Supplemental Material

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for *IFNL3* (*IL28B*) genotype and peginterferon alpha based regimens

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CPIC Updates

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines are published in full on the PharmGKB website (www.pharmgkb.org). Relevant information will be periodically reviewed and updated guidelines will be published online.

Focused Literature Review

A literature search of the PubMed (1966 to January 2013) and Ovid MEDLINE (1950 to January 2013) database using the keywords ((IL28B OR interleukin 28) AND (peginterferon OR pegylated-interferon alfa OR PEG/IFN) AND genotype) was performed. Only articles available in English were reviewed.

Other genes affecting PEG-interferon response

Many studies over the last three decades have evaluated genetic predictors of Hepatitis C virus (HCV) treatment response. Although the *IFNL3* genotype has emerged as the strongest predictor of treatment response, a recent systematic review found that more than forty genes have been associated with treatment response or treatment-related adverse events (1). The review did not attempt to validate the individual studies suggesting associations but was meant to provide awareness of the research. Other than the *IFNL3* genotype, these studies have not reported a consistent genetic association with HCV treatment response. Gene Ontology analysis categorized these genes into major groups of genes associated with the immune response, the inflammatory response, and the response to the virus (Table S1).

Available Genetic Test Options

Commercially available genetic testing options change over time. An updated and fully linked table is available at http://www.pharmgkb.org/gene/PA134952671#tabview=tab0&subtab=34. Furthermore, the Genetic Testing Registry (GTR) provides a central location for voluntary submission of genetic test information by providers and is available at http://www.ncbi.nlm.nih.gov/gtr/. However, at the time of the writing of this manuscript no genetic test information was available on the GTR website for *IFNL3*.

Levels of Evidence linking genotype to phenotype

The evidence summarized in Supplemental Table S4 has been graded using the three tiered system required by the Clinical Pharmacogenetics Implementation Consortium:

High: Evidence includes consistent results from well-designed, well conducted studies.

Moderate: Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence.

Weak: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.

Every effort was made to present evidence from high-quality studies, which provided the framework for the strength of therapeutic recommendations in Table 2.

Strength of Recommendations

Overall, the dosing recommendations are simplified to allow rapid interpretation by clinicians. We chose to use a slight modification of a transparent and simple system for just three categories for recommendations adopted from the rating scale for evidence-based recommendations on the use of retroviral agents (http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf): strong, where "the evidence is high quality and the desirable effects clearly outweigh the undesirable effects"; moderate, in which "there is a close or uncertain balance" as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects; and optional, in which the desirable effects are closely balanced with undesirable effects and there is room for differences in opinion as to the need for the recommended course of action.

Strong recommendation for the statement

Moderate recommendation for the statement

Optional recommendation for the statement

Supplemental Table S1. Genes associated with HCV treatment response (1)

Immune response	Inflammatory response	Response to the virus
CCR5	*APOE*	*IFNAR1*
CTLA4	*CCR5*	*IFNAR2*
CYP27B1	*IL6*	*IFNγ*
HLA-A	*IL10*	*IL6*
HLA-B	*MBL2*	*CCL5*
HLA-C	*CCL5*	*TNF*
HLA-DQB1	*TGFB1*	*TLR7*
HLA-DRB1	*TNF*	*TNK2*
HFE	*TRL7*	*MAPKAPK3*
IL6		*ADAR*
IL10		*OASL*
KIR2DL3		*EIF2AK2*
MBL2		*MX1*
TGFB1		*PSMB8*
TNF		*SPP1*
TLR7		

Supplemental Table S2. Frequencies of genotypes/alleles in major race/ethnic groups

Genotype	Caucasian (n=2042)	Asian (n=1518)	African American (n=491)	Hispanic (n=191)
rs12979860 : CC	0.38 (n=772)	0.77 (n=1166)	0.15 (n=72)	0.31 (n=60)
rs12979860 : CT	0.50 (n=1029)	0.21 (n=323)	0.48 (n=237)	0.48 (n=91)
rs12979860 : TT	0.12 (n=241)	0.02 (n=29)	0.37 (n=182)	0.21 (n=40)
rs12979860: C allele	0.63	0.87	0.39	0.55

Frequencies were calculated using the genotype information from subjects in studies by *Ge D et al* (2) and *Thompson AJ et al* (3) for Caucasians, African Americans and Hispanics and study by *Kobayashi M* (4) for Asians.

Supplemental Table S3. Frequency of genotypes/alleles by individual publications for rs12979860

Reference	Race	Study subject	CC (%)	CT (%)	TT (%)	Total (N)
Ramos *et al*. (2012) (5)	European & African		21 (32)	29 (44)	16 (24)	66
Falleti *et al*. (2012) (6)	Caucasian		76 (37)	130 (63)		206
El-Awady *et al*. (2012) (7)	Egyptian	Healthy control	48 (48)	38 (38)	14 (14)	100
		Spontaneous clearance	72 (86)	6 (7)	6 (7)	84
		Chronic HCV	14 (13)	83 (75)	13 (12)	110
		End stage liver disease	0 (0)	88 (80)	30 (20)	118
Xie *et al*. (2012) (8)	Chinese	Healthy control	85 (85)	13 (13)	2 (2)	100
		CHC patient	122 (55.5)	80 (36.4)	18 (8.1)	220
Riva *et al*. (2012) (9)	Caucasian	Sustained virological response (SVR)	28 (28)	59 (59)	13 (13)	100
		Nonsponse (NR)	0	60 (85)	11 (15)	70
Ramos *et al*. (2012) (10)	Brazilian	Acute hepatitis C with viral clearance	16 (88.9)	0 (0.0)	2 (11.1)	18
		Chronic hepatitis C	36 (30.3)	61 (51.3)	22 (18.5)	119
Poordad *et al*. (2012) (11)		Untreated-PR48	64 (29)	116 (53)	37 (17)	217
		Untreated-BOC RGT	77 (35)	103 (46)	42 (19)	222
		Untreated-BOC/PR48	55 (26)	115 (54)	44 (21)	214
		Treatment-failure-PR48	13 (25)	29 (56)	10 (19)	52

		Treatment-failure-BOC RGT	28 (28)	62 (62)	11 (11)	101
		Treatment-failure-BOC/PR48	22 (21)	66 (62)	18(17)	106
Fabris *et al*. (2012) (12)	Caucasian	With minimal or no fibrosis	26 (28)	54 (58)	13 (14)	93
		With chronic HCV infection and abnormal levels of transaminase	52 (36)	74 (52)	17 (12)	143
Martin-Carbonero *et al*. (2012) (13)	Spain	Chronic hepatitis B	29 (59)	17 (35)	3 (6)	49
		Spontaneous HBV clearance	22 (45)	21 (42)	6 (12)	49
Asselah *et al*. (2012) (14)	Egyptian, European, Sub-Saharan African	All patients	43 (26.2)	85 (51.8)	36 (22)	164
		Treated patients	22 (26.8)	43 (52.4)	17 (20.8)	82
Cariani *et al*. (2011) (15)	Caucasian		36.50%	47.60%	15.90%	170
Golden-Mason *et al*. (2011) (16)	African American		15.63%	40.62%	43.75%	55
	Caucasian		50.00%	34.62%	15.38%	46
Luo *et al*. (2013) (17)		Severe Fibrosis	1 (5)	13(65)	4(30)	30
		Mild Fibrosis	5 (50)	2 (20)	3(30)	
De la Fuente *et al*. (2013) (18)	Egyptian	Drug: Respnder	45 (71.4)	13 (20.6)	5 (7.9)	100
		Drug: Non-responder	9 (24.3)	21(56.7)	7(18.9)	

Shaker and Sakik (2012) (19)	Caucasian		17(27)	34(53)	13(20)	64
Ramos *et al*. (2012) (10)			17(27%)	39(63%)	6(10%)	68
Falleti *et al*. (2011) (20)		Control	11.20%	41.80%	47%	629
		Hepatitis Patients	14.60%	52.80%	32.60%	
Fonseca-Coronado *et al*. (2011) (21)		Donor	3	5	22	50
		Patient	16	0	4	
Bitetto *et al*. (2011) (22)	Caucasian	Drug: Responder	14(10.4%)	60(44.8%)	60 (44.8%)	211
		Drug: Non-responder	10(13.0%	51(66.2%)	16(20.8%)	
Ito *et al*. (2011) (23)	Japanese		4(1.4%)	85(29.6%)	198(69%)	287
Neukam *et al*. (2011) (24)	German &Spanish	acute	7(8.8%)	35(43.8%)	38(47.5%)	587
		chronic	46(9.5%)	243(44.7%)	218(45.8%)	
Ochi *et al*. (2011)(25)	Asian	HCV 1b	31(1.9%)	367(23%)	1198(75.1%)	2432
		HCV 2a	10(1.8%)	92(16.6%)	452(81.6%)	
		control	2(0.7%)	44(15.6%)	236(83.7%)	
Fabris *et al*. (2011) (26)	Italian	control	35(10.2%)	145(42.1%)	164(47.7%)	756
		Viral cirrhosis	8(5.8%)	58(42.0%)	72(52.2%)	
		Non-viral cirrhosis	38(13.9%)	137(50%)	99(36.1%)	
Langhans *et al*. (2011)(27)	Caucasian	Control	5	36	59	400
		Acute hepatitis	16	37	47	
		Chronic hepatitis	11	44	45	
		Self	7	39	54	
Clausen *et al*. (2011) (28)	Danish	Virus Clarence	0	15 (32%)	32 (68%)	206
		infection	30 (19%)	67 (42%)	62 (39%)	

Mangia *et al*. (2010)(29)	Caucasian	HCV infection	40(15%)	128((48%)	100(37%)	446
		control	14(8%)	90(51%)	74(42%)	
Thompson *et al*. (2010)(3)	Caucasian		139	596	436	1171
	African American		42	146	112	300
	Hispanic		34	56	26	116
Ge *et al*. (2009) (2)	Caucasian		336	433	102	871
	African American		30	91	70	191
	Hispanic		26	35	14	75
Kobayashi *et al*. (2012)(4)	Asian		1166	323	29	1518
			CC (%)	**CT/TT (%)**		**Total N**
Rizk and Derbala (2012) (30)	White & Black		13 (40%)	20 (60%)		33
Yuan *et al*. (2012) (31)		Viral Type 1	15(20%)	25(33.33%)		75
		Viral Type 3	8(10.67%)	8(10.67%)		
		Viral Type 4	5(6.67%)	4(5.33%)		
		1y4	2(2.67%)	3(4%)		
			C allele (%)	**T allele (%)**		**Total N**
Shi *et al*. (2012) (32)	Han Chinese	Healthy control	325 (95)	17 (5.0)		171
		Persistent HCV infection	1008 (95.3)	50 (4.7)		529
		Spontaneously cleared the virus	383 (97.7)	9 (2.3)		196

Supplemental Table S4. Evidence linking genotype with phenotype

Type of experimental model	Major findings	References	Level of evidence*
Clinical	*IFNL3* rs12979860 (CC genotype) is associated with increased SVR rates in HCV genotype 1 patients treated with PEG-IFNα and RBV therapy	McCarthy *et al*. (2010) (33) Montes-Cano *et al*. (2010) (34) Stattermayer *et al*. (2011) (35) Liao *et al*. (2011) (36) Chen *et al*. (2011) (37) Galmozzi *et al*. (2011) (38) Sarrazin *et al*. (2011) (39) Reiberger *et al*. (2011) (40) Bitetto *et al*. (2011) (22) de Rueda *et al*. (2011) (41) Darling *et al*. (2011) (42) Hayes *et al*. (2011) (43) Lin *et al*. (2011) (44) Patel *et al*. (2011) (45) Shi *et al.* (2012) (46) Ladero et al. (2012)(47)	High
Clinical	*IFNL3* rs8099917 (TT genotype) is associated with increased SVR rates in HCV genotype 1 patients treated with PEG-IFNα and RBV therapy	Stattermayer *et al*. (2011) (35) Tanaka *et al*. (2009) (48) Suppiah *et al*. (2009) (49) Rauch *et al*. (2010) (50) Abe *et al*. (2010) (51) Sinn *et al*. (2011) (52) Hayes *et al*. (2011) (43) Fukuhara *et al*. (2010) (53) Kurosaki *et al*. (2011) (54)	High
Clinical	*IFNL3* rs8099917 (TT genotype) is associated with increased SVR rates in HCV genotype 1 patients treated with PEG- PEG-IFNα and RBV therapy	Stattermayer *et al*. (2011) (35) Tanaka *et al*. (2099) (48) Suppiah *et al*. (2009)(49) Rauch *et al*. (2010) (50) Abe *et al*. (2010) (51) Sinn *et al*. (2011) (52) Hayes *et al*. (2011) (43) Fukuhara *et al*. (2010) (53) Kurosaki *et al*. (2011) (54)	High
Clinical	*IFNL3* rs12980275 (AA genotype) is associated with increased SVR rates in HCV genotype 1 patients treated with PEG-IFNα and RBV therapy	Fattovich *et al*. (2011) (55)	Moderate

Clinical	*IFNL3* rs12979860 is associated with early viral kinetics in patients infected with HCV during PEG- PEG-IFNα and RBV therapy	Naggie *et al*. (2012) (56) Howell *et al*. (2012) (57) Lindh *et al*. (2011) (58) Bochud *et al*. (2011) (59) Chu *et al*. (2012) (60)	Moderate
Clinical	*IFNL3* rs12979860 (CC genotype) is associated with increased SVR rates in HCV genotype 2 patients treated with PEG-IFNα and RBV therapy	Mangia *et al*. (2010) (29) Sarrazin *et al*. (2011) (39) Bitetto *et al*. (2011) (22) de Rueda *et al*. (2011) (41)	Moderate
Clinical	*IFNL3* rs8099917 (TT genotype) is associated with increased SVR rates in HCV genotype 2 patients treated with PEG-IFN/RBV therapy	Kawaoka *et al*. (2011) (61) Sinn *et al*. (2011) (52) Sarrazin *et al*. (2011) (39) Shi *et al*. (2012) (46)	Moderate
Clinical	*IFNL3* rs12979860 (CC genotype) is associated with increased SVR rates in HCV genotype 3 patients treated with PEG-IFNα and RBV therapy	Mangia *et al* (2010) (29) Scherzer *et al*. (2011) (62) Sarrazin *et al*. (2011) (39) Moghaddam *et al* (2011) (63) Bitetto *et al*. (2011) (22) de Rueda *et al*. (2011) (41)	Moderate
Clinical	*IFNL3* rs8099917 (TT genotype) is associated with increased SVR rates in HCV genotype 3 patients treated with PEG- PEG-IFNα and RBV therapy	Scherzer *et al*. (2011) (62) Sarrazin *et al*. (2011) (39) Shi *et al*. (2012) (46)	Moderate
Clinical	*IFNL3* rs12979860 (CC genotype) is associated with increased SVR rates in HCV genotype 4 patients treated with PEG-IFNα and RBV therapy	Stattermayer *et al*. (2011) (35) Ge *et al*. (2009) (2) Kawaoka *et al*. (2011) (61) Reiberger *et al*. (2011) (40) Bitetto *et al*. (2011) (22) de Rueda *et al*. (2011) (41) Shi *et al*. (2012) (46) Asselah *et al*. (2012) (14)	High
Clinical	*IFNL3* rs8099917 (TT genotype) is associated with increased SVR rates in HCV genotype 4 patients treated with PEG-IFNα and RBV therapy	Stattermayer *et al*. (2011) (35)	Low

Clinical	*IFNL3* rs12979860 is associated with spontaneous clearance of acute HCV	Thomas *et al*. (2009)(64) Ruiz-Extremera *et al*. (2011) (65) Tillmann *et al*. (2010) (66) Knapp *et al*. (2011) (67)	Moderate
Clinical	*IFNL3* rs8099917 is associated with spontaneous clearance of acute HCV infection	Rauch *et al*. (2010) (50)	Low
In vitro	Effect of *IFNL3* variation on *IFNL3* gene expression	Ge *et al*. (2009) (2) Suppiah *et al*. (2009) (49) Honda *et al*. (2010) (68) Urban *et al*. (2010) (69)	Moderate
In vitro	Effect of *IFNL3* variation on intrahepatic interferon-stimulated genes (ISG) expression	Honda *et al*. (2010) (68) Urban *et al*. (2010) (69) Dill *et al*. (2011) (70) Abe *et al*. (2011) (71) McGilvray *et al*. (2012) (72)	Moderate
In vitro	IFN lamda-3 inhibits HCV replication	Ank *et al*. (2006) (73)	Low

Evidence Review Table: IL28B = interleukin-28-beta; SVR = Sustained Virologic Response; HCV = Hepatitis C Virus; PEG-IFNα = Pegylated Interferon; RBV = Ribavirin; ISG = Interferon-Stimulated-Genes.

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