Pre-treatment and on-treatment predictors for decisions of anti-HCV therapy

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Overview

- What do we mean by “Treatment”?
- What types of predictors are there?
- What do we know about prediction of SVR?
- Do we need predictors?

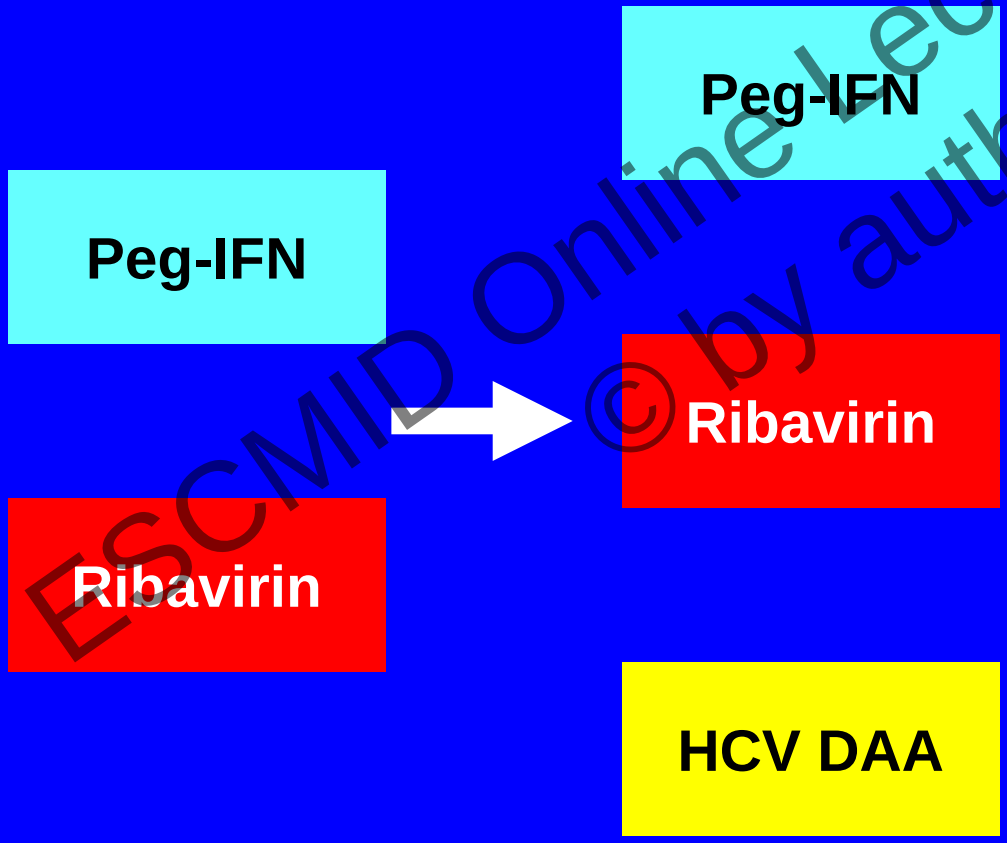
Treatment

2001 - 2011 standard of care

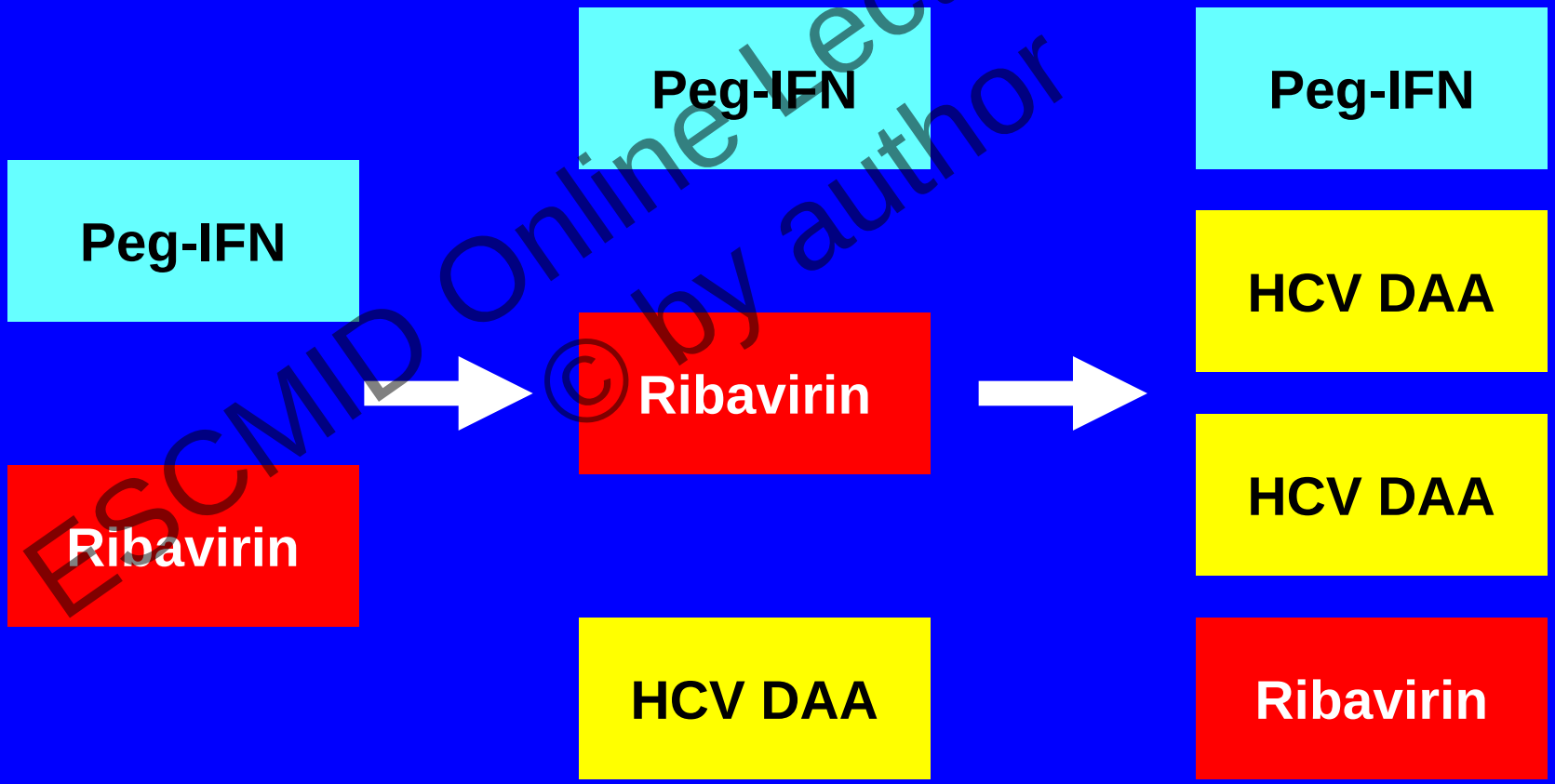
Peg-IFN

Ribavirin

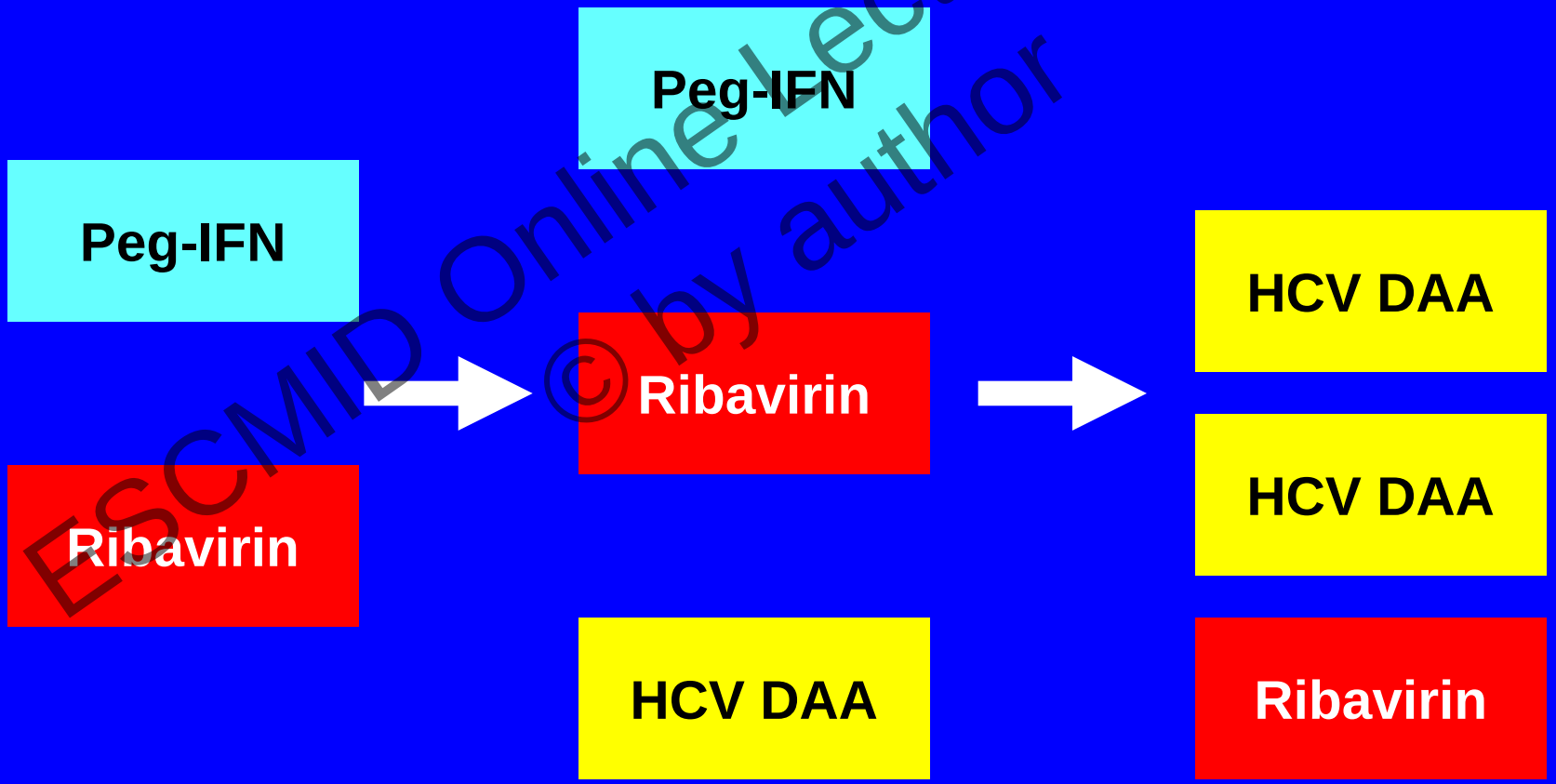
2012 Standard of Care



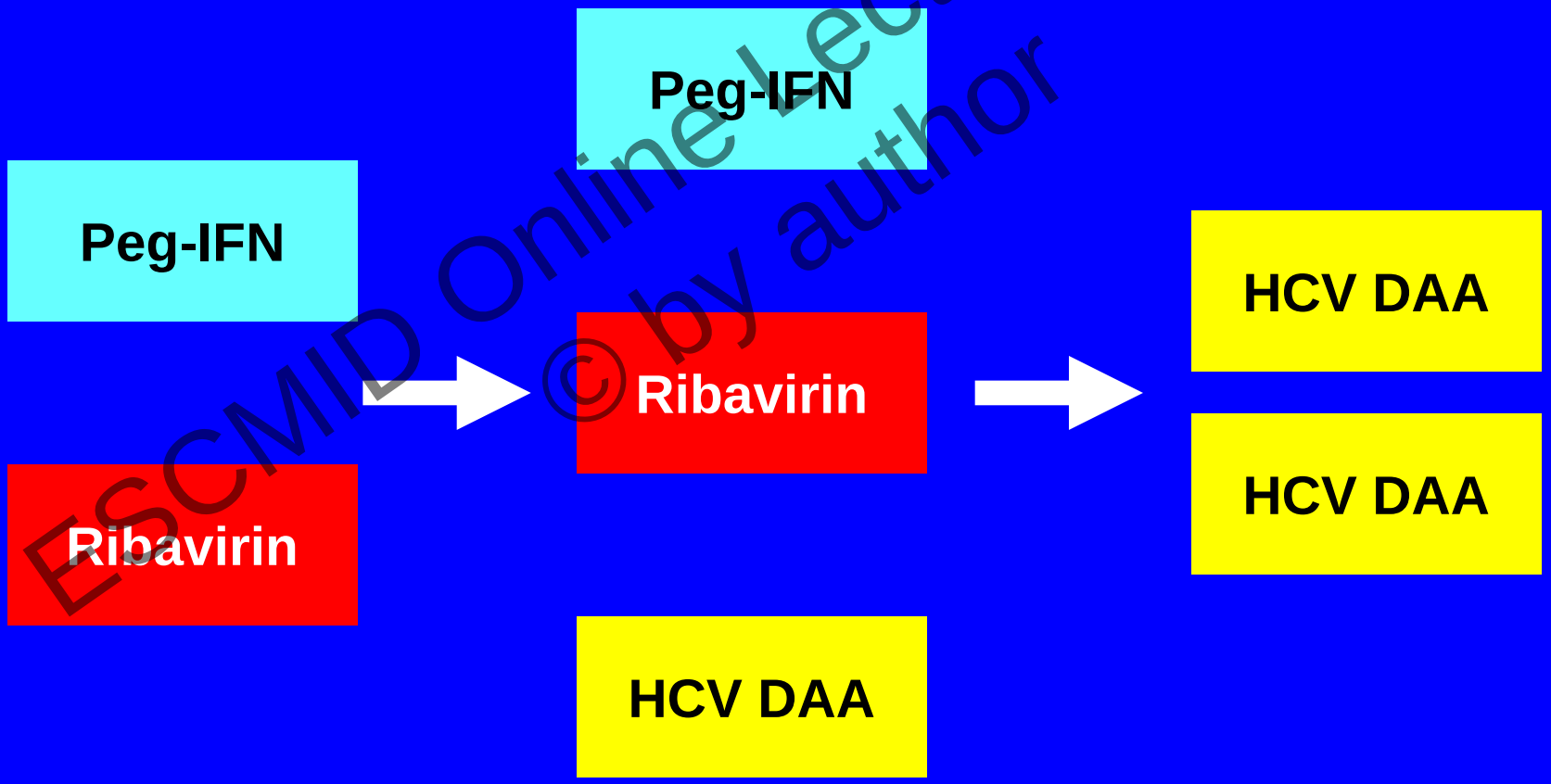
The future: Quadruple therapy ……



The future: ….all oral, interferon-free ….



The future: ….. All oral, multiple DAAs



Changing treatment modalities

- PEG + RV
  - The most studied
- PEG + RV + DAAs
  - Some data emerging
- DAAs
  - Very little data available

Changing treatment modalities

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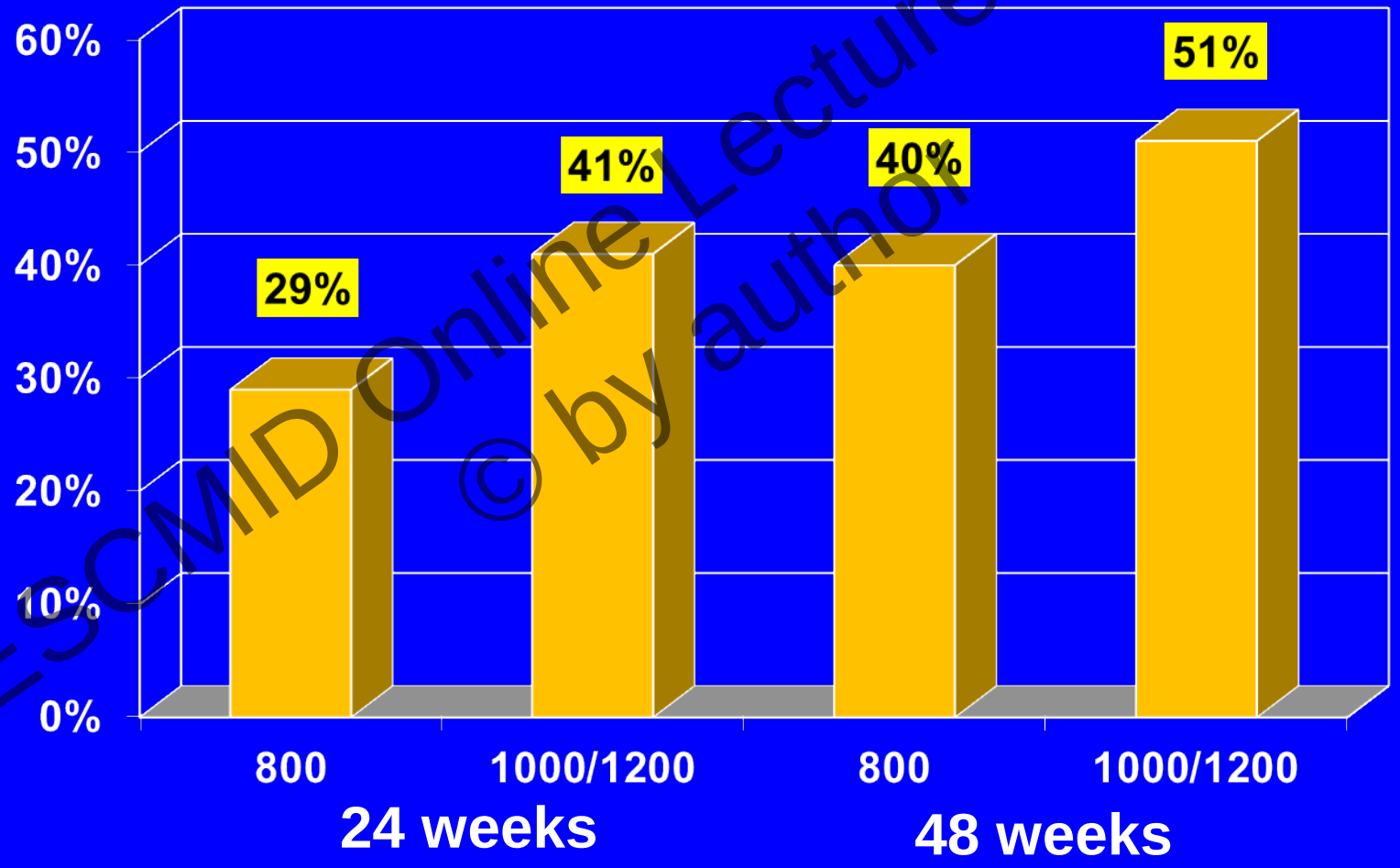
Predictors

Host factors	Viral factors

Predictors: PEG + RV

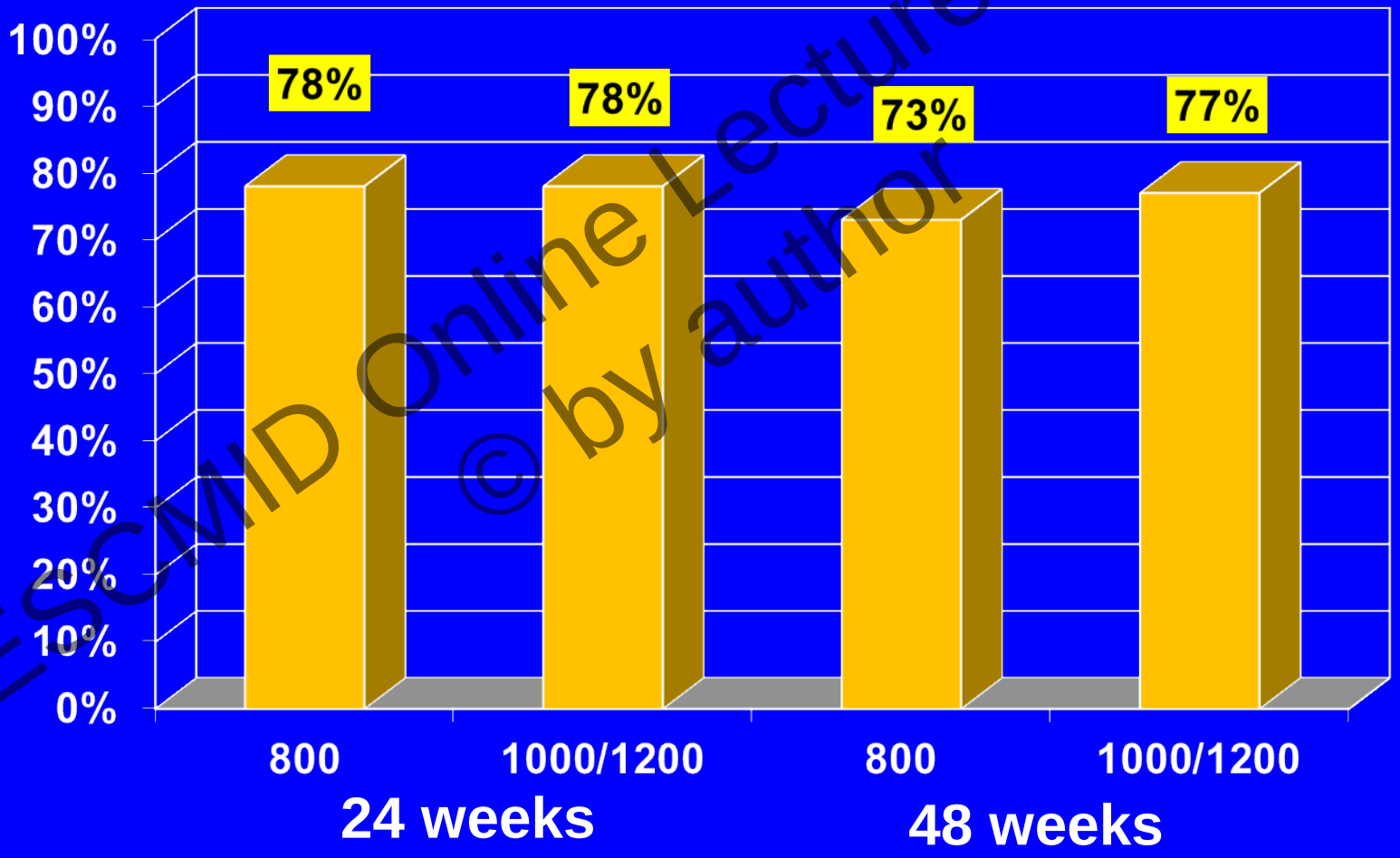
Host factors	Viral factors
	Viral genotype

PEG-IFN alpha2a & Ribavirin Genotype 1



Hadziyannis EASL 2002

PEG-IFN alpha2a & Ribavirin
Genotype non-1 (mainly 2 & 3)



Hadziyannis EASL 2002

Predictors: PEG + RV

Host factors	Viral factors
	Viral genotype

Biological basis for differential sensitivity amongst viral genotypes was – and remains - unknown

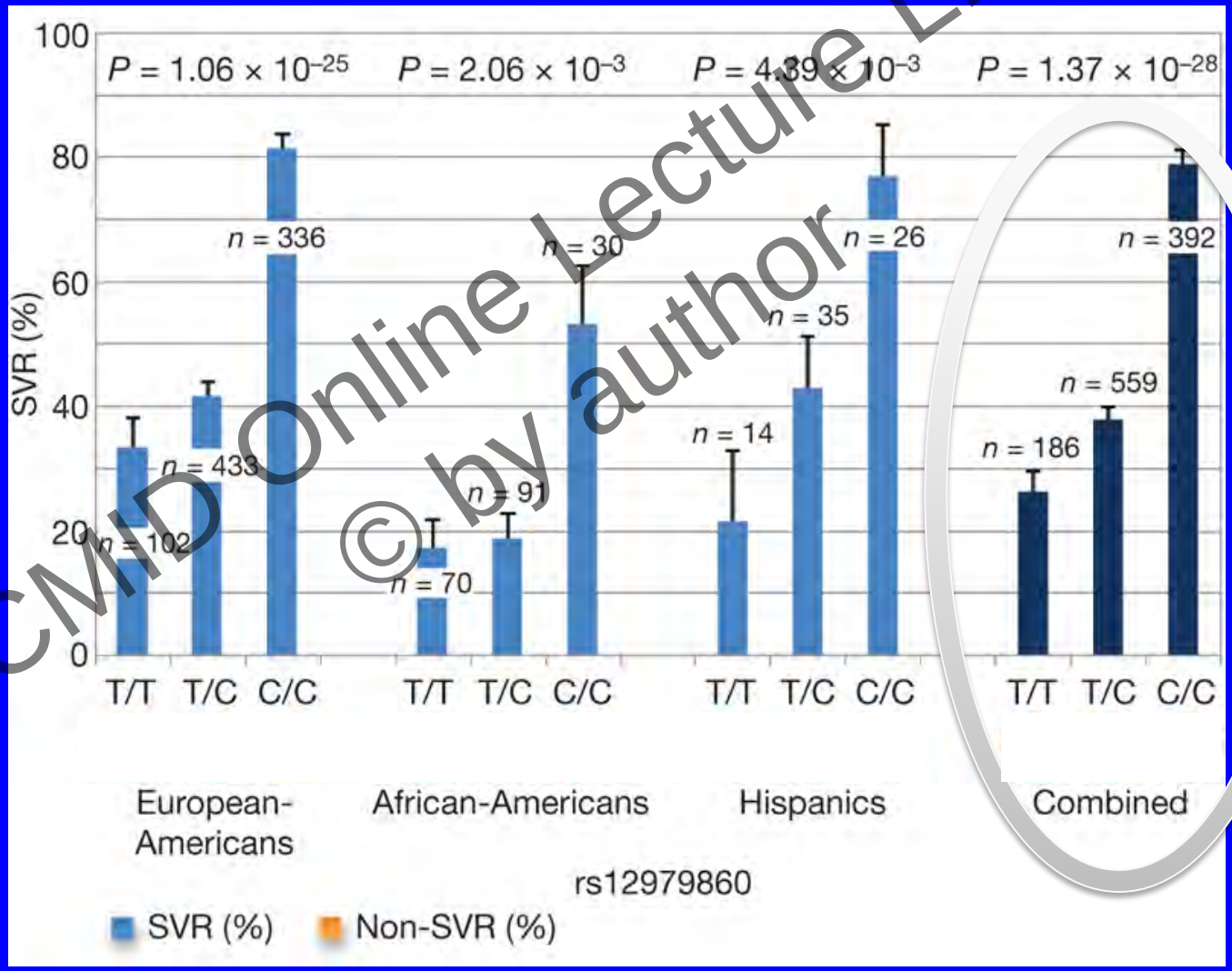
Predictors: PEG + RV

Host factors	Viral factors
Host genotype – IL28B	Viral genotype

IL-28B: Host Genetic Studies

- 4 large GWAS in high impact journals all replicating strong association between SNPs tagging IL28B (a.k.a. IFN-λ3) gene locus, and response to therapy
- Different ethnic groups
  - African American, Hispanic, European, Japanese

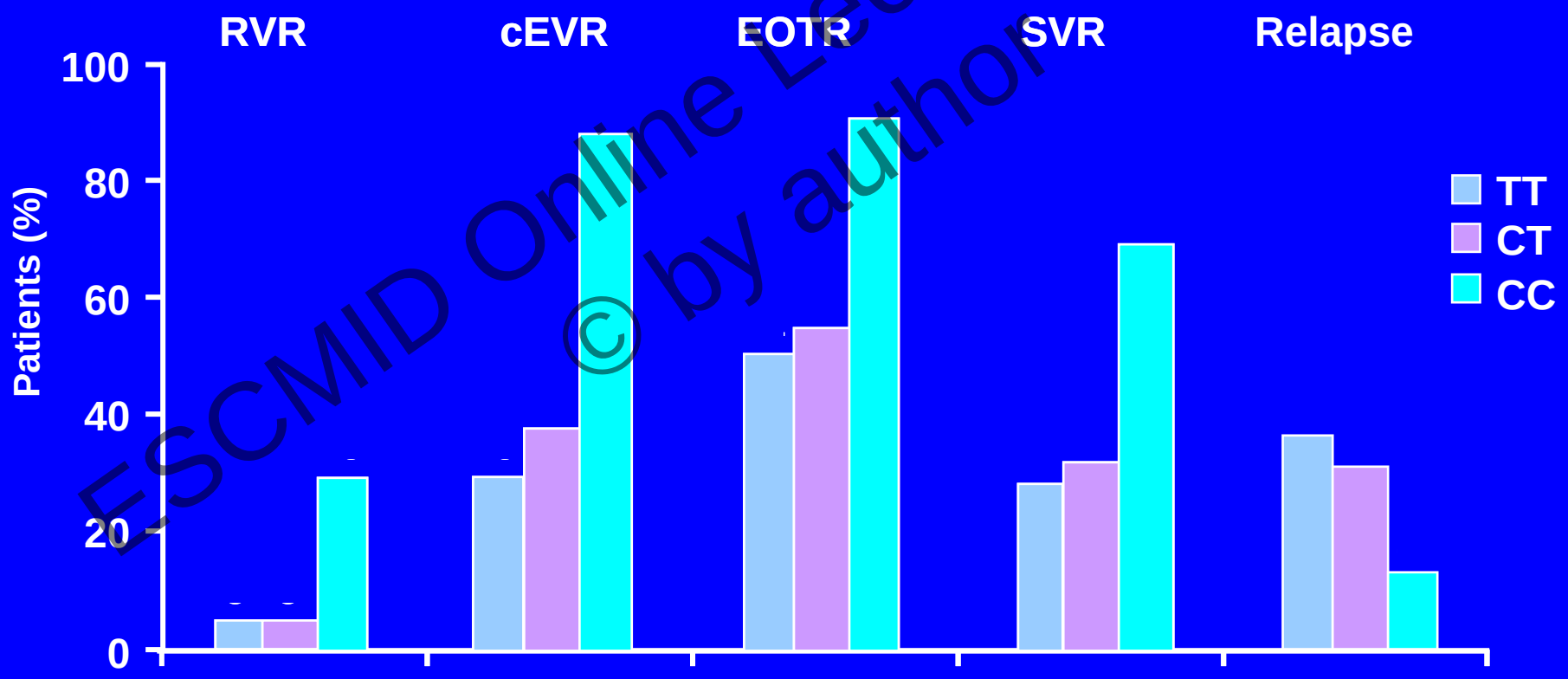
SVR Rates by IL-28B Genotype



DL Ge *et al.* *Nature* **461**, 399-401 (2009) doi:10.1038/nature08309

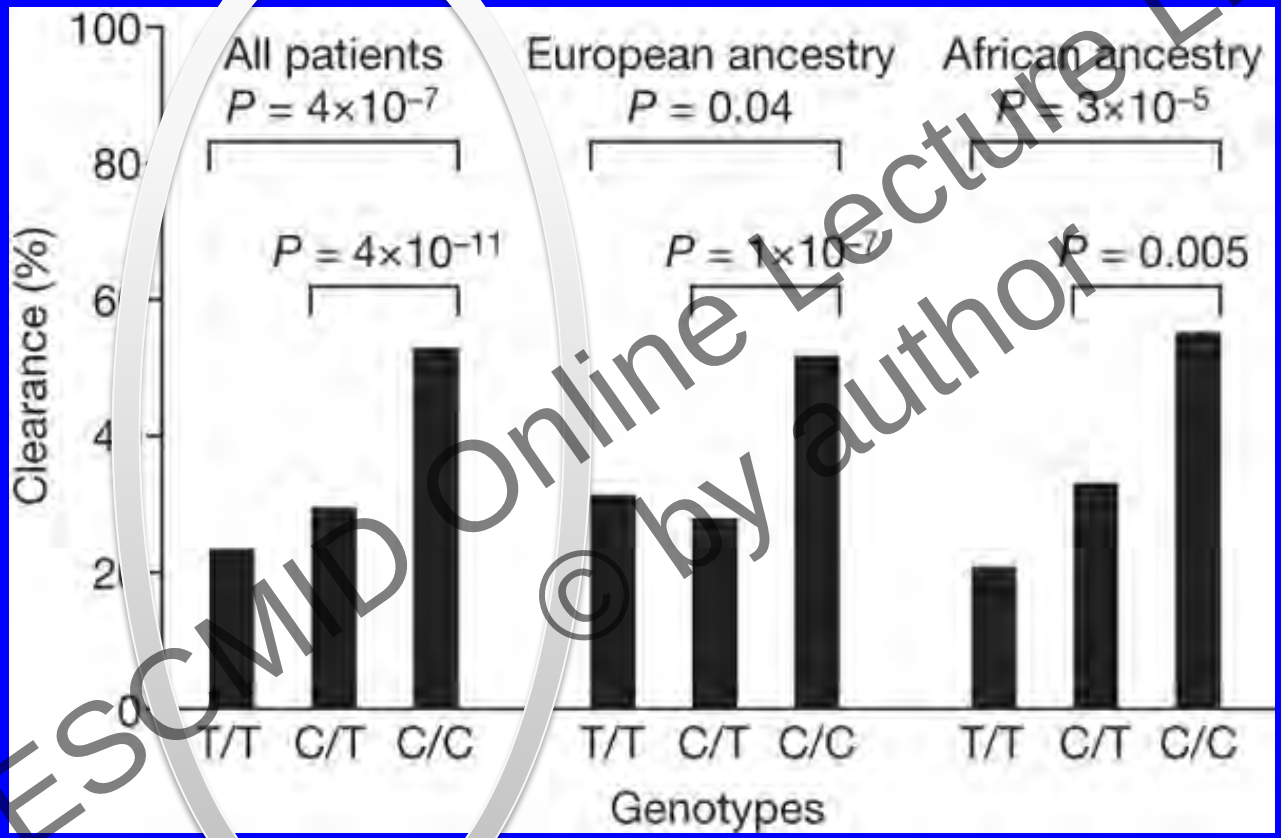
Host *IL28B* genotype associated with time to response and SVR

Caucasian GT1, naive patients
48 wk treatment with peginterferon alfa-2a/RBV or peginterferon alfa-2b/RBV



Thompson AJ, et al. Gastroenterology 2010; 139:120–129

SPONTANEOUS HCV CLEARANCE BY GENOTYPE



DL Thomas *et al. Nature* **461**, 798-801 (2009) doi:10.1038/nature08463

IL28B IS MORE COMMON IN ETHNIC GROUPS WITH POOR OUTCOMES

Thomas et.al., Nature, 2009

IL28B and HCV genotype 3

- ? Good allelle enriched in patients with geno 3a
  - Hepatology and Gastroenterolgy 2010
- IL28B polymorphisms not associated
  - Rauch et al Gastro 2010
- Il28B allelles linked to outcome in those without a RVR
  - McHutchinson Gastroenterology 2010

Predictors: PEG + RV

Host factors	Viral factors
Host genotype – IL28B	Viral genotype

IL28B genotype is associated with:

- Treatment response in HCV genotype 1 patients
- Spontaneous clearance of infection

Link with treatment response in HCV genotype 3 infection is weak

Underlying mechanisms unclear

Predictors: PEG + RV

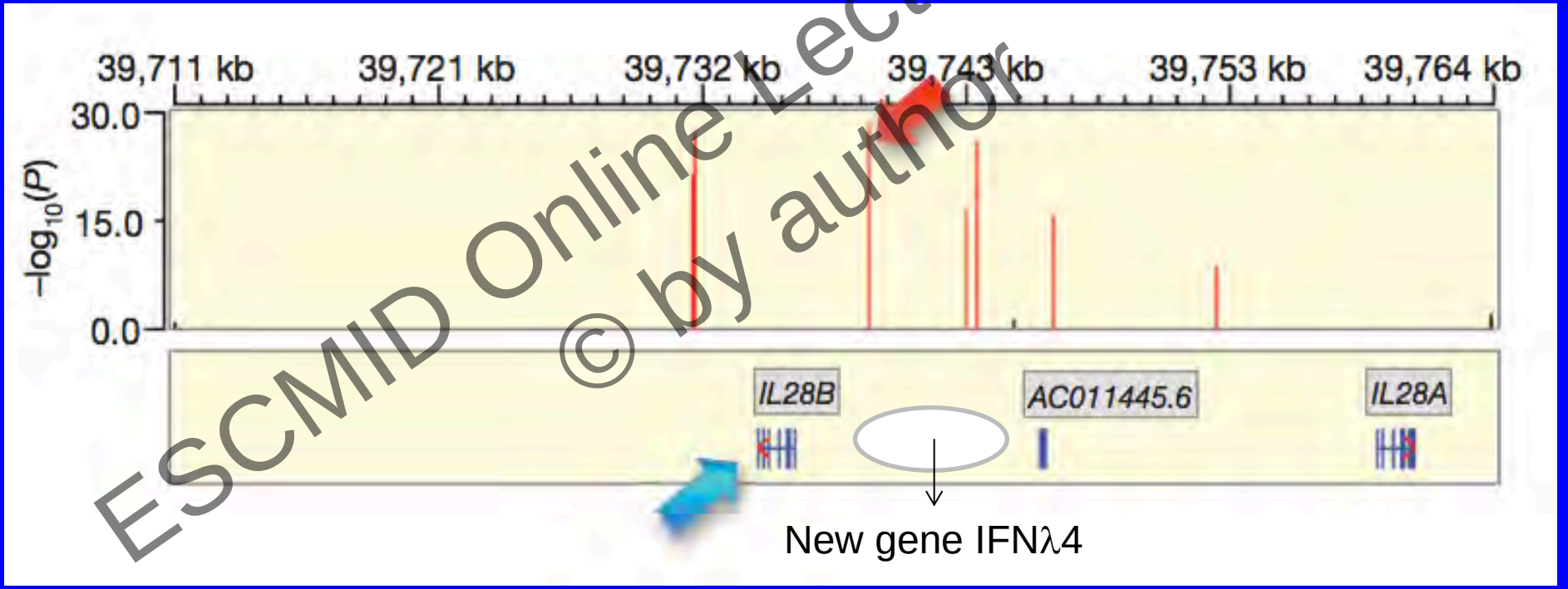
Host factors	Viral factors
Host genotype – IL28B	Viral genotype
Host genotype – IFN λ4	

nature genetics

A variant upstream of *IFNL3* (*IL28B*) creating a new interferon gene *IFNL4* is associated with impaired clearance of hepatitis C virus

Ludmila Prokunina-Olsson[1], Brian Muchmore[1], Wei Tang[1], Ruth M Pfeiffer[2], Heiyoung Park[3], Harold Dickensheets[4], Dianna Hergott[1,5], Patricia Porter-Gill[1], Adam Mumy[1], Indu Kohaar[1], Sabrina Chen[6], Nathan Brand[1], McAnthony Tarway[1], Luyang Liu[1], Faruk Sheikh[4], Jacquie Astemborski[7], Herbert L Bonkovsky[8], Brian R Edlin[9,10], Charles D Howell[11], Timothy R Morgan[12,13], David L Thomas[7,14], Barbara Rehermann[3], Raymond P Donnelly[4] & Thomas R O'Brien[5]

GENOMIC OVERVIEW OF CHROMOSOME 19



DL Ge *et al. Nature* **461**, 399-401 (2009) doi:10.1038/nature08309

Lupberger J et al. Hepatology 2013 58: 439-441

Predictors: PEG + RV

Host factors	Viral factors
Host genotype – IL28B	Viral genotype
Host genotype – IFN λ4	

Other host genes may also impact on treatment response:
HLA-C, HLA-E, NK KIR, ITPA (RV-anaemia)

The search for better host genetic markers in HCV g3 infection continues

Predictors: PEG + RV

Host factors	Viral factors
Host genotype – IL28B	Viral genotype
Host genotype – IFN λ4	**Baseline viral load**

Variation in cut-off definition (high versus low):

400,000 IU/ml 600,000 IU/ml 800,000 IU/ml

More pronounced effect in HCV g1 infection

Predictors: PEG + RV

Host factors	Viral factors
Host genotype – IL28B	Viral genotype
Host genotype – IFN λ4	Baseline viral load
Liver fibrosis	

Cirrhotics do not respond as well

Fibrotest at baseline has been reported to be predictive of SVR

Predictors: PEG + RV

Host Factors	Viral factors
Host genotype – IL28B	Viral genotype
Host genotype – IFN λ4	Baseline viral load
Liver fibrosis	
Age	
Body Mass Index	
HIV co-infection	

Better response associated with:

- Younger age
- Lower BMI
- Mono-infection

Predictors: PEG + RV

Host Factors	Viral factors
Host genotype – IL28B	Viral genotype
Host genotype – IFN λ4	Baseline viral load
Liver fibrosis	
Age	
Body Mass Index	
HIV co-infection	
IP-10 levels	

Lower preRx interferon inducible protein 10 (CXCL10) levels associated with higher SVR rates

Other serum markers include RANTES, apo B-100, γGT

Predictors: PEG + RV

Host Factors	Viral factors
Host genotype – IL28B	Viral genotype
Host genotype - IFNλ4	Baseline viral load
Liver fibrosis	
Age	
Body Mass Index	
HIV co-infection	
IP 10 levels	
Vitamin D status	

Vit D receptor polymorphisms associate with low Vit D levels and low SVR rates

Vit D supplementation may or may not ↑ SVR - CONTROVERSIAL

Vit B12 supplementation, Vit A deficiency

Predictors: PEG + RV

Host Factors	Viral factors
Host genotype – IL28B	Viral genotype
Host genotype - IFNλ4	Baseline viral load
Liver fibrosis	**Viral sequence**
Age	
Body Mass Index	
HIV co-infection	
IP 10 levels	
Vitamin D status	

IFN sensitivity determining region (ISDR) NS5a
IFN/RV resistance determining region (IRRDR) NS5a
Core positions 70, 75 and 91

All of above may be genotype dependent

Predictors: PEG + RV Clinical use?

Ferenci et al. Liver International Dec 2013

		Points		Points		Points		Points
Age	<35	2	35-45	1	>45	0		
BMI	<20	2	20-22	1	>22	0		
Viral load	<100k	3	100-400k	2	400-800k	1	>800k	0
Platelets	>150x10^9	1	<150x10^9	0				
ALN	>3ULN	1	<3ULN	0				
AST	<1ULN	1	>1ULN	1				

Score	No. patients	SVR %
0-2	1029	35.0
3-4	698	54.9
≥5	382	76.7

Predictors: PEG + RV

Host Factors	Viral factors	On Rx factors
Host genotype – IL28B	Viral genotype	**Response at 4 weeks**
Host genotype - IFNλ4	Baseline viral load	
Liver fibrosis		
Age		
Body Mass Index		
HIV co-infection		
IP 10 levels		
Vitamin D status		

Rapid Virological Response is the strongest predictor of SVR

Rapidity of viral load decline may determine length of therapy and defines stopping rules

Predictors of treatment failure

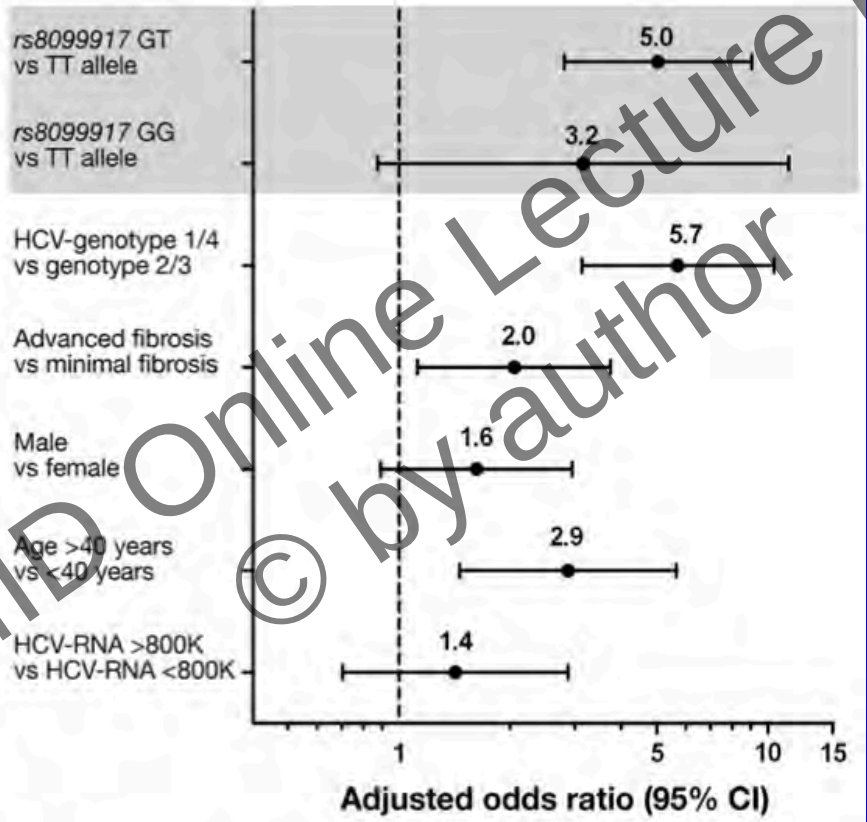


Figure 3. Predictors of failure to respond to pegylated IFN-α and ribavirin therapy. Carriers of the *rs8099917* G-risk genotypes had a higher risk of failing to respond to HCV treatment. ORs were calculated by allele and were adjusted for HCV genotypes, fibrosis stage, sex, age, baseline HCV viral load, and the first 2 ancestry principal components.

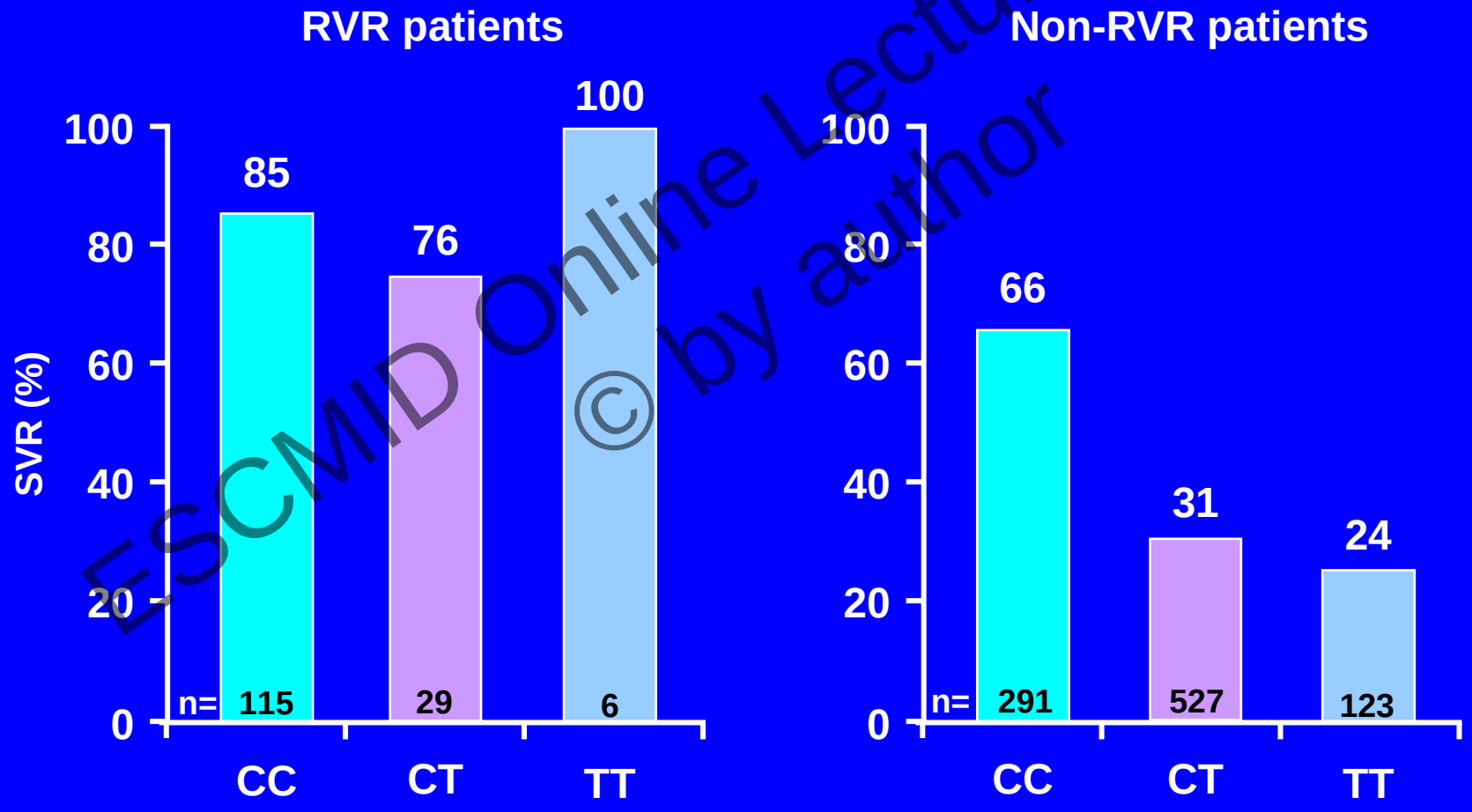
RVR vs no RVR

OR is around 7.0

Rauch et.al., Gastroenterology, 2010

IL28B CC patients with an RVR have similar SVR rates to non-CC patients with an RVR

Caucasian GT1, naive patients
48 wk treatment with peginterferon alfa-2a/RBV or peginterferon alfa-2b/RBV



Thompson AJ, et al. Gastroenterology 2010; 139:120–129

Changing treatment modalities

- PEG + RV
  - The most studied
- **PEG + RV + DAAs**
  - Some data emerging
- DAAs
  - Very little data available

Predictors: PEG + RV + DAA

Host Factors	Viral factors	On Rx factors
		Response at 4 weeks

Rapid Virological Response is the strongest predictor of SVR

Rapidity of viral load decline determines length of therapy (RGT) and defines stopping rules

Predictors: PEG + RV + DAA

Host Factors	Viral factors	On Rx factors
	Viral genotype	Response at 4 weeks

DAAs may be genotype specific – aim is for pangenotypic activity

Predictors: PEG + RV + DAA

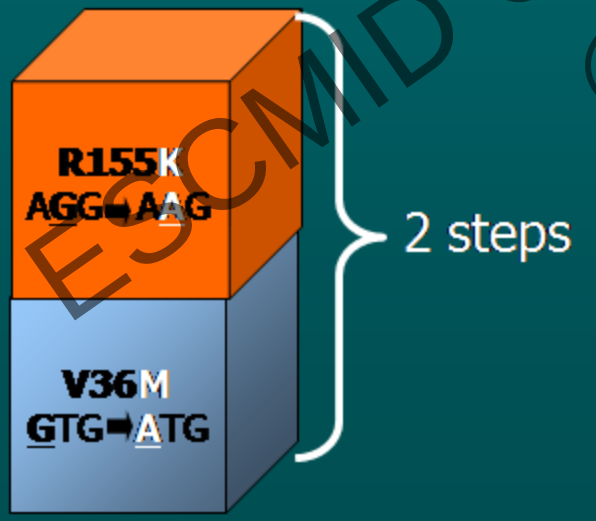
Host Factors	Viral factors	On Rx factors
	Viral genotype – and subtype	Response at 4 weeks

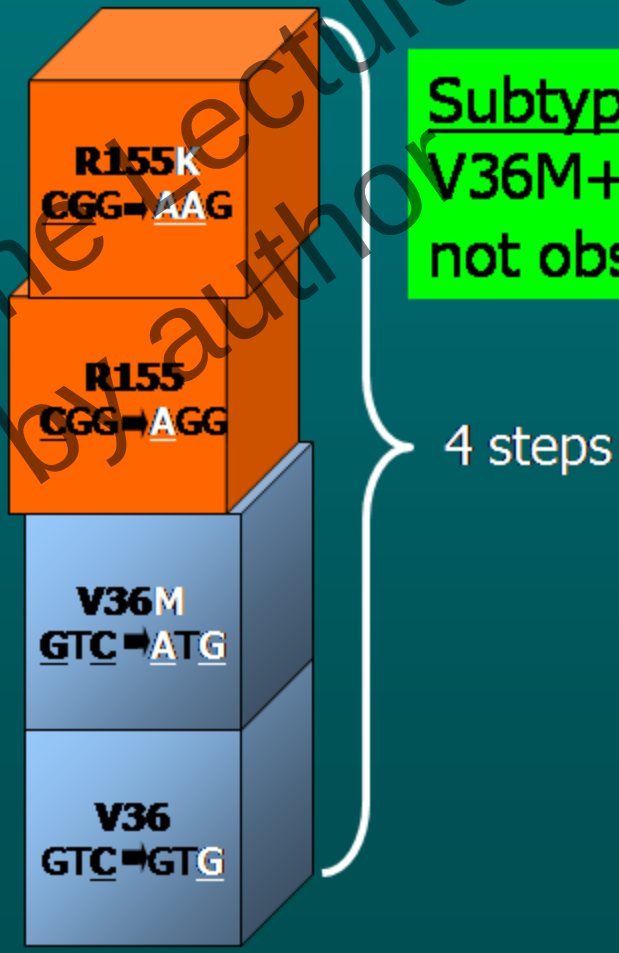
G1b responds better than g1a to many DAAs

Higher genetic barrier to resistance

Clinical Implications of Genetic Barrier to Resistance – Acquisition of NS3 Inhibitor Resistant Variant V36M+R155K

Subtype 1a
V36M+R155K variant observed clinically[1,2]





Subtype 1b
V36M+R155K variant not observed clinically

McHutchison JG. *N Engl J Med.* 2009; 360; 18 1827-1838
Hezode C. *N Engl J Med.* 2009; 360; 18 1839-1850

Predictors: PEG + RV + DAA

Host Factors	Viral factors	On Rx factors
	Viral genotype and subtype	Response at 4 weeks
	Baseline viral load – less important	

Predictors: PEG + RV + DAA

Host Factors	Viral factors	On Rx factors
Host genotype – IL28B – less important	Viral genotype	Response at 4 weeks
	(Baseline viral load)	

IL28B may be helpful in allowing shortening of therapy in patients who achieve RVR and have favourable genotype

May also help in predicting SVR in patients who do NOT achieve eRVR

Predictors: PEG + RV + DAA

Host Factors	Viral factors	On Rx factors
(Host genotype – IL28B)	Viral genotype	Response at 4 weeks
Host genotype - IFNλ4 – less well studied	(Baseline viral load)	

Predictors: PEG + RV + DAA

Host Factors	Viral factors	On Rx factors
(Host genotype – IL28B)	Viral genotype	Response at 4 weeks
Liver fibrosis	(Baseline viral load)	

Most trials involving DAAs do not have large numbers of cirrhotics

Response is not as good in cirrhosis

Predictors: PEG + RV + DAA

Host Factors	Viral factors	On Rx factors
(Host genotype – IL28B)	Viral genotype	Response at 4 weeks
Liver fibrosis	(Baseline viral load)	
Age		
Body Mass Index		
HIV co-infection		

Predictors: PEG + RV + DAA

Host Factors	Viral factors	On Rx factors
(Host genotype – IL28B)	Viral genotype	Response at 4 weeks
Liver fibrosis	(Baseline viral load)	
Age		
Body Mass Index		
HIV co-infection		
Previous treatment response		

Responder relapsers versus
Partial Responders versus
Non-responders

REALIZE TPR Re-Rx

SVR rates REALIZE

	Relapsers	Partial responders	Null responders	Overall ITT
	n = 354	n = 124	n = 184	n = 662
Telaprevir treatment arms	86% (245/286)	57% (55/97)	31% (47/147)	65% (346/530)
	Pooled analysis 78% (300/383)			
Control	24% (16/68)	15% (4/27)	5% (2/37)	17% (22/132)

No difference between lead in (delayed start) and simultaneous start

Changing treatment modalities

- PEG + RV
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  - Some data emerging
- **DAAs**
  - Very little data available

Predictors: DAAs (+/- ribavirin)

Host Factors	Viral factors	On Rx factors
Host genotype – IL28B	Viral genotype	Response at 4 weeks
Host genotype - IFNλ4	Baseline viral load	
Liver fibrosis		
Age		
Body Mass Index		
HIV co-infection		
IP 10 levels		
Vitamin D status		

Predictors: DAAs (+/- ribavirin)

Host Factors		Viral factors		On Rx factors	
Host genotype – IL28B	X	Viral genotype	X	Response at 4 weeks	X
Host genotype - IFNλ4	X	Baseline viral load	X		
Liver fibrosis	√				
Age	X				
Body Mass Index	X				
HIV co-infection	?				

Predictors: DAAs

- SVR rates will be so high (>95%), it will not be possible to identify predictors
- Agents will be pangenotypic
- There will be no need for on-treatment monitoring – just start, then test for SVR12
- Patients with end-stage liver disease may not do so well
- Trials in HIV co-infection awaited

Predictors: Do we need them?

- Depends on cost and availability of DAAs
- If there are restrictions on who can access DAAs, then it will become imperative to identify patients who could/could not be treated with IFN/RV based regimens

Summary

- Numerous host and viral factors have been identified as predictors of response to PEG/RV based therapy
- On treatment viral kinetics is the strongest single predictor of overall response
- Simple, multi-parameter models allowing accurate prediction of SVR may be clinically useful in the transition period to universal use of DAAs

Acknowledgements for slides

- Dr Ellie Barnes, Oxford
- Prof Graham Foster, London
- Prof Christophe Hezode, Paris
- Prof William Rosenberg, London