Hepatitis C – Monitoring and Complications (and Treatment!)

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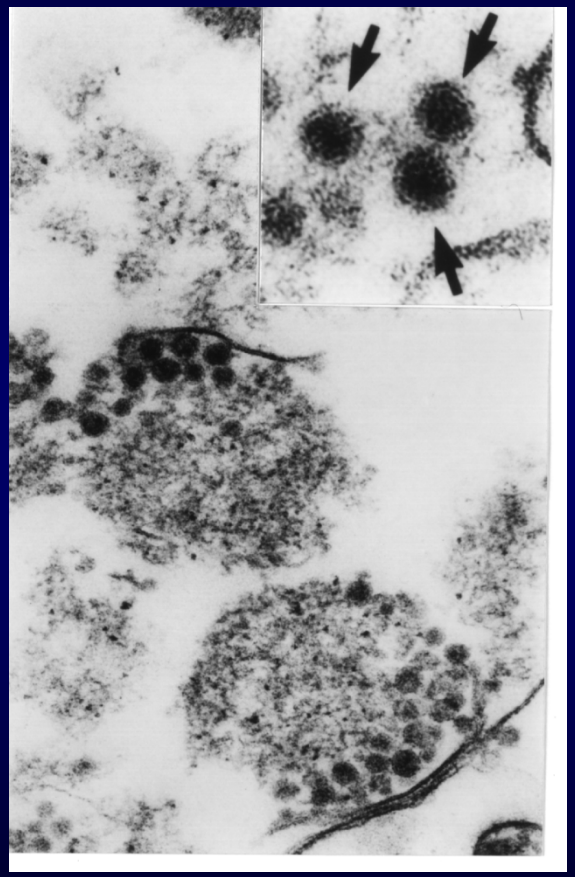
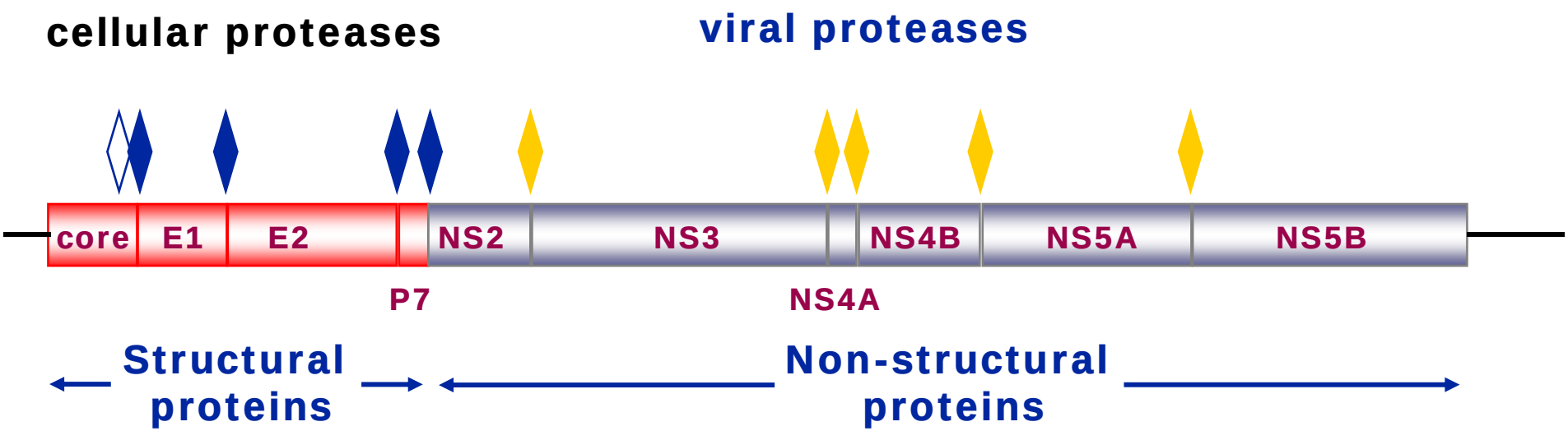
Hepatitis C Virus

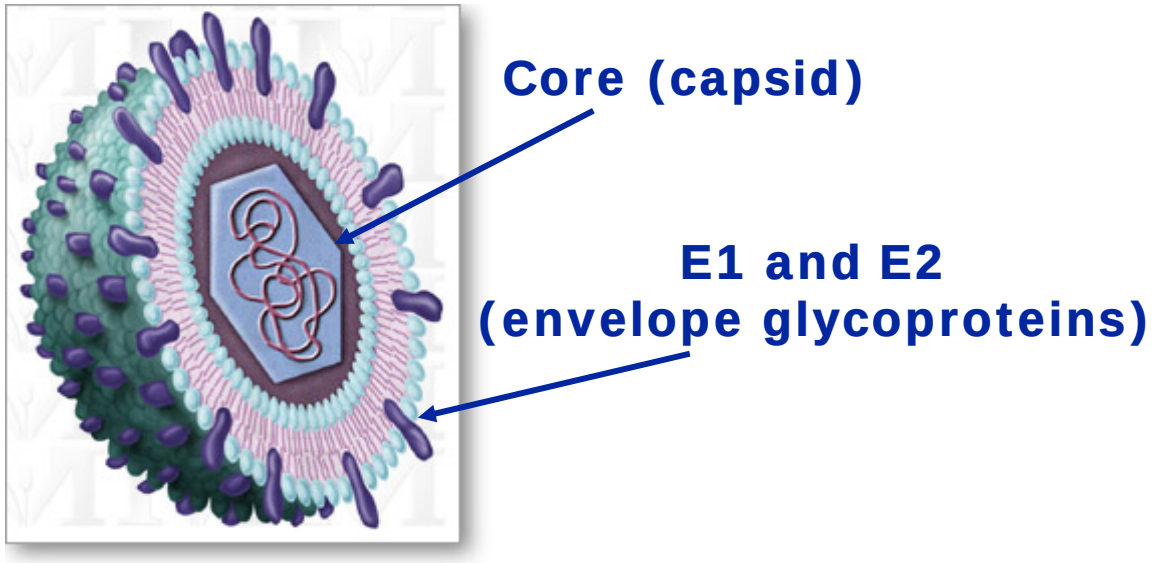


Shimizu *et al*., 1996

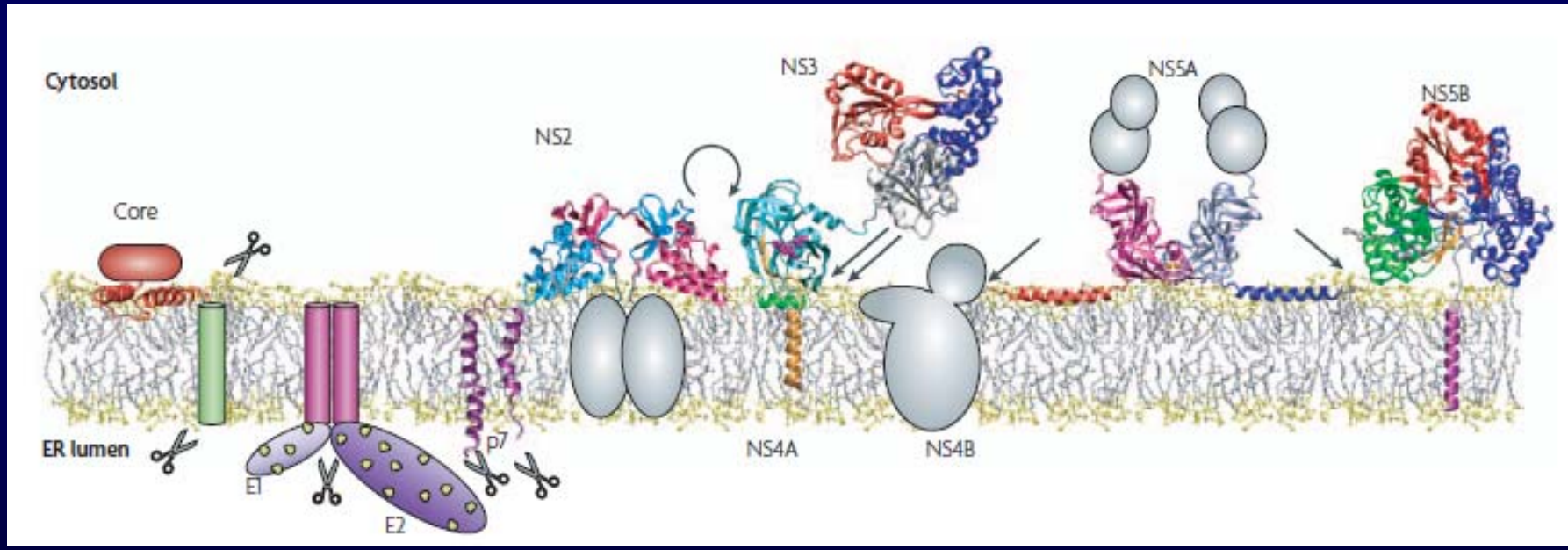
- Positive single strand RNA virus
- *Flaviviridae* family, *Hepacivirus* genus
- 9.6 kbp genome
- ~3000 amino acid polyprotein
- 60 nm enveloped virions
- Lipo-viral particles
- Until recently, unable to grow in cell culture

Features of the HCV Genome





HCV Proteins - ER Membrane Associations

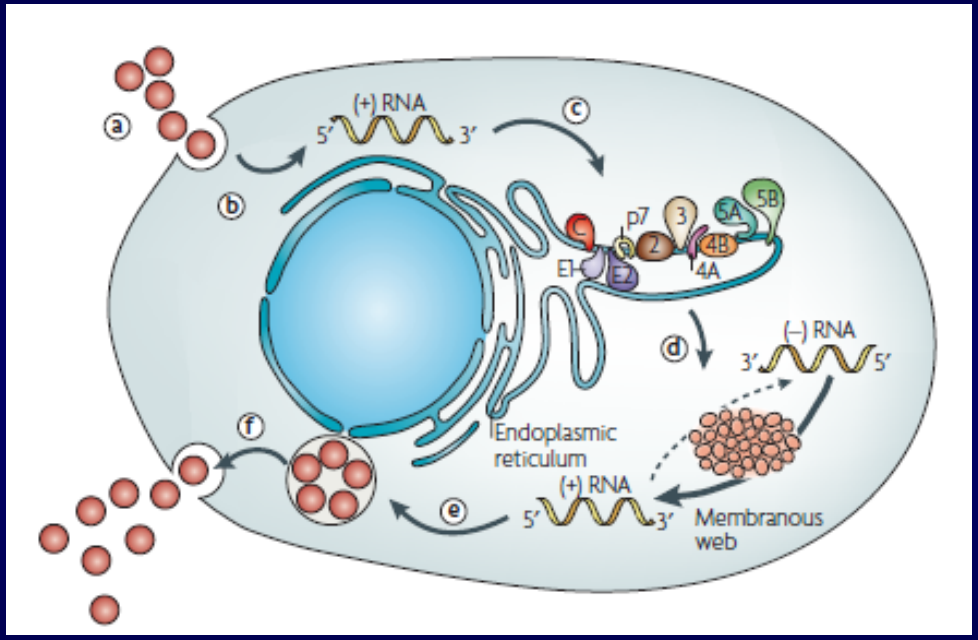


Moradpour et al, 2007

HCV Proteins

Core	Highly basic core protein
E1*gp31	Envelope glycoprotein, heterodimer in virion
E2* gp70	Envelope glycoprotein, heterodimer in virion
p7	Cleaved from E2, behaves as ion channel
NS2	Serine protease (NS2/3)
NS3	serine protease, helicase and NTPase activities
NS4A	cofactor essential for NS3 serine protease activity
NS4B	induces a membranous replication complex at the ER
NS5A	serine phosphoprotein, interacts with cell pathways
NS5B	RNA Polymerase – (RNA dependent)

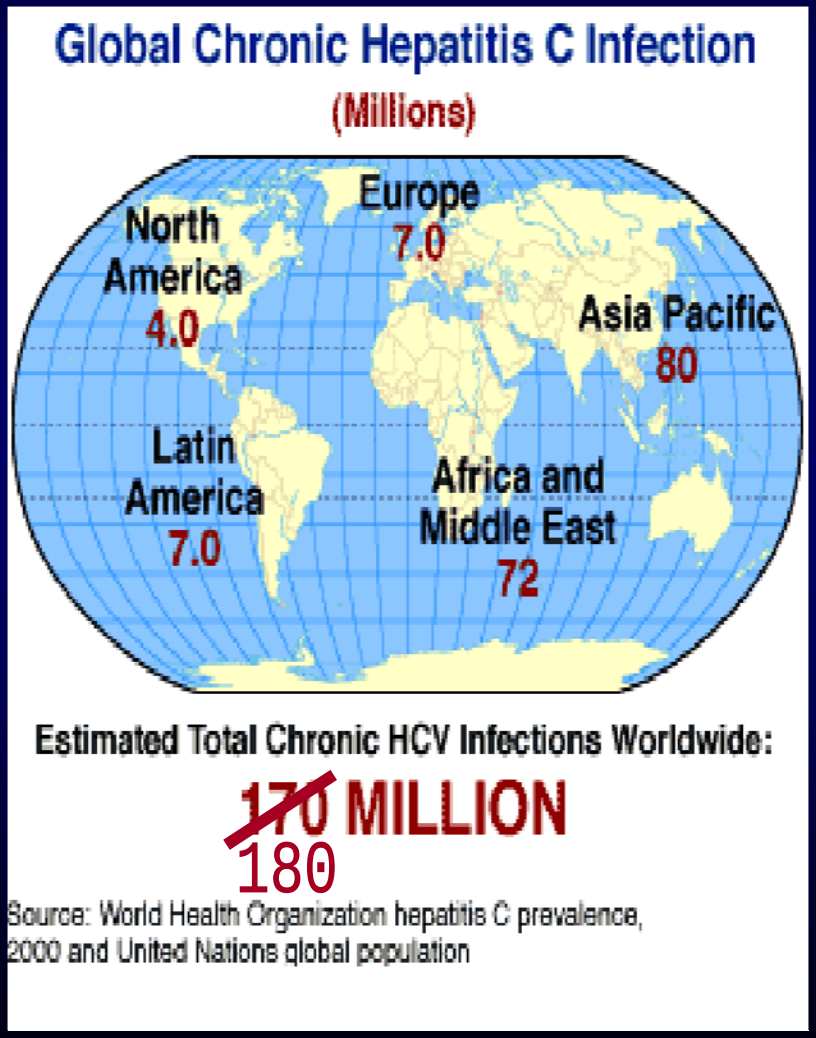
HCV – Life Cycle



Moradpour et al, 2007

- Cytoplasmic replication
- Replication complexes at ER
- Membranous web induced by NS4B
- Interactions with lipid metabolism
- Some export via VLDL pathway

Hepatitis C - Epidemiology



- 3% prevalence worldwide (1% Australia, USA, UK)
- Causes more deaths than HIV in the USA, Australia
- Main cause of cirrhosis requiring liver transplant: Australia, USA, UK
- 3 to 4 million new cases per year (most IDU here)

Global Distribution of HCV Genotypes

Genotypes	1-3	Worldwide
Genotypes	4 & 5	Africa
Genotype	6	Asia

Webster *et al*.,2000

Hepatitis C - Transmission

- Source
  - human blood
  - blood contaminated body fluids
  - ?infected lymphocytes
- Route
  - inoculation
  - Sexual transmission rare, but reported (well described in HIV +ve MSM)
  - vertical transmission 5% (at birth)

Typical Course of HCV Infection

- Minor (anicteric) acute illness
  - 20-40% virus clearance
  - 60-80% chronic viral replication
- Chronic HCV
  - 20-30% no evidence of disease
  - 60-80% chronically elevated LFTs
  - 3-9% develop cirrhosis over 20-30y
  - HCC 1-3% per year once cirrhotic

Metabolic Complications of HCV

- Steatosis – HCV Genotype 3
- Insulin resistance – HCV Genotype 1
  - Predicts progression, poor response to interferon-based treatment
- Mechanisms are poorly understood
  - effects of HCV core on metabolic pathways?
  - chronic inflammation?

Monitoring HCV

- Infection
  - Anti-HCV antibodies, antigen (ELISA)
  - Detect HCV RNA by RT-PCR
  - Quantitative PCR, genotype
- Disease
  - LFTs (especially ALT)
  - Liver biopsy (Fibroscan)
  - HCC screen (ultrasound, AFP)

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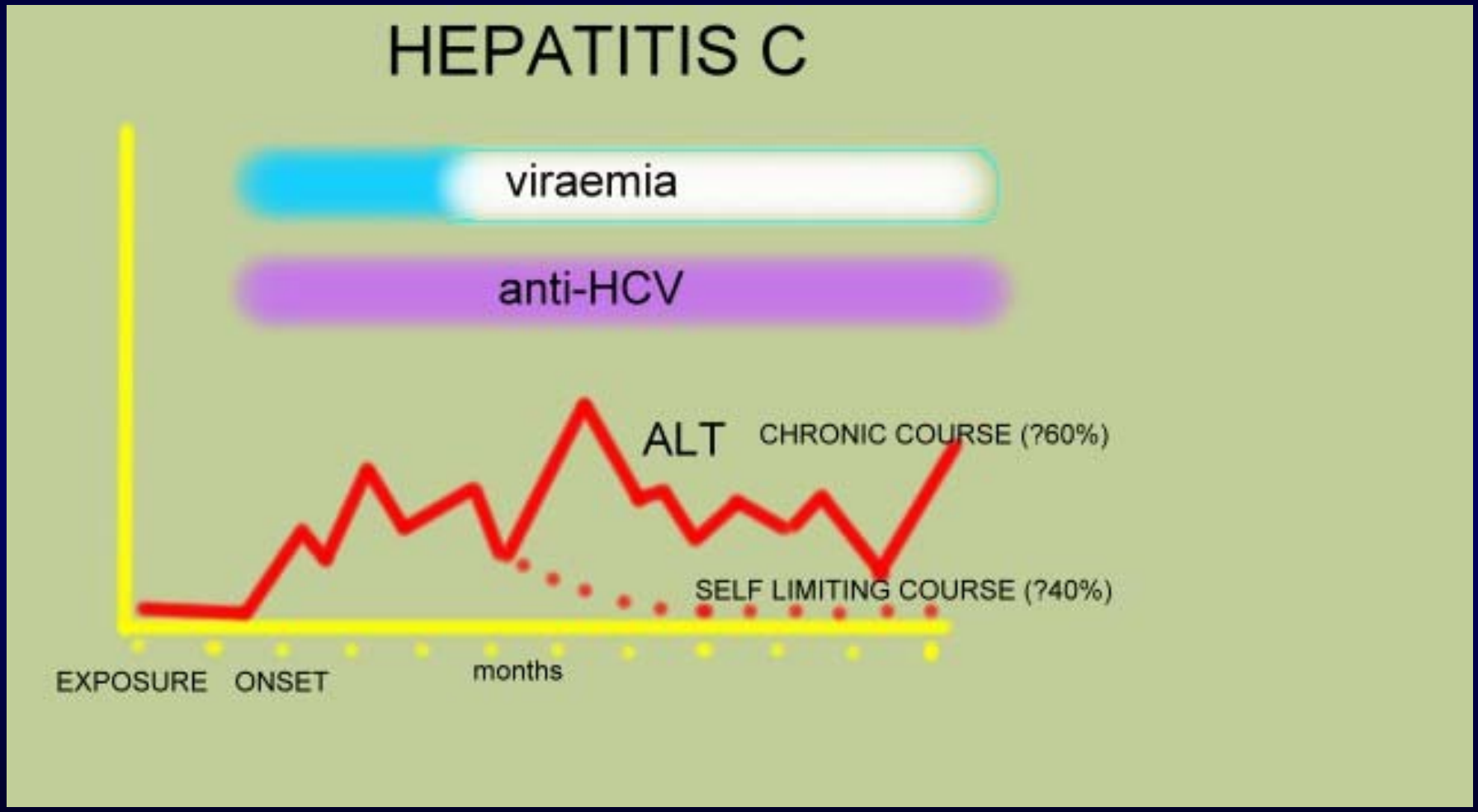
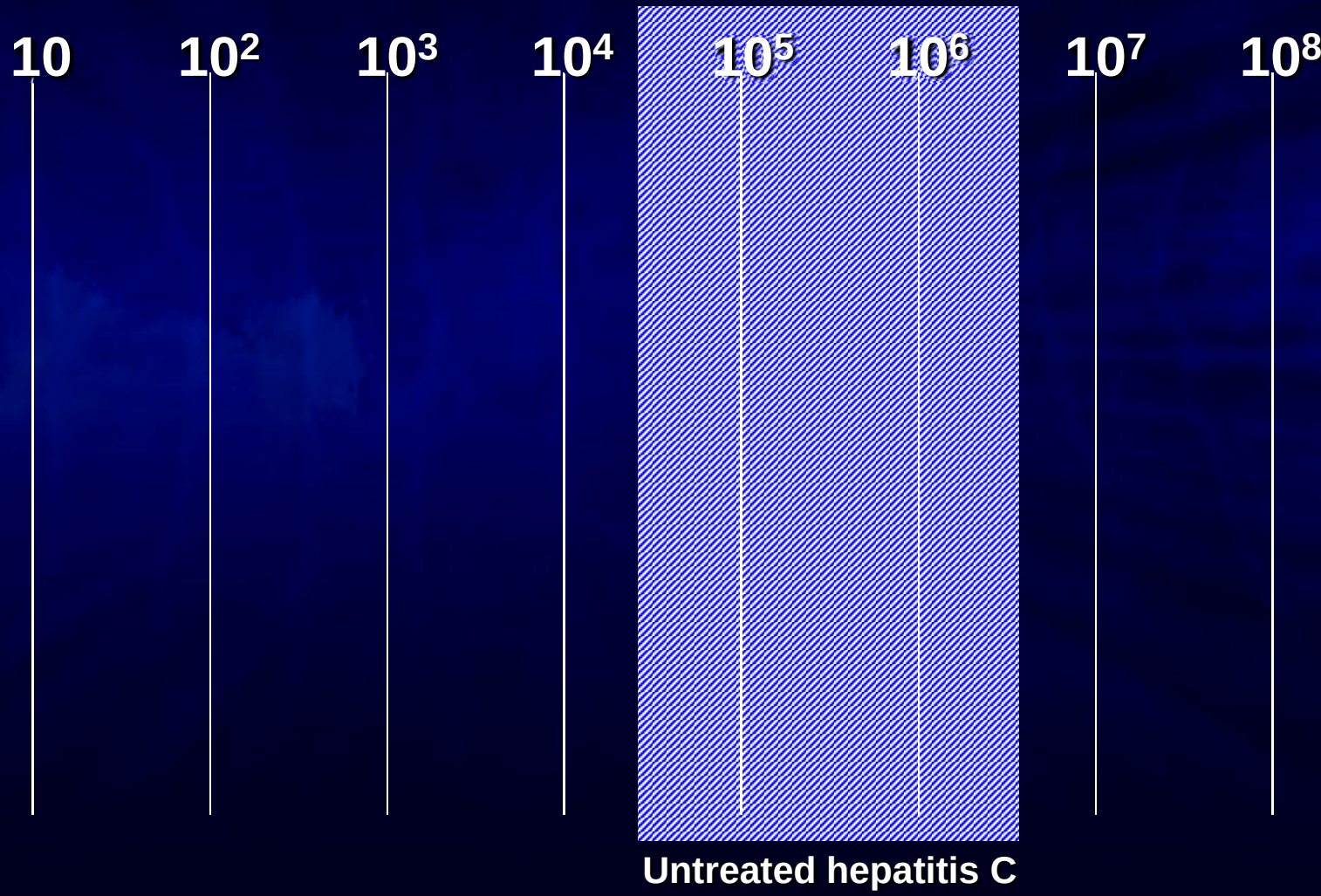
Serum Markers of HCV



Ranges of Linear Quantification of HCV RNA Assays (IU/ml)



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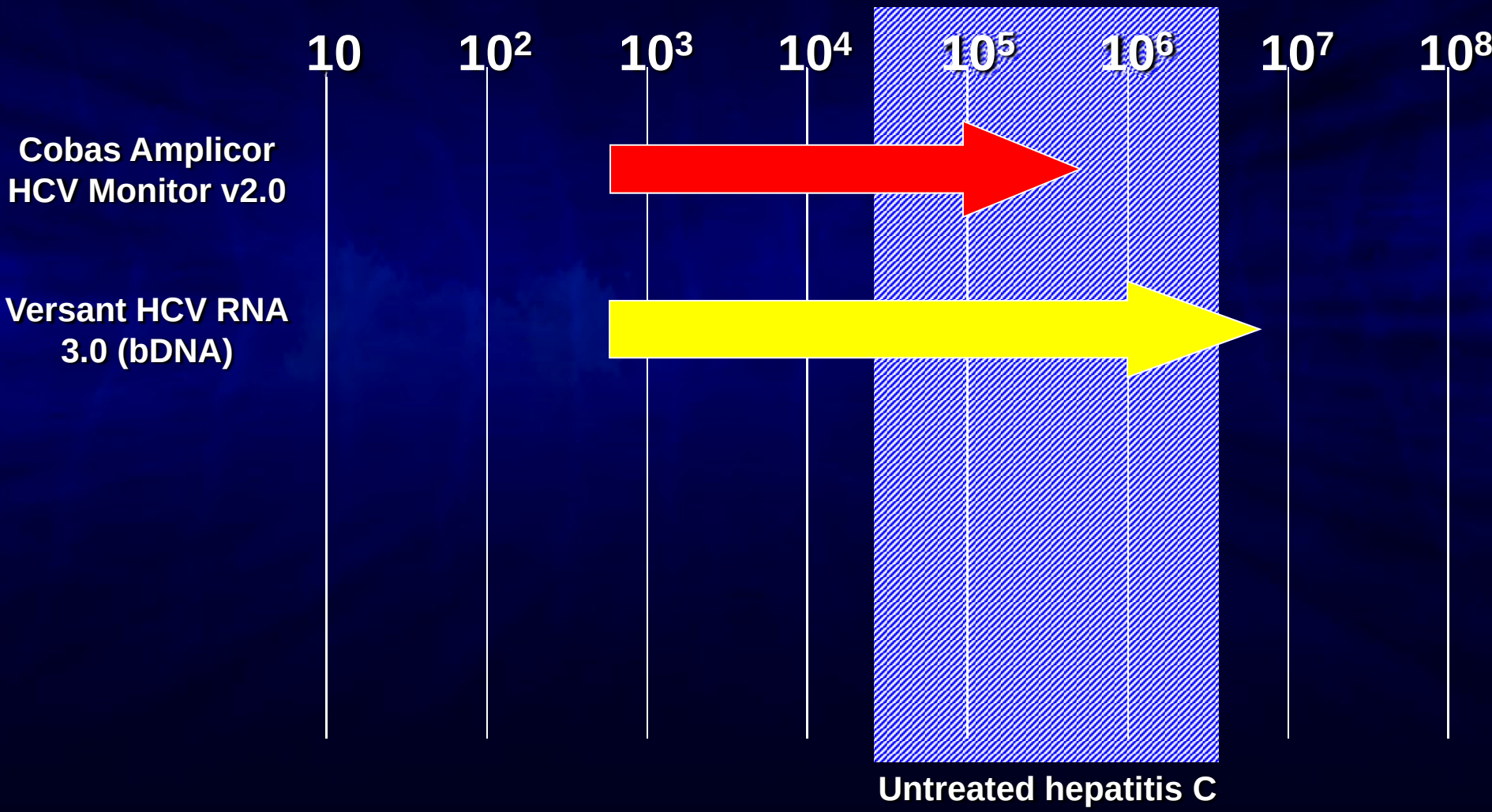

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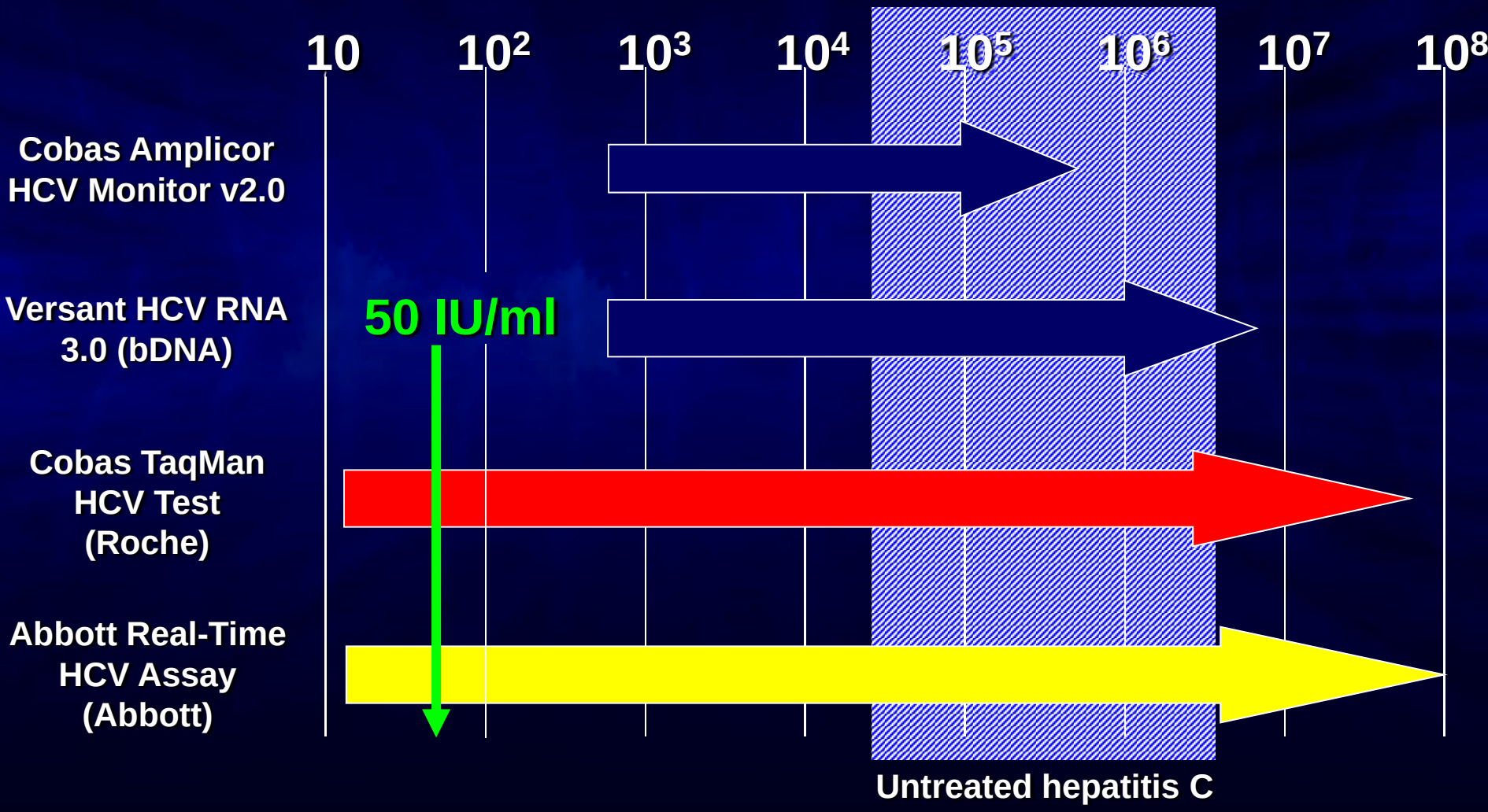

Roche Real-Time PCR

Cobas Ampliprep®

Cobas Taqman®

Cobas Ampliprep®/Cobas Taqman® (CAP/CTM) platform

Real-Time PCR Quantification

- Automation
  - sample preparation
  - PCR cycling, nucleic acid quantification
- Improved sensitivity
- No carryover contamination
- Extended dynamic range of quantification
- Precision and reproducibility

That sounds great!

… but is there a catch?

Cost!! (Medicare restrictions)

- HCV PCR (qualitative)
  - $92.80
  - 4 × per year on treatment (or 1 × per year)
- HCV PCR (quantitative – viral load)
  - $181.45
  - 2 × per year
- HCV Genotype
  - $206.20
  - 1 × per year

Monitoring HCV

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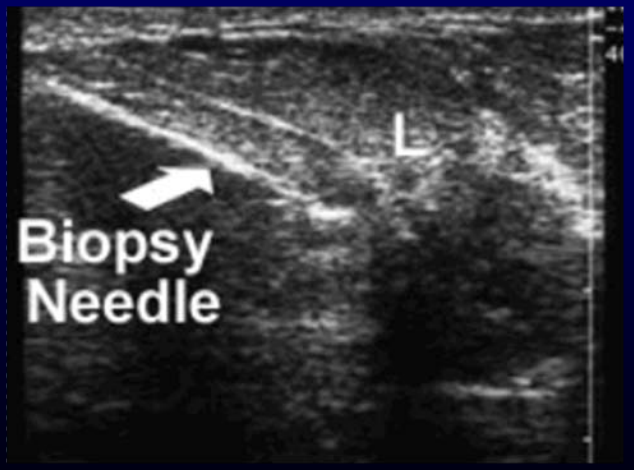
Liver Biopsy



Biopsy - Metavir Score

Activity

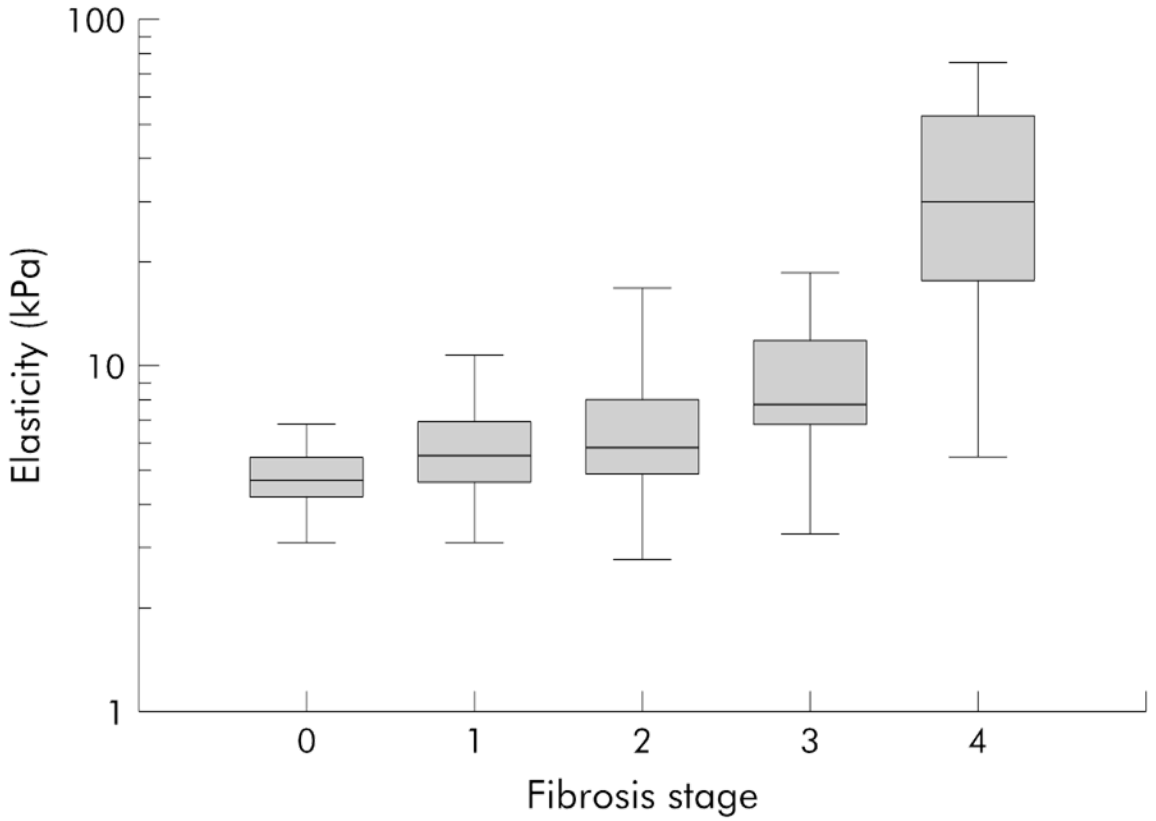
- A0 = no activity
- A1 = mild activity
- A2 = moderate activity
- A3 = severe activity

Fibrosis

- F0 = no fibrosis
- F1 = portal fibrosis without septa
- F2 = few septa
- F3 = numerous septa without cirrhosis
- F4 = cirrhosis

Fibroscan - Transient Elastography

Fibroscan - correlation



Gut 2006;55:403–408

Fibroscan – predictive value

Table 2 Cut off values of liver stiffness according to fibrosis stage for a positive predictive value of at least 90%

	Moderate (F⩾2)	Severe (F⩾3)	Cirrhosis (F=4)
Cut off	7.2	12.5	17.6
PPV	90	90	91
NPV	52	80	92
Sensitivity	64	65	77
Specificity	85	95	97
PLR	4.2	13.7	28.4

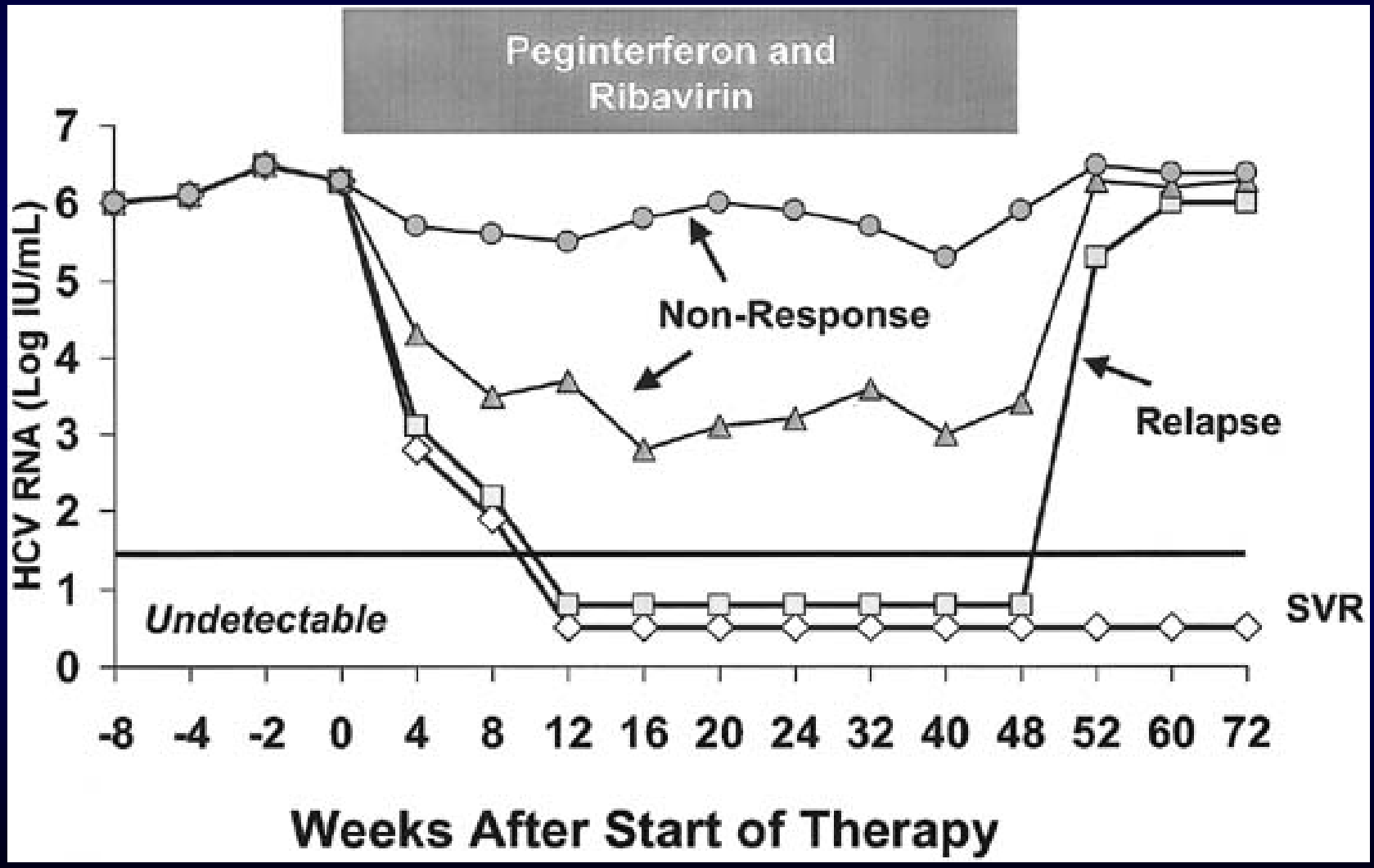
PPV, positive predictive value; NPV, negative predictive value; PLR, positive likelihood ratio.

Gut 2006;55:403–408

HCV - Treatment

- Interferon (pegylated), ribavirin
- “Cure” - Sustained Virological Response
- Treatment & outcome depend on genotype
- Genotypes 1 (4, 5, 6)
  - 48 weeks treatment
  - 50% SVR
- Genotypes 2, 3
  - 24 weeks treatment
  - 80% SVR

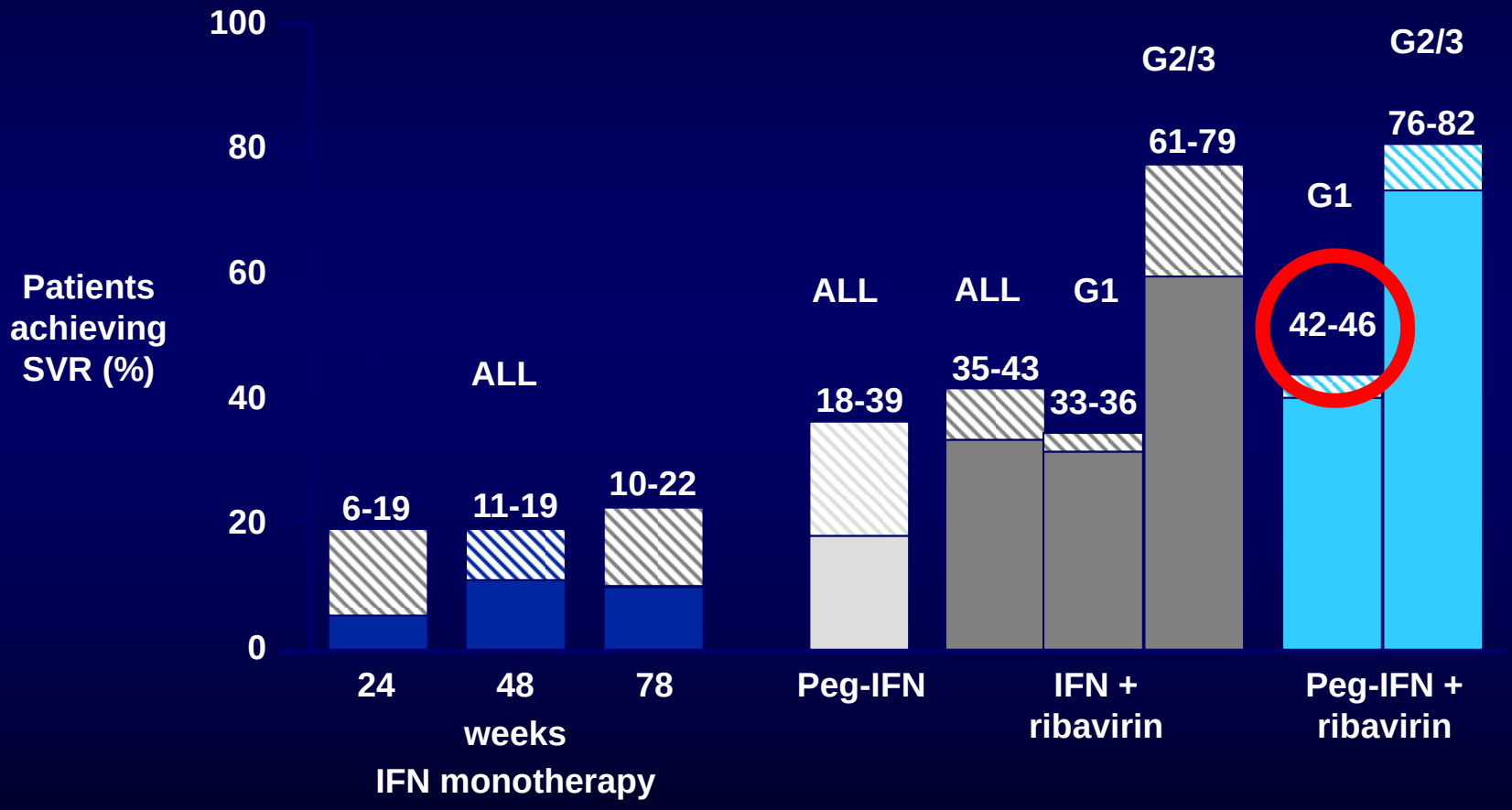
Hepatitis C Treatment Outcomes



Factors associated with SVR

- Genotype 2 or 3 (not 1, 4)
- Lower HCV viral load
- Milder degree of fibrosis (F0-F1 vs. F3-4)
- Lower body weight / Insulin resistance
- Younger age
- Adherence to treatment
- Female
- Asian > Caucasian > African

Evolution of SVR rates



*Range of values reported;
lower bar represents lower value

Manns, Foster et al., Nature Reviews Drug Discovery 2007

Genome-wide association studies
Treatment response

- **Genetic variation in IL28B is associated with response to PEG-IFN and ribavirin treatment**
  - **SNP rs12979860**
    - » **Ge D, et al. Nature 2009; 461:399-401 (United States)**
  - **SNP rs8099917**
    - » **Suppiah V, et al. Nat Genet 2009; 41:1100-04 (Australia)**
    - » **Tanaka Y, et al. Nat Genet 2009; 41:1105-09 (Japan)**
    - » **Rauch A, et al. Gastroenterology 2010: January 7 (Switzerland)**

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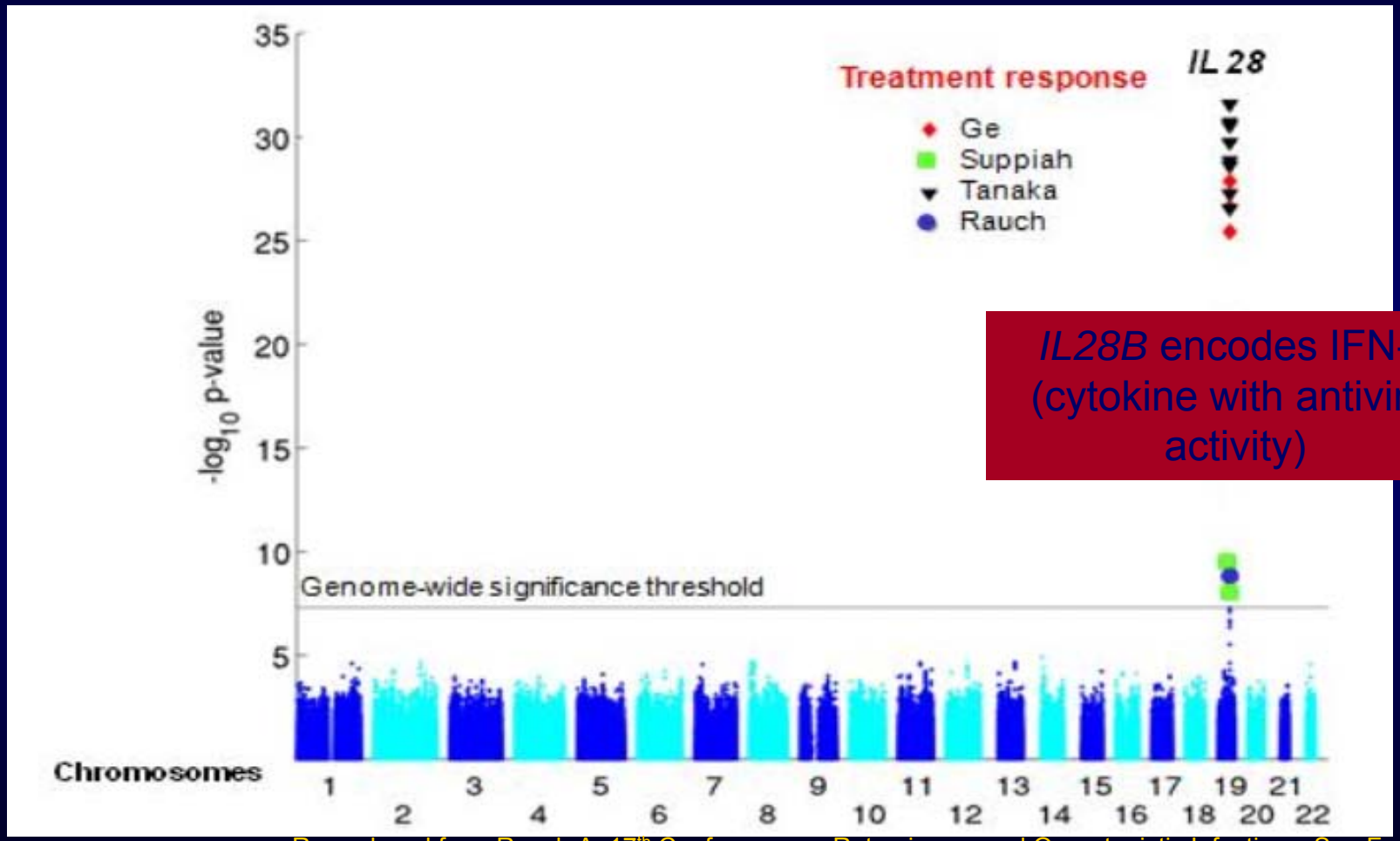
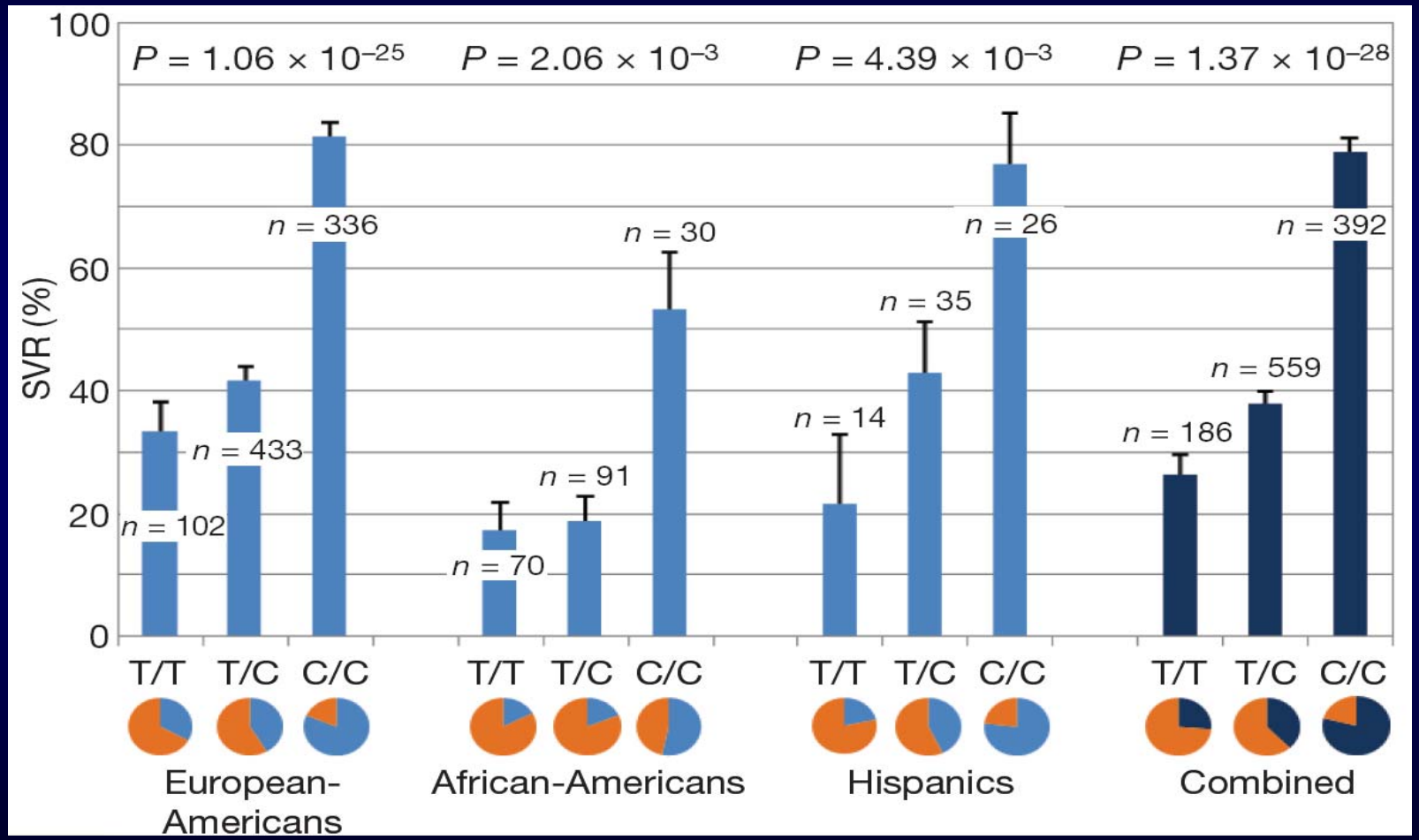
Genetic variation in IL28B and HCV response



IL28B encodes IFN-λ (cytokine with antiviral activity)

Reproduced from Rauch A. 17th Conference on Retroviruses and Opportunistic Infections. San Francisco, United States, 2010. Ge D, et al. *Nature* 2009; 461:399-401. Suppiah V, et al. *Nat Genet* 2009; 41:1100-04. Tanaka Y, et al. *Nat Genet* 2009; 41:1105-09. Rauch A, et al. *Gastroenterology* 2010: January 7.

Association of rs12979860 with SVR



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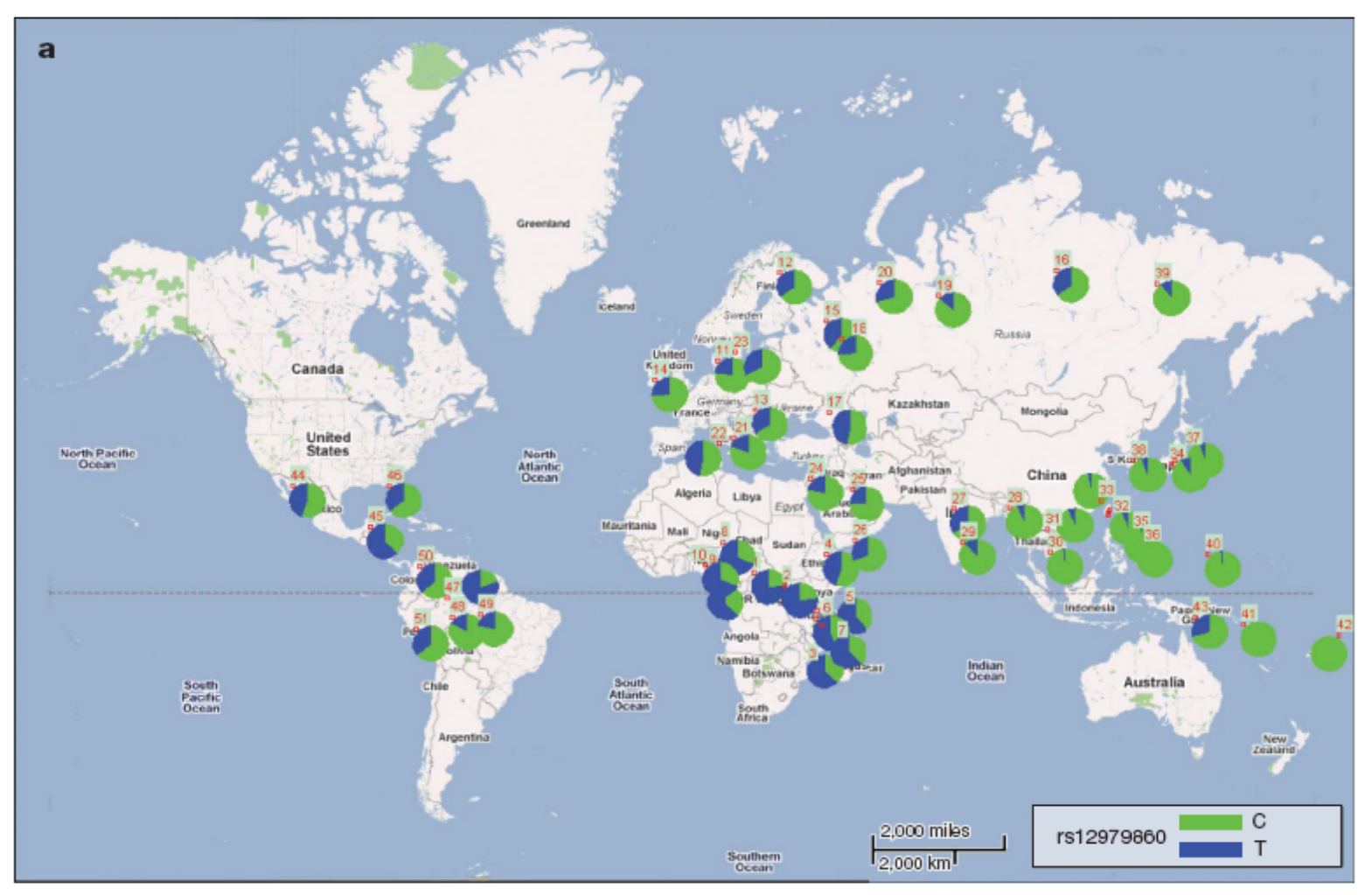
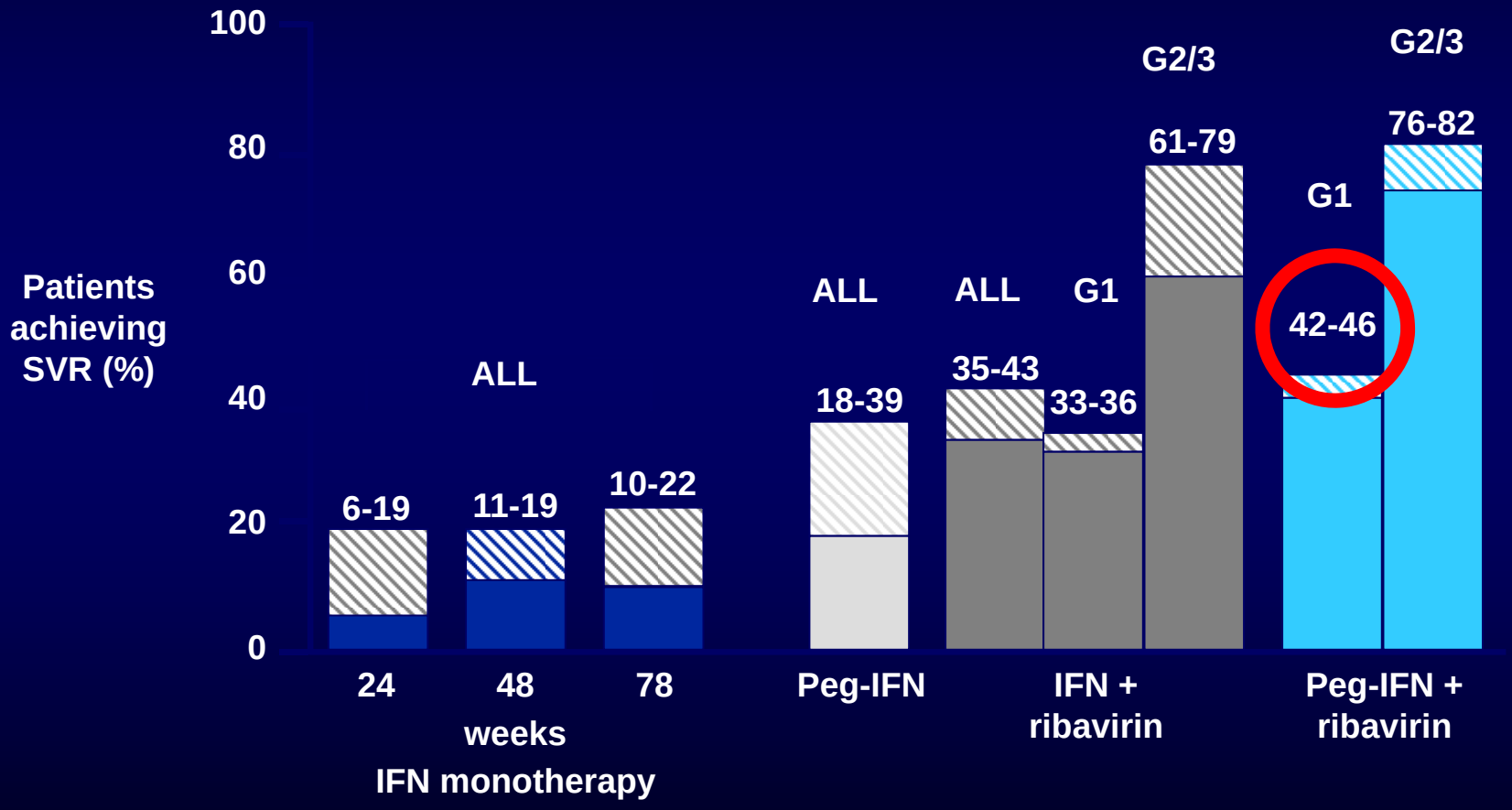
Favourable IL28B polymorphism is common in Asia



Thomas D, et al. *Nature* 2009; 461:798-801

Evolution of SVR rates



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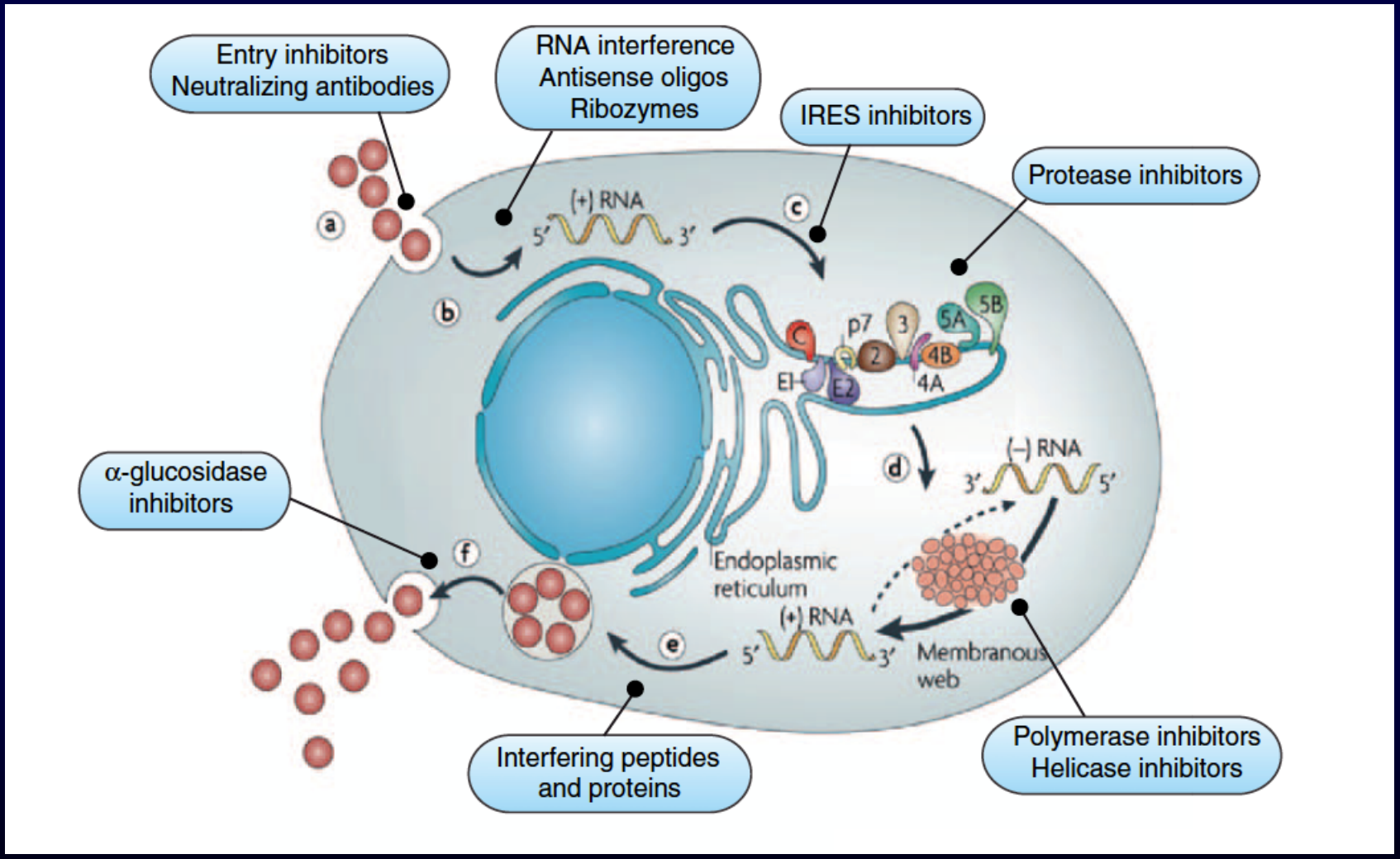
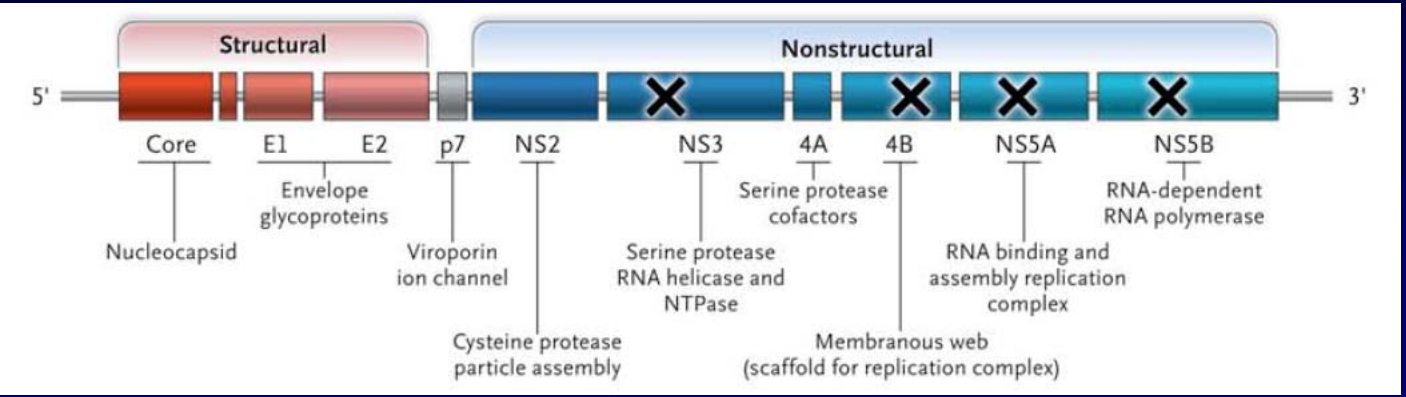
Potential New Drug Targets



Pockros, PJ (2010, Therap Adv Gastro, 3:191–202)

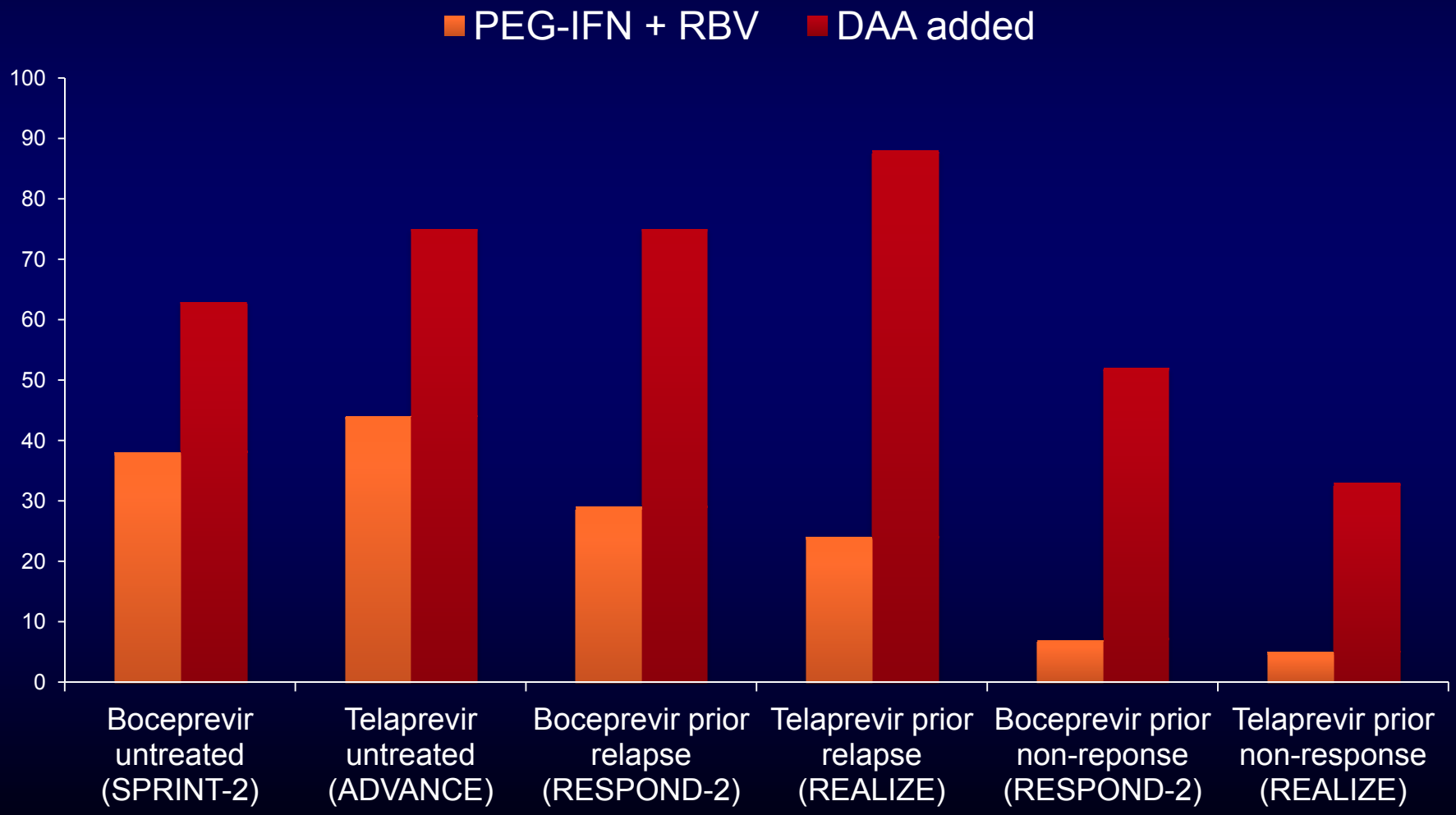
Direct Acting Antivirals (DAAs)



- **NS3/4A protease inhibitors**
  - **telaprevir, boceprevir**
- **NS5B polymerase inhibitors**
  - **Nucleoside analogues**
  - **Non-nucleoside analogues**
- **NS5A inhibitors**

Rosen, H. R. (2011, NEJM, 364:2429–2438)

Phase 3 Studies (NEJM, 2011)



Conclusions – Hepatitis C

- Hepatitis C is now a curable disease
  - Screen high risk patients and refer for Rx
- HCV PCR is key marker of active infection
- 70-80% SVR gt 2/3 with PEG-IFN/RBV
- 45% SVR gt 1 with PEG-IFN/RBV (30-70% IL28B)
- 70-80% SVR gt 1 when adding DAA
- IFN-free treatment likely to become a reality in the next 5 years
- 90% SVR with 12 weeks of IFN-free oral treatment may soon be possible