Goals for Treatment and Predicting Response

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Outline

- Rationale and goals for treatment (SVR, disease progression, survival)
- Viral factors that predict response to therapy (HCV genotype, HCV RNA level)
- Host factors that predict response to therapy (race, age, sex, *IL28B* genotype)
- Combined factors (degree of fibrosis)

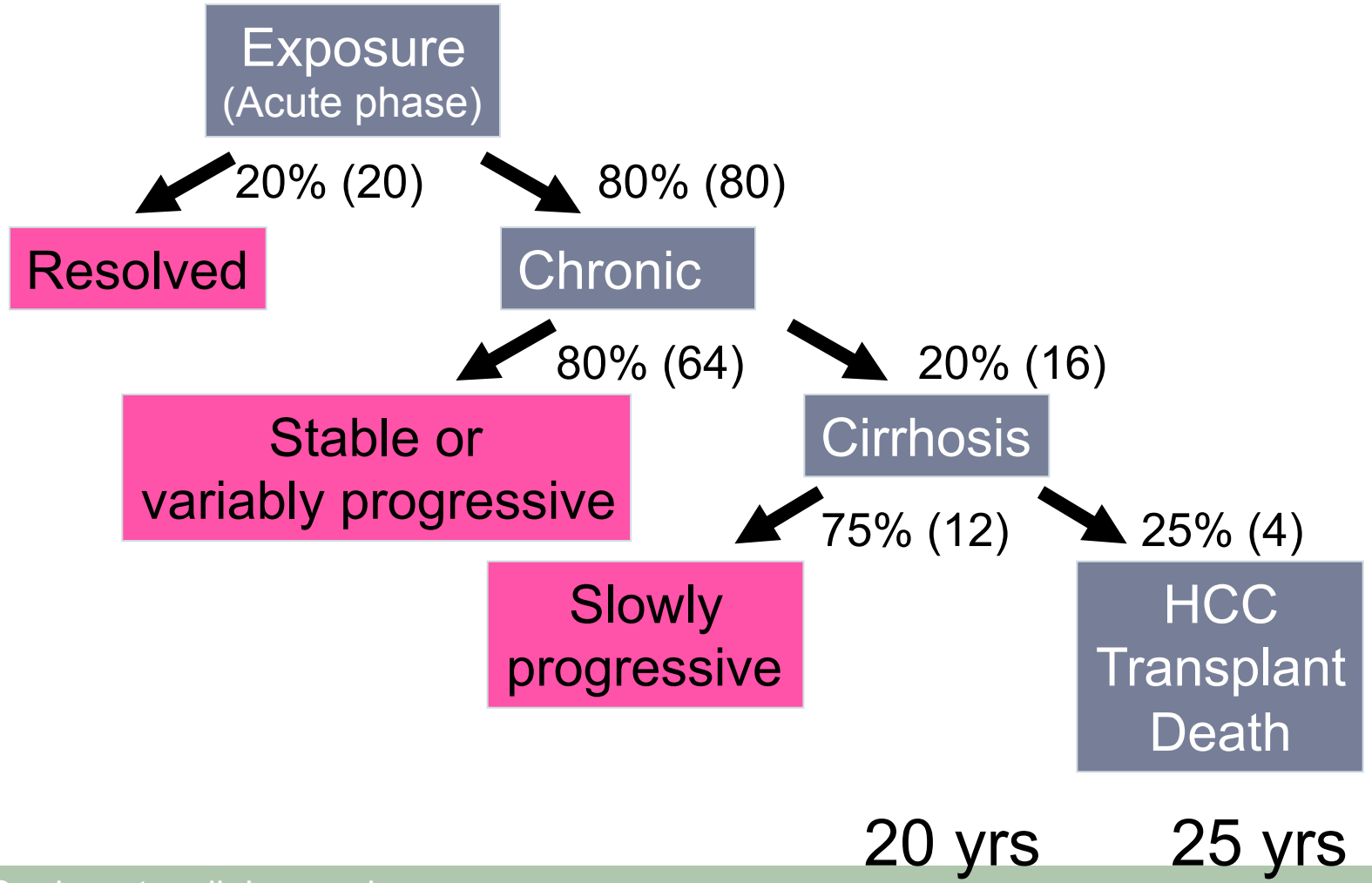
HCV = hepatitis C virus; SVR = sustained virologic response

Rationale and Goals for Treatment (SVR, Improve Histology, Survival)

Rationale and Goals for Treatment

- Chronic HCV is a progressive disease that can produce significant morbidity and mortality if left untreated
- HCV RNA virus without latent, stable intermediate
- Requires continuous replication
- SVR is possible and connotes clinical cure
- Defined as clearance of HCV RNA 24 weeks after completion of a course of antiviral therapy
  - SVR 12 weeks after discontinuation of treatment equates to SVR 24 weeks after discontinuation of treatment

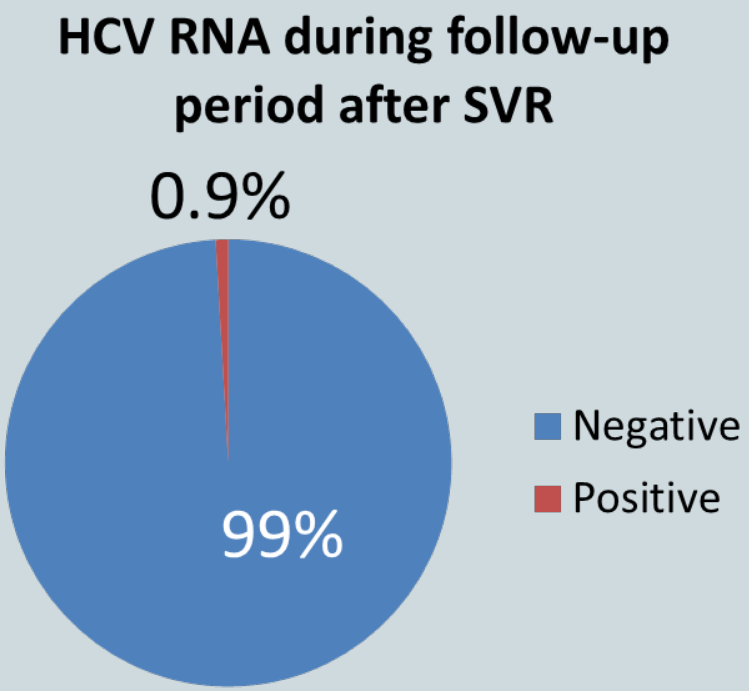
Natural History of Chronic HCV



HCC = hepatocellular carcinoma

An SVR is Truly Sustained

- Cohort study
- Patients from 9 trials
- HCV: 1243 patients
- HIV/HCV: 100 patients
- Follow-up: mean 3.9 yrs (range, 0.8-7.1 yrs)
- 0.9% HCV RNA positive after treatment ended



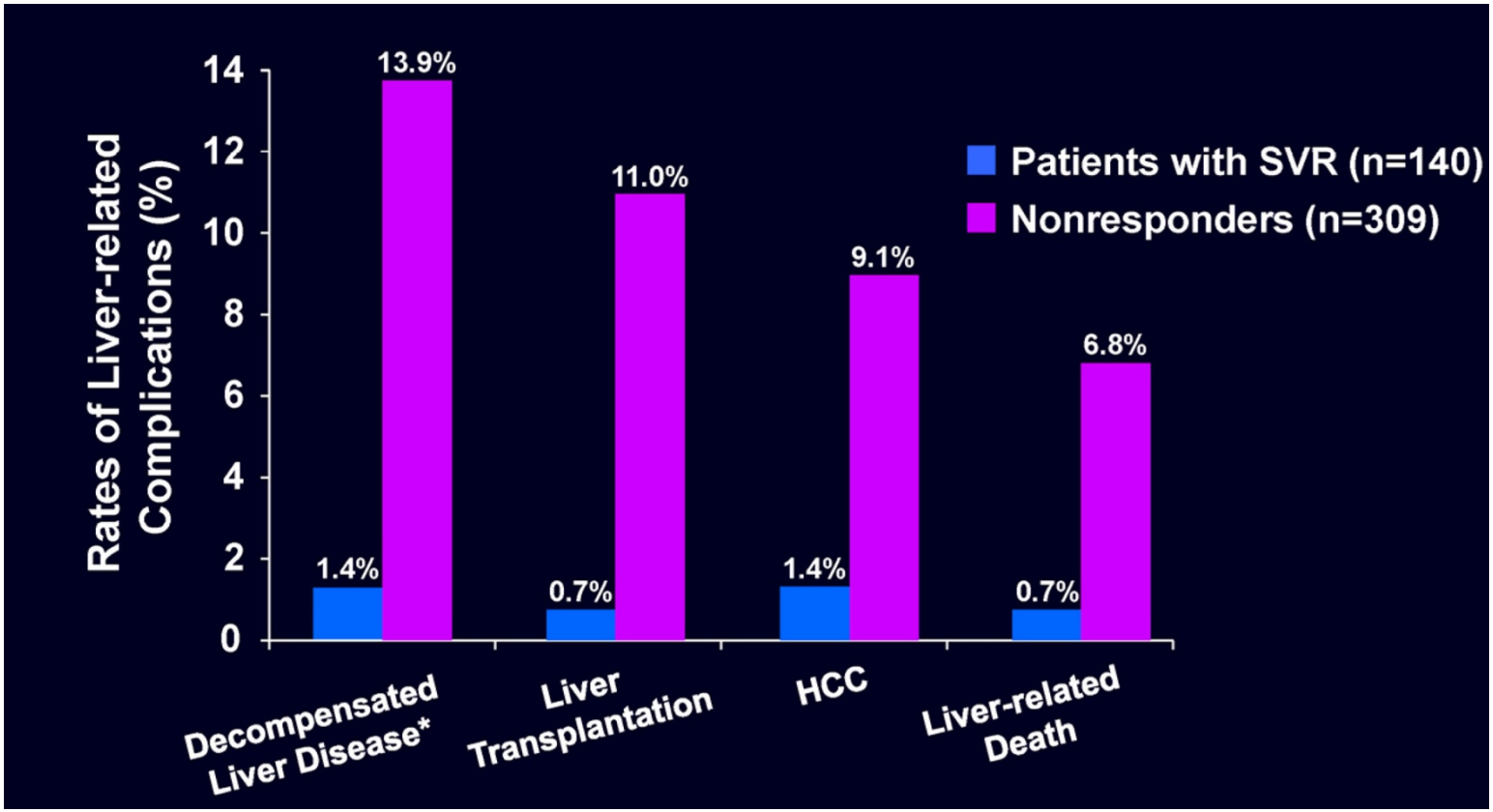
Swain MG. *Gastro,* 2010

Impact of SVR on Natural History in Patients With Advanced Fibrosis

- Improved outcomes in patients who achieve SVR
  - All-cause mortality
  - Liver-related mortality
  - Liver cancer
  - Liver failure or need for liver transplantation
  - Reduce insulin resistance and diabetes mellitus

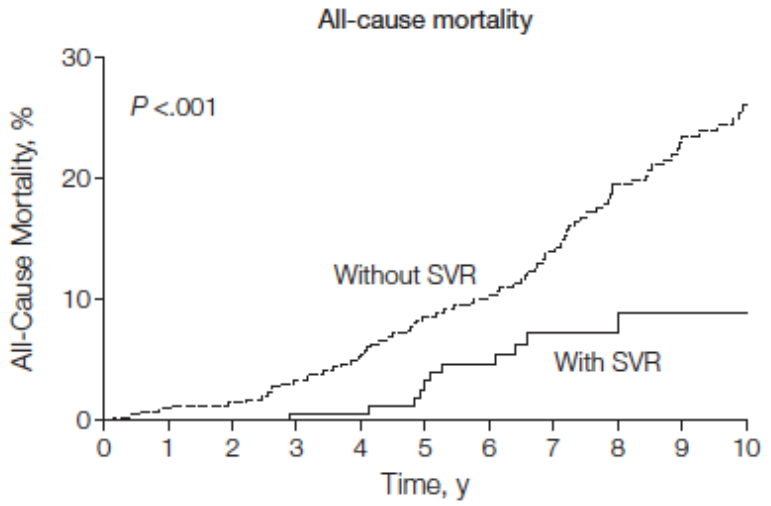
SVR Reduces Liver-Related Complications

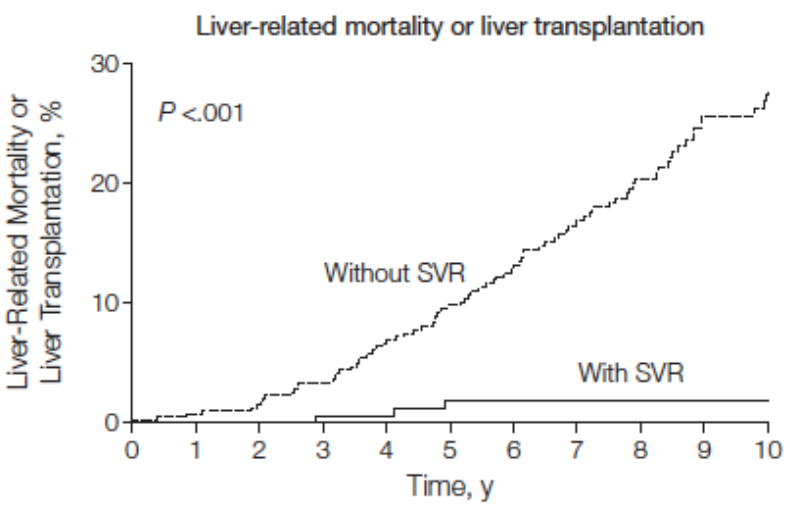
- HALT-C Cohort (patients with bridging fibrosis/cirrhosis)
- Median follow-up 85.8 months (SVR) and 78.4 months (non-SVR)



Morgan T. *Hepatology*. 2010;52(3):833-44.

SVR Reduces All-Cause and Liver-Related Mortality





Outcomes	With SVR: Events, No.	With SVR: Observation Period, Person-Years	With SVR: Rate per 100 Person-Years (95% CI)	Without SVR: Events, No.	Without SVR: Observation Period, Person-Years	Without SVR: Rate per 100 Person-Years (95% CI)	*P* Value[b]
Any event[a]	18	1260	1.43 (0.77-2.09)	169	2921	5.79 (4.91-6.66)	<.001
All-cause mortality	13	1283	1.01 (0.46-1.56)	100	3410	2.93 (2.36-3.51)	<.001
Liver-related mortality or liver transplantation	3	1283	0.23 (<0.01-0.50)	103	3120	3.20 (2.58-3.82)	<.001

van der Meer A, *JAMA*, 2013

Baseline Factors Predictive of SVR With an HCV PI Plus PegIFN and RBV therapy

Viral factors

- HCV RNA level
- HCV genotype (GT; 1 vs 2,3)
- GT 1 subtype (1a vs 1b)

Host factors

- Race and ethnicity
- Gender
- Interleukin 28B genotype (CC vs CT or TT)
- Body mass index (BMI)

Combined

- Liver histology

PI = protease inhibitor; PegIFN = peginterferon alfa; RBV = ribavirin

Baseline Predictors of SVR: SPRINT-2

Effect	Odds Ratio (95% CI)	*P* value
Baseline HCV RNA: ≤ 400,000 vs > 400,000	11.6 (1.5, 87.8)	.02
IL28B rs12979860: CC vs TT	2.6 (1.3, 5.1)	.006
IL28B rs12979860: CC vs CT	2.1 (1.2, 3.7)	.01
IL28B rs12979860: CT vs TT	1.2 (0.7, 2.2)	.48
Cirrhosis: no vs yes	4.3 (1.6, 11.9)	.004
Genotype: 1b vs 1a	2.0 (1.2, 3.4)	.005
Race: non-black vs black	2.0 (1.1, 3.7)	.03
BMI: ≤ 30 vs > 30	1.6 (1.0, 2.5)	.07

CI = confidence interval

Viral Factors that Predict Response to Therapy (HCV Genotype, HCV RNA level)

Viral Factors

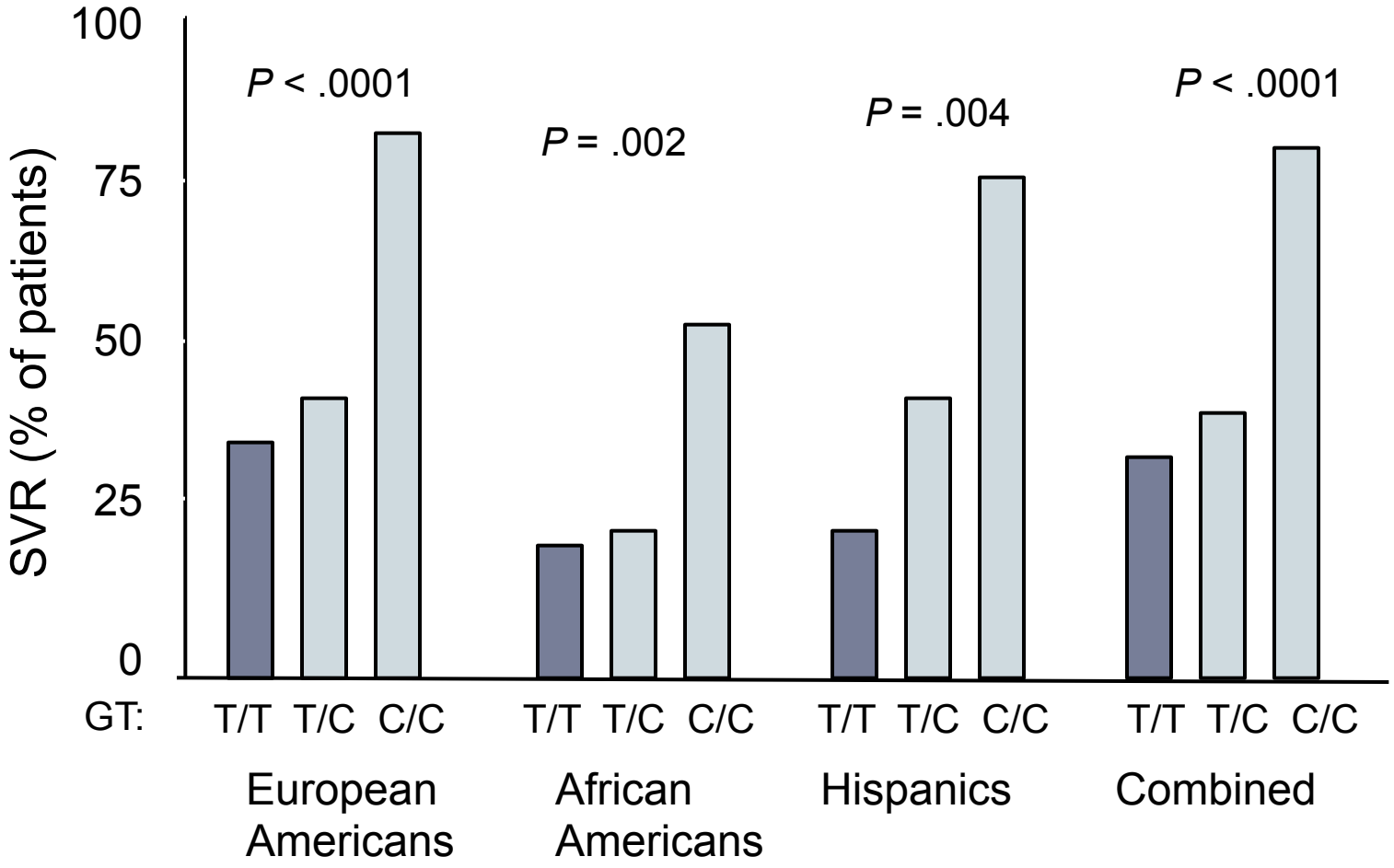
- Genotype
  - Current therapies (PegIFN/RBV/PI) centered on GT 1
  - Standard of care for GT 2,3: PegIFN and RBV
- Subtype
  - SVR rates higher for GT 1b vs 1a
  - 1a - lower barrier to emergence of resistant variants for HCV PIs
- HCV RNA level
  - Higher HCV RNA associated with slightly diminished SVR
  - Effect strong

Host Factors that Predict Response to Therapy (Race, Age, Sex, *IL28B* Genotype)

Host Factors

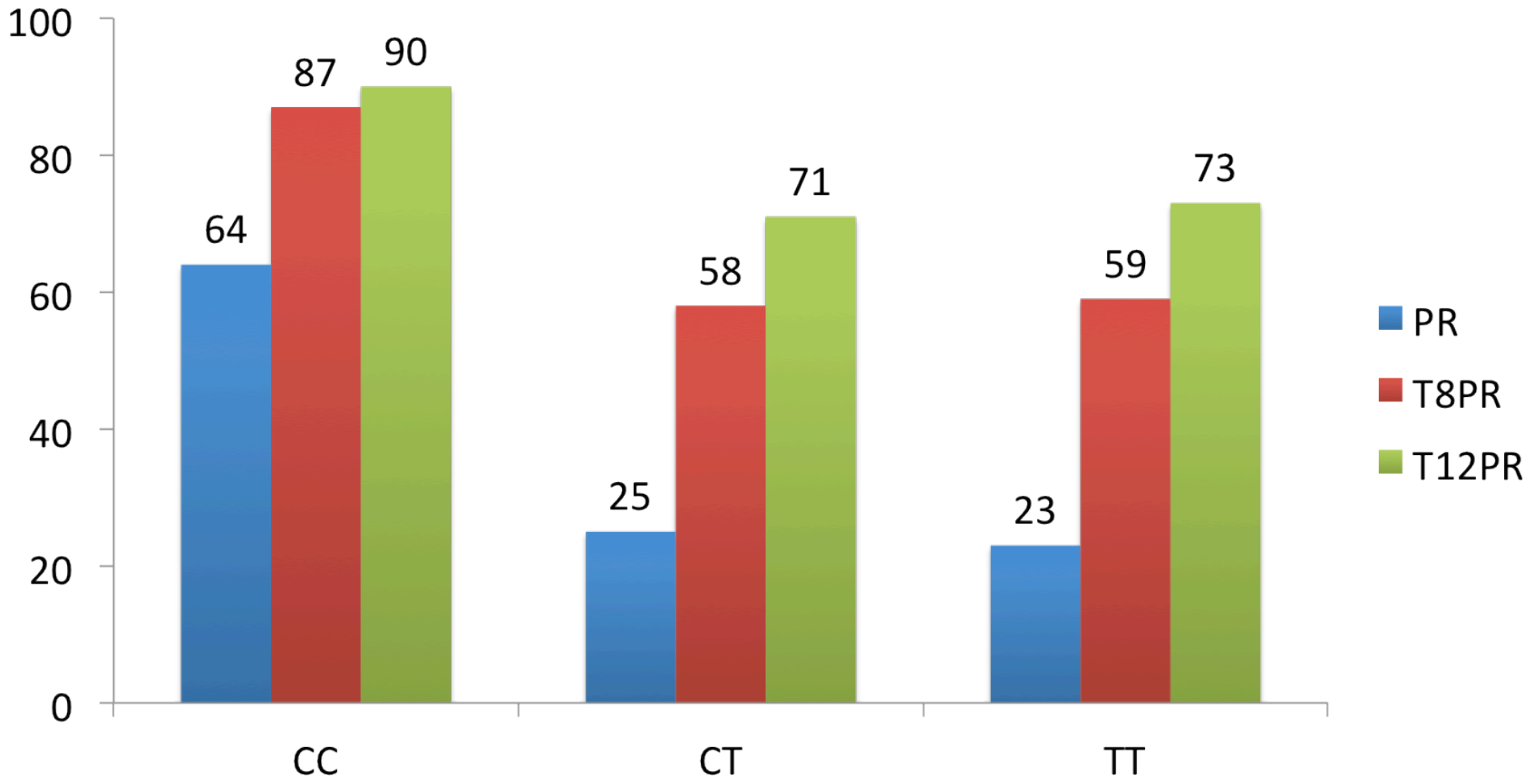
- Race (non-black > black)
- Age (younger > older)
- Sex (F > M)
- *IL28B* GT (CC > CT, TT for the rs12979860 single nucleotide polymorphism [SNP])
  - Strongest predictor of PegIFN and RBV response in GT 1, but effect less stark with PegIFN and RBV plus a PI

SVR to PegIFN and RBV Profoundly Influenced by *IL28B* Genotype



Ge D et al. *Nature.* 2009;461(7262):399-401.

SVR According to *IL28B:* PegIFN, RBV, and Telaprevir



Jacobson et al. EASL, 2011; PR = peginterferon alfa and ribavirin; T = telaprevir

Degree of Fibrosis and Predicting Treatment Response

Combined Factors

- Extent of fibrosis
  - Patients without cirrhosis more responsive than patients with cirrhosis
- Mechanism unclear
  - Pharmacokinetic and pharmacodynamic considerations with distorted architecture
  - Cirrhosis associated with innate and adaptive immune deficits
- Decision to treat patients with cirrhosis must be weighed against projected response rate and potential for adverse effects
- Similarly, deferral of treatment may be considered in patients without cirrhosis with the impending approval of direct-acting antivirals (DAAs)

Summary

- Cure of HCV achievable
- SVR associated with significant clinical benefit
  - Slows or reverses disease progression
  - Reduces hepatic and all-cause mortality
  - Improves extrahepatic manifestations
- Host, viral, and mixed factors all influence success of treatment with PegIFN, RBV, and a PI
- Discussion of these factors should take place in preparation for treatment
- Availability of potent DAA combination regimens will dilute the effect of these predictors

End

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