Published in final edited form as:

Infect Dis Clin North Am. 2012 December ; 26(4): 863–877. doi:10.1016/j.idc.2012.08.010.

IL28B polymorphisms as a pre-treatment predictor of response to HCV treatment

Christoph T. Berger, MD^{1,2} and Arthur Y. Kim, MD³

¹Ragon Institute of Massachusetts General Hospital, Massachusetts Institute of Technology and Harvard Medical School ²Department of Internal Medicine and Department of Biomedicine, University Hospital Basel, Switzerland ³Division of Infectious Diseases, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts 02114, USA

SYNOPSIS

In recent years, genome-wide association studies (GWAS) all identified polymorphisms located near the gene encoding the interferon-lambda beta subunit (also known as IL28B) that turned out to be the best predictor of response to pegylated interferon plus ribavirin for chronic HCV genotype 1 infection. This association was extended to spontaneous clearance of HCV, suggesting shared mechanisms of both treatment and natural control of this virus. African-Americans were discovered to harbor the favorable host genotype at a lower rate than Caucasian counterparts, thus in part explaining the previous observation that they cleared HCV less successfully. In addition to the biologic implications for innate immunity and HCV, a variety of clinical studies have suggested possible translation to a useful genetic test for practitioners. Herein we review the discovery, biology, and potential clinical applications that have stemmed from the seminal observation that IL-28B polymorphisms are a main predictor of HCV clearance.

Keywords

IL28B; pharmacogenomics; antiviral; type III interferon; interferon-lambda

INTRODUCTION

Approximately 170 million individuals, or about 2–3% of the world's population, are chronically infected with the hepatitis C virus (1). With the approval of interferon alpha for HCV treatment in 1991, infection could be successfully cured in only a fraction of patients. The first combination treatment with ribavirin (RBV) and replacement of conventional interferon with pegylated interferon alpha (PEG-IFNa) led to dramatically increased treatment success rates over the past decade. Still about half of all affected individuals fail to clear the virus despite this treatment (2). Several viral and host factors -specifically, infection with HCV genotype 1 and 4, higher magnitude of viral titers, male gender,

© 2012 Elsevier Inc. All rights reserved.

Arthur Y. Kim, MD (corresponding), Massachusetts General Hospital, 55 Fruit Street/Cox 5, Boston, MA 02114, USA, akim1@partners.org, Tel: +1 617 724 3230; fax: +1 617 726 5411. Christoph T. Berger, MD, University Hospital Basel, Department of Internal Medicine Outpatient Clinic, Petersgraben 4, Basel, 4051, Switzerland, bergerc@uhbs.ch, Tel: +41 61 328 6631; fax: +41 61 265 5515.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

advanced liver fibrosis and African ancestry- were associated with poor treatment response rates (3). Stratification based on such risk factors consequently led to personalized treatment strategies that varied mostly in the duration of treatment (2). Since PEG-IFNa/RBV is hampered by its long duration and the high burden of side effects, even more accurate predictors of outcome would help clinicians optimize treatment plans and duration.

This motivated several genome wide association studies (GWAS) aimed at identifying protective host genetic factors associated with successful treatment response and/or spontaneous HCV clearance. In 2009 and 2010 several groups independently reported single nucleotide polymorphisms (SNP) near the interleukin-28 beta subunit (IL-28B) gene that were dramatically associated with both sustained virological response to PEG-IFNa/RBV and spontaneous viral clearance in the absence of therapy (4–7). IL28B genotyping quickly became available both in research and clinical settings and a large number of studies investigating the impact of the IL28B genotype have been published since the first reports. Just as these discoveries heralded a new era in HCV treatment based on pharmacogenomic testing, several questions remain regarding the utility of IL28B genotype testing in clinical practice.

GWAS to Detect Host Genetic Factors in HCV Identifies a SNP Linking IL28B to Treatment Response

The human genome spans more than 3 billion base pairs with an overall conservation rate of >99%. GWAS test a set of more than 500'000 SNP that commonly occur in a population (e.g. >5%), and SNP frequencies are compared between a cohort of individuals with a specific condition or disease outcome and respective controls (8). Importantly, in most cases the SNPs that are detected are in fact not contained within the genes involved in the different outcome, but rather are often upstream or downstream and therefore are 'tags' of the genes themselves. Thus once a SNP is detected, a subsequent fine mapping of the area of interest is warranted. Moreover, since several SNP in that area can tag the same gene, testing for "linkage disequilibrium" (the degree these SNP are linked on the same chromosome) is crucial. Overall, a genome-wide approach's major advantage is that associations can be screened for in an unbiased and hypothesis-free manner, contrary to studies where target genes are specifically selected and thus by design prevents the discovery of new and unexpected genetic associations.

The first independent GWAS were performed in patients receiving PEG-IFNa/RBV for genotype 1 HCV infection and discovered two SNPs (rs12979860 and rs8099917) on chromosome 19 which were located in close proximity to the IL-28b gene, a type III interferon with antiviral and immunomodulatory effects (4–7). These were some of the strongest associations identified in any GWAS to date (9). In the first study, being homozygous for the favorable SNP of rs12979860 (C/C genotype), depending on the ethnic background, resulted in an odds ratio of 5.6–7.3 compared to the C/T or T/T genotype to achieve SVR. This favorable effect was strongest in Caucasians, but was found to be independent of gender, ethnicity, liver fibrosis or pretreatment viral loads. The beneficial SNP was much more common in Caucasians compared to individuals of African descent, and accounted for roughly 50% of the difference in the treatment response between these two groups (4). Interestingly, homozygosity for the favorable allele of rs12979860 was also associated with natural or "spontaneous" clearance of infection, suggesting shared mechanisms of viral control between both types of clearance (10). These host genotypes do not influence control of other chronic viruses such as human immunodeficiency virus-1 (HIV-1) or hepatitis B virus (HBV) (11, 12).

Subsequently, three additional GWAS conducted in Australian, Japanese and Swiss HCV cohorts identified another SNP, rs8099917, in the IL28B genomic region that was

significantly associated with treatment response (5–7). Importantly, this SNP is in strong linkage with rs12979860 and was the second strongest SNP identified in the study by *Ge et al.* before correcting for rs12979860 (4). Furthermore, rs12979860 was not or only partially assessed in the other GWAS, thus explaining why top hits differed (13).

Several lines of evidence indicate that the IL28B gene is the causative gene for the difference in viral clearance: i) the IL28B gene lies in close proximity to both identified SNPs (rs12979860 and rs8099917), ii) subsequent fine mapping of the IL28B gene region identified two SNPs of potential importance in linkage disequilibrium with the above SNPs. One of them a non-synonymous change in the gene (rs8103142) resulting in a lysine to arginine substitution at position 70 (K70R), and another SNP (rs28416813) only 37 base pairs upstream of the IL28B translation initiation site (7, 14), iii) the favorable IL28B genotype associates with increased IL28B levels, suggesting a functional importance of the protein (15), and iv) previous studies indicated similar functional properties of type III IFN and type I IFN (16), providing biological plausibility that IL28B may be beneficial in HCV clearance. This immediate plausibility contrasts with genetic associations found by GWAS for other diseases, where the links to pathogenesis are often not immediately obvious.

Biology, Function and Clinical Application of Type III Interferon in Clinical Trials

IL28B is a cytokine of the type III IFN family, with IL28A and IL29 being the other members. Several cell types are capable of expressing IL28B in response to viral infections. Dendritic cells and macrophages, as well as primary hepatocytes and hepatic tumor lines have been shown to produce IL28B following contact with HCV (17–20). IL28B signals through a heterodimeric receptor composed of one part IL-28R α (also called IL-28R1) and one part IL-10R2 (21–23). The IL-28R α is expressed at high levels on hepatocytes, suggesting that IL28B is involved in antiviral activity in the infected liver (17, 23, 24). In fact, type III interferons inhibit HCV replication in vitro comparable to type I interferon (25, 26). Other cell types, including B lymphocytes and T lymphocytes, have been reported to express this receptor at varying levels and thus additional immunomodulatory functions compared to type I interferon are likely (23, 24). However, exactly how and to what extent, IL28B directly contributes to HCV clearance in vivo remains poorly understood. IL28B shares several functional characteristics with type I interferon, including antiviral activity and immunomodulatory function (21, 22, 27, 28).

The strong genetic link between IL28B genotype and HCV clearance, alongside the strong IL28B production seen in natural HCV infection in primates (29), supports the idea that IL28B might be a potential treatment for HCV infection (16). Currently, there are no data available from IL28B trials. However, preliminary results from clinical trials with another type III IFN, IL29, structurally and functionally very similar to IL28B, show early promise as effective antiviral therapy. In 86% of the treatment naive-patients who received combined pegylated IL29 and RBV for 4 weeks there was a relevant decrease in HCV viral load observed (30). Intriguingly, compared to PEG-IFN α treatment, it seems that many of the adverse effects seen with PEG-IFN α therapy are not induced by type III interferon, likely explained by the restricted expression of interferon-lambda receptors to certain cell types compared to those of interferon-alfas, which are expressed on virtually all cell types (30). Phase II trials comparing IL29 and PEG-IFN α are currently ongoing (Genzyme/Bristol Myers. clinical trials gov).

IL28B homozygosity for the favorable allele is linked to rapid virologic response

Despite this strong evidence for an important role of IL28B in HCV treatment response, the phenotype that explains the different outcomes remains largely unknown. One study looked at the viral suppression in the first 24h after treatment initiation and found that the favorable

genotype was highly predictive of rapid decline of viremia (31). In line with this, rapid virological response (RVR) rate was significantly higher in individuals with the favorable genotype (32). This could mechanistically be explained by studies looking at the gene expression profiles in HCV, suggesting that the favorable genotype has lower pretreatment ISG expression, a state that predicts response rate to IFNa treatment even better than the IL28B genotype alone (33). However, individuals with RVR had the highest rate of SVR, independent of the host IL28B genotype, suggesting that other (IL28B independent) mechanisms may help to achieve a positive outcome in some individuals with nonfavorable IL28B genotypes.

Predictive Value of IL28B genotype in Non-Genotype 1 Infection

As described, the first GWAS on factors predicting HCV SVR focused on those with genotype 1, the most common genotype in the developed world. Determining the influence of IL28B host polymorphisms on non-genotype 1 outcomes was the next logical extension of these findings, as treatment of genotype 1 with PEG-IFNa/RBV has much lower SVR rates (40–45%) than genotype 2 or 3 (65–82%) (3, 34). This was addressed in a large randomized, controlled trial in 268 HCV genotype 2/3 infected individuals that compared treatment with PEG-IFNa/RBV for 24 weeks ('SOC group') vs. 12 weeks if they had a rapid virologic response or 24 weeks if they did not achieve RVR ('response guided group'). In this setting the favorable IL28B allele was only associated with SVR in individuals without RVR in the SOC group but did not affect RVR in either group (35). Similarly, Moghaddam *et al.* found no impact of the IL28B genotype on SVR in a cohort of 281 genotype 3 infected individuals (except between the C/C and T/T carriers) (36), however, having both favorable alleles of IL28B was associated with RVR in this study, a finding confirmed by others (36, 37). Several other studies supported a lack of association of IL28B genotype with SVR in genotype 2/3 infection (38–40), including a large Asian study focusing on genotype 2 only (40). Conversely, others reported that the favorable allele predicts SVR (particularly after failure to achieve RVR) in genotype 2/3 infection (41) and that a beneficial effect of the favorable IL28B allele on SVR might be strongest in genotype 2b (38, 42). The lower rates of nonresponse in genotype 2/3 infection may have reduced power to detect significant differences. Taken together, data suggest that any beneficial effect of the favorable IL28B genotype for genotype 2/3 would be at lower strength compared to genotype 1 infection.

In Western countries HCV *genotype 4* is rare, but represents the most common genotype in some areas including Egypt, which has one of the highest HCV prevalence worldwide. Previously, several small studies that included genotype 4 infected individuals consistently reported effects of the IL28B genotype comparable to those seen in genotype 1 HCV infection (5, 43, 44). These findings were now recently confirmed in two larger trials including 112 and 82 genotype 4 infected individuals, respectively (45, 46). In one study by *De Nicola et al.* homozygote carriers of the good IL28B allele had a SVR rate of 88% compared to 38%, and showed no relapses (vs. 36% in the CT/TT group) (45). *Asselah et al.* found similar associations with clearance rates of 81.8% in the CC carriers vs. 46.5% and 29.4% in the CT and TT carriers respectively (46).

Finally, *genotype 5* is most prevalent in South Africa or Syria, but clusters have also been reported in Spain, Belgium and France. Because of its relative rarity, genotype 5 is often neglected in clinical trials. In 49 infected individuals of Caucasian descent, there were no differences in the SVR rate by IL28B genotype (47). Whether this lack of association is due to small sample size or due to the older age and higher fibrosis grade in these genotype 5 infected individuals remains elusive.

In summary, IL28B genotype strongly predicts treatment response in HCV genotype 1 and 4 infection, may or may not predict response in genotype 2 and 3, and more data are needed to

determine prediction of response in genotype 5. Thus, we recommend that IL28B testing only be performed for genotype 1 and 4 infections.

Predictive value of IL28B in special populations and potential utility in liver transplantation for HCV

The discovery of IL28B SNPs and their influence in viral clearance was first discovered in patients who were monoinfected with HCV alone. Subsequently the finding was rapidly extended to specialized populations such as those with co-existing HIV-1 infection (5, 44, 48–51). In perinatal studies, no association was found with the rate of HCV transmission but the same host genotypes are associated with spontaneous clearance in children (52).

In the post-transplant setting for HCV, infection of the newly placed graft is virtually universal and cases of spontaneous clearance are extraordinarily rare; due to their rarity IL28B genotypes have yet to be linked to this outcome. For interferon-based treatment outcomes in the post-transplant setting, several studies show that if either the donor or recipient IL28B genotype was favorable, SVR rates were improved, but even more so when both donor and recipient were favorable (53–56). These studies suggest that the mechanisms by which IL28B genotypes influence treatment response are more likely to be related to innate responses than adaptive responses, given the significant defects in the latter induced by exogenous immunosuppression post-transplant. Moreover, they suggest the possibility of allocating liver grafts based on favorable donor IL28B genotype to those with HCV to enhance the likelihood of response to interferon-based therapies. Further information is required before such allocation can be implemented, including the IL28B's role in the rapid fibrosis progression observed in the post-transplant setting. IL28B genotypes favorable for treatment response could lead to better viral control and/or slower progression or to more brisk inflammation and rapid progression. Thus far early post-transplant studies suggest that recipient alleles unfavorable for treatment response are associated with more rapid progression (53, 57) but that the opposite may hold for the donor IL28B genotypes (58). Whether patients homozygous for the favorable allele experience more rapid disease progression in the non-transplant setting remains an open question (59).

Utility of host IL28B genotyping for acute genotype 1 infection

Since IL28B genotype is also a strong predictor of spontaneous resolution of HCV in genotype 1 infection (10), there may be a role for testing in the setting of acute infection when the outcome is yet to be determined. In particular testing may help select individuals that would profit most from immediate treatment (IL28B genotypes suggesting progression to chronic infection) or that would be given a chance to be observed to see if spontaneous clearance occurs, thus saving treatment (IL28B favorable genotype). Interestingly favorable genotype was associated with symptoms during acute HCV, which is also a predictor of spontaneous clearance (60, 61). Patients might initially defer treatment knowing that spontaneous clearance rates might be as high as 64 % with CC rs12979860 genotype (61) and initiate only if serial viral titers suggest that the patient will not clear. By contrast, the low spontaneous clearance rate in individuals with the unfavorable IL28B genotype (24% in the heterozygote CT and 6% in the homozygote, TT) is a strong argument to treat these individuals as early as possible, especially if not symptomatic (61, 62). The counterargument to testing in the acute setting is that IL28B is an imperfect predictor of spontaneous clearance; up to 36% of the individuals with the favorable genotype will not clear infection and that treatment response to PEG-IFNa-based regimens is generally higher if started in acute HCV infection. Finally, IL28B does not predict SVR when PEG-IFNa is applied in the acute phase and thus has diminished utility (60).

A recent model-based analysis contradicted such IL28B-guided approaches, showing that immediate treatment of all acutely infected individuals (independent of IL28B genotype and presence of HCV related symptoms) may be the best approach to reduce the development of chronic HCV roughly by half (63). The currently available data therefore suggest, that IL28B genotype in acute HCV infection should not be used as a sole argument to withhold early treatment in individuals with the favorable genotype (2), but could rather be used in conjunction with other predictors of clearance (Table 1) to help clinicians and patients to weigh the individual chance of spontaneous resolution against potential treatment-associated side effects. Finally, while generating predictive models is informative (64) clearly prospective studies are needed to generate evidence-based recommendations.

Utility of host IL28B genotyping for chronic genotype 1 infection in the DAA era

Recently, several trials of new direct acting antivirals (DAA) have generated exciting results with increased SVR in treatment-naïve subjects as well as relapsers (for recent reviews on the topic see (65, 66). Intriguingly, preliminary data suggest that these agents might be successful even in IFN-free treatment regimens (67). These drugs will revolutionize HCV treatment and combination treatments promise effective treatments of previously refractory HCV infection in the near future. Data from available studies on DAAs indicate an increased SVR rate independent of the IL28B genotype, but specifically HCV infected individuals with the unfavorable IL28B genotypes showed the largest increase in SVR when a DAA was added to the treatment (68, 69). Thus, one might argue that DAAs should be part of every HCV treatment strategy in the future for genotype 1 and thus the discovery of the IL28B genotype came a little too late (70, 71).

However, it is more likely that IL28B plays a role even in the current DAA era (with interferon) and beyond. There remain several potential applications of IL28B testing to individualize treatments in specific HCV patient subgroups. Because of the differences in treatment outcome depending on the viral genotype and other individual factors (Table 1), clinicians treating HCV-infected individuals are experienced in using such genetic predictors and biomarkers to select the appropriate RBV dose and treatment length. The reproducible and strong association of favorable HCV outcome in various clinical settings with the good IL28B allele, as well as relatively easy testing and broad availability of the test, holds promise for its applicability in clinical decision-making.

The most obvious application of IL28B genotype testing could be to identify subjects who might profit the most of the addition of a protease inhibitor to PEG-IFNa/RBV. A potential approach could be to immediately add a PI to PEG-IFNa/RBV in patients with a non-favorable IL28B genotype, whereas treat those with favorable IL28B genotypes initially with PEG-IFNa/RBV alone. For individuals with the good IL28B genotype DAAs could be made available as add-on treatment for those not achieving initial RVR (72). Since protease inhibitor treatment is expensive (about 1100–4300 \$/week, depending on the agent) such an approach would reduce overall costs (73).

Optimizing the treatment duration has been one of the hot topics in HCV research. While genotype 1 infection is usually treated for 48 weeks, those with RVR can be reduced to 24 weeks (2). Similarly, although a 24-week duration of therapy is used in genotype 2 and 3 infection, the length of treatment can be shortened to 12 to 16 weeks if RVR is achieved (2, 74). Not surprisingly, the IL28B genotype has been shown to affect RVR in two large trials of boceprevir/PEG-IFNa/RBV (RESPOND-2 / SPRINT-2) and thus might be used to predict if shorter treatment duration would be an option (75, 76). A counterargument is since RVR is the stronger predictor of SVR than IL28B, genotyping may not change clinical practice—in other words, success during the initial period of therapy trumps the genetic predictor and can render it unnecessary. Similarly, retrospective analysis of individuals with the favorable

genotype that did not achieve RVR showed no evidence that in these patients shorter treatment duration of 24 weeks would suffice (77).

A few studies have also looked at whether IL28B genotype can be used to intensify treatment dose or duration. In fact, a higher dose of PEG-IFNa resulted in higher response rate in individuals with previous treatment failure heterozygous for the IL28B allele vs. those homozygous for the bad allele (78). For individuals infected with genotype 2 or 3 current standard of care is a 24-week treatment course of PEG-IFNa/RBV and addition of the currently available DAAs is not necessary due to high efficacy in their absence (genotype 2) and lack of predicted activity (genotype 3). Nonetheless, IL-28B testing may predict whether certain individuals with the non-favorable host genotype should consider treatment extension from the usual 24 to 48 weeks (35). Similarly, in genotype 1 and 4 infection treatment extension to 72 weeks in non- or slow-responders with the non-favorable IL28B genotype might increase SVR substantially to PEG-IFNa/RBV alone (13% vs. 61%) although this strategy is likely unpalatable in the DAA era (79). However, it is likely that this might be different in the setting of triple therapy including a DAA, where 12 weeks of treatment resulted in 100% SVR in individuals with the good genotype vs. 40% and 20% in heterozygote or homozygote bad allele carriers (80).

Summary/Conclusions

In sum, pretreatment determination of IL28B genotype in patients chronically infected with genotype 1 may assist the decision process by supplying the provider and patient some insight into the expected outcome on so-called “triple therapy”. A host IL28B genotype may affect a decision regarding whether a specific patient should be treated or not with current available therapies: a more favorable genotype may favor an initially less intensive approach with PEG-IFNa/RBV and using viral kinetics to guide use of an additional protease inhibitor. In contrast, a less favorable genotype may require a more aggressive approach upfront or even consideration of deferral until even newer treatment paradigms are available. For patients already motivated or in need of therapy, early viral kinetics remain better predictors than IL28B and thus testing may not change the decision to treat; however testing may still affect duration of therapy. Since data from prospective and randomized trials are lacking to date, most of these applications remain speculative and their utility requires confirmation.

Finally, the role of IL28B in the future era of interferon-free regimens remains to be determined. A key component of future studies using interferon-free strategies will be close study of those with unsuccessful treatment due to nonresponse or relapse and whether IL28B’s mechanisms will influence these results. Due to the fundamental role of IL28B as a predictor of HCV clearance, the initial reports of relapse while on interferon-free therapy (67), and the possibility of using interferon-based strategies as salvage for interferon-free ones, testing for IL28B polymorphisms is likely to retain relevance even as therapeutic paradigms evolve.

REFERENCES

1. Alter MJ. Epidemiology of hepatitis C virus infection. *World J Gastroenterol*. 2007; 13(17):2436–2441. [PubMed: 17552026]
2. Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology*. 2011; 54(4):1433–1444. [PubMed: 21898493]
3. McHutchison JG, Lawitz EJ, Shiffman ML, et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. *N Engl J Med*. 2009; 361(6):580–593. [PubMed: 19625712]

4. Ge D, Fellay J, Thompson AJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. *Nature*. 2009; 461(7262):399–401. [PubMed: 19684573]
5. Rauch A, Kutalik Z, Descombes P, et al. Genetic variation in IL28B is associated with chronic hepatitis C and treatment failure: a genome-wide association study. *Gastroenterology*. 2010; 138(4): 1338–1345. 1345 e1–7. [PubMed: 20060832]
6. Suppiah V, Moldovan M, Ahlenstiel G, et al. IL28B is associated with response to chronic hepatitis C interferon-alpha and ribavirin therapy. *Nat Genet*. 2009; 41(10):1100–1104. [PubMed: 19749758]
7. Tanaka Y, Nishida N, Sugiyama M, et al. Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. *Nat Genet*. 2009; 41(10): 1105–1109. [PubMed: 19749757]
8. Pearson TA, Manolio TA. How to interpret a genome-wide association study. *JAMA*. 2008; 299(11):1335–1344. [PubMed: 18349094]
9. Hindorff L, MacArthur J, Wise A, et al. A Catalog of Published Genome-Wide Association Studies. 2012
10. Thomas DL, Thio CL, Martin MP, et al. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. *Nature*. 2009; 461(7265):798–801. [PubMed: 19759533]
11. Martin MP, Qi Y, Goedert JJ, et al. IL28B polymorphism does not determine outcomes of hepatitis B virus or HIV infection. *J Infect Dis*. 2010; 202(11):1749–1753. [PubMed: 20977343]
12. Salgado M, Kirk GD, Cox A, et al. Protective interleukin-28B genotype affects hepatitis C virus clearance, but does not contribute to HIV-1 control in a cohort of African-American elite controllers/suppressors. *AIDS*. 2011; 25(3):385–387. [PubMed: 21099664]
13. Balagopal A, Thomas DL, Thio CL. IL28B and the control of hepatitis C virus infection. *Gastroenterology*. 2010; 139(6):1865–1876. [PubMed: 20950615]
14. de Castellarnau M, Aparicio E, Parera M, et al. Deciphering the interleukin 28B variants that better predict response to pegylated interferon-alpha and ribavirin therapy in HCV/HIV-1 coinfectd patients. *PLoS One*. 2012; 7(2):e31016. [PubMed: 22328925]
15. Langhans B, Kupfer B, Braunschweiler I, et al. Interferon-lambda serum levels in hepatitis C. *J Hepatol*. 2011; 54(5):859–865. [PubMed: 21145813]
16. Donnelly RP, Dickensheets H, O'Brien TR. Interferon-lambda and therapy for chronic hepatitis C virus infection. *Trends Immunol*. 2011; 32(9):443–450. [PubMed: 21820962]
17. Pagliaccetti NE, Robek MD. Interferon- λ in the Immune Response to Hepatitis B Virus and Hepatitis C Virus. *Journal of Interferon & Cytokine Research*. 2010; 30(8):585–590. [PubMed: 20645875]
18. Coccia EM, Severa M, Giacomini E, et al. Viral infection and Toll-like receptor agonists induce a differential expression of type I and λ interferons in human plasmacytoid and monocyte-derived dendritic cells. *European Journal of Immunology*. 2004; 34(3):796–805. [PubMed: 14991609]
19. Megjugorac NJ, Gallagher GE, Gallagher G. IL-4 enhances IFN- λ 1 (IL-29) production by plasmacytoid DCs via monocyte secretion of IL-1Ra. *Blood*. 2010; 115(21):4185–4190. [PubMed: 20233967]
20. Mihm S, Frese M, Meier V, et al. Interferon type I gene expression in chronic hepatitis C. *Lab Invest*. 2004; 84(9):1148–1159. %U <http://dx.doi.org/10.1038/labinvest.3700135>. [PubMed: 15208644]
21. Kotenko SV, Gallagher G, Baurin VV, et al. IFN- λ s mediate antiviral protection through a distinct class II cytokine receptor complex. *Nat Immunol*. 2003; 4(1):69–77. [PubMed: 12483210]
22. Sheppard P, Kindsvogel W, Xu W, et al. IL-28, IL-29 and their class II cytokine receptor IL-28R. *Nat Immunol*. 2003; 4(1):63–68. [PubMed: 12469119]
23. Witte K, Gruetz G, Volk HD, et al. Despite IFN- λ receptor expression, blood immune cells, but not keratinocytes or melanocytes, have an impaired response to type III interferons: implications for therapeutic applications of these cytokines. *Genes Immun*. 2009; 10(8):702–714. [PubMed: 19798076]
24. Doyle SE, Schreckhise H, Khuu-Duong K, et al. Interleukin-29 uses a type I interferon-like program to promote antiviral responses in human hepatocytes. *Hepatology*. 2006; 44(4):896–906. [PubMed: 17006906]

25. Marcello T, Grakoui A, Barba-Spaeth G, et al. Interferons alpha and lambda inhibit hepatitis C virus replication with distinct signal transduction and gene regulation kinetics. *Gastroenterology*. 2006; 131(6):1887–1898. [PubMed: 17087946]
26. Robek MD, Boyd BS, Chisari FV. Lambda interferon inhibits hepatitis B and C virus replication. *J Virol*. 2005; 79(6):3851–3854. [PubMed: 15731279]
27. O'Brien TR. Interferon-alfa, interferon-lambda and hepatitis C. *Nat Genet*. 2009; 41(10):1048–1050. [PubMed: 19749756]
28. Zhang L, Jilg N, Shao RX, et al. IL28B inhibits hepatitis C virus replication through the JAK-STAT pathway. *J Hepatol*. 2011
29. Thomas E, Gonzalez VD, Li Q, et al. HCV infection induces a unique hepatic innate immune response associated with robust production of type III interferons. *Gastroenterology*. 2012; 142(4):978–988. [PubMed: 22248663]
30. Muir AJ, Shiffman ML, Zaman A, et al. Phase 1b study of pegylated interferon lambda 1 with or without ribavirin in patients with chronic genotype 1 hepatitis C virus infection. *Hepatology*. 2010; 52(3):822–832. [PubMed: 20564352]
31. Bochud PY, Bibert S, Negro F, et al. IL28B polymorphisms predict reduction of HCV RNA from the first day of therapy in chronic hepatitis C. *J Hepatol*. 2011; 55(5):980–988. [PubMed: 21354446]
32. Thompson AJ, Muir AJ, Sulkowski MS, et al. Interleukin-28B polymorphism improves viral kinetics and is the strongest pretreatment predictor of sustained virologic response in genotype 1 hepatitis C virus. *Gastroenterology*. 2010; 139(1):120–129. e18. [PubMed: 20399780]
33. Dill MT, Duong FH, Vogt JE, et al. Interferon-induced gene expression is a stronger predictor of treatment response than IL28B genotype in patients with hepatitis C. *Gastroenterology*. 2011; 140(3):1021–1031. [PubMed: 21111740]
34. Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet*. 2001; 358(9286):958–965. [PubMed: 11583749]
35. Mangia A, Thompson AJ, Santoro R, et al. An IL28B polymorphism determines treatment response of hepatitis C virus genotype 2 or 3 patients who do not achieve a rapid virologic response. *Gastroenterology*. 2010; 139(3):821–827. 827 e1. [PubMed: 20621700]
36. Moghaddam A, Melum E, Reinton N, et al. IL28B genetic variation and treatment response in patients with hepatitis C virus genotype 3 infection. *Hepatology*. 2011; 53(3):746–754. [PubMed: 21374656]
37. Lindh M, Lagging M, Farkkila M, et al. Interleukin 28B gene variation at rs12979860 determines early viral kinetics during treatment in patients carrying genotypes 2 or 3 of hepatitis C virus. *J Infect Dis*. 2011; 203(12):1748–1752. [PubMed: 21606533]
38. Kawaoka T, Hayes CN, Ohishi W, et al. Predictive value of the IL28B polymorphism on the effect of interferon therapy in chronic hepatitis C patients with genotypes 2a and 2b. *J Hepatol*. 2011; 54(3):408–414. [PubMed: 21112660]
39. Scherzer TM, Hofer H, Staettermayer AF, et al. Early virologic response and IL28B polymorphisms in patients with chronic hepatitis C genotype 3 treated with peginterferon alfa-2a and ribavirin. *J Hepatol*. 2011; 54(5):866–871. [PubMed: 21145807]
40. Yu ML, Huang CF, Huang JF, et al. Role of interleukin-28B polymorphisms in the treatment of hepatitis C virus genotype 2 infection in Asian patients. *Hepatology*. 2011; 53(1):7–13. [PubMed: 21254157]
41. Sarrazin C, Susser S, Doehring A, et al. Importance of IL28B gene polymorphisms in hepatitis C virus genotype 2 and 3 infected patients. *J Hepatol*. 2011; 54(3):415–421. [PubMed: 21112657]
42. Sakamoto N, Nakagawa M, Tanaka Y, et al. Association of IL28B variants with response to pegylated-interferon alpha plus ribavirin combination therapy reveals intersubgenotypic differences between genotypes 2a and 2b. *J Med Virol*. 2011; 83(5):871–878. [PubMed: 21360545]
43. Staettermayer AF, Stauber R, Hofer H, et al. Impact of IL28B genotype on the early and sustained virologic response in treatment-naïve patients with chronic hepatitis C. *Clin Gastroenterol Hepatol*. 2011; 9(4):344–350. e2. [PubMed: 20728570]

44. Rallon NI, Naggie S, Benito JM, et al. Association of a single nucleotide polymorphism near the interleukin-28B gene with response to hepatitis C therapy in HIV/hepatitis C virus-coinfected patients. *AIDS*. 2010; 24(8):F23–F29. [PubMed: 20389235]
45. De Nicola S, Aghemo A, Rumi MG, et al. Interleukin 28B polymorphism predicts pegylated interferon plus ribavirin treatment outcome in chronic hepatitis C genotype 4. *Hepatology*. 2012; 55(2):336–342. [PubMed: 21932415]
46. Asselah T, De Muynck S, Broet P, et al. IL28B polymorphism is associated with treatment response in patients with genotype 4 chronic hepatitis C. *J Hepatol*. 2012; 56(3):527–532. [PubMed: 21951981]
47. Antaki N, Bibert S, Kebbewar K, et al. IL28B polymorphisms do not predict response to therapy in chronic hepatitis C with HCV genotype 5. *Gut*. 2012
48. Pineda JA, Caruz A, Rivero A, et al. Prediction of response to pegylated interferon plus ribavirin by IL28B gene variation in patients coinfecting with HIV and hepatitis C virus. *Clin Infect Dis*. 2010; 51(7):788–795. [PubMed: 20804372]
49. Dayyeh BK, Gupta N, Sherman KE, de Bakker PI, Chung RT. IL28B alleles exert an additive dose effect when applied to HCV-HIV coinfecting persons undergoing peginterferon and ribavirin therapy. *PLoS One*. 2011; 6(10):e25753. [PubMed: 22003405]
50. Labarga P, Barreiro P, Mira JA, et al. Impact of IL28B polymorphisms on response to peginterferon and ribavirin in HIV-hepatitis C virus-coinfected patients with prior nonresponse or relapse. *AIDS*. 2011; 25(8):1131–1133. [PubMed: 21537116]
51. Neukam K, Camacho A, Caruz A, et al. Prediction of response to pegylated interferon plus ribavirin in HIV/hepatitis C virus (HCV)-coinfecting patients using HCV genotype, IL28B variations, and HCV-RNA load. *J Hepatol*. 2012; 56(4):788–794. [PubMed: 22173157]
52. Ruiz-Extremera A, Munoz-Gamez JA, Salmeron-Ruiz MA, et al. Genetic variation in interleukin 28B with respect to vertical transmission of hepatitis C virus and spontaneous clearance in HCV-infected children. *Hepatology*. 2011; 53(6):1830–1838. [PubMed: 21413051]
53. Charlton MR, Thompson A, Veldt BJ, et al. Interleukin-28B polymorphisms are associated with histological recurrence and treatment response following liver transplantation in patients with hepatitis C virus infection. *Hepatology*. 2011; 53(1):317–324. [PubMed: 21254179]
54. Coto-Llerena M, Perez-Del-Pulgar S, Crespo G, et al. Donor and recipient IL28B polymorphisms in HCV-infected patients undergoing antiviral therapy before and after liver transplantation. *Am J Transplant*. 2011; 11(5):1051–1057. [PubMed: 21466653]
55. Fukuhara T, Taketomi A, Motomura T, et al. Variants in IL28B in liver recipients and donors correlate with response to peg-interferon and ribavirin therapy for recurrent hepatitis C. *Gastroenterology*. 2010; 139(5):1577–1585. 1585 e1–3. [PubMed: 20708617]
56. Lange CM, Moradpour D, Doehring A, et al. Impact of donor and recipient IL28B rs12979860 genotypes on hepatitis C virus liver graft reinfection. *J Hepatol*. 2011; 55(2):322–327. [PubMed: 21147186]
57. Graziadei IW, Zoller HM, Schloegl A, et al. Early viral load and recipient interleukin-28B rs12979860 genotype are predictors of the progression of hepatitis C after liver transplantation. *Liver Transpl*. 2012; 18(6):671–679. [PubMed: 22298465]
58. Duarte-Rojo A, Veldt BJ, Goldstein DD, et al. The Course of Posttransplant Hepatitis C Infection: Comparative Impact of Donor and Recipient Source of the Favorable IL28B Genotype and Other Variables. *Transplantation*. 2012
59. Barreiro P, Pineda JA, Rallon N, et al. Influence of interleukin-28B single-nucleotide polymorphisms on progression to liver cirrhosis in human immunodeficiency virus-hepatitis C virus-coinfected patients receiving antiretroviral therapy. *J Infect Dis*. 2011; 203(11):1629–1636. [PubMed: 21592993]
60. Grebely J, Petoumenos K, Hellard M, et al. Potential role for interleukin-28B genotype in treatment decision-making in recent hepatitis C virus infection. *Hepatology*. 2010; 52(4):1216–1224. [PubMed: 20803561]
61. Tillmann HL, Thompson AJ, Patel K, et al. A polymorphism near IL28B is associated with spontaneous clearance of acute hepatitis C virus and jaundice. *Gastroenterology*. 2010; 139(5):1586–1592. 1592 e1. [PubMed: 20637200]

62. Grebely J, Matthews GV, Dore GJ. Treatment of acute HCV infection. *Nat Rev Gastroenterol Hepatol*. 2011; 8(5):265–274. [PubMed: 21423258]
63. Deuffic-Burban S, Castel H, Wiegand J, et al. Immediate vs. delayed treatment in patients with acute hepatitis C based on IL28B polymorphism: A model-based analysis. *J Hepatol*. 2012
64. Ochi H, Hayes CN, Abe H, et al. Toward the establishment of a prediction system for the personalized treatment of chronic hepatitis C. *J Infect Dis*. 2012; 205(2):204–210. [PubMed: 22124128]
65. Barritt, ASt; Fried, MW. Maximizing opportunities and avoiding mistakes in triple therapy for hepatitis C virus. *Gastroenterology*. 2012; 142(6):1314–1323. e1. [PubMed: 22537438]
66. Welsch C, Jesudian A, Zeuzem S, Jacobson I. New direct-acting antiviral agents for the treatment of hepatitis C virus infection and perspectives. *Gut*. 2012; 61(Suppl 1):i36–i46. [PubMed: 22504918]
67. Lok AS, Gardiner DF, Lawitz E, et al. Preliminary study of two antiviral agents for hepatitis C genotype 1. *N Engl J Med*. 2012; 366(3):216–224. [PubMed: 22256805]
68. Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med*. 2011; 364(25):2405–2416. [PubMed: 21696307]
69. Poordad F, McCone J Jr. Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med*. 2011; 364(13):1195–1206. [PubMed: 21449783]
70. Hofmann WP, Zeuzem S. A new standard of care for the treatment of chronic HCV infection. *Nat Rev Gastroenterol Hepatol*. 2011; 8(5):257–264. [PubMed: 21468124]
71. Jensen DM, Pol S. IL28B genetic polymorphism testing in the era of direct acting antivirals therapy for chronic hepatitis C: ten years too late? *Liver Int*. 2012; 32(Suppl 1):74–78. [PubMed: 22212576]
72. Fried M, Buti M, Dore G. Efficacy and safety of TMC435 in combination with peginterferon alfa 2a and ribavirin in treatment-naïve genotype-1 HCV patients: 24-week interim results from the PILLAR study. *Hepatology*. 2010; 52(4 Suppl) LB-5.
73. Liu S, Cipriano LE, Holodniy M, Owens DK, Goldhaber-Fiebert JD. New protease inhibitors for the treatment of chronic hepatitis C: a cost-effectiveness analysis. *Ann Intern Med*. 2012; 156(4): 279–290. [PubMed: 22351713]
74. Guidelines E. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. *J Hepatol*. 2011; 55(2):245–264. [PubMed: 21371579]
75. Zeuzem S, Asselah T, Angus P, et al. Efficacy of the protease inhibitor BI 201335, polymerase inhibitor BI 207127, and ribavirin in patients with chronic HCV infection. *Gastroenterology*. 2011; 141(6):2047–2055. quiz e14. [PubMed: 21925126]
76. Bacon BR, Gordon SC, Lawitz E, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. *N Engl J Med*. 2011; 364(13):1207–1217. [PubMed: 21449784]
77. Huang CF, Huang JF, Yang JF, et al. Interleukin-28B genetic variants in identification of hepatitis C virus genotype 1 patients responding to 24 weeks peginterferon/ribavirin. *J Hepatol*. 2012; 56(1):34–40. [PubMed: 21703176]
78. Chevaliez S, Hezode C, Soulier A, et al. High-dose pegylated interferon-alpha and ribavirin in nonresponder hepatitis C patients and relationship with IL-28B genotype (SYREN trial). *Gastroenterology*. 2011; 141(1):119–127. [PubMed: 21439960]
79. Pearlman BL, Ehleben C. The IL-28B genotype predicts which slow-responding hepatitis C-infected patients will benefit from treatment extension. *Am J Gastroenterol*. 2011; 106(7):1370–1371. [PubMed: 21731027]
80. Bronowicki J, Hezode C, Bengtsson L, et al. 100% SVR in IL28B SNP rs12979860 C/C patients treated with 12 weeks of telaprevir, peginterferon and ribavirin in the PROVE2 trial *EASL 2012*. Barcelona Spain. 2012
81. McHutchison JG, Manns MP, Muir AJ, et al. Telaprevir for previously treated chronic HCV infection. *N Engl J Med*. 2010; 362(14):1292–1303. [PubMed: 20375406]
82. Gao B, Hong F, Radaeva S. Host factors and failure of interferon-alpha treatment in hepatitis C virus. *Hepatology*. 2004; 39(4):880–890. [PubMed: 15057887]

83. Lim SR, Qin X, Susser S, et al. Virologic escape during danoprevir (ITMN-191/RG7227) monotherapy is hepatitis C virus subtype dependent and associated with R155K substitution. *Antimicrob Agents Chemother*. 2012; 56(1):271–279. [PubMed: 22064535]
84. Vispo E, Rallon NI, Labarga P, Barreiro P, Benito JM, Soriano V. Different impact of IL28B polymorphisms on response to peginterferon-alpha plus ribavirin in HIV-positive patients infected with HCV subtypes 1a or 1b. *J Clin Virol*. 2012
85. Walsh MJ, Jonsson JR, Richardson MM, et al. Non-response to antiviral therapy is associated with obesity and increased hepatic expression of suppressor of cytokine signalling 3 (SOCS-3) in patients with chronic hepatitis C, viral genotype 1. *Gut*. 2006; 55(4):529–535. [PubMed: 16299039]
86. Muir AJ, Bornstein JD, Killenberg PG. Peginterferon alfa-2b and ribavirin for the treatment of chronic hepatitis C in blacks and non-Hispanic whites. *N Engl J Med*. 2004; 350(22):2265–2271. [PubMed: 15163776]
87. Dev AT, McCaw R, Sundararajan V, Bowden S, Sievert W. Southeast Asian patients with chronic hepatitis C: the impact of novel genotypes and race on treatment outcome. *Hepatology*. 2002; 36(5):1259–1265. [PubMed: 12395338]
88. Lo, Re V., 3rd; Teal, V.; Localio, AR.; Amorosa, VK.; Kaplan, DE.; Gross, R. Relationship between adherence to hepatitis C virus therapy and virologic outcomes: a cohort study. *Ann Intern Med*. 2011; 155(6):353–360. [PubMed: 21930852]
89. Lo Re V 3rd, Amorosa VK, Localio AR, et al. Adherence to hepatitis C virus therapy and early virologic outcomes. *Clin Infect Dis*. 2009; 48(2):186–193. [PubMed: 19086908]
90. Romero AI, Lagging M, Westin J, et al. Interferon (IFN)-gamma-inducible protein-10: association with histological results, viral kinetics, and outcome during treatment with pegylated IFN-alpha 2a and ribavirin for chronic hepatitis C virus infection. *J Infect Dis*. 2006; 194(7):895–903. [PubMed: 16960776]
91. Casrouge A, Decalf J, Ahloulay M, et al. Evidence for an antagonist form of the chemokine CXCL10 in patients chronically infected with HCV. *J Clin Invest*. 2011; 121(1):308–317. [PubMed: 21183794]
92. Petta S, Camma C, Scazzone C, et al. Low vitamin D serum level is related to severe fibrosis and low responsiveness to interferon-based therapy in genotype 1 chronic hepatitis C. *Hepatology*. 2010; 51(4):1158–1167. [PubMed: 20162613]
93. Bitetto D, Fattovich G, Fabris C, et al. Complementary role of vitamin D deficiency and the interleukin-28B rs12979860 C/T polymorphism in predicting antiviral response in chronic hepatitis C. *Hepatology*. 2011; 53(4):1118–1126. [PubMed: 21480318]
94. Honda M, Sakai A, Yamashita T, et al. Hepatic ISG expression is associated with genetic variation in interleukin 28B and the outcome of IFN therapy for chronic hepatitis C. *Gastroenterology*. 2010; 139(2):499–509. [PubMed: 20434452]
95. Asahina Y, Tsuchiya K, Muraoka M, et al. Association of gene expression involving innate immunity and genetic variation in interleukin 28B with antiviral response. *Hepatology*. 2012; 55(1):20–29. [PubMed: 21898478]
96. McGilvray I, Feld JJ, Chen L, et al. Hepatic Cell-Type Specific Gene Expression Better Predicts HCV Treatment Outcome Than IL28B Genotype. *Gastroenterology*. 2012; 142(5):1122–1131. e1. [PubMed: 22285807]
97. Khakoo SI, Thio CL, Martin MP, et al. HLA and NK cell inhibitory receptor genes in resolving hepatitis C virus infection. *Science*. 2004; 305(5685):872–874. [PubMed: 15297676]
98. Dring MM, Morrison MH, McSharry BP, et al. Innate immune genes synergize to predict increased risk of chronic disease in hepatitis C virus infection. *Proc Natl Acad Sci U S A*. 2011; 108(14):5736–5741. [PubMed: 21402922]
99. Suppiah V, Gaudieri S, Armstrong NJ, et al. IL28B, HLA-C, and KIR variants additively predict response to therapy in chronic hepatitis C virus infection in a European Cohort: a cross-sectional study. *PLoS Med*. 2011; 8(9):e1001092. [PubMed: 21931540]
100. de Rueda PM, Lopez-Nevot MA, Saenz-Lopez P, et al. Importance of host genetic factors HLA and IL28B as predictors of response to pegylated interferon and ribavirin. *Am J Gastroenterol*. 2011; 106(7):1246–1254. [PubMed: 21670772]

101. Vidal-Castineira JR, Lopez-Vazquez A, Alonso-Arias R, et al. A predictive model of treatment outcome in patients with chronic HCV infection using IL28B and PD-1 genotyping. *J Hepatol.* 2012
102. Liu CH, Liang CC, Liu CJ, et al. Interleukin 28B genetic polymorphisms and viral factors help identify HCV genotype-1 patients who benefit from 24-week pegylated interferon plus ribavirin therapy. *Antivir Ther.* 2012; 17(3):477–484. [PubMed: 22301466]
103. Rallon NI, Soriano V, Naggie S, et al. IL28B gene polymorphisms and viral kinetics in HIV/hepatitis C virus-coinfected patients treated with pegylated interferon and ribavirin. *AIDS.* 2011; 25(8):1025–1033. [PubMed: 21505315]
104. Scherzer TM, Stattemayer AF, Strasser M, et al. Impact of IL28B on treatment outcome in hepatitis C virus G1/4 patients receiving response-guided therapy with peginterferon alpha-2a (40KD)/ribavirin. *Hepatology.* 2011; 54(5):1518–1526. [PubMed: 22006276]
105. O'Bryan JM, Potts JA, Bonkovsky HL, Mathew A, Rothman AL. Extended interferon-alpha therapy accelerates telomere length loss in human peripheral blood T lymphocytes. *PLoS One.* 2011; 6(8):e20922. [PubMed: 21829595]

KEY POINTS

- Polymorphisms related to the gene encoding IL-28B are the strongest genetic predictors of HCV clearance, both by interferon-based treatment or by the natural immune system
- IL-28B belongs to the interferon-lambda family and plays a plausible biological role in antiviral defenses
- The predictive capacity of IL-28B is thus far strongest for HCV genotypes 1 and 4
- The effects of IL-28B extend into special populations with HCV such as those with HIV-1 coinfection and liver transplant recipients
- IL-28B polymorphisms will continue to play a role as a clinical pharmacogenomic test in the current direct-acting antiviral era and may be relevant as interferon-free regimens are developed

Table 1

Viral and host factors predicting treatment response to interferon-based regimens in HCV

Predictor of better treatment response	Ref.
Viral	
RVR (negative viral load at week 4 on therapy) *	(3)
HCV genotype 2/3	(3, 64)
Low baseline viremia	(3, 64)
Female gender	(3, 82)
Viral polymorphisms, i.e. baseline predominating resistance mutations	(83)
Genotype 1b versus 1a	(83, 84)
Host	
Demographic	
Normal BMI	(85)
Younger age	(64, 82)
Caucasian or East Asian ethnicity	(3, 86, 87)
Adherence to antiviral medications	(88, 89)
Serum Markers	
Low IP10 levels	(90, 91)
Cytokine levels	(82)
High vitamin D3 levels	(92, 93)
Intrahepatic factors	
Absence or low liver fibrosis	(3)
Low pretreatment hepatic ISG expression *	(33, 94)
High RIG1/ISG15	(95)
Factors in immune cells	
MxA Gene expression in Macrophages	(96)
Genetic Factors	
IL28B genotype *	(4–7)
KIR genotype	(97–99)
HLA DQB1	(100)
PD-1 Polymorphism	(101)

* Factors associated with IL28B genotyping, others are independent

Abbreviations used:

BMI (Body mass index)

HLA (human leukocyte antigen)

IL28B (interleukin–28-beta subunit)

IP10 (inducible protein–10)

ISG (interferon-stimulated genes)

KIR (killer-immunoglobulin-like receptors)

MxA (myxovirus-resistance protein A)

PD-1 (programmed death–1)

RVR (rapid virologic response or a negative HCV RNA at week 4 after initiation of therapy)

RIG-I (retinoic acid-inducible gene I)
ISG15 (interferon-stimulated gene 15)
ITPA (inosine triphosphatase)
RBV (ribavirin)

Table 2

Arguments or potential applications for and against IL28B testing in the clinical setting

“Pro” IL28B genotype testing

- Allows pre-treatment prediction of response to PEG-IFNa (4–7)
- Shorter treatment might be an option in non-GT1 infected with the favorable IL28B genotype (102–104)
- Treatment intensification in non-RVR with non-favorable IL28B GT (35)
- Adding a DAA to PEG-IFNa/RBV in GT1 infected individuals with the non favorable IL28B genotype (2)
- Shorter triple therapies in the presence of the favorable IL28B genotype (80)
- Longer treatment (72 weeks) of GT1/4 in slow responders increases SVR rate (79)
- Consider retreatment of GT1 infection with treatment failure and the favorable IL28B genotype (105)

“Against” IL28B genotype testing

- Viral kinetics (especially RVR) are better predictors of SVR than the IL28B genotype (3); i.e. in non-RVR with the good genotype treatment probably cannot be shortened (77)
- Not enough data to withhold DAA in the favorable IL28B genotype (2)
- Negative predictive value is too low to really chose not to treat based on the expected SVR (6)
- In the near future everybody will receive triple therapy because SVR might be up to 100% after only 12 weeks of triple therapy in the good IL28B genotype (80)