Hepatitis C Pharmacogenetics: State of the Art in 2010

Nezam H. Afdhal,1 John G. McHutchison,2 Stefan Zeuzem,3 Alessandra Mangia,5 Jean-Michel Pawlotsky,6 Jeffrey S. Murray,7 Kevin V. Shinya,3 Yasuhiro Tanaka,8 David L. Thomas,9 David R. Booth,10 and David B. Goldstein,3 for the Pharmacogenetics and Hepatitis C Meeting Participants

In 2009, a correlated set of polymorphisms in the region of the interleukin-28B (IL28B) gene were associated with clearance of genotype 1 hepatitis C virus (HCV) in patients treated with pegylated interferon-alfa and ribavirin. The same polymorphisms were subsequently associated with spontaneous clearance of HCV in untreated patients. The link between IL28B genotype and HCV clearance may impact decisions regarding initiation of current therapy, the design and interpretation of clinical studies, the economics of treatment, and the process of regulatory approval for new anti-HCV therapeutic agents.

(HEPATOTOLOGY 2011;53:336-345)

The current standard of care for chronic infection with hepatitis C virus (HCV) is 24 or 48 weeks of therapy with pegylated interferon-alfa (PEG-IFN) and ribavirin (RBV). Response to therapy is variable, and viral and host characteristics can influence whether patients achieve a sustained virological response (SVR), defined as having undetectable serum HCV RNA at 24 weeks after cessation of treatment. Viral genotype is a predictor of response: patients infected with genotype 1 virus who are treated for 48 weeks with PEG-IFN and RBV have a 40%-50% likelihood of having an SVR, whereas patients with genotype 2 or 3 virus have an SVR rate of 70%-80% after only 24 weeks of PEG-IFN and RBV therapy. Patient genetic ancestry is also a factor in treatment outcome. African American patients with chronic HCV have an almost 50% reduction in SVR rates with PEG-IFN and RBV compared with non-Hispanic patients of European ancestry, and the difference is not explained by socio-demographic characteristics or compliance to treatment.1,2 Other factors predictive of response to PEG-IFN and RBV include hepatitis C viral load as well as patient age, sex, weight, liver fibrosis stage, and adherence to therapy. Because PEG-IFN and RBV can cause burdensome adverse effects and treatment is prolonged, clinicians often weigh the various viral and host characteristics for each patient before initiating treatment.

In 2009, reports from three genome-wide association studies described several highly correlated common single nucleotide polymorphisms (SNPs) in the vicinity of three IFN-λ genes as being highly predictive of response to PEG-IFN and RBV therapy in patients with genotype 1 HCV.3-5 The three genes encode IFN-λ1 (IL29), IFN-λ2 (IL28A), and IFN-λ3 (IL28B). The same set of SNPs was subsequently associated with natural clearance of HCV.6,7

To discuss the implications of the novel pharmacogenetic data on hepatitis C treatment, a meeting of representatives from leading academic medical centers, government agencies, and the pharmaceutical and biotechnology industries took place in Alexandria, VA, on June 4 and 5, 2010. The focus of the meeting was to critically appraise current evidence on the association between genetic markers and response to PEG-IFN and RBV therapy and to provide guidance for incorporating...
genetic data into clinical decision-making and drug development. We report here the current data on IL28B in HCV and the panel’s recommendations for establishing priorities for IL28B research. In addition, recommendations for incorporating genetic data into clinical care and development of therapeutics are outlined.

### Predictive Endpoints of IL28B SNPs

The initial published analyses describing genome-wide associations of IL28B SNPs and response to PEG-IFN and RBV were derived from several global populations recruited in different clinical trials (Table 1). All three studies reached similar conclusions that underscored the strong predictive effect of IL28B genotype on response in treatment-naïve patients.

**United States.** The first published report came from Ge et al.3 who analyzed 1,131 genotype 1 HCV patients for predictors of response to 48 weeks of treatment with PEG-IFN and RBV. Adherence to therapy was a criterion for inclusion: all patients achieving SVR were included, and nonresponders had to be >80% adherent to PEG-IFN and RBV. For the analysis, genetic ancestry was determined explicitly by genetic inference, not self-reporting. Polymorphism rs12979860, which is upstream of the IL28B gene on chromosome 19, was strongly associated with SVR, both among patients of European ancestry (P = 1.06 × 10^{-3}) and African American patients (P = 2.06 × 10^{-3}). IL28B encodes IFN-κ3, a cytokine distantly related to type 1 (α and β) IFNs and the IL-10 family. A set of other variants was also reported as being associated with response, and in patients of European ancestry they were not statistically distinguishable from rs12979860. The C allele at rs12979860 was positively associated with SVR. In patients of European ancestry, 80% of patients with the C/C genotype cleared the virus, whereas only 30% with the T/T genotype did so. The C/C genotype was also more common in European Americans (39%) than African Americans (16%). The difference in allele frequency between these population groups explains approximately half of the difference in response rates between patients of African American versus European ancestry.

<table>
<thead>
<tr>
<th>Table 1. IL28B SNPs and Predictive Rates in Various Populations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Total Population</strong></td>
</tr>
<tr>
<td>rs12979860</td>
</tr>
<tr>
<td>Ge et al.3</td>
</tr>
<tr>
<td>No. of patients</td>
</tr>
<tr>
<td>C/C</td>
</tr>
<tr>
<td>T/C</td>
</tr>
<tr>
<td>T/T</td>
</tr>
<tr>
<td>Thompson et al.6</td>
</tr>
<tr>
<td>No. of patients</td>
</tr>
<tr>
<td>C/C</td>
</tr>
<tr>
<td>T/C</td>
</tr>
<tr>
<td>T/T</td>
</tr>
<tr>
<td>Tanaka et al.4</td>
</tr>
<tr>
<td>No. of patients</td>
</tr>
<tr>
<td>T/T</td>
</tr>
<tr>
<td>G/G</td>
</tr>
<tr>
<td>Suppiah et al.5</td>
</tr>
<tr>
<td>No. of patients</td>
</tr>
<tr>
<td>T/T</td>
</tr>
<tr>
<td>T/G</td>
</tr>
<tr>
<td>G/G</td>
</tr>
</tbody>
</table>

*P = 1.37 × 10^{-28} for T/T versus C/C. 
†P = 1.01 × 10^{-25} for T/T versus C/C. 
‡P = 2.06 × 10^{-3} for T/T versus C/C. 
§P = 4.39 × 10^{-3} for T/T versus C/C. 
||P < 0.0001 for T/T versus C/C. 
*P < 0.0001 for T/T versus C/C. 
#P = 0.249 for T/T versus C/C. 
**P = 1.18 × 10^{-18} for G/G or G/T versus T/T. 
††P = 7.75 × 10^{-4} for G/G versus T/T.
intent-to-treat basis, meaning that patients were included regardless of adherence. Ethnicity was determined by patient self-reporting. Although including all subjects regardless of adherene does not result in the most powered study design for discovering gene variants influencing therapeutic efficacy, it provides a more accurate picture of the relevance of genotypic information in the clinic, where adherence is variable. Among patients of European ancestry (n = 1,171), SVR was attained by 27% with the T/T genotype, 33% with the C/T genotype, and 69% with the C/C genotype. Among African American patients (n = 300), SVR was attained by 13% with the T/T genotype, 15% with the C/T genotype, and 48% with the C/C genotype. The presence of only one C allele conferred little benefit in treatment response, as was true in the analyses performed by Ge et al.\(^3\) and in the studies of spontaneous clearance reported by Thomas et al.\(^4\) African American patients with the C/C genotype had a significantly higher rate of SVR than European Americans who were non-C/C, indicating that genetic background is more important than ethnicity. However, response rates were lower for African Americans in each genotype category. In a logistic regression analysis of pretreatment (baseline) factors, \(\text{IL28B}\) status (C/C versus non-C/C) was the strongest predictor of SVR (odds ratio \([\text{OR}]\) 5.2; 95% confidence interval \([\text{CI}]\) 4.1-6.7). When on-treatment parameters were considered, rapid virological response (RVR, HCV RNA negativity at week 4) was the strongest predictor of SVR, but only a minority of patients (14% of Caucasians) had rapid response. In patients that did have RVR, \(\text{IL28B}\) remained strongly predictive of SVR, even at 4 weeks after treatment initiation.

Asia. To identify host genes associated with response to PEG-IFN and RBV, Tanaka et al.\(^4\) conducted a genome-wide association study in treatment-adherent Japanese patients with HCV genotype 1 infection. Among the 154 patients, 82 had virological nonresponse (defined as <2 \(\log_{10}\) IU/mL reduction in serum HCV RNA at week 12 of treatment), and 72 had a virological response. Two SNPs, rs12980275 and rs8099917, both of which are near \(\text{IL28B}\), were strongly associated with both virological nonresponse \((P = 1.93 \times 10^{-13} [\text{OR} 20.3]\) and \(P = 3.11 \times 10^{-15} [\text{OR} 30.0]\), respectively) and SVR. Interestingly, the predictive value of these variants in the Japanese study appears to be stronger than what was observed in the studies of African American and European American patients.

The associations were replicated in an independent cohort, and in further fine mapping of the region, seven SNPs near \(\text{IL28B}\) (rs8103142, rs28416813, rs4803219, rs8099917, and rs7248668) showed the most significance. Analysis of linkage disequilibrium (statistical association) among these SNPs showed that all were highly correlated, and there were few grounds for distinguishing them, although rs8099917 was the most significant. It should be noted that rs12979860 was not tested in this study, but it is within the group of associated SNPs (Fig. 1).

Real-time quantitative polymerase chain reaction assays in peripheral blood mononuclear cells showed modestly lower \(\text{IL28B}\) expression levels in individuals carrying the minor alleles of rs8099917 \((P = 0.015)\), suggesting that variable \(\text{IL28B}\) expression is associated with a response to PEG-IFN and RBV treatment, although this conclusion remains controversial (see “Mechanisms of Action of Lambda IFNs and Role of \(\text{IL28B}\)” below).

Australia. Suppiah et al.\(^5\) conducted a genome-wide association study of SVR to PEG-IFN and RBV combination therapy in 293 Australian individuals with genotype 1 chronic hepatitis C. The most significantly associated SNPs were then tested in a larger independent cohort of Europeans from the United Kingdom, Germany, Italy, and Australia (N = 555). SVR was associated with the SNP rs8099917 (combined \(P = 9.25 \times 10^{-9} [\text{OR} 1.98; 95% \text{CI} 1.57-2.52]\)).

**\(\text{IL28B}\) for Other HCV Genotypes and in the Context of Coinfection**

**HCV Genotypes 2 and 3.** Although the original studies of \(\text{IL28B}\) polymorphisms were performed in patients with genotype 1 HCV, more recently the association of rs12979860 on response to treatment with PEG-IFN and RBV has been characterized in a cohort of genotype 2 or 3 patients.\(^9\) The patient population consisted of 268 Caucasian patients (genotype 2, n = 213; genotype 3, n = 55) who participated in a multi-center randomized controlled trial from 13 clinical sites in Italy. Patients were randomly assigned to groups that received therapy of either variable or standard (24 weeks) duration. Patients in the variable group who had an RVR (HCV RNA negativity at week 4) were treated for 12 weeks; those without an RVR were treated for 24 weeks. Of patients with the C/C genotype, 82% had an SVR, compared with 75% for genotype C/T and 58% for genotype T/T \((P = 0.0046\) for trend). In contrast to previous observations in North American patients with genotype 1 HCV,\(^3,8\) the SVR rate for genotype C/T patients was intermediate between genotype C/C and T/T patients, suggesting...
the possibility of a more additive effect of the C allele than in the previous setting. Differences between IL28B genotypes were greatest among patients who did not have an RVR. Among the 61% of patients who had RVR, SVR was >70% in all IL28B genotype groups, and the IL28B genotype was not associated with SVR. In contrast, for patients who did not attain RVR, there was a significant difference in SVR on the basis of IL28B genotype.

**Human Immunodeficiency Virus Coinfection.** In a study of patients from two clinical trials at eight major hospitals in Switzerland, the rs8099917 minor allele was associated with progression to chronic HCV infection (OR 2.31; 95% CI 1.74-3.06; \( P = 6.07 \times 10^{-5} \)).\(^7\) The association was observed in HCV monoinfected patients (OR 2.49; 95% CI 1.64-3.79; \( P = 1.96 \times 10^{-5} \)) and patients coinfected with HCV and human immunodeficiency virus (OR 2.16; 95% CI 1.47-3.18; \( P = 8.24 \times 10^{-7} \)). Among all patients, the risk allele was identified in 24% of those with spontaneous HCV clearance, 32% who responded to therapy, and 58% who did not respond (\( P = 3.2 \times 10^{-10} \)). The strongest association in failure to respond was in patients with HCV genotypes 1 or 4.

**Choosing a Variant for Diagnosis.** Multiple polymorphisms around the IL28B gene are strongly associated with response to standard of care for chronic hepatitis C (Fig. 1), thus raising the issue of which variant or variants to use diagnostically. For patients of European ancestry,\(^3,5\) the rs12979860 (*), the initial variant discovered by Ge et al.\(^3\) The remaining variants represent the findings by Tanaka et al.,\(^4\) with the primary associated variant, rs8099917 (†), identified by Tanaka et al. and Supphai et al.\(^5\) Compared with the other variants, the rs12979860 variant is much stronger predictor of response in individuals of African ancestry; therefore, this single variant would be the best diagnostic in global populations.

**Spontaneous Clearance of HCV**

To determine the potential effect of rs12979860 variation on natural resolution of HCV infection, Thomas et al.\(^6\) genotyped this variant in HCV cohorts comprising individuals who spontaneously cleared the virus (n = 388) or had persistent infection (n = 620). The C/C genotype strongly enhanced resolution of HCV infection, with similar clearance rates among individuals of both European and African ancestry. Clearance rates for genotype C/C were approximately double those for T/T and implicate IL28B as having a primary role in resolving HCV infection. The rs8099917 genotype T/T has also been strongly associated with spontaneous resolution of HCV infection in Swiss cohorts.\(^7\)

**IL28B Genotype and Viral Kinetics**

Variation in IL28B appears to influence the kinetics of viral response to therapy. The first 24 to 48 hours after initiation of IFN-alpha therapy is characterized by a rapid dose-dependent decline in viral load, known as the first phase decline, which represents direct inhibition of viral replication.\(^10\) In patients who respond to therapy, after \( \approx 24-48 \) hours, the viral decline enters a second phase of relatively slow exponential decay, which represents elimination of infected cells. Patients who are not responsive to therapy have a plateau or even a rebound in viral load during this second phase.

After initiation of PEG-IFN and RBV therapy, patients with the C/C genotype at rs12979860 have a greater HCV RNA decline from days 0-28 than patients with the C/T or T/T genotype.\(^8\) Further studies show that the difference can be detected in the first 48 hours of treatment (Fig. 2).\(^11,12\) Among patients...
with the C/C genotype, Caucasians but not African Americans have greater HCV RNA declines than the other genotypes during the second phase (days 7-28).

Mechanisms of Action of Lambda IFNs and Role of IL28B

The specific mechanisms of how variations in IL28B SNPs affect HCV suppression remain unknown. However, IL28A, IL28B, and IL29, also called type 3 or lambda IFNs, are induced by viral infection and have antiviral activity.13 All three interact with a heterodimeric class II cytokine receptor that consists of IL10Rβ and IL28Ra (IFNλR1)14,15 (Fig. 3). Lambda IFNs inhibit HCV replication in vitro16,17 and may protect against other RNA-containing viruses in vivo.13,18 Lambda IFNs are thought to produce intracellular responses similar to those of IFN-α but are more specific in their tissue targets because of restricted receptor expression. This has led some to hypothesize that lambda IFNs have similar antiviral activity as IFN-α, but with fewer adverse effects. Supporting this hypothesis are results from an open-label study of PEG-IFN-λ1 (IL29) in patients with genotype 1 HCV, in which weekly dosing had antiviral activity and was well tolerated.19 However, larger, blinded studies are needed to further evaluate the safety and efficacy of lambda IFNs.

As for type 1 IFNs, expression of lambda IFNs occurs predominantly in antigen-presenting cells such as macrophages and dendritic cells.13,20 Within the liver, the receptor for lambda IFNs is predominantly expressed in hepatocytes.21 The kinetics of signal transduction appear to differ between type 1 and type 3 IFNs, with type 3 IFN showing slower activation onset and prolonged duration of activity compared with type 1.16 However, type 1 and type 3 stimulate similar pathways, with receptor binding resulting in phosphorylation of the kinases JAK1 and Tyk2, activation of the transcription factor complex containing STAT1, STAT2, and IFN regulatory factor 9, and up-regulation of a similar set of interferon-stimulated genes (ISGs).16,18

Improved viral clearance could result from alterations in IL28B expression, messenger RNA splicing, half-life, or cytokine-receptor affinity or specificity. The responder haplotype of rs8099917 has been weakly associated with higher expression levels of IL28A and IL28B in peripheral blood mononuclear cells.4,5 However, in the SNP expression database http://humangenome.duke.edu/software, no difference in peripheral blood mononuclear cell expression of IL28B on the basis of rs12979860 genotype has been noted. In addition, in two independent studies,22,23 no differences in levels of intrahepatic IL28B gene expression on the basis of IL28B genotype were observed. Further studies are needed to elucidate the causal variants and the biological mechanisms underlying the association between IL28B genotype and HCV treatment response.

The expression of hepatic ISGs has been associated with treatment response and has more recently been strongly associated with genetic variation in IL28B. In one study, gene expression profiles were analyzed in liver tissue from 91 patients with chronic hepatitis C who received PEG-IFN and RBV combination therapy.22 Genetic variation in host rs8099917 was determined, and the expression of ISGs was evaluated in all samples. Hepatic ISGs were associated with the IL28B polymorphism (OR 18.1; P < 0.001), and their expression was significantly higher in patients with the minor genotypes (T/G or G/G), which were associated with nonresponse to treatment, than in those with the major genotype (T/T). Because rs8099917 strongly
correlates with rs12979860, this implies that the poor-response minor allele T at rs12979680 is associated with higher ISG expression than the good-response C allele. (It is important to note that which alleles are associated with good and bad response depends on which marker variant is considered). Similarly, in RNA expression analyses from liver biopsies of 61 North American patients with chronic HCV, 164 transcripts were differentially expressed on the basis of rs12979860 genotype.\(^{23}\) The IFN signaling pathway was the most enriched canonical pathway with differential expression \((P < 10^{-5})\), and most genes had higher expression in livers of individuals carrying the poor-response non-C/C genotypes.

**Clinical Role for Pharmacogenetics in Hepatitis C**

*IL28B* genotyping has multiple potential roles for current practice. For example, treatment-naïve patients with the C/C genotype at rs12979860 may decide to undergo PEG-IFN and RBV therapy given their relatively high likelihood of SVR. Patients with the T/T genotype at rs12979860 and no indications of serious liver problems may wait for new direct antiviral agents to become available, because T/T genotypes have a poor likelihood of IFN responsiveness. *IL28B* genotype may also be considered in conjunction with virological response at week 4; patients with poor viral kinetics and T/T genotype at rs12979860 may decide to stop therapy.

Although *IL28B* genotyping is highly predictive of SVR at the population level in HCV genotype 1 patients, its predictive power at the individual patient level is far from absolute. Therefore, *IL28B* genotyping should not be the sole factor in deciding on a treatment strategy. Some patients have SVR despite having an unfavorable genotype. In addition, although evidence suggests that *IL28B* genotyping is the strongest pretreatment indicator of response, the on-treatment
variable of RVR at week 4 is an even stronger predictor. These factors suggest that if \( IL28B \) genotyping is used, it should be considered along with other baseline predictors of response and virological status at week 4.

An attractive scenario is that patients with favorable \( IL28B \) genotyping but HCV genotype 1 virus may be able to reduce treatment time from 48 weeks. Although this issue is a priority of future studies, at this time, there is insufficient data to recommend shortening the duration of standard of care.

Another clinical advance is the recent identification of two inosine triphosphatase (\( ITPA \)) polymorphisms known to be functionally responsible for \( ITPA \) deficiency and strongly protective against RBV-induced hemolytic anemia. \(^{24} \) \( ITPA \) genotyping could help guide clinical decision-making, especially for patients in whom treatment with RBV is avoided or relatively contraindicated because of the high risk for developing anemia.

It is unclear whether \( IL28B \) genotyping will be relevant in the context of direct antiviral therapy. The effects of \( IL28B \) genotype appear to be most substantial during the first phase of viral decline. Therefore, direct antivirals that have swift, potent effects on viral load may diminish the influence of \( IL28B \) genotyping in predicting SVR. However, direct antivirals achieve reductions in viral load by a variety of mechanisms, and it should not be assumed that \( IL28B \) genotyping will have the same implications with different therapies or treatment strategies. The lack of data regarding whether \( IL28B \) genotype is predictive of response when directly acting antivirals are added to IFN and RBV makes a definitive statement on combination treatment difficult. Knowledge of \( IL28B \)'s effect in patients taking directly acting antivirals is a priority for research and clinical care.

**Pharmacoeconomics: Implications of Tailored Therapy**

Both the process of \( IL28B \) genotyping and the possibility of tailored therapy affect the pharmacoeconomics of hepatitis C therapy. An important consideration regarding \( IL28B \) genotyping is whether it will be covered by health care plans. Coverage of genotyping could enhance clinical decision-making. However, coverage of treatment should not be based on genotyping alone. It is hoped that clinical and patient advocacy groups will insist that \( IL28B \) status is not used to deny treatment, especially given that its informative value is not absolute.

In the context of drug development, tailored therapy has several potential implications. Segmenting the treatment population may reduce the overall size of the market; however, this may not necessarily limit profit. Throughout the world, treatment for HCV has poor patient uptake, often because of patient concerns about efficacy and tolerability. Pharmacogenetics could make a drug more appealing to a specific group of patients, such as African Americans with a C/C genotype at rs12979860. Knowing how pharmacogenetic testing could affect the size of the marketplace, the segmenting of the treatment population, and the clinical need is critical for important considerations such as pricing, therapeutic substitutions, competition, and orphan drug status.

**Role of Pharmacogenetics in Clinical Trials**

In North America, a commercial test for \( IL28B \) genotyping is now available and costs approximately $300.\(^{25} \) Given the strength of \( IL28B \) genotyping as a pretreatment indicator of response to current hepatitis C therapy, investigators of trials of novel therapeutic agents combined with a PEG-IFN backbone would be advised to at minimum collect samples at baseline for retrospective genotyping. Establishing study designs with stratification on the basis of \( IL28B \) genotype can prevent enrichment of favorable or unfavorable genotypes in comparator cohorts. In such cases, a novel therapeutic agent is at risk for failing to reach noninferiority or superiority claims against standard of care with PEG-IFN and RBV.

Obtaining informed patient consent for genetic information is essential in elucidating relationships between genotype and response to therapy; however, patients and institutional review boards can have concerns regarding providing consent. Given the increasing clinical significance of pharmacogenomics, the US Food and Drug Administration is in the process of developing a clinical pharmacogenomics guidance, which will be available online. The panel recognized the importance of educating institutional review boards on the critical role and potential patient benefits of pharmacogenomic testing in clinical trials.

**Perspective of the US Food and Drug Administration**

From the perspective of regulatory agencies, pharmacogenetics can be a factor in drug development, labeling, and eventual clinical use in the marketplace. The potential applications of pharmacogenetics-informed HCV trials are listed in Table 2. At present, it is recommended that samples for pharmacogenetic testing be stored at the outset of a clinical trial.

There are two avenues for obtaining pharmacogenetic testing information on a product label: the first
is through codevelopment of drug and test, and the second is through postapproval label updates. Linked codevelopment provides the best opportunity to obtain evidence of clinical use for both test and drug. In this case, the evidence in support of product labeling often comes from prospective hypotheses, randomized controlled trials, and replication. The sponsor assumes primary responsibility for generating evidence.

For postapproval label updates with genetic information, evidence of clinical use often comes from observational analyses, case-control or cohort studies (versus randomized controlled trials), and retrospective analyses. The data are not always generated by a pharmaceutical sponsor and are often added to labeling because of a safety issue, such as the occurrence of an adverse event that becomes apparent with widespread product use. Common occurrences leading to label updates include frequent or severe clinical events, the further understanding of disease pathology and drug target (biological plausibility), clinical validation in prospective studies, or the presence of actionable recommendations. An example of this would be genetic testing prior to abacavir in human immunodeficiency virus therapy. The framework for evaluating the value of a genetic test is outlined in Table 3.

### Table 3. Considering the Value of a Genetic Test

<table>
<thead>
<tr>
<th>Framework</th>
<th>Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical situation</td>
<td>What is the medical need?</td>
</tr>
<tr>
<td>Marker association</td>
<td>What is the strength of the association?</td>
</tr>
<tr>
<td>Clinical variables</td>
<td>What nongenetic variable is associated with the response?</td>
</tr>
<tr>
<td>Clinical course</td>
<td>What is the clinical course in marker-positive patients?</td>
</tr>
<tr>
<td>Cost</td>
<td>What is the value of the test? Is it cost-effective?</td>
</tr>
</tbody>
</table>

Currently, the US Food and Drug Administration considers IL28B genotyping in the treatment of chronic HCV as advisable but not necessary.

### Future Directions and Priorities

IL28B genotyping will almost certainly drive the hepatitis C treatment setting toward a more tailored approach. However, the role and importance of pharmacogenetics in hepatitis C treatment is multifaceted and evolving. Actions that would benefit research and clinical care include having a uniform and more intuitive nomenclature for the IL28B SNPs and the creation of a central data repository for reporting genotypic and phenotypic correlations to treatment response. Priorities for research studies are numerous (Table 4) and include understanding the mechanics of lambda IFNs in HCV suppression and detailing the cost-effectiveness of response-guided therapy that includes IL28B genotyping. Collaboration between academia, industry, and governing bodies will help move the priorities forward and should hasten advances in clinical care.

### Financial support:

The costs of this meeting were sponsored by Abbott Laboratories, Abbott Park, IL; Anadys Pharmaceuticals, Inc., San Diego, CA; Bristol-Myers Squibb, Princeton, NJ; Genentech, Inc., Hoboken, NJ; Gilead Sciences, Inc., Foster City, CA; Globe-Immune, Inc., Louisville, CO; Human Genome Sciences, Inc., Rockville, MD; Idera Pharmaceuticals, Inc., Cambridge, MA; LabCorp, Burlington, NC; Liver Institute for Education and Research, NJ; Medtronic, Inc., Minneapolis, MN; Merck & Co., Inc., Kenilworth, NJ; Monogram Business Sciences, Inc., South San Francisco, CA; Pharmasset, Inc., Princeton, NJ; Roche Laboratories, South San Francisco, CA; Roche Molecular Diagnostics, Pleasanton, CA; Roche Pharmaceuticals, Palo Alto, CA; Scynexis, Inc., Durham, NC; Tibotec BVBA, Beerse, Belgium; Tibotec, Inc., Titusville, NJ; Vertex Pharmaceuticals, Inc., Cambridge, MA; and Virco BVBA, Beerse, Belgium.

### Potential conflicts of interest:

John G. McHutchison, Kevin V. Shianna, and David B. Goldstein are coinventors of patents commercially protecting the use of IL28B and ITPA genetic variation to predict
treatment response and anemia for patients undergoing treatment for chronic hepatitis C infection. Nezam H. Afdhal reports the following financial relationships: Abbott Laboratories (consulting, advisory arrangements), Anadys Pharmaceuticals (consulting, advisory arrangements), Bristol-Myers Squibb (consulting, speakers’ bureau, research grants), Gilead Sciences, Inc. (consulting, speakers’ bureau, research grants), Human Genome Sciences, Inc. (consulting, advisory arrangements, research grants), Idera Pharmaceuticals, Inc. (consulting), Liver Institute for Education and Research (director), Merck & Co., Inc. (consulting, advisory arrangements, research grants), Pharmasset, Inc. (consulting), Scynexis, Inc. (consulting), Tibotec BVBA (advisory arrangements), Titusville, NJ; Kevin A. Schulman, Duke University Medical Center, Durham, NC; Jean-Michel Pawlotsky, Jean-Michel Pawlotsky reports the following financial relationships: Merck & Co., Inc. (advisory arrangements), Roche Molecular Diagnostics (advisory arrangements), Roche Pharmaceuticals (advisory arrangements, speakers’ bureau, travel grants), Tibotec BVBA (advisory arrangements, speakers’ bureau), Vertex Pharmaceuticals, Inc. (advisory arrangements, speakers’ bureau), Virco BVBA (advisory arrangements). Kevin V. Shianne reports the following financial relationships: Merck & Co., Inc. (intellectual property). Yasuhiro Tanaka reports the following financial relationships: Bristol-Myers Squibb (research grants), Roche Molecular Diagnostics (advisory arrangements), Roche Pharmaceuticals (advisory arrangements, speakers’ bureau, travel grants), Tibotec BVBA (advisory arrangements, speakers’ bureau), Vertex Pharmaceuticals, Inc. (advisory arrangements, speakers’ bureau), Virco BVBA (advisory arrangements).

Appendix

The participants of the Pharmacogenetics and Hepatitis Meeting are as follows: Jeroen Aerssens, Tibotec BVBA, Beerse, Belgium; Nezam H. Afdhal, Beth Israel Deaconess Medical Center, Boston, MA; Steven M. Anderson, Laboratory Corporation of America/ Monogram Biosciences, Research Triangle Park, NC; Shashi G. Amur, Debra Birnkrant, Jeffrey S. Murray, Sarah M. Robertson, Kimberly A. Struble, Kathleen Whittaker, US Food and Drug Administration, Silver Spring, MD; David Apelian, GlobelImmune, Inc., Louisville, CO; Jim Appleman, Anadys Pharmaceuticals, Inc., San Diego, CA; Robert D. Arbeit, Idera Pharmaceuticals, Inc., Cambridge, MA; M. Michelle Berrey, Pharmasset, Inc., Princeton, NJ; David R. Booth, University of Sydney, Sydney, Australia; Martyn Bothfield, Shelley George, Vertex Pharmaceuticals, Inc., Cambridge, MA; Clifford Brass, Merck & Co., Inc., Kenilworth, NJ; Jenny Brews, Paul Clark, John G. McHutchison, Susanna Naggie, Keyur Patel, Alexander J. Thompson, Duke Clinical Research Institute, Durham, NC; Scott C. Brun, Abbott Laboratories, Abbott Park, IL; Mary Carrington, SAIC-Frederick, National Cancer Institute, Frederick, MD; Sophia Chao, Stephen J. Rossi, Roche Molecular Diagnostics, Pleasanton, CA; Gavin Clougherty, Abbott Molecular, Des Plaines, IL; Eoin P. Coakley, Monogram Biosciences, Inc., South San Francisco, CA; Jacques Fellay, David B. Goldstein, Kevin V. Shianne, Thomas J. Urban, Duke University Medical Center, Durham, NC; Hawazin Faruki, LabCorp, Burlington, NC; Sam Hopkins, Scynexis, Inc., Durham, NC; Nigel Hughes, Tibotec–Virco BVBA, Beerse, Belgium; Christina Kish, Genentech, Inc., Hoboken, NJ; Bruce Kreter, Bristol-Myers Squibb, Princeton, NJ; William A. Lee, Gilead Sciences, Inc., Foster City, CA; T. Jake Liang, Emmanuel Thomas, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD; Uri Lopatin, Roche Pharmaceuticals, Palo Alto, CA; Ven Manda, Rachael Scherer, William Van Antwerp, Medtronic, Inc., Minneapolis, MN; Alessandra Mangia, IRCCS Casa Sollievo della Sofferenza Hospital, San Giovanni Rotondo, Italy; Masashi Mizokami, National Center for Global Health and Medicine, Chiba, Japan; David Oldach, Gilead Sciences, Inc., Durham, NC; Jean-Michel Pawlotsky, Hopital Henri Mondor, University of Paris EST, Creteil, France; Gastón Picchio, Tibotec, Inc., Titusville, NJ; Kevin A. Schulman,
References


