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Rob Goldin

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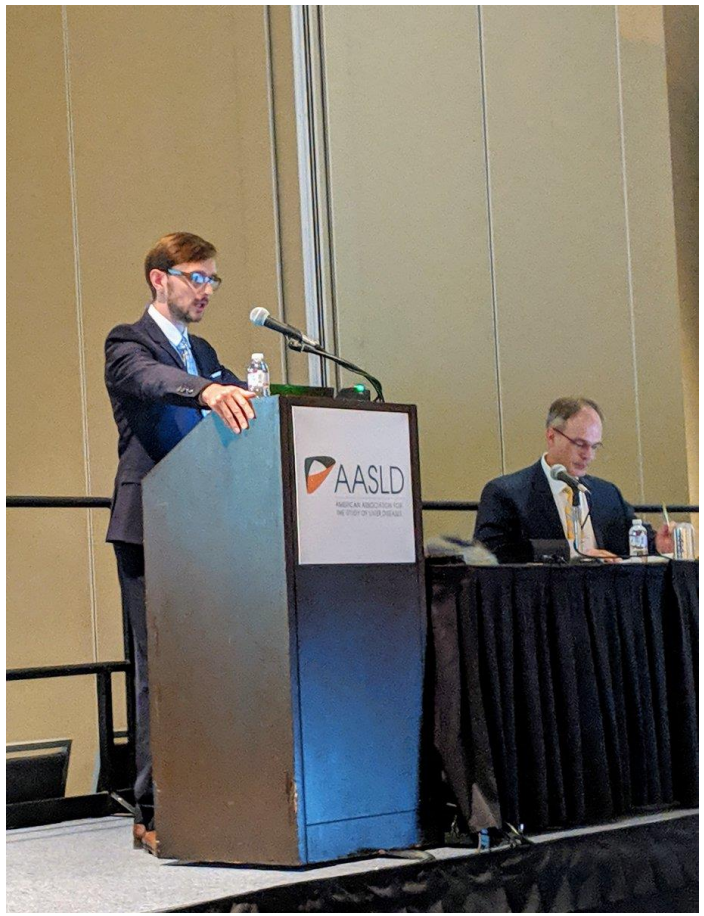
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THE LIVER MEETING®
2018 SAN FRANCISCO
NOVEMBER 9-13
Tuesday's Weather
65°
partly cloudy with
a chance of meatballs

General

The “omes”

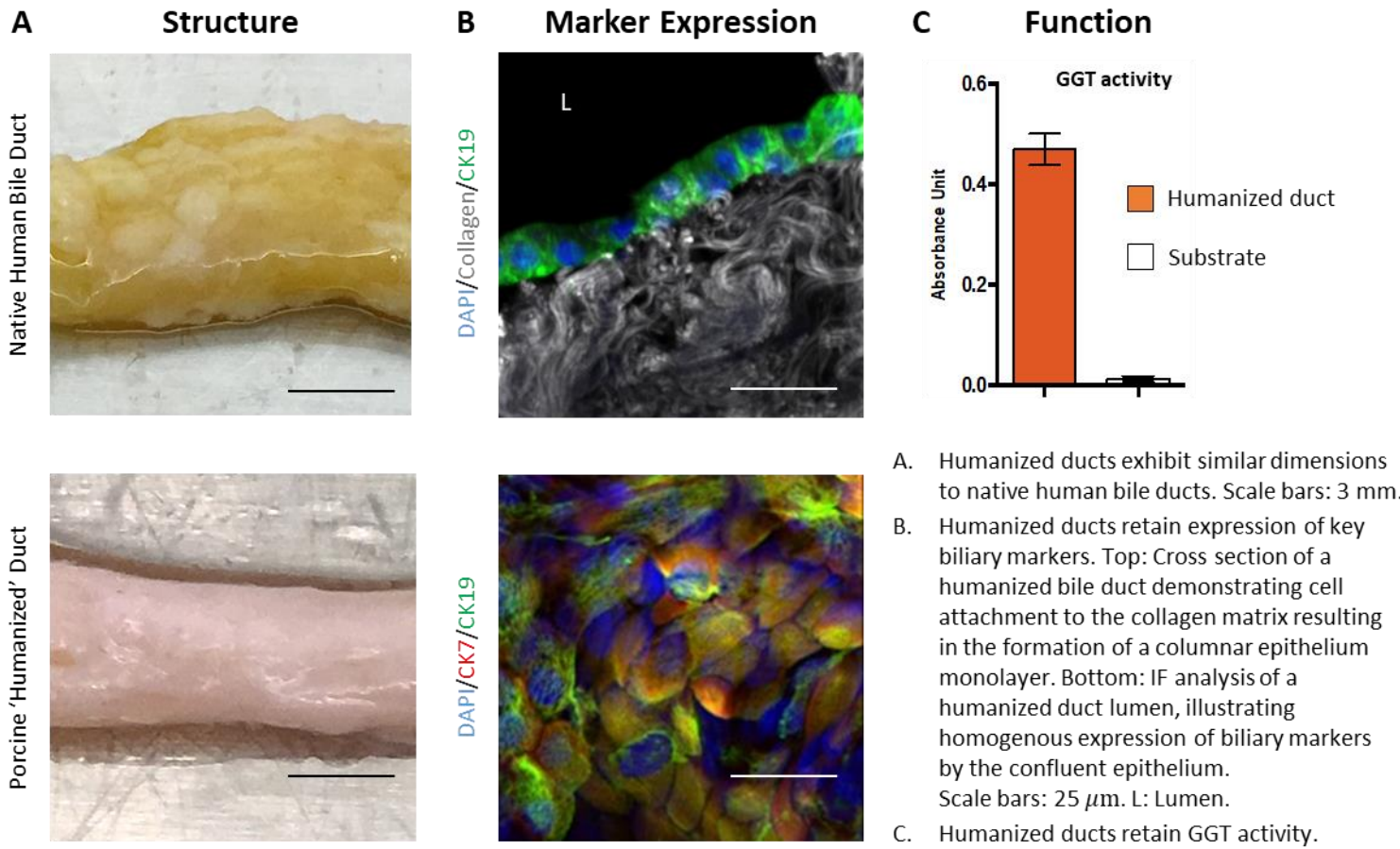
Generation of bio-engineered biliary tissue using primary cholangiocytes and decellularized bile ducts

Aim:
Generation of human-size tissue-engineered bile ducts

Methods:
'Humanized' bile ducts were generated by seeding primary Extrahepatic Cholagiocytes Organoids (ECOs) on decellularized pig bile ducts.

Conclusions:
Humanized bile ducts are compatible with surgical manipulation, they allow adequate transfer of oxygen and nutrients across their wall while retaining key biliary markers and function following long-term culture and demonstrate a unique potential for advancing bile duct tissue engineering from proof-of-principle studies in small animal models to constructs compatible with large animal studies and clinical translation.

Brevini T, et al., Abstract 20

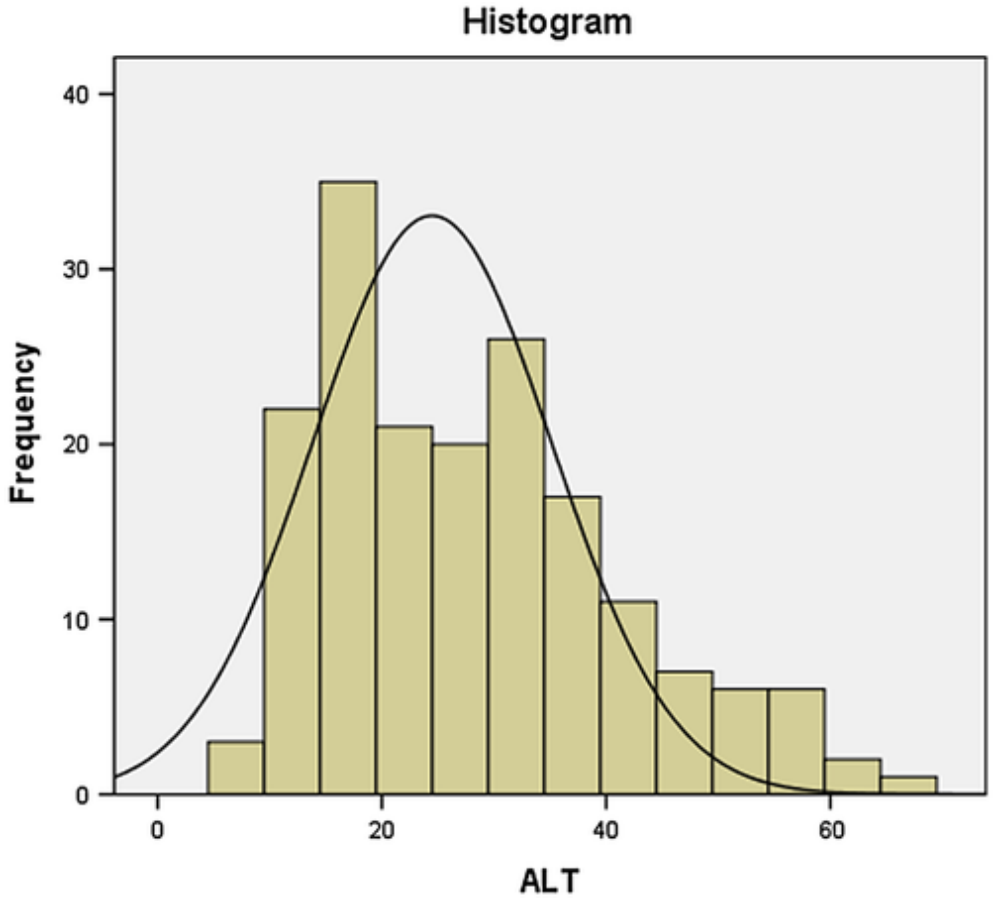


A. Humanized ducts exhibit similar dimensions to native human bile ducts. Scale bars: 3 mm.

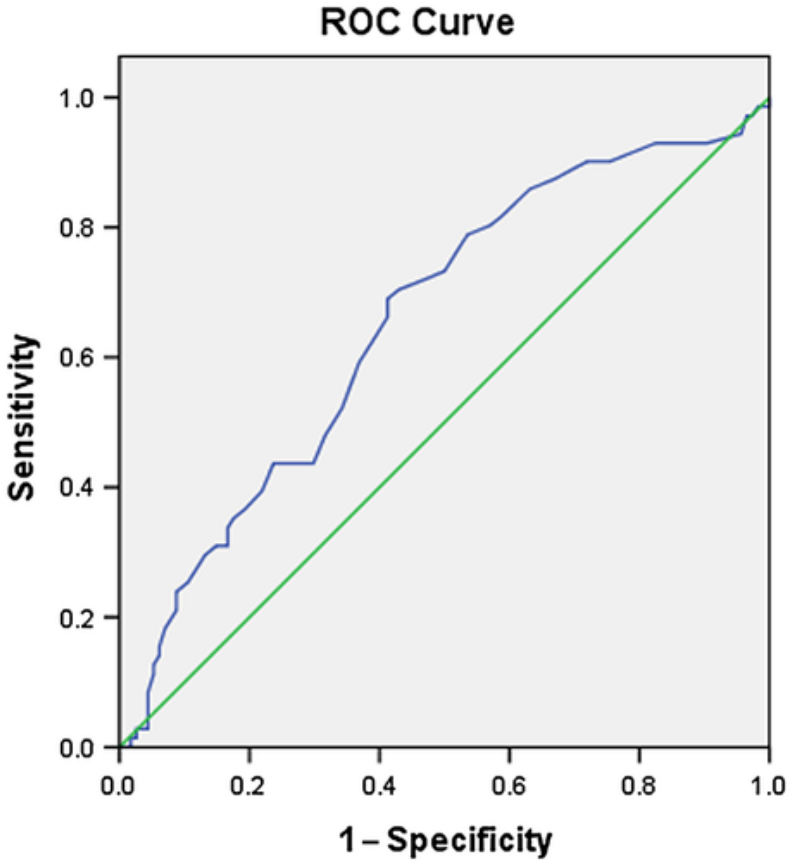
B. Humanized ducts retain expression of key biliary markers. Top: Cross section of a humanized bile duct demonstrating cell attachment to the collagen matrix resulting in the formation of a columnar epithelium monolayer. Bottom: IF analysis of a humanized duct lumen, illustrating homogenous expression of biliary markers by the confluent epithelium.
Scale bars: 25 μm. L: Lumen.

C. Humanized ducts retain GGT activity.

Misconception: You Can’t Have Liver Disease With Normal Liver Chemistries

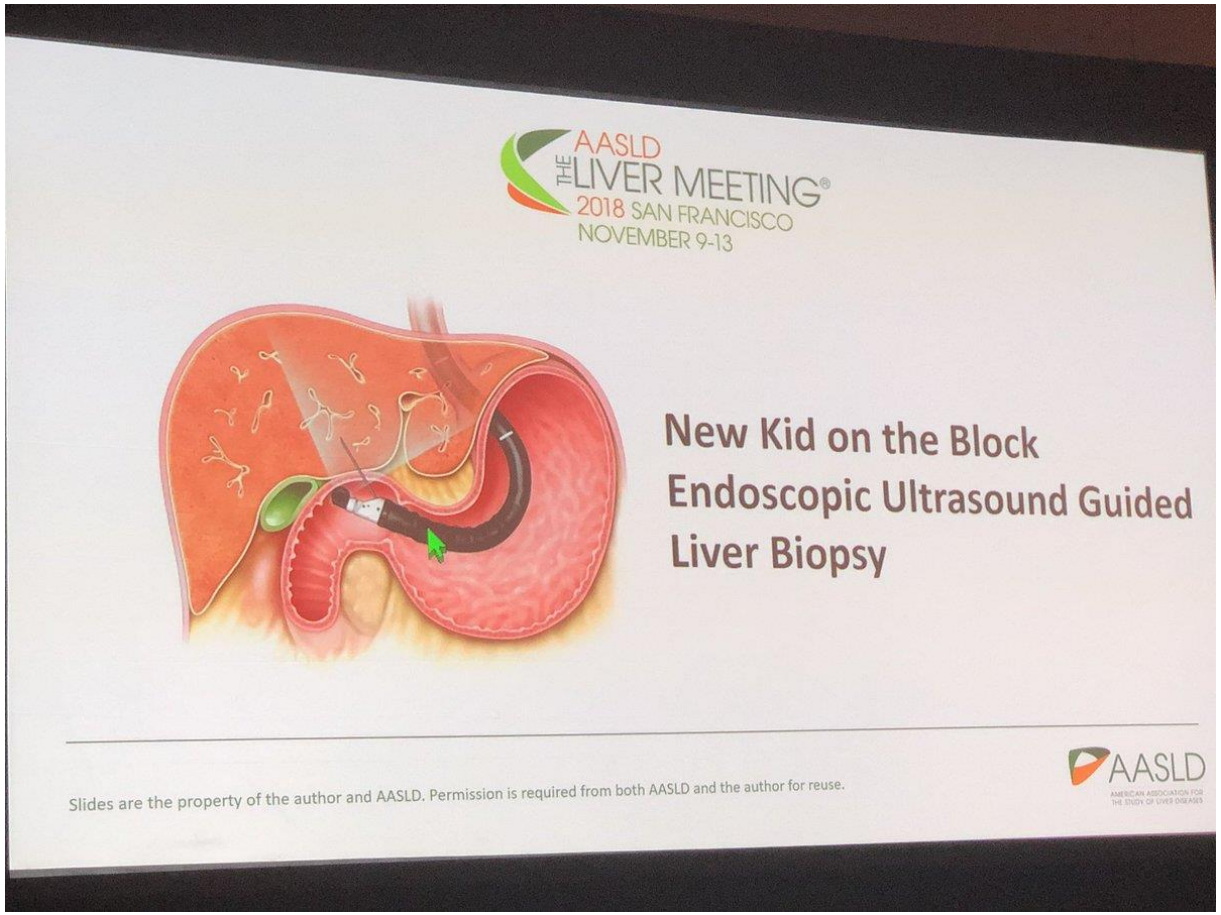


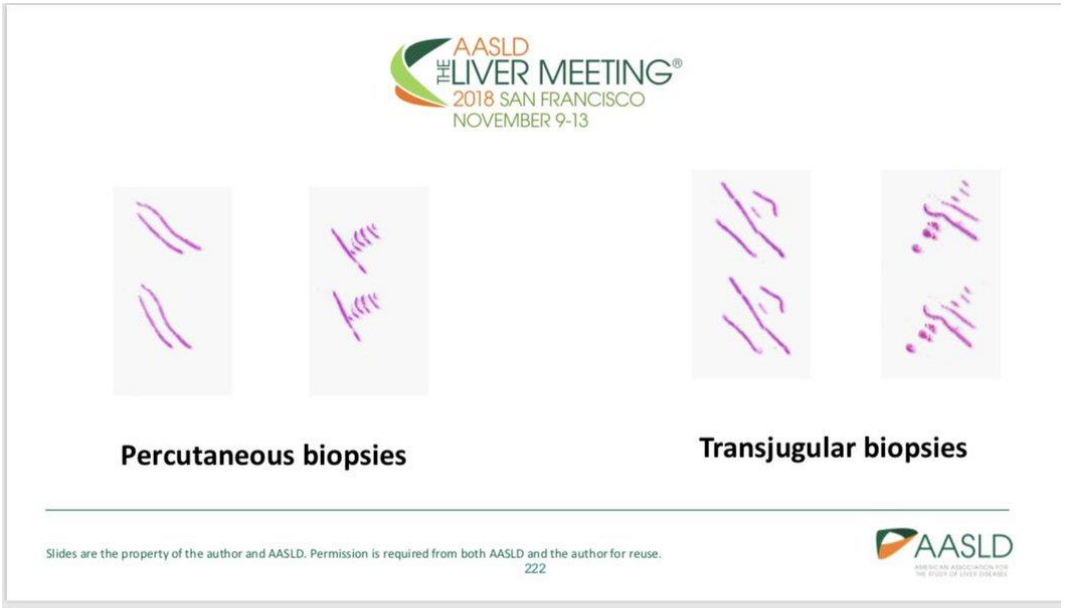
ALT values in 177 overweight patients undergoing bariatric surgery.

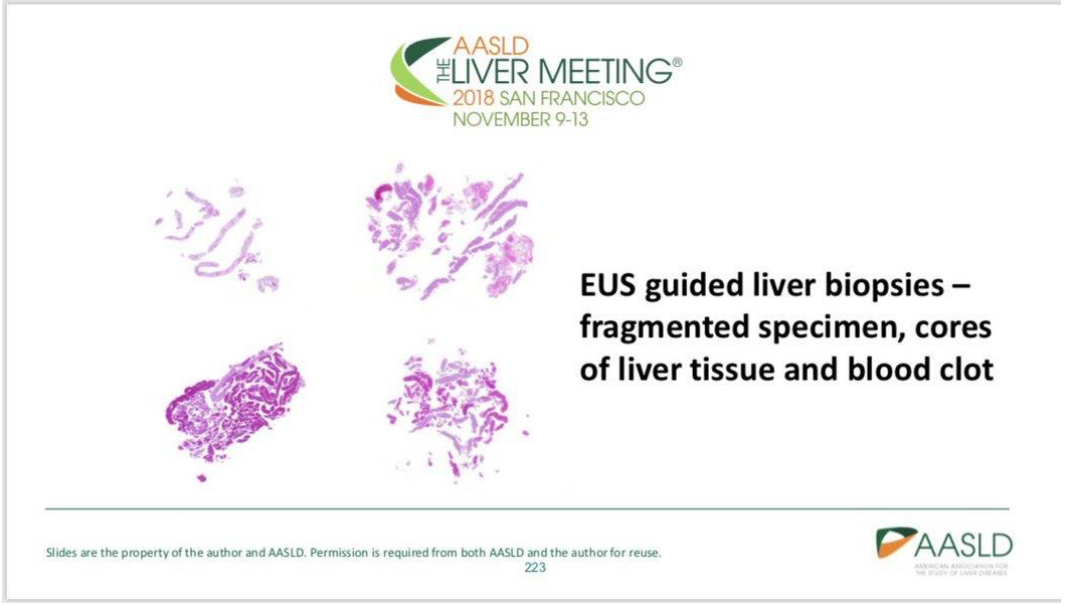


ROC curve for ALT in discriminating the presence of nonalcoholic steatohepatitis in patients undergoing bariatric surgery (AUC = 0.653).

EUS guided Liver Biopsy





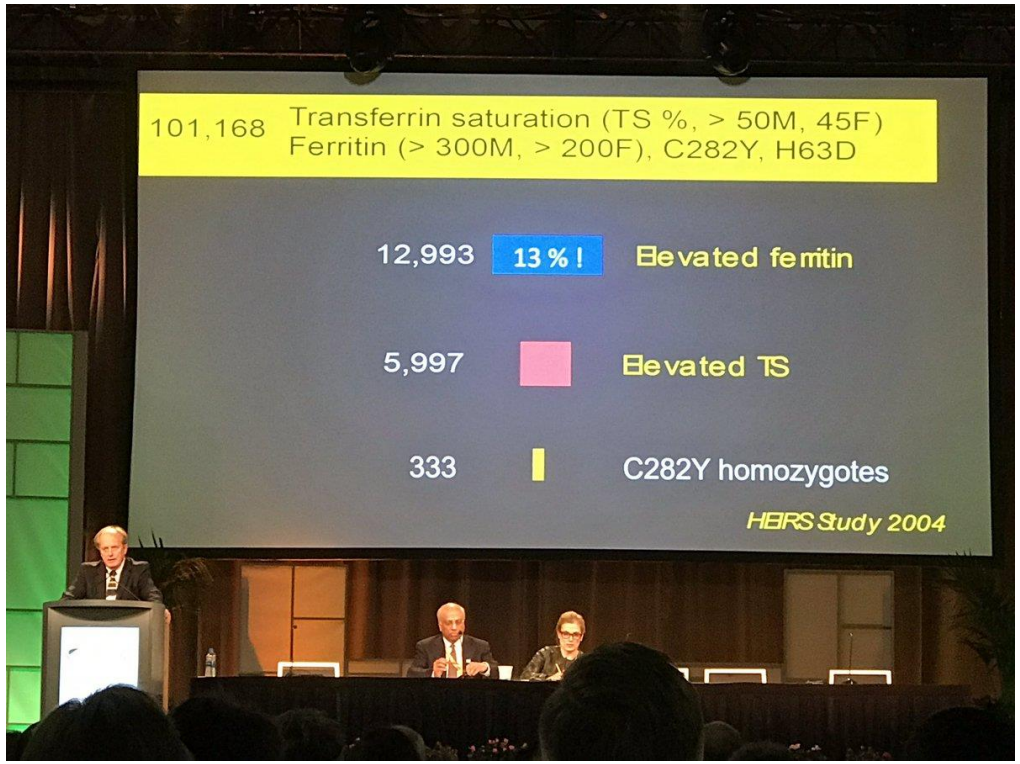


"EUS liver biopsy vs transjugular and percutaneous.

Fragmented biopsies obtained by EUS are not ideal for medical liver evaluation. "

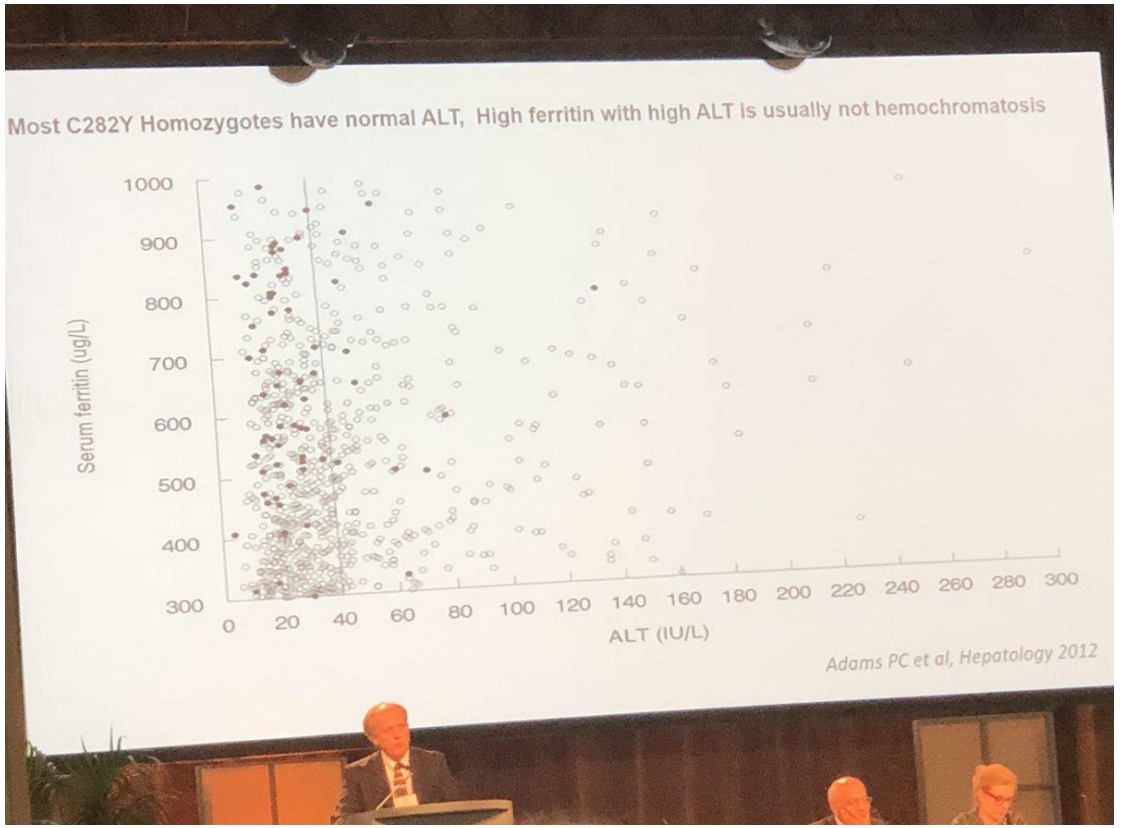
Metabolic

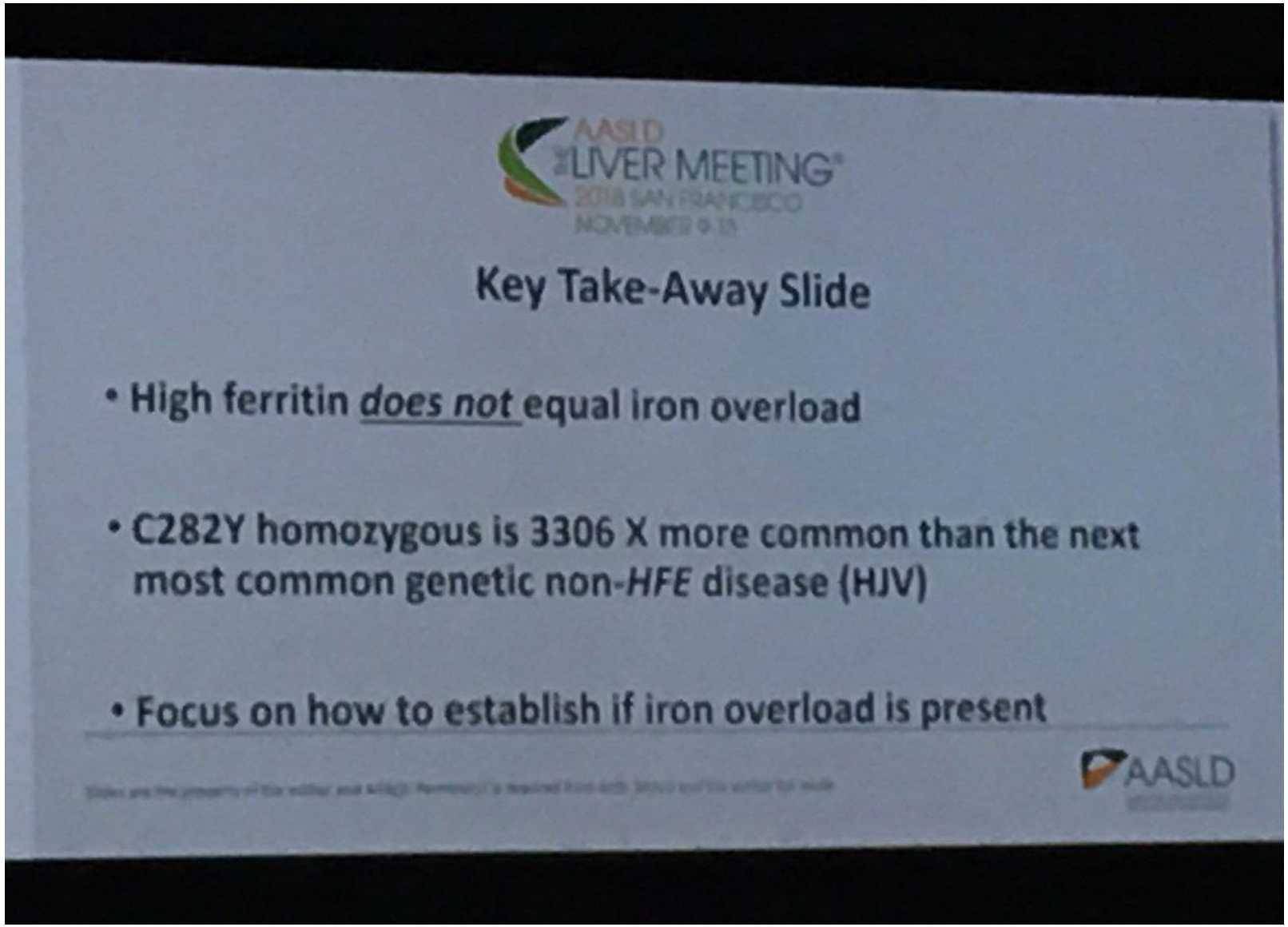
“An elevated ferritin does not always equal hemochromatosis”



Acton, Ronald T. et al "Geographic and Racial/Ethnic Differences in *HFE* Mutation Frequencies and Iron Phenotypes in the Hemochromatosis and Iron Overload Screening (HEIRS) Study." *Blood* 104.11 (2004

If your patient has a high ferritin AND elevated ALT, he/she likely does NOT have hemochromatosis!
Most C282Y homozygotes have normal ALT.

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Key Take-Away Slide
• High ferritin *does not* equal iron overload
• C282Y homozygous is 3306 X more common than the next most common genetic non-*HFE* disease (HJV)
• Focus on how to establish if iron overload is present
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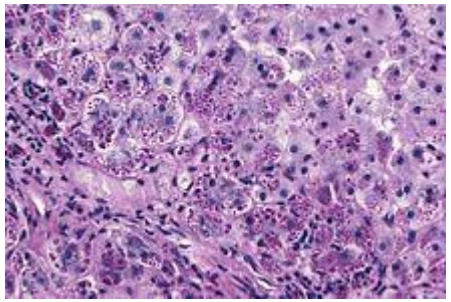
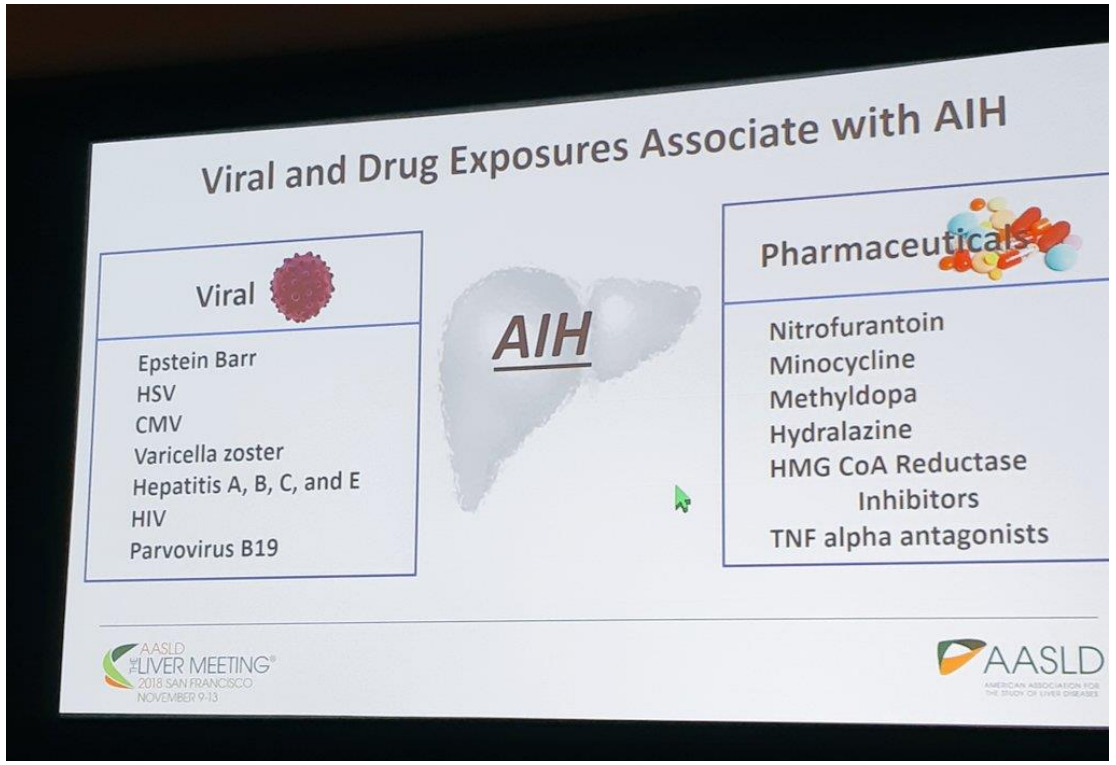
Alpha-1 antitrypsin deficiency

- 94 adults with classic genotype ‘PI*ZZ’ AATD
- The prevalence of clinically significant liver fibrosis (F ≥ 2) was 35%.
- Metabolic syndrome was associated with the presence of clinically significant fibrosis.
- Additionally, the presence of accumulated abnormal AAT in hepatocytes, portal inflammation, and hepatocellular degeneration were associated with clinically significant fibrosis.

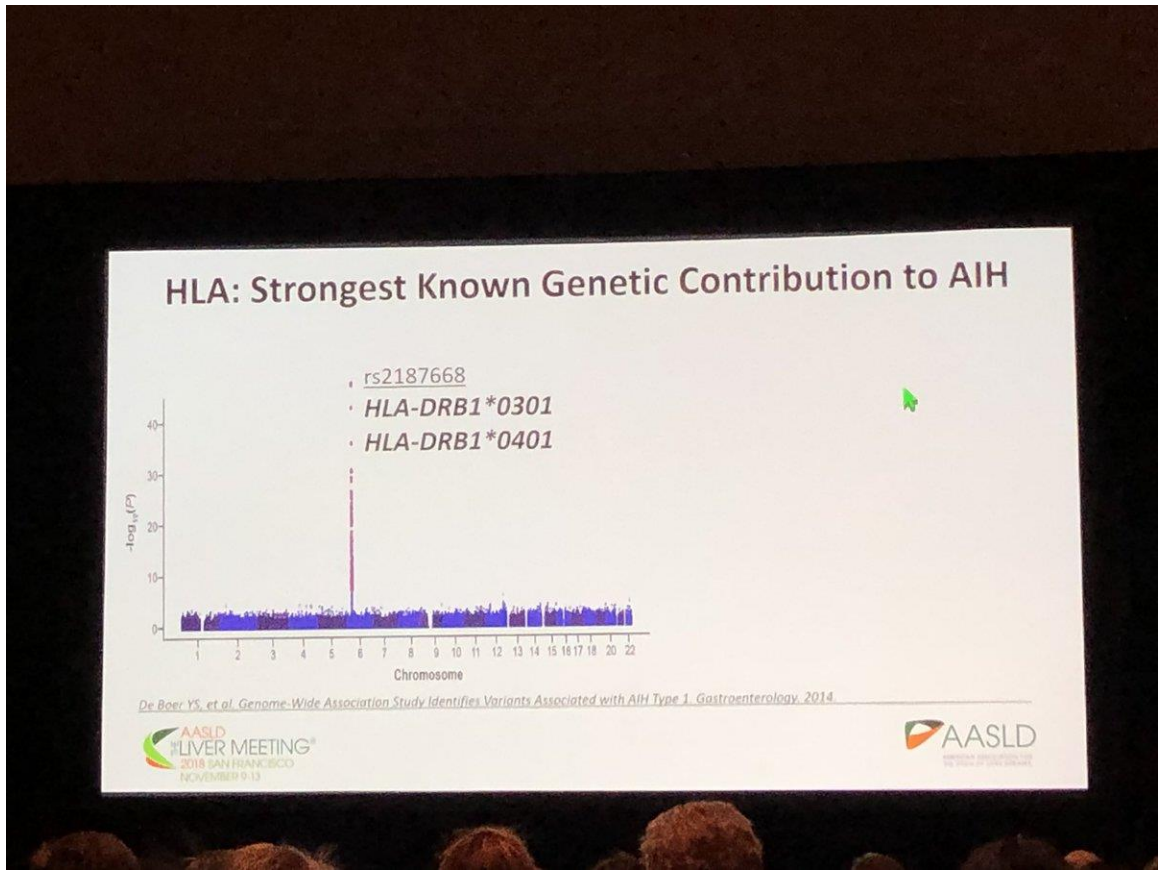


Autoimmune hepatitis

Viral and Drug Exposures Associated with AIH

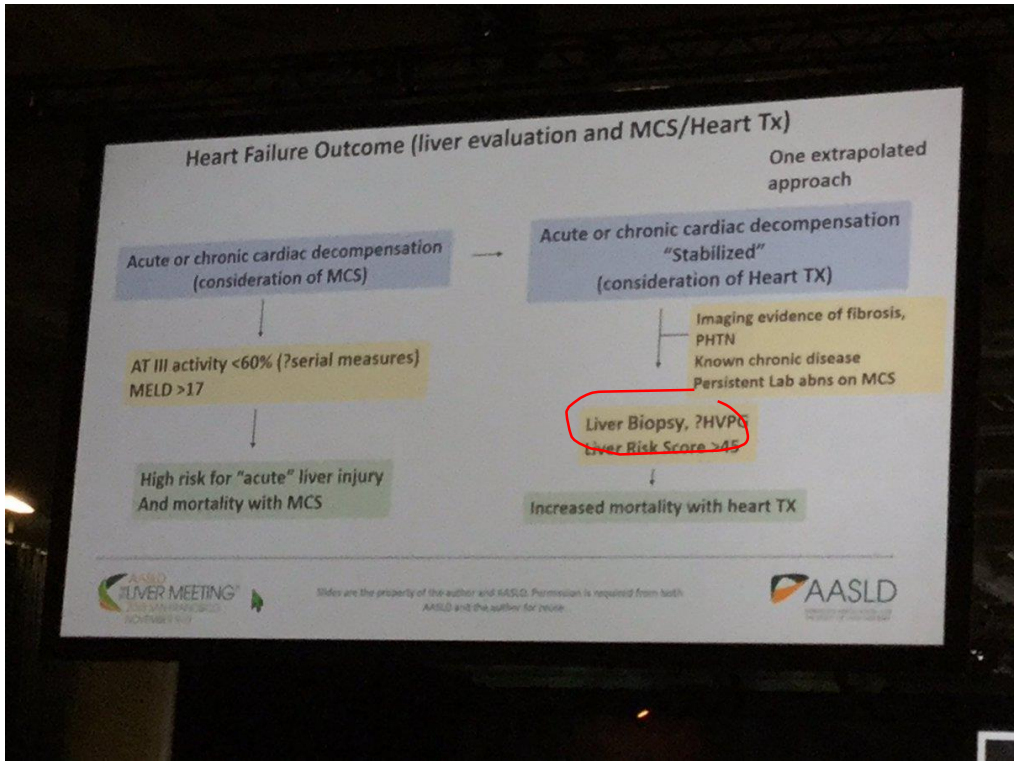


HLA Strongest Known Genetic Contribution to AIH

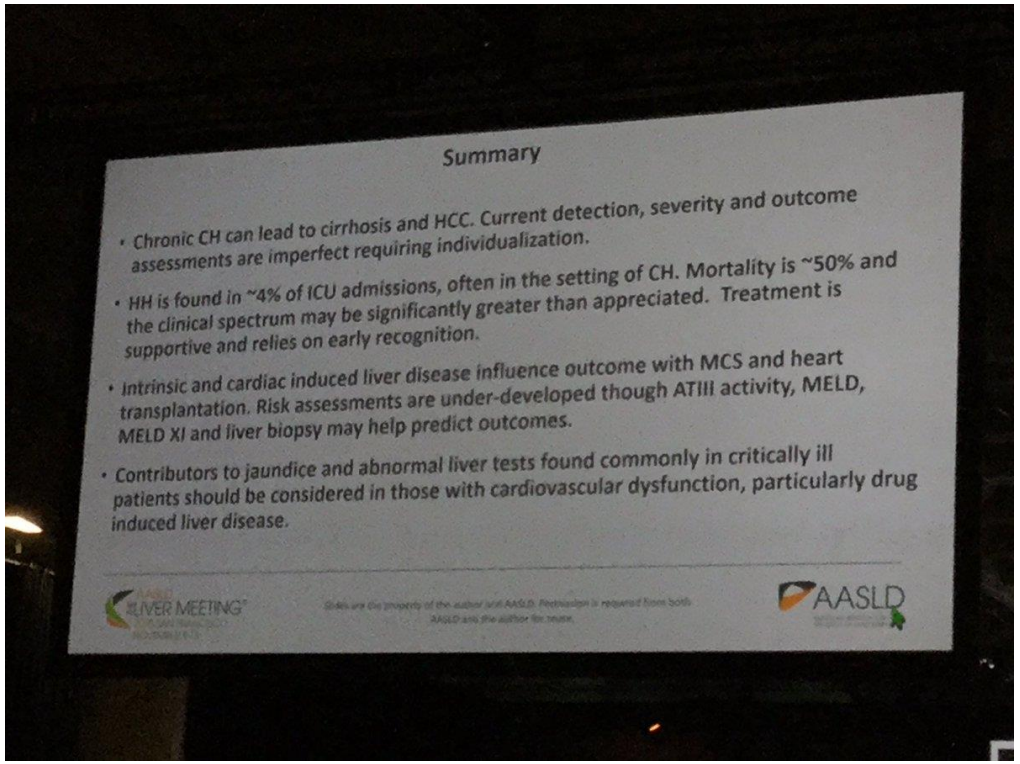


Vascular Disease

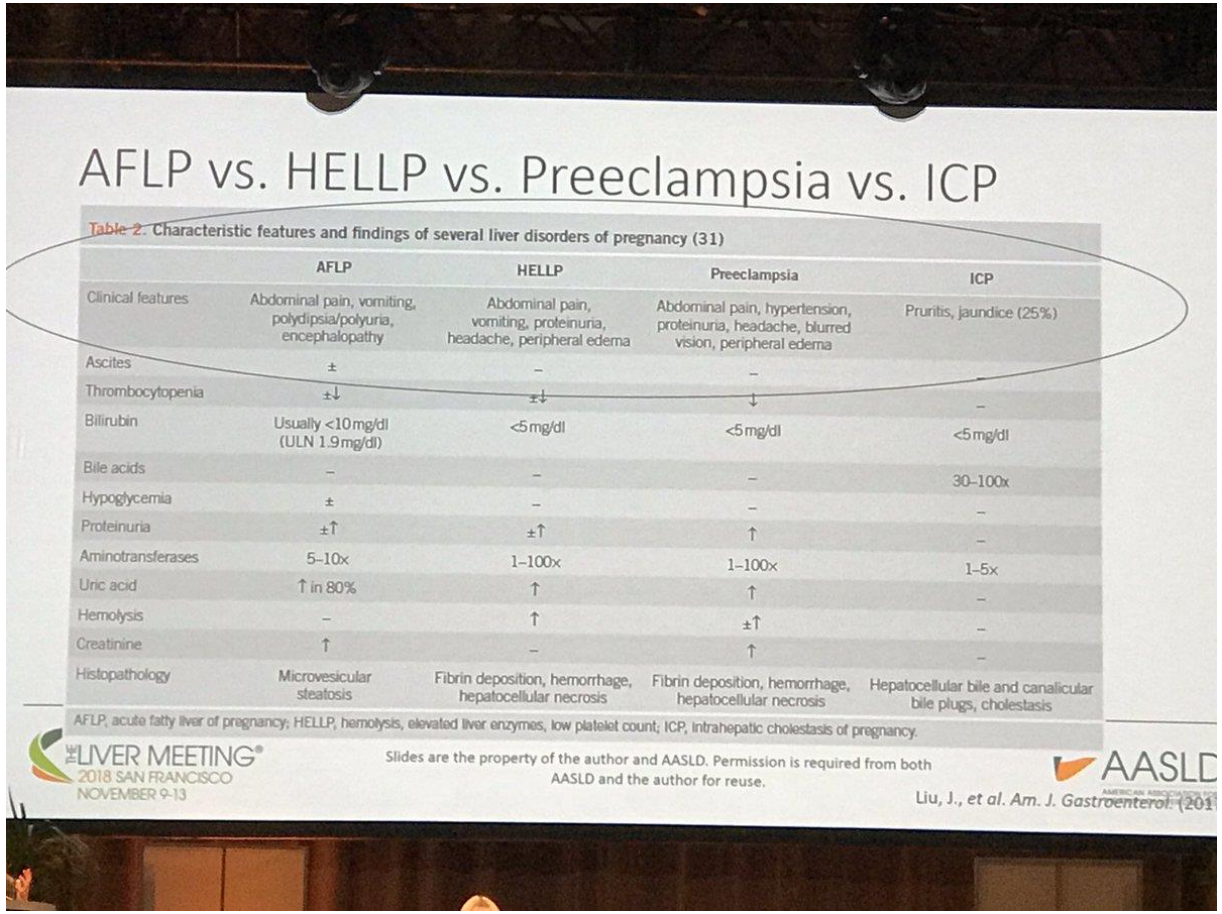
Heart Disease and Cardiac Failure



Heart Disease in Cardiac Failure

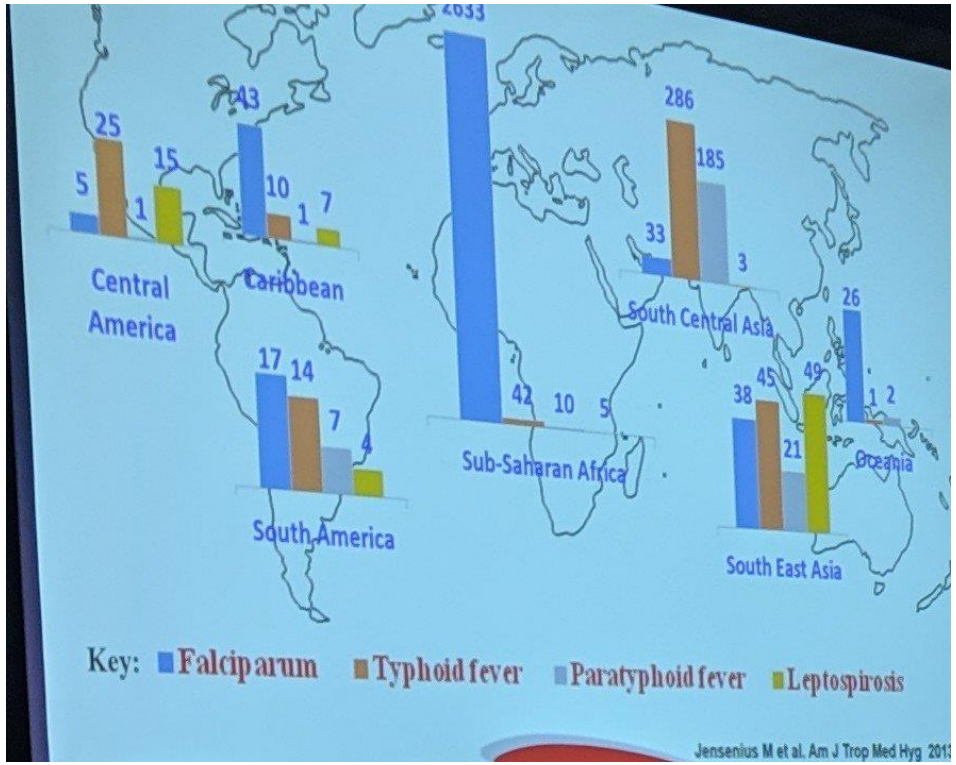


Liver Disease in Pregnancy

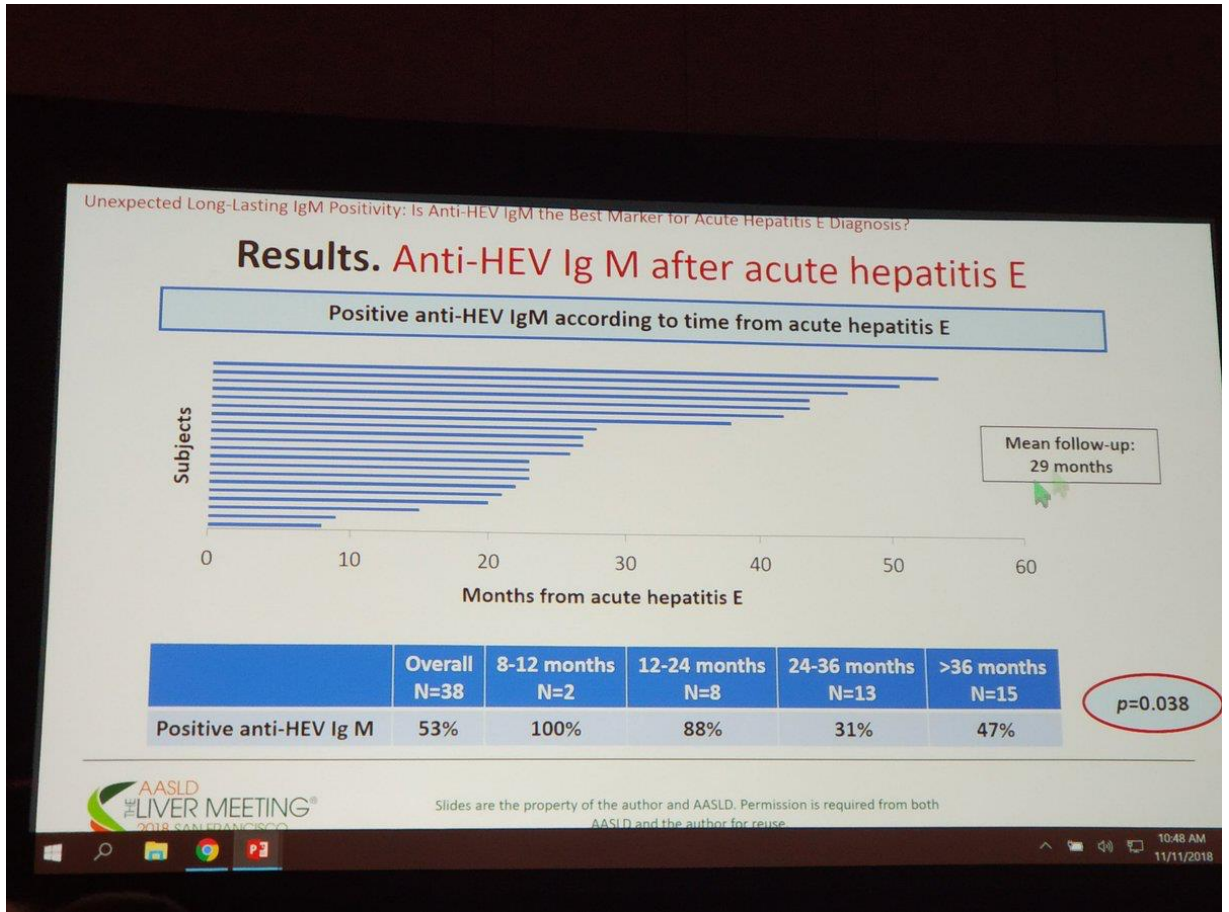


Infectious Diseases

Fever, hepatitis, hepatosplenomegaly and cytopenias are common symptoms of malaria, dengue, typhoid and leptospirosis



HEV IgM persists after acute infection. >50% positive 2.5 years after acute infection. Bear in mind when diagnosing HEV as cause of acute hepatitis



Mycobacterium chimaera Hepatitis

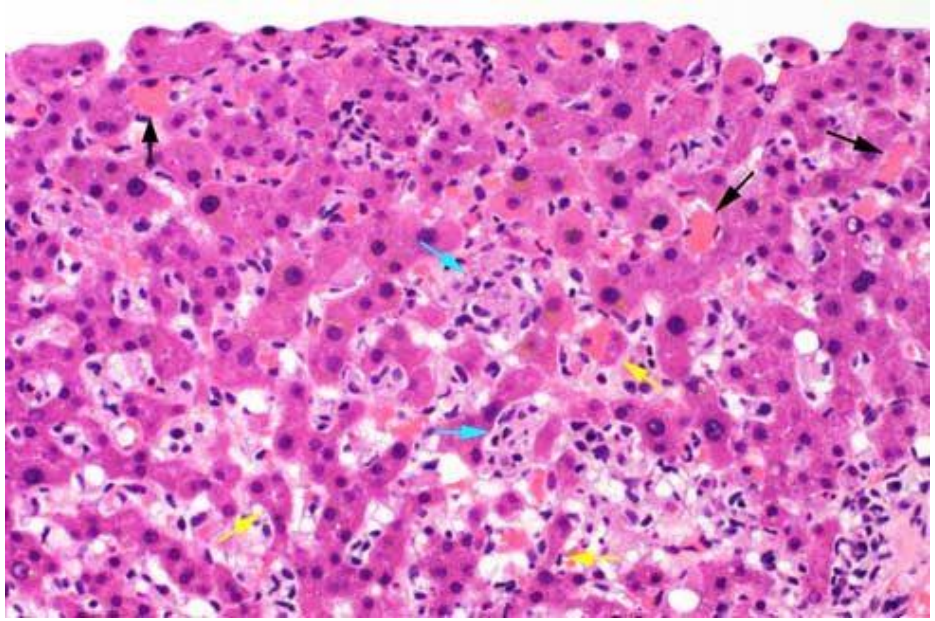
- In 2015, an outbreak of disseminated *M. chimaera* disease was described in European patients after undergoing open-heart surgery in which contaminated heater-cooler water units were used.
- High mortality
- Pathology:

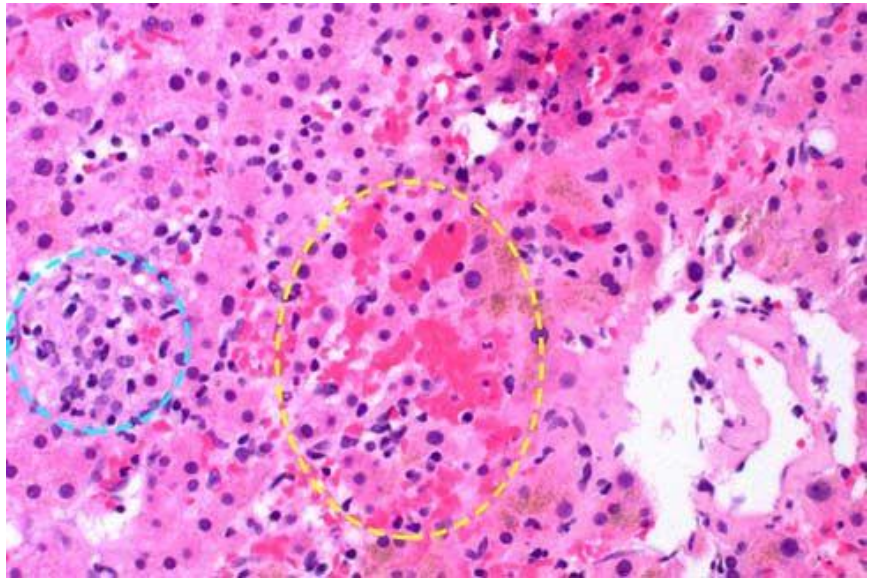
- small, ill-formed collections of sinusoidal histiocytes with rare multinucleated giant cells, and

- scattered architectural changes of venous outflow obstruction

American Journal of Surgical Pathology: October 22, 2018

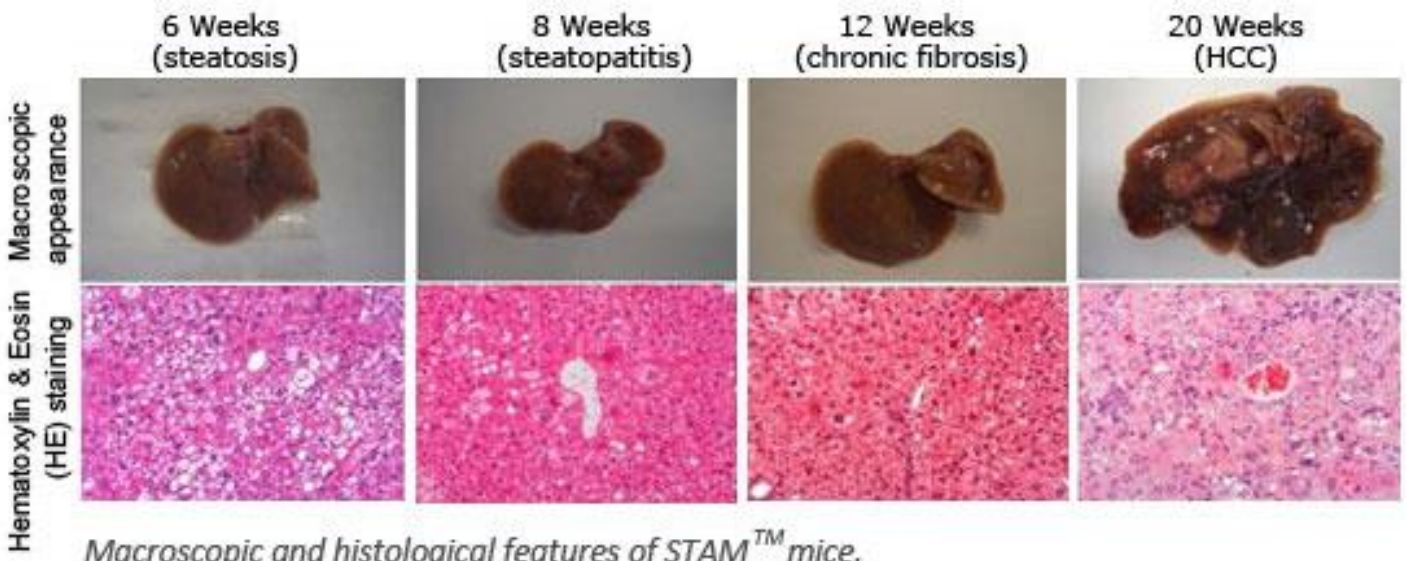
Mycobacterium chimaera Hepatitis





Fatty liver disease

Mouse models of liver disease



Macroscopic and histological features of STAM™ mice.
The mice develop steatosis at 6 weeks, steatohepatitis at 8 weeks, chronic fibrosis at 12 weeks and HCC at 20 weeks of age.

- “Among studies published in gastroenterology/hepatology journals, 53% provided a pathologist's analysis of NASH. This proportion was less (43–44%) in metabolism, pharmacology, and other journals”

- “some authors had “invented” their own version of NAS, misnaming it as the “NASH activity score,” or in some instances, eliminating the hepatocellular injury component conferred by scoring hepatocyte ballooning.”

Mouse models of non-alcoholic steatohepatitis: A reflection on recent literature. Journal of Gastroenterology and Hepatology, 33: 1312–1320.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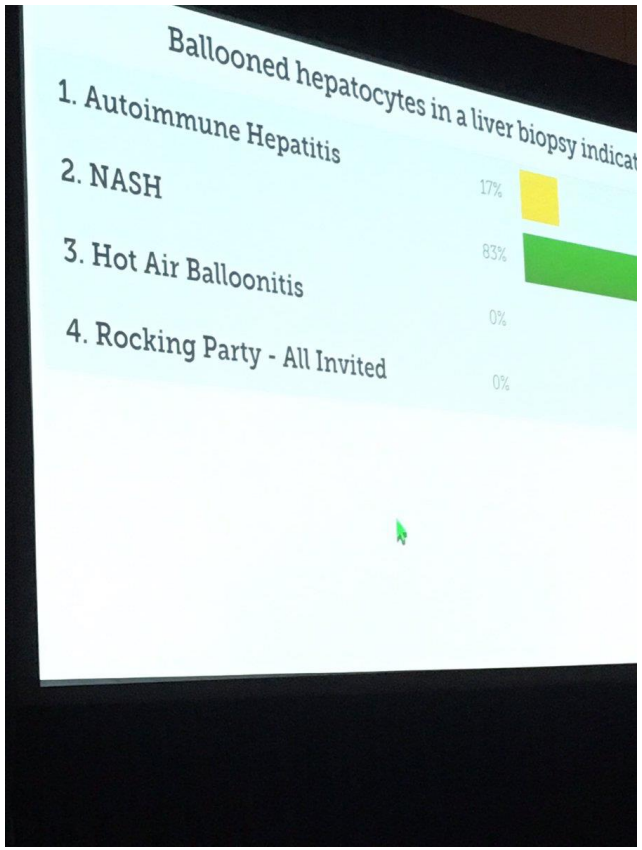
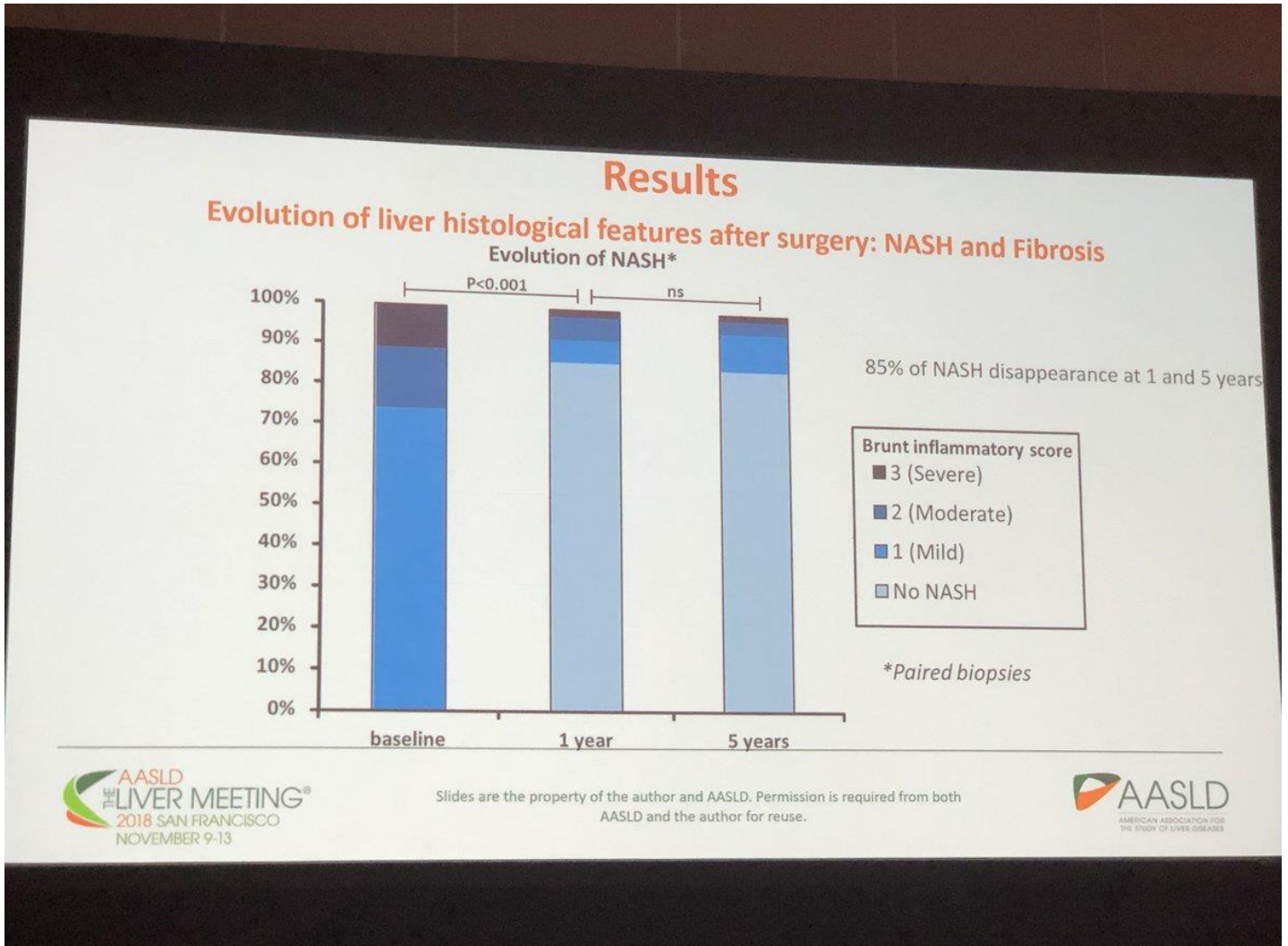
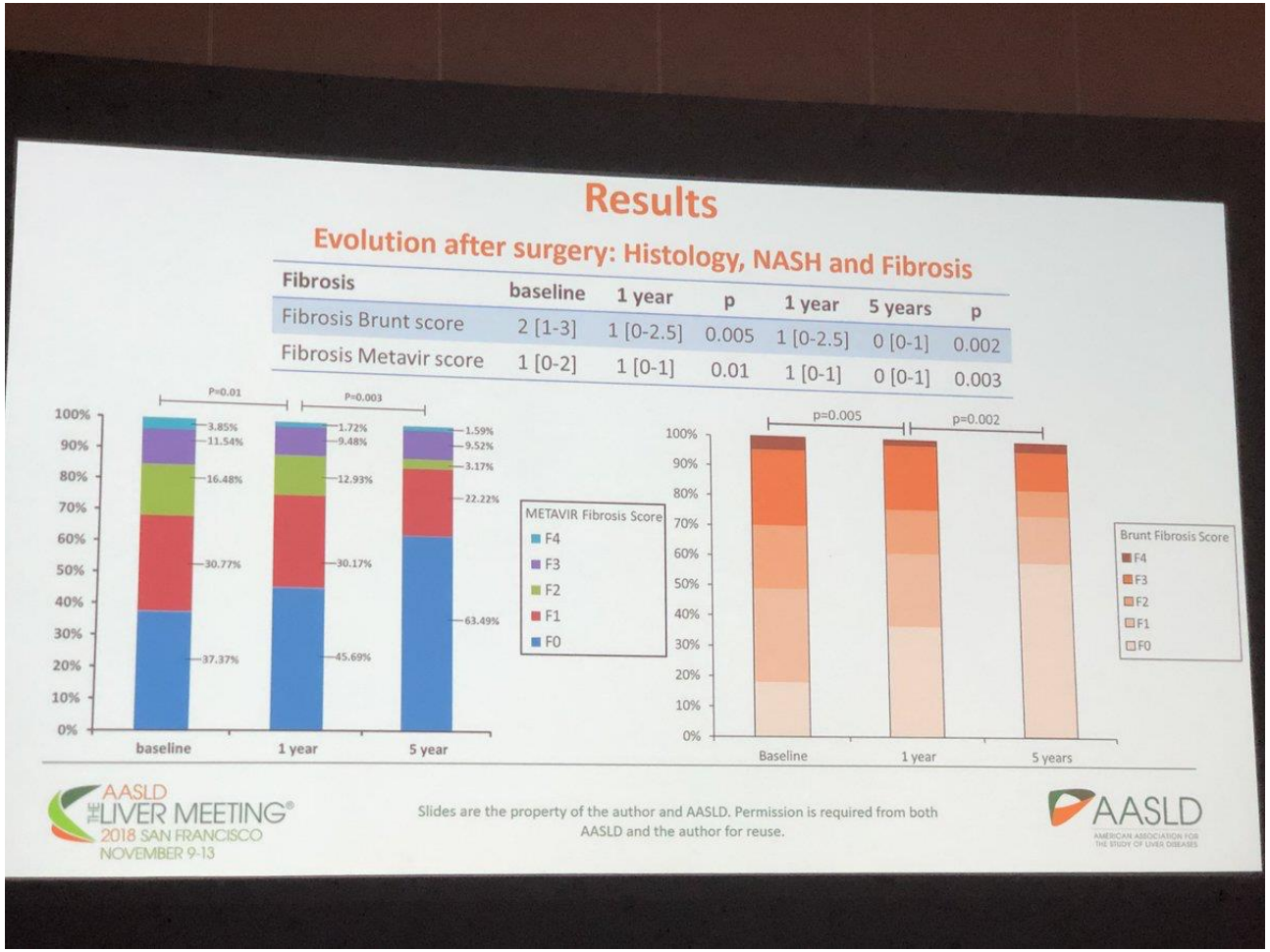

Ballooned hepatocytes in a liver biopsy indicat
1. Autoimmune Hepatitis
17%
2. NASH
83%
3. Hot Air Balloonitis
0%
4. Rocking Party - All Invited
0%

Response to bariatric surgery: Inflammation



Response to bariatric surgery: Fibrosis

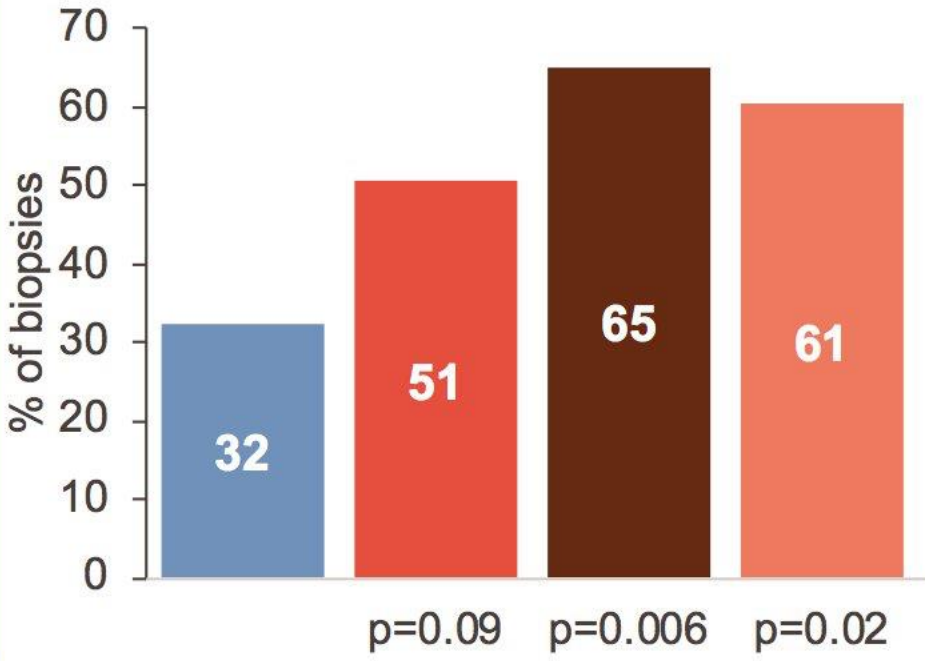


How do we assess the response to treatment?

2-Point NAS Reduction

with at least a 1-pt reduction in ballooning or inflammation

(% of liver biopsies)

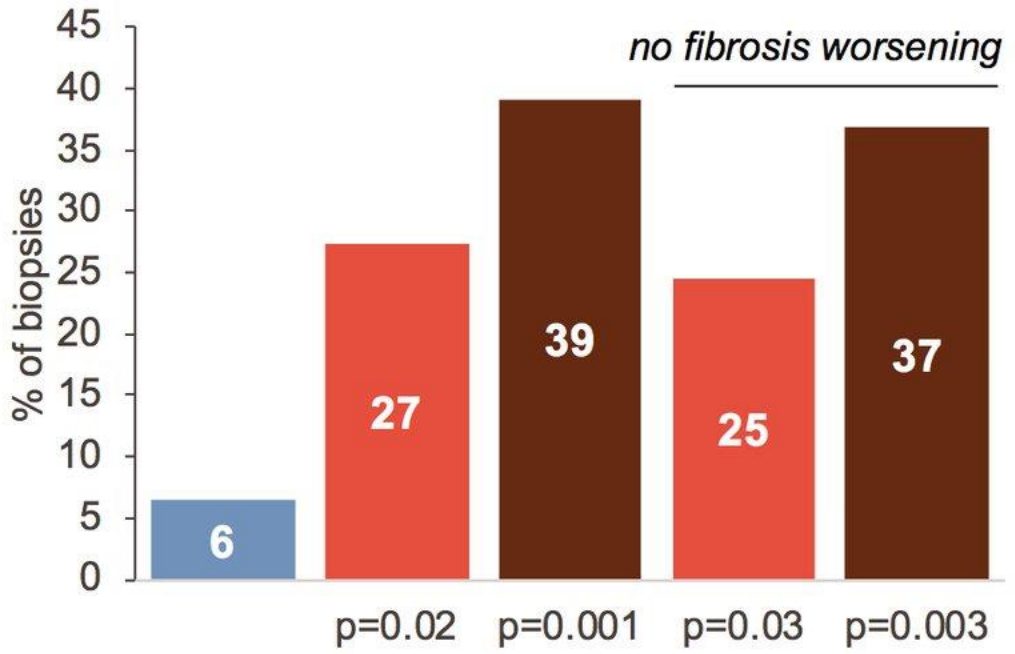


How do we assess the response to treatment?

NASH Resolution

ballooning=0, inflammation =0, 1 with at least 2-point reduction in NAS

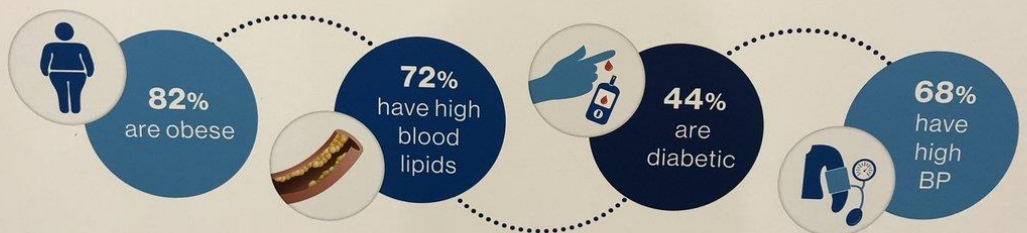
(% of liver biopsies)



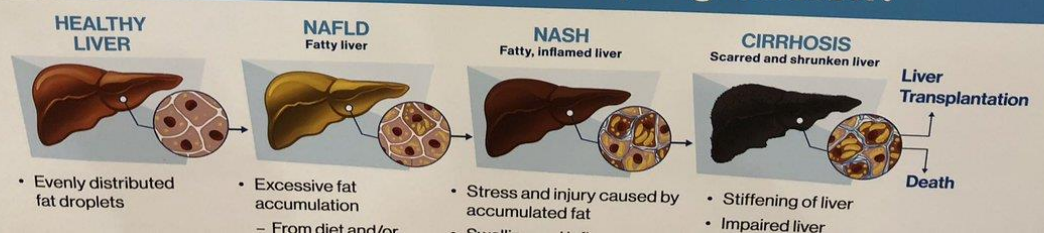
NASH is usually asymptomatic. It may progress to cirrhosis undetected. In symptomatic patients, symptoms vary from fatigue to discomfort in the upper right side of the abdomen.[3]

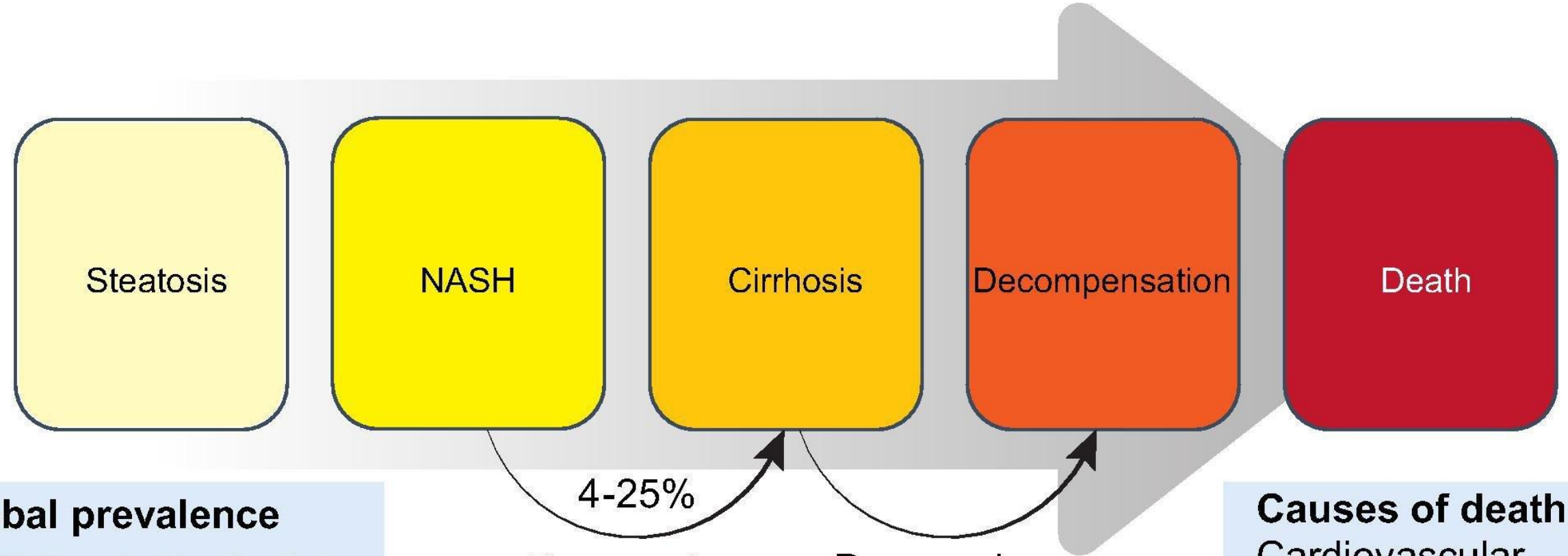
Is NASH a widespread disease?

The global prevalence of NAFLD is ~25% and the prevalence of NASH among NAFLD patients ranges from 10% to 59%. Moreover, out of the total patients diagnosed with NASH, approximately:[1,5]



What are the stages of NASH progression?[2]





Global prevalence

NAFLD: 25% of adults
Diabetes: 425 million
Obesity: 671 million
Overweight: 1.3 billion

Causes of death

Cardiovascular
Malignancy
Liver (1-2%)
HCC progression:
1% per year

Slow fibrosis progression rates in placebo-treated randomized controlled trial participants with NASH predict low rates of cirrhosis development.

Slow fibrosis progression in placebo-treated patients with NASH in RCTs predict low rates of cirrhosis

Aim:

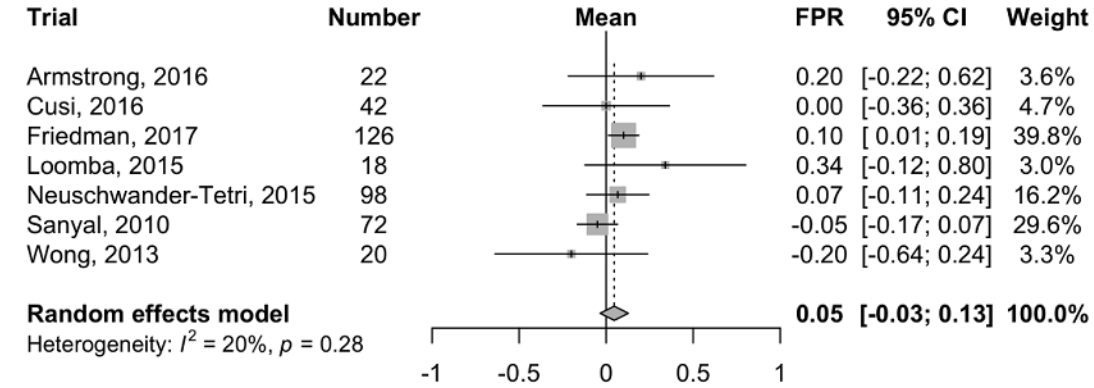
To estimate the proportion of individuals with NASH that will develop cirrhosis

Methods:

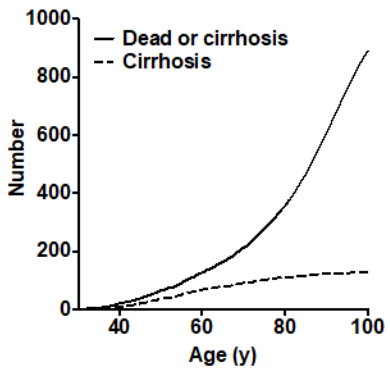
- Systematic review and meta-analysis of fibrosis progression rates (FPR) in placebo-treated participants in RCTs
- RCT FPR were used to model progression to cirrhosis in simulated 1000-patient populations
- Competing mortality from natural causes modelled to reflect increased mortality in patients with NASH

Conclusions:

Current natural history models of NASH may greatly overestimate rates of cirrhosis development



Pooled FPR 0.05 stages per year in low risk of bias RCTs



Roskilly A, et al., Abstract 33

- Fibrosis progression rates in placebo treated randomised controlled trial participants with NASH are significantly lower than in non-randomised repeat biopsy studies.
- In simulation models this predicts fewer than 1 in 25 individuals with NASH will develop cirrhosis in their lifetime, a 7-fold reduction in the proportion of individuals estimated to develop cirrhosis when compared with non-randomised studies.
- Current natural history models may overestimate the impact of NASH on the development of cirrhosis.

Non-Alcoholic Steatohepatitis Predicts Adverse Liver-Related Outcomes and Death in Chronic Hepatitis B Patients

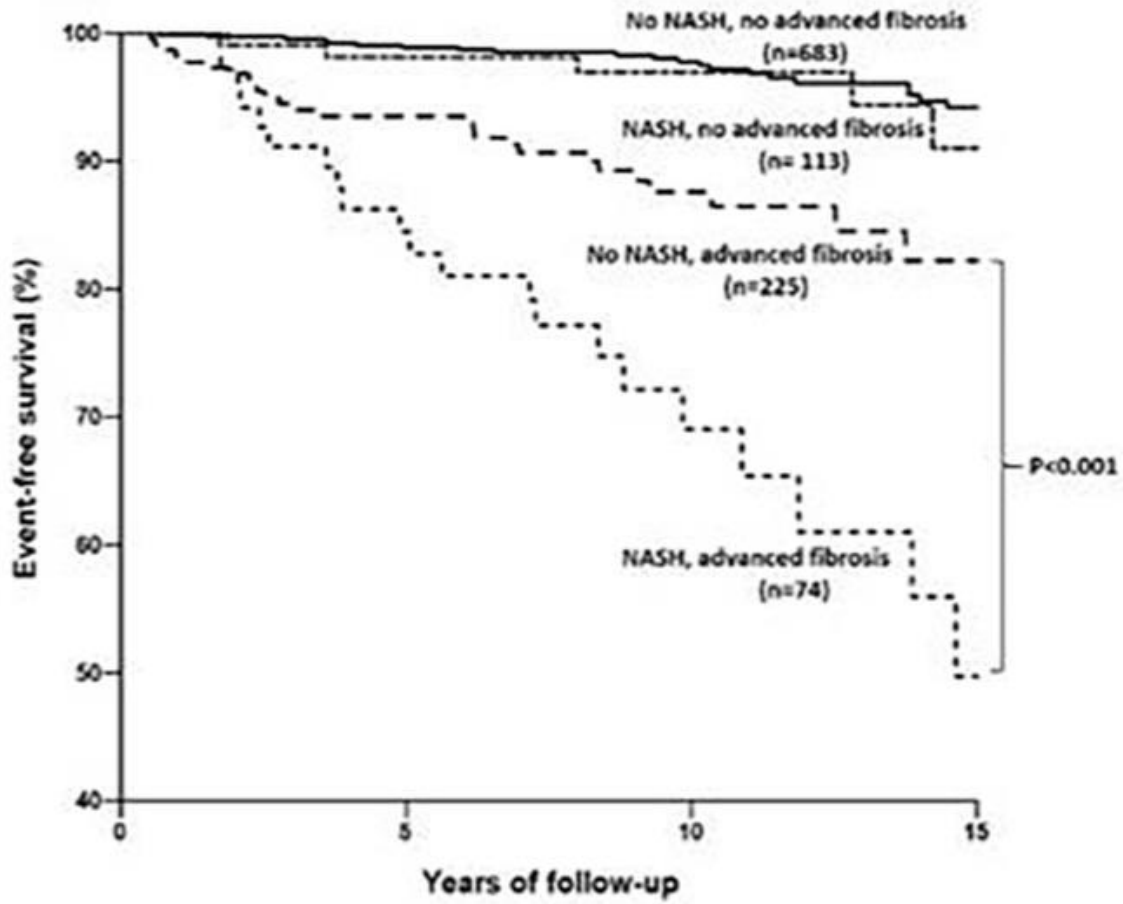
- patients with concomitant NASH and CHB had

more advanced fibrosis, and

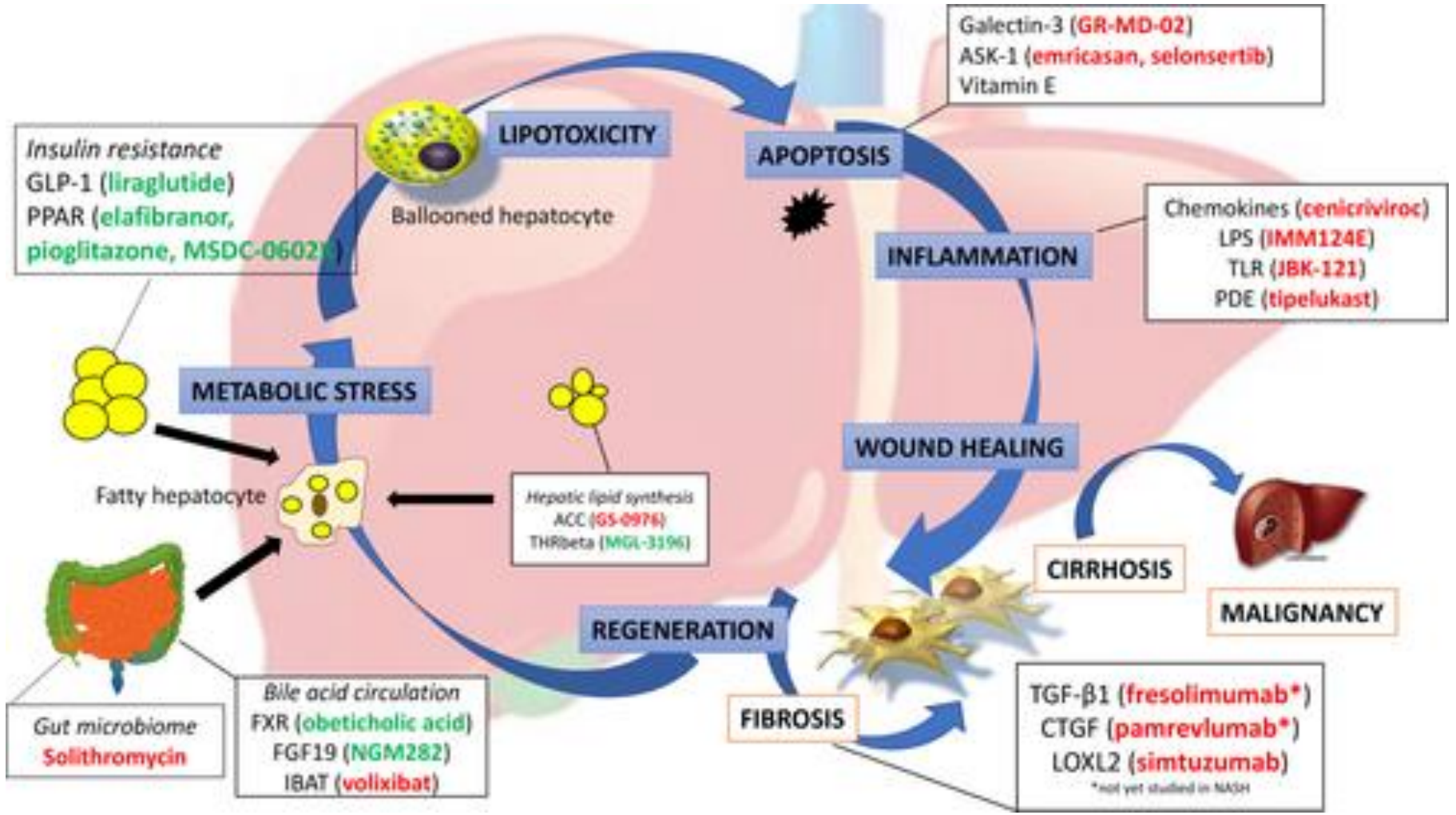
shorter time to development of liver-related outcomes or death.

- patients with advanced fibrosis, with superimposed NASH had

poorer clinical outcomes in our cohort.


No NASH, no advanced fibrosis
(n=683)
NASH, no advanced fibrosis
(n= 113)
No NASH, advanced fibrosis
(n=225)
NASH, advanced fibrosis
(n=74)
P<0.001
Event-free survival (%)
100
90
80
70
60
50
40
0
5
10
15
Years of follow-up

Disease pathways and molecular mechanisms of nonalcoholic steatohepatitis




Currently Available Interventions
AASLD NAFLD Guidance
• Pioglitazone only for patients with biopsy proven NASH
• Discuss risks and benefits
• Not recommended for patients without biopsy proven disease
• It is premature to consider GLP-1 agonists to specifically treat liver disease in patients with NASH
• Vitamin E may be considered for non diabetic adults with biopsy proven NASH
• Discuss risks and benefits
• Not recommended for diabetics, NALFD without biopsy or cirrhosis
• Other medications like UCDA and omega 3 fatty acids should not be used as a specific treatment for NAFLD
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Cancer

The incidence of malignancies in non-alcoholic fatty liver disease (NAFLD)

Aim:

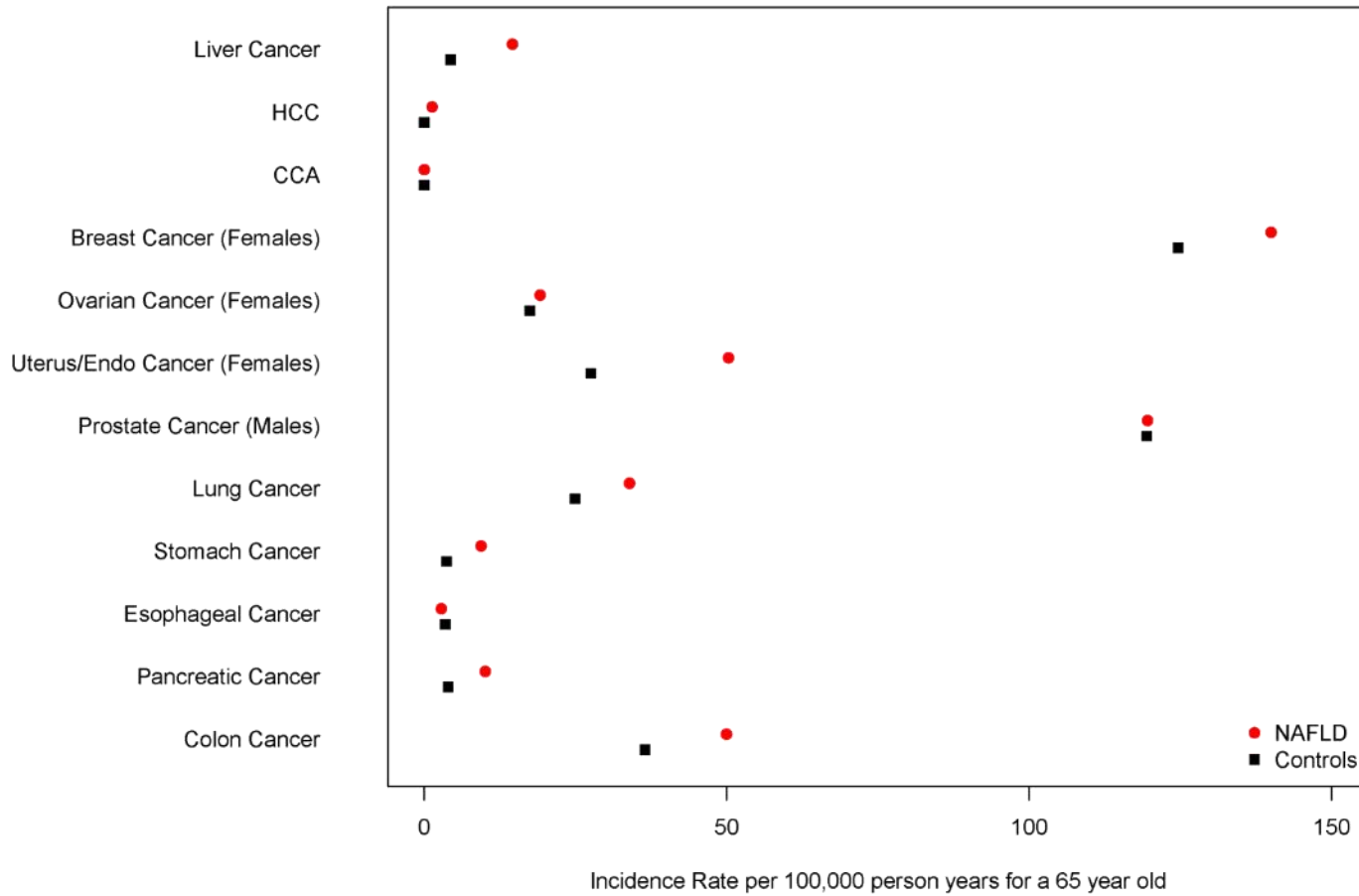
To determine the incidence of cancer diagnosis in NAFLD compared to controls in a U.S. community

Methods:

A community cohort of all adults diagnosed with NAFLD and age- and sex-matched controls in Olmsted County, Minnesota, between 1997 and 2014

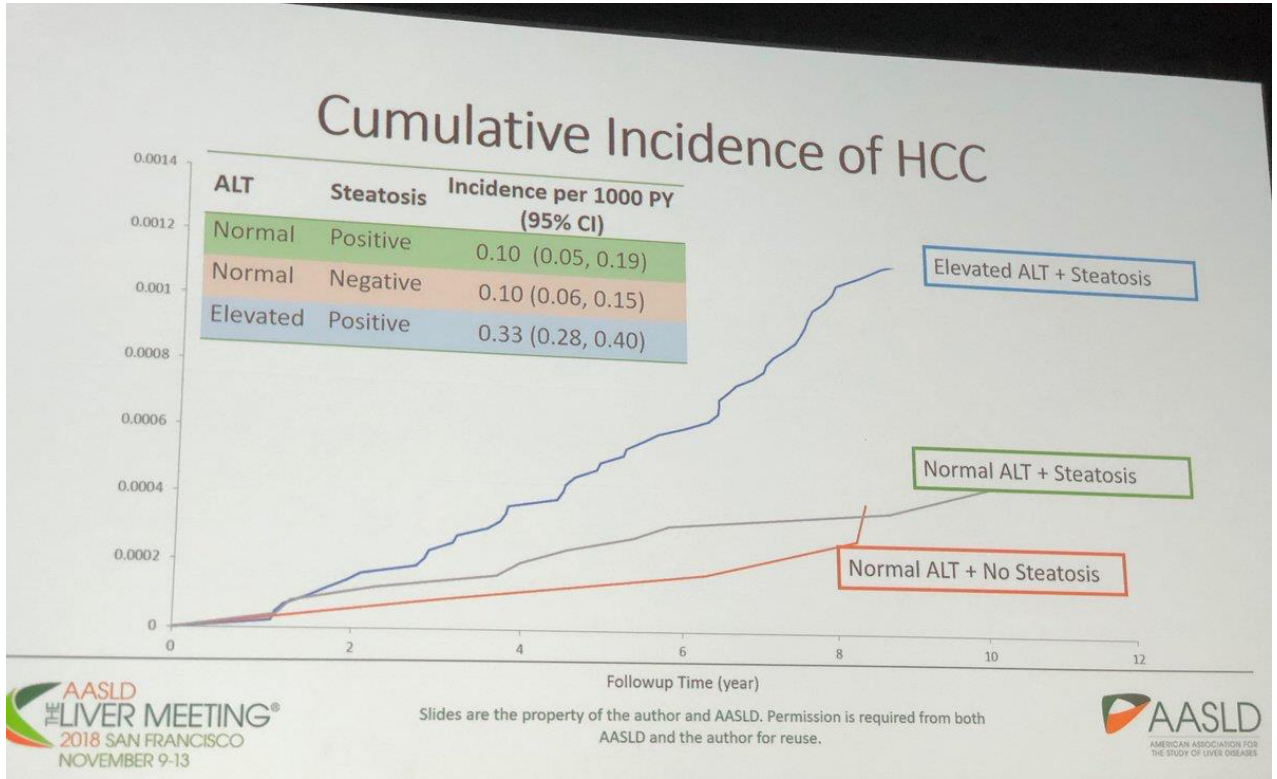
Conclusions:

The incidence of malignancy among NAFLD patients was higher than among controls across most types of cancers, with the largest relative increase noted in liver cancer, followed by stomach and pancreas.

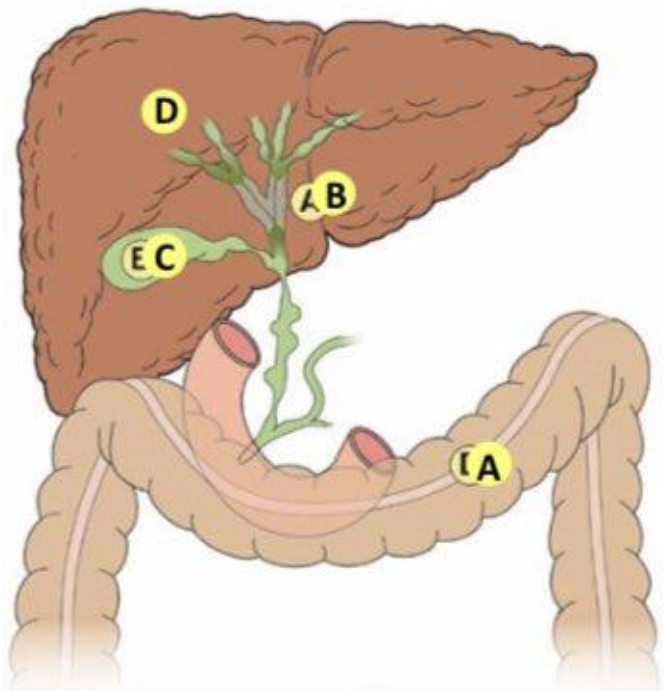


Allen A, et al., Abstract 31

Low risk of hepatocellular carcinoma in patients with NAFLD and normal ALTs in a cohort.



PSC: *A premalignant condition*



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A **Colorectal Cancer Associated with IBD (CRC)**
- 20 yr cumulative risk after IBD diagnosis ~6%
- PSC + IBD involving colon ↑ 10x vs ulcerative colitis

B **Cholangiocarcinoma (CCA)**
- 400 x ↑ risk vs general population
- ~10-15% may develop during disease course

C **Gallbladder cancer (GBC)**
- 1-4% lifetime risk

D **Hepatocellular Carcinoma (HCC)**
- Most series ≤2% even among those with cirrhosis

Weismuller TJ, et al. Gastroenterology 2017; Boonstra K, et al. Hepatology 2013; Beuers U, et al. J Hepatol 2009; Zenouzi R, et al. Clin Gastroenterol Hepatol 2014; Harnois DS, et al. J Hepatol 1994 .

Molecular classification and potential therapeutic targets in extrahepatic cholangiocarcinoma (eCCA)

Aims:

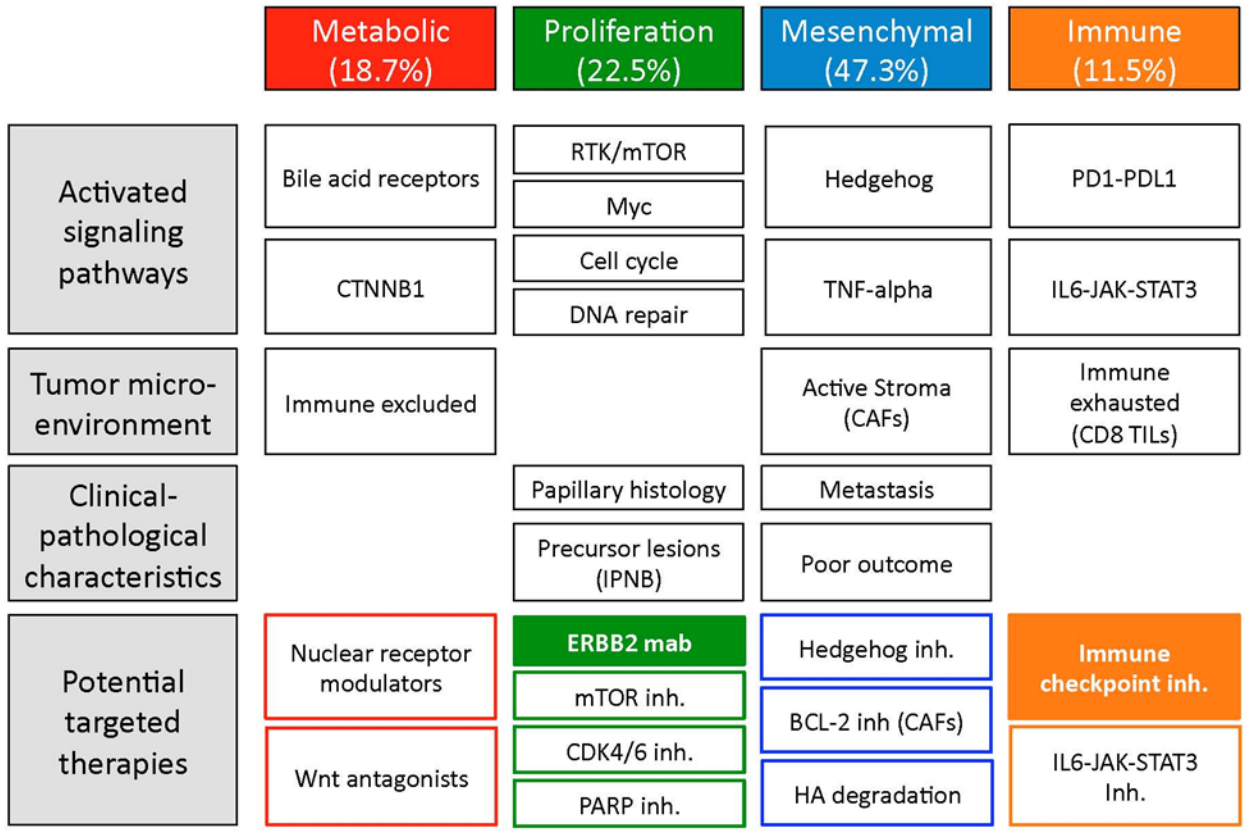
- Provide a molecular classification of eCCA.
- Define the landscape of genomic aberrations in eCCA.
- Translate the molecular features of eCCA into the clinic.

Methods:

- A total of 189 FFPE primary eCCA treated by resection were retrospectively collected at 7 international centers.
- Whole gene expression profiling was performed and data was submitted to unsupervised clustering by NMF consensus.

Conclusions:

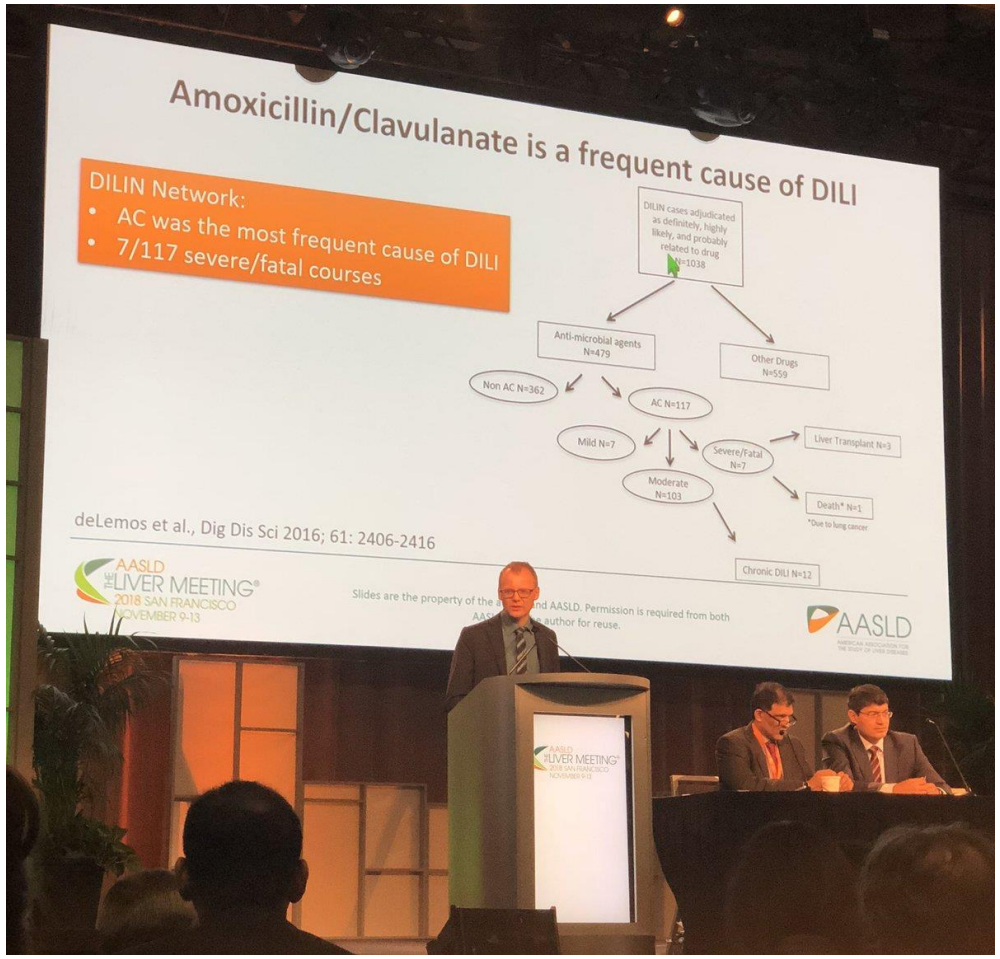
- Transcriptome-based classification of eCCA identifies four distinct molecular subtypes that correlate with clinico-pathological characteristics.

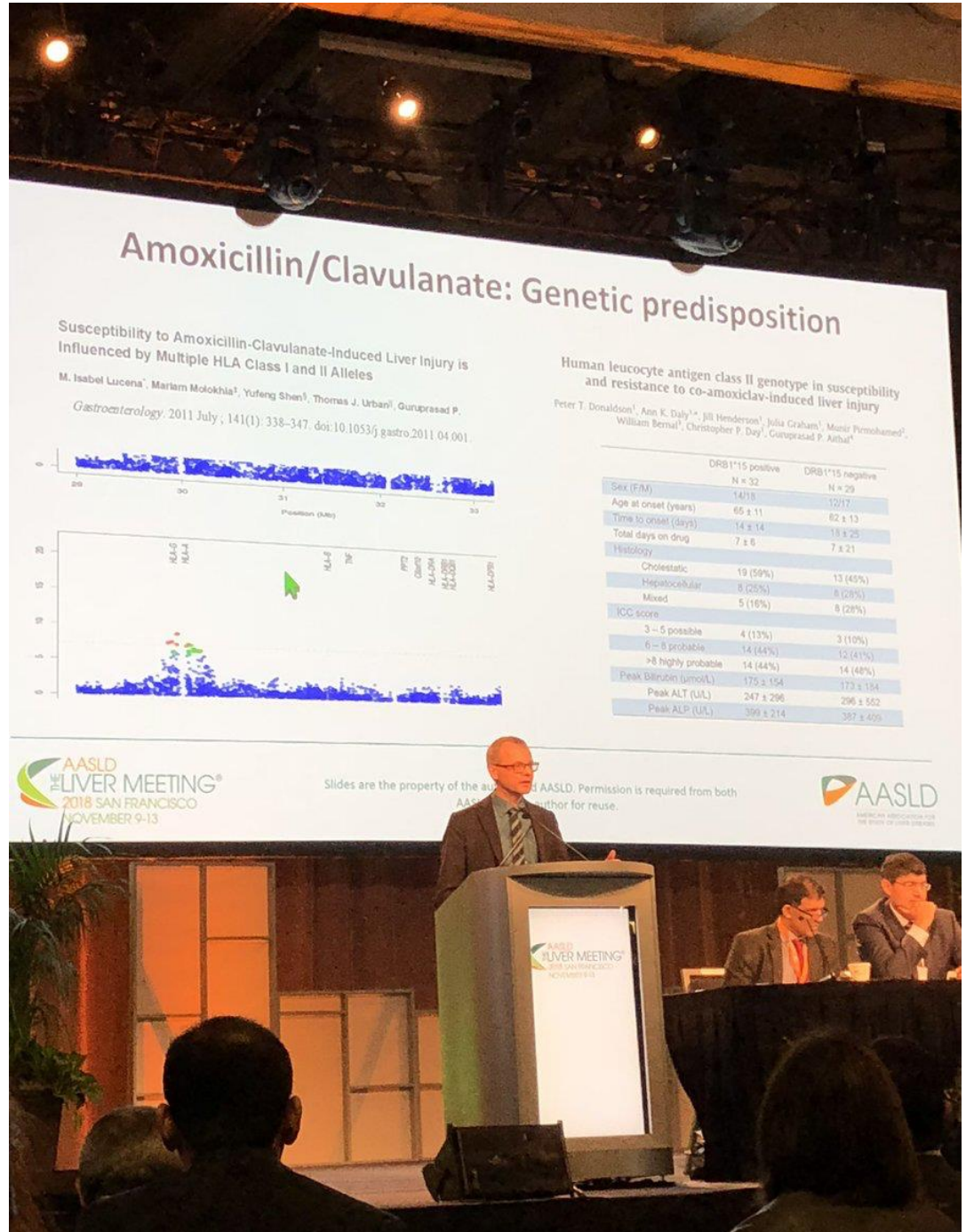


Montal R, et al., Abstract 28.

Drugs

What is the most common cause of Drug Induced Liver Injury? Amoxicillin-Clavulanate! What is mechanism? Thought to be immune-mediated!




Amoxicillin/Clavulanate: Genetic predisposition
Susceptibility to Amoxicillin-Clavulanate-Induced Liver Injury is Influenced by Multiple HLA Class I and II Alleles
M. Isabel Lucena, Mariam Molokhia, Yufeng Shen, Thomas J. Urban, Guruprasad P.
Gastroenterology. 2011 July ; 141(1): 338–347. doi:10.1053/j.gastro.2011.04.001.
Human leucocyte antigen class II genotype in susceptibility and resistance to co-amoxiclav-induced liver injury
Peter T. Donaldson, Ann K. Daly, Jill Henderson, Julia Graham, Munir Pirmohamed, William Bernal, Christopher P. Day, Guruprasad P. Aithal
DRB1*15 positive N = 32
DRB1*15 negative N = 29
Sex (F/M) 14/18 12/17
Age at onset (years) 65 ± 11 62 ± 13
Time to onset (days) 14 ± 14 18 ± 25
Total days on drug 7 ± 6 7 ± 21
Histology
Cholestatic 19 (59%) 13 (45%)
Hepatocellular 8 (25%) 8 (28%)
Mixed 5 (16%) 8 (28%)
ICC score
3 – 5 possible 4 (13%) 3 (10%)
6 – 8 probable 14 (44%) 12 (41%)
>8 highly probable 14 (44%) 14 (48%)
Peak Bilirubin (μmol/L) 175 ± 154 173 ± 184
Peak ALT (U/L) 247 ± 296 296 ± 552
Peak ALP (U/L) 399 ± 214 387 ± 409
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Clinically Significant Hepatotoxicity Due to Immune Checkpoint Inhibitors Is Rare but Leads to Treatment Discontinuation in a High Proportion

- During the study period, 5,762 patients received ICIs; 1.7% exhibited either moderate or severe ICI-HT.
- Among ICI recipients, clinically significant ICI-HT was rare but led to permanent discontinuation of ICI treatment in the majority (69%) of cases.
- ICI-HT was not associated with liver failure, presumably due to prompt recognition and management.
- Combination of CTLA-4 and PD-1/L-1 was not associated with more severe HT.
- Patients with underlying liver disease did not appear to be at higher risk for more severe ICI-HT.

The future?

A Genomic Approach to Idiopathic Liver Disease in Adults: New Insights into Disease Pathogenesis and New Interventions at Bedside

Whole exome sequencing led to a diagnosis in 5 of 19 cases (26%), identifying four monogenic disorders in five unrelated individuals, with an impact in patient's management beyond family counselling in nearly all diagnosed cases.

Example

A 32 year-old female was found to suffer from undiagnosed familial partial lipodystrophy type 3 for 18 years.

Knowledge of genotype led to initiation of leptin replacement therapy 13 months ago with subsequent normalization of liver transaminases and substantial decrease in triglycerides level and daily insulin requirements.


I'M A LIVER
NOT A FIGHTER