Ujian Diagnostik
Viral Load , Genotyping , Fibroscan

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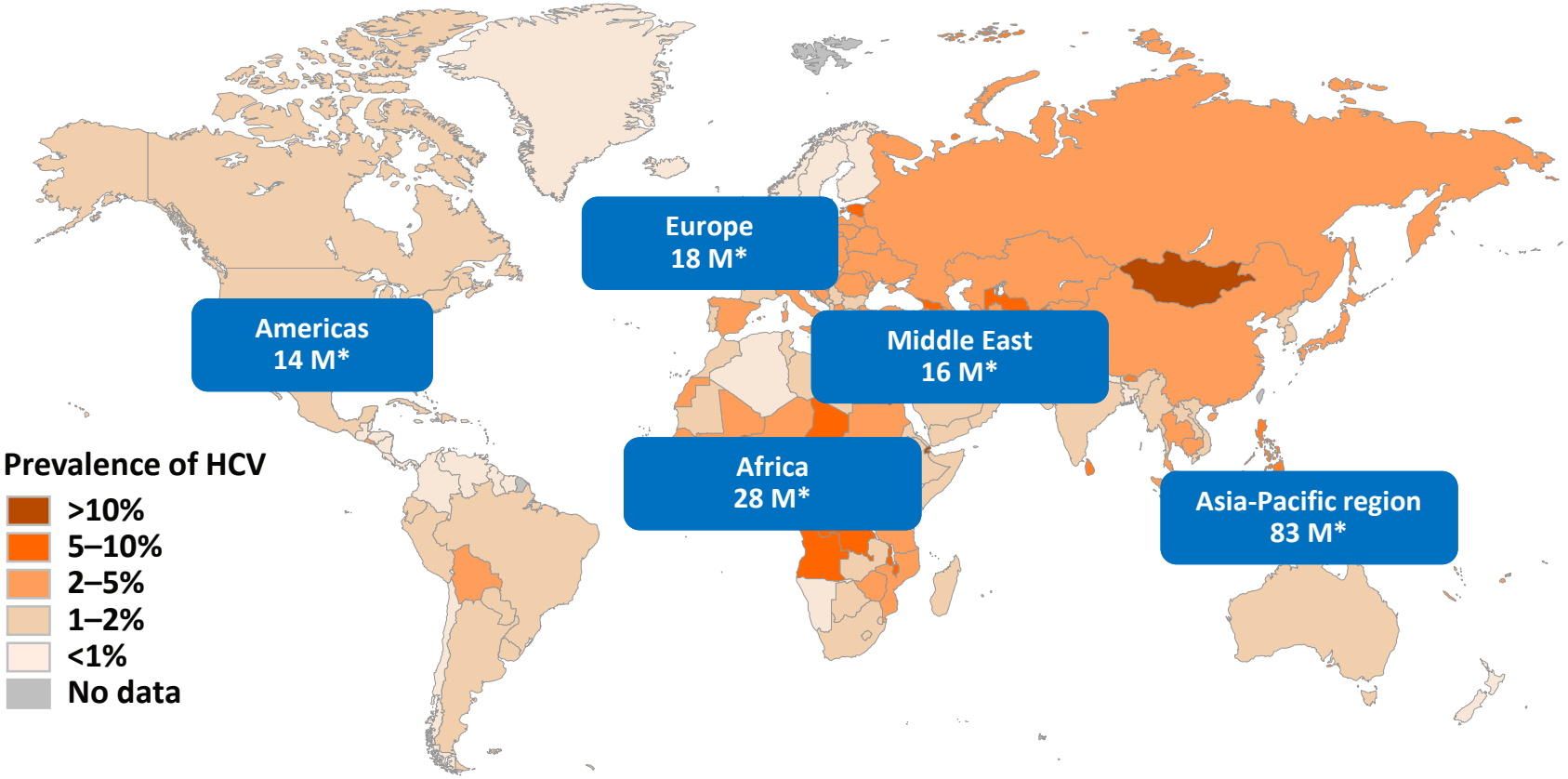
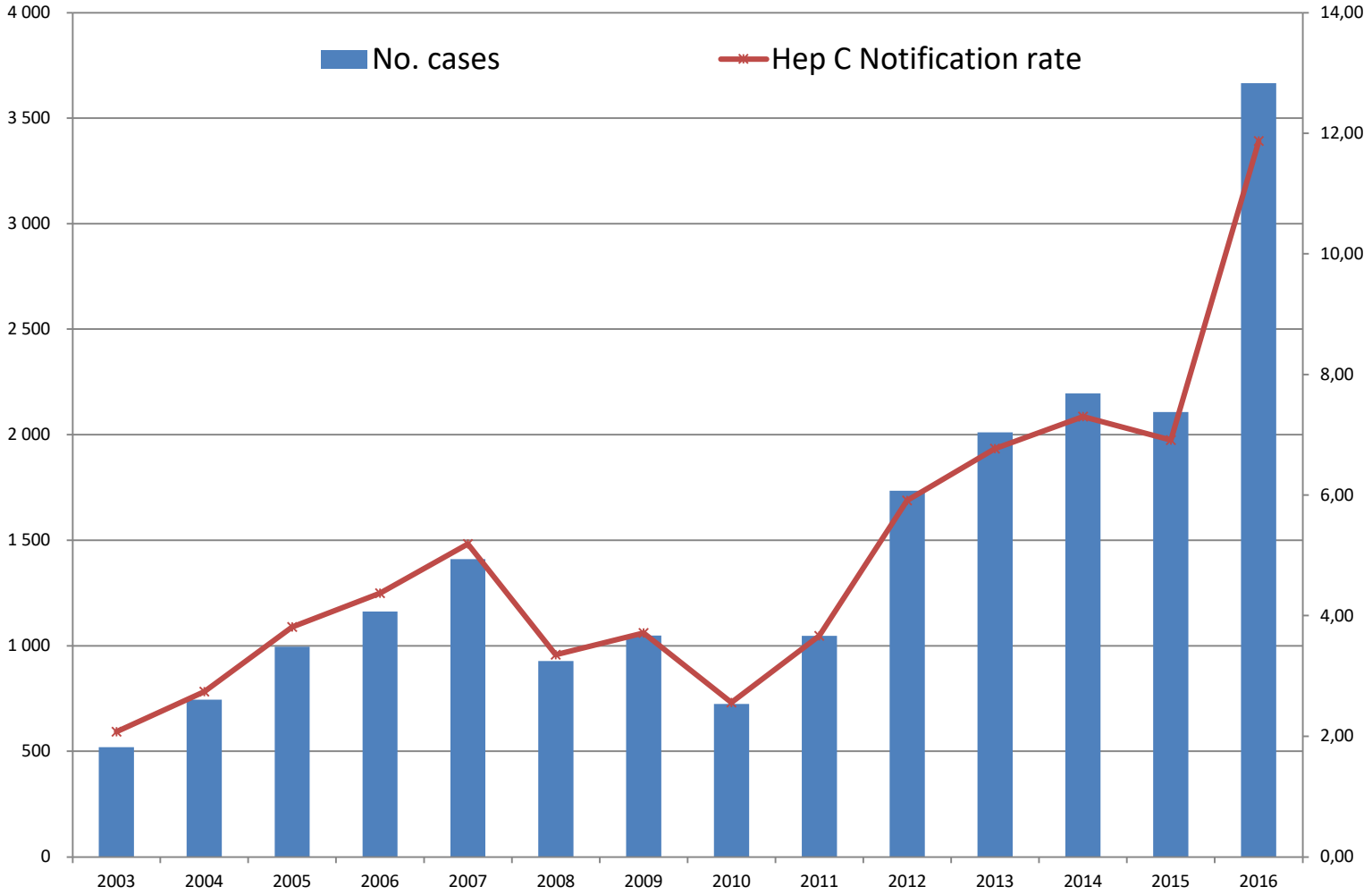
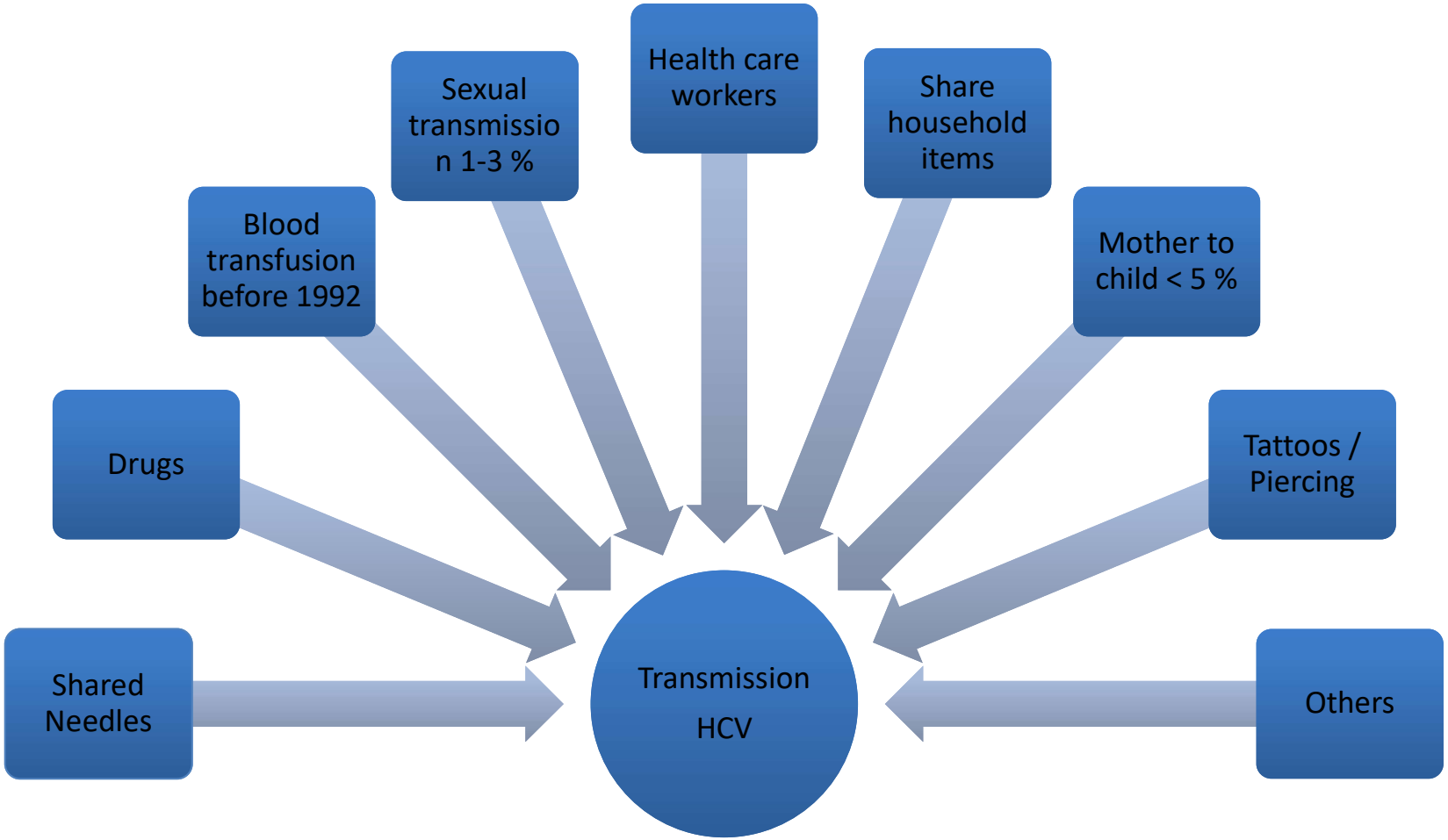
HCV Distribution Across the World



* Estimated number of chronically infected individuals (2010).
Lavanchy D. Clin Microbiol Infect. 2011; 17:107–115; CDC:
http://wwwnc.cdc.gov/travel/yellowbook/2012/chapter-3-infectious-diseases-related-to-travel/hepatitis-c.htm;
WHO Prevention and control of viral hepatitis infection http://who.int/csr/disease/hepatitis/GHP_Framework_En.pdf?ua=1.

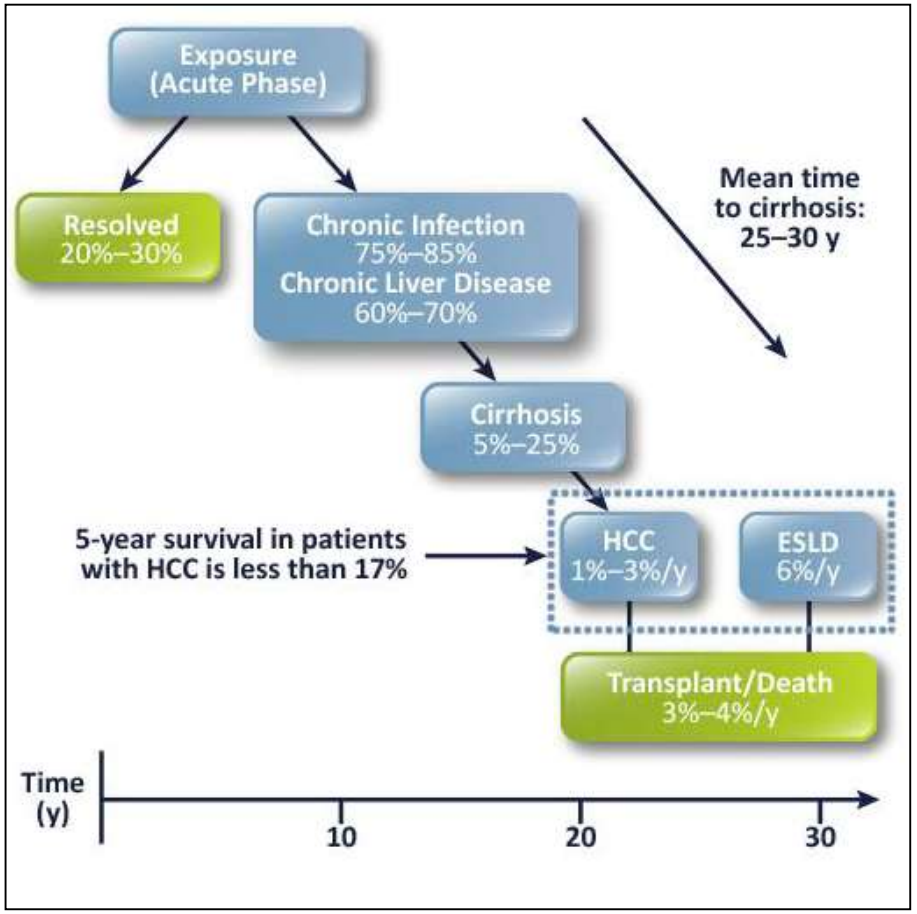

No. cases
Hep C Notification rate
4 000
3 500
3 000
2 500
2 000
1 500
1 000
500
0
14,00
12,00
10,00
8,00
6,00
4,00
2,00
0,00
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016

Transmission and Prevention

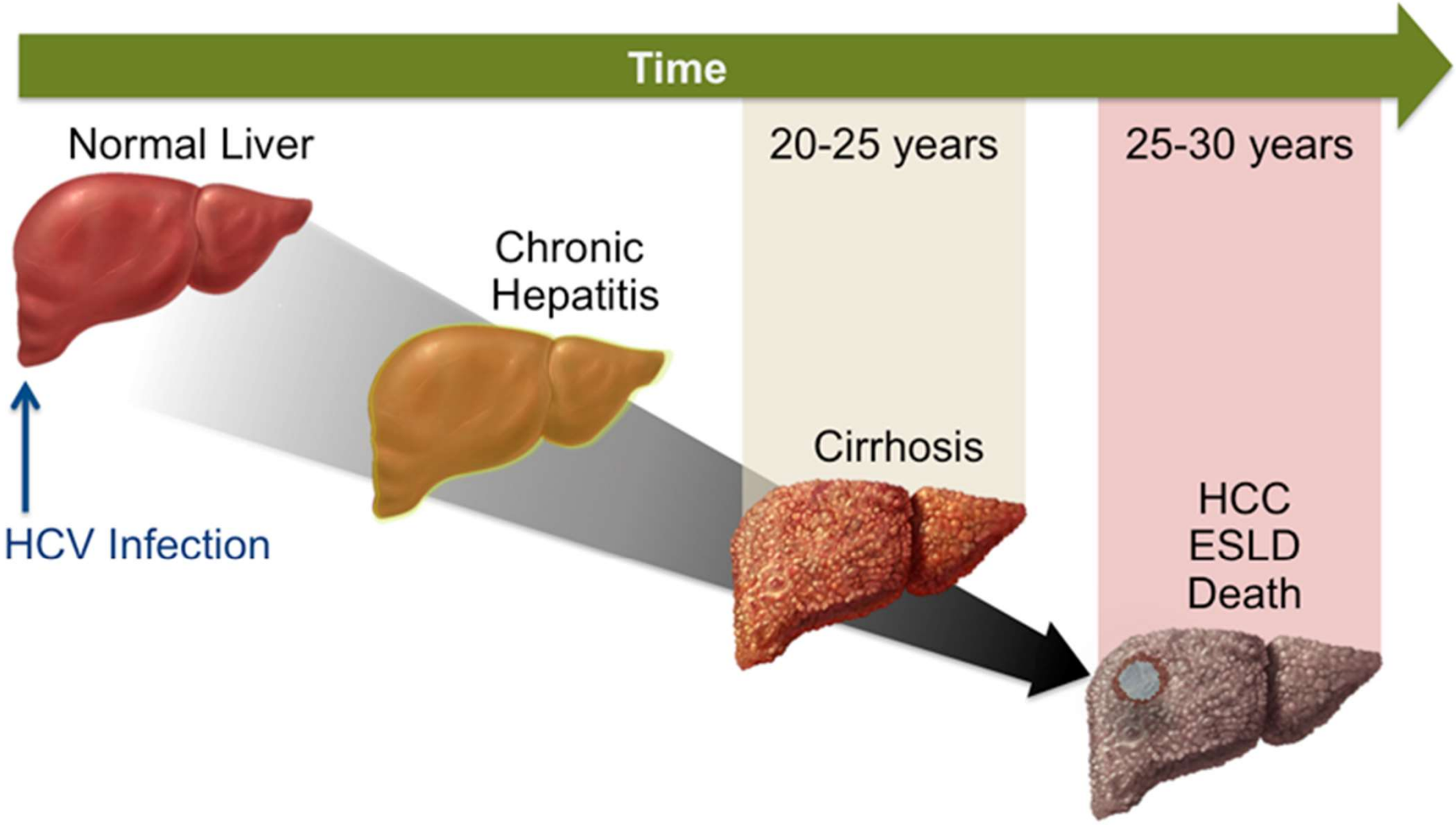


Natural History of HCV Infection Overview

- Majority of patients with acute HCV infection develop chronic hepatitis C
- Chronic HCV infection sequelae
- Progressive liver fibrosis leading to cirrhosis
- End-stage liver disease (ESLD)
- Hepatocellular carcinoma (HCC)

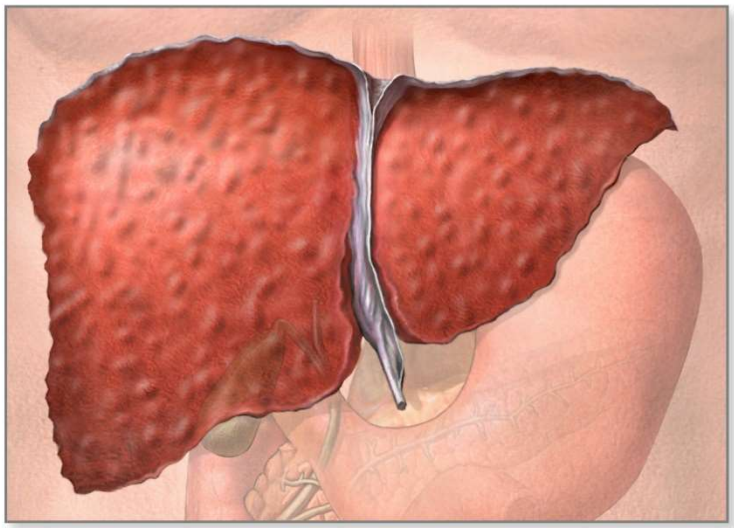


Howlader N, et al. SEER Cancer Statistics Review, 1975-2010, National Cancer Institute. Bethesda, MD, based on November 2012 SEER data submission, posted to the SEER web site, April 2013.
Ghany MG, Strader DB, Thomas DL, et al. Hepatology. 2009;49(4):1335–1374.


Time
Normal Liver
20-25 years
25-30 years
Chronic
Hepatitis
Cirrhosis
HCC
ESLD
Death
HCV Infection

Cirrhosis Overview

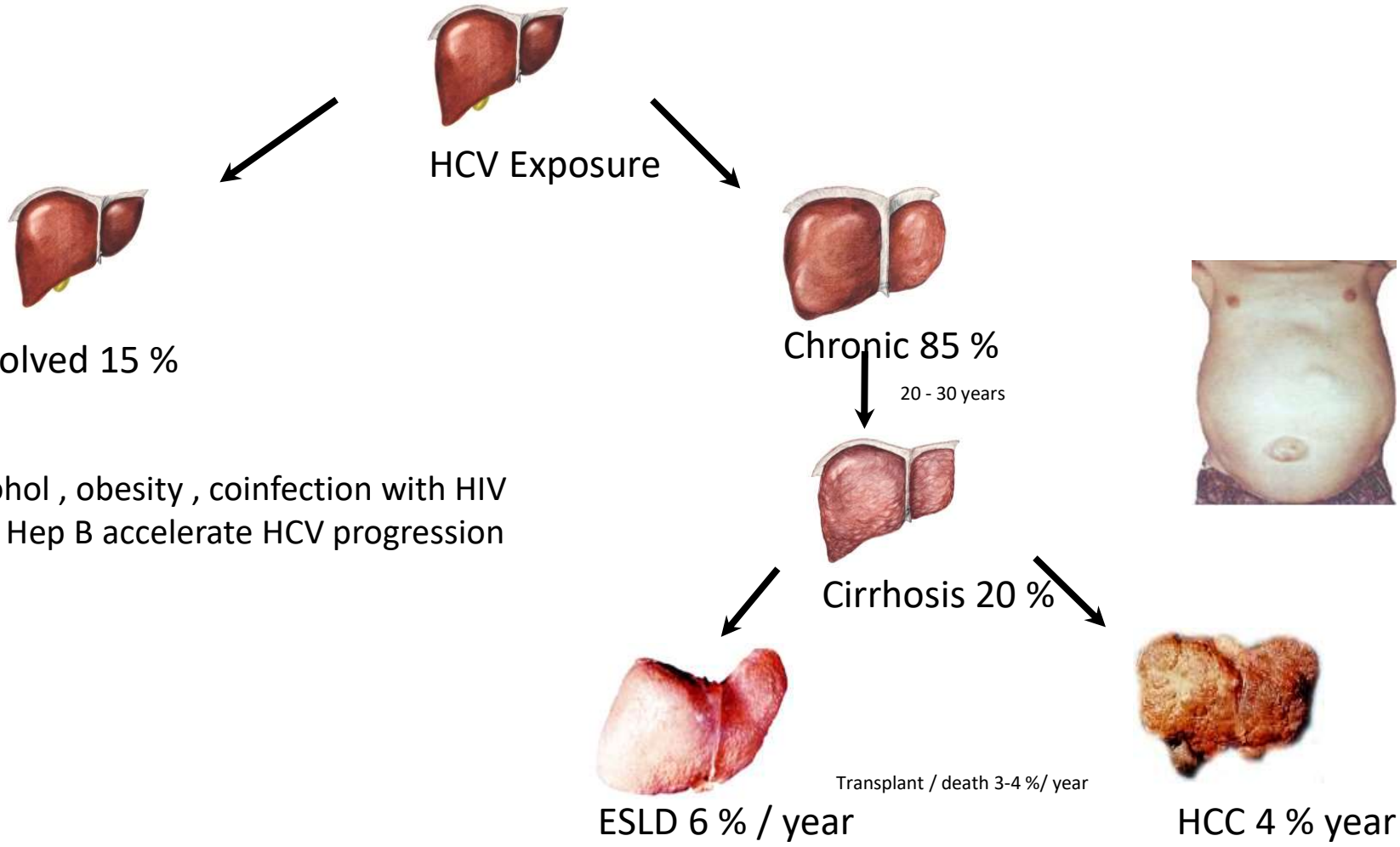
- HCV disease progression to cirrhosis is often clinically silent
- Some patients are not diagnosed with HCV until the complications of end-stage liver disease become apparent
- The natural history of cirrhosis is characterized by an initial phase (compensated), followed by a rapidly progressive phase marked by complications (decompensated)



A.D.A.M.

Garcia-Tsao et al. Goldman's Cecil Medicine. 24th ed. Philadelphia, PA: Saunders; 2012:999-1007.
Kochar et al. Andreoli and Carpenter's Cecil Essentials of Medicine. 8th ed. Philadelphia, PA: Saunders Elsevier; 2010:478-487.
O'Leary et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th ed. Philadelphia, PA: Saunders Elsevier; 2010:1313-1335.
Chen et al. Int J Med Sci. 2006;3(2):47-52.

The NATURAL HISTORY OF HCV INFECTION IN UNTREATED PATIENTS



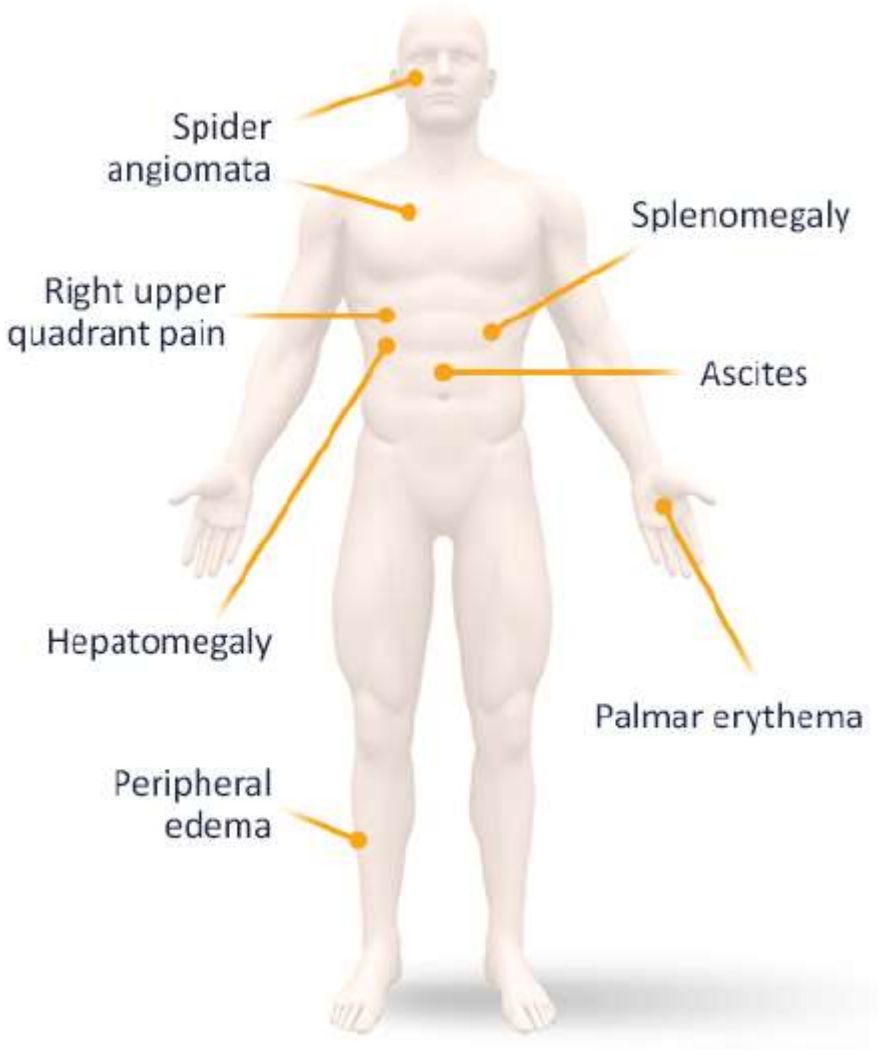
% = percent of original group;
ESLD, End-Stage Liver Disease.

Di Bisceglie AM, et al. Hepatology 2000; 31:1014–1018;
Chen SL, Morgan TR. Int J Med Sci. 2006; 3:47–52.

Signs and Symptoms of Liver Disease

- The signs and symptoms of liver disease are varied and often vague
  - 60-70% no discernable symptoms
  - 20-30% (+) jaundice
  - 10-20% nonspecific symptoms

- Common presenting symptoms and signs of liver disease include:
  - Fatigue
  - Pruritus
  - Jaundice
  - Nausea



Martin P. Approach to the patient with liver disease. In: Goldman's Cecil Medicine. 24th ed. 2012:952–956.

HCV Antibody

- When a person is exposed to HCV, the immune system produces proteins called antibodies against the virus. It usually takes the immune system a few weeks to develop enough antibodies to be detected by an antibody test, but it could take as long as six months.
- There are two commercial antibody tests used to detect HCV antibodies— HCV EIA (HCV ELISA) and CIA. The most common HCV antibody test is the HCV EIA or ELISA.
- A positive HCV antibody test will only confirms that someone has been infected with the hepatitis C virus at one time; an HCV RNA viral load test will need to be performed to find out if someone is actively infected with the hepatitis C virus.

HCV Antibody

- Once people are exposed to hepatitis C, they will retain HCV antibodies for life even if the body is able to eliminate the hepatitis C virus either naturally or if the person is cured by medical treatment.
- It is also important to remember that HCV antibodies do not protect people from infection or reinfection of hepatitis C.

Interpretations of HCV assay

Anti-HCV	HCV RNA	Interpretations
Positive	Positive	Acute or chronic HCV infection (to differentiate: history and clinical context)
Positive	Negative	Resolution of HCV-acute HCV already with low viraemia
Negative	Positive	•Early acute HCV •HCV in immunosupressed •False positive HCV RNA
Negative	Negative	Absence of HCV infection.

*HCV RNA can be detected by 2 weeks of exposure
*Anti HCV – 8- 12 weeks

HCV Antibody

- HCV ELISA immunoassay (EIA)
- Most common antibody test
- Positive antibody test indicates exposure
- Does not indicate active Hepatitis C infection

HCV Viral Load

- A viral load test measures the amount of HCV RNA (genetic material) in the blood. This test is used to confirm active HCV infection.

- There are two types of viral load tests:

1. Qualitative:

Measures the presence of the virus in the blood. This type of test is usually used to confirm initial and chronic infection with HCV.

- If HCV RNA is detected, a positive result is reported

If HCV RNA is not detected, the test result is negative

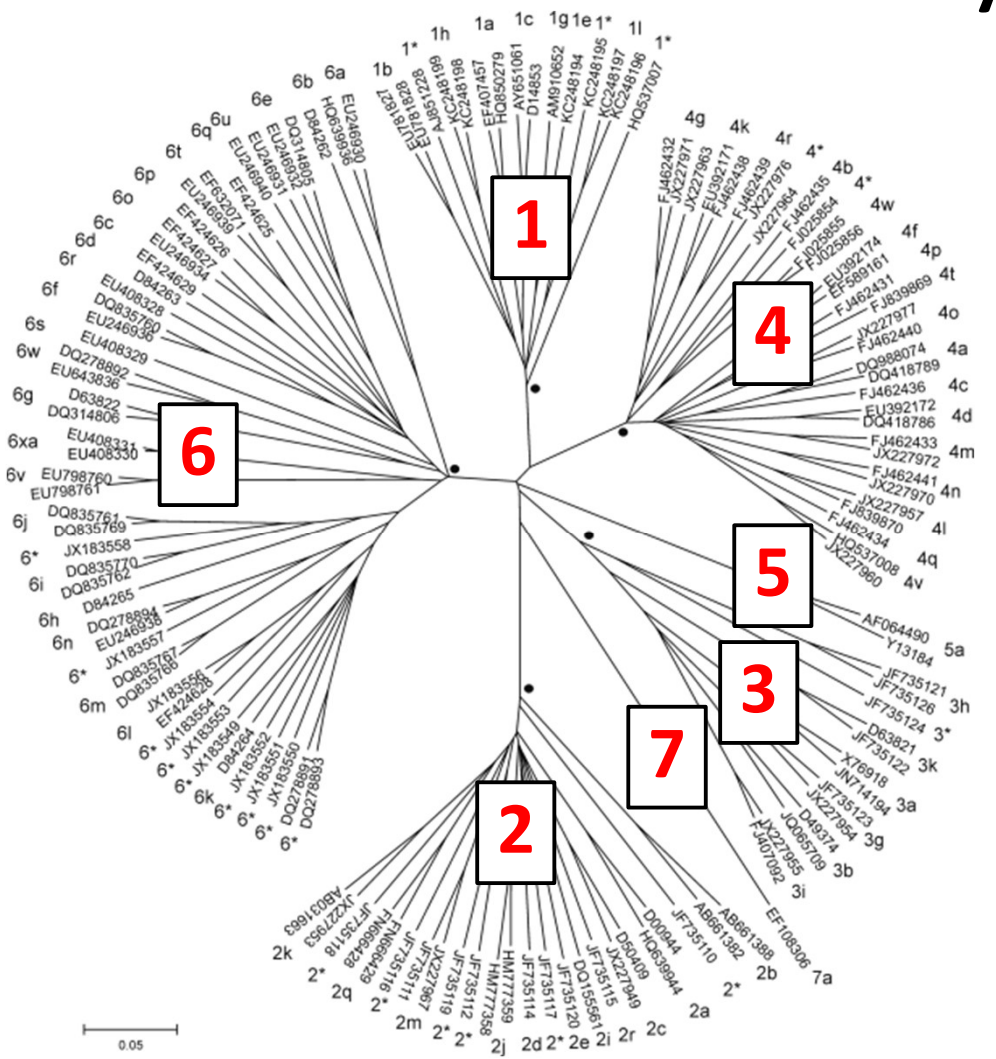
2. Quantitative:

Measures the amount of virus in the blood. This test generally is used for HCV treatment to determine if a patient is responding or has responded to treatment.

- Scientific studies have not found any correlation between viral load and disease progression.

- A viral load test requires a blood sample.

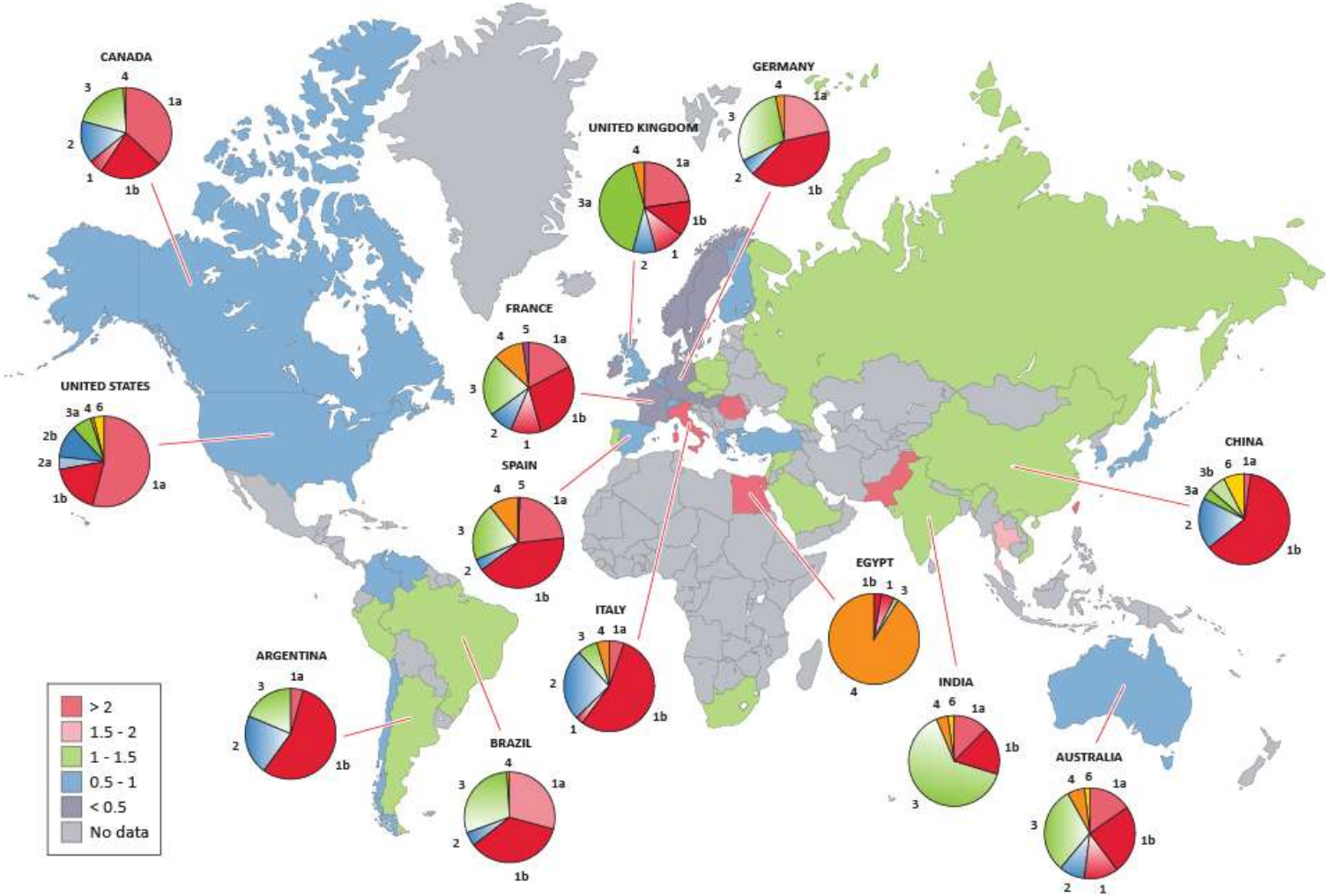
HCV is a Genetically Diverse Virus



Hepatitis C virus is classified into **7** distinct genotypes and **67** subtypes

Smith DB, et al. Hepatology. 2014;59:318–327. HCV Sequence Database (http://hcv.lanl.gov).

Geographical Distribution of HCV Genotypes 1–6*



* The region of endemicity for GT7 remains to be definitively established5

1. Alberti A, Negro F. Liver Int. 2011;31(suppl 2):1–3; 2. Kershenobich D et al. Liver Int. 2011;31(suppl 2):18–29;
3. Cornberg M et al. Liver Int. 2011;31(suppl 2):30–60; 4. Negro F et al. Liver Int 2011; 31 Suppl 2:1–3;
5. Smith DB, et al. Hepatology 2014; 59:318–327.

HCV Genotype/Subtype

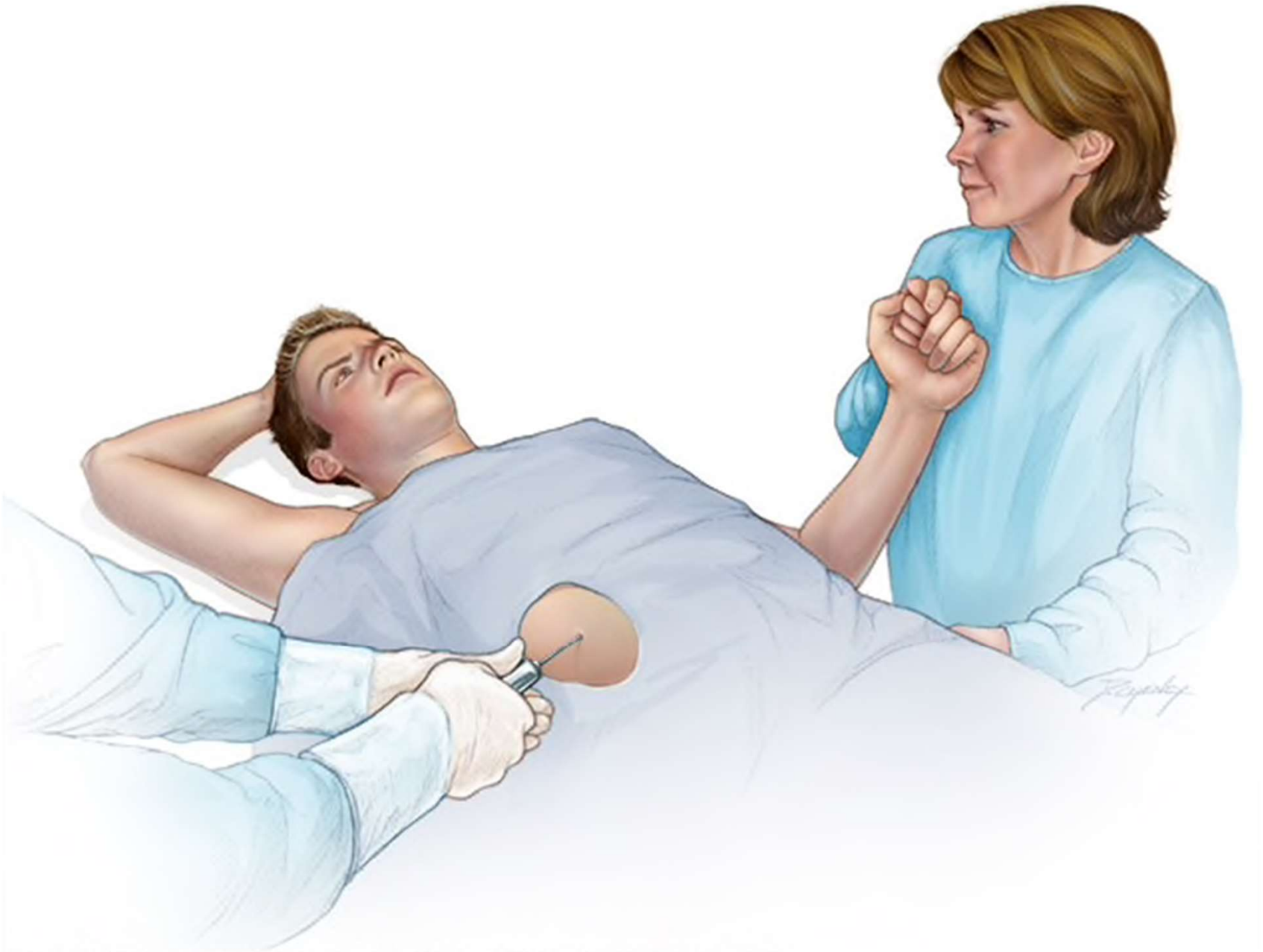
- There are several strains of hepatitis C, called genotypes. These strains are very similar but have enough genetic diversity to classify them into seven major genotypes: 1, 2, 3, 4, 5, 6 and 7.
- Genotype 1 is the most common genotype (70-75%) in the United States, followed by genotypes 2 and 3 (25-30%). Genotypes 4, 5, 6 and 7 are less prevalent in the United States.
- In Malaysia the most common Genotype is Genotype 3 , followed by Genotype 1

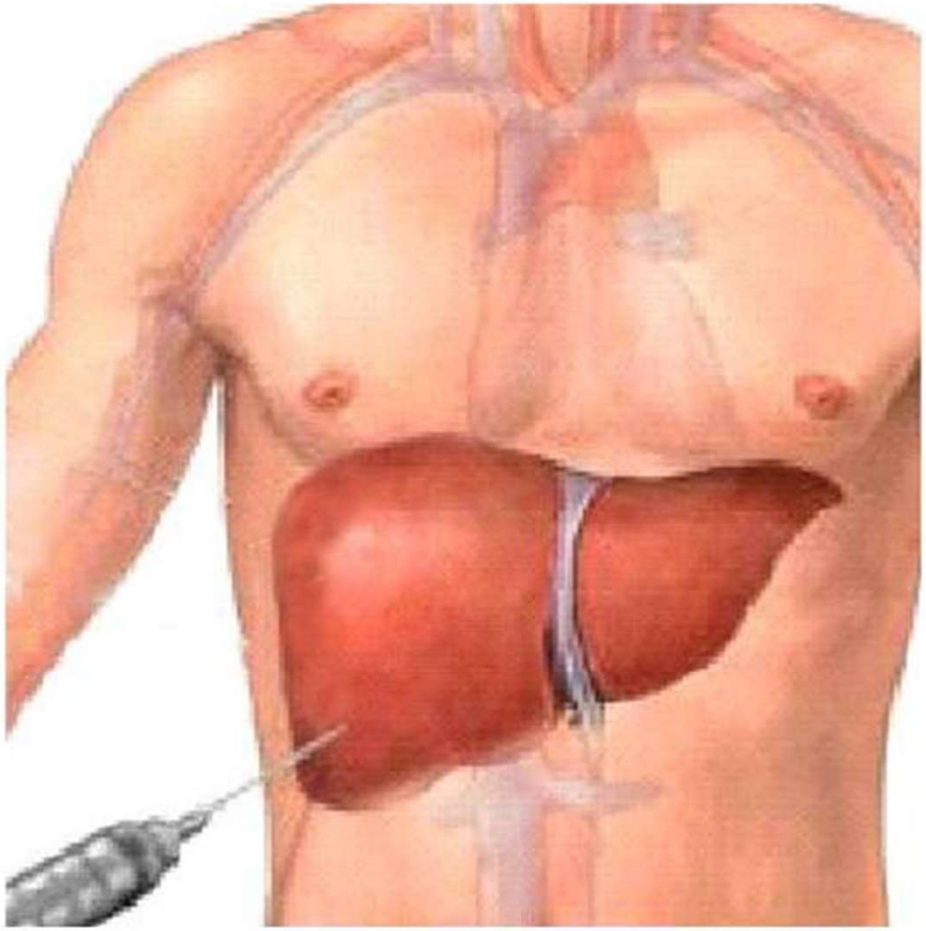
HCV Genotype/Subtype

- A genotype/subtype test is generally given to someone who is considering HCV medical treatment and is only performed once since a person's genotype remains the same throughout the course of the disease unless they become re-infected with another genotype.
- Genotype and subtype tests require a blood sample

Liver Biopsy

- The actual procedure to extract the liver specimen only takes a few seconds. After the procedure a patient will be required to lie on their right side (where the needle was inserted) for a few hours so that they can be monitored. About 30-50% of people experience mild to moderate pain.
- Complications from a liver biopsy rarely occur (1 in 1,000 biopsies or less). If necessary, people can ask their medical professional for a mild tranquilizer before a biopsy and for pain medication after the procedure.

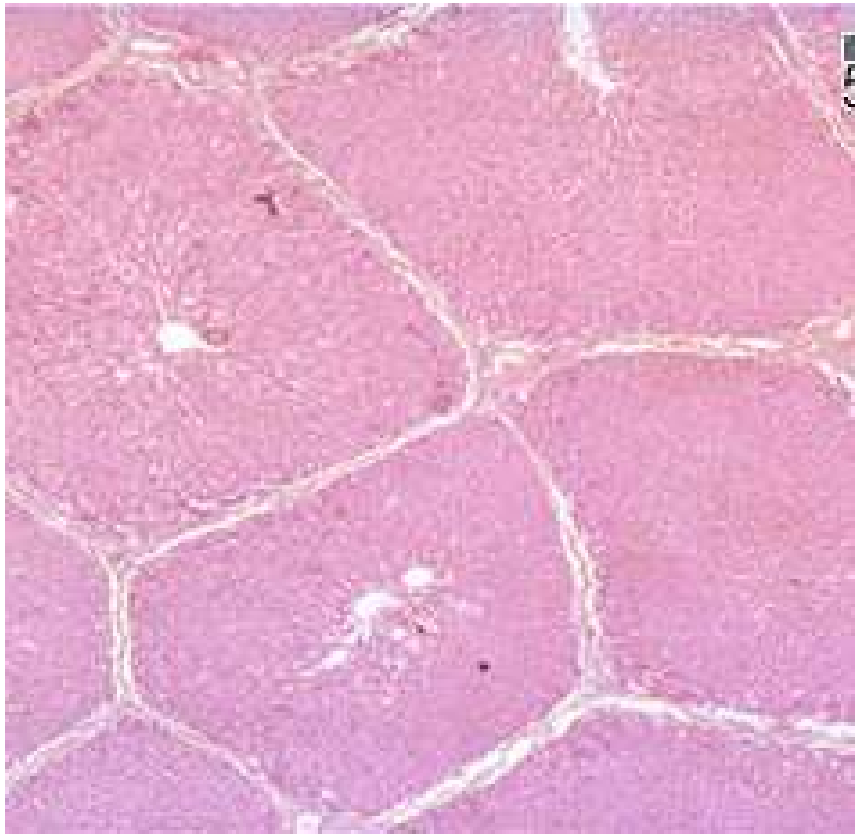




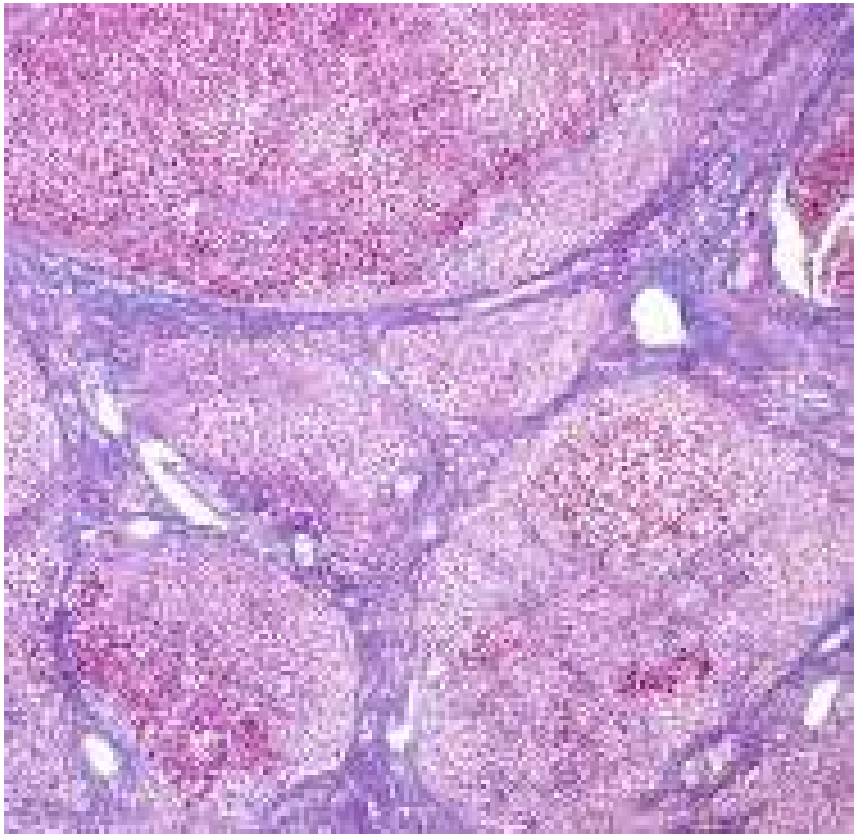
Liver Biopsy

- The liver biopsy is generally only performed once, but it may be performed every 5-7 years to gauge disease progression. Due to the cost and the potential health risks the alternatives listed below are replacing the percutaneous liver biopsy.

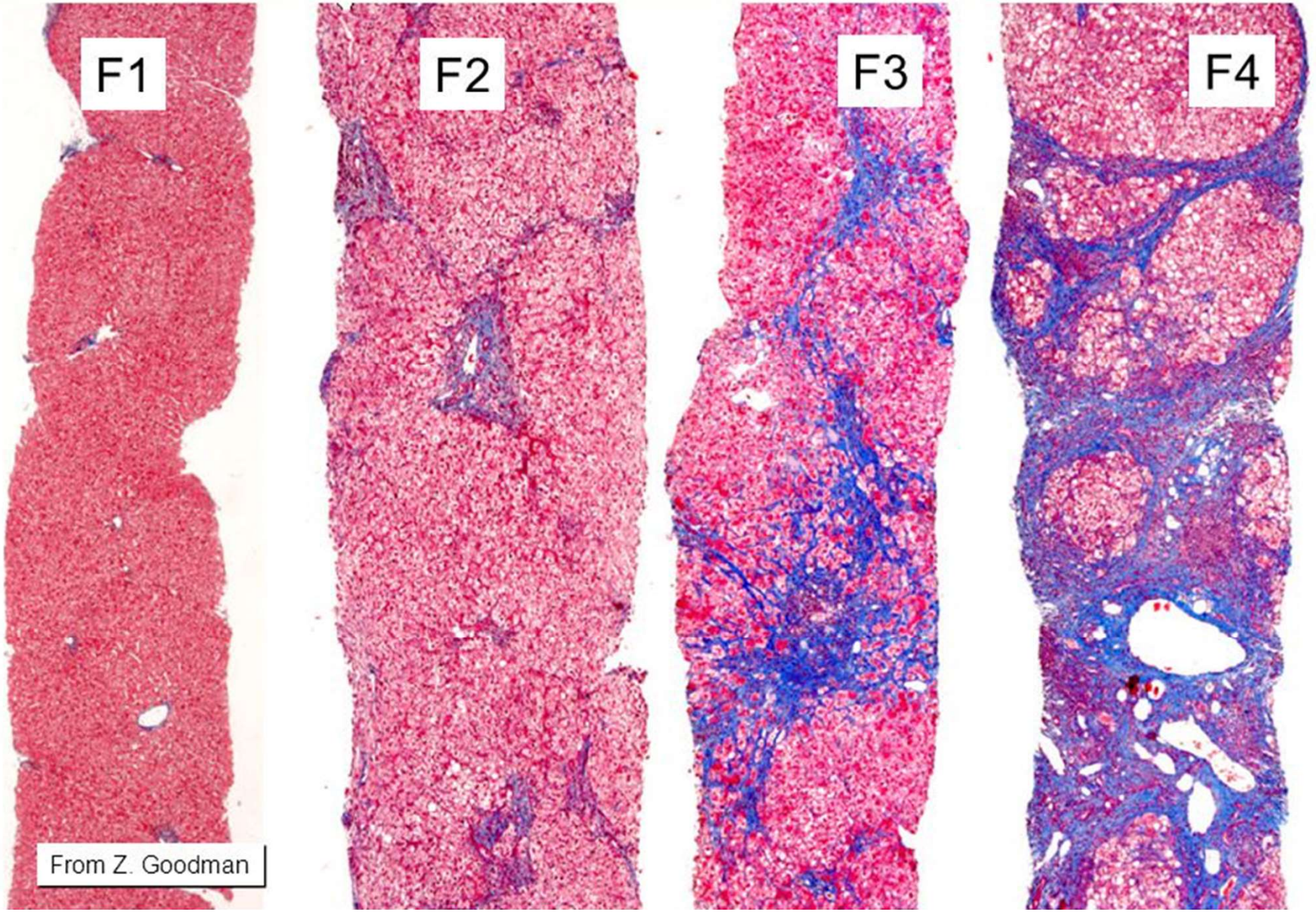
Normal



Cirrhosis



Liver biopsy : METAVIR scoring system



METAVIR Grading and Staging System

- Most popular staging system
- Quantifies inflammation and fibrosis
  - Inflammation is graded from 0 to 3 (none, mild, moderate, severe)
  - Fibrosis is scored from 0 to 4
    - 0: No fibrosis
    - 1: Portal fibrosis
    - 2: Portal fibrosis with septa formation
    - 3: Bridging fibrosis (can be focal, diffuse, or marked)
    - 4: Cirrhosis

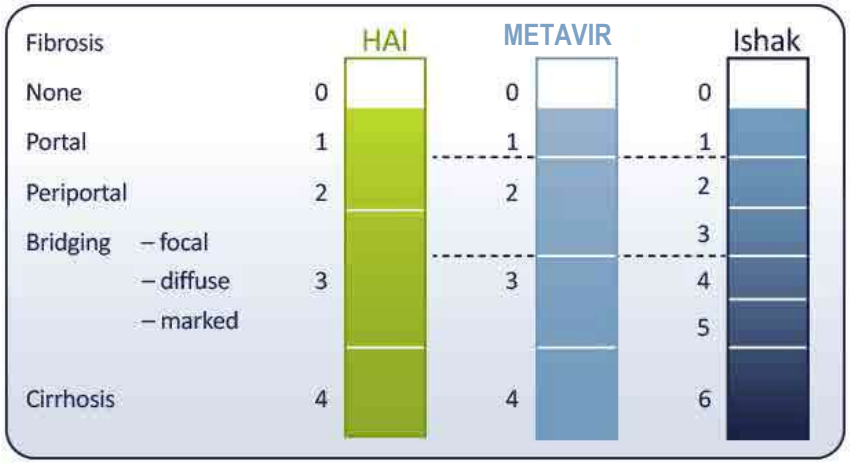


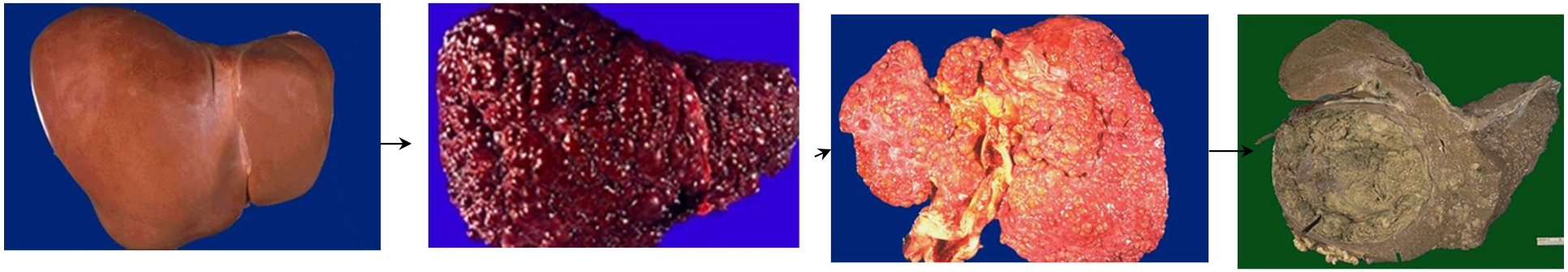
Illustration adapted from O'Leary JG, Davis GL. Hepatitis C. In: Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management. 9th ed. Philadelphia, PA: Saunders, Elsevier Inc.; 2010:1313–1335.

Kochar R, Fallon MB. Laboratory tests in liver disease. In: Andreoli and Carpenter's Cecil Essentials of Medicine. 8th ed. Philadelphia, PA: Saunders Elsevier; 2010:456–459.

Staging of Liver Disease

- There are various models used to grade and stage the degree of liver damage.
- The Metavir is widely used because it is simple, and easy to use and understand.
- There are, however, other scoring systems available such as the Knodell that are much more complex.

PROGRESSION OF CIRRHOSIS



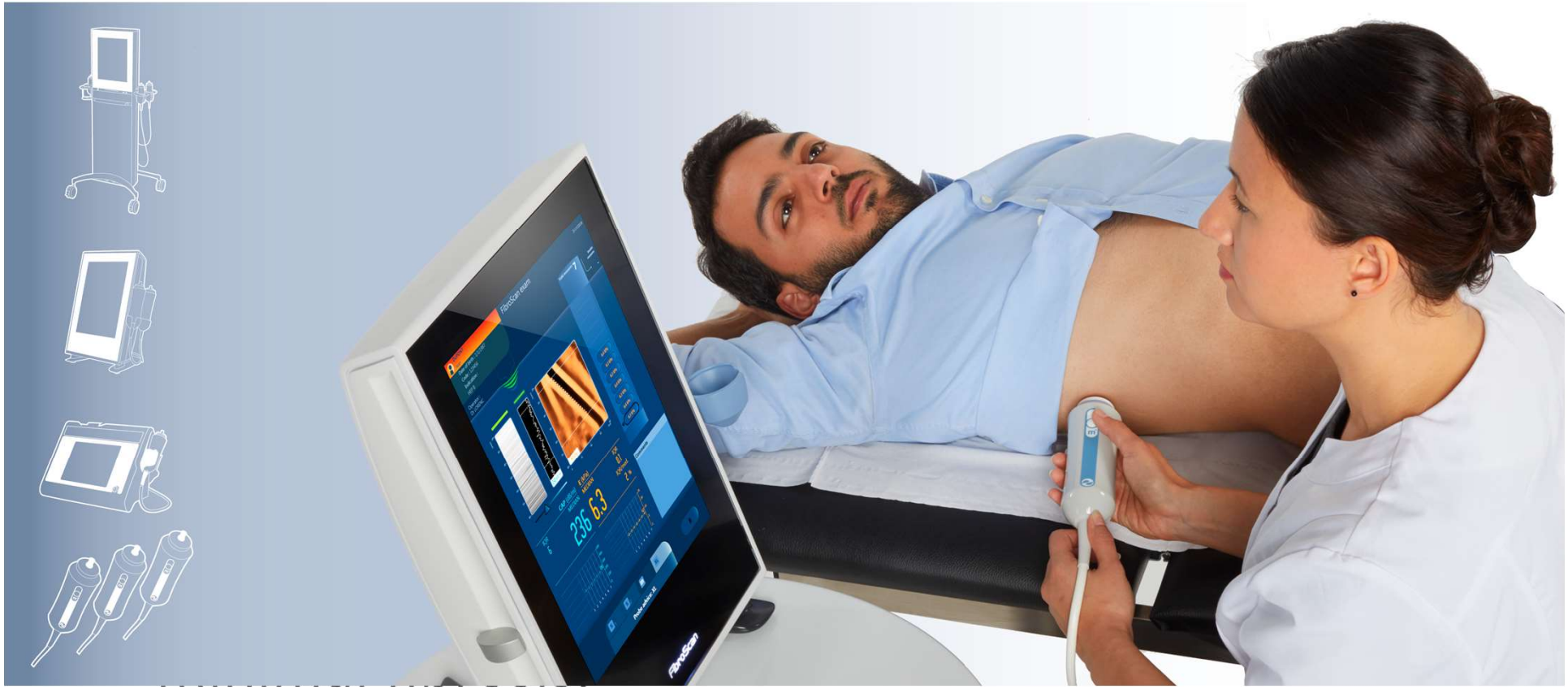
Liver Biopsy

- Gold Standard in determining health of the liver
- Measure of inflammation
- Extent of scarring
- Non Invasive tests – may not be as accurate

Fibroscan

- The Fibroscan is an approved painless imaging test that is used to evaluate the amount of scarring (if any) of the liver.
- While the Fibroscan isn't 100% accurate, it has been shown to have a very high degree of accuracy for predicting mild fibrosis, severe fibrosis and cirrhosis.
- It is less likely to distinguish between no or minimal fibrosis.
-

Fibroscan



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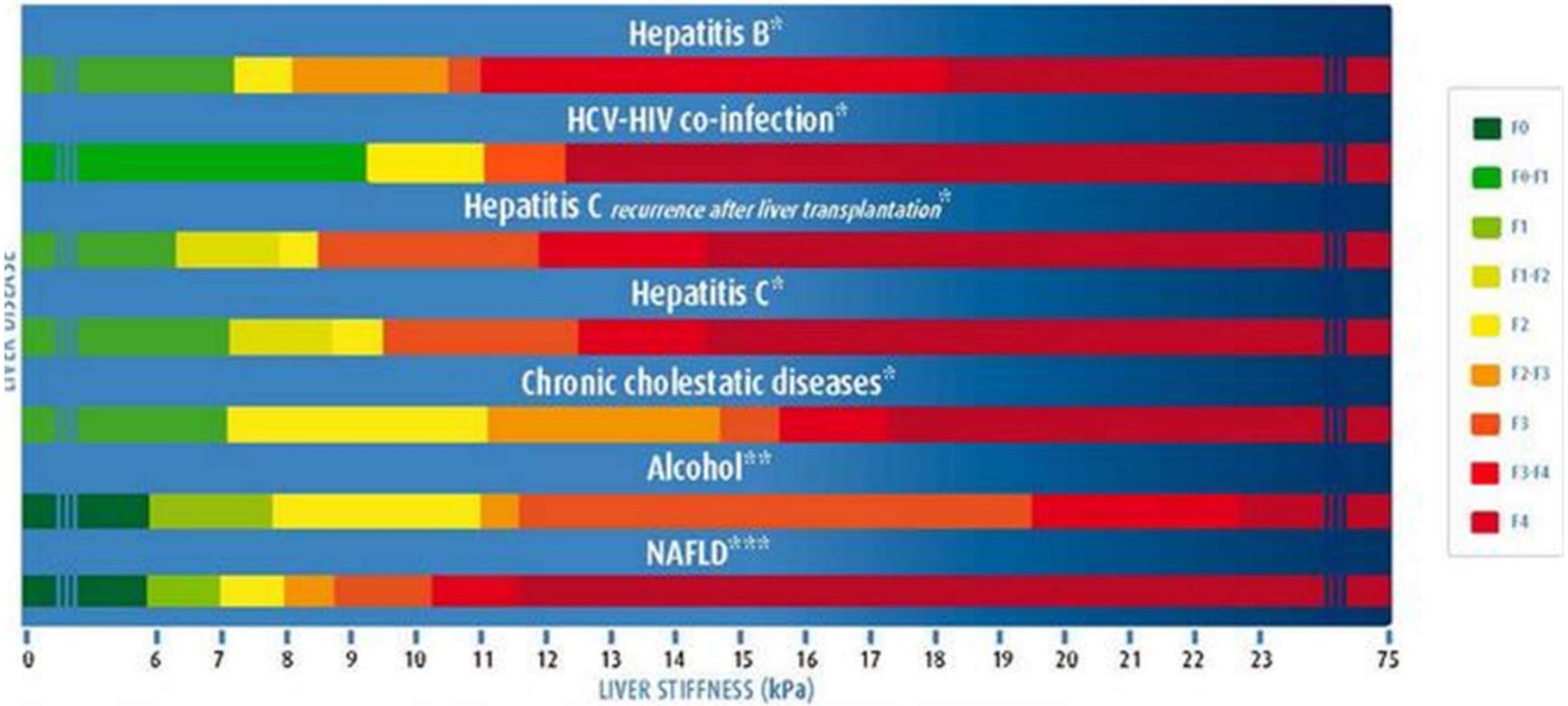
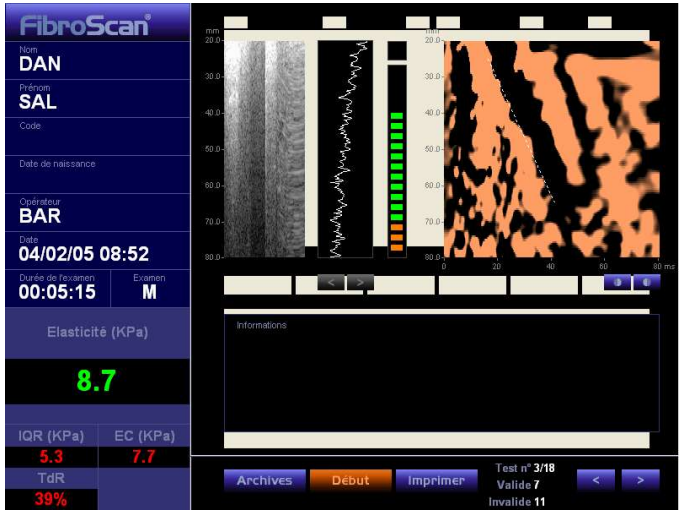

Hepatitis B*
HCV-HIV co-infection*
Hepatitis C recurrence after liver transplantation*
Hepatitis C*
Chronic cholestatic diseases*
Alcohol**
NAFLD***
0
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
75
LIVER STIFFNESS (kPa)
F0
F0-F1
F1
F1-F2
F2
F2-F3
F3
F3-F4
F4

Interpretation of fibroscan

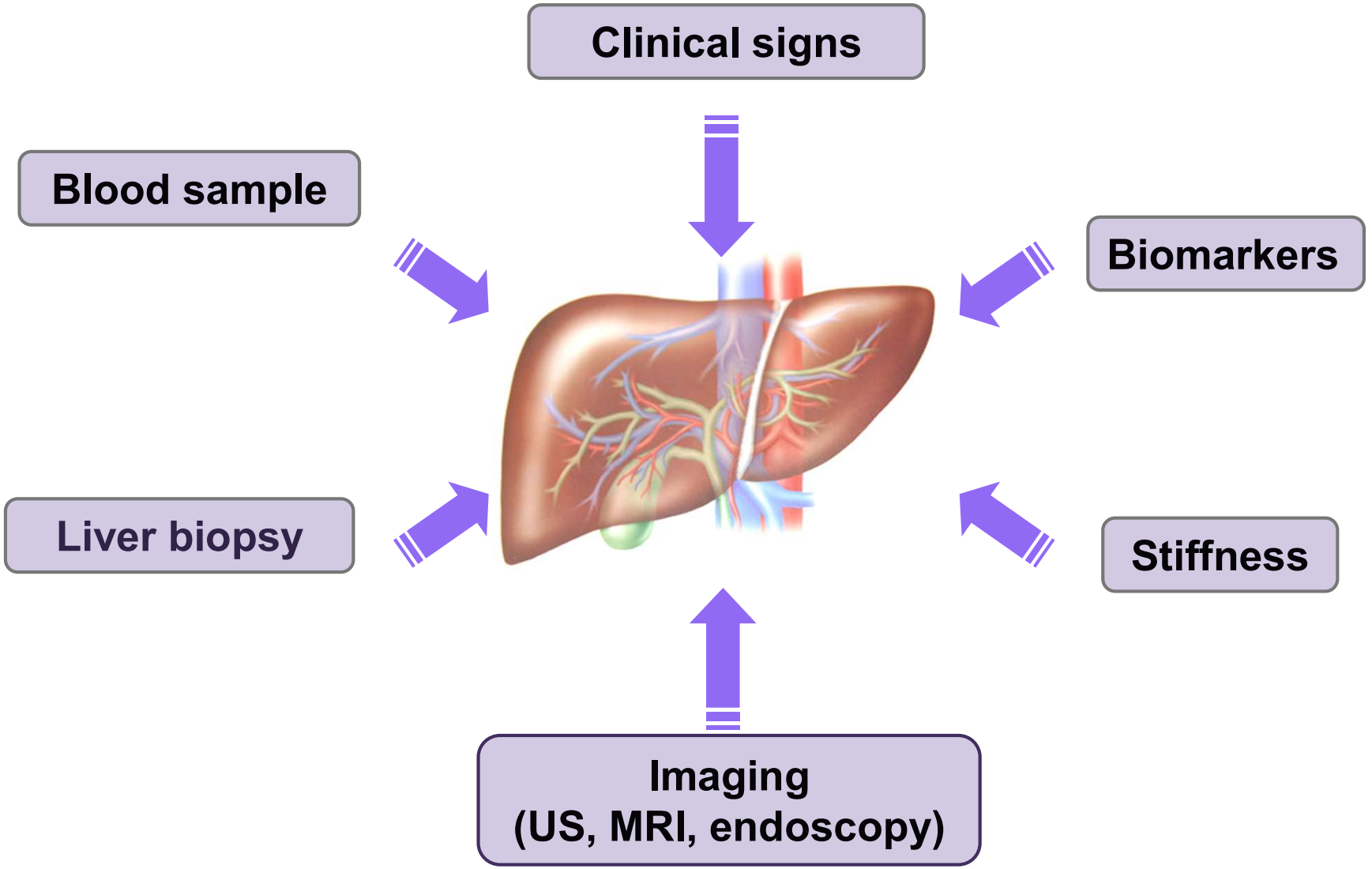
- Median value
- IQR < 21 - 30% of median value
- Number of measurements - 10



In Clinical Practise

- Interpretation is always by an expert according to clinical context
- Quality criteria of fibroscan (10 values, IQR)
- Quality criteria of biomarkers (haemolysis..)
- Combination
- Repeat if discordance
- Useful for diagnosis , follow up , prognosis

Today: useful with other parameters



Challenges in fibrosis staging for patients with HCV infection: invasive versus non-invasive tests

Invasive tests

Liver biopsy

- ✓ Considered by some as the Gold standard
- ✘ Patient burden of invasive procedure
- ✘ Expensive
- ✘ Carry risk of potentially life-threatening complications
- ✘ Difficulties obtaining patient consent
- ✘ Misclassification of Metavir stage as high as 25%

Non-invasive tests

Transient elastography

APRI

FIB-4

FibroSURE™ (US) or FibroTest™ (Europe)

ARFI

MRE

- ✓ Reduces burden for patients
- ✘ Less clinical experience
- ✘ Lack of distinction between different stages of intermediate fibrosis (F0–3)

APRI = aspartate aminotransferase/platelet ratio index;
ARFI = accoustic radiation force impulse imaging;
FIB-4 = Fibrosis 4 score; MRE = magnetic resonance elastography.

Cohen EB & Afdhal NH. J Clin Gastroenterol 2010; **44:**637–645.
Kim MY, et al. World J Gastroenterol 2014; **20:**4300–4315.
Nudo CG, et al. Gastroenterol Hepatol 2008; **4:**862–870.
Bedossa P, et al. Hepatology 2003; **38:**449–1457.

… Thank You …

QUIZ 1

- Presence of HCV Antibody always indicate active Hepatitis C infection.

QUIZ 2

- What is the most common Genotype in Malaysia ?

QUIZ 3

- Fibroscan is a simple and painless procedure to evaluate amount of scarring .