

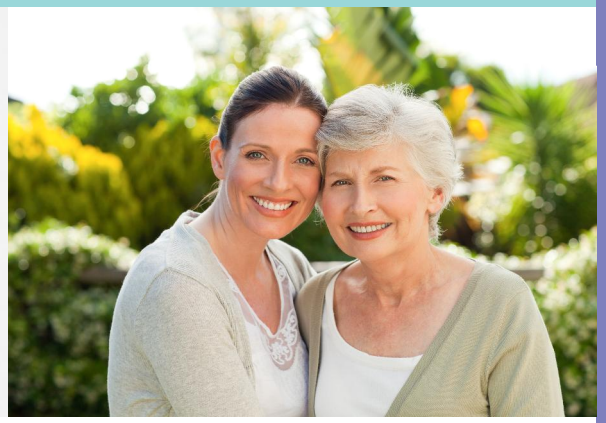

Ask the Experts
Patient Education Program

Autoimmune Liver Diseases

Talal Adhami, M.D., HCMBA., AGAF., FAASLD

April 26, 2017

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LIVER FUNCTIONS

Liver is made of liver cells, with well defined functions, bile duct cells responsible for draining the bile, and eliminating cholesterol, toxins and certain metals

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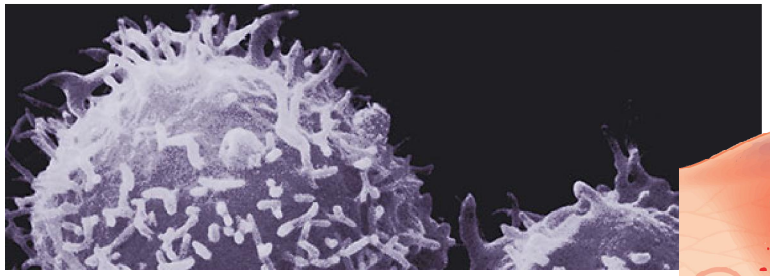
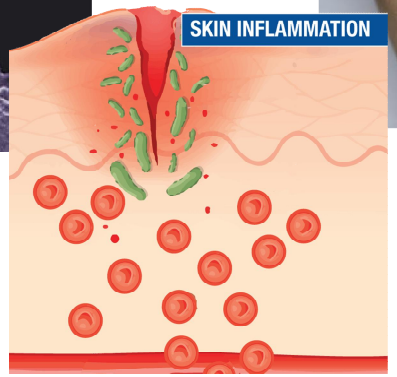
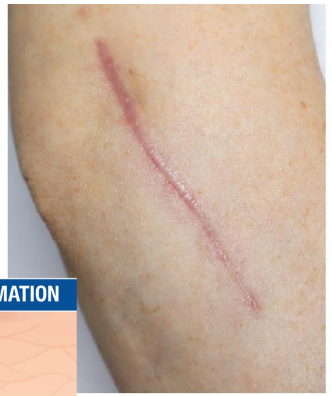
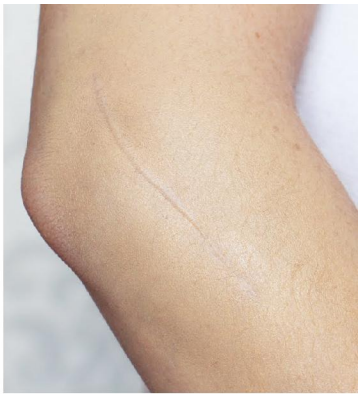
Injury and Healing

- Immune system to heal and clean up and repair the injured site
- Immune systems is triggered by insult causes injury and cell death in normal cases
- Shuts off as soon as the repair process is over









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Injury and Healing

- Autoimmune liver diseases occur when the immune system does not recognize a liver component as self and starts attacking it

- Injury, inflammation, cell death, liver dysfunction, healing scar tissue deposition (fibrosis) leading to cirrhosis

What is Autoimmune Liver Disease

- Autoimmune hepatitis is a long lasting disease
- Body's **immune** system attacks the liver and **causes** inflammation and damage (mainly scarring)
- Autoimmune hepatitis is a serious condition that may worsen over time if not treated.
- Autoimmune hepatitis can lead to cirrhosis and liver failure.

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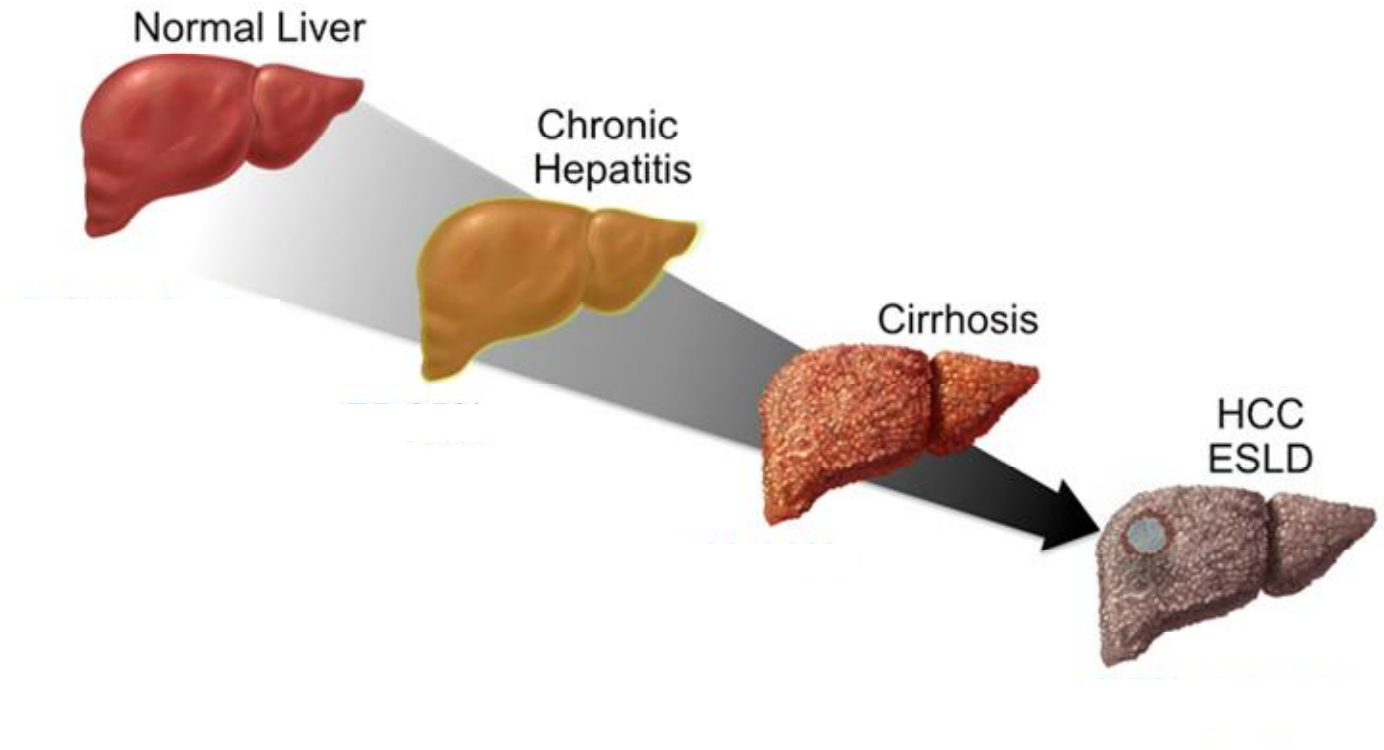
Disease Progression



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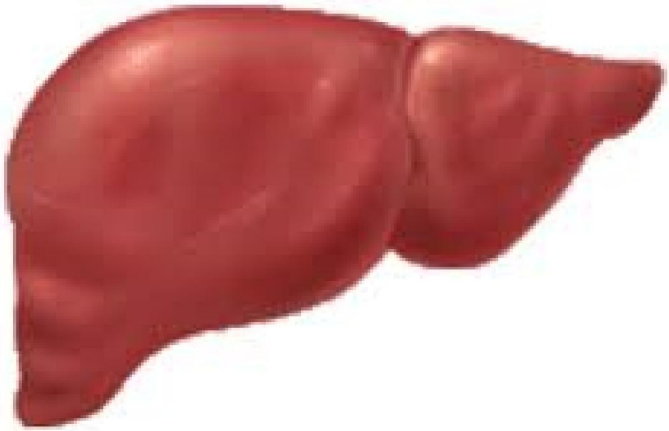

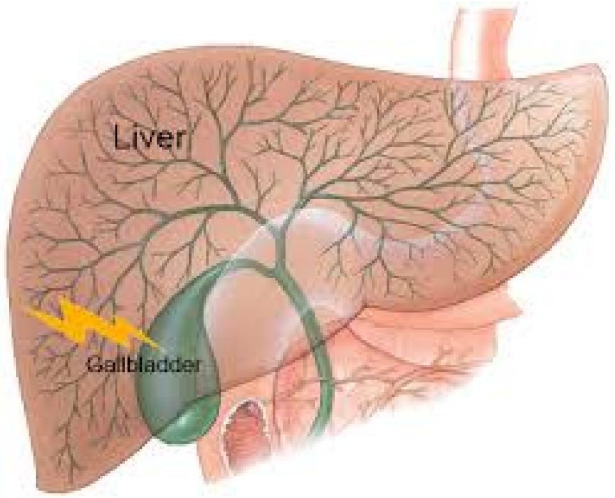

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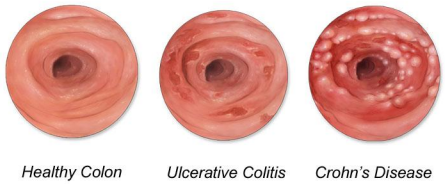
Disease Type and Treatment

- 4 major Categories
  - Autoimmune hepatitis (AIH)
  - Primary Biliary Cholangitis (PBC)
  - Primary Sclerosing Cholangitis (PSC)
  - Combination of the above

- Prevalence: 2-3/100,000
- Females (8x) >>>> male (except in PSC)

- Associated with other conditions
  - Thyroiditis
  - Rheumatoid Arthritis
  - Inflammatory bowel diseases
  - Vitiligo



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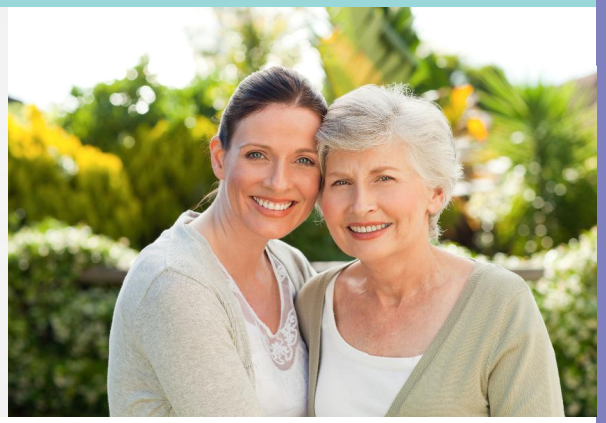
Disease Type and Treatment

Treatment is effective especially in early stages (except PSC)

- Immunosuppression
- Bile Acid
- Liver transplantation





Ask the Experts
Patient Education Program

Liver Transplantation

Teresa Diago Uso, M.D.
April 26, 2017

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Milestones

1954 – kidney transplant

1966 – pancreas transplant

1967 – liver transplant

1981 – heart / lung

1983 – cyclosporin approved

1983 – single lung transplant

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1983

Liver transplantation is approved as a therapeutic modality by NIH Consensus Conference

National Institutes of Health Consensus Development Conference Statement: Liver Transplantation—June 20–23, 1983

Since performance of the first human orthotopic liver transplantation in 1963, over 340 such operations have been carried out in four medical centers in the United States and Western Europe. Additional liver transplantation procedures have been performed in other parts of the world, and more recently in several other American medical centers. Although extremely demanding and expensive, the operation has been shown to be technically feasible, and interpretable results have been reported from all four primary transplant centers. These clearly demonstrate that liver transplantation offers an alternative therapeutic approach which may prolong life in

(1) ARE THERE GROUPS OF PATIENTS FOR WHOM TRANSPLANTATION OF THE LIVER SHOULD BE CONSIDERED APPROPRIATE THERAPY?

Liver transplantation is a promising alternative to current therapy in the management of the late phase of several forms of serious liver disease. Candidates include children and adults suffering from irreversible liver injury who have exhausted alternative medical and surgical treatments, and are approaching the terminal phase of their illness. In many forms of liver disease, the precise

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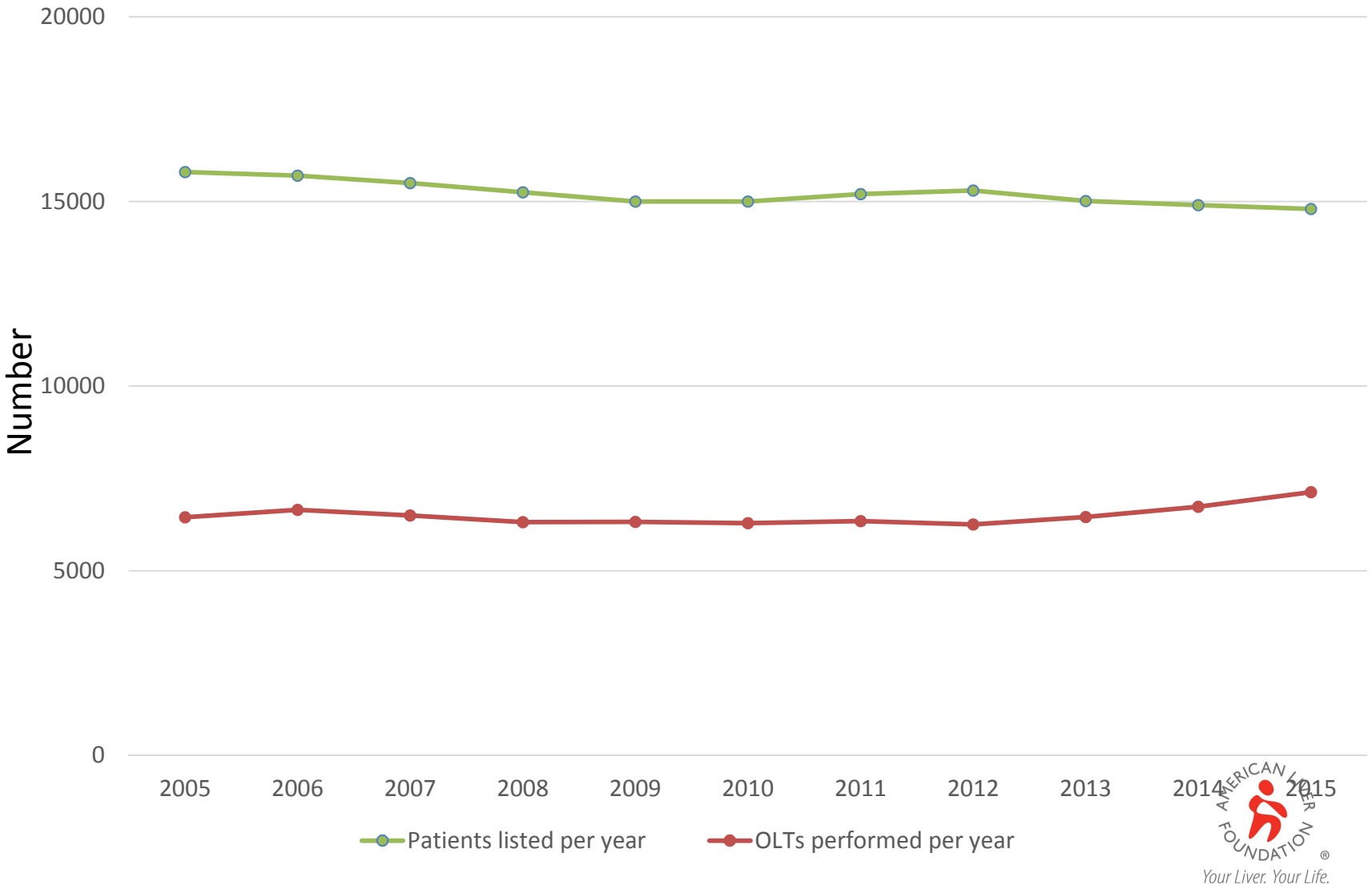
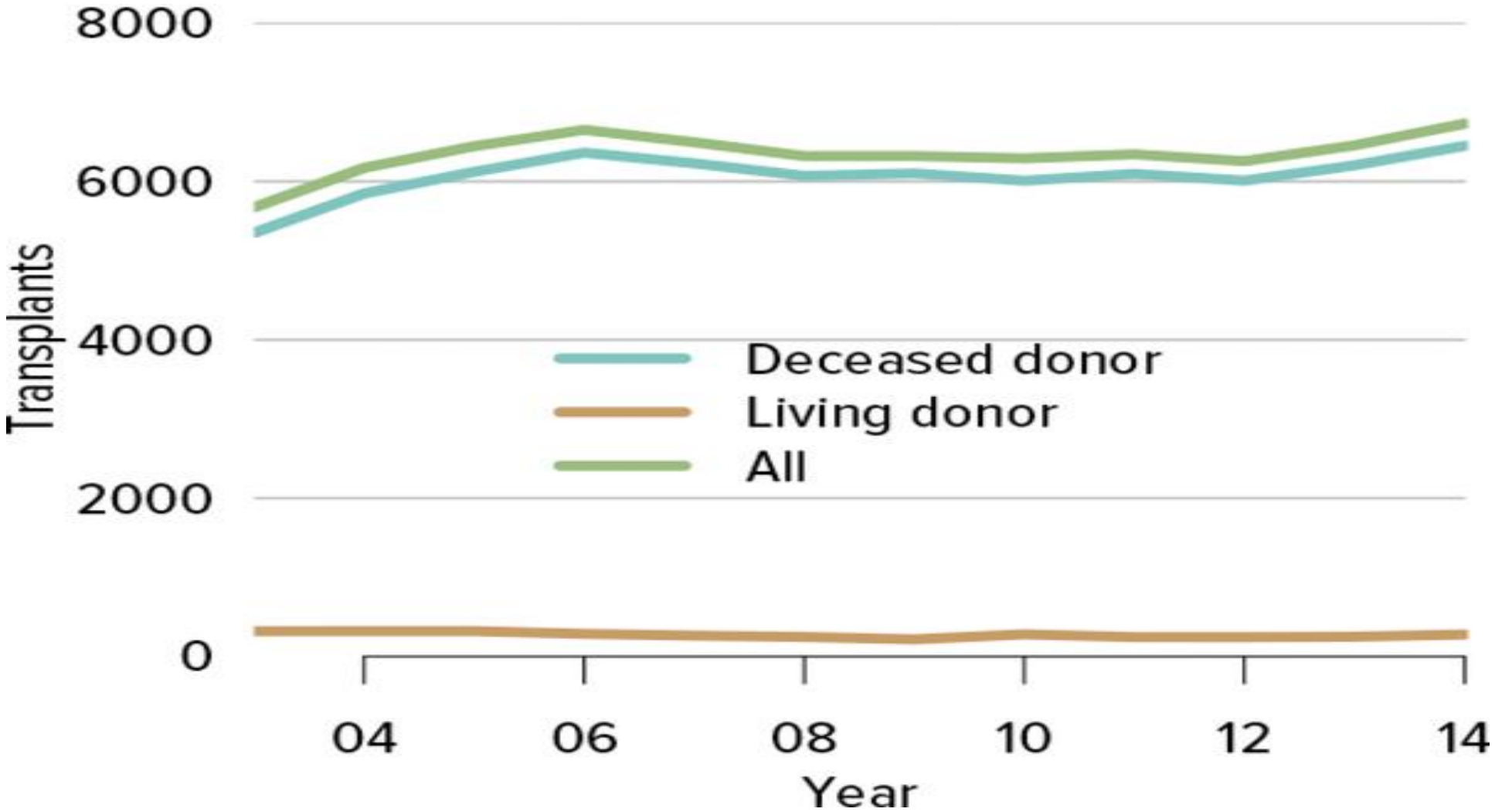
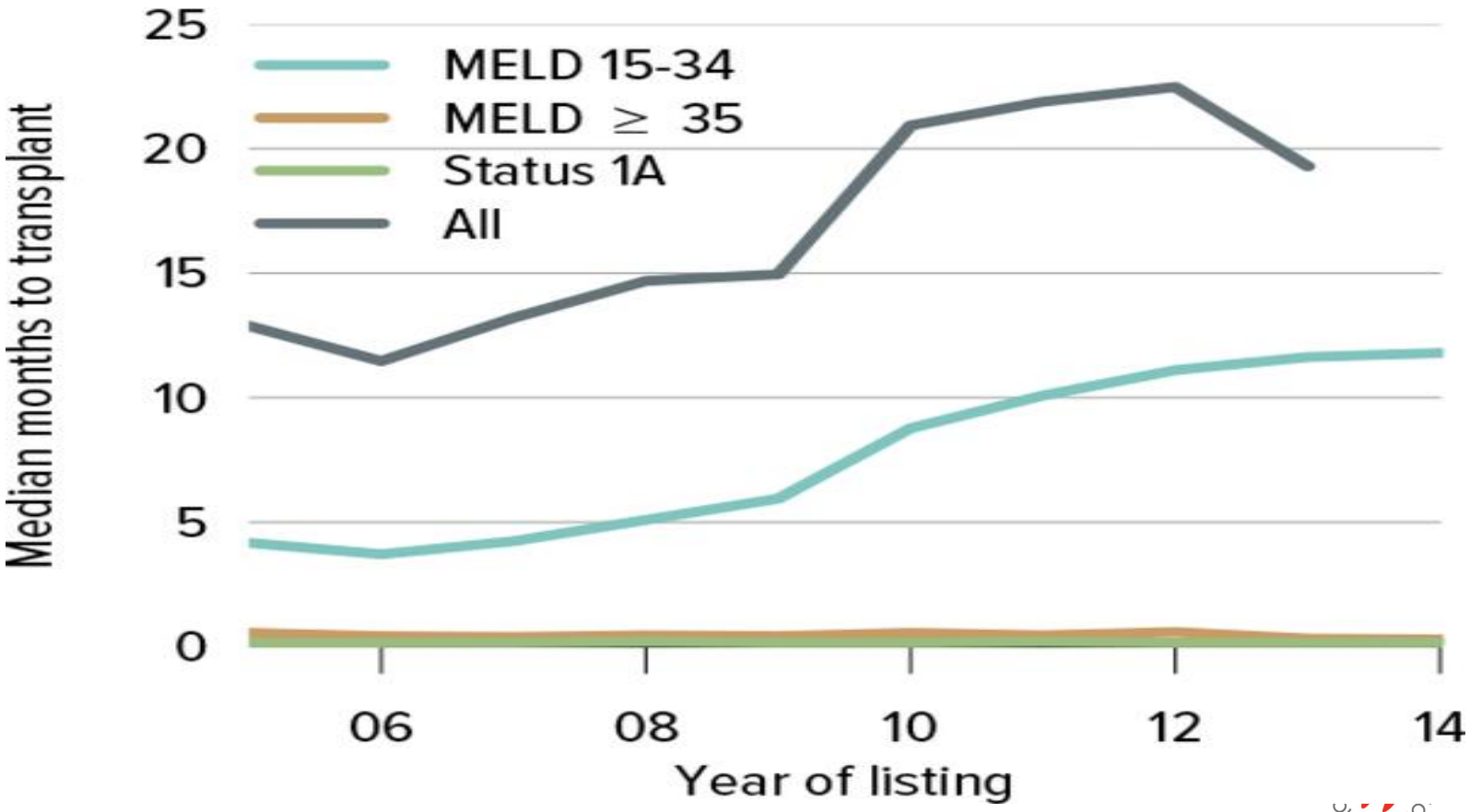
Waiting list



Transplants



Waiting time



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Liver Transplantation

Liver transplantation should be reserved to those that have exhausted standard medical and surgical therapies.

Liver transplantation is a form of treatment, and as such was designed for those with **life threatening** complications of end stage liver disease.

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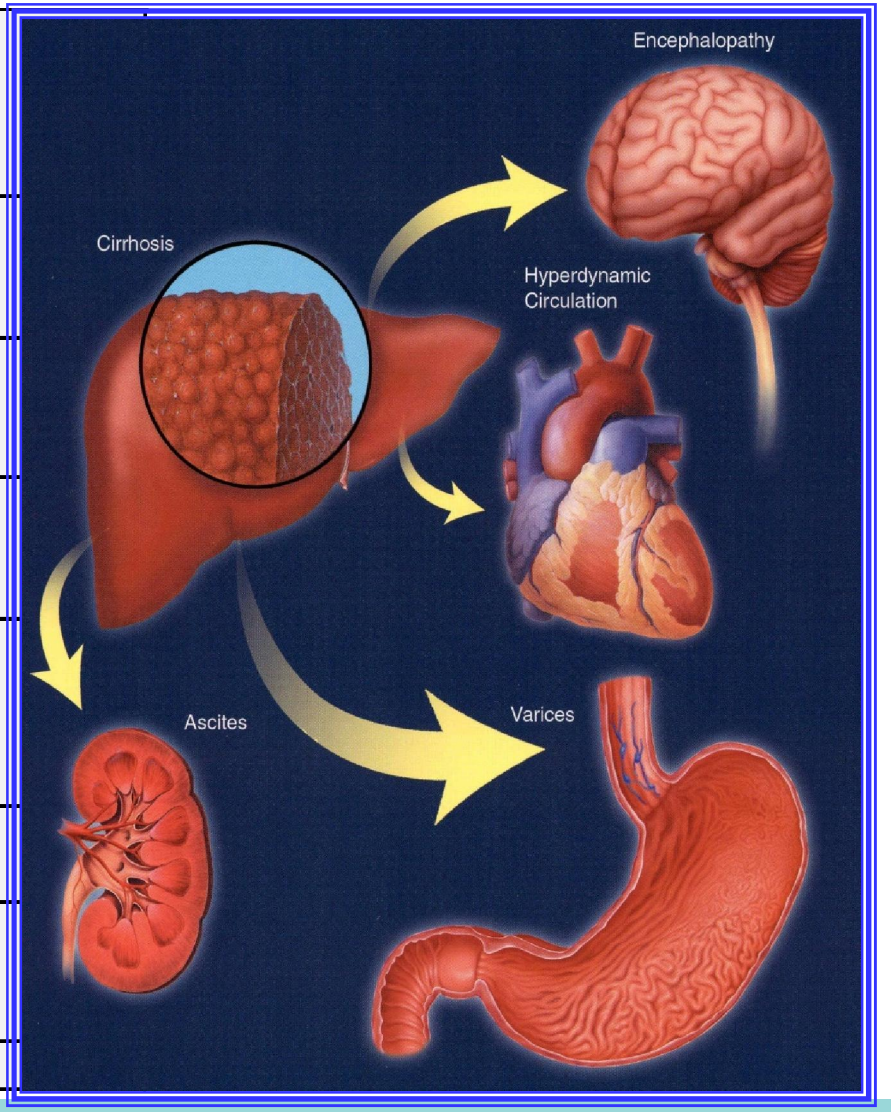
Complications of Liver Dysfunction and Cirrhosis

- Portal hypertension
  - Esophageal varices
  - Ascites
  - Splenomegaly
- Cardiovascular dysfunction
  - Cardiomyopathy
  - Hyperdynamic circulation
- Pulmonary dysfunction
  - Arterial hypoxemia from pulmonary shunts
  - Pulmonary hypertension
- Synthetic dysfunction
  - Coagulopathy
  - Hypoalbuminemia
- Renal dysfunction
  - Hepatorenal syndrome
  - Platelet dysfunction and coagulopathy
  - Electrolyte disturbances
- Neurologic dysfunction
  - Hepatic encephalopathy
- Excretory dysfunction
  - Jaundice
  - Pruritis
- Risk of malignancy



Indications for LTX

- **Fulminant or sub-fulminant liver disease**
  - Hepatitis B
  - Acetaminophen toxicity
  - Idiosyncratic drug toxicity
  - Hepatitis A
  - Adenovirus
  - Mushroom toxicity
  - Acute Wilson's disease
  - Acute Budd-Chiari syndrome
  - Trauma or iatrogenic injury
  - Acute failure of previously transplanted liver

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Indications for LTx

- **Chronic end-stage liver disease**
  - Chronic Hepatitis C
  - Non-alcoholic steatohepatitis (NASH)
  - Alcoholic liver disease
  - Autoimmune hepatitis
  - Primary biliary cirrhosis
  - Secondary biliary cirrhosis
  - Primary sclerosing cholangitis
  - Biliary atresia
  - Cryptogenic cirrhosis
  - Chronic Hepatitis B

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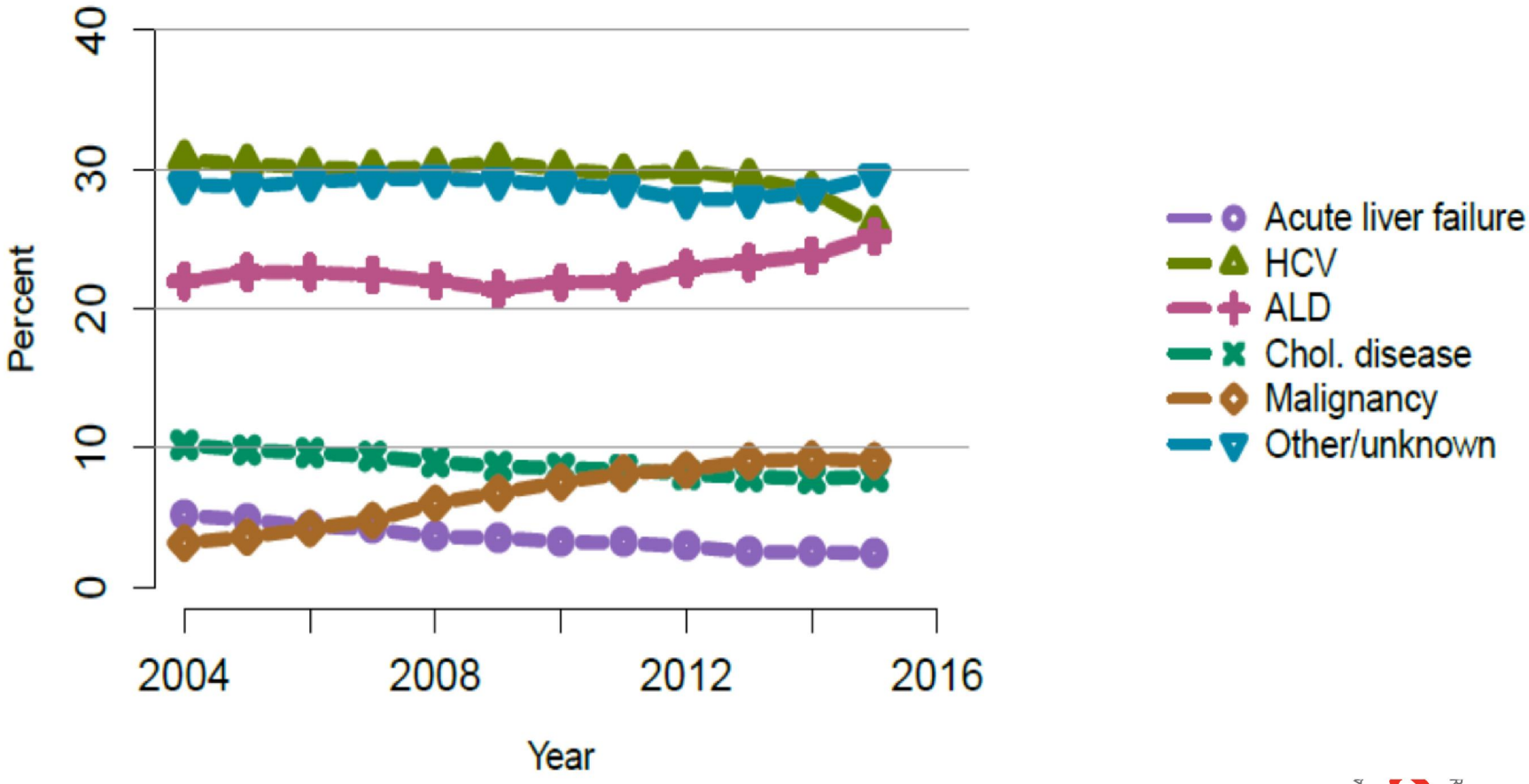
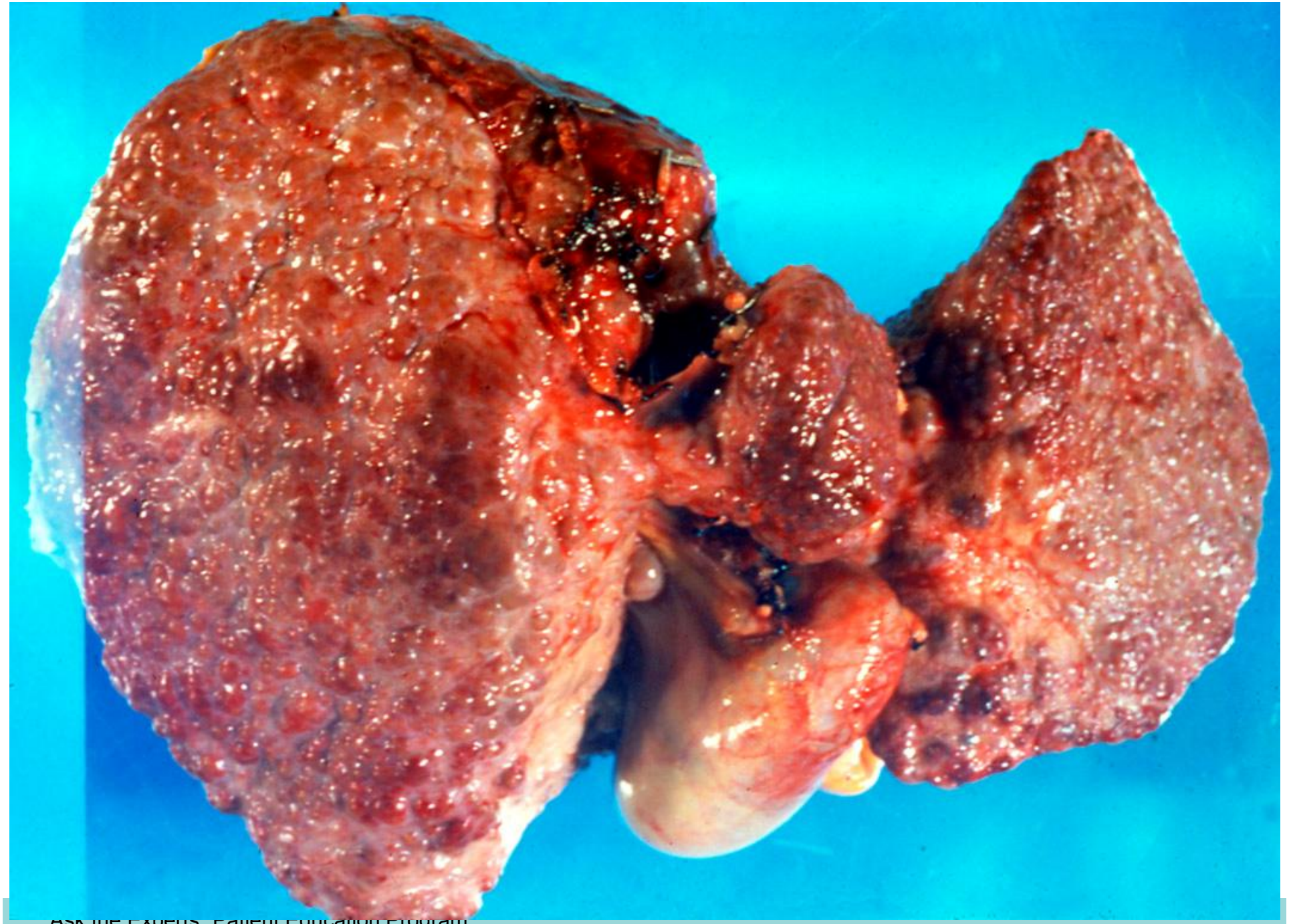
Indications for LTX

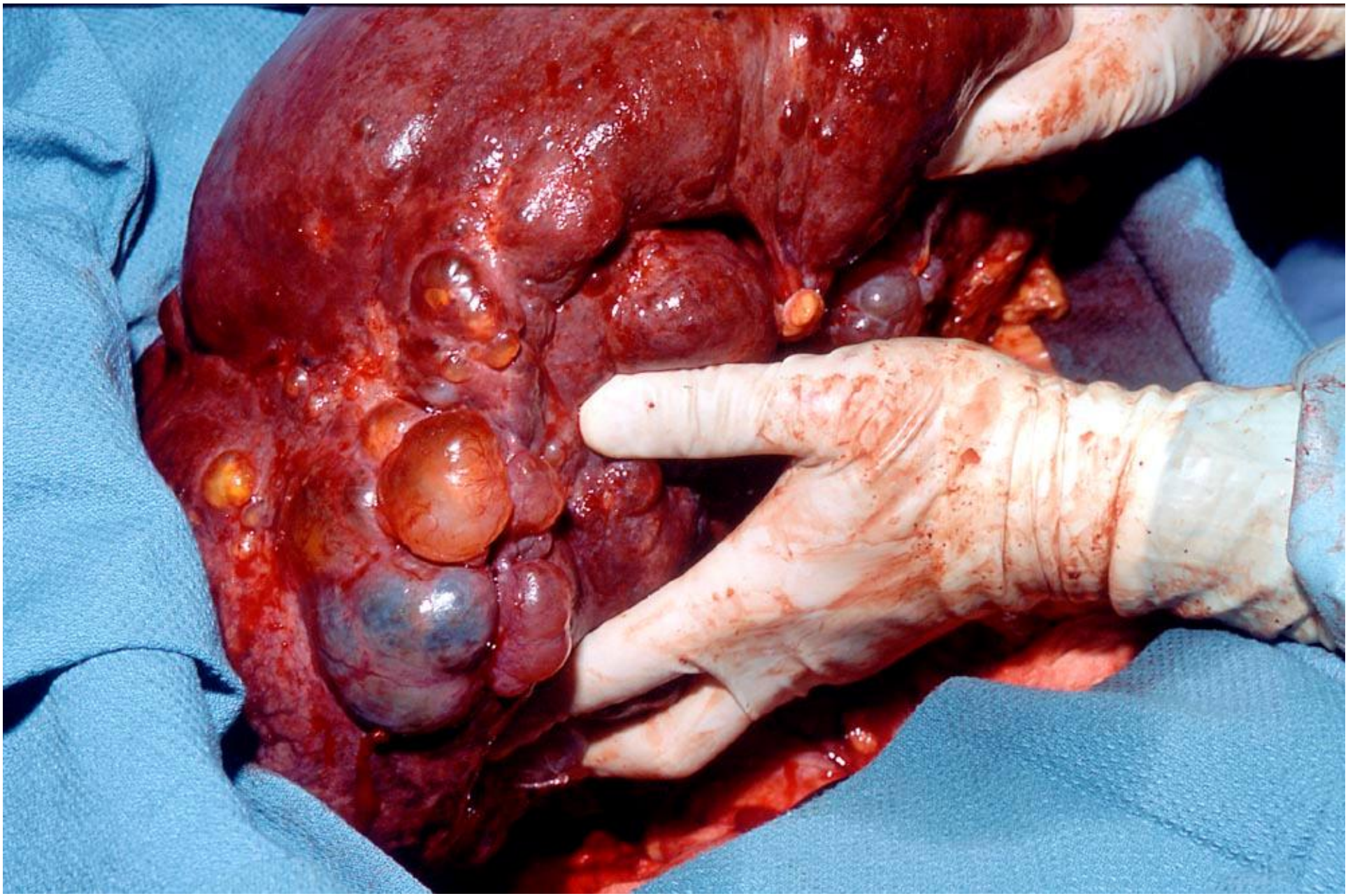
- **Metabolic liver disease**
  - Wilson's disease
  - Alpha-1 antitrypsin deficiency
  - Hemochromatosis
  - Tyrosinemia
  - Hyperoxalosis
  - Familial polyneuropathy - amyloidosis
  - Crigler-Najjar syndrome
- **Malignancies**
  - Hepatocellular carcinoma
  - Metastatic neuroendocrine tumors
  - Hepatic Epithelioid Hemangioendothelioma
  - Cholangiocarcinoma
  - Metastatic colorectal cancer to the liver!!!!!

Waiting list by diagnosis



Kim, AJT, 2017





Contraindications for LTx

- Extrahepatic sepsis
- Advanced cardiopulmonary failure
- Multisystem organ failure
- Inability or unwillingness to comply with post-transplant medical therapy
- Active substance abuse ?
- Advanced age (physiologic) ?
- Extrahepatic malignancy (except for skin/colorectal) ?

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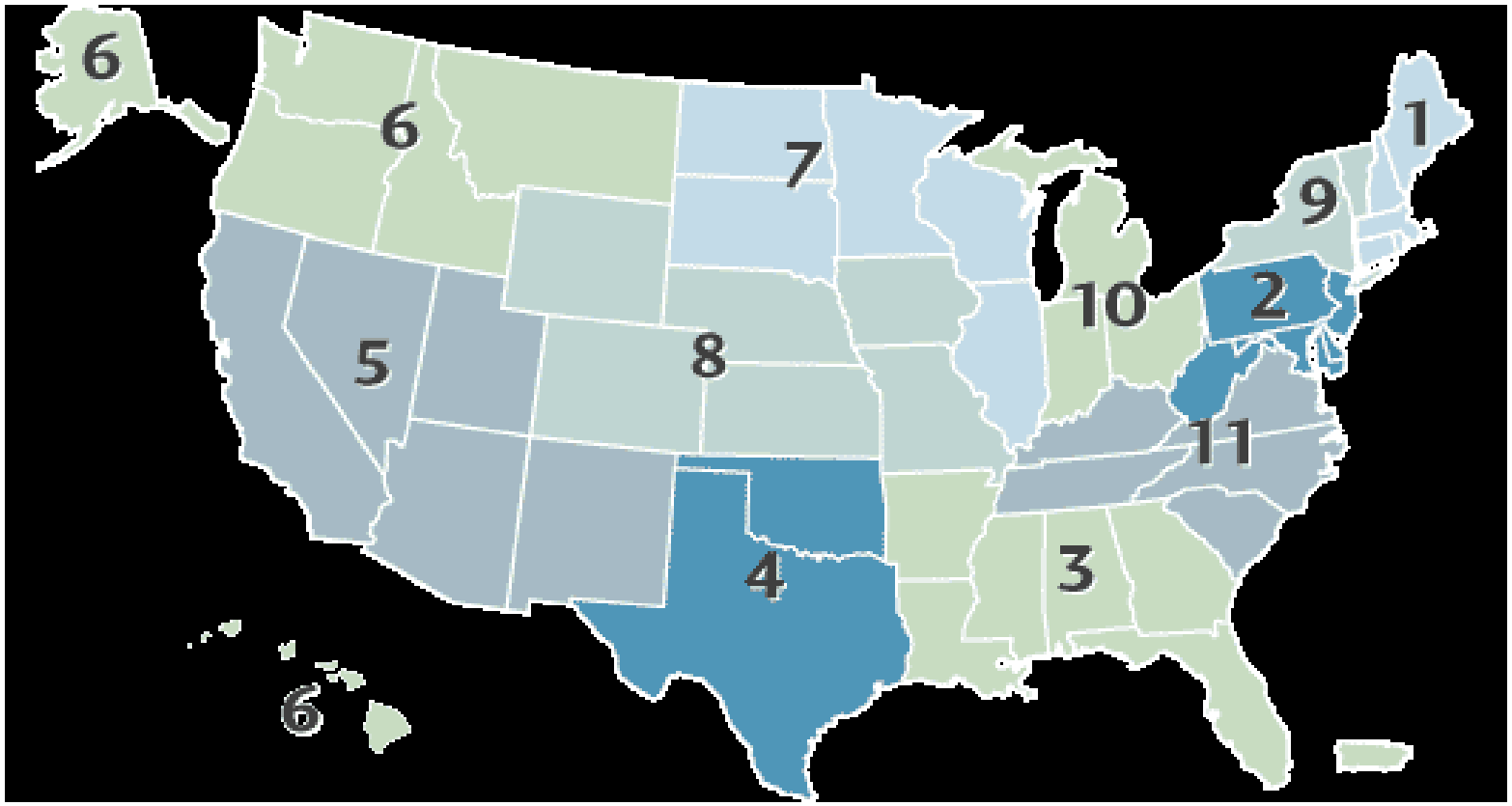
Model for End-Stage Liver Disease (MELD)

- MELD - predict mortality while waiting for LTx
- Based on four objective clinical lab values:

  Bilirubin, INR, creatinine, Na

UNOS regions

United Network for Organ Sharing



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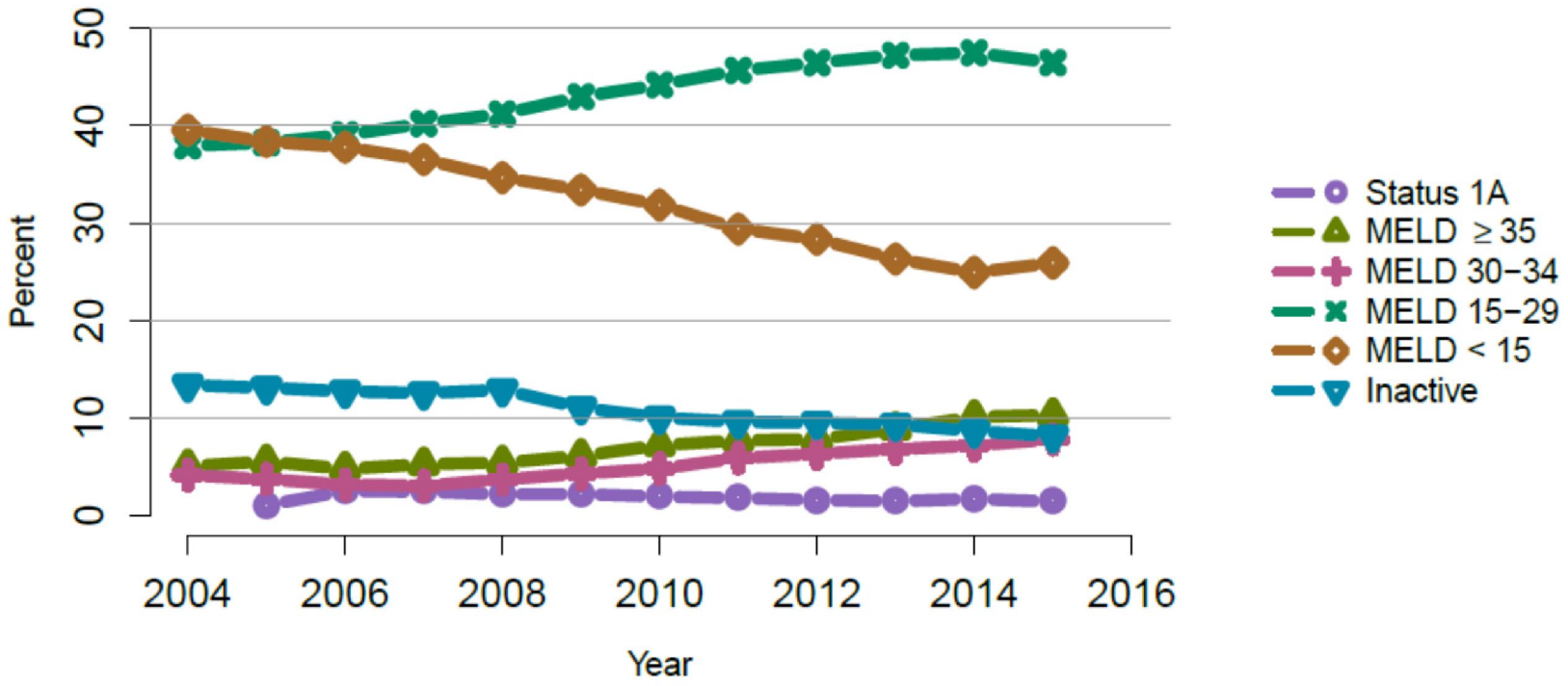
Waiting list by MELD score



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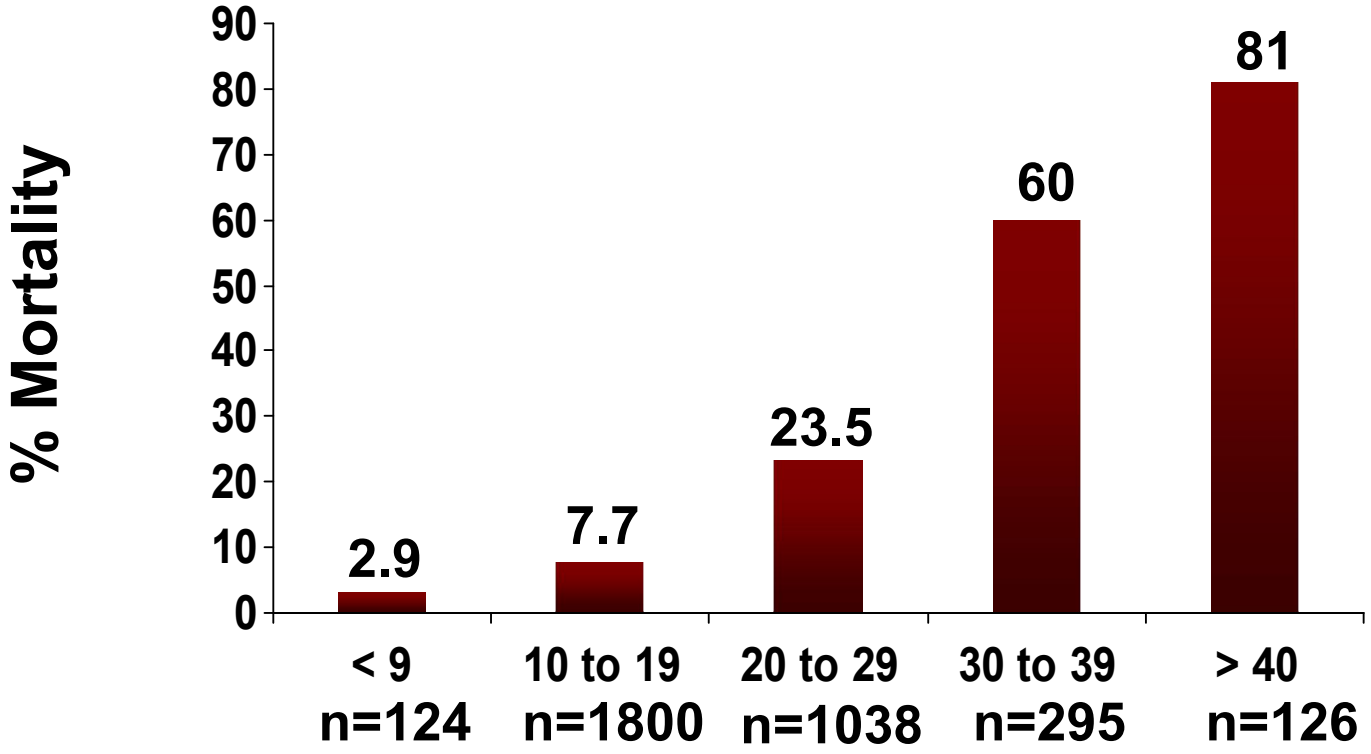
Kim, AJT, 2017

3-Month Mortality Based on Listing MELD Score



Wiesner R. Gastroenterology 2003;124:91-96

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MELD Exceptions

- HCC
- Hepatopulmonary syndrome
- Cholangiocarcinoma
- Cystic fibrosis
- Familial amyloid polyneuropathy
- Portopulmonary hypertension
- Primary hyperoxaluria

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UNOS criteria for OLT for HCC (Milan Criteria)

- Single tumor less than 5 cm
- Three or less tumors each less than 3 cm
- Absence of macrovascular invasion or distant metastases

Mazzaferro V, et al. *N Engl J Med.* 1996;334:693-699.

Hepatocellular Carcinoma (HCC

- The most common primary liver malignancy, the sixth most common cancer worldwide, and the third most common cause of cancer death.
- Affects 3.7 men per 100,000 per year and 2.0 women per 100,000 per year in the United States.
- Since the 1980s, the incidence of HCC in the US has tripled.
- The age distribution has shifted to a younger age: the greatest increases are in the age group 45 – 60 years old.

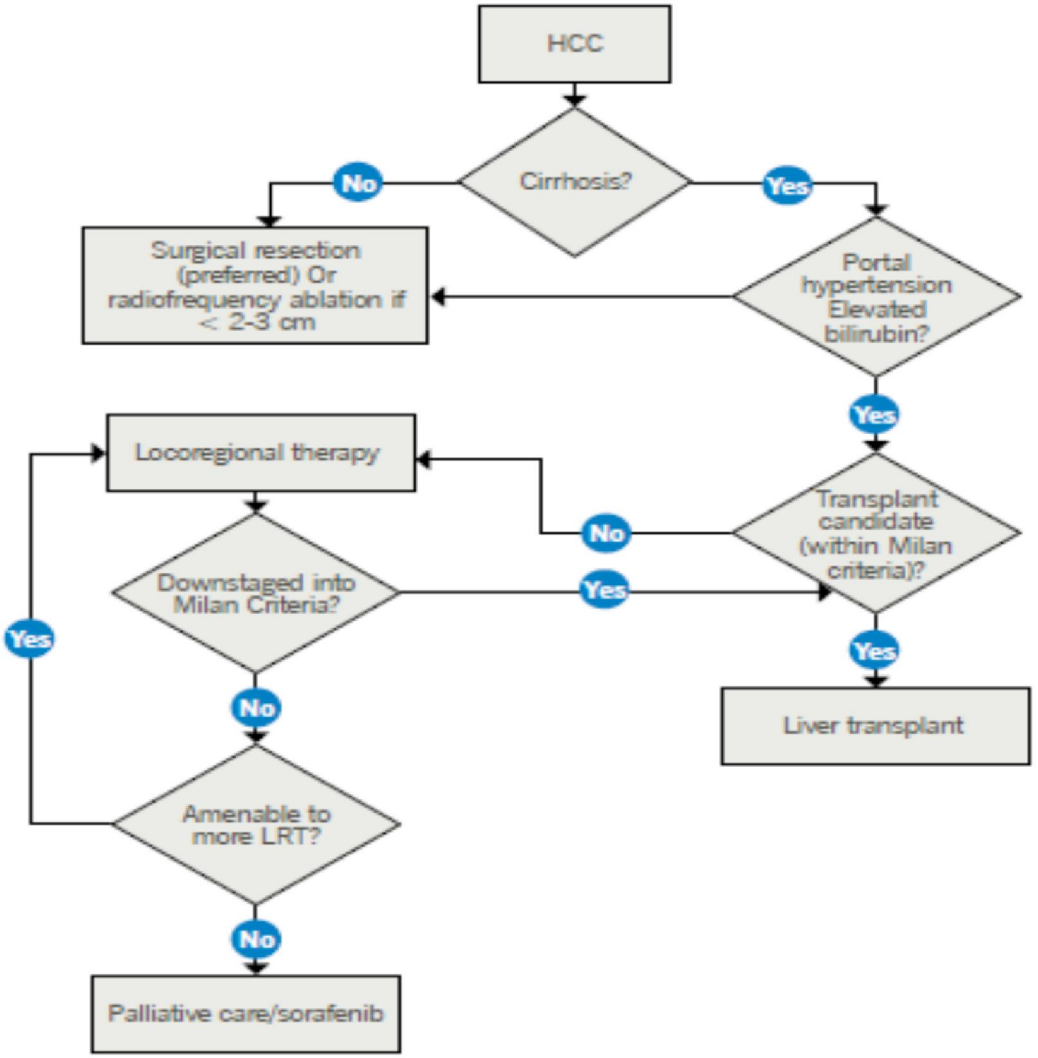
Elserag HB, Kanwal F. *Hepatology*. 2014; 60(5):1767-75
Ferlay J, et al. *Int J Cancer*. 2010; 127(12):2893-2917

Management of Early HCC

- As outlined by the BCLC staging classification: Treatment options are defined by disease characters and functional capacity.
- Curative options for HCC include: Resection, RFA, and transplantation
- Resection is considered safe: Perioperative mortality is in the order of less than 1%, however outcomes are limited by the high recurrence rates.
- Transplantation is limited by the paucity of available organs.

Sapisochin G, et al. *World J Hepatol.* 2014;6(11):766-75
Llovet JM, et al. *Lancet*. 2003; 362(9399):1907-17.

Simplified management for HCC



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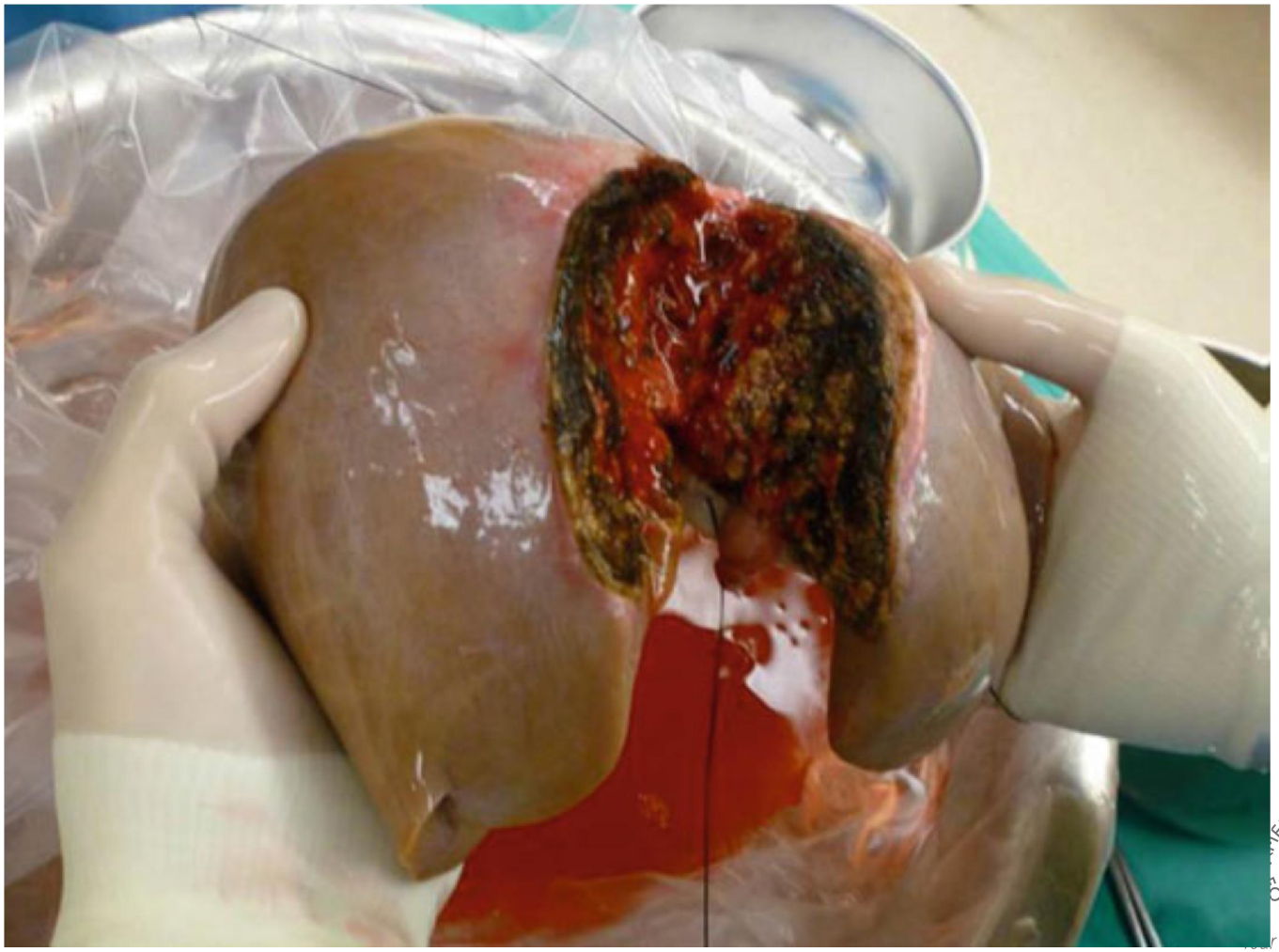
LIVER TRANSPLANTATION FOR HCC
(within Milan Criteria)

- 1 year survival 80-90 %
- 5 years survival 65-75 %
- Recurrence rates were 6.1%, 12.7%, and 15% at 1- , 3- , and 5- years respectively

Liver Transplantation

- Deceased donor
  - Whole
  - Split
- DCD donor
- Domino donor
- Living related donor
- HCV +ve donor

Left lateral, tri-segment split



LDLT vs. cadaveric graft

Advantages

- Assures a healthy organ with minimal preservation damage
- Independence from long cadaveric waiting list
- Optimizes the timing of transplantation
- Helps alleviate the severe shortage of cadaveric livers and death on the waiting list

Disadvantages

- Finite risk of donor morbidity and mortality
- Both operation are technically complex
- The program is extremely labor-intensive
- Reputational risk

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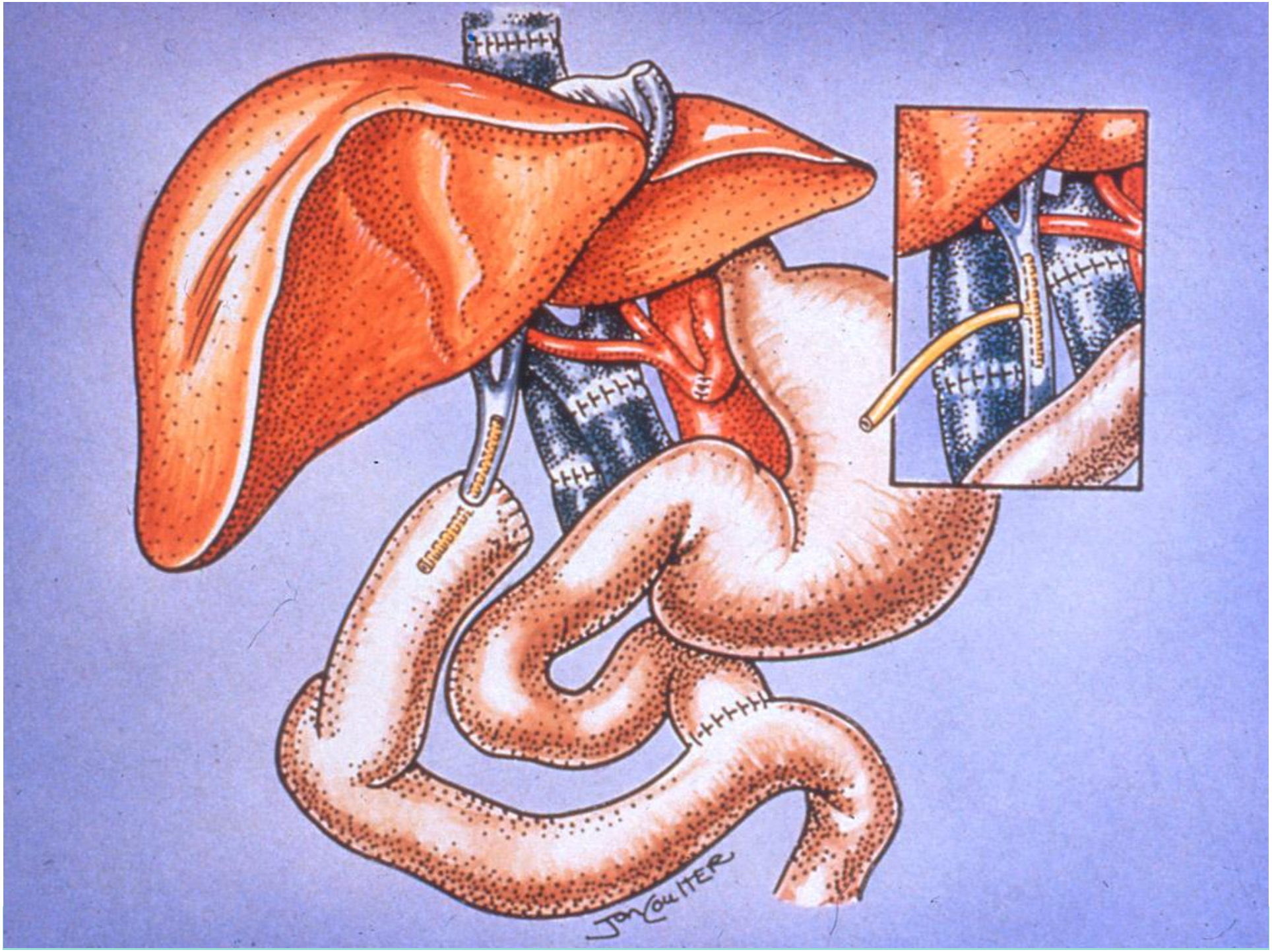

JON COULTER

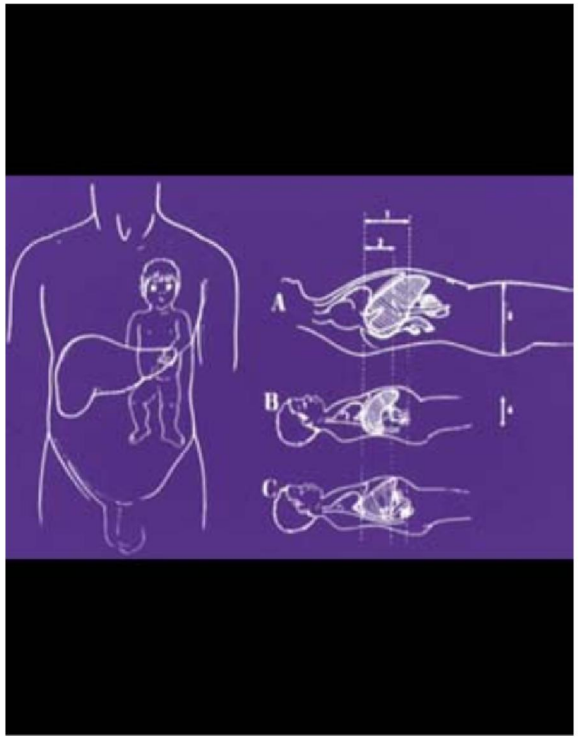
Live donor liver transplantation

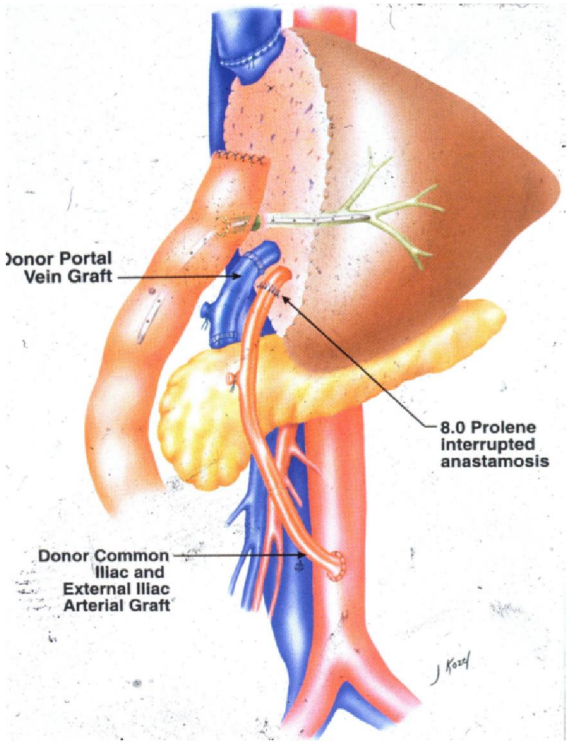
1988

Raia in Brazil is first to perform living donor liver transplant - mother to child but unsuccessful

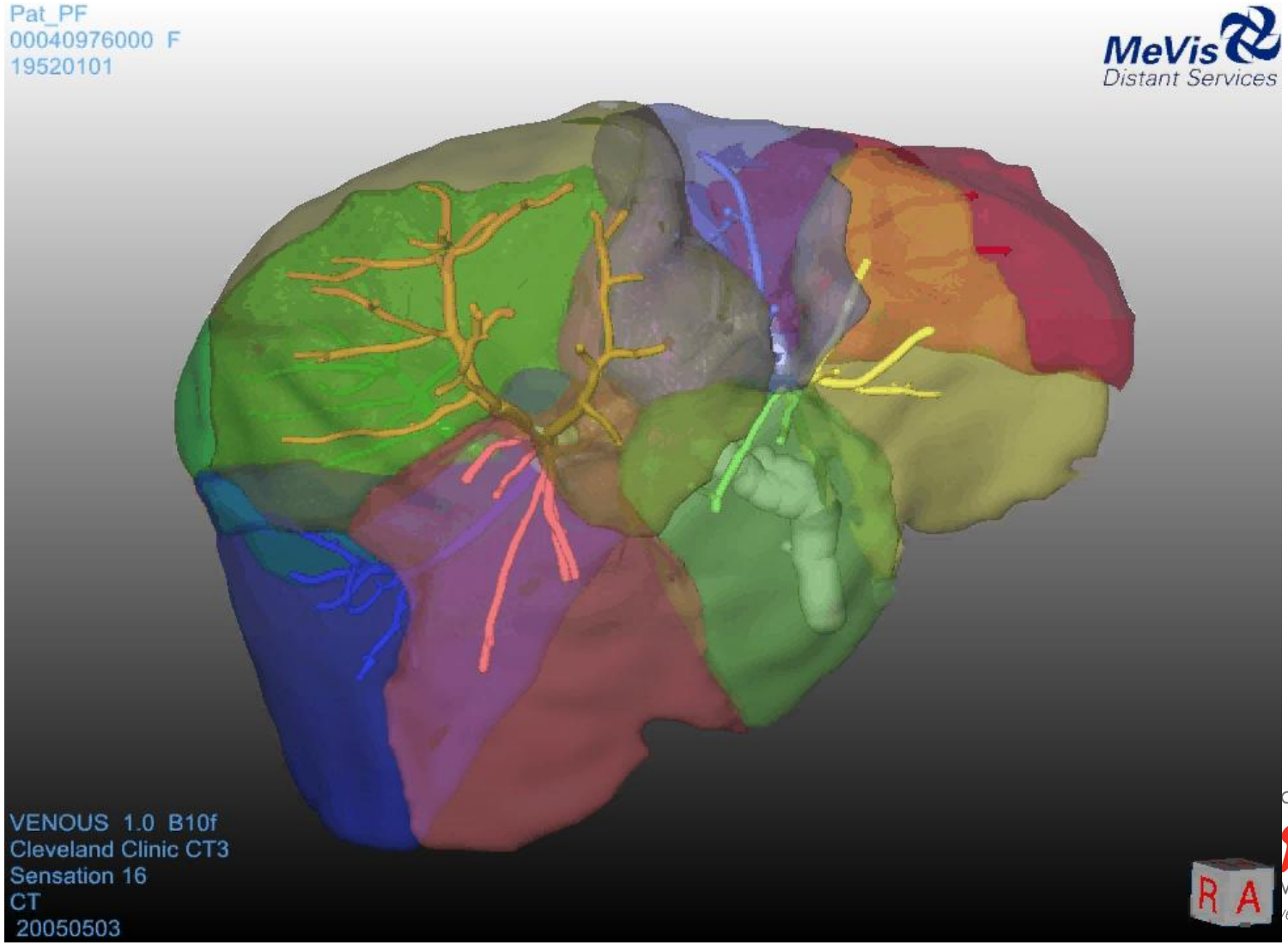
1989

Strong and Lynch perform first successful LRD in Australia

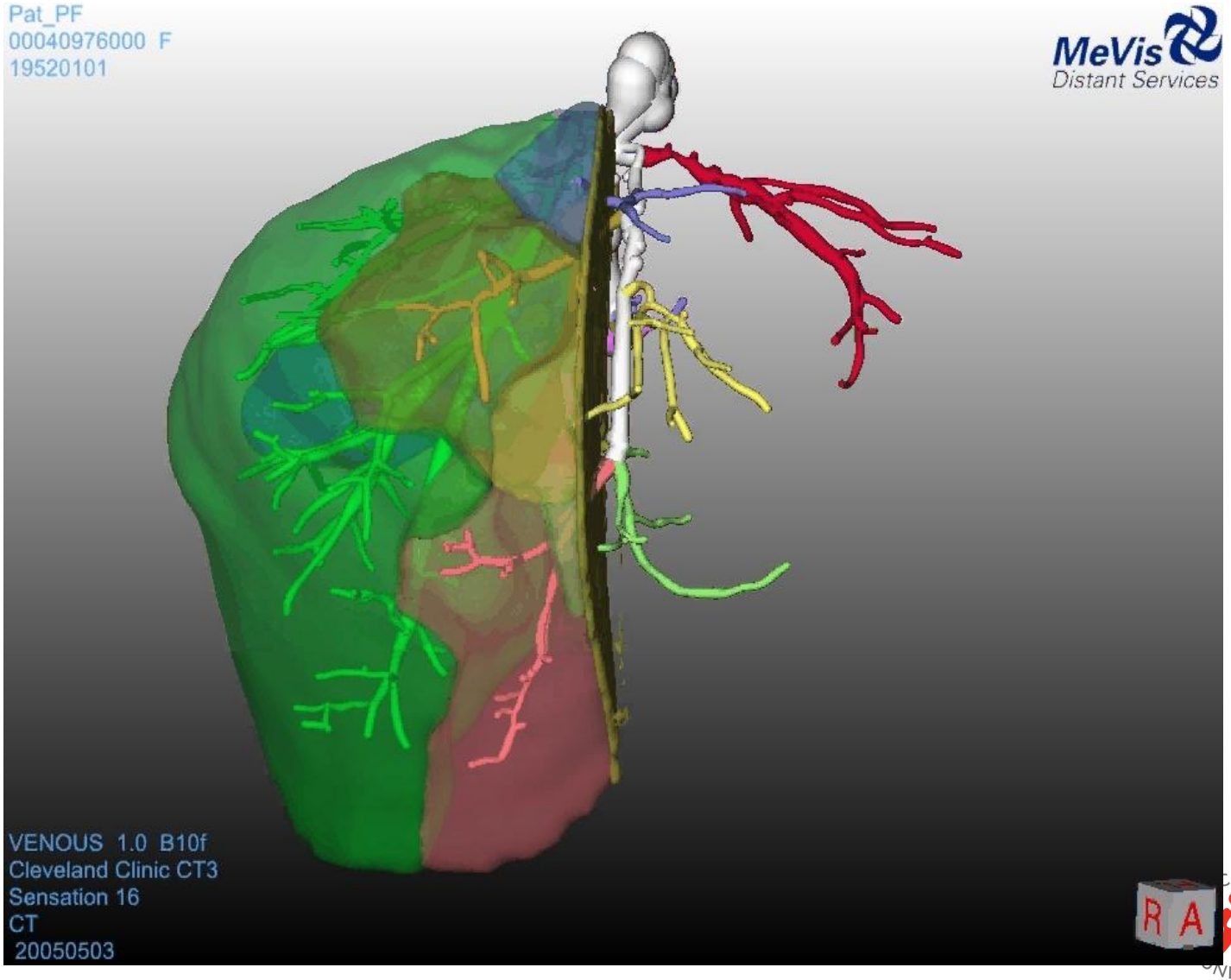




Segmental Anatomy



Right liver graft



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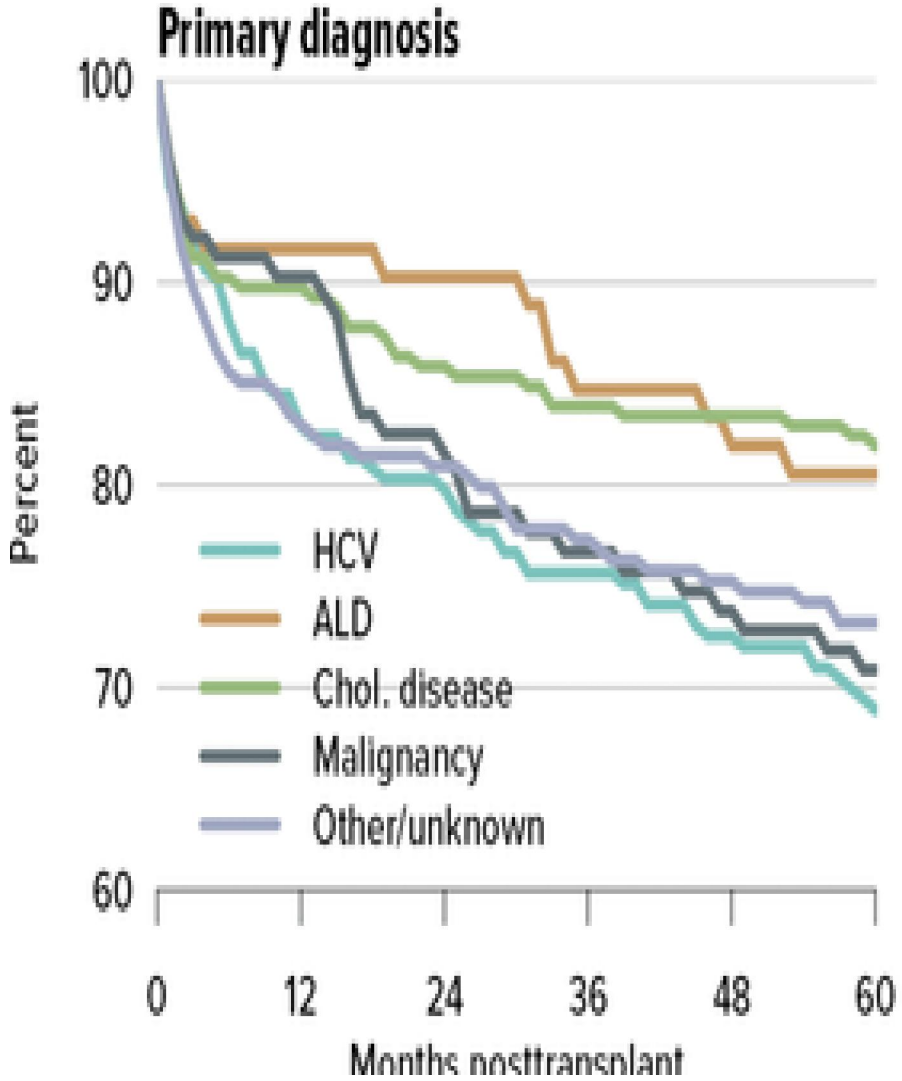
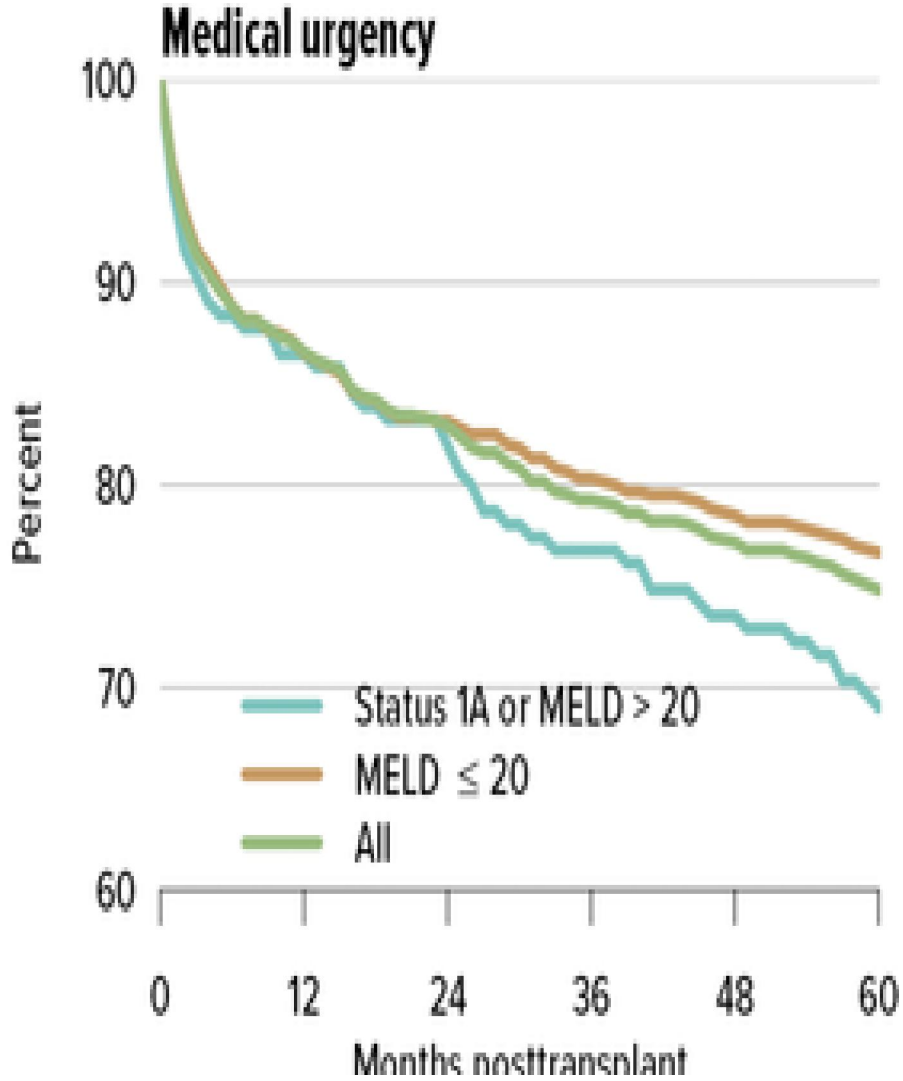
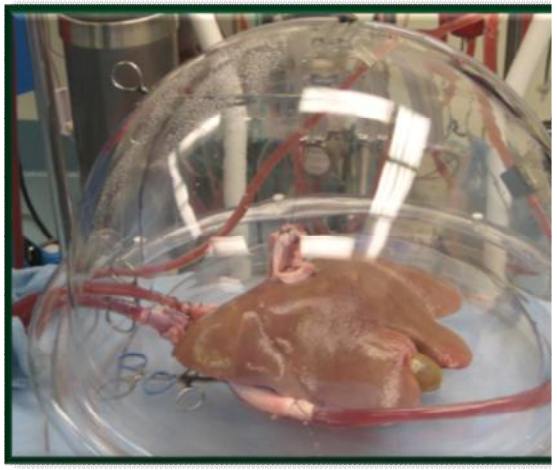
Survival

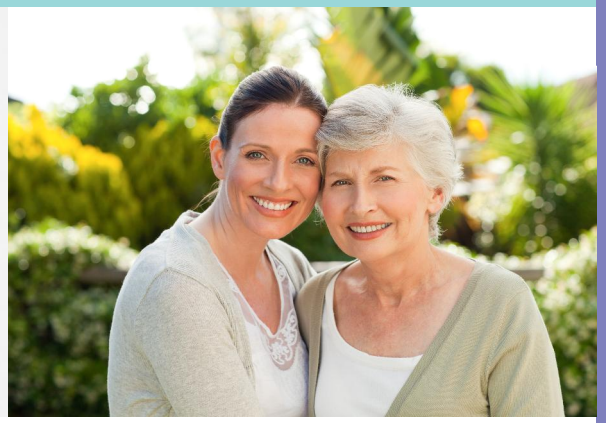

Primary diagnosis
Percent
100
90
80
70
60
HCV
ALD
Chol. disease
Malignancy
Other/unknown
0
12
24
36
48
60
Months posttransplant


Medical urgency
Percent
100
90
80
70
60
Status 1A or MELD > 20
MELD ≤ 20
All
0
12
24
36
48
60
Months posttransplant

Future







Ask the Experts
Patient Education Program

Current Developments in Treatment and Care

Stanley Martin Cohen, MD, FAASLD, FACG
April 26, 2017

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Liver Biopsy Without the Needle

(FibroSCAN or ultrasound elastography)

FibroScan slides courtesy of Sandhill Scientific, Inc.

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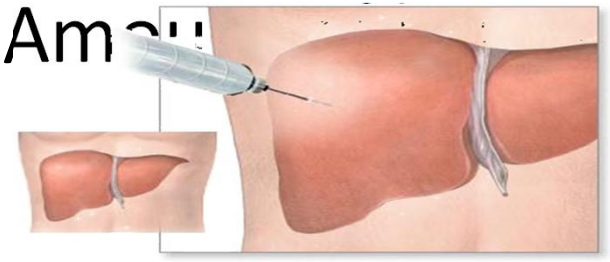
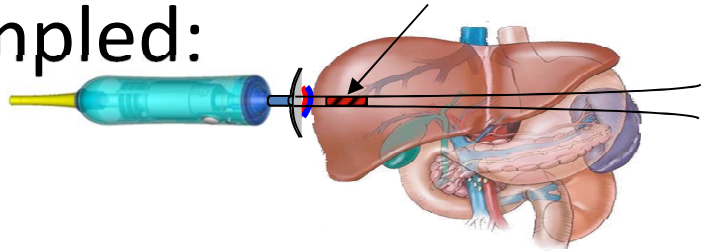
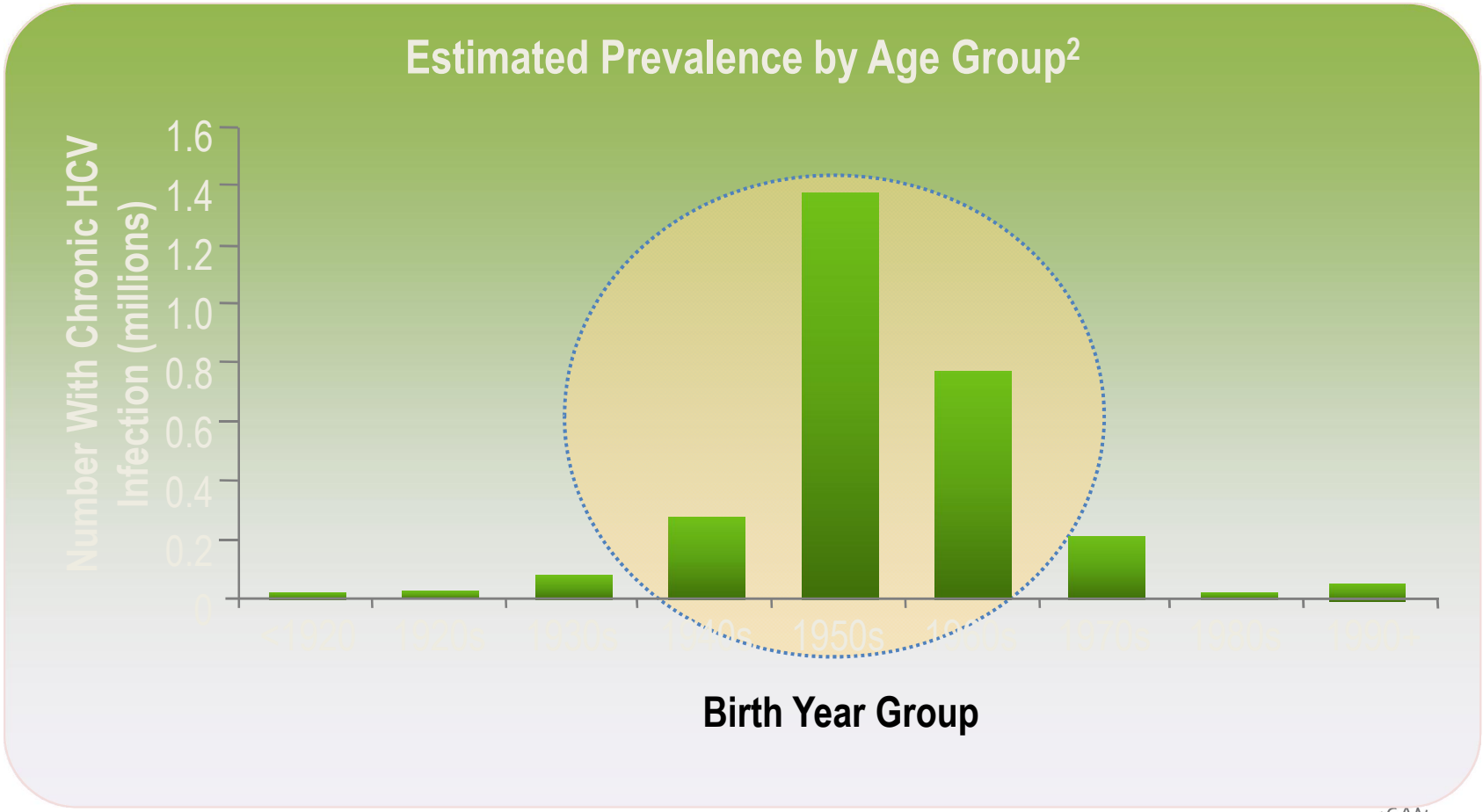
FibroScan Advantages

- Easy to use
- FDA-approved
- Can be done by trained RN's, MA's, techs, etc
- Can be used to follow serial exams
- Am[illegible]mpled:





Baby Boomers Account for 70-80% of HCV



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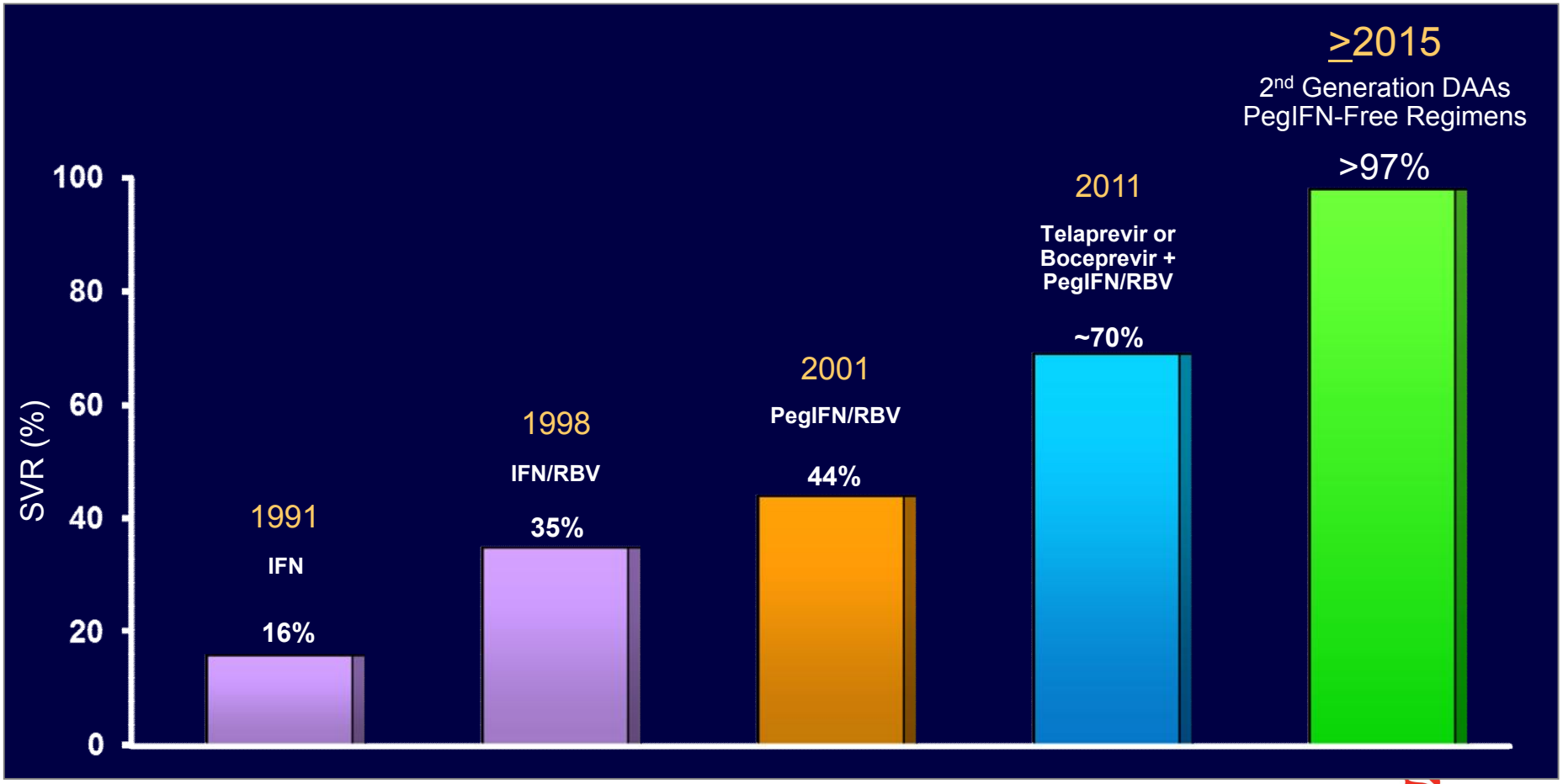
CDC Screening Guidelines for Hepatitis C

- **The Centers for Disease Control and Prevention (CDC) has issued draft guidelines recommending a one-time anti-HCV antibody test for all baby boomers (those born from 1945 through 1965) in an effort to identify these undiagnosed individuals.**

Centers for Disease Control and Prevention. http://www.cdc.gov/nchhstp/newsroom/HepTestingRecsPressRelease2012.html. Accessed May 23, 2012.

Chronic HCV Therapy (Genotype 1): Advances in Raising Cure Rates



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Hepatitis C
(Advances in cure rates, genotype 1)

Elbasvir + Grazeprevir (C-EDGE)	Sofosbuvir + Ledipasvir (ION1/3)	Dasabuvir, Ombitasvir, Paritaprevir/ ritonavir (Sapphire-1)	Simeprevir + Sofosbuvir (Optimist)	Sofosbuvir + Velpatasvir (Astral-1)	Daclatasvir + Sofosbuvir (Ally-2)
Zepatier	**Harvoni**	**Viekira**	**Olysio/Sovaldi**	**Epclusa**	**Daklinza/Sovaldi**
95%	97-99%	95%	97%	98%	96%

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Curing Hepatitis C: The Benefits

- "Sustained viral response" or SVR or Cure
  - Durable
    - 99% stay HCV negative for >10 years
  - Biopsy can get better
  - Decreased risk of getting cirrhosis
  - Decreased risk of cirrhosis getting worse
  - Decreased risk of liver cancer
  - Decreased mortality

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Hepatitis B

	Peg-IFN 2a 180 mcg qwk 48 wk	Lamivudine 100 mg qd 48-52 wk	Adefovir 10 mg qd 48 wk	Entecavir 0.5 mg qd 48 wk	Telbivudine 600 mg qd 52 wk	Tenofovir 300 mg qd 48 wk
Loss of serum HBV DNA	63%	60-73%	51%	90%	88%	93%
Normalization of ALT	38%	60-79%	72%	78%	74%	76%
Histologic improvement	59% (at 72 wks)	60-66%	64%	70%	67%	N/A

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Fatty Liver and NASH

- The most common liver disease in the US

- Risk factors:
  - Obesity
  - Diabetes
  - High lipids (cholesterol/triglycerides)

- Treatments:
  - Weight loss, diet, exercise
  - Control of blood sugar
  - Control of lipids
  - ??????????????????????????????????

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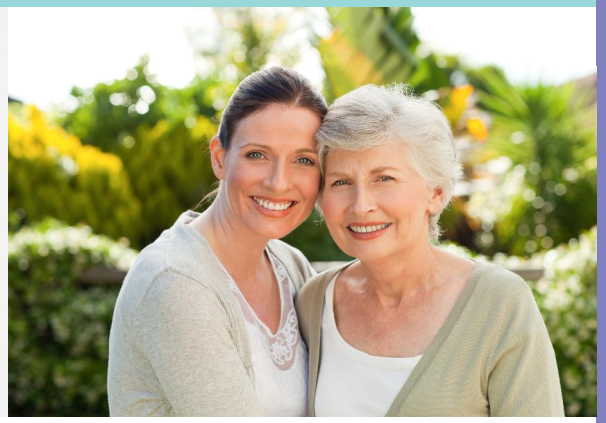

Ask the Experts
Patient Education Program

LIVER WELLNESS

Mousab Tabbaa, MD - ALF MAC Chair - President, North Shore Gastroenterology & Endoscopy Centers

April 26, 2017

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WELLNESS

LEONARDO DA VINCI

Leonardo di ser Piero da Vinci
Italian High Renaissance
painter
sculptor
architect
musician
scientist
mathematician
engineer
astronomer
designer
inventor
anatomist
geologist
cartographer
botanist
writer
and party planner

Born: April 15, 1452
Died: May 2, 1519

THE 7 DA VINCIAN PRINCIPLES

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Patient perspective
LIVER WELLNESS= WELLNESS

- HEALTHY DIET: ***What to eat?***
  Coffee?
  Alcohol?
- EXERCISE: ***How much?***
  What type?
- Toxins ***:*** ***Polypharmacy?***
  over-the-counters?
  Herbal supplements?

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DOCTOR PERSPECTIVE
Liver Wellness

- Understanding genetic makeup
- Addressing environmental factors
- Predicting response to environmental factors based on genetic makeup
- Predicting response to therapy and intervention
- Predicting side-effects (hepatotoxicity)
- Discovering pre-clinical “silent” injury

Definitions

Pharmacogenomics(genetics): Application of knowledge of genetic variation to predict therapeutic response or adverse events to a particular medication. Generally applies to germ line mutations (some apply to somatic mutations in tumor tissue)

Personalized Medicine as it pertains to the field of PGx:
Right treatment in a right dose for right patient at right time.

Genetic variants

- **Can modify treatment response**
  - Some variants exhibit faster or greater response
  - Some variants exhibit less or no response
- **Can predict or cause adverse drug reactions**
  - Skin reactions
  - Drug induced liver injury
  - Hyperbilirubinemia

INCREASED BMI IS BAD FOR YOU!

- Coronary artery disease
- Hypertension
- Increased cholesterol and triglycerides
- Diabetes
- Atherosclerosis
- Strokes
- Peripheral vascular disease
- Dementia
- Fatty liver and Cirrhosis
- Arthritis
- Impotence
- Cancer of various organs

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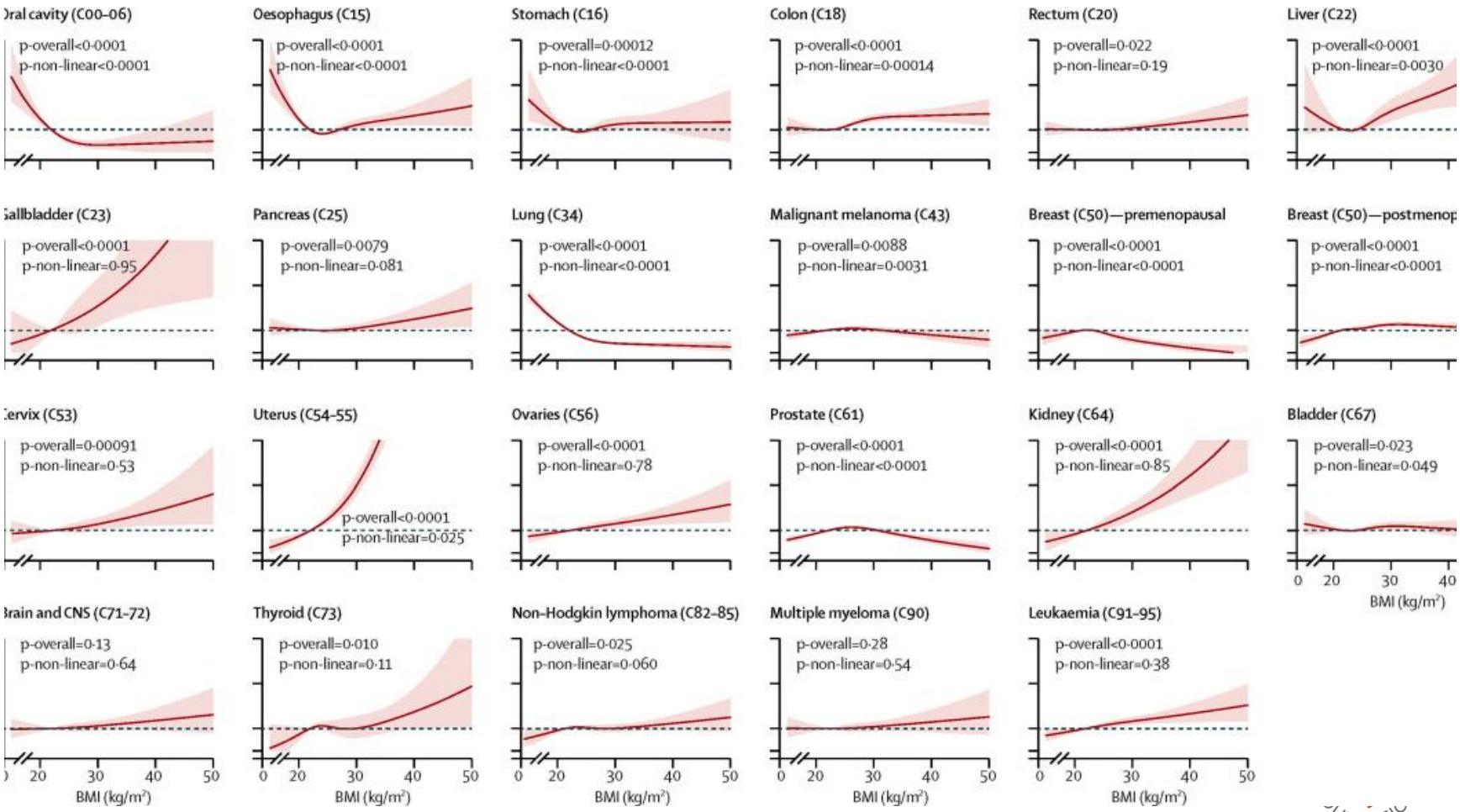
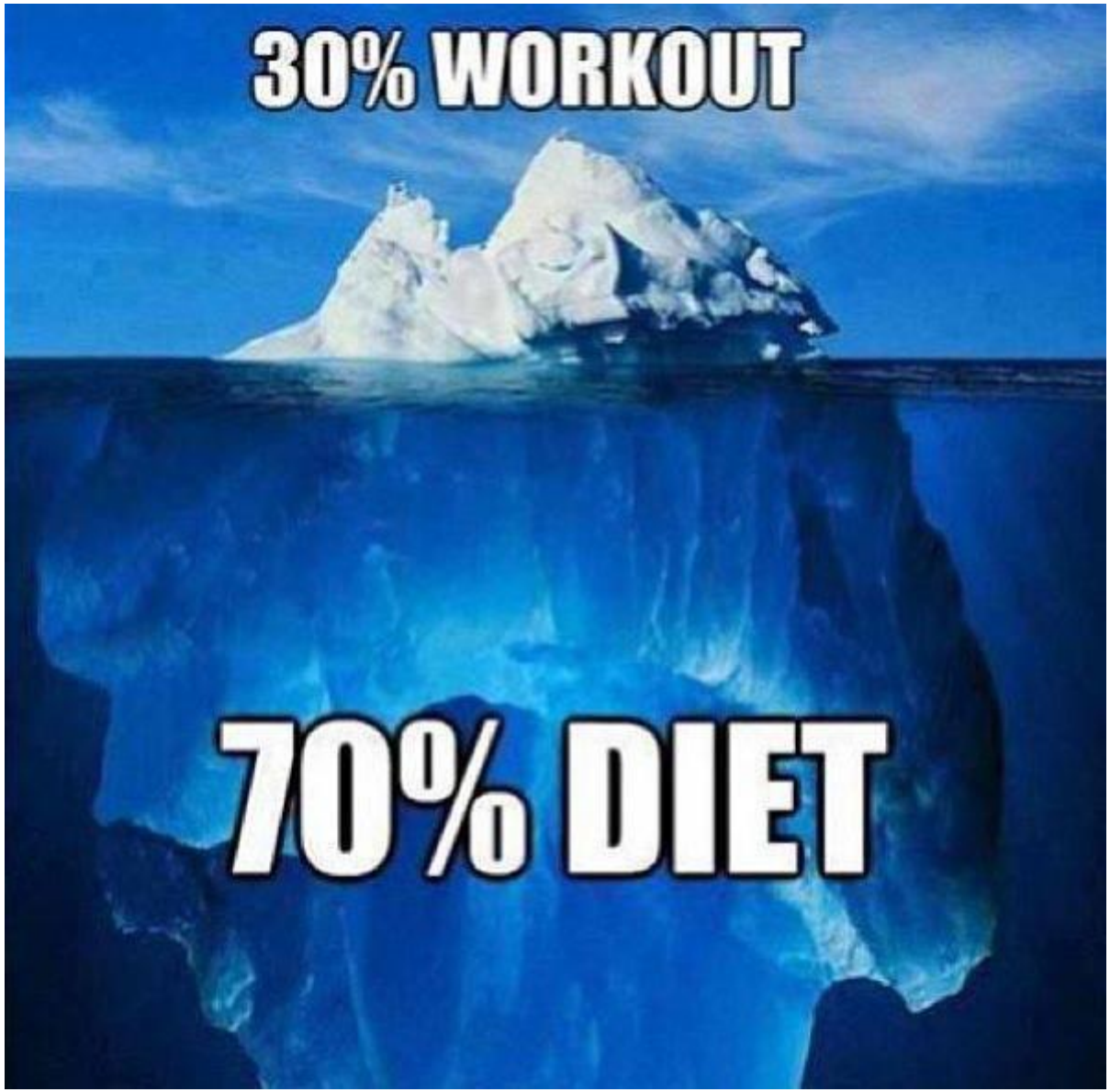
Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies.





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EXERCISE

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Effect of aerobic exercise training dose on liver fat and visceral adiposity

Shelley E. Keating, Daniel A. Hackett, Helen M. Parker, Helen T. O'Connor, James A. Gerofi, Amanda Sainsbury, Michael K. Baker, Vivienne H. Chuter, Ian D. Caterson, Jacob George, Nathan A. Johnson

Jourrnal of Hepatology, July 2015, Volume 63, Issue 1, Pages 174–182

Study Design

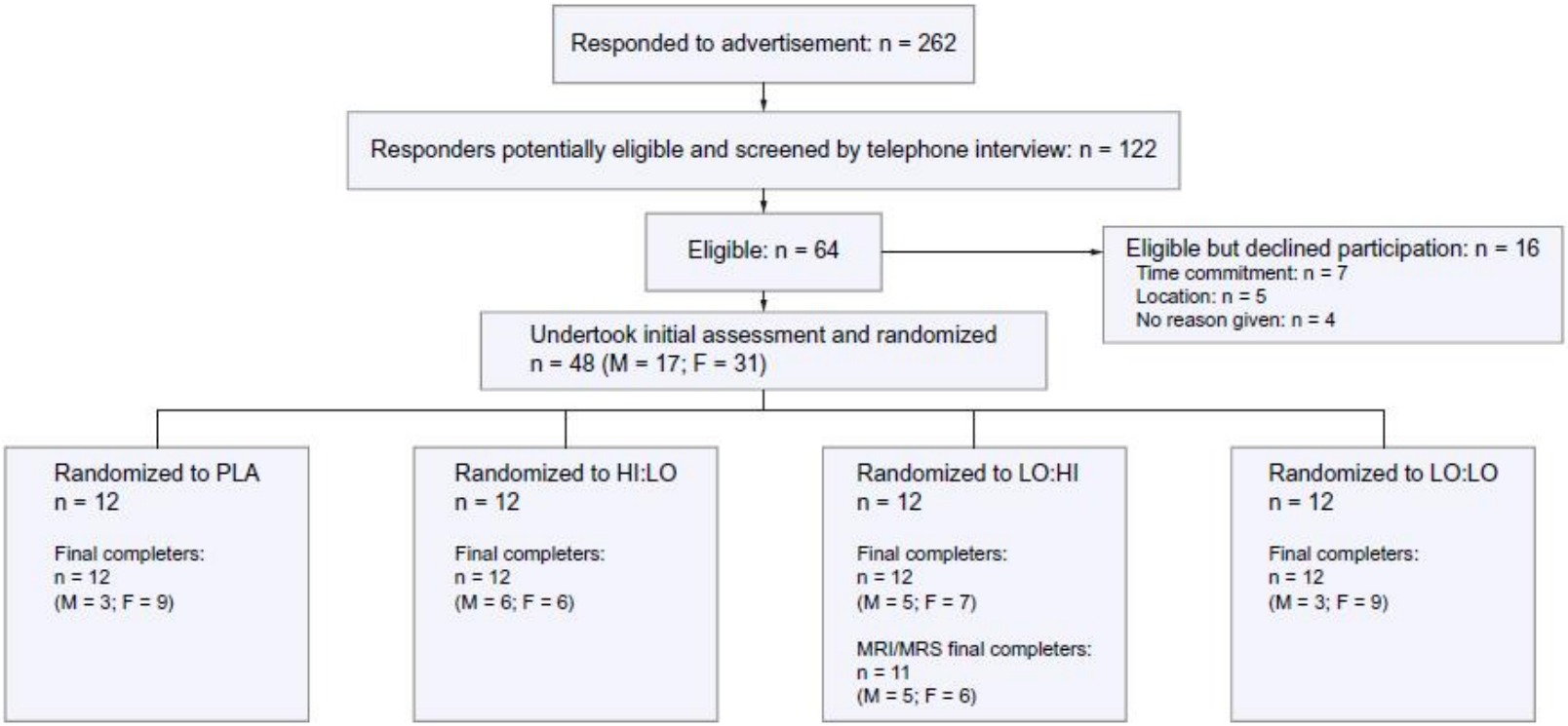

Fig. 1. Flowchart showing the study process. M, male; F, female; HI:LO, high intensity, low volume aerobic exercise; LO:HI, low to moderate intensity, high volume aerobic exercise; LO:LO, low to moderate intensity, low volume aerobic exercise; PLA, Placebo control group; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy.

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Study Conclusion

- All exercise doses (levels), irrespective of volume(minutes/week) or intensity(50-70% of maximum aerobic capacity) were effective in reducing liver fat and visceral adipose tissue by small but clinically important amount in previously inactive, overweight or obese adults.
- These changes were observed even without clinically significant weight loss.
- There was no difference between different exercise regimens for these benefits

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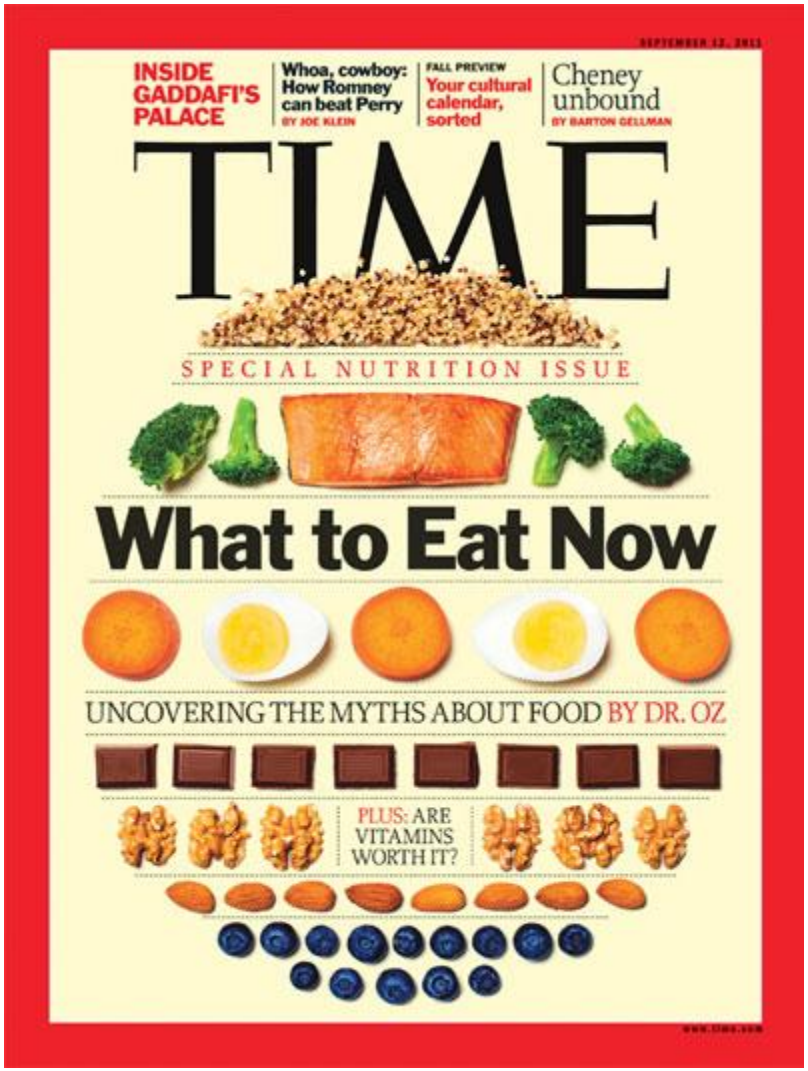
Exercise & Improvement of NAFLD: Practical Recommendations

- **There is good quality evidence to support that regular exercise is beneficial in reducing the risk of NAFLD**
- **Both aerobic and resistance training regimen are equally effective in reducing liver fat in individuals with NAFLD even in the absence of weight loss**
- **There are no data to support that exercise alone without weight loss can improve or reverse NASH. *Hence, lifestyle interventions utilizing both exercise and caloric restriction inducing weight loss (loosing approximately 5–10% of body weight) are needed to improve NASH.***
- **The United States Department of Health and Human Services exercise recommendations may lower liver fat but based upon our expert opinion more stringent exercise regimen coupled with dietary interventions may be needed to induce improvement in liver histologic features associated with NASH.**

editorial by Loomba and cortez-Pinto



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Western dietary pattern and fast food

- ↑ Consumption of fructose, soft drinks, meat, saturated fat
- ↓ Consumption of fiber, PUFA, fish or omega-3 and vitamins

In one study > twice a week = 4.5 kg extra body weight = ↑ two fold greater insulin resistance

In other study: 18 healthy young students with at last 2 fast food meals aday for 4 weeks
11 had elevated ALT at one week

❖ In clinical evaluations of subjects with ↑ ALT

Questions about
- Alcohol and soft drink
- Recent excessive intake of fast food

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Mediterranean diet

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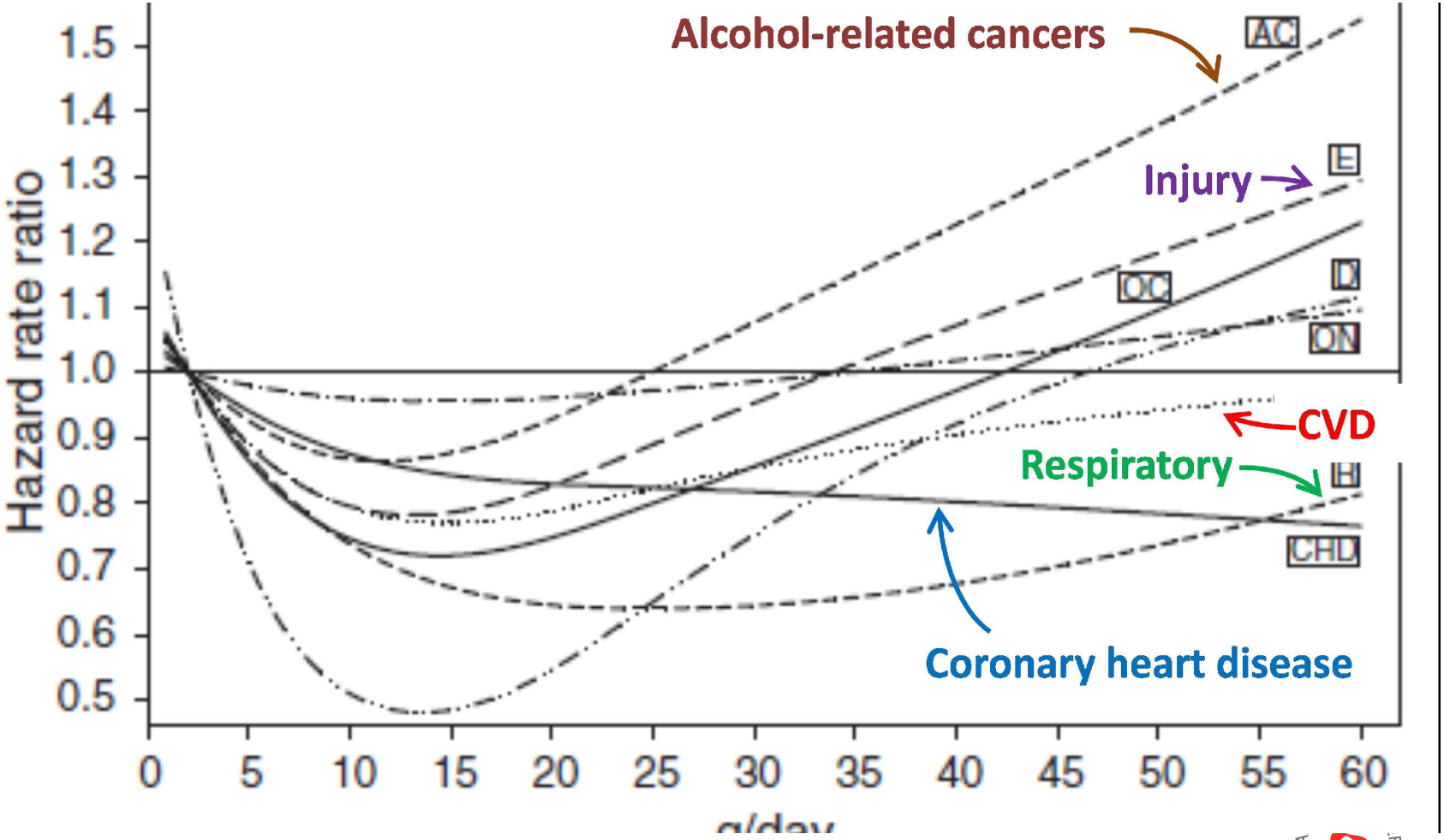
ALCOHOL


Alcohol-related cancers
AC
Injury
IJ
OC
D
ON
CVD
Respiratory
H
CHD
Coronary heart disease
Hazard rate ratio
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0
5
10
15
20
25
30
35
40
45
50
55
60
g/day

Alcohol Consumption and the Risk of Cancer
A Meta-Analysis

Vincenzo Bagnardi, Ms.C., Marta Blangiardo, Ms.C., Carlo La Vecchia, M.D., and Giovanni Corrao, Ph.D.

- Alcohol consumption has been linked to an increased risk for various types of cancer.
- A combined analysis of more than 200 studies assessing the link between alcohol and various types of cancer (i.e., a meta-analysis) sought to investigate this association in more detail.
- This meta-analysis found that alcohol most strongly increased the risks for cancers of the oral cavity, pharynx, esophagus, and larynx.
- Statistically significant increases in risk also existed for cancers of the stomach, colon, rectum, liver, female breast, and ovaries.
- Concurrent tobacco use, which is common among drinkers, enhances alcohol's effects on the risk for cancers of the upper digestive and respiratory tract.
- The analysis did not identify a threshold level of alcohol consumption below which no increased risk for cancer was evident.

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What do we recommend our patients with NAFLD about alcohol use?

- Heavy alcohol consumption has many harmful effects including those on liver and should be discouraged regardless whether an individual has NAFLD or not.
- Emerging epidemiological data suggest that light to moderate drinking may have favorable effects from a liver standpoint. But most studies are cross-sectional in nature and utilized surrogates such as aminotransferases and liver imaging.

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What do we recommend our patients with NAFLD about alcohol use?

- Furthermore, it is not clear if cardiovascular and metabolic benefits of light to moderate alcohol consumption observed in general population are extended to those with NAFLD and NASH.
- There are emerging studies to suggest that even light alcohol consumption may increase the risk of cancers (e.g., breast and colon).
- ***Until further data from rigorously conducted prospective studies become available, we believe that individuals with NAFLD should avoid alcohol consumption of any type or amount.***

AJG.2012July;107(7):976-978

COFFEE

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Coffee consumption and liver function

- Drinking moderate amounts of coffee may help to reduce the risk of liver cancer, and the risk of developing liver cancer falls as coffee consumption rises.
- Moderate coffee consumption may also be related to a slower progression of liver disease. Patients with a higher coffee consumption have been found to display a milder course of fibrosis, especially in alcoholic liver disease.
- The association between moderate coffee consumption and a slower rate of fibrosis has also been seen in patients with hepatic fibrosis, cirrhosis, non-alcoholic liver disease and Hepatitis C.
- It is not yet clear whether, and to what extent, caffeine may be responsible for the reduction in risk of developing these diseases.
- Several different coffee components are being investigated. Kahweol and cafestol, naturally-occurring compounds in coffee, are being studied for their anti-carcinogenic effects, while the anti-viral properties of chlorogenic and caffeic acids are also under investigation.

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coffee&health

from the institute for scientific information on coffee

- K Friedrich et al, 2016. Coffee consumption protects against progression in liver cirrhosis and increases long term survival after liver transplantation, Journal of Gastroenterology and Hepatology, published online ahead of print.
- O J Kennedy et al, 2016, Systematic review with meta-analysis: coffee consumption and the risk of cirrhosis, Alimentary Pharmacology and Therapeutics, published online ahead of print.
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- F Liu et al, 2015. Coffee Consumption Decreases Risks for Hepatic Fibrosis and Cirrhosis: A Meta-Analysis, PLOS One, published online ahead of print.
- V Gupta et al, 2015. Oily fish, Coffee and Walnuts: Dietary Treatment for non-alcoholic fatty iver disease, World Journal of Gastroenterology, Volume 21 (37)
- S Zelber-Sagi et al, 2014. Coffee consumption and nonalcoholic fatty liver onset: a prospective study in the general population. Translational Research, published online ahead of print.
- V W Setiawan et al, 2014, Association of Coffee Intake with Reduced Incidence of Liver Cancer and Death from Chronic Liver Disease in the US Multiethnic Cohort, Gastroenterology, published online ahead of print.
- F Morisco et al, 2014. Coffee and liver health. Journal of Clinical Gastroenterology, Volume 48, Supplement 1: S87-90
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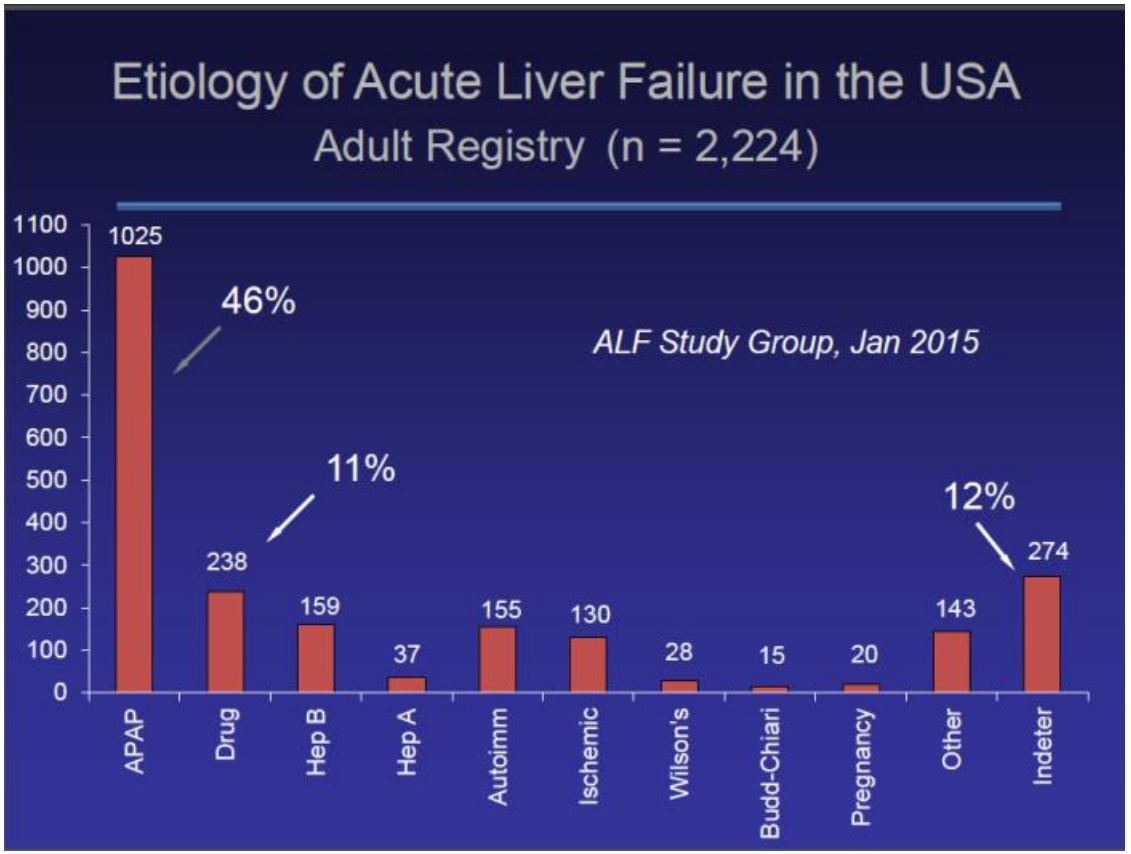
DRUGS & LIVER INJURY



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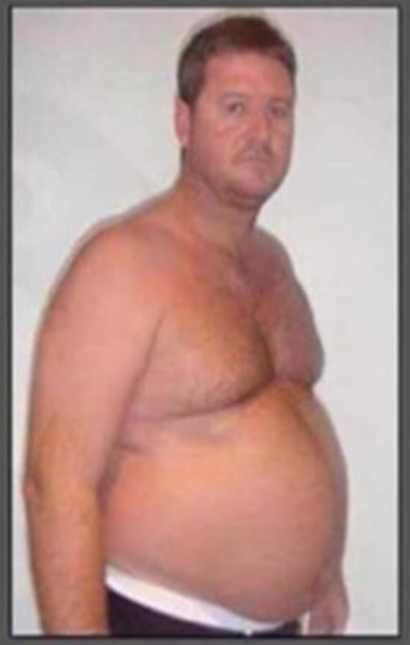
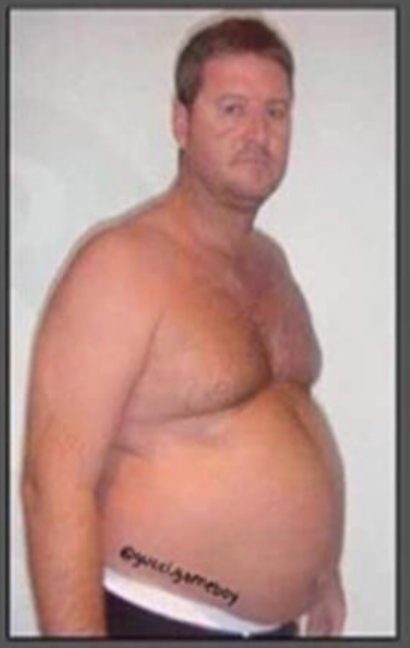
Before



After



In only 6 weeks of drinking FitTea™ Robert lost $500

FATAL COMBINATION

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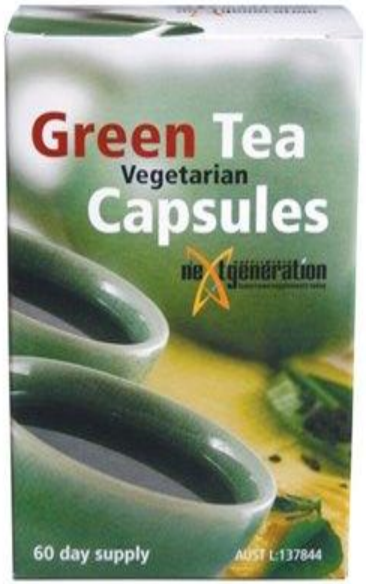
The Ubiquity of Green Tea (Extract)



Liver Injury due to Green Tea Extract

- Over 50 reported clinical cases of liver injury
- No clear relationship between GTE dose and severity of liver injury *(Navarro, 2009)*
- Mechanism of injury conjectural
- Typical picture
  - Viral hepatitis like picture
  - Very high ALT elevations
  - Hepatocellular jaundice

Why is there risk of DILI from HDS?

- Inappropriate use
- Inherent toxicity
- Adulteration and contamination
- Herb-drug interactions
- Individual susceptibility