately
  → Preventative and early guideline adherent care
- Disparity in access to transplant
  → Facilitate access
  → Special programs (e.g. Hispanic Program, African American Transplant Access Program (AATAP)
  → Outreach clinics
  → Education for primary care providers
- Bias in selection for transplantation
  → Anti-bias training
  → Use measurable metrics (e.g. frailty measure)
  → Education (e.g. alcohol use disorder, obesity)
- Management of Waitlisted Patients
  → Setting of expectations, feed-back loop clinician/patient

Ethical challenges – Summary

- Liver transplant provides excellent and curative solution for patients with cirrhosis
- Ethical challenges exist throughout the transplant process
- Evidence-based study is essential
- New ethical challenges will continue to arise
- To provide best care, ethical challenges need to be confronted and solutions need to be implemented and constantly improved

THANK YOU