Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 9/1/24**
(See policy history boxes for previous effective dates)

Title: Interferon Lambda 3 (IFNL3) Testing to Predict Response to Treatment of Hepatitis C Virus (HCV) Infection

Description/Background

Inflammation of the liver caused by Hepatitis C virus (HCV) infections, may result in liver fibrosis and cirrhosis. HCV infections are estimated to affect 2% to 3% of the world's population, including 2.7 to 4.1 million individuals in the United States. Most individuals with HCV become infected after needle-stick injuries, the sharing of hypodermic needles, blood transfusions prior to standard HCV screening, or insufficient infection control in healthcare settings. Many patients with acute HCV infections do not initially exhibit clinical symptoms, and up to 25% will clear the virus spontaneously. However, 75% to 85% of infected individuals progress to having chronic HCV. Clinically, chronic HCV may be associated with abdominal pain, abdominal swelling, jaundice, itching, fatigue, changes in urine or stool color, and nausea or vomiting. Chronic HCV infections result in a significantly increased risk for liver fibrosis, cirrhosis, and hepatocellular carcinoma, and are the most common reason for liver transplantation.

HCV is classified based on the DNA sequence of the virus, since this sequence may be highly variable between HCV patients. HCV is grouped into 6 major genotypes (different versions of DNA sequence), each of which has a different geographic distribution. HCV genotypes 1, 2, and 3 account for the vast majority of HCV cases in the United States and Europe, with genotype 1 being the most common. Until recently, the standard treatment for HCV infections of all genotypes was a combination of pegylated interferon alpha (PegIFN) and ribavirin (RBV). However, newer treatment regimens involving PegIFN, RBV, and a direct-acting protease inhibitor—a combination referred to as "triple therapy"—increase the chance of viral response in patients with HCV genotype 1.

Studies designed to identify genetic variants associated with an increased likelihood of response to PegIFN/ RBV therapy have been conducted with the goal of identifying the most

appropriate candidates for treatment with these medications. These studies identified 2 single nucleotide polymorphisms (SNPs; single base pair changes in DNA sequence) near the interleukin 28B gene (*IL28B*). *IL28B* is located on chromosome 19 at band q13.13 and encodes the cytokine interferon lambda 3. Based on these associations, tests examining 1 or both *IL28B* SNPs are now clinically available.

IL28B SNP testing for HCV treatment response may be performed using a variety of methods, including allele-specific polymerase chain reaction (PCR)-based assays. Currently, evidence supporting *IL28B* SNP genotypes as predictors of response to triple therapy (PegIFN, RBV, and a protease inhibitor) are limited.

***While the official name for *IL28B* is now interferon lambda 3 (*IFNL3*), the former name *IL28B* is used in this report for consistency with the medical literature.**

Regulatory Status

No approvals for *IL28B* SNP testing for HCV were identified on the FDA website on January 18, 2013 (search 510(k) Premarket Notification using keywords *IL28B*; *HCV*; *hepatitis C*; 510(k) Premarket Notification). Genetic tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA) of 1988 (FDA CLIA). All 3 laboratories that provide genetic testing for SNPs upstream of *IL28B* for HCV have current CLIA certifications, including ARUP Laboratories (ARUP CLIA), LabCorp (LabCorp CLIA), and Mayo Medical Laboratories (Mayo CLIA).

Medical Policy Statement

Interferon Lambda 3 (IFNL3) testing to predict response to treatment of hepatitis C virus (HCV) Infection is experimental/investigational. It has not been scientifically demonstrated to improve patient clinical outcomes.

Inclusionary and Exclusionary Guidelines

N/A

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

N/A

Other codes (investigational, not medically necessary, etc.):

81283

Rationale

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

INTERFERON LAMBDA 3 (*IFNL3*) TESTING TO PREDICT RESPONSE TO TREATMENT OF HEPATITIS C VIRUS (HCV) INFECTION

Clinical Context and Test Purpose

IL28B SNP testing for HCV treatment response may be performed using a variety of methods, including allele-specific polymerase chain reaction (PCR)-based assays. Testing for the rs12979860 C/T and rs8099917 T/G SNPs located upstream of *IL28B* may be performed for any HCV patient being considered for treatment with PegIFN and RBV, with or without a protease inhibitor.

The following **PICOs** were used to select literature to inform this review.

Population

Testing for the rs12979860 C/T and rs8099917 T/G SNPs may be considered for HCV individuals being evaluated for treatment with PegIFN and RBV (with or without a protease inhibitor), particularly those with HCV genotype 1.

Intervention

The intervention of interest is testing for SNPs, including testing for the rs12979860 CT and rs8099917 T/G SNPs.

Comparator

Clinical alternatives to *IL28B* SNP testing include an assessment of possible treatment response based on HCV genotype, viral load, degree of fibrosis, and host characteristics, including patient sex, patient age, patient ethnicity, body mass index, alcohol use, and the presence of metabolic syndrome or menopause.

Outcomes

The general outcomes of interest are to predict the response to treatment of hepatitis C infection prior to PegIFN and RBV.

Analytically Valid

Several studies have evaluated the analytical validity of *IL28B* SNP testing. Ito and colleagues (2011) compared 5 different methods for the detection of SNPs located near *IL28B*

(rs12979860, rs8099917, rs11881222, and rs8103142).[1] Samples from 292 Japanese HCV patients were tested for each SNP using direct sequence analysis, high-resolution melting analysis (HRM), hybridization probe analysis, the PCR-based InvaderPlus assay (Invader Chemistry), and an allele-specified TaqMan PCR assay. The HRM assay was subsequently excluded because of 5 (1.7%) genotyping failures. For the rs12979860 SNP, all 4 methods identified 198 C/C patients, 85 C/T patients, and 4 T/T patients, for a concordance rate of 100%. For the rs8099917 SNP, direct sequence analysis identified 204 T/T patients, 79 T/G patients, and 4 G/G patients. The remaining 3 methods identified 202 T/T patients, 81T/G patients, and 4 G/G patients, resulting in a concordance rate of 99.3%. To resolve the discrepant results obtained for the rs8099917 SNP, direct sequence analysis was repeated using alternative sequencing primers. This analysis identified a novel minor SNP present in the forward primer and revealed that the 3 other methods correctly identified the 2 patients as T/G carriers. The concordance for the remaining 2 SNPs was 100% for all 4 methods.

A group from ARUP Laboratories compared 2 different methods for the analysis of rs12979860 and rs8099917: an allele-specific single nucleotide extension assay and a fluorescence resonance energy transfer (FRET) probe assay. Genomic DNA samples from 152 individuals were used to assess the performance of the 2 protocols. A subset of 25 samples was also evaluated by direct sequence analysis. The concordance between the single nucleotide extension assay, the FRET assay, and sequencing was 100%. For the FRET assay, the analytical sensitivity and specificity for the rs12979860 SNP were 100% (95% confidence interval [CI], 96.5% to 100%) and 100% (95% CI, 96.1% to 100%), respectively. The analytical sensitivity and specificity for the rs8099917 SNP were 100% (95% CI, 94.4% to 100%) and 100% (95% CI, 97.3% to 100%), respectively.

Reynolds and colleagues (2012) compared an allele-specific TaqMan-based PCR assay designed to analyze the rs12979860 SNP with direct sequence analysis.[2] Both methods were used to test 48 genomic DNA samples obtained from the Coriell Institute. The results for these 48 samples were 100% concordant between the TaqMan assay and sequencing. A beta distribution was subsequently used to determine that the 99% and 95% lower confidence limits were 91.03% and 94.07%, respectively. A subset of 24 samples was further analyzed using a commercially available test from LabCorp Inc. One DNA specimen was genotyped as T/T by the LabCorp assay and as C/T by both direct sequence analysis and the TaqMan assay, yielding a concordance rate of 95.9% (23 of 24).

Clinically Valid

Multiple genome-wide association studies (GWAS) have independently identified SNPs near the *IL28B* gene that are associated with response to treatment with PegIFN and RBV dual therapy in patients with chronic HCV. The main findings are summarized below in Table 1.

Table 1. GWAS Studies Identifying SNPs Near IL28B as Predictors of PEGIFN/RBV Treatment Response for Chronic HCV.

Study	Population	SNP & Alleles[a]	% SVR (by SNP Genotype)	Likelihood of PegIFN/RBV Tx Response
Ge et al. (2009)[3]	1137 European American, African American, and Hispanic pts w/HCV genotype 1	rs12979860, C/T	C/C: 79% C/T: 38% T/T: 26%	OR for SVR in C/C vs. C/T and T/T: 7.3 (95% CI, 5.1-10.4) in European Americans, 6.1 (95% CI, 2.3-15.9) in African Americans, and 5.6 (95% CI, 1.4-22.1) in Hispanics[b]

Suppiah et al. (2009)[4]	848 white Australian pts w/HCV genotype 1	rs8099917, T/G	T/T: 56% T/G: 36% G/G: 31%	OR for SVR in T/T vs. T/G and G/G: 3.36 (95% CI, 2.15-5.35; $p=7.06x10^{-8}$)[c]
Tanaka et al. (2009)[5]	142 Japanese pts w/HCV genotype 1	rs8099917, T/G	T/T: 64% T/G: 13% G/G: 0%	OR for SVR in T/T vs. T/G and G/G: 36.5 (95% CI, 11.6-114.6; $p=5.00x10^{-14}$)[d]
Rauch et al. (2010)[6]	465 Swiss pts w/HCV genotypes 1 (n=188), 2 (n=60), 3 (n=162), or 4 (n=34), or w/unspecified HCV genotype (n=21)	rs8099917, T/G	T/T: 68% T/G: 29% G/G: 3%	OR for tx failure in G/G and G/T vs. T/T: 5.19 (95% CI, 2.90-9.30; $p=3.11x10^{-8}$)
Ochi et al. (2011)[7]	2104 Japanese or Taiwanese pts w/HCV genotypes 1b (n=1562) or 2a (n=542)	rs8099917, T/G	T/T: 51.8% T/G: 29.4% G/G: 18.4%	OR for SVR in T allele carriers: 3.0 (95% CI, 2.4-3.8; $p=1.0x10^{-20}$); OR for SVR in T carriers w/HCV genotype 1b: 3.5 (95% CI, 2.6-4.6; $p=1.2x10^{-18}$); OR for SVR in T carriers w/HCV genotype 2a: 2.1 (95% CI; 1.3-3.2; $p=1.6x10^{-3}$)

CI: confidence interval; HCV: hepatitis C virus; OR, odds ratio; PegIFN, pegylated interferon alpha; pt(s): patient(s); RBV: ribavirin; SNP: single nucleotide polymorphism; SVR, sustained virological response; tx: treatment

[a] Patients carry either a cytosine © or a thymine (T) at SNP rs12979860, and a T or a guanosine (G) at SNP rs8099917.

[b] Corresponding relative risks (RR) for SVR in C/C vs. C/T and T/T were 2.0 (95% CI, 1.8-2.3) in European Americans, 3.0 (95% CI, 1.9-4.7) in African Americans and 2.1 (95% CI, 1.4-3.2) in Hispanics.

[c] OR for SVR in a replication cohort of 555 HCV patients was 1.59 (95% CI, 1.21-2.11; $p=9.39x10^{-4}$). Using a dominant model of inheritance, the rs8099917 G allele predicted nonresponse with a sensitivity, specificity, and positive predictive value (PPV) of 57%, 63%, 64%, respectively.

[d] OR for SVR in a replication cohort of 172 HCV patients was 25.1 (95% CI, 10.0-63.1; $p=1.00x10^{-14}$)

The data summarized above in Table 1 indicate that the odds ratio (OR) for achieving SVR among HCV genotype 1patients carrying the rs12979860 C/C genotype was 5.6 for Hispanic individuals, 6.1 for African American individuals, and 7.3 for European Americans. While the studies reporting an association with the rs8099917 SNP presented their data in different ways (e.g., an OR for SVR in C/C patients of 3.35 versus an OR for treatment failure in G/G and G/T patients of 5.19), the data consistently show a strong association between the T/T genotype and an increased likelihood of PegIFN/RBV treatment response. These studies suggest that rs12979860 and rs8099917 genotypes may facilitate the identification of HCV patients more likely to respond to PegIFN/RBV treatment, prior to treatment initiation.

Clinical Utility

A single study, by Liu et al, 2012b, of cost-effectiveness was identified.[8] Markov modeling was used to assess the cost-effectiveness of *IL28B* SNP testing for the treatment of patients with chronic HCV. Three treatment strategies were considered: dual therapy (PegIFN and RBV) without *IL28B* SNP testing; triple therapy (PegIFN, RBV, and a protease inhibitor) without *IL28B* SNP testing; and *IL28B*-guided triple therapy stratifying patients with a rs12979860 C/C genotype to dual therapy and those with non-C/C genotypes to triple therapy. Sex-, age-, and race-specific non-HCV mortality data were obtained from the 2006 United States life tables. Data regarding the effectiveness of standard HCV therapy were obtained from the intention-to-treat cohorts from the IDEAL study. Data regarding the effectiveness of triple therapy were obtained from the ADVANCE (A New Direction in HCV Care: A Study of Treatment-Naïve Hepatitis C Patients with Telaprevir) and SPRINT-2 clinical trials. Costs were adjusted to 2010 dollars, with an estimated weekly cost of $1100 for boceprevir and $4100 for telaprevir. Using the above model, universal triple therapy was found to cost $51,500 per quality-adjusted life-year (QALY) for patients with advanced fibrosis and $102,600 per QALY for those with mild

fibrosis. In contrast, *IL28B*-guided triple therapy cost $36,300 per QALY and $70,100 per QALY, respectively. Incremental cost-effectiveness ratios (ICERs) for *IL28B*-guided boceprevir therapy were $62,900 per QALY for patients with mild fibrosis and $32,800 per QALY for those with advanced fibrosis. ICERs for universal triple therapy with boceprevir were $102,600 per QALY for patients with mild fibrosis and $51,500 per QALY for those with advanced fibrosis. ICERs for *IL28B*-guided telaprevir therapy were $86,800 per QALY for patients with mild fibrosis and $45,300 per QALY for those with advanced fibrosis. ICERs for universal triple therapy with telaprevir were $102,400 per QALY for patients with mild fibrosis and $54,100 for those with advanced fibrosis. According to the authors, these findings suggest that universal triple therapy and *IL28B*-guided triple therapy may both be cost-effective when using the least expensive protease inhibitor.

No studies evaluating the impact of *IL28B* SNP testing on patient management or health outcomes were identified.

Studies Evaluating Response to Dual Therapy with Interferon-Alpha and Ribavirin

Numerous studies have evaluated the associations identified in the previous GWAS studies. Studies evaluating the associations between *IL28B* SNP genotype and response to PegIFN/RBV dual therapy in at least 300 patients with chronic HCV genotype 1 are summarized below in Table 2.

Table 2. Relationship Between *IL28B* SNPs rs12979860 and rs8099917 and SVR in HCV Genotype 1 Patients Treated with PegIFN/RBV Therapy

Study	Pt Population	SNP Genotype Frequencies	% of Pts w/SVR by Genotype	Likelihood of SVR by Genotype	Other Relevant Findings
Thompson et al. (2010)[9]	1628 pts, including 1171 white, 300 African American, 116 Hispanic, and 41 pts of other ethnic backgrounds **Baseline characteristics:** 61% male; 85.6% >40 yrs; median viral load 6.2-6.5 log10 IU/mL; 13.1% w/ advanced fibrosis or cirrhosis **Tx duration:** 48 wks	**rs12979860 (white pts):** C/C: 37% C/T: 51% T/T: 12% **rs12979860 (African American pts):** C/C: 14% C/T: 49% T/T: 37% **rs12979860 (Hispanic pts):** C/C: 29% C/T: 48% T/T: 22% (*P*<0.0001 for difference in C/C genotype across 3 ethnic groups) **rs8099917:** Not evaluated	**rs12979860 (white pts):** C/C: 69% C/T: 33% T/T: 27% (*P*<0.0001 for C/C Vs. C/T and T/T) **rs12979860 (African American pts):** C/C: 48% C/T: 15% T/T: 13% (*P*<0.0001 for C/C Vs. C/T and T/T) **rs12979860 (Hispanic pts):** C/C: 56% C/T: 38% T/T: 27%	**rs12979860:** OR of SVR for C/C vs. C/T or T/T: 5.2 (95% CI, 4.1-6.7; *P*<0.0001 [MV]) **rs8099917:** Not evaluated	**rs12979860 genotype for predicting SVR (C/C vs. non-C/C):** Sensitivity: 56% (95% CI, 52%-60%) Specificity: 79% (95% CI, 76%-82%) PPV: 69% (95% CI, 65%-74%) NPV: 68% (95% CI, 65%-71%) C/C genotype was also associated w/a greater chance of RVR (*P*<0.0001 for whites; *P*<0.02 for African Americans and Hispanics).

			(*P*=0.09 for C/C vs. C/T; *P*=0.02 for C/C Vs. T/T) **rs8099917:** Not evaluated		
Hayes et al. (2011)[10]	813 Japanese pts **Baseline characteristics:** 56.5% male;median age 58 yrs (range, 51-65); median viral load 6.5 log10 IU/mL (range, 6.1-6.9); 51.8% w/ advanced fibrosis or cirrhosis **Tx duration:** 48 wks	**rs12979860:** C/C: 71.6% C/T: 25% T/T: 3.3% **rs8099917:** T/T: 72.3% T/G: 24.5% G/G: 3.1%	**rs12979860:** C/C: 53.4% C/T: 25.1% T/T: 14.8% **rs8099917:** T/T: 52.9% T/G: 25.6% G/G: 12%	**rs12979860:** OR of SVR for C/C Vs. C/T or T/T: 4.98 (95% CI, 2.81-8.82; $P=4\times10^{-8}$ [MV]) **rs8099917:** OR of SVR for T/T Vs. T/G or G/G: 3.53 ($P=1.77\times10^{-13}$ [UV])	rs12979860 C/C genotype was also an independent predictor for change in viral load by week 4 of tx ($P=1.4\times10^{-8}$ [MV]).
Kurosaki et al. (2011)[11]	496 Japanese pts (including 98 pts from Tanaka et al., 2009) **Baseline characteristics:** 50% male; mean age 57.1±9.9 yrs; 82% w/ viral load >600,000 IU/mL; 24% w/advanced fibrosis or cirrhosis **Tx duration:** ≥24 wks	**rs12979860:** Not evaluated **rs8099917:** T/T: 70% T/G: 29% G/G: 1%	**rs12979860:** Not evaluated **rs8099917:** T/T: 50% T/G: 14% G/G: 0% (*P*<0.0001 for T/T Vs. T/G)	**rs12979860:** Not evaluated **rs8099917:** OR of SVR for T/T Vs. T/G or G/G: 7.41 (95% CI, 4.05-13.6; *P*<0.0001 [MV])	A model for the prediction of SVR (including rs8099917 genotype, platelet count, viral load, and variants in the ISDR region of the virus) yielded a sensitivity of 78% and a specificity of 70% (ROC AUC, 0.782).
Stättermayer et al. (2011)[12]	392 Austrian pts **Baseline characteristics:** 57.7% men; mean age 45.3±11.4 yrs; mean viral load 5.96±0.75 log10 IU/mL; 31.3% (89/284)w/advanced fibrosis or cirrhosis **Tx duration:** 24-72 wks	**rs12979860:** C/C: 34.8% C/T: 51.6% T/T: 13.7% **rs8099917:** T/T: 58.9% T/G: 37.1% G/G: 4%	**rs12979860:** C/C: 79.1% C/T: 43.8% T/T: 41.2% **rs8099917:** T/T: 67.6% T/G: 38.4% G/G: 40.0%	**rs12979860:** OR of SVR for T allele carriers: 0.143 (95% CI, 0.077-0.265; *P*<0.0001 [MV]) **rs8099917:** NR	**Prediction of SVR in rs12979860 C/C carriers:** Sensitivity: 49.5% Specificity: 85.7% PPV: 80.5% NPV: 58.8% **Prediction of SVR in rs8099917 G/G carriers:** Sensitivity: 68.3% Specificity: 61.7% PPV: 71.6% NPV: 57.9%
Suppiah et al. (2011)[13]	910 pts representing 6 different cohorts from Australia and Europe **Baseline characteristics:** 62.5% male; mean age 40.9 yrs for responders and 45.7 yrs for nonresponders;	**rs12979860:** NR **rs8099917 for responders:** T/T: 62% T/G: 33.7% G/G: 4.3% **rs8099917 for nonresponders:** T/T: 42.7% T/G: 50.3% G/G: 6.9%	**rs12979860:** NR **rs8099917:** T/T: 54.9% T/G: 35.9% G/G: 34%	**rs12979860:** NR **rs8099917:** OR for T/T genotype in pts w/no SVR: 0.46 (95% CI, 0.35-0.60; $P=1.27\times10^{-8}$); OR for T/G genotype in pts w/ no SVR: 2.0 (95% CI,	**Prediction of failure to achieve SVR:** G/G genotype: Sensitivity: 7% Specificity: 96% PPV: 66% NPV: 46% Carriage of G allele: Sensitivity: 57% Specificity: 62% PPV: 64%

	fibrosis and viral load measurements NR **Tx duration:** 48 wks, except for pts w/ <2 log decrease in HCV RNA at 12 wks			1.52-2.63; $P=7.35\times10^{-7}$); OR for no SVR in carriers of G allele: 2.19 (95% CI, 1.67-2.88; $P=1.27\times10^{-8}$)	NPV: 55%
Akuta et al. (2012a)[14]	490 Japanese pts, only 219 of whom had data regarding SNP genotype **Baseline characteristics:** 63.3% men; median age 54 yrs (range, 20-75 yrs); median viral load 6.4 log10 IU/mL (range, 2.2-7.7); rate of advanced fibrosis NR	**rs12979860:** Not evaluated **rs8099917:** T/T: 68.5% T/G: 29.7% G/G: 1.8%	**rs12979860:** Not evaluated **rs8099917:** T/T: 63% T/G or G/G: 26%	**rs12979860:** Not evaluated **rs8099917:** OR of SVR for T/T Vs. T/G or G/G: 16.7 (95% CI, 4.54-61.3; $P<0.001$ [MV])	**rs8099917:** OR for ETR in T/T pts Vs. T/G or G/G pts: 18.2 (95% CI, 6.29-52.6; $P<0.001$ [MV])
Amanzada et al. (2012)[15]	305 pts (97% white) **Baseline characteristics:** 55% male; mean age 52±13 yrs; 18.7% of pts w/ biopsy w/ moderate fibrosis to cirrhosis; baseline viral load NR **Tx duration:** ≥24 wks	**rs12979860:** C/C:34.1 % C/T: 46.2% T/T: 19.7% **rs8099917:** T/T: 48.2% T/G: 37.7% G/G: 14.1%	**rs12979860:** C/C: 64.4% C/T: 37.6% T/T: 23.3% **rs8099917:** T/T: 54.4% T/G: 38.3% G/G: 23.3%	**rs12979860:** OR of SVR for C/C Vs. C/T: 3.0 (95% CI,1.8-5.1); OR of SVR for C/C vs. T/T: 5.9 (95% CI, 2.9-12.2) **rs8099917:** OR of SVR for T/T Vs. T/G: 1.9 (95% CI, 1.2-3.2); OR of SVR for T/T vs. G/G: 3.9 (95% CI, 1.8-8.6)	**rs12979860:** Rate of SVR in pts w/ C/C and anemia by wk 4 of tx was 81%; OR for anemic C/C pts to achieve SVR was 4.4 (95% CI, 1.8-10.4), compared w/ C/C pts w/o anemia.
Fischer et al. (2012)[16]	942 white European pts (including pts from Suppiah et al., 2009) **Baseline characteristics:** 58.8% male; mean age 47.6±10.7 yrs; 70.2% w/ baseline viral load ≥400,000 IU/mL; 48% (387/807) w/ moderate to severe fibrosis **Tx duration:** 93% tx'd for 48 wks; 7% tx'd for >48 wks (up to 72 wks)	**rs12979860:** C/C: 34% C/T: 52% T/T: 14% **rs8099917:** T/T: 55.6% T/G: 39.8% G/G: 4.6%	**rs12979860:** C/C: 68% C/T: 46% T/T: 41% **rs8099917:** T/T: 62% T/G: 42% G/G: 35%	**rs12979860:** OR of SVR for C/C vs. T/T: 4.87 (95% CI, 2.82-8.40; $P=1.3\times10^{-8}$) **rs8099917:** OR of SVR for T/T vs. G/G: 3.45 (95% CI, 1.48-8.07; $P=0.004$)	**rs12979860:** OR of tx failure for C/T vs. C/C: 3.35 (95% CI, 2.31-4.86; $P=1.9\times10^{-10}$) **rs8099917:** OR of tx failure for T/G vs. T/T: 2.91 (95% CI, 2.07-4.09; $P=1.4\times10^{-9}$)
Howell et al. (2012)[17]	361 pts, including	**rs12979860 (white pts):**	**rs12979860 (all pts):**	**rs12979860 (white**	rs12979860 C/C

	188 white Americans and 173 African Americans **Baseline characteristics:** 65.7% male; mean age 46.3-49.2 yrs; mean baseline viral load 6.3-6.6 log10 IU/mL; median Ishak fibrosis score 2.0* **Tx duration:** Up to 48 wks	C/C: 45.7% C/T: 44.2% T/T: 10.1% **rs12979860 (African American pts):** C/C: 11.6% C/T: 54.9% T/T: 33.5% **rs8099917:** Not evaluated	C/C: 61.3% C/T: 34.3% T/T: 26.0% **rs12979860 (white pts):** C/C: ~65%† C/T: ~45%† T/T: ~30%† **rs12979860 (African American pts):** C/C: ~40%† C/T: ~25%† T/T: ~25%† **rs8099917:** Not evaluated	**pts):** OR of SVR for C/C vs. C/T or T/T: 2.3 (95% CI, 1.3-4.2; *P*=0.004 [MV]) **rs12979860 (African American pts):** OR of SVR for C/C vs. C/T or T/T: 1.6 (95% CI, 0.8-3.1; *P*=0.21 [MV]) **rs8099917:** Not evaluated	genotype was also an independent predictor of declines in HCV RNA at days 0-2 (*P*<0.0001) and days 7-28 (*P*=0.011)

AUC, area under the curve; CI, confidence interval; ETR, end-of-treatment (response); HCV, hepatitis C virus; ISDR, interferon sensitivity determining region; IU/mL, international units per milliliter; MV, multivariate analysis; NPV, negative predictive value; NR, not reported; OR, odds ratio; PPV, positive predictive value; pt(s), patient(s); ROC, receiver operating characteristics; RVR, rapid virological response; SVR, sustained virological response; tx, treatment or therapy; tx'd, treated; UV, univariate analysis
*The Ishak fibrosis score rates the level of fibrosis from 0 (no fibrosis) to 6 (cirrhosis probable or definite) (Standish et al., 2006).
†Data was presented as a bar graph. Precise rate of SVR was not reported.

The studies summarized above indicate that the rate of SVR in PegIFN/RBV-treated HCV genotype 1 patients with an rs12979860 C/C genotype ranged from 48% to 79.1%.[9,10,12,16,17] In comparison, the rates of SVR in C/T and T/T patients were 15% to 46% and 13% to 41.2%, respectively. The rates of SVR tended to be lower in African American populations than in those of European or Asian descent. Consistent with these findings, the OR for SVR in PegIFN/RBV-treated HCV genotype 1 patients with a C/C genotype ranged from 1.6 in an African American population to 4.98 in an Asian population, with all but a single African American population showing a statistically significant difference in treatment response among patients with the various genotypes. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of an rs12979860 C/C genotype for the prediction of SVR were 49.5% to 56%, 79% to 85.7%, 69% to 80.5%, and 58.8% to 68%, respectively (Thompson et al., 2010; Stättermayer et al., 2011).[9,12] The data also show that the rate of SVR in PegIFN/RBV-treated HCV patients with an rs8099917 T/T genotype ranged from 50% to 67.6%.[10-14,17] The rates of SVR in patients with T/G or G/G genotypes ranged from 14% to 42% and 0% to 35%, respectively. The corresponding OR for SVR in T/T patients ranged from 3.53 to 16.7. The sensitivity, specificity, PPV, and NPV of an rs8099917 T/T genotype for the prediction of SVR were 68.3%, 61.7%, 71.6%, and 57.9%, respectively.[12]

SUMMARY OF EVIDENCE

Currently available evidence suggests that *IL28B* SNP testing may provide helpful information regarding the likelihood of response to PegIFN/RBV treatment in patients with chronic HCV. Additional prospective studies involving well-defined patient populations with sufficient clinical information are needed to confirm these associations and to better understand the correlations between genotype and response to the various treatment regimens. In addition to *IL28B* SNP genotype, there are multiple viral and host factors known to be predictive of treatment response in patients with chronic HCV. At the present time, the interactions between these factors and their combined effect on treatment response are not fully understood. Therefore, the evidence is insufficient to determine the effects of the technology on health outcomes and is considered experimental/investigational in nature.

SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS

American Association of the Study of Liver Diseases (AASLD)[18]
In updated guidelines for the treatment of patients with a chronic HCV genotype 1 infection, the AASLD stated that SNP genotypes near *IL28B* are a strong pretreatment predictor of SVR to dual therapy with PegIFN and RBV, as well as triple therapy with PegIFN, RBV, and a protease inhibitor. As such, they recommend that *IL28B* SNP testing be considered in cases where additional information is needed regarding the likelihood of patient response or the duration of treatment that may be required.

European Association of the Study of the Liver (EASL)[19]
In their recently updated clinical practice guidelines for the treatment of HCV, the EASL stated that *IL28B* SNP testing may assist treating physicians in assessing the probability of a patient's response to treatment with PegIFN and RBV. The level of evidence rating for this recommendation was moderate, with a weak grading for the recommendation.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this policy are listed in Table 3.

Table 3. Summary of Key Active Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
Unpublished			
NCT02297126	A prospective trial to assess cost and clinical outcomes of a clinical pharmacogenomics program.	6000	June 2018
NCT01437969	Pharmacogenomics study on IL28B genetic variants in Italian patients with HCV infection Naïve to treatment.	500	Sept 2012
NCT01441804	A randomized trial of 24-week vs. 48-week courses of peginterferon plus ribavirin for patients with genotype 1 hepatic C and IL28B CC polymorphism.	200	Aug 2014

NCT: national clinical trial

Government Regulations
National:
No national coverage determination available for IFNL3 testing.

Local:
No local coverage determination available for IFNL3 testing.

Code 81283 has a fee listed in the 2024 CMS Laboratory Fee Schedule.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are

updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Transplant-Liver
- Transplant Liver-Kidney (Combined)
- Radiofrequency Ablation of Primary or Metastatic Liver Tumors
- Specialty Pharmacy Medication Guideline for Hepatitis C Use of Interferons and Ribavirin (pharmacy policy)

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through May 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
9/1/18	6/19/18	6/19/18	Joint policy established
9/1/19	6/18/19		Routine policy maintenance, no change in policy status.
9/1/20	6/16/20		Routine policy maintenance, no change in policy status.
9/1/21	6/15/21		Routine policy maintenance, no change in policy status.
9/1/22	6/21/22		Routine policy maintenance, no change in policy status.
9/1/23	6/13/23		Routine policy maintenance, no change in policy status. Vendor managed: N/A (ds)
9/1/24	6/11/24		Routine policy maintenance, no change in policy status. Vendor managed: N/A (ds)

Next Review Date: 2nd Qtr. 2025

Pre-Consolidation Medical Policy History

Original Policy Date	Comments
BCN:	Revised:
BCBSM:	Revised:

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: INTERFERON LAMBDA 3 (IFNL3) TESTING TO PREDICT RESPONSE TO TREATMENT OF HEPATITIS C VIRUS (HCV) INFECTION

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered.
BCNA (Medicare Advantage)	See government section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.