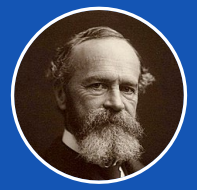
Swiss Re

Hepatic Diseases

Nicola Charlton MD MPH DBIM, R&D

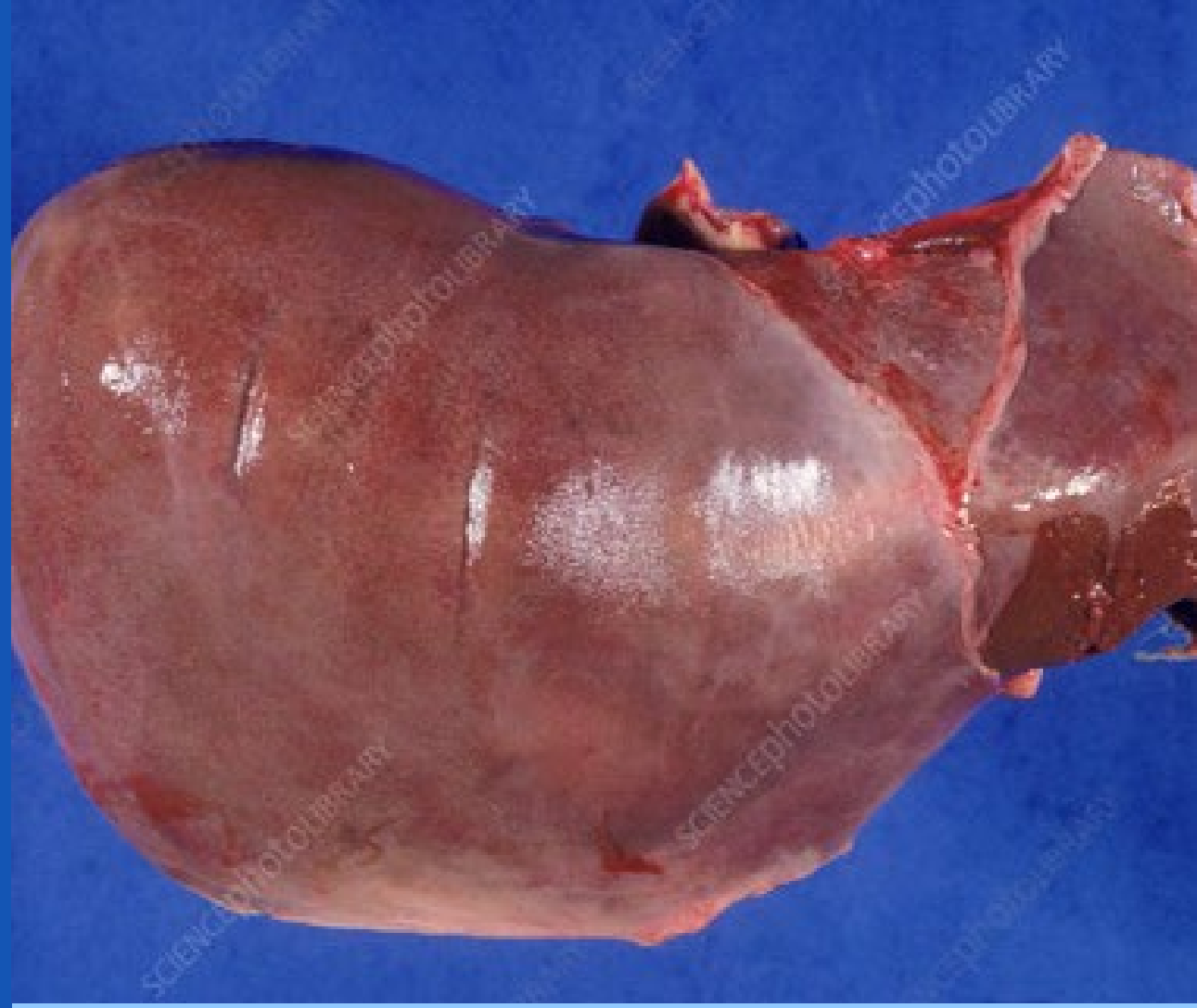
Is life worth living? It all depends on the liver.



William James

Liver– Pathophysiology

The largest organ in the body ,responsible for toxin breakdown and neutralization, energy regulation, energy storage, produces immune system components, creates proteins, breakdown old red blood cells, makes Bile which help with food breakdown. Only organ known to regenerate itself



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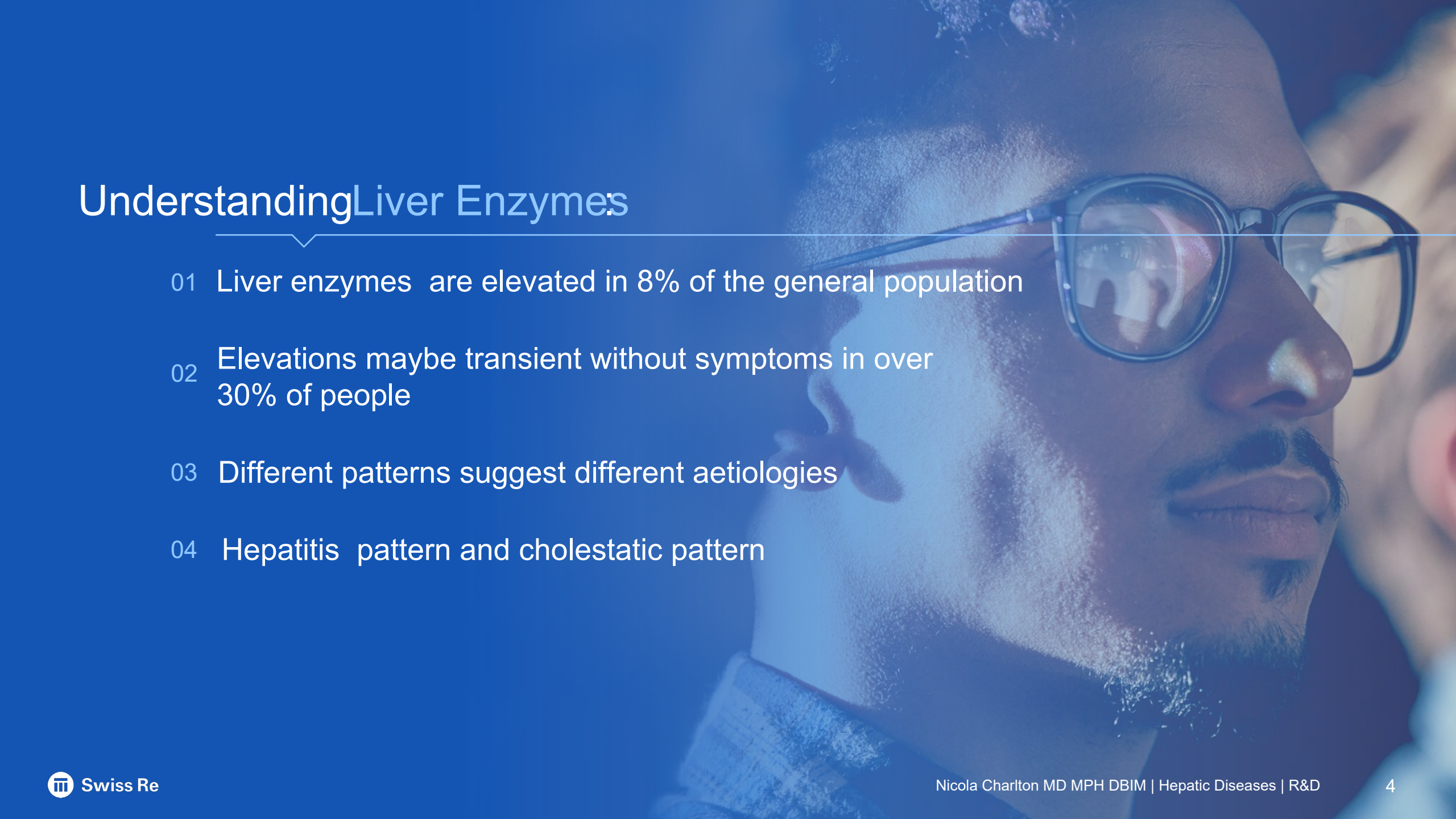
Understanding Liver Enzymes:

01 Liver enzymes are elevated in 8% of the general population

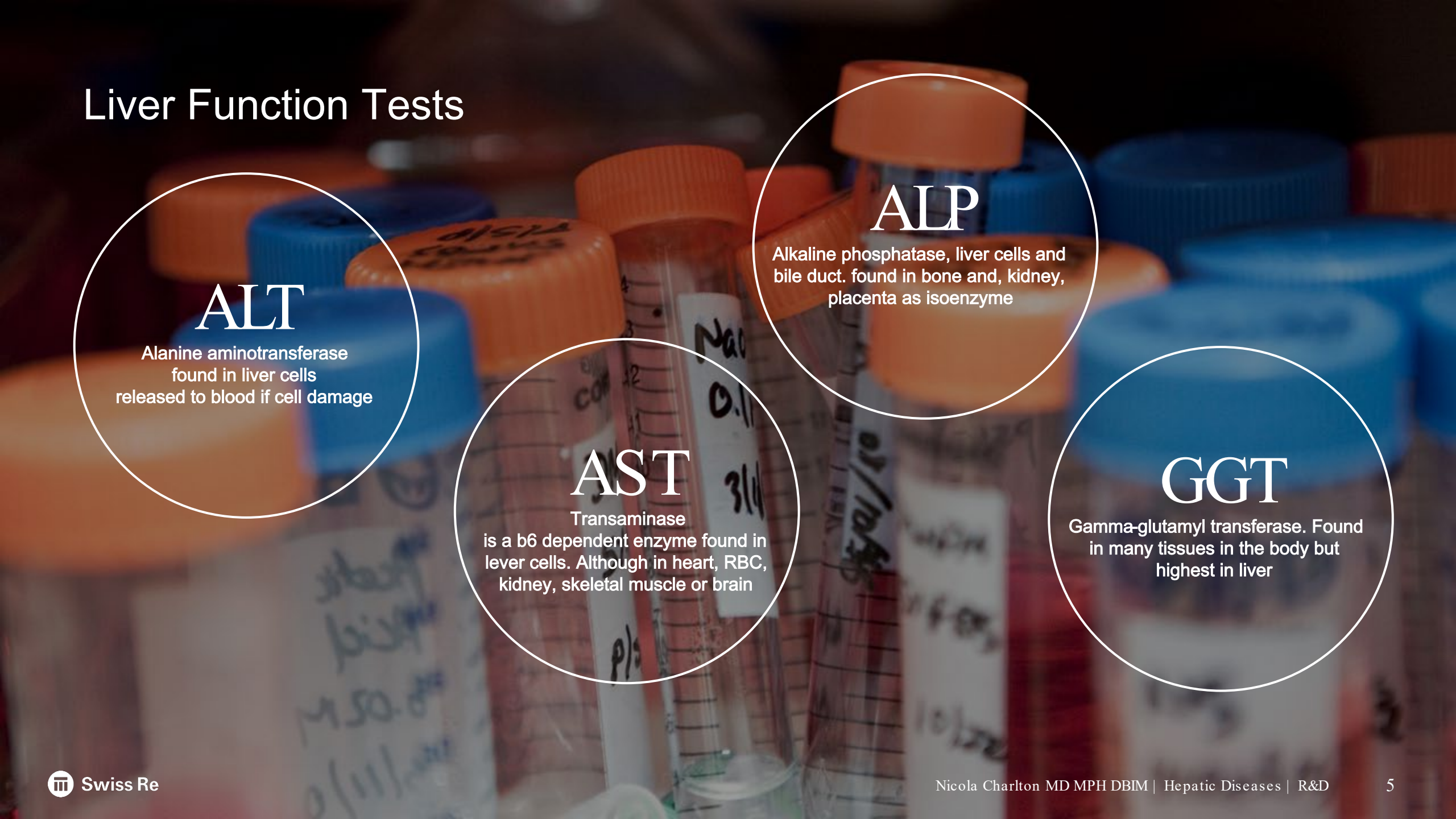
02 Elevations maybe transient without symptoms in over 30% of people

03 Different patterns suggest different aetiologies

04 Hepatitis pattern and cholestatic pattern



Liver Function Tests



ALT

Alanine aminotransferase
found in liver cells
released to blood if cell damage

ALP

Alkaline phosphatase, liver cells and bile duct. found in bone and, kidney, placenta as isoenzyme

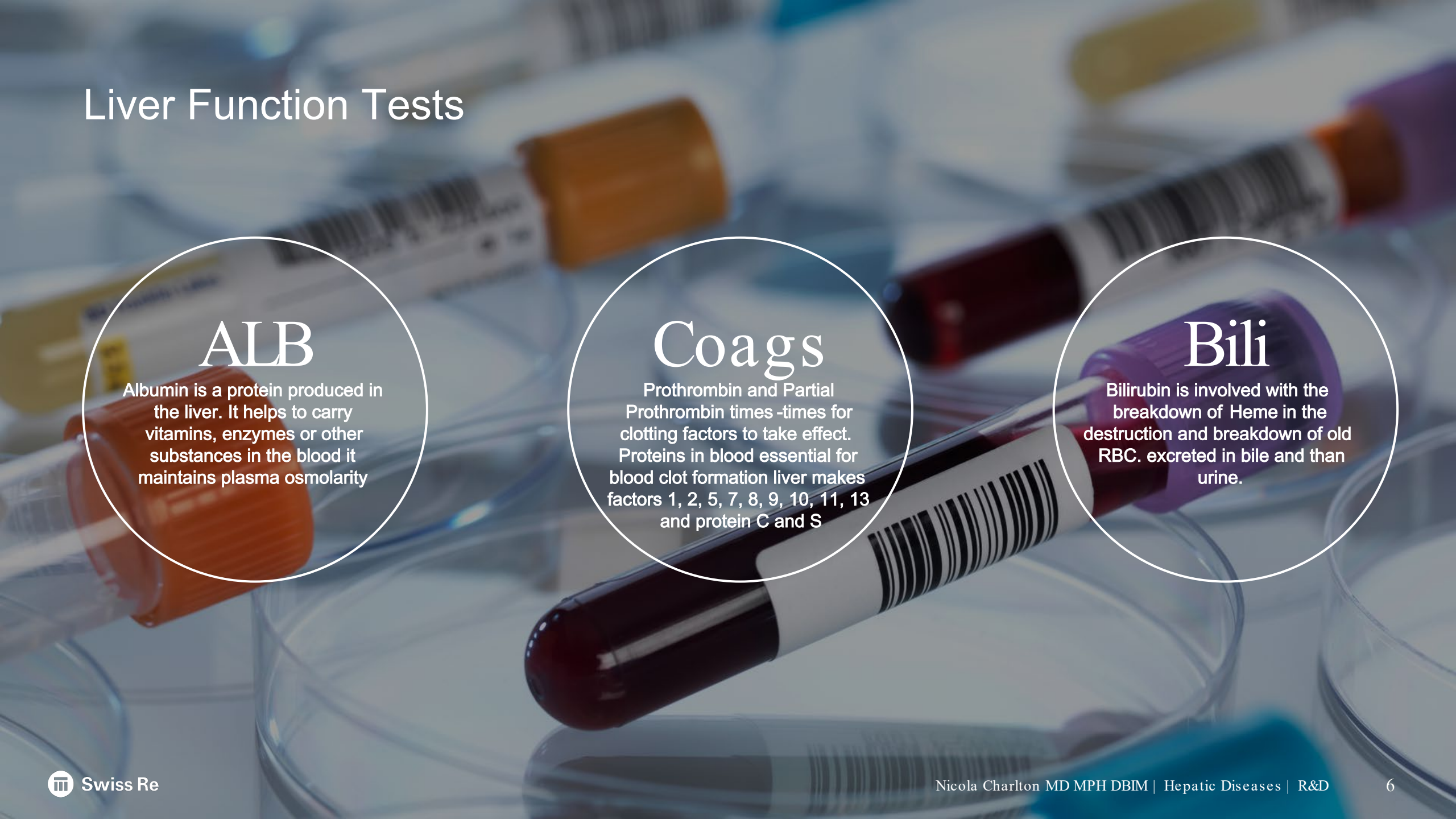
AST

Transaminase
is a b6 dependent enzyme found in lever cells. Although in heart, RBC, kidney, skeletal muscle or brain

GGT

Gamma-glutamyl transferase. Found in many tissues in the body but highest in liver

Liver Function Tests



ALB

Albumin is a protein produced in the liver. It helps to carry vitamins, enzymes or other substances in the blood it maintains plasma osmolarity

Coags

Prothrombin and Partial Prothrombin times -times for clotting factors to take effect. Proteins in blood essential for blood clot formation liver makes factors 1, 2, 5, 7, 8, 9, 10, 11, 13 and protein C and S

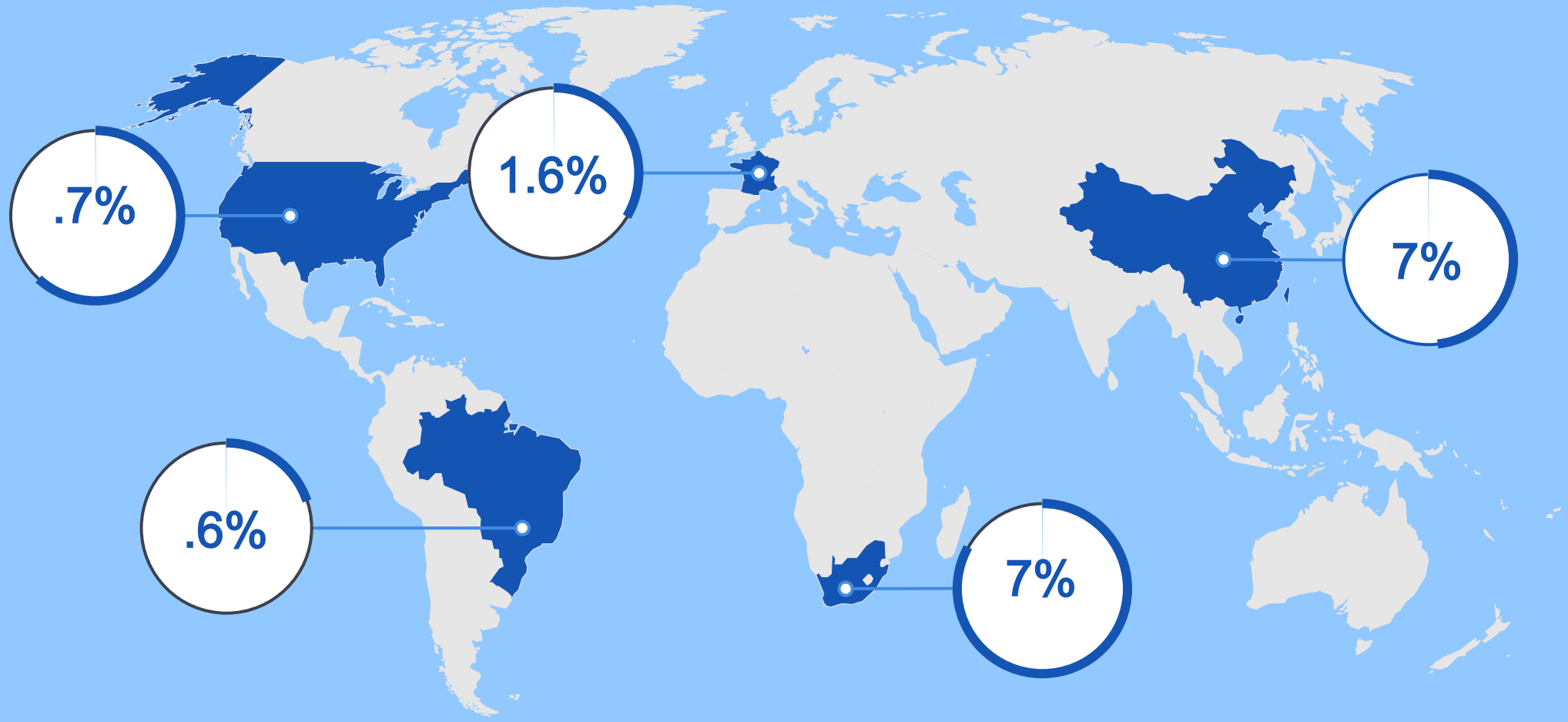
Bili

Bilirubin is involved with the breakdown of Heme in the destruction and breakdown of old RBC. excreted in bile and than urine.

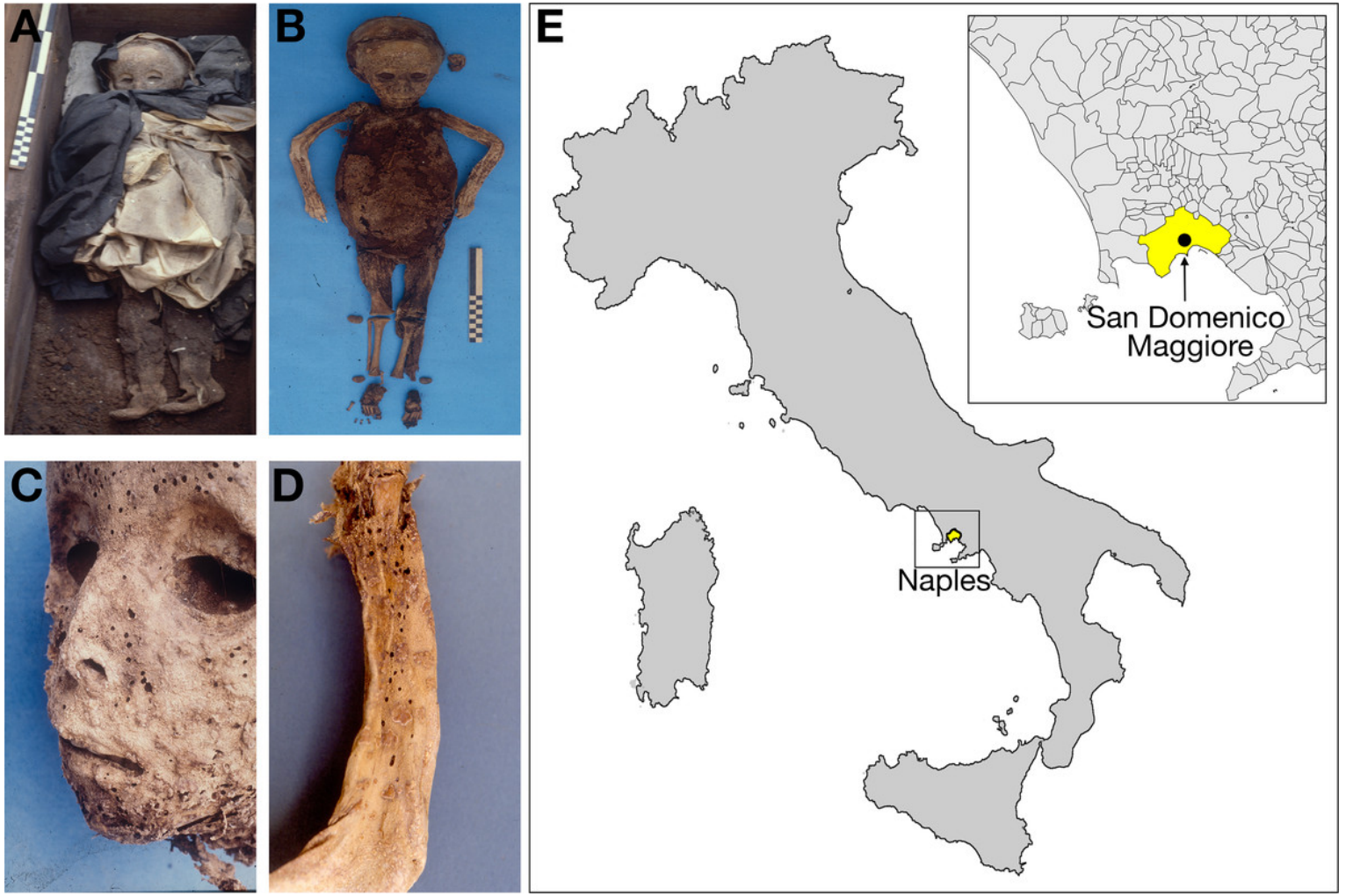
Hepatitis


GI illness
no chronic state
vaccine preventable
blood borne
½ developed chronic infection
drinking contaminated water
or milk
undercooked vegetables,
shellfish
Hepatitis A
Hepatitis B
Hepatitis C
Hepatitis D
Hepatitis E
acute and chronic infection
vaccine preventable
causes cirrhosis and liver
cancer
infected blood
occurs in those with a
Hepatitis B infection
HVB-HVD most severe form of
chronic hepatitis

Hepatitis B Prevalence 1B infected Globally

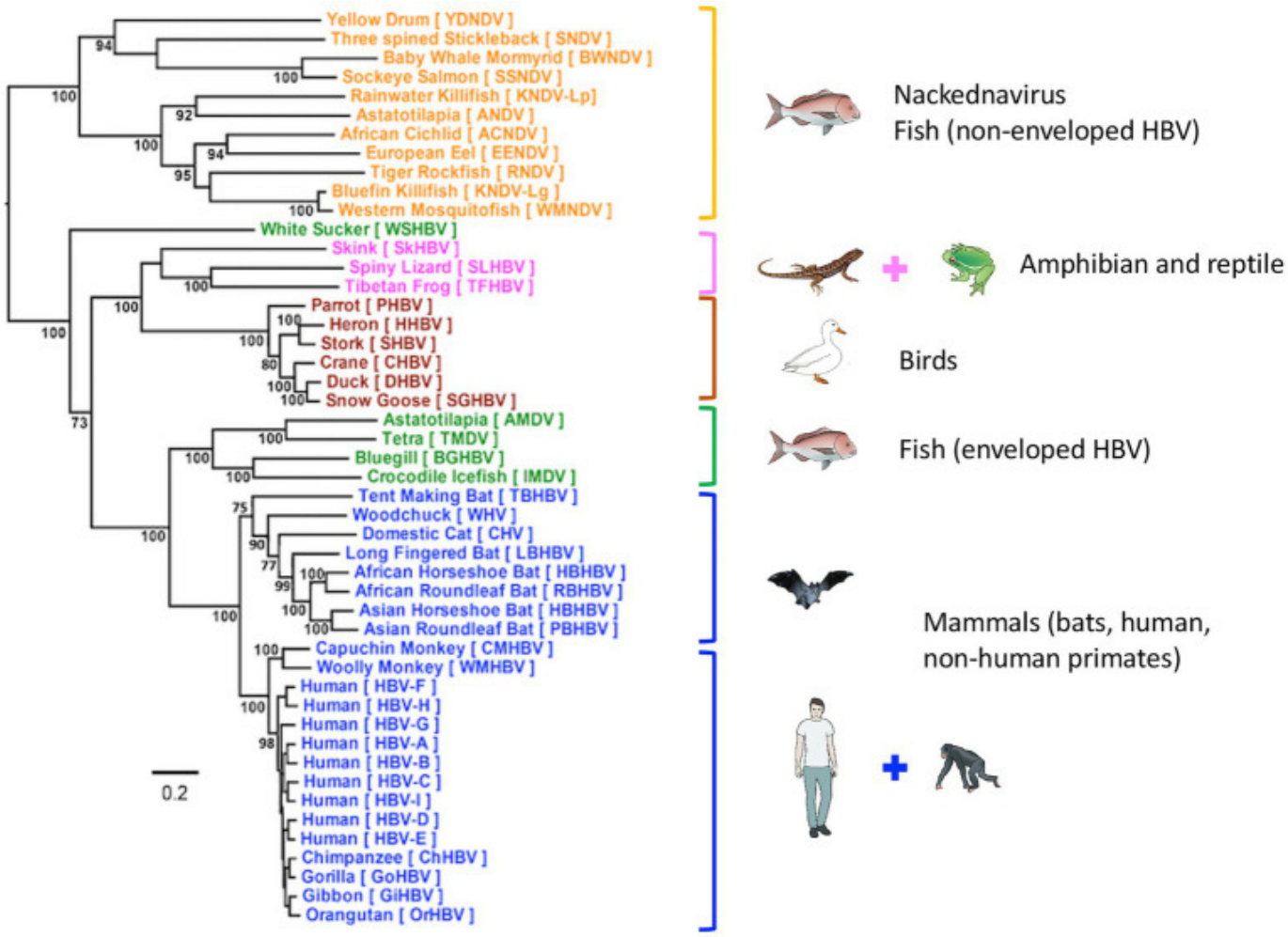


Mummy: Overwhelming infection Hepatitis B

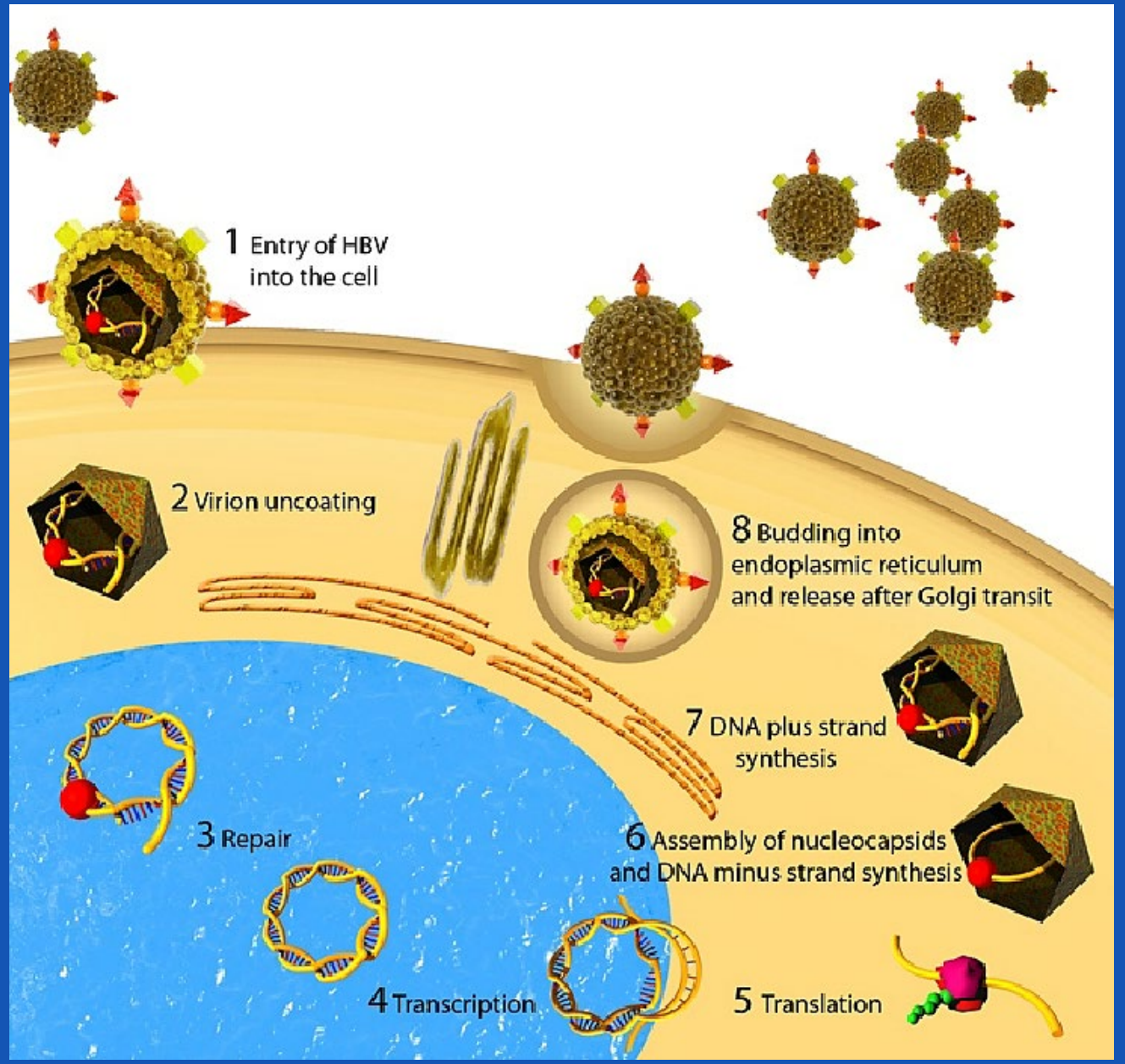


Evolution of Hepatitis B

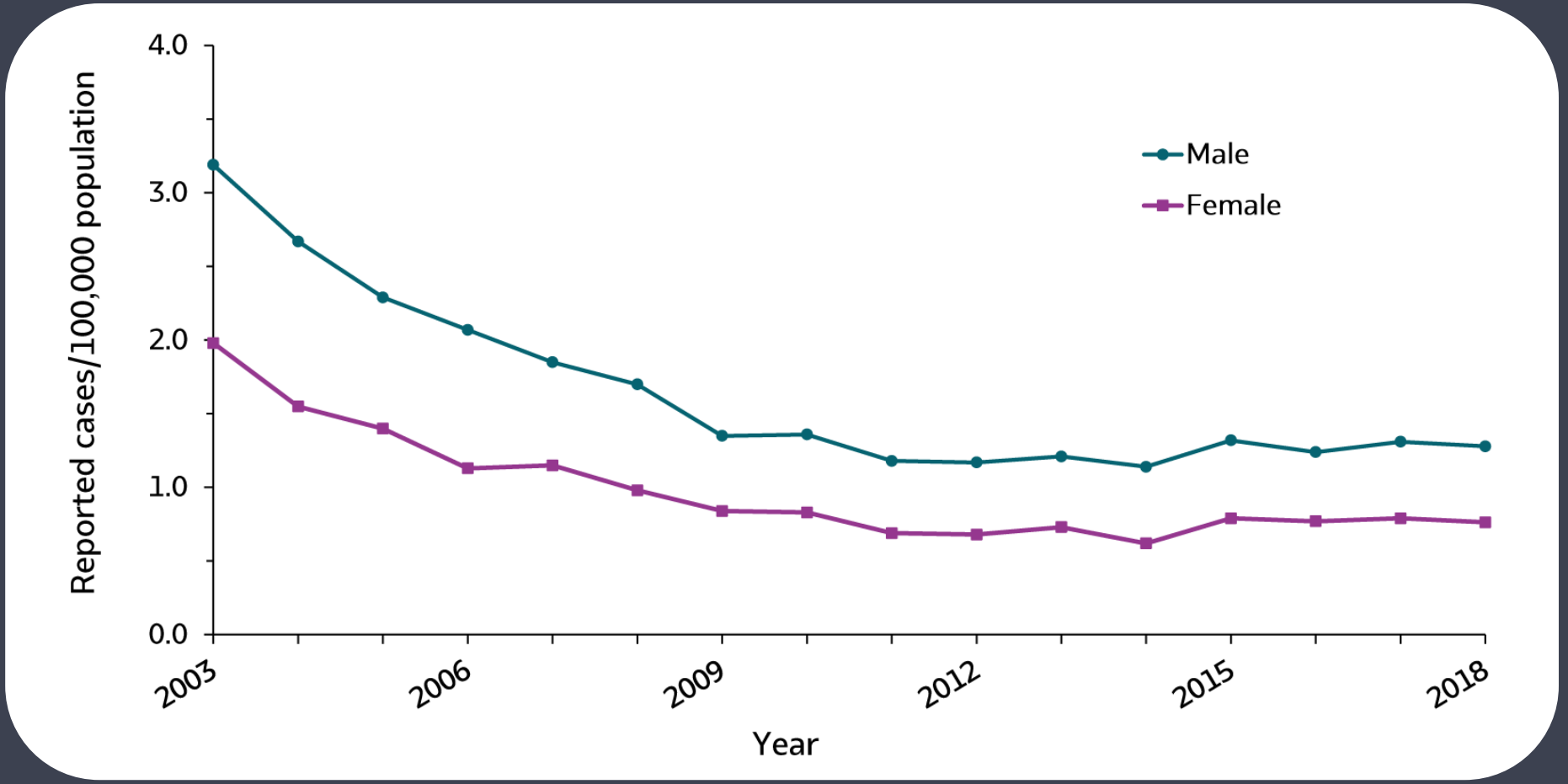
- Recent discovery of ancient HBV sequences in fossilized remains of humans dating back to the Neolithic period around 7,000 years ago.
- Metagenomic analysis identified a number of African non-human primate HBV sequences in the oldest samples collected, indicating that human HBV may have at some stage, evolved in Africa following zoonotic transmissions from higher primates and moved out to other areas of the world



Lifecycle of Hepatitis B



Hepatitis B: CDC



Hepatitis B

- Hepatitis B 5 -10% adults,30% -50% children and 90% babies do not clear viral infection,
- 100x more infective than HIV
- HBV over 1M deaths a year globally
- 5,000 -6,000 chronic liver disease from HBV
- Vaccine preventable

Common serologic patterns in hepatitis B virus infection and their interpretation.

HBsAg	Anti-HBs	Anti-HBc	HBeAg	Anti-HBe	Interpretation
+	–	IgM	+	–	Acute hepatitis B
+	–	IgG[1]	+	–	Chronic hepatitis B with active viral replication
+	–	IgG	–	+	Inactive HBV carrier state (low HBV DNA level) or HBeAg-negative chronic hepatitis B with active viral replication (high HBV DNA level)
+	+	IgG	+ or –	+ or –	Chronic hepatitis B with heterotypic anti-HBs (about 10% of cases)
–	–	IgM	+ or –	–	Acute hepatitis B
–	+	IgG	–	+ or –	Recovery from hepatitis B (immunity)
–	+	–	–	–	Vaccination (immunity)
–	–	IgG	–	–	False-positive; less commonly, infection in remote past

[1]Low levels of IgM anti-HBc may also be detected.

Source : Current Medical Diagnosis and Treatment 2018

Changing Classification

Chronic hepatitis B	HBeAg positive		HBeAg negative		
	Phase 1	Phase 2	Phase 3	Phase 4	Phase 5
Chronic HBV infection	Chronic HBV infection	Chronic hepatitis B	Chronic HBV infection	Chronic hepatitis B	Resolved HBV infection
HBsAg	High	High/ intermediate	Low	Intermediate	Negative
HBeAg	Positive	Positive	Negative	Negative	Negative
HBV DNA	>10^7 IU/mL	10^4–10^7 IU/mL	<2,000 IU/mL*	>2,000 IU/mL	<10 IU/mL‡
ALT	Normal	Elevated	Normal	Elevated†	Normal
Liver disease	None/minimal	Moderate/ severe	None	Moderate/ severe	None§
Old terminology	Immune tolerant	Immune reactive HBeAg positive	Inactive carrier	HBeAg negative chronic hepatitis	HBsAg negative /anti-HBc positive

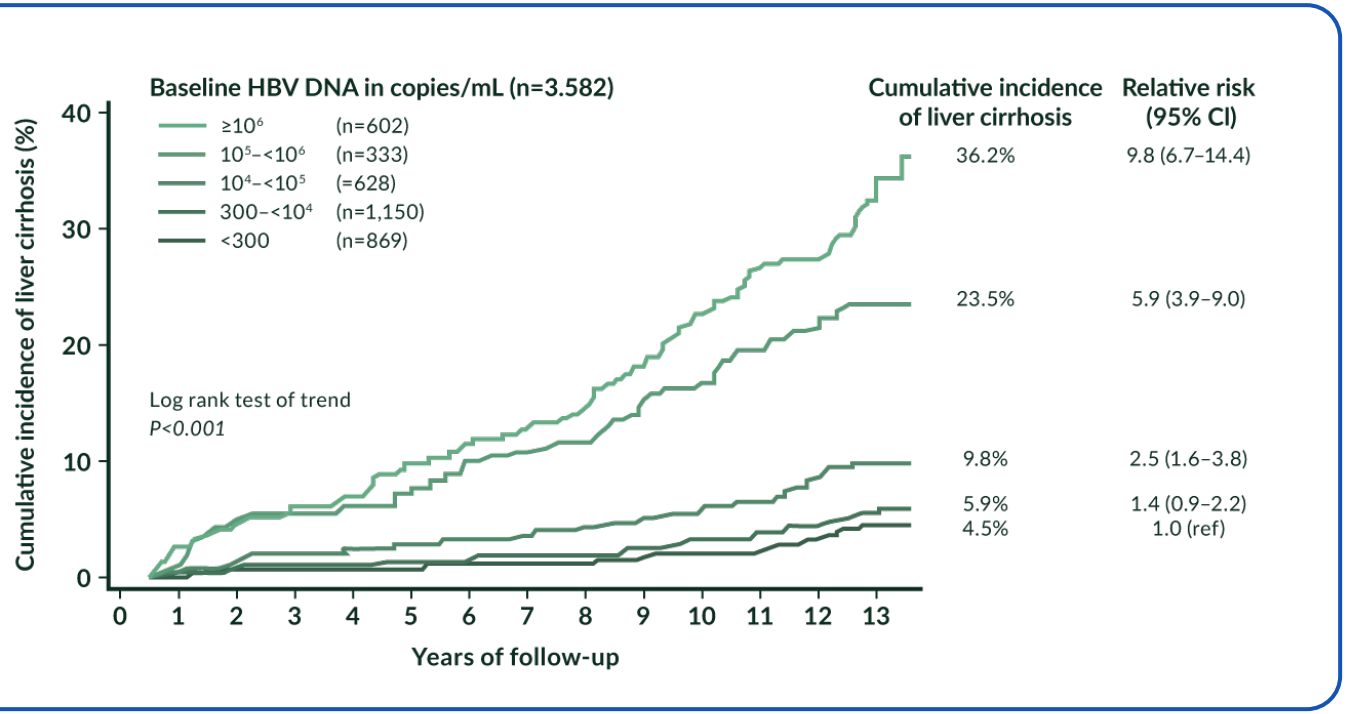
Cleveland Clinic
Hepatology Section

*HBV DNA levels can be between 2,000 and 20,000 IU/mL in some patients without signs of chronic hepatitis.
†Persistently or intermittently, based on traditional ULN (~40 IU/L). ‡cccDNA can frequently be detected in the liver.
§Residual HCC risk only if cirrhosis has developed before HBsAg loss.
EASL CPG HBV. J Hepatol 2017;67:370–98

Hepatitis B

- Exposure: immunoglobulin
- Acute infection: supportive therapy
- Chronic infection: persistence of infection longer than 6 months
- Therapy chronic hepatitis B aim is hepatitis virus DNA replication to be supressed and prevent or improve liver inflammation and fibrosis.
- Immunological cure - supresses virus and the loss of the hepatitis b surface antigen
- Successful therapies - pegylated interferon alfa -2a,entecavir,and tenofovir are first line options
- No inactive carrier state

Long-term outcomes in hepatitis B: the REVEAL-HBV study



Serum HBVDNA level has been shown to be significantly and independently associated with incidence of hepatocellular carcinoma (HCC) and cirrhosis and liver-related mortality across a biological gradient. It is also a major predictor of HBsAg seroclearance

Chen, C. J., Yang, H. I., Iloeje, U. H., & Yang, H. I. (2007). Long-term outcomes in hepatitis B: the REVEAL-HBV study. *Clinics in liver disease*

Treatment for Hepatitis B

TREATMENT FOR CHRONIC INFECTION:

- **No curative treatment** , but tries to delay or prevent development of complications like liver damage and cirrhosis. There two types of treatment currently given:
- ***INTERFERON:*** Similar to interferon produced in the body. It boosts immune system to fight infection and is given weekly.
- ***ANTIVIRAL DRUGS:*** e.g Lamivudine, tenofovir etc, they try to stop the virus multiplication in the body. Drug combinations maybe taken.
- Treatment is usually continued for years and patient regularly monitored.
- **NOTE:** Resistance to drugs may also develop.

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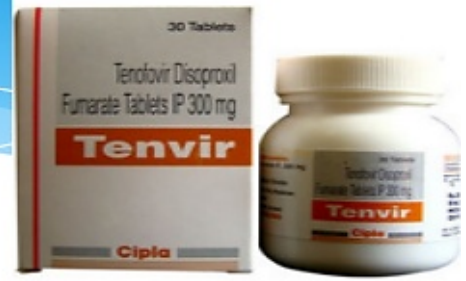
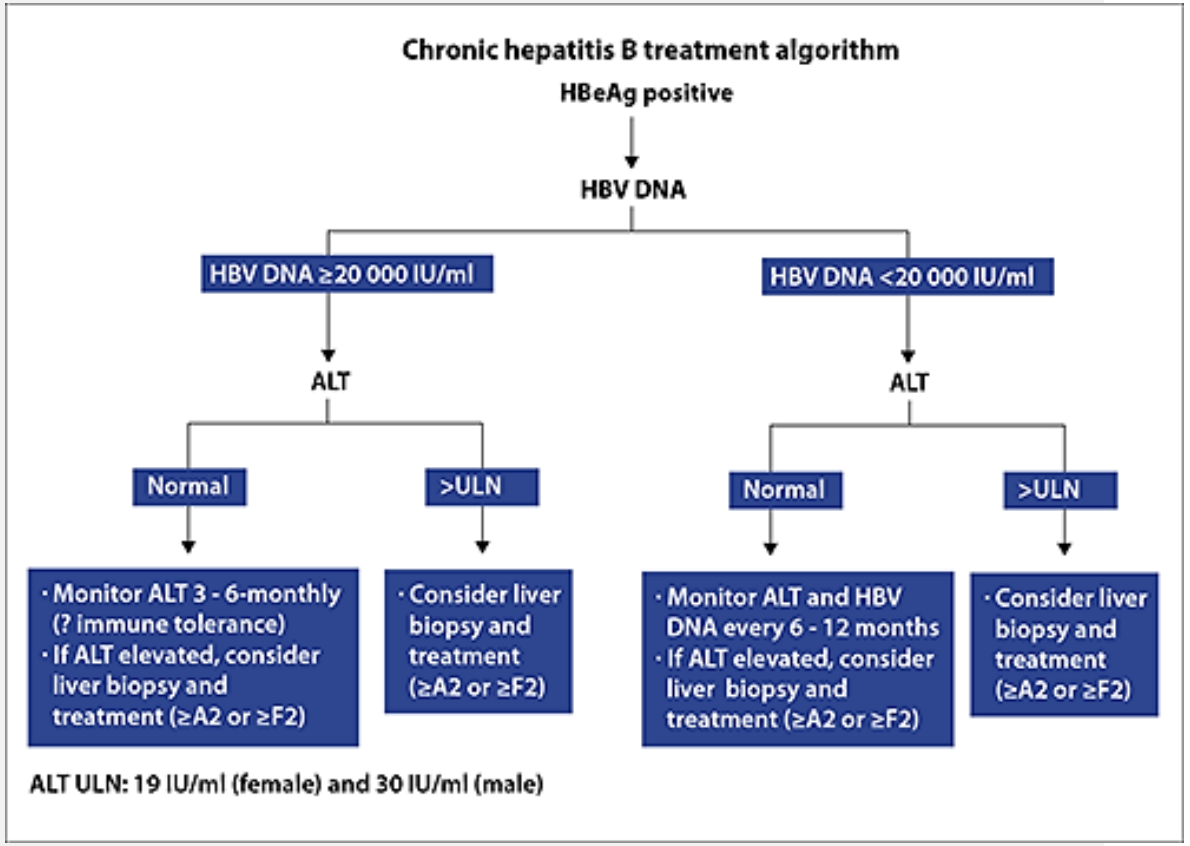
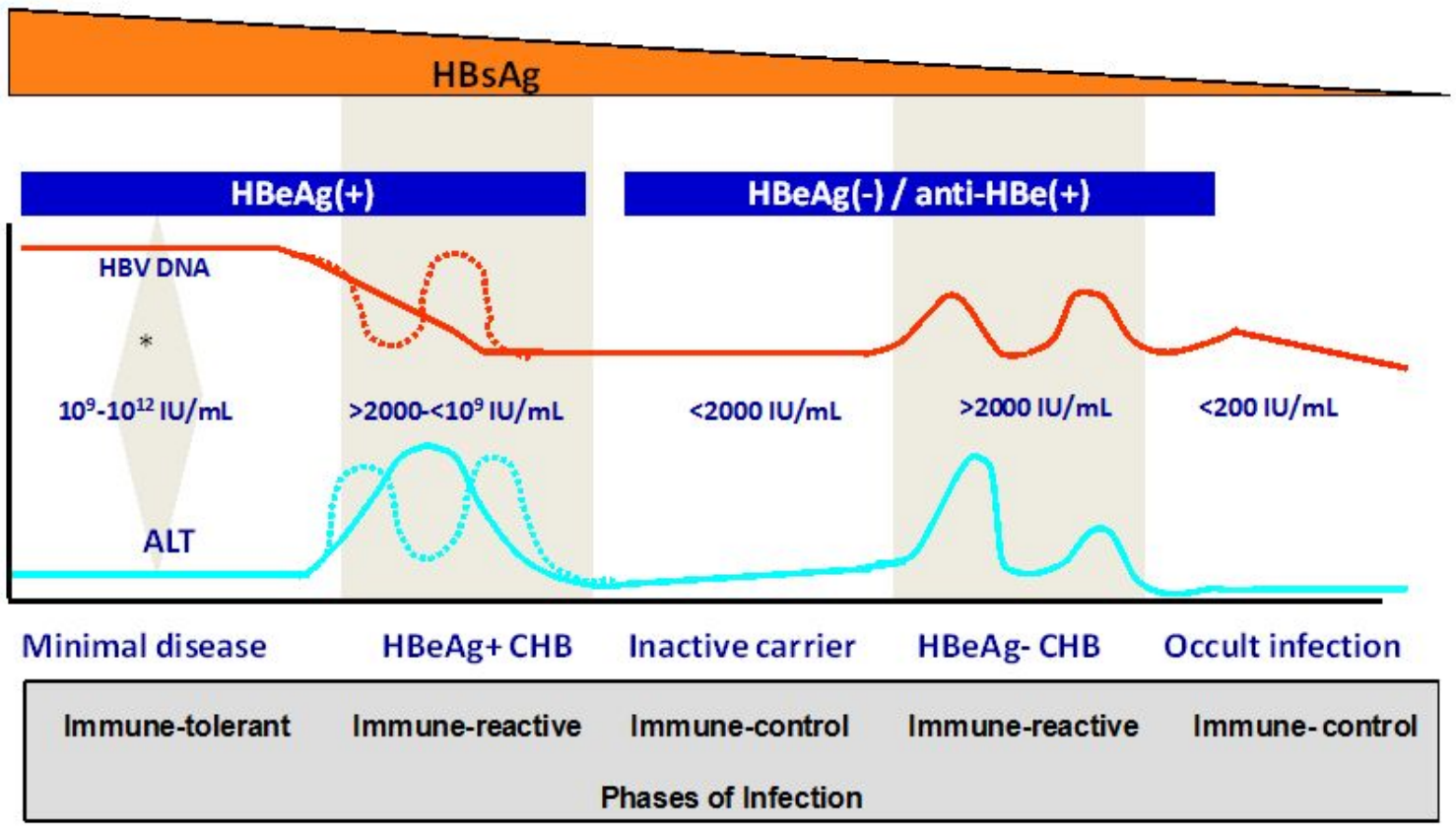


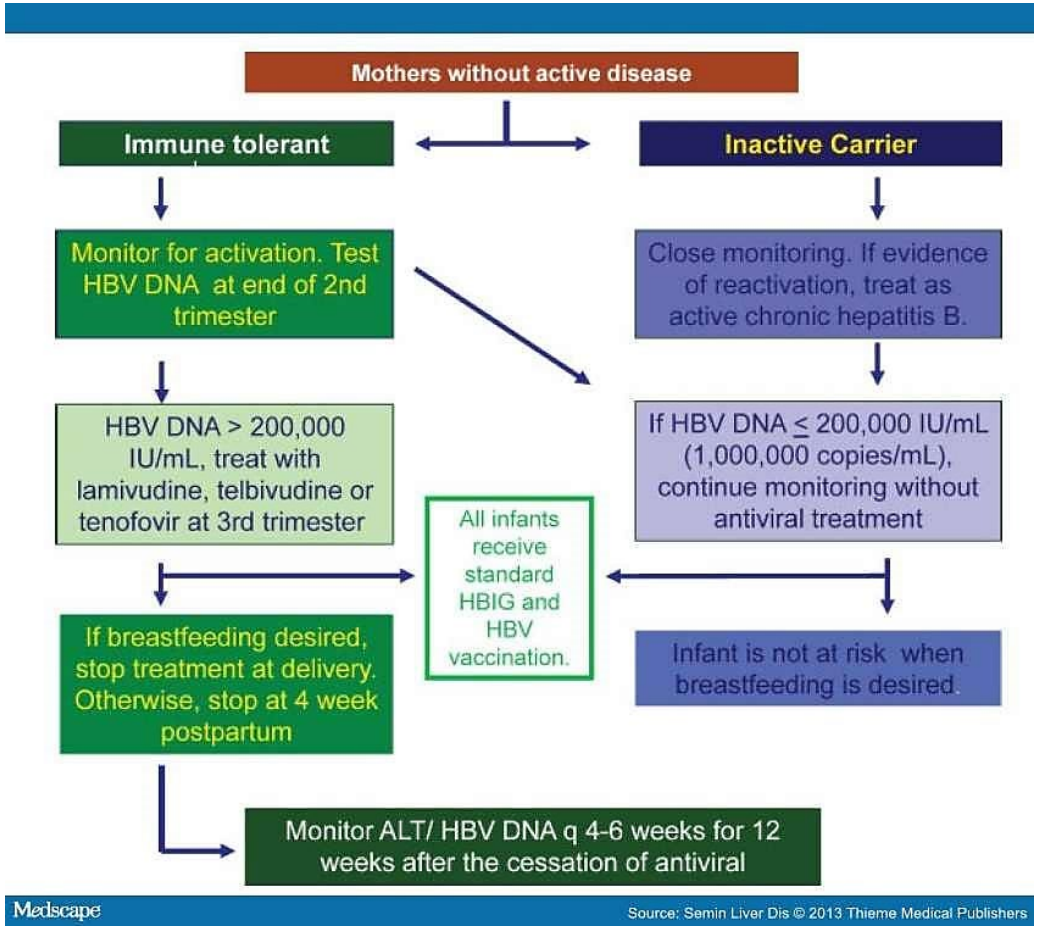
http://www.mayoclinic.org/

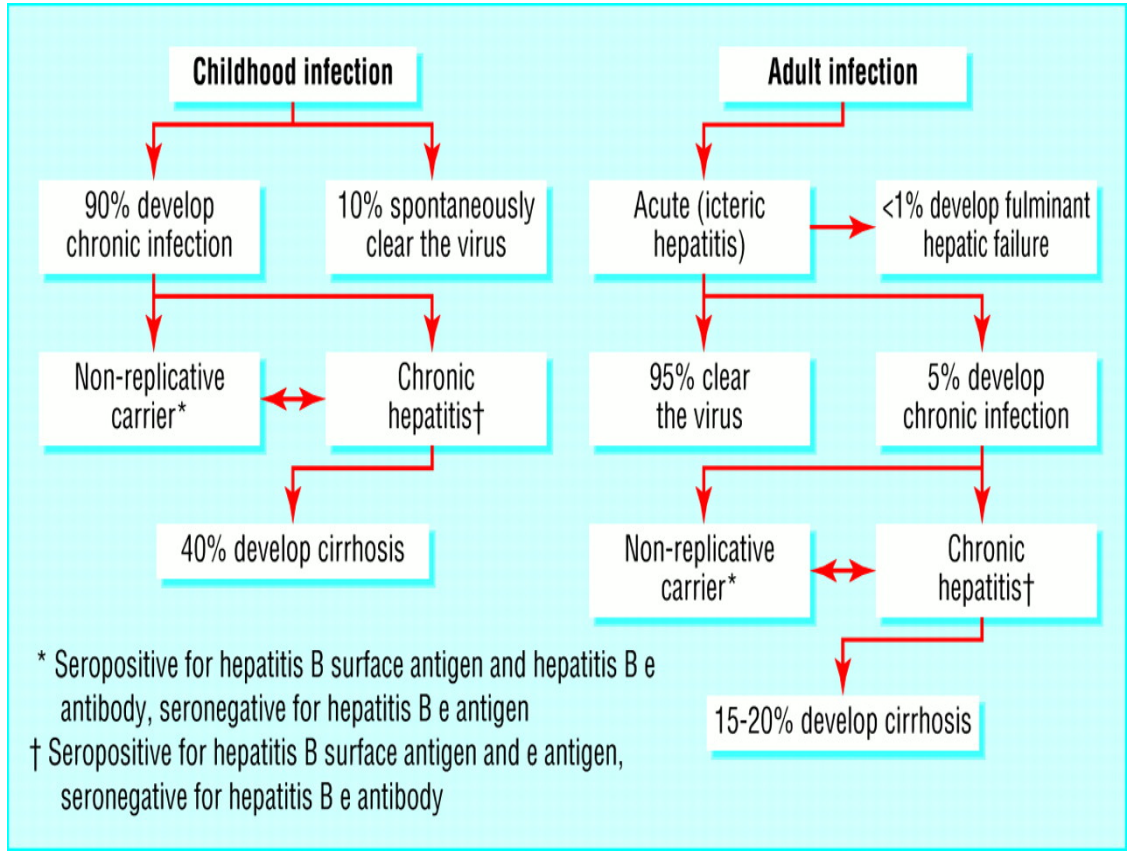


Endpoints of Hepatitis B Treatment

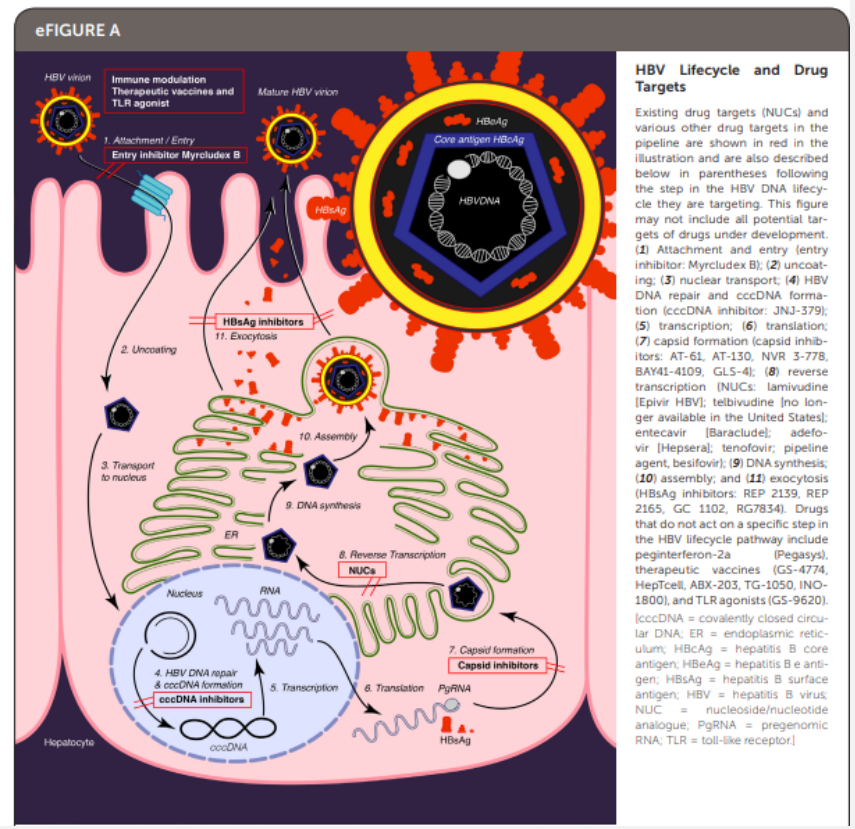


Hepatitis B in Pregnancy





Hepatitis B: Screening, Prevention, Diagnosis, and Treatment



Screening guidelines for HCC

All patients with cirrhosis (any age)

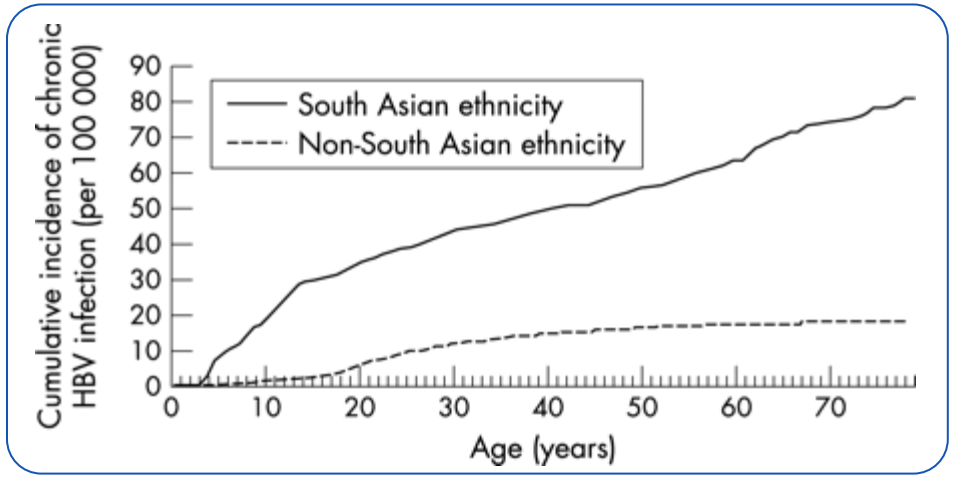
Patients with HBsAg

Asian females >50 yr	Males >40 yr
Africans/North American Blacks >20 yr	Family history of HCC
Non-Asians/Black females >50 yr	Non-Asians/Black males >40 yr with active disease[a]

Notes: [a]HBV-DNA >100,000 copies/mL and/or elevated ALT. Data from Bruix et al.[5]
Abbreviations: HCC, hepatocellular carcinoma; HBV, hepatitis B virus; ALT, alanine transaminase; yr, years.

Hepatitis B: Screening, Prevention, Diagnosis, and Treatment; Thad Wilkins, MD, MBA; Rashid Sahay, MD, MA; and Mary Carpenter, PharmD Medical College of Georgia at Augusta University, Augusta, Georgia

Vaccination Against Hepatitis B



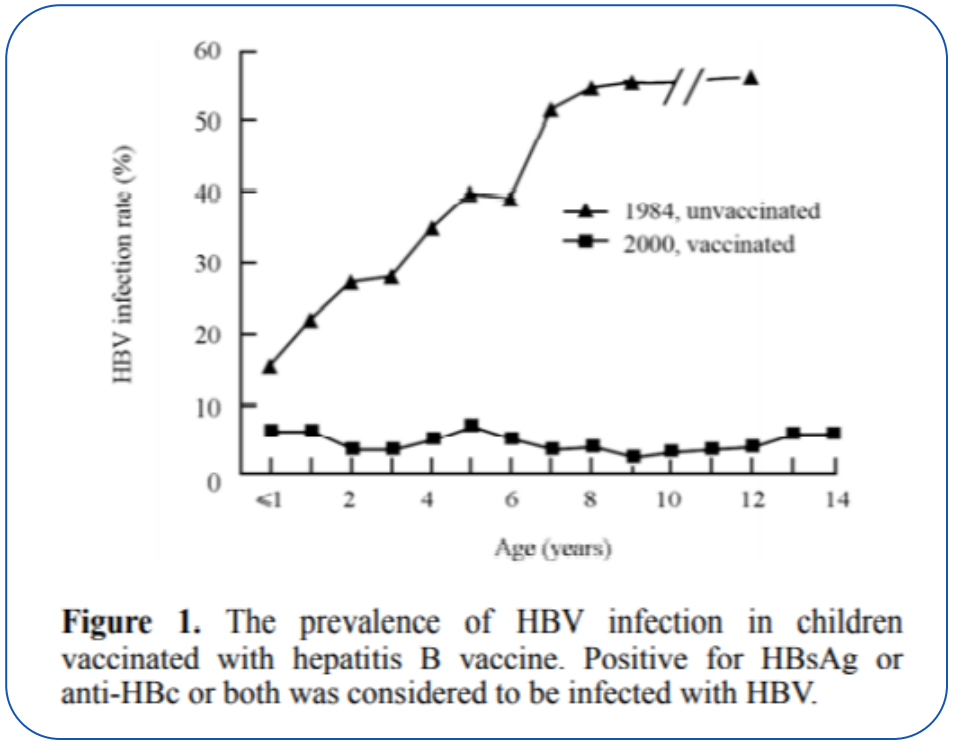


Figure 1. The prevalence of HBV infection in children vaccinated with hepatitis B vaccine. Positive for HBsAg or anti-HBc or both was considered to be infected with HBV.

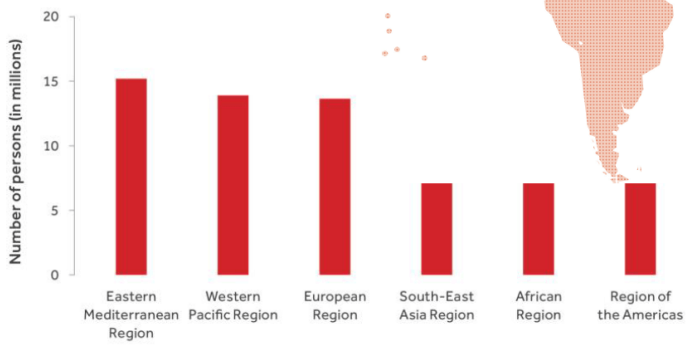
Chin Med J 2009;122(1):98 -10; Vaccination against hepatitis B

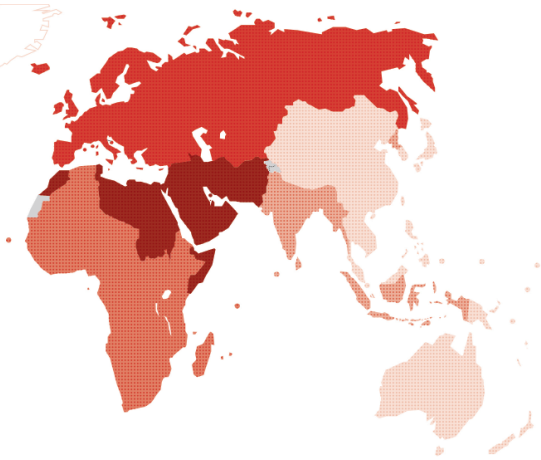
Hepatitis C

STATUS OF HEPATITIS C

HCV

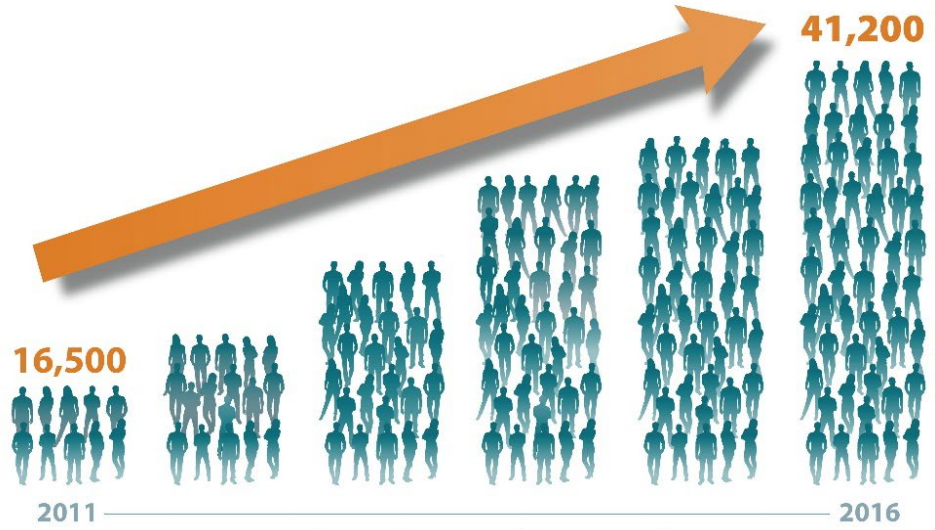
Incidence:
1.75 million new infections / year
(Unsafe health care and injection drug use)





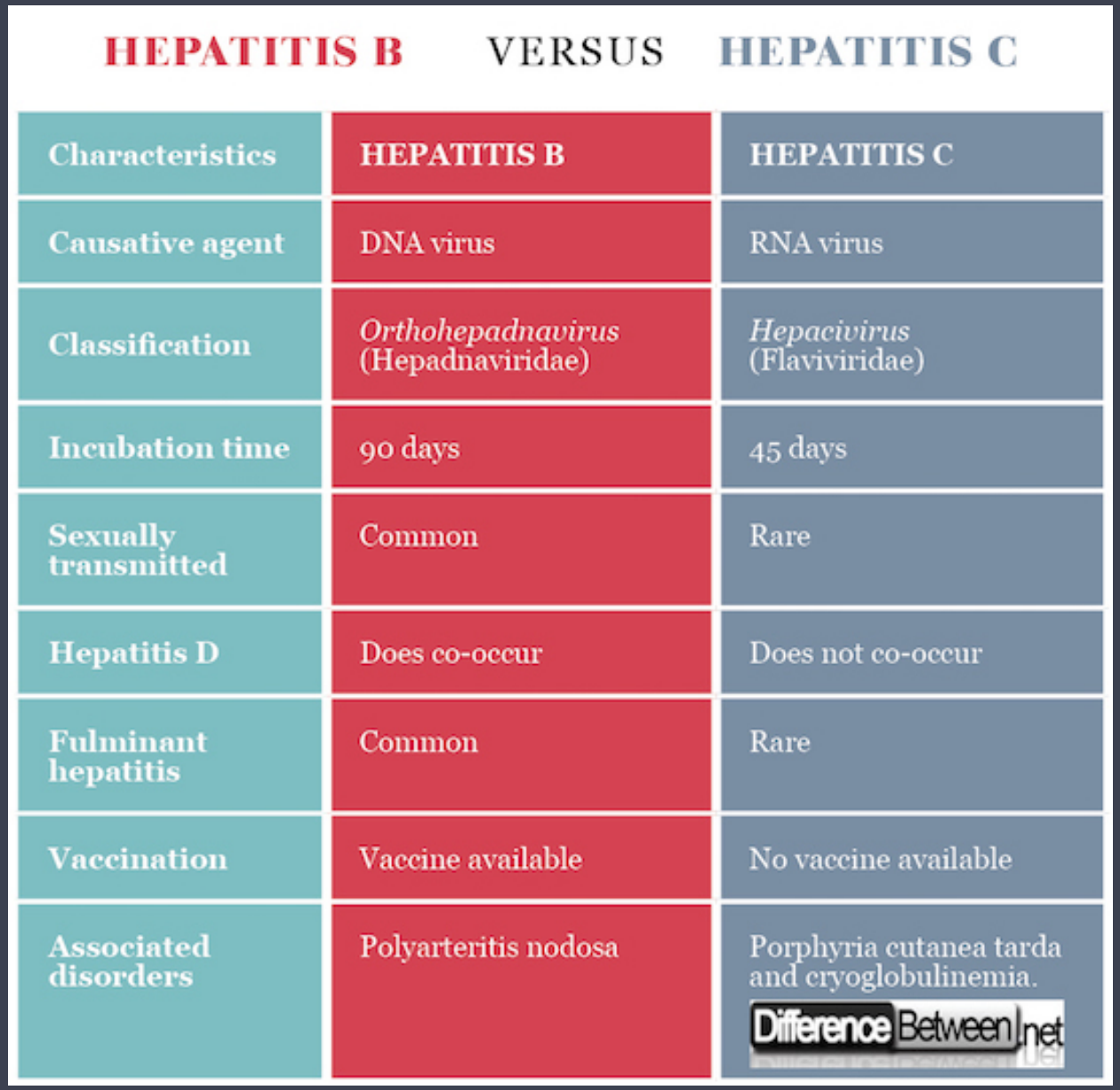
Prevalence:
71 million infected, all regions

IN THE SHADOW OF THE OPIOID CRISIS, NEW HEPATITIS C INFECTIONS HAVE INCREASED



Visit www.cdc.gov/hepatitis for more information

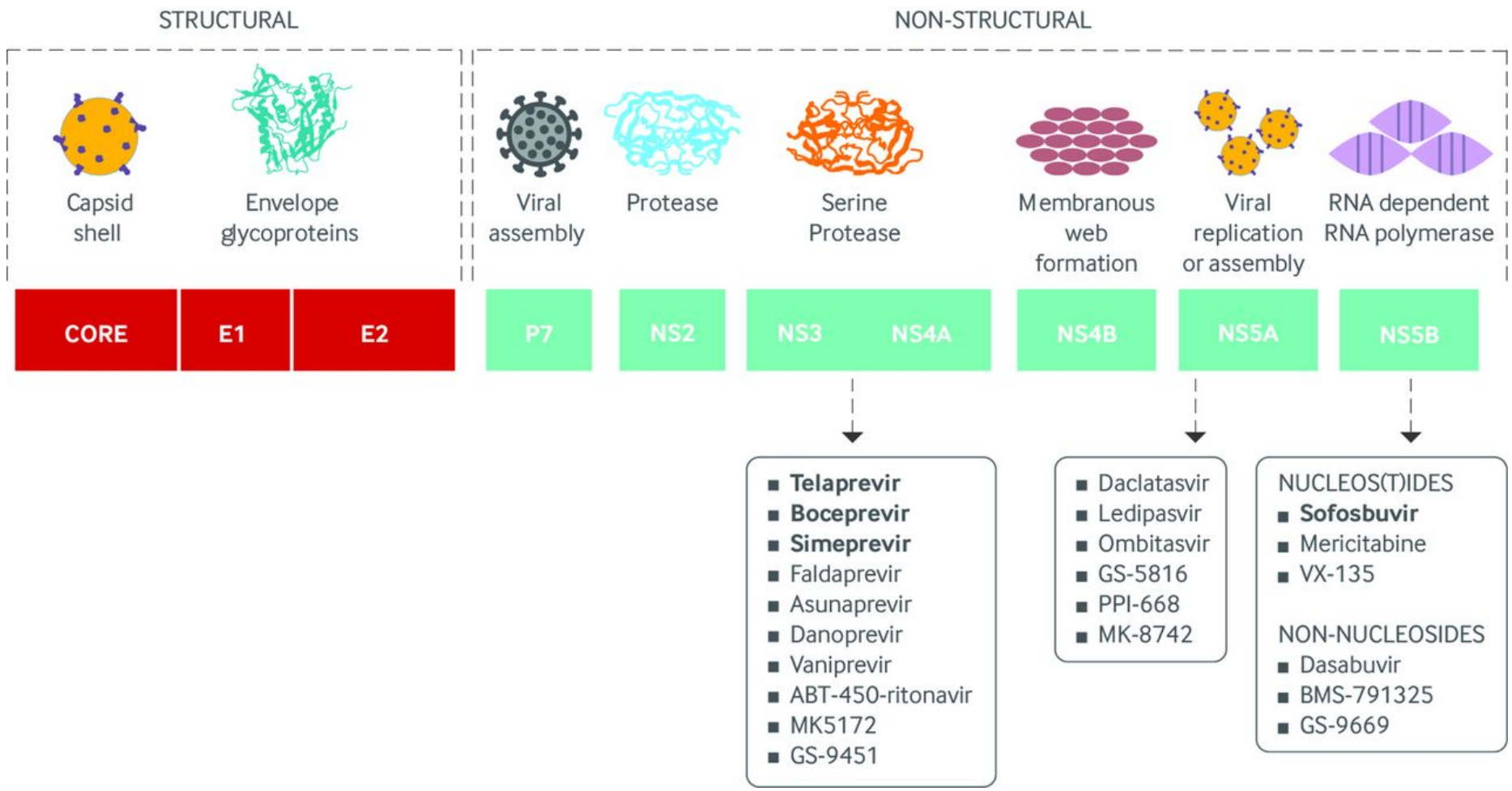
Difference Between Hepatitis B and Hepatitis C



HEPATITIS B VERSUS HEPATITIS C

Characteristics	HEPATITIS B	HEPATITIS C
Causative agent	DNA virus	RNA virus
Classification	*Orthohepadnavirus* (Hepadnaviridae)	*Hepacivirus* (Flaviviridae)
Incubation time	90 days	45 days
Sexually transmitted	Common	Rare
Hepatitis D	Does co-occur	Does not co-occur
Fulminant hepatitis	Common	Rare
Vaccination	Vaccine available	No vaccine available
Associated disorders	Polyarteritis nodosa	Porphyria cutanea tarda and cryoglobulinemia.

Hepatitis C therapies – BMJ



Hepatitis C

Summary of recommended preferred regimens with treatment durations*

Persons without cirrhosis

	Daclatasvir/ sofosbuvir	Ledipasvir/ sofosbuvir	Sofosbuvir/ ribavirin
Genotype 1	12 weeks	12 weeks[a]	
Genotype 2			12 weeks
Genotype 3	12 weeks		24 weeks
Genotype 4	12 weeks	12 weeks	
Genotype 5		12 weeks	
Genotype 6		12 weeks	

Persons with cirrhosis

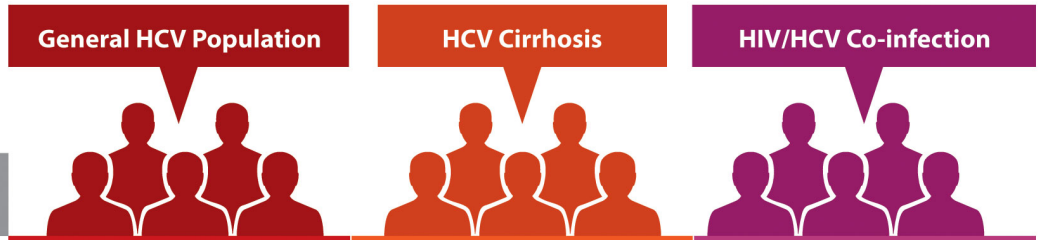
	Daclatasvir/ sofosbuvir	Daclatasvir/ sofosbuvir/ ribavirin	Ledipasvir/ sofosbuvir	Ledipasvir/ sofosbuvir / ribavirin	Sofosbuvir/ ribavirin
Genotype 1	24 weeks	12 weeks	24 weeks	12 weeks[b]	
Genotype 2					16 weeks
Genotype 3		24 weeks			
Genotype 4	24 weeks	12 weeks	24 weeks	12 weeks[b]	
Genotype 5			24 weeks	12 weeks[b]	
Genotype 6			24 weeks	12 weeks[b]	

* Treatment durations are adapted from the 2015 guidelines of the American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL).

[a] Treatment may be shortened to 8 weeks in treatment-naive persons without cirrhosis if their baseline HCV RNA level is below 6 million (6.8 log) IU/mL. The duration of treatment should be shortened with caution.

[b] If platelet count <75 x 10^3/µL, then 24 weeks' treatment with ribavirin should be given.

Table. Effect of Sustained Virologic Response on All-Cause Mortality*



	General HCV Population	HCV Cirrhosis	HIV/HCV Co-infection
5-year Mortality Rate (95% CI)			
SVR	1.98 (1-3.45)	4.9 (3.45-7.28)	1.49 (0.5-2.96)
Non-SVR	7.75 (5.86-10.98)	15.88 (11.44-21.8)	11.44 (6.33-19.31)
Adjusted HR (SVR; 95% CI)	0.33 (0.23-0.46)	0.26 (0.18-0.37)	0.21 (0.1-0.45)

*Adapted from Simmons et al.; meta-analysis of 31 studies (n = 33,360).

Abbreviations: CI, confidence interval; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HR, hazard ratio; SVR, sustained virologic response.

10-year Cumulative Incidence

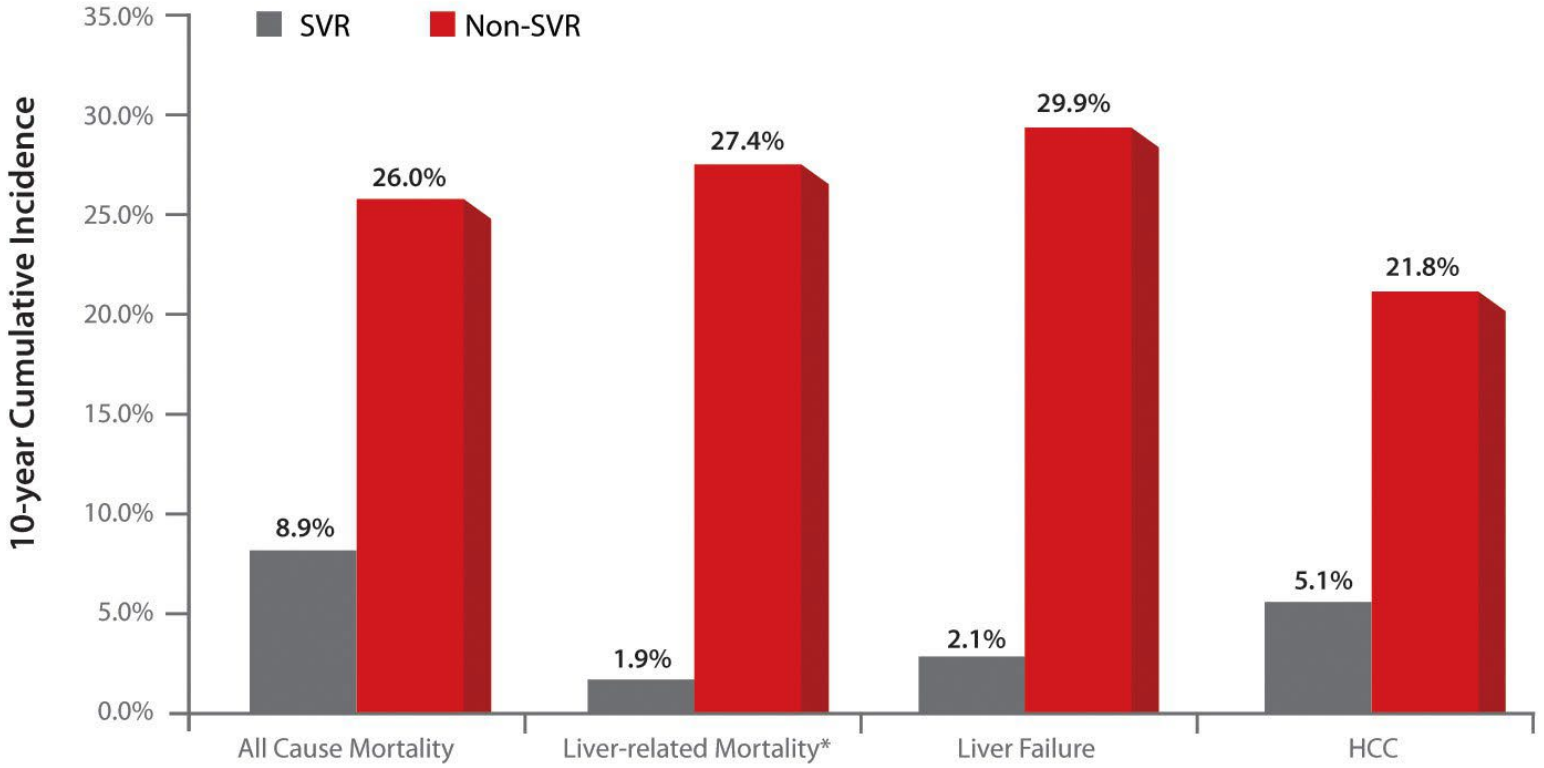
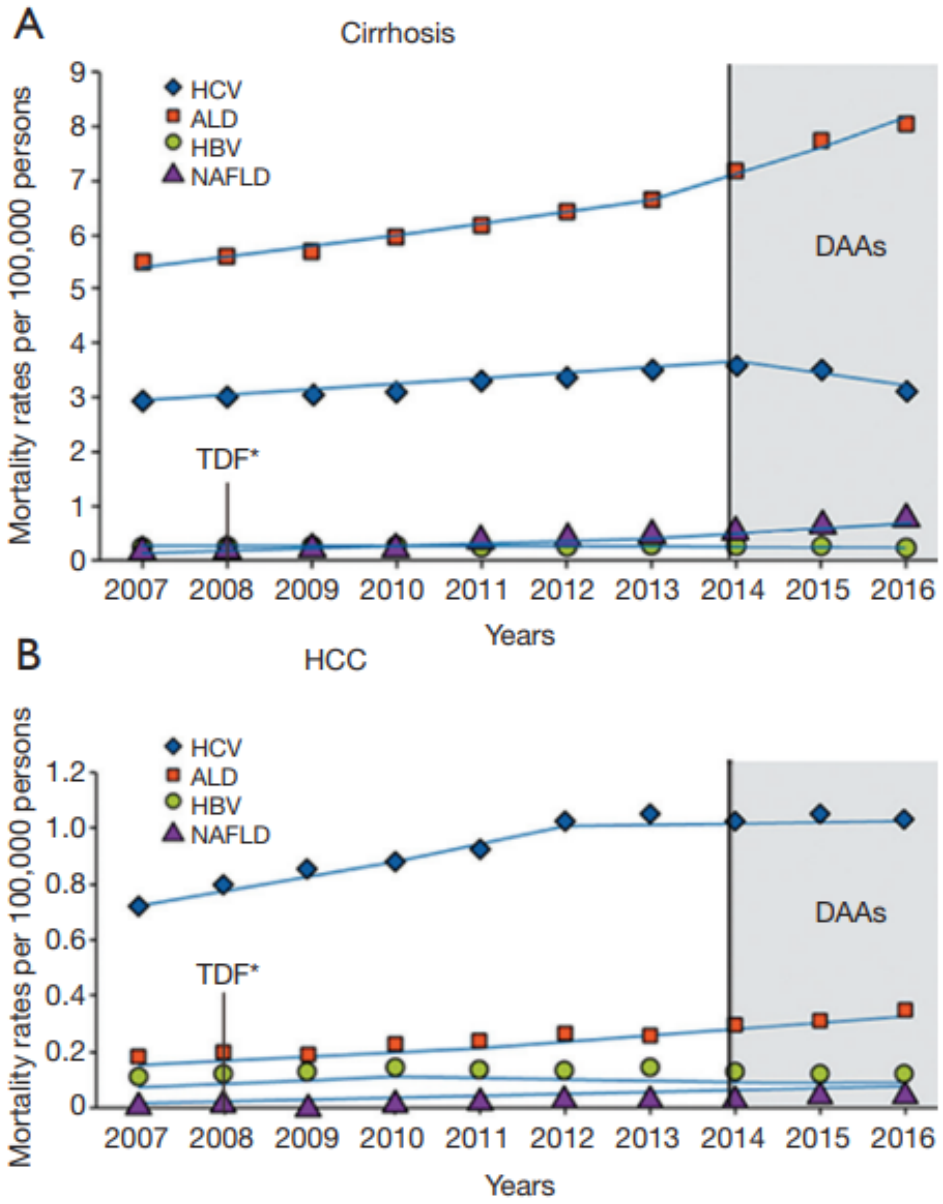


Figure 2. 10-year cumulative incidence of outcomes based on a large, long-term cohort follow-up study of patients with advanced hepatic fibrosis who underwent antiviral therapy (n = 530); adapted from van der Meer et al. *Liver related mortality includes need for liver transplantation.

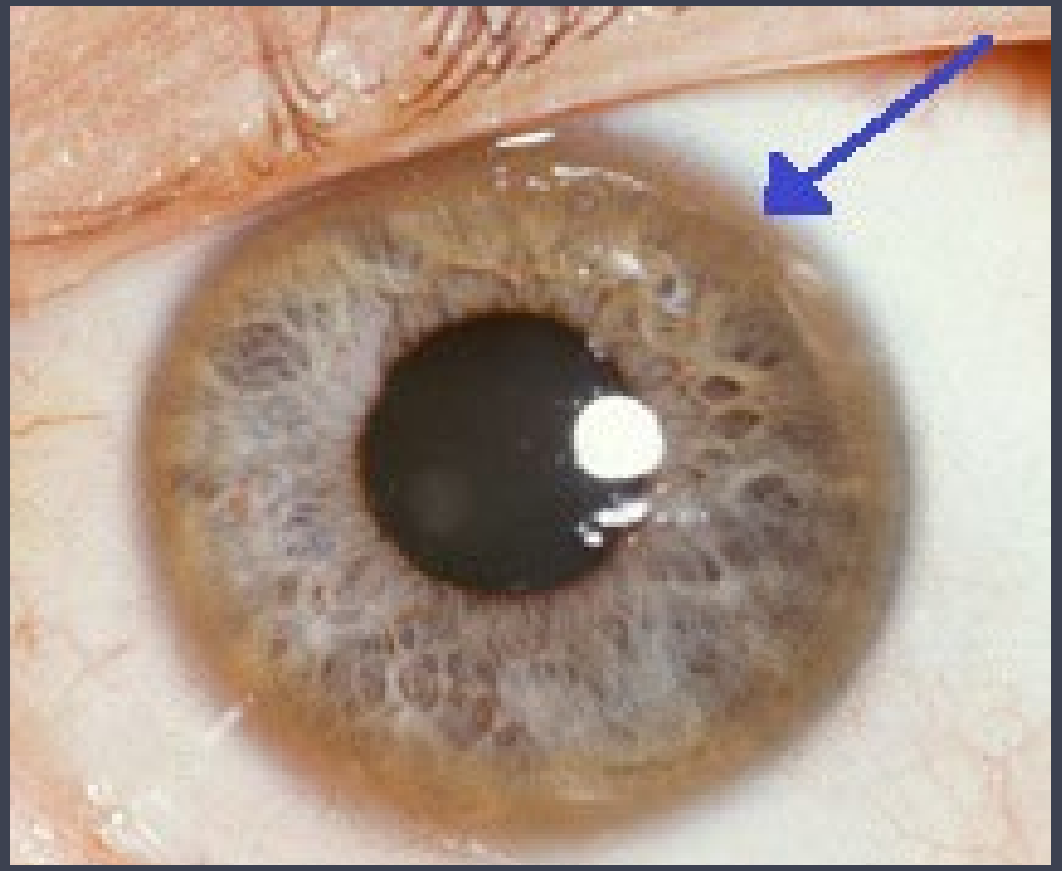
Mortality from Cirrhosis and Hepatocellular Carcinoma before and after anti-virals



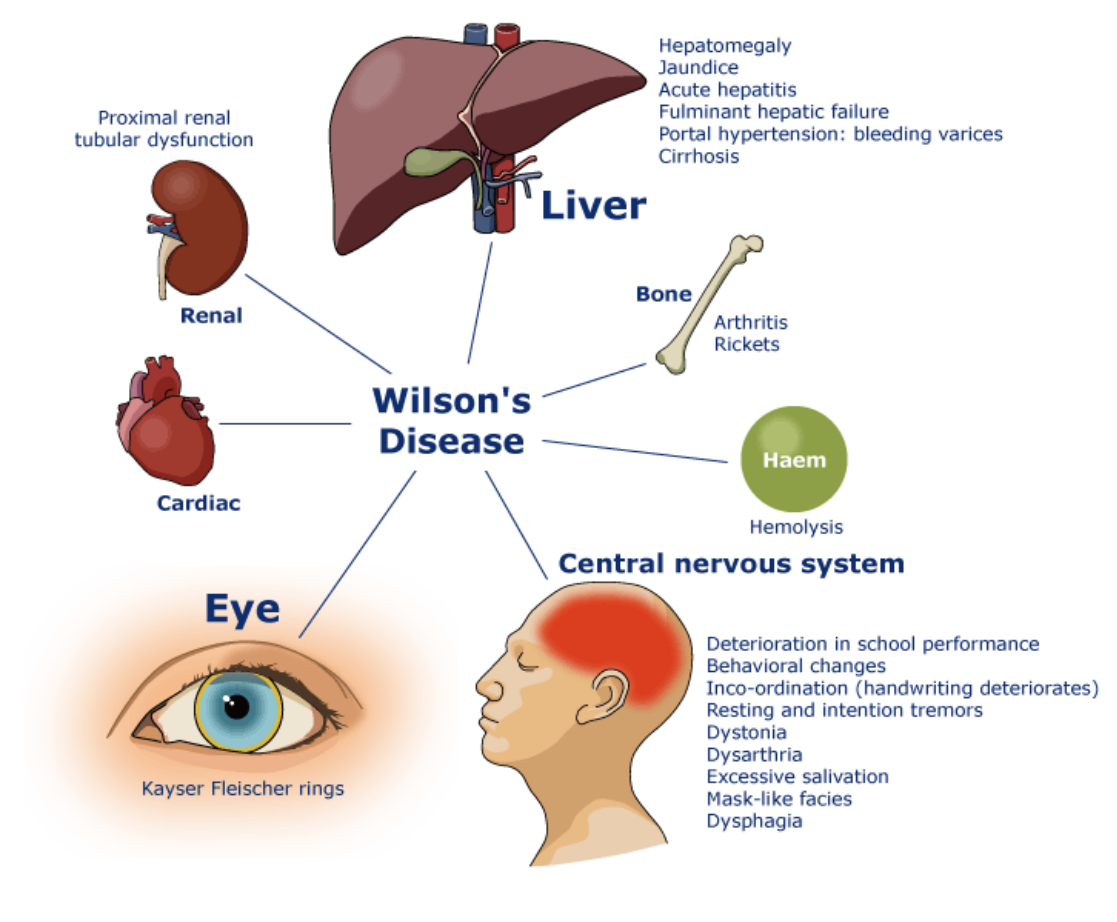
Mortality from Cirrhosis and Hepatocellular Carcinoma before and after anti-virals HepatoBiliary Surg Nutr 2019;8(3):307-310 | http://dx.doi.org/10.21037/hbsn.2019.01.21

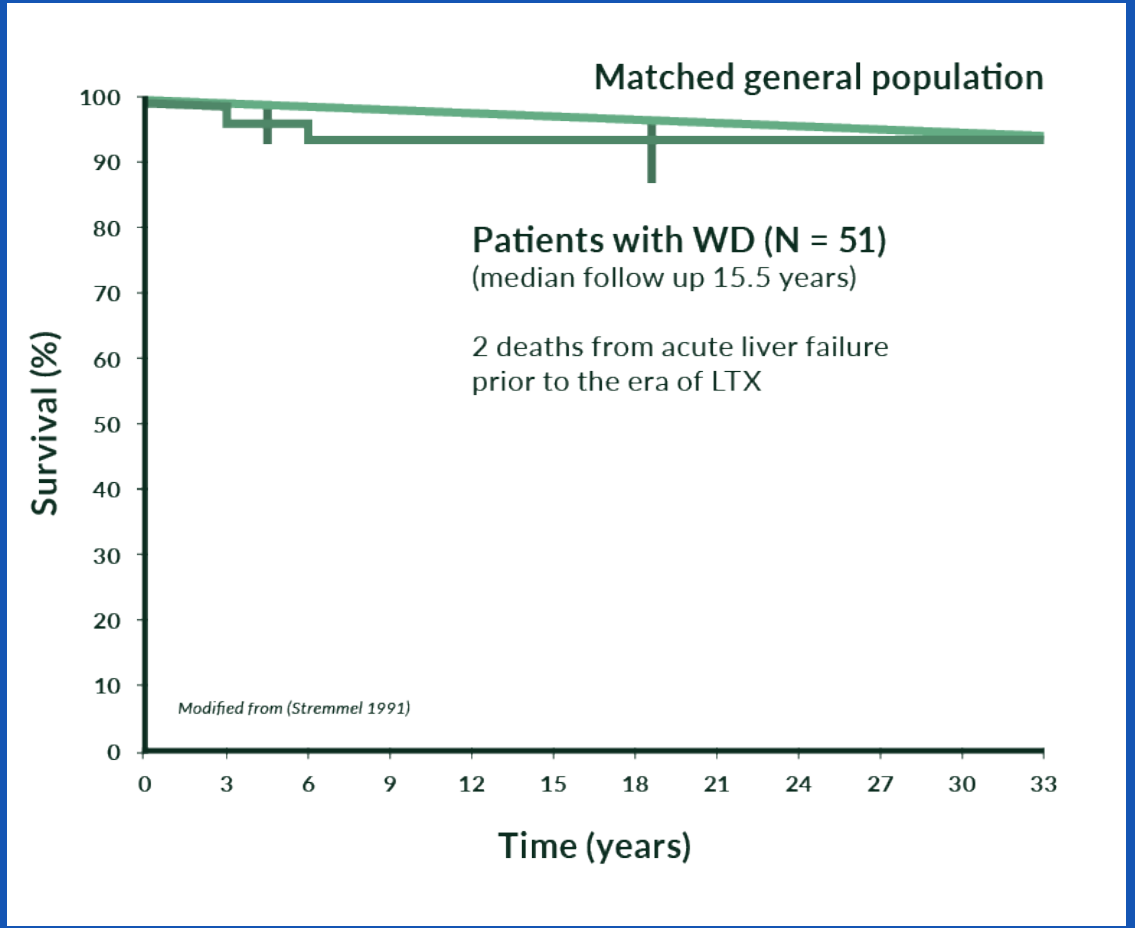
Wilson's Disease

- Autosomal recessive disorder of copper metabolism
- 30% have cirrhosis on diagnosis
- 30,000-40,000 people worldwide
- 2,000-3,000 cases in US
- 1:0 a carrier
- Ceruloplasmin protein helps excrete copper from body
- Affects liver, kidneys, nervous systems, rbc's-haemolytic anaemia
- Parkinsonism, mood disorders
- Kayser-fleischer ring-golden ring around cornea



Wilson's Disease (Eurowilson)





Hemochromatosis

- Autosomal recessive causes increase in iron absorption
- Iron accumulates as ferritin and hemosiderin in various organs
- Liver, pancreas, heart, joints, skin, thyroid
- Cirrhosis, diabetes, cardiomyopathy, arthritis
- Diagnosis
- Elevated serum iron and serum ferritin
- Elevated iron saturation (transferrin saturation)
- Decreased total iron-binding capacity -tbic
- Liver biopsy-shows iron concentration
- Genetic testing
- Treatment phlebotomy

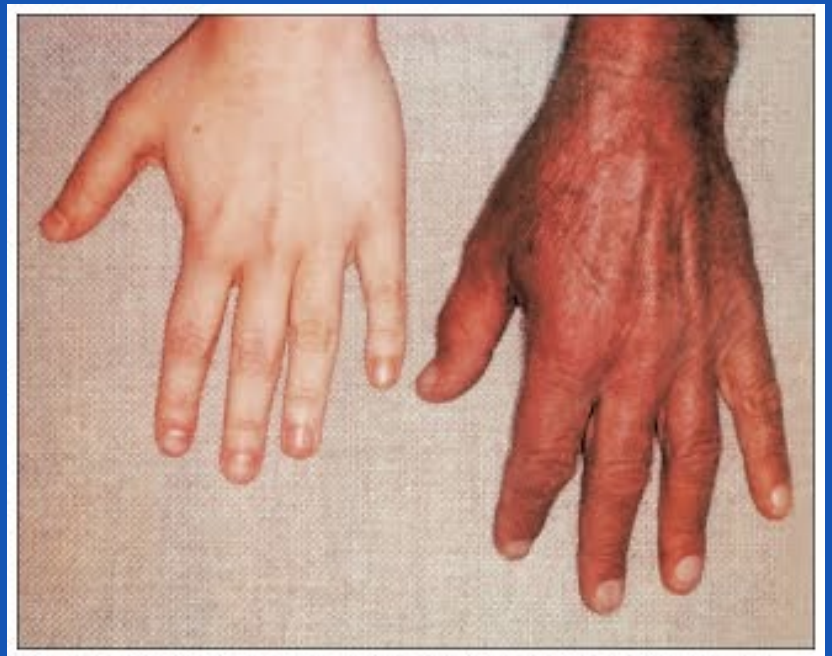
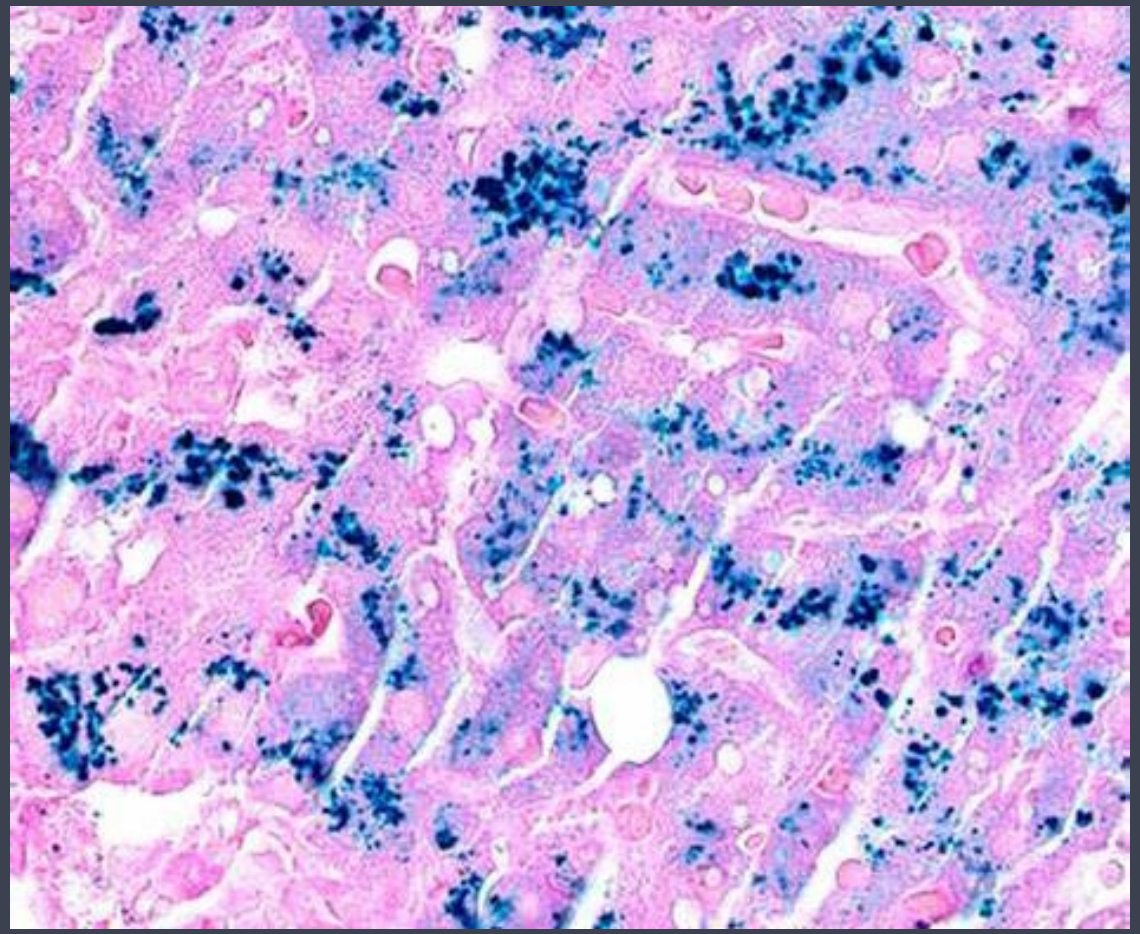
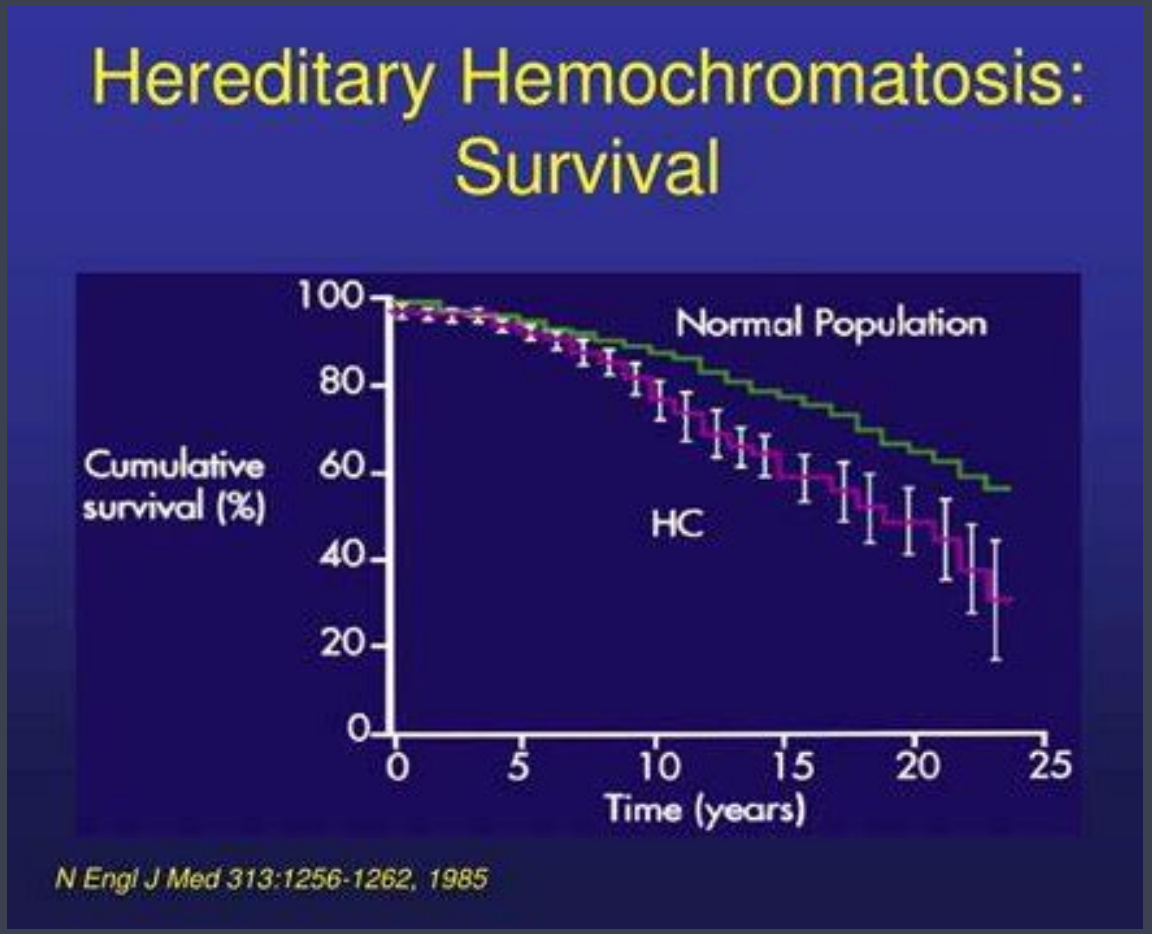


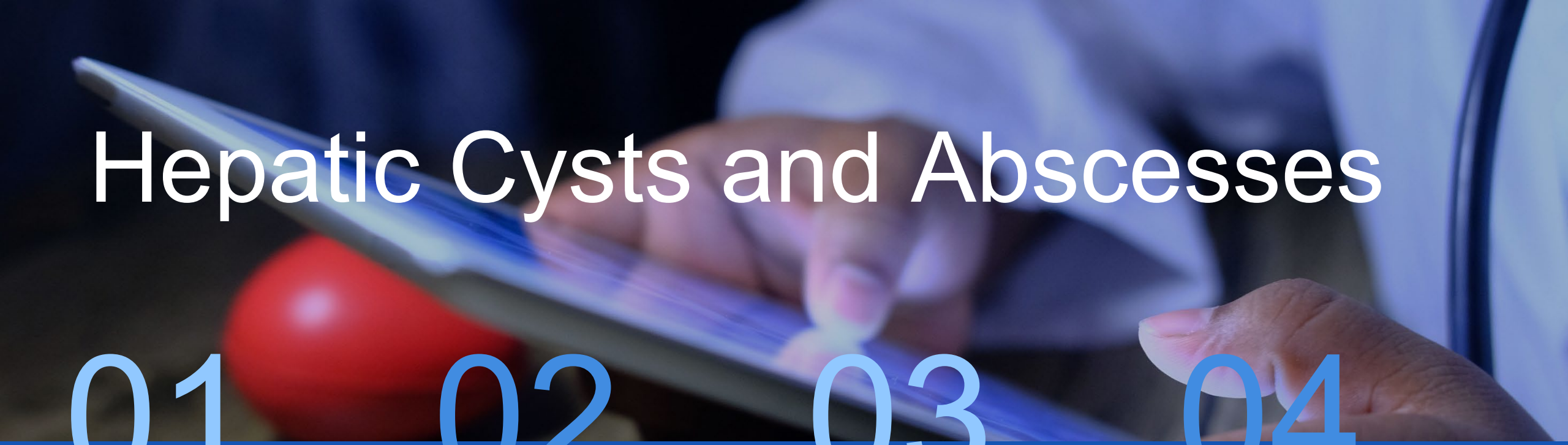
Figure 1 – The hand on the right is that of a 60-year-old white man with hereditary hemochromatosis. It is shown next to the hand of an unaffected person for comparison. The hyperpigmentation—characteristically golden brown or bronze—is generalized, but appears most prominently on sun-exposed or traumatized areas.

(Courtesy of Eugene Wong, MD, and Peter Peropoulos, MD.)

Hemochromatosis







Hepatic Cysts and Abscesses

01

Polycystic Liver Cysts

Autosomal dominant, usually associated with polycystic kidney disease, treatment usually unnecessary

02

Hydatid Liver Cysts

Tapeworm infection

03

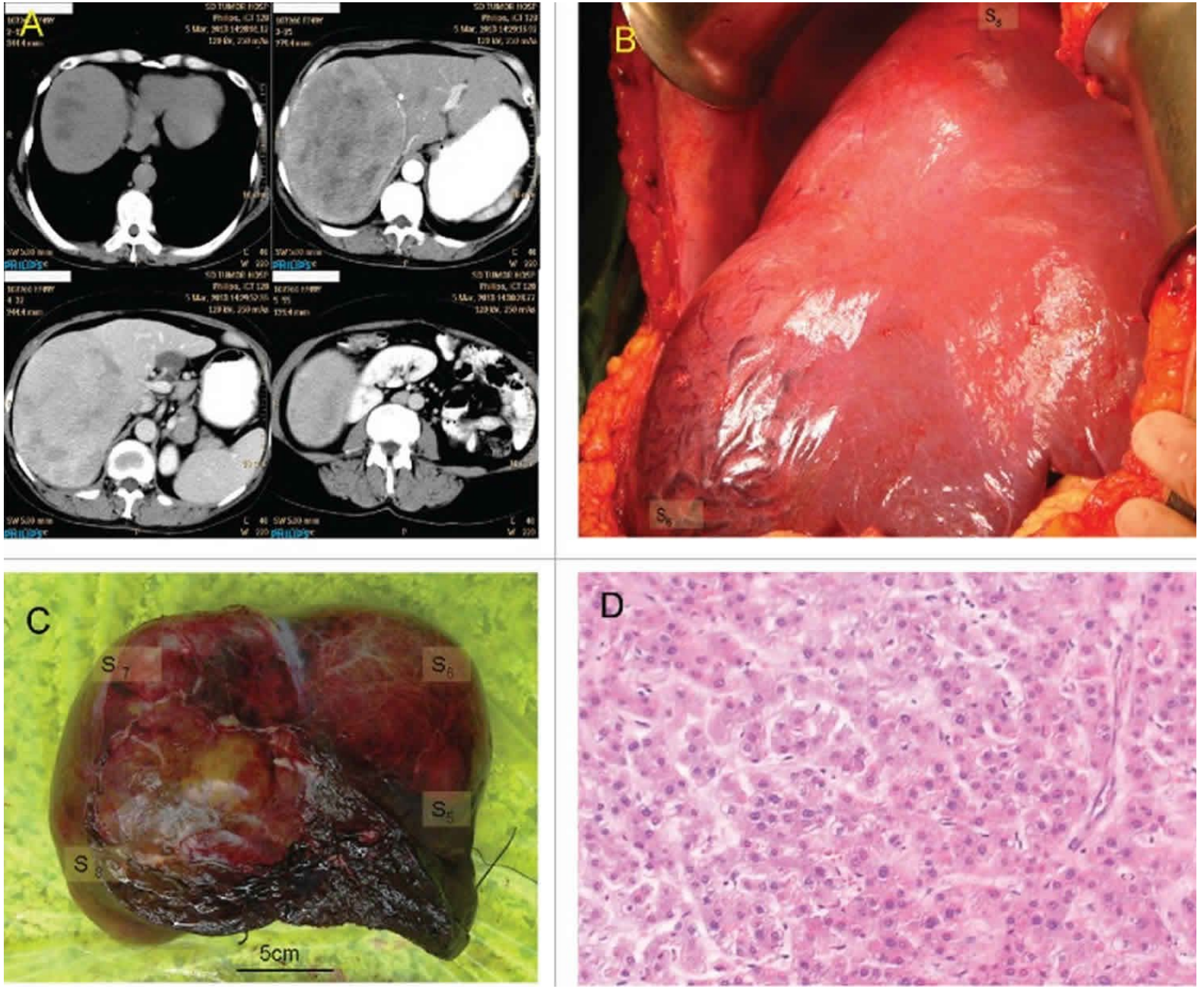
Pyogenic Abscess

04

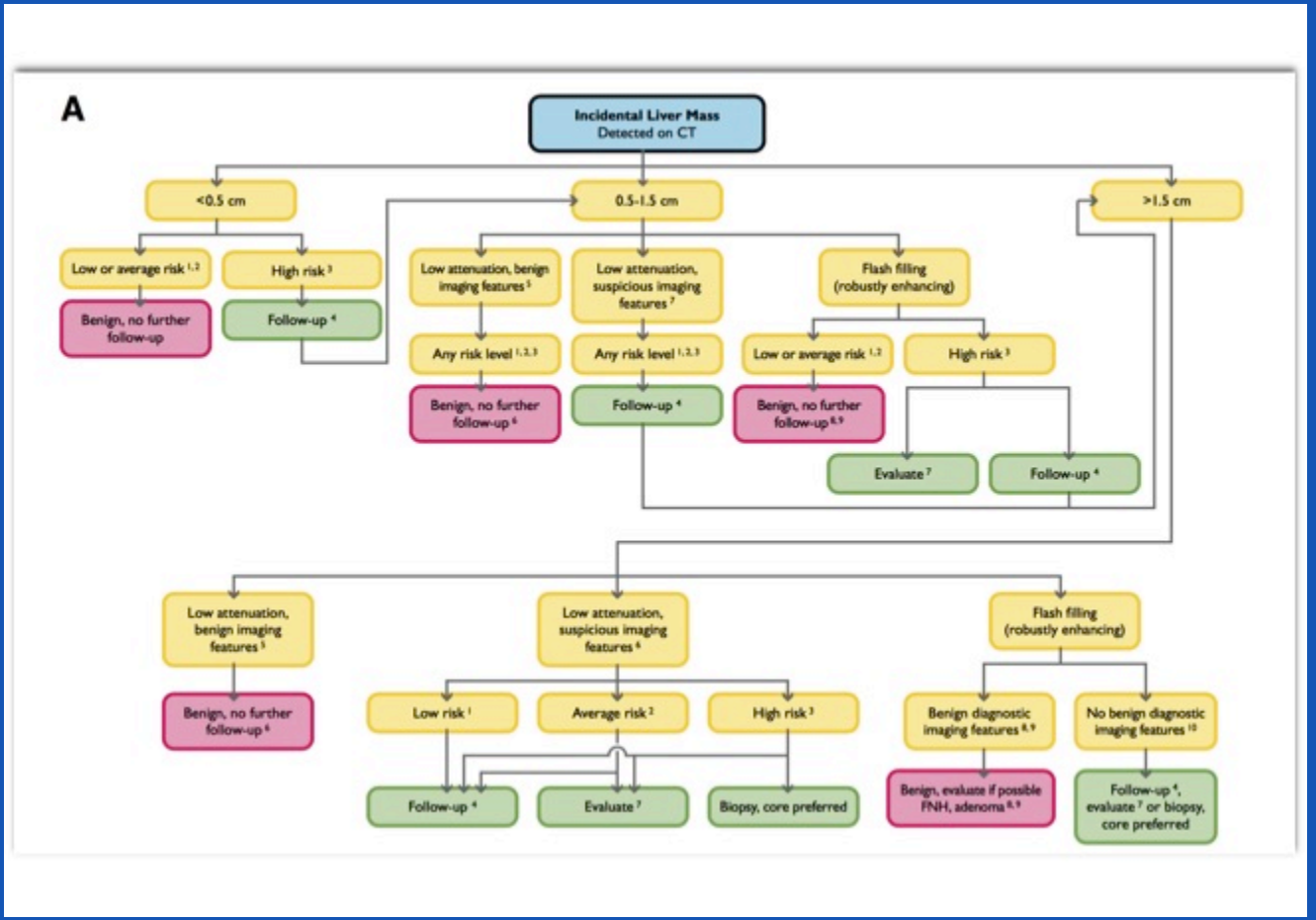
Amoebic Liver Abscess-entamoeba Histolytica

Hepatic Adenoma

- Generally benign
- Women 15-40 years
- Oral contraceptives, anabolic steroids
- Malignant transformation is low
- Resection if greater than 5 cm
- May rupture



Incidental Liver Lesions



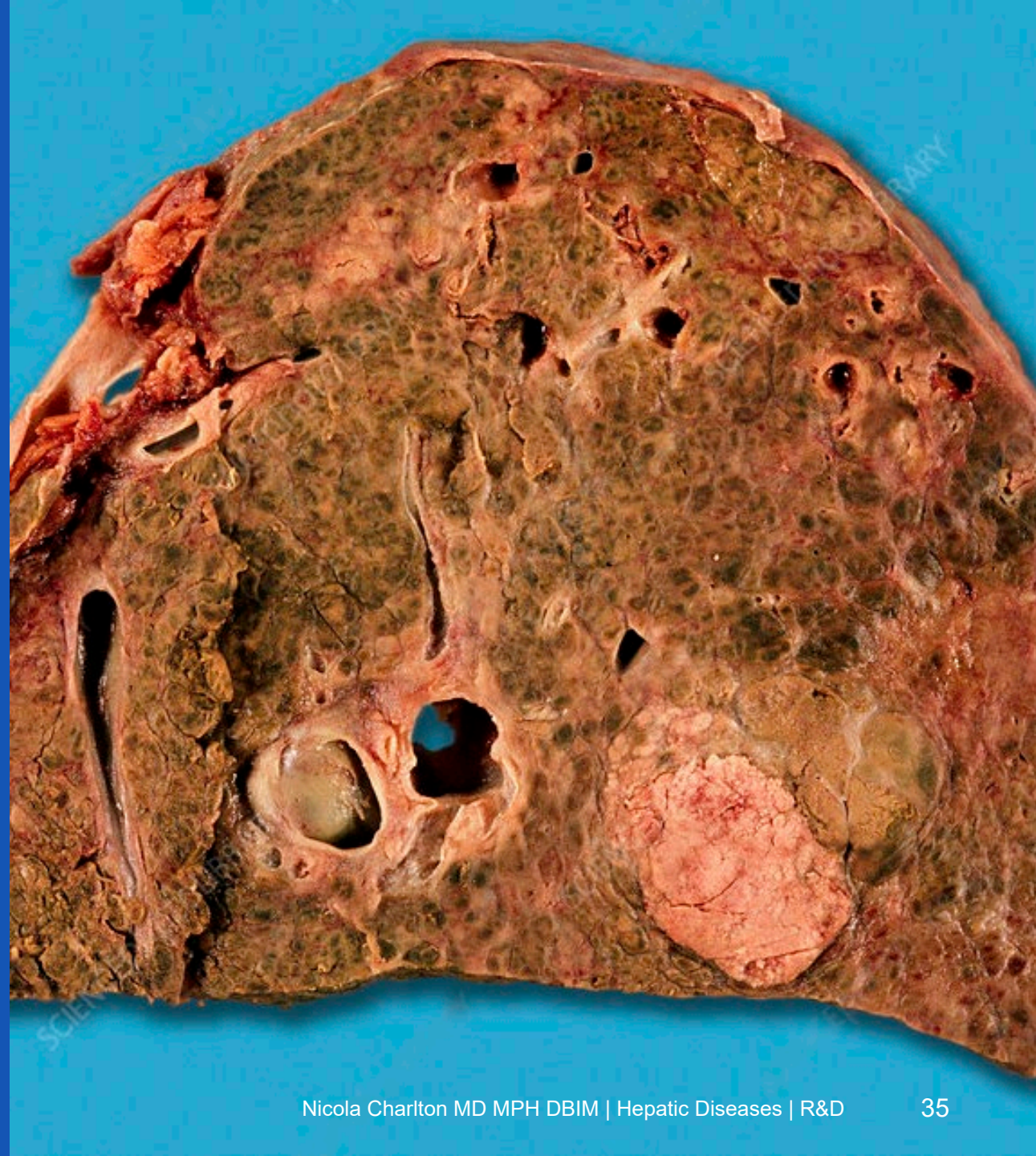
Hepatocellular carcinoma

80% of primary liver cancers

Majority of HCC in Africa and Asia

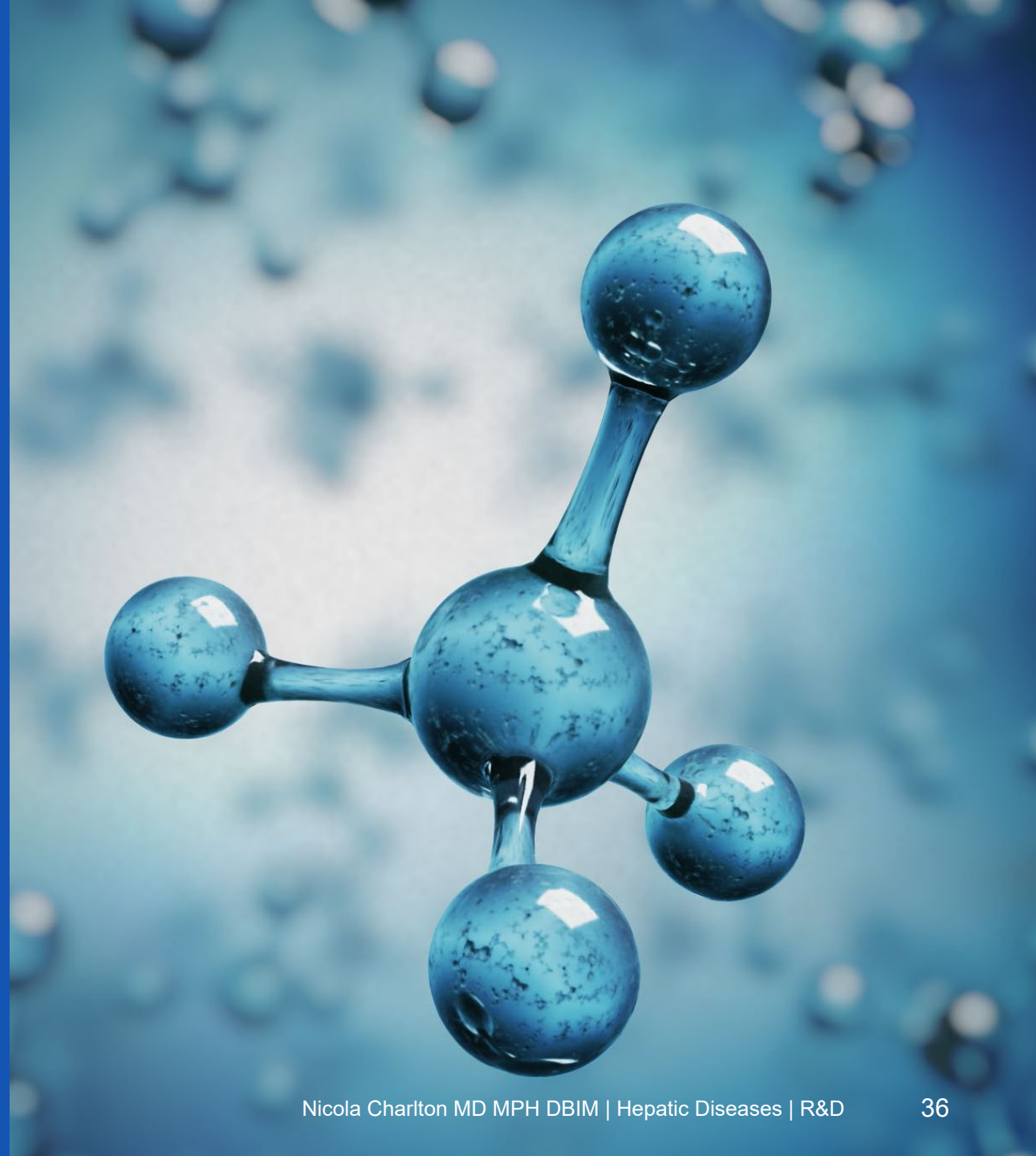
2 types - Fibrolamellar and non-Fibrolamellar which is caused by hepatitis B and C

Causes-cirrhosis, chemical cargcinogens,hemochromatosis,Wilson’s disease, hepatic adenoma, cigarette smoking



Autoimmune Hepatitis

- Autoimmune: body attack your own cells
- Female/male 4:1
- HLA- genes on chromosome 6 – part of immune system-abnormalities of self -proteins {HLA-DR3 and HLA-DR4]
- Hashemites' thyroiditis, Celiac and Graves disease
- Asymptomatic to cirrhosis
- ALT and AST elevated
- Type 1- 80% -ANA,ASMA adulthood
- Type 2- ANLKM-1 – young women, more severe prognosis



Metabolic Fatty Liver Disease [MAFLD]

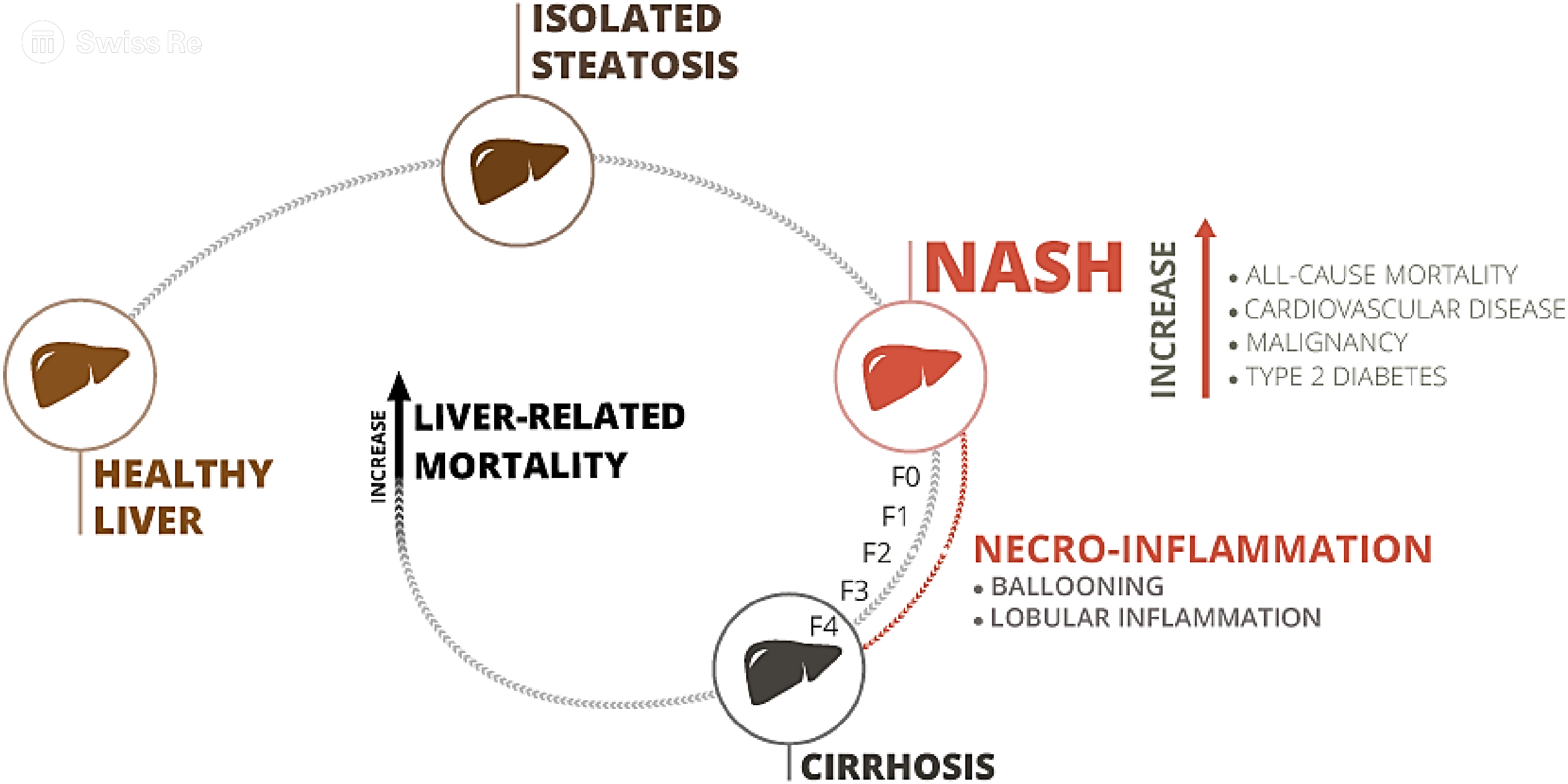
Changing terminology from alcoholic vs non-alcoholic distinction- 20-25% of adults population affected or 1.5 B

Autoimmune hepatitis

Chronic cholangiopathies

Increasing as viral hepatis is decreasing and vaccination rates improve

Fibrosis is reversable as after successful bariatric surgery or viral hepatitis treatment.

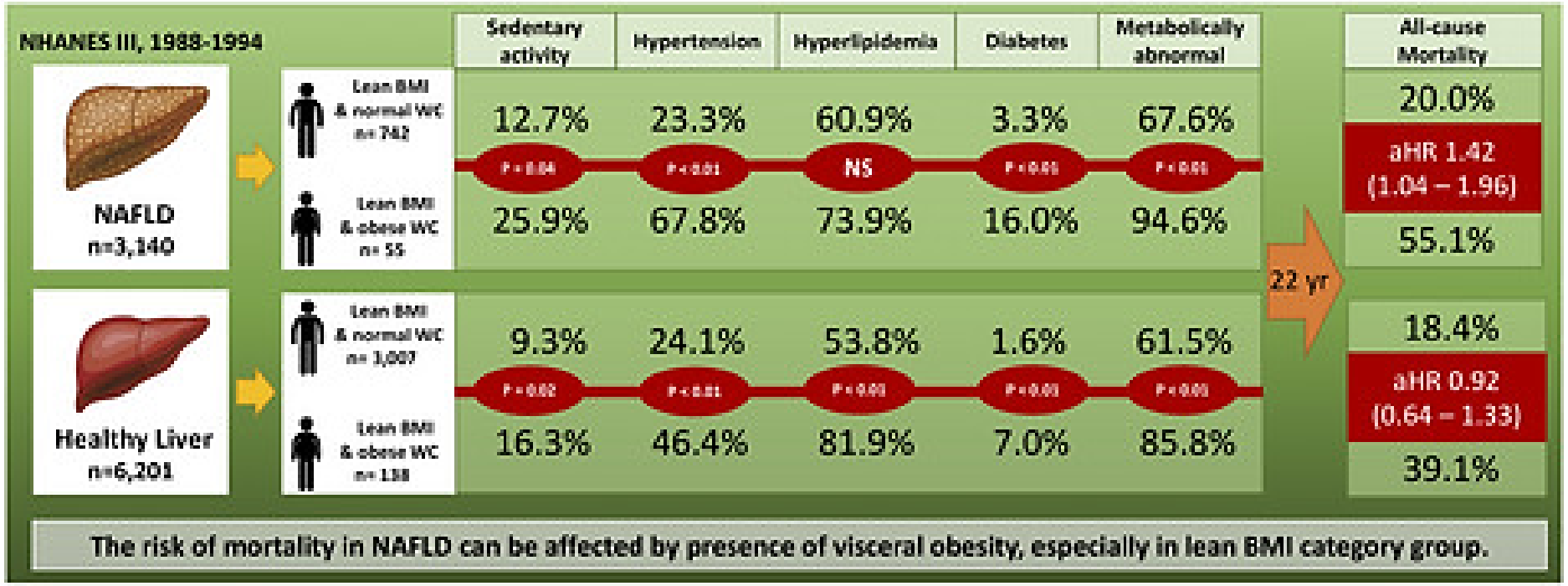

ISOLATED STEATOSIS
NASH
INCREASE
• ALL-CAUSE MORTALITY
• CARDIOVASCULAR DISEASE
• MALIGNANCY
• TYPE 2 DIABETES
HEALTHY LIVER
INCREASE
LIVER-RELATED MORTALITY
F0
F1
F2
F3
F4
NECRO-INFLAMMATION
• BALLOONING
• LOBULAR INFLAMMATION
CIRRHOSIS

Epidemiology of Non-Alcoholic Fatty liver Disease

- NAFLD- most common liver disorder in the Western industrialized countries ,about 30-35%
- Risk factors- Metabolic Syndrome: central obesity, type 2 diabetes, dyslipidaemia, insulin resistance, NAFLD is “de facto” to be a part of the metabolic syndrome
- Associated factors of disease progression: older age, elevated BMI,ETOH consumption
- Natural history of NASH/ NAFLD mirrors metabolic syndrome- CVD is primary
- Progression to cirrhosis and hepatocellular cancer still small -3%-5% over 30-50 years rather than 20-30 with infectious causes
- Progression fibrosis: about 50% stable,30% progress and 20% improve
- HCC-NASH less often diagnoses than in those with Hepatitis C and can develop without cirrhosis

  Inflammation + steatosis= steatohepatitis
- Metabolic-associated steatohepatitis

Mortality and BMI and waist Circumference in NAFLD



Golabi, et al. *Hepatol Commun*, 2020.

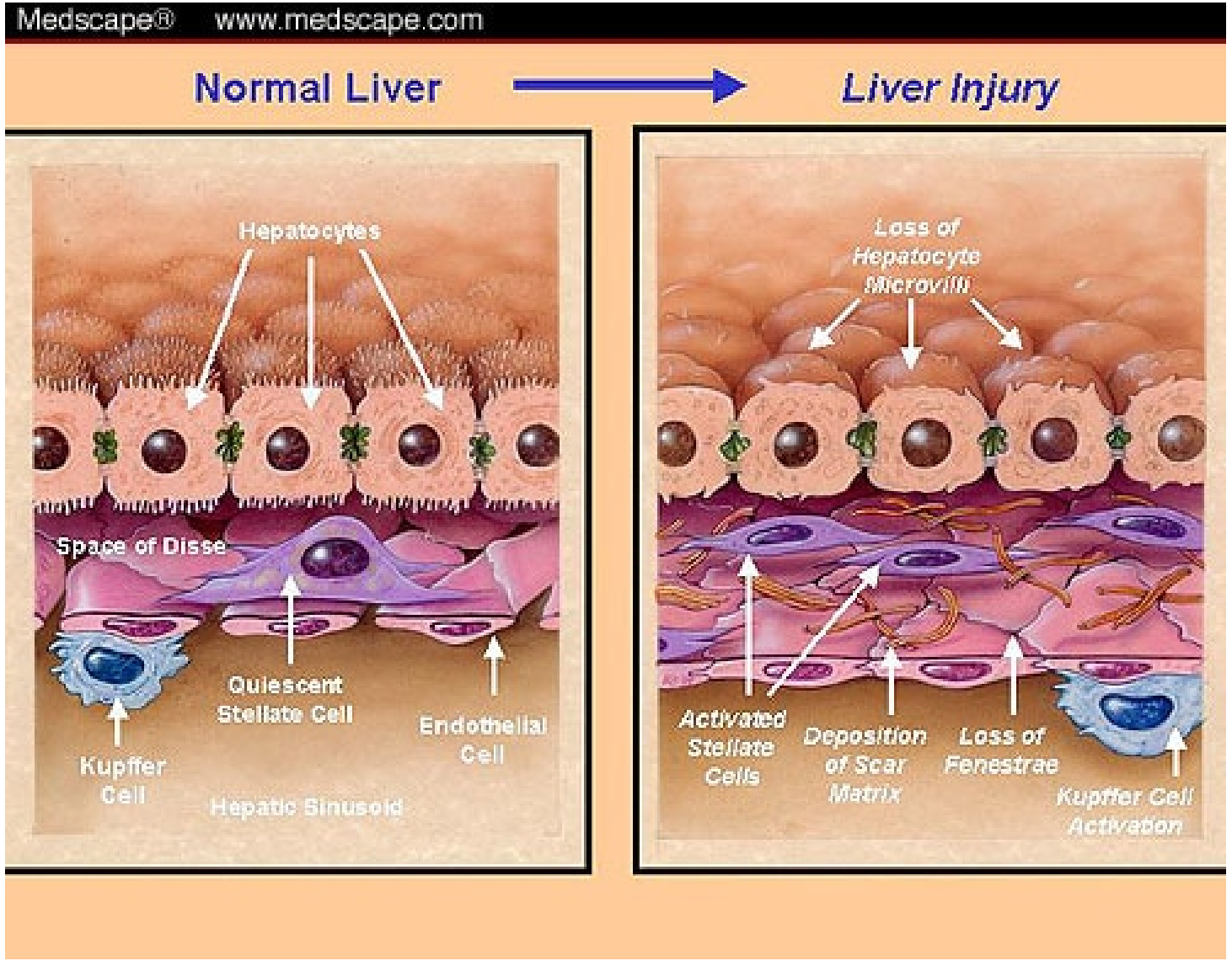
HEPATOLOGY COMMUNICATIONS

Fibrosis

- Chronic liver injury
- Fibrosis is a wound healing response to damaged tissue
- Major cause of global mortality and morbidity
- Most common cause is viral hepatitis
- Non-alcoholic and alcoholic liver disease-metabolic liver disease
- Several months to years, not clear when becomes non-reversable
- Activated stellate cells and fibroblasts
- Balance of matrix production and matrix degradation
- Liver architecture changes
- Increase in ALT and AST
- Fibrosis needs to proceed HCC but how fibrosis promotes cancer is unclear

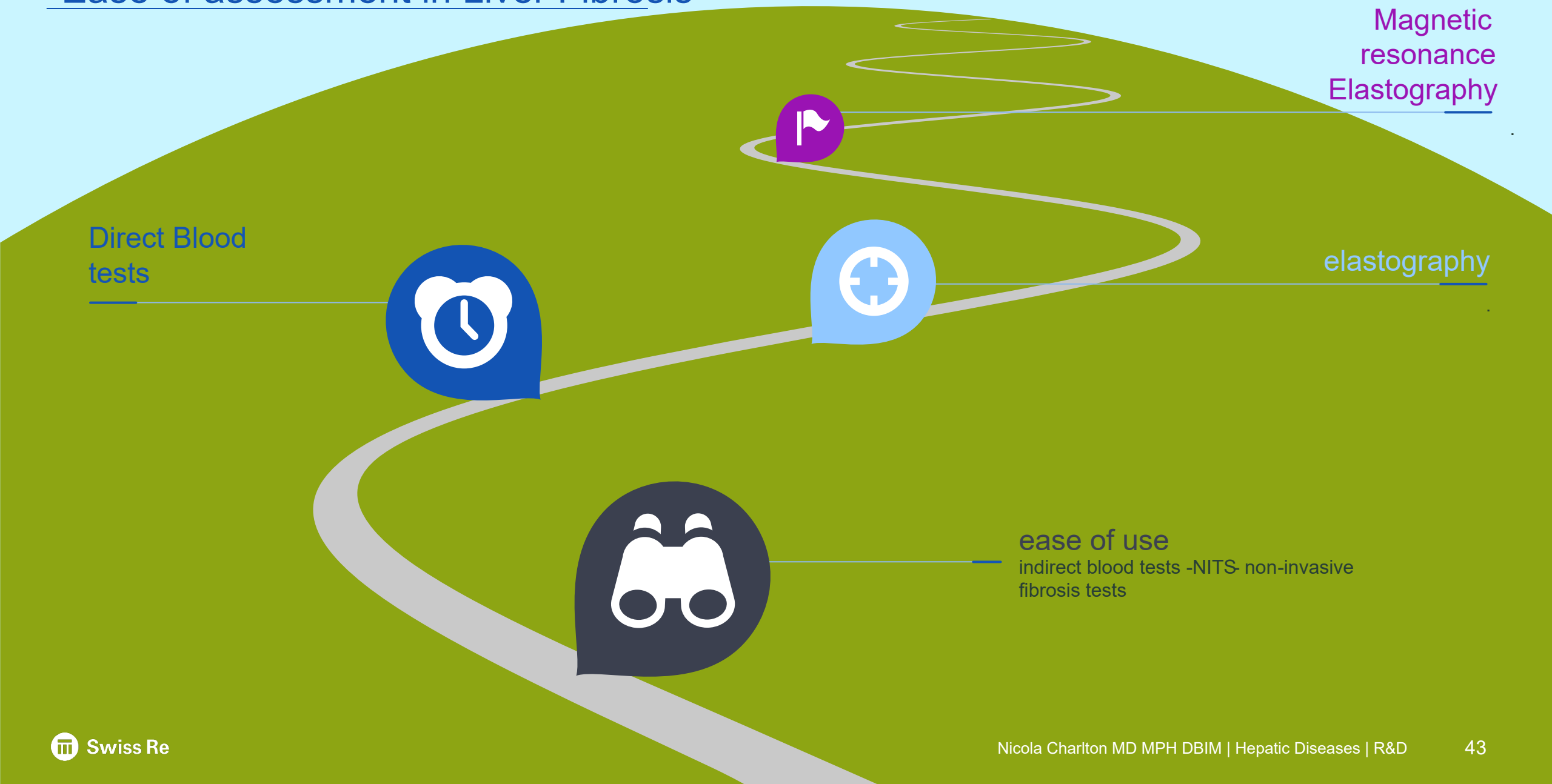
Hepatic Fibrosis:

Role of Hepatic Stellate Cell Activation



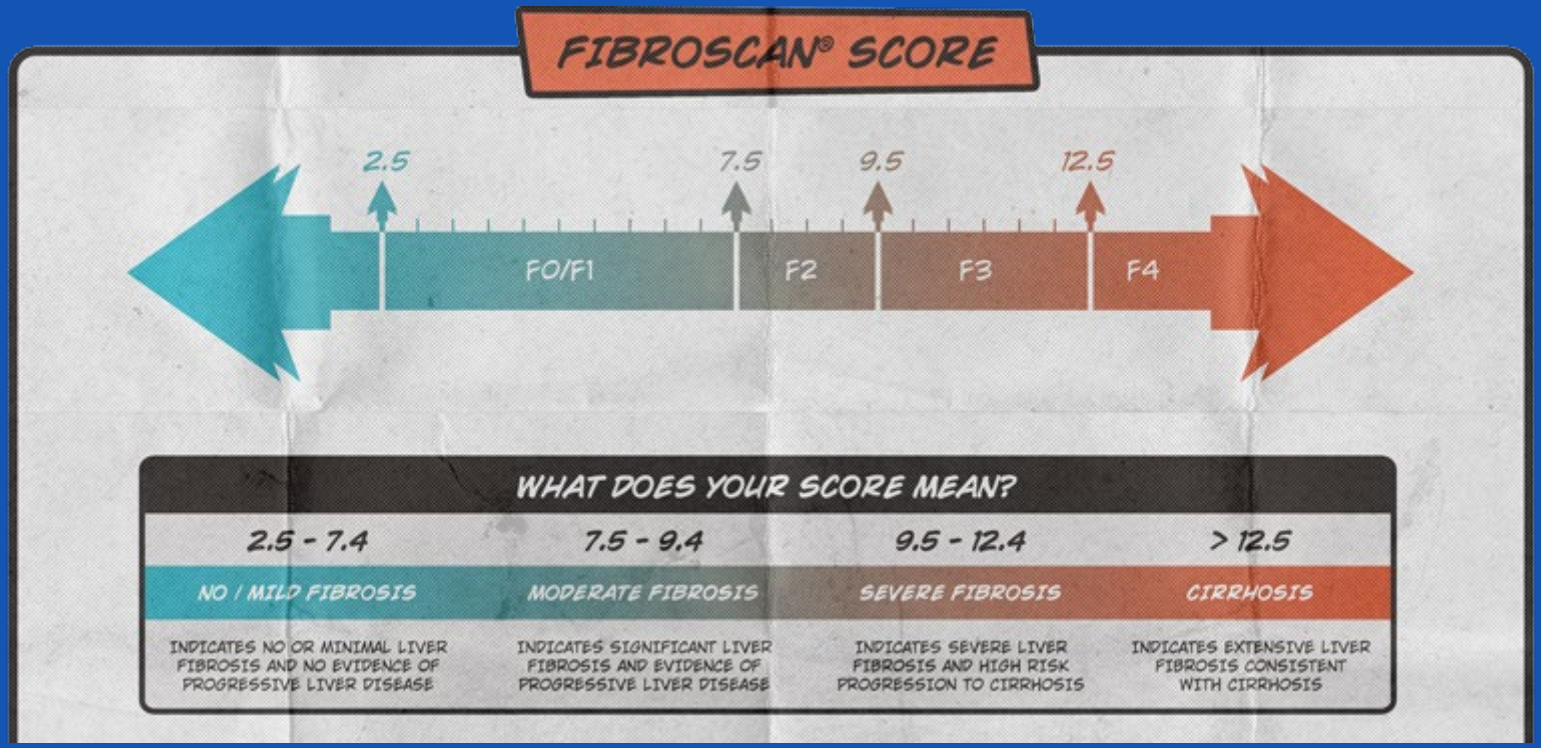
Hepatic Fibrosis- Role of Hepatic Stellate Cell Activation Medscape- Jul 16, 2002.

Ease of assessment in Liver Fibrosis



Fibrosis Scores: Non-Invasive

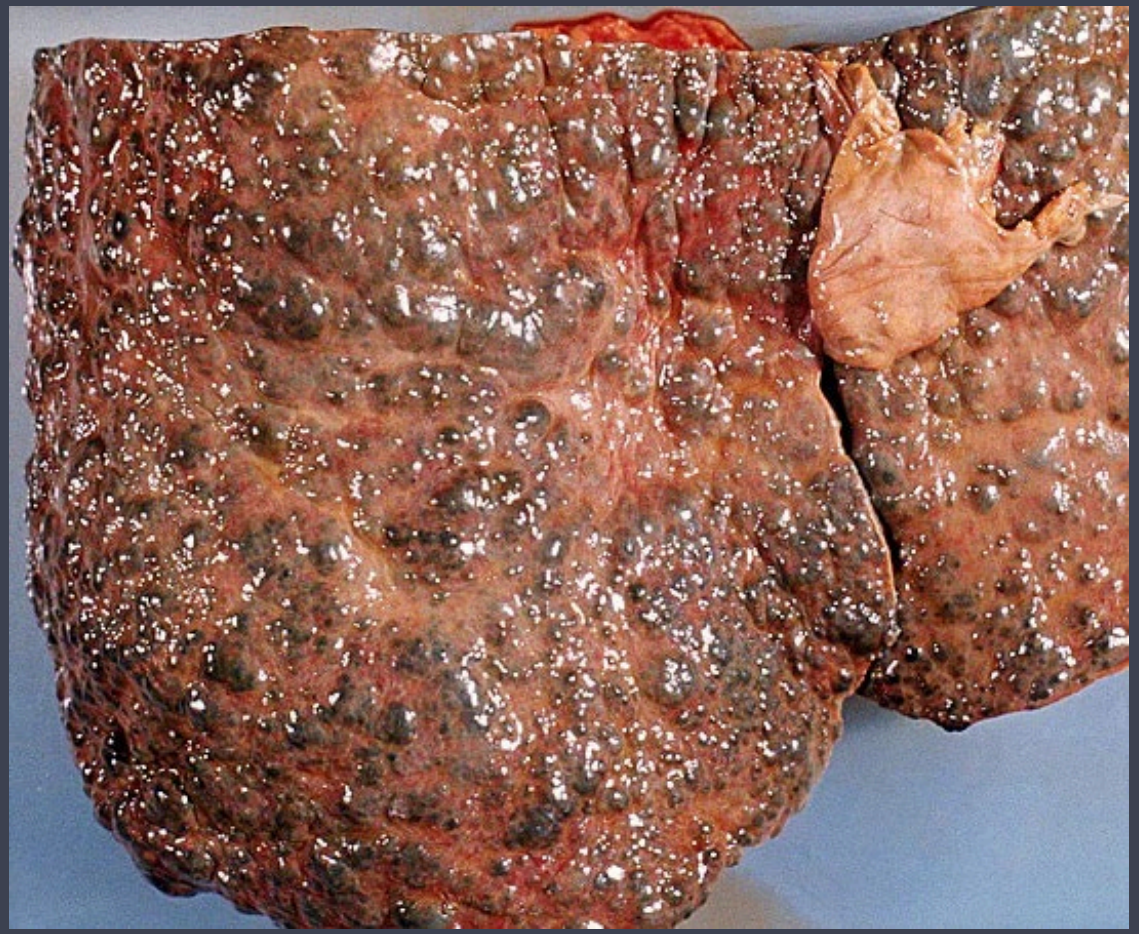
- NAFLD Fibrosis Score
- Fibrosis-4
- Bard score
- AST to PLT Ratio (APRI)
- AST to ALT Ratio (AAR)
- FibroMeter
- eLIFT
- HEPAMET Score
- FibroTest



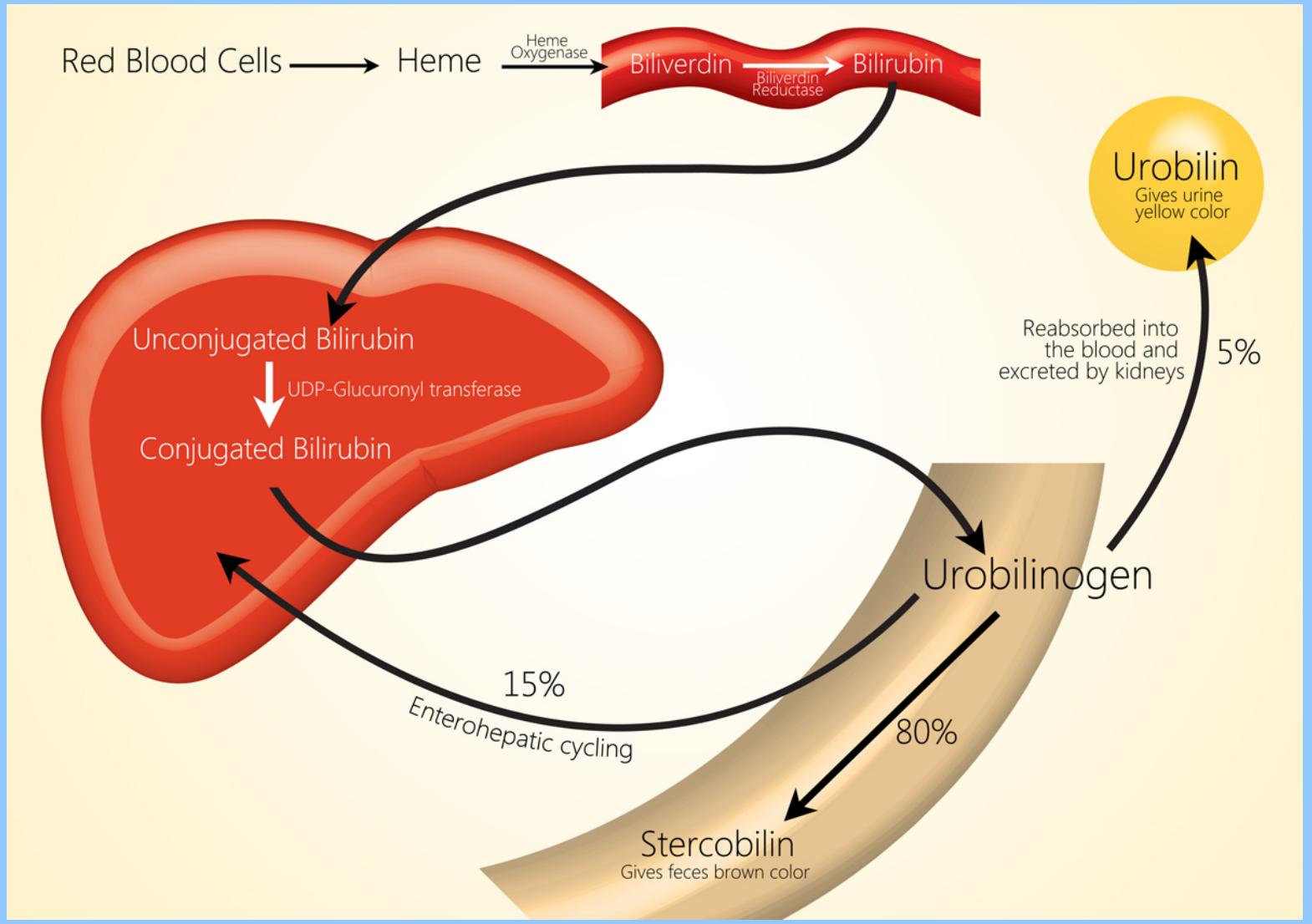
Cirrhosis

- Chronic liver disease: where fibrosis replaced damaged or dead hepatocytes
- Irreversible
- Alcoholic liver disease is most common
- Chronic hepatis B and C
- Drugs: methotrexate, acetaminophen toxicity
- Liver biopsy is gold standard diagnosis

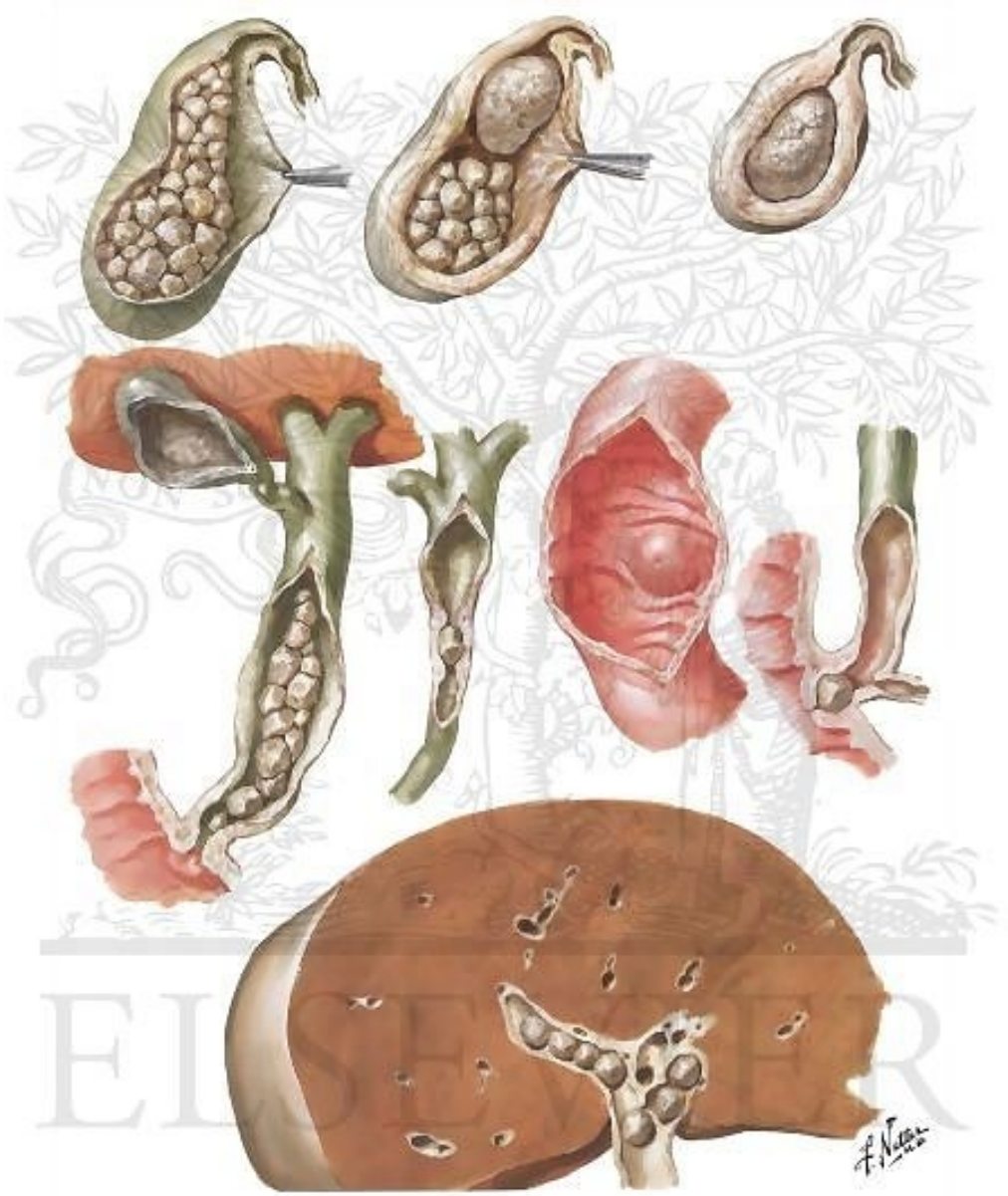
Child-Pugh score predicts severity: ascites, bilirubin, encephalopathy, inr ratio, albumin



Bilirubin Metabolism



Cholithiasis
Choledochal Lithiasis, Intrahepatic Stones

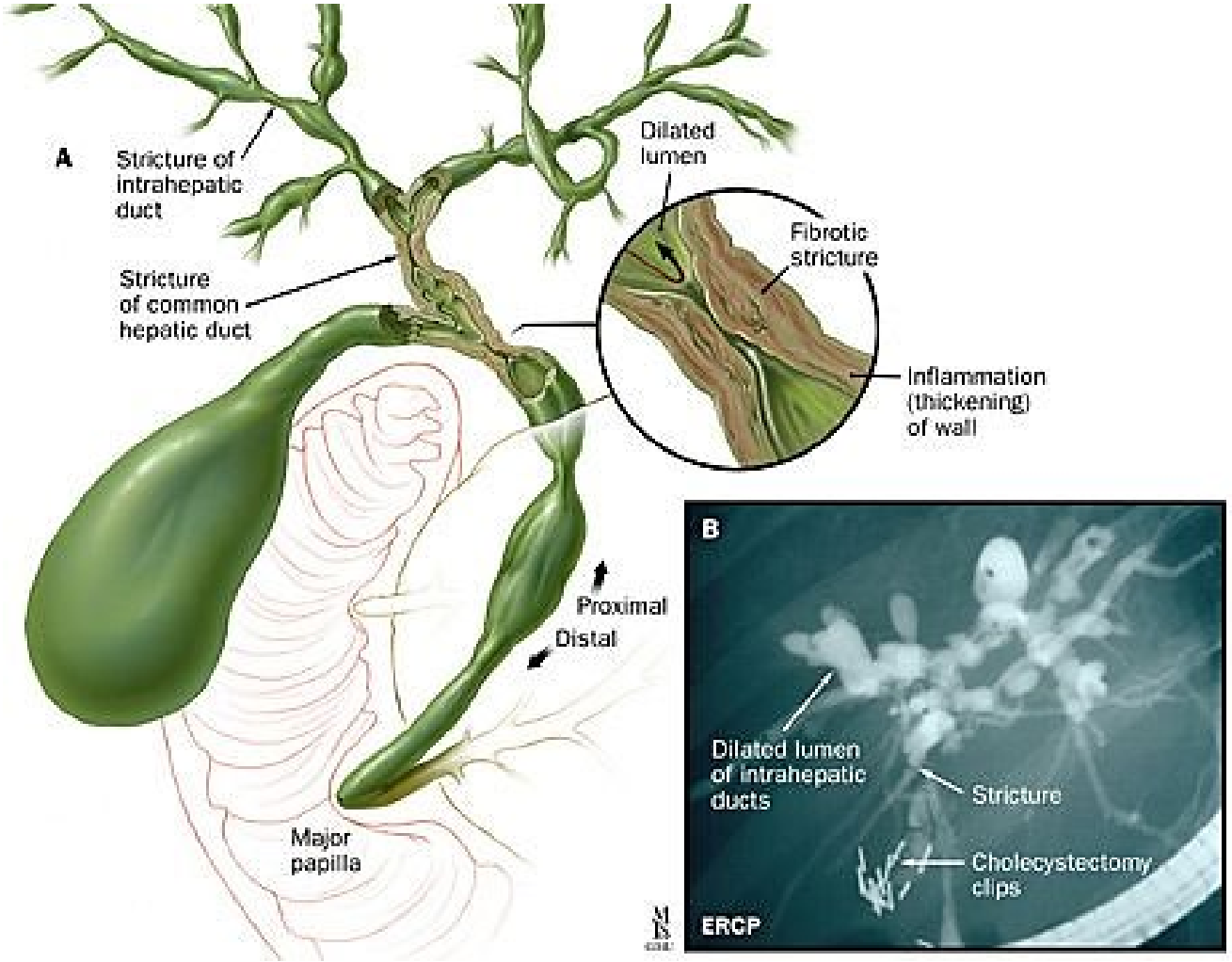


Primary Biliary Cholangitis (PBC)

- Autoimmune disease were T cells of the immune system attack the cells that line the bile ducts of the liver
- Associated with other autoimmune diseases; interplay of genetics and environment leads to loss of self-tolerance
- Male: female is 9:1 ratio
- Makes antibodies to mitochondria or AMA ,which is elevated in the blood- molecular mimicry
- Bile leaks out of cells and cause inflammation
- Destroyed cells eventually cause fibrosis than cirrhosis
- Rarely lead to liver cancer
- Generally found in an asymptomatic phase from elevated liver enzymes on routine blood tests
- Secondary PBC: same clinical picture but damaged bile duct cells from a tumour so similar picture but no anti- mitochondrial antibodies

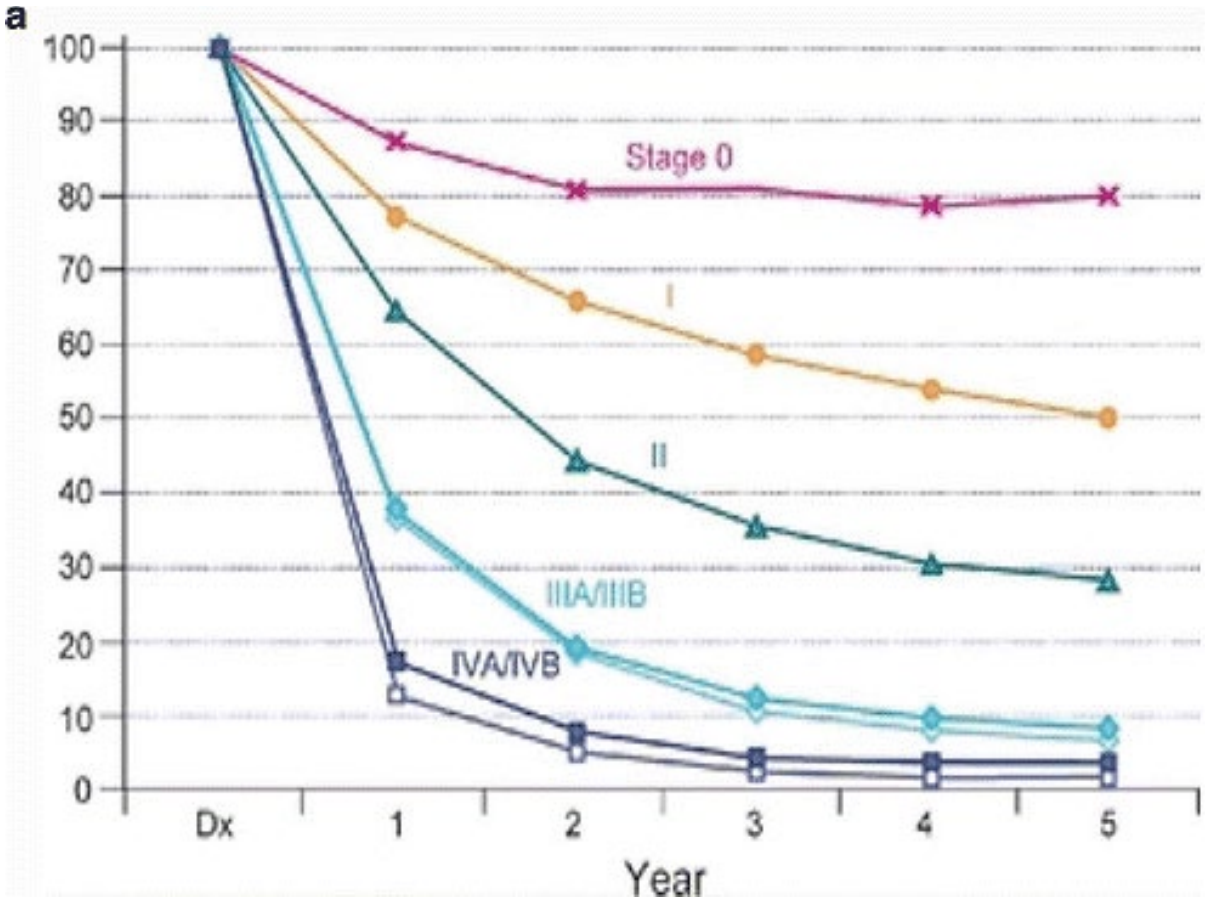
PBC

- Diagnosis 2/3 : evidence of cholestasis with an alp elevation, presences of the ama autoantibody (10% are neg), histologic evidence of destruction of liver cells
- Associated with other autoimmune diseases
- DDX: drug induced liver disease, sarcoidosis, amyloidosis of liver
- Medications slow progression and people who have a biochemical response criteria do very well with a normal life expectancy
- GLOBE score: serum bilirubin, alp, age at onset, platelet count after one year of therapy, albumin: estimates the difference in survival



Gallbladder Cancers

- Generally advanced when found, only 1in 5 are in an early stage
- 4,500 deaths in US a year from gallbladder cancer
- Rare and mainly adenocarcinomas
- Papillary adenocarcinoma- better prognosis
- Gallbladder polyps maybe pre-cancerous and most over 10mm are resected. less than 10mm very few are cancerous UNLESS has PBC
- 1% of removed gallbladders have a positive cancer on pathology
- Porcelain gallbladders: contiguous calcification is a marker of cancer not segmental



Liver Regeneration and Liver Transplant

- The only organ that can completely regrow
- Second most common transplant after kidney
- The transplant survival very good short-term but still poor long-term with most effects from the immunosuppressive drugs causing malignancy
- 7,000 in US a year
- Regeneration of liver possible even if 50% removed
- Biliary cells become stem cells for the hepatocyte
- Regeneration in mass not necessarily size

Prometheus

Any questions?

Swiss Re

Thank you!

Contact us

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