CPIC Guideline Update on PharmGKB

For: "Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Ivacaftor Therapy in the Context of *CFTR* Genotype"

Date: June 2017

URL: http://www.pharmgkb.org/guideline/PA166114461

Description: The FDA-approved drug label for ***ivacaftor*** has been updated to include an additional 23 *CFTR* variants, bringing the total number of indicated variants to 33:

E56K (rs397508256)	L206W (rs121908752)	S945L (rs397508442)	D1152H (rs75541969)
P67L (rs368505753)	R347H (rs77932196)	S977F (rs141033578)	G1244E (rs267606723)
R74W (rs115545701)	R352Q (rs121908753)	F1052V (rs150212784)	S1251N (rs74503330)
D110E (rs397508537)	A455E (rs74551128)	K1060T (rs397508513)	S1255P (rs121909041)
D110H (rs113993958)	S549N (rs121908755)	A1067T (rs121909020)	D1270N (rs11971167)
R117C (rs77834169)	S549R (rs121908757, rs121909005)	G1069R (rs200321110)	G1349D (rs193922525)
R117H (rs78655421)	G551D (rs75527207)	R1070Q (rs78769542)	
G178R (rs80282562)	G551S (rs121909013)	R1070W (rs202179988)	
E193K (rs397508759)	D579G (rs397508288)	F1074L (rs186045772)	

Consequently, the CPIC guideline annotation on PharmGKB, including Table 1 and Figure 1, has been updated to include these variants.

Please see the updated guideline at: http://www.pharmgkb.org/guideline/PA166114461

The variant listed above was not discussed in the 2014 guideline publication that follows.

CPIC Guideline Update on PharmGKB

For: "Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Ivacaftor Therapy in the Context of *CFTR* Genotype"

Date: May 2016

URL: http://www.pharmgkb.org/guideline/PA166114461

Description:

The FDA-approved drug label for ***ivacaftor*** has been updated to include the *CFTR* variant R117H (rs78655421). Consequently, the CPIC guideline annotation on PharmGKB, including Table 1 and Figure 1, has been updated to include this variant. Additionally, the updated drug label indicates ivacaftor use for patients 2 years and older; previously it was indicated only for patients 6 years and older.

Please see the updated guideline at: http://www.pharmgkb.org/guideline/PA166114461

The variant listed above was not discussed in the 2014 guideline publication that follows. Additionally, the 2014 CPIC guideline dosing recommendations were published prior to the age change on the FDA-approved drug label, and are therefore written for patients age 6 years or older.

CPIC Guideline Update on PharmGKB

For: "Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Ivacaftor Therapy in the Context of *CFTR* Genotype"

Date: April 2014

URL: http://www.pharmgkb.org/guideline/PA166114461

Description:

After the submission and review of this CPIC guideline, the FDA-approved drug label for ***ivacaftor*** has been updated to include additional variants. Consequently, the CPIC guideline annotation on PharmGKB, including Table 1 and Figure 1, has been updated to include the following *CFTR* variants: G1244E (rs267606723), G1349D (rs193922525), G178R (rs80282562), G551S (rs121909013), S1251N (rs74503330), S1255P (rs121909041), S549N (rs121908755) and S549R (rs121908757 and rs121909005).

Please see the updated guideline at: http://www.pharmgkb.org/guideline/PA166114461

The specific variants listed above were not discussed in the 2014 guideline publication that follows.

Supplemental Material

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Ivacaftor Therapy in the context of *CFTR* Genotype

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Literature Review

We searched the PubMed database (1966 to June 2013 and Ovid MEDLINE (1950 to June 2013) for keywords ((((((((((((((((((cftr) OR atp binding cassette sub family g member 7) OR atp binding cassette sub family g, member 7) OR atp binding cassette transporter subfamily a member 7) OR atp-binding cassette, subfamily c member 7) OR camp-dependent chloride channel) OR channel conductance-controlling atpase) OR cystic fibrosis transmembrane conductance regulator) OR cystic fibrosis transmembrane conductance regulator) OR atp-binding cassette AND (sub-family c, member 7)) OR ABC35) OR ABCC7) OR CF) OR cftr/mrp) OR MRP7) OR tnr-cftr) OR dJ760C5.1) OR OTTHUMP00000196524)) AND (((ivacaftor) OR vx-770) OR kalydeco) and ((ivacaftor) OR vx-770) OR Kalydeco. Results were limited to those available in English.

Available Genetic Test Options

Commercially available genetic testing options change over time. Below is some information that may assist in evaluating options. Some laboratories offering clinical testing may be listed at: http://pharmgkb.org/views/viewGeneticTests.action. 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/.

Genetic Test Interpretation

Diagnosis of Cystic Fibrosis

Prenatal CF screening is offered during pregnancy as part of newborn screens in all fifty states in the US. Most newborn screening tests incorporate genetic testing of common *CFTR* variants with serum tests of CFTR function (serum trypsinogen levels, which reflect CFTR function in the pancreas). Positive newborn screens are typically followed up with sweat testing (measuring the concentration of chloride in sweat, which is elevated in CF) and frequently with confirmatory genetic testing (that typically includes many more CF-causing variants than are usually captured in various newborn screening panels). Commercially available genetic tests often offer tiered testing, initially screening for common *CFTR* variants followed by more extensive panels,

culminating in full *CFTR* gene sequencing. The diagnosis of CF is made by clinical evidence of CF disease (eg: failure to thrive, recurrent respiratory infections, chronic sinusitis) coupled with two CF causing variants in *CFTR* and/or evidence of CFTR dysfunction (ie: elevated sweat chloride). While genetic testing identifies >95% of disease-causing variants in *CFTR*, the diagnosis of CF does not require identifying two *CFTR* variants. Furthermore, a rising number of newborns have abnormal newborn screens, but fail to meet the full diagnostic criteria for CF. Examples include patients with only one well characterized variant and intermediate sweat chloride testing (i.e. above the normal range, but failing to cross the threshold established to diagnose CF), or patients with polymorphisms in the *CFTR* gene of unknown clinical significance (identified during full *CFTR* gene sequencing). These patients are categorized as having CFTR-Related Metabolic Syndrome, and are often followed in CF clinics to determine if they eventually meet full diagnostic criteria (ie: elevated sweat chloride levels above the CF diagnostic threshold, abnormal nasal potential difference measurements and CF-associated disease manifestations).

Genetic test panels

The Cystic Fibrosis Mutation Database and CFTR2 websites provide a comprehensive resource of known variants within the *CFTR* gene (http://www.genet.sickkids.on.ca/GenomicDnaSequencePage.html and http://www.cftr2.org/). Numerous companies and clinics offer testing of specific *CFTR* variants or sequence analysis – see PharmGKB (http://www.pharmgkb.org/views/viewGeneticTests.action) and the Genetic Test Registry (GTR) for further information (http://www.ncbi.nlm.nih.gov/gtr). The American College of Medical Genetics (ACMG) recommends a panel of 23 variants for population screening of CF carrier status (Supplemental Table S1). This was originally established in 2001 as a standard panel of 25 known CF-causing variants with an allele frequency of equal to or more than 0.1% in the USA (1), and revised to 23 variants in 2004 as a consequence of new information on allele frequencies and experience in clinical practice (2, 3). The panel includes the F508del and G551D variants (2).

Levels of Evidence

The evidence summarized in Supplemental Table S5 is graded using a scaled modified slightly from Valdes et al. (4)

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.

Strength of Recommendations

CPIC's dosing recommendations are based on weighting the evidence from a combination of preclinical functional and clinical data, as well as on some existing disease-specific consensus guidelines (5).

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. Common *CFTR* Variants[a] and Class

Legacy Name[b]	Amino Acid Position[b, c]	cDNA Position[b, d, g]	Reference Sequence ID[b]	Class[e]
ΔF508 (also known as F508del)	p.Phe508del	c.1521_1523delCTT or c.1520_1522delTCT	rs113993960[f] (CTT deletion) rs199826652[f] (TCT deletion)	II, VI
G542X	p.Gly542Ter	c.1624G>T	rs113993959	I
G551D	p.Gly551Asp	c.1652G>A	rs75527207	III
N1303K	p.Asn1303Lys	c.3909C>G	rs80034486	II
W1282X	p.Trp1282Ter	c.3846G>A	rs77010898	I
R117H	p.Arg117His	c.350G>A	rs78655421	IV
R553X	p.Arg553Ter	c.1657C>T	rs74597325	I
1717-1G->A	N/A	c.1585-1G>A	rs76713772	I
621+1G->T	N/A	c.489+1G>T	rs78756941	I
2789+5G->A	N/A	c.2657+5G>A	rs80224560	V
3849+10kbC->T	N/A	c.3717+12191C>T	rs75039782	V
R1162X	p.Arg1162Ter	c.3484C>T	rs74767530	I
G85E	p.Gly85Glu	c.254G>A	rs75961395	II
3120+1G->A	N/A	c.2988+1G>A	rs75096551	I
ΔI507	p.Ile507del	c.1519_1521delATC	rs121908745	II
1898+1G->A	N/A	c.1766+1G>A	rs121908748	I
3659delC	p.Thr1176Thrfs frameshift	c.3528delC	rs121908747	I
R347P	p.Arg347Pro	c.1040G>C	rs77932196	IV
R560T	p.Arg560Thr	c.1679G>C	rs80055610	III
R334W	p.Arg334Trp	c.1000C>T	rs121909011	IV
A455E	p.Ala455Glu	c.1364C>A	rs74551128	V
2184delA	p.Lys684Asnfs frameshift	c.2052delA	rs121908746	I
711+1G->T	N/A	c.579+1G>T	rs77188391	I
5T	N/A (intron 9)	c.1210-12T(5_9) (AJ574948.1:g152T(5_9)[g], (poly-T tract variations; 5T, 7T or 9T).	rs200454589[h]	V

[a]This list of *CFTR* genotypes includes the 23 *CFTR* variants recommended by the American College of Medical Genetics (ACMG) Cystic Fibrosis Carrier Screening Working Group that should be tested to determine carrier status as a part of population screening programs (2). The

5T variant is not included in this list; however, it has been added here to provide further information regarding this polymorphism.
[b]Information sourced from dbSNP http://www.ncbi.nlm.nih.gov/projects/SNP/ and/ or http://www.genet.sickkids.on.ca/Home.html or http://www.cftr2.org/acmg_mutations.php (accessed 3rd April 2013).
[c]Protein reference sequence NP_000483.3.
[d]cDNA reference sequence NM_000492.3. The positions given take into account that the initiation codon begins at position 133, therefore for example c.1521_1523 is position 1653_1655 on reference sequence NM_000492.3.
[e]As defined in (6).
[f] The F508del *CFTR* variant can result from a CTT deletion at cDNA position NM_000492.3.c.1521_1523 (rs113993960) or a TCT deletion at cDNA position NM_000492.3.c.1520_1522 (rs199826652). Both result in the same sequence change: ATC ATC TTT GGT GTT > ATC ATT GGT GTT, corresponding to a deletion of Phe at amino acid position 508. Here we include both rsIDs from dbSNP which result in the same deletion of Phe at position 508; rs113993960 is deletion CTT, the cDNA reference position name that is referred to on the CFTR1 website (c.1521_1523delCTT) and is flagged on dbSNP as "with pathogenic allele" due to its association with cystic fibrosis. Rs199826652 is deletion TCT and is more likely to be called in sequencing data due to the left justification of indels; hence this has a minor allele frequency from 1000 genomes.
[g]See reference (7) for more details regarding exon numbering and correct nomenclature for nucleotide repeat sequences.
[h]This rsID describes the 7T and 9T repeats but not 5T.

Supplemental Table S2. Frequencies[1] of alleles in Cystic Fibrosis patients by major race/ethnic groups[2]

CFTR Variant	Caucasian	Mediter-ranean	South American	African	Middle Eastern	Mexican
ΔF508	0.65692	0.48487	0.38614	0.41734	0.20802	0.43580
G542X	0.02271	0.05282	0.03543	0.01656	0.01579	0.06462
G551D	0.02069	0.00205	0.00347	0.02489	0.001361	0.00434
N1303K	0.01173	0.03778	0.00914	0.00203	0.07527	0.01762
W1282X	0.00875	0.01069	0.01283	0.00060	0.07512	0.00176
R117H	0.01581	0.00538	-	0.03045	0.00963	0.00188
R553X	0.01220	0.00541	0.01137	0.01972	0.00108	0.00812
1717-1G->A	0.00754	0.00847	0.00671	0.01358	0	0.02117
621+1G->T	0.00633	0.01308	0.00691	0.00370	0.00278	0.00587
2789+5G->A	0.00212	0.01156	0.00408	-	0.01846	-
3849+10kbC->T	0.00292	0.00214	0.00652	0.00057	0	0.01440
R1162X	0.00456	0.02655	0.01657	0.00374	0.01390	0.00552
G85E	0.00226	0.00564	0.01595	-	0.00278	0.00458
3120+1G->A	0.00292	0.00237	0.01599	0.07632	0.04971	0.00787
ΔI507	0.00306	0.00322	0.00227	0.00636	0	0.00714
1898+1G->A	0.00141	0.00132	-	0.01030	-	-
3659delC	0.00443	0	-	-	-	0.00148
R347P	0.00352	0.00268	-	0.00020	-	0.00040
R560T	0.00333	0	-	0.00211	0	0
R334W	0.00150	0.01134	0.01520	0.00543	0.00933	0.02608
A455E	0.00262	0	-	0	-	0.00017

2184delA	0.00131	0.00123	-	0.00017	0.02842	-
711+1G->T	0.00190	0.00577	-	-	0.05810	-

[1]Average frequencies are reported based on the average from the actual numbers of subjects with each allele reported in multiple studies. See Supplemental Table S3 for details and references.
[2]Race/ethnic group designations correspond to those indicated in Supplemental Table S3.

Supplemental Table S3. *CFTR* minor allele frequencies in cystic fibrosis patients

Pooled Grouping	Ethnicity	*CFTR* variants minor allele frequency (%)																							Total patients
		F508del	G542X	G551D	N1303K	W1282X	R117H	R553X	1717-1G->A	621+1G->T	2789+5G->A	3849+10kbC->T	R1162X	G85E	3120+1G->A	I507del	1898+1G->A	3659delC	R347P	R560T	R334W	A455E	2184delA	711+1G->T	
African	Afro-American (8)	31.0	0.9	0.9	0.5	0.0	0.0	1.4	0.9	0.0	0.0	0.0	0.5	0.0	8.8	0.0	0.0	0.0	0.0	0.5	0.5	0.0	0.0	0.9	108
African	Afro-American (9)	48.0	0.7	0.7	0.0	0.0	0.0	0.0	0.7	0.0	-	0.0	-	-	12.2	0.7	-	-	0.0	0.0	0.7	0.0	-	-	74
African	Afro-American (10)	60.6	-	6.1	-	-	12.1	3.0	-	-	-	-	-	-	0.0	-	3.0	-	-	-	-	-	0.0	-	33
African	Afro-American (11)	25.0	3.6	3.6	0.0	0.0	-	3.6	3.6	-	-	-	0.0	-	-	0.0	-	-	-	-	-	-	-	-	14
African	Afro-American (2)	44.1	1.5	1.2	0.4	0.2	0.1	1.9	0.4	1.1	0.0	0.2	0.7	0.1	9.6	1.9	0.1	0.1	0.1	0.2	0.5	0.0	0.1	0.0	-
Average African		**41.73**	**1.66**	**2.49**	**0.20**	**0.06**	**3.05**	**1.97**	**1.39**	**0.37**	**0.00**	**0.06**	**0.37**	**0.06**	**7.63**	**0.64**	**1.03**	**0.03**	**0.02**	**0.21**	**0.54**	**0.00**	**0.02**	**0.46**	**-**
Caucasian	American (12)	75.3	1.9	1.9	1.5	0.4	0.8	0.0	1.1	1.1	-	-	-	0.8	-	0.0	-	-	-	0.8	-	1.1	-	3.0	139
Caucasian	American (9)	66.2	2.3	2.0	1.3	2.7	0.5	1.0	0.4	0.8	-	0.6	-	-	0.0	0.1	-	-	0.3	0.2	0.1	0.1	-	-	4357
Caucasian	American (11)	60.5	6.2	3.8	1.9	0.5	-	0.5	1.9	-	-	-	0.0	-	-	0.0	-	-	-	-	-	-	0.0	-	105
Caucasian	American (11)	66.7	16.7	0.0	0.0	0.0	-	0.0	0.0	-	-	-	8.3	-	-	0.0	-	-	-	-	-	-	0.0	-	6
Caucasian	American (13)	75.9	2.4	2.4	1.2	1.6	0.6	0.8	0.4	1.2	0.5	0.4	0.4	0.2	0.1	1.5	0.2	0.4	0.4	0.5	0.2	0.1	0.2	0.1	1969
Caucasian	American (13)	68.9	2.2	2.1	1.3	1.4	0.8	1.0	0.5	1.9	0.5	0.7	0.1	0.4	0.1	0.3	0.1	0.3	0.5	0.3	0.1	0.5	0.1	0.8	-
Caucasian	American (14)	74.0	1.5	1.5	3.0	1.0	0.5	2.0	1.5	1.5	1.0	0.5	-	0.5	-	-	1.0	-	-	-	-	0.5	0.5	0.5	100
Caucasian	American (15)	70.1	6.0	5.0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	139
Caucasian	American (2)	72.4	2.3	2.3	1.3	1.5	0.7	0.9	0.5	1.6	0.5	0.6	0.2	0.3	0.1	0.9	0.2	0.3	0.5	0.4	0.1	0.3	0.2	0.4	-
Caucasian	Australian (16)	70.9	2.3	4.6	1.5	-	13.8	0.4	0.4	1.9	0.4	0.4	0.4	-	0.4	0.8	-	0.8	0.4	-	-	-	0.4	-	261

Caucasian	Austrian (17)	63.7	2.1	1.1	0.6	0.2	0.2	0.4	0.2	0.4	0.0	0.0	1.9	0.0	0.0	0.0	0.0	0.2	0.4	0.0	0.0	0.0	0.0	0.0	-
Caucasian	Austrian (18)	74.6	2.4	1.6	-	0.0	-	0.0	0.8	-	0.0	0.0	0.0	-	-	0.0	-	-	1.6	-	0.0	-	-	-	63
Caucasian	Belarusian (17)	38.5	0.0	0.0	0.0	15.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-
Caucasian	Belgian (17)	75.5	2.7	0.2	2.9	1.5	0.4	1.0	1.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.0	0.0	0.2	0.4	0.2	0.0	-
Caucasian	Belgian (19)	74.2	1.6	0.0	2.4	-	-	2.4	2.4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	62
Caucasian	British (17)	75.3	1.7	3.1	0.5	0.2	0.5	0.5	0.6	0.9	0.0	0.1	0.0	0.2	0.0	0.3	0.5	0.1	0.1	0.4	0.0	0.0	0.0	0.0	-
Caucasian	British (20)	75.3	1.7	3.1	0.5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Caucasian	Bulgarian (21)	65.6	3.1	0.0	5.3	0.8	-	-	0.4	-	0.4	1.1	-	0.8	-	-	-	-	1.1	-	-	-	0.4	-	131
Caucasian	Bulgarian (17)	64.2	4.7	0.0	5.1	0.8	0.0	0.0	0.8	0.4	0.8	0.8	0.0	2.0	0.0	0.0	0.0	0.0	2.4	0.0	0.0	0.0	0.0	0.0	-
Caucasian	Canadian (22)	58.7	1.9	2.6	0.7	0.7	0.7	0.4	0.5	1.1	-	-	-	-	-	0.5	-	0.1	0.1	0.5	0.3	0.2	-	-	538
Caucasian	Canadian (23)	63.2	1.6	4.5	0.4	0.0	14.6	0.8	1.6	1.2	0.8	2.4	0.0	0.8	1.2	0.4	0.4	0.0	0.0	0.0	0.4	0.8	0.4	0.4	124
Caucasian	Czech (17)	69.7	2.1	3.4	2.6	0.5	0.2	0.2	0.3	0.2	0.3	0.3	0.3	0.2	0.0	0.0	1.9	0.2	0.9	0.0	0.2	0.0	0.0	0.0	-
Caucasian	Danish (17)	87.2	0.6	0.1	1.0	0.1	0.3	0.0	0.0	0.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.6	0.0	0.0	0.3	0.0	0.0	0.0	-
Caucasian	Dutch (17)	74.4	1.3	0.1	0.9	0.7	0.1	1.2	1.5	0.0	0.0	0.0	0.9	0.0	0.0	0.1	0.0	0.1	0.1	0.0	0.0	3.3	0.0	0.0	-
Caucasian	English (24)	42.3	-	7.7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	13
Caucasian	Estonian (17)	64.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-
Caucasian	Estonian (25)	51.7	0.0	0.0	0.0	0.0	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-	0.0	0.0	1.7	0.0	0.0	0.0	0.0	0.0	0.0	30
Caucasian	Ex-Yugoslavian (17)	70.0	3.0	0.0	1.0	0.5	0.0	0.0	0.0	0.5	0.0	0.0	3.0	0.0	0.0	0.0	0.0	0.0	0.5	0.0	0.0	0.0	0.0	0.0	-
Caucasian	Finnish (17)	46.2	1.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-
Caucasian	Finnish (26)	36.3	1.0	0.0	0.0	0.0	2.0	0.0	0.0	0.0	0.0	0.0	1.0	0.0	0.0	0.0	0.0	5.9	0.0	0.0	0.0	0.0	0.0	0.0	51
Caucasian	French (27)	68.9	3.3	0.3	1.8	1.5	0.1	0.8	1.3	0.1	-	-	0.5	0.3	-	0.3	0.1	0.3	0.4	-	0.4	0.1	0.1	0.7	600
Caucasian	French (28)	63.9	5.8	0.4	0.7	0.4	-	0.4	1.5	0.4	-	-	0.7	0.4	-	1.1	0.0	0.4	0.4	-	1.1	-	1.1	-	137
Caucasian	French (29)	67.2	2.9	1.0	2.1	0.9	0.0	0.9	1.3	-	-	0.4	0.4	-	-	0.7	-	-	-	-	-	-	-	0.4	3710
Caucasian	French (17)	66.8	3.1	0.5	1.4	0.6	0.0	0.9	1.6	0.1	0.1	0.1	0.4	0.1	0.3	0.6	0.1	0.2	0.2	0.0	0.2	0.0	0.1	0.1	-

Caucasian	French (30)	67.9	2.5	0.7	2.0	0.6	-	0.8	1.2	-	0.6	-	0.4	-	-	0.5	-	-	-	-	-	-	0.3	-	-
Caucasian	French (31)	70.5	1.7	3.0	3.0	0.4	1.7	0.9	0.9	0.9	0.9	-	-	-	-	0.9	-	-	-	-	-	-	-	-	117
Caucasian	French (32)	74.8	0.6	3.7	1.4	0.4	0.5	0.4	1.0	0.6	0.8	0.0	0.1	0.3	0.1	0.4	0.0	0.0	0.1	0.0	0.0	-	0.1	-	389
Caucasian	German (33)	72.0	1.4	1.0	2.3	0.7	0.3	2.3	0.9	0.1	0.9	1.0	0.3	-	-	0.1	-	0.6	1.6	-	0.3	0.1	0.3	-	-
Caucasian	German (17)	72.7	1.1	0.7	1.3	0.2	0.1	1.9	0.5	0.1	0.1	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.5	0.0	0.2	0.1	0.4	0.0	-
Caucasian	German (34)	66.8	4.1	0.5	2.7	-	0.0	3.2	1.8	-	-	-	0.0	-	-	0.0	-	-	-	-	-	0.0	-	-	110
Caucasian	German (35)	71.5	1.2	0.9	1.3	-	-	1.9	0.4	-	-	0.4	-	-	-	-	-	-	0.6	-	-	-	0.4	-	641
Caucasian	Hungarian (17)	43.9	1.8	0.0	1.8	1.8	0.0	0.0	1.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-
Caucasian	Hungarian (36)	64.3	1.2	0.0	1.2	1.2	-	2.4	1.2	0.0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	42
Caucasian	Irish (37)	72.5	1.0	6.9	0.4	-	2.0	0.0	0.6	0.8	-	-	-	-	-	0.4	-	0.4	-	0.8	-	-	-	-	253
Caucasian	Irish (38)	76.7	0.0	8.4	0.0	-	13.4	-	-	0.5	-	-	-	-	-	-	-	0.5	-	-	-	-	-	-	101
Caucasian	Irish (39)	75.8	0.5	8.1	0.0	-	2.9	0.2	2.3	0.1	-	-	-	0.1	-	0.5	0.2	-	-	0.5	-	-	-	-	-
Caucasian	Irish (17)	72.7	1.0	6.9	0.4	0.0	2.0	0.0	0.6	0.8	0.0	0.0	0.0	0.0	0.0	0.4	0.0	0.4	0.0	0.8	0.0	0.0	0.0	0.0	-
Caucasian	Irish (40)	58.0	1.7	4.0	0.4	-	2.1	0.2	-	1.7	-	-	-	-	-	0.8	-	0.2	-	2.5	-	-	-	-	124
Caucasian	Irish (41)	68.0	2.2	5.1	0.0	0.0	4.1	0.5	-	2.2	0.0	0.0	0.0	0.0	0.0	1.7	-	0.0	-	2.9	-	-	-	0.0	206
Caucasian	Irish (32)	77.4	0.5	7.1	0.3	0.0	2.7	0.1	0.6	1.4	0.0	0.2	0.1	0.2	0.0	0.7	0.1	0.1	0.0	2.1	0.1	-	0.1	-	770
Caucasian	Norwegian (17)	66.7	0.6	1.2	0.6	0.0	3.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-
Caucasian	Norwegian (42)	62.2	0.7	2.0	1.0	0.3	4.1	0.3	-	0.3	-	0.3	0.3	-	-	0.3	-	1.7	-	-	-	-	-	-	148
Caucasian	Polish (17)	66.2	2.3	0.7	2.0	0.2	0.0	1.4	1.6	0.0	0.0	0.5	0.0	0.0	0.0	0.5	0.0	0.0	0.5	0.9	0.0	0.0	0.0	0.0	-
Caucasian	Portuguese (17)	44.5	1.3	0.0	0.7	0.0	0.0	0.0	0.0	0.2	0.0	0.0	0.2	0.2	0.0	0.2	0.0	0.0	0.0	0.0	0.7	0.0	0.0	0.2	-
Caucasian	Reunion Island (43)	52.2	0.7	1.4	0.0	-	-	-	0.7	-	-	-	-	-	8.0	-	-	-	-	-	-	2.2	-	-	69
Caucasian	Romanian (17)	42.0	0.0	0.0	0.0	2.0	0.0	4.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-
Caucasian	Russian (17)	61.8	0.7	0.2	0.4	0.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.0	0.9	0.0	0.2	0.0	-
Caucasian	Scottish (44)	68.9	5.5	7.1	0.0	-	2.5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	183
Caucasian	Scottish (45)	82.1	1.7	6.8	0.0	-	0.0	0.9	0.9	0.9	-	-	-	-	-	0.9	-	-	-	0.0	-	-	-	-	-

Caucasian	Slovakian (17)	55.9	7.5	0.0	3.5	1.6	0.0	4.3	0.0	0.0	0.0	1.2	0.0	0.0	0.0	0.0	0.4	0.0	1.2	0.0	0.0	0.0	0.0	0.0	-
Caucasian	Swedish (17)	73.3	0.6	0.0	0.0	0.0	0.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	3.0	0.0	0.0	0.0	0.0	0.0	0.0	-
Caucasian	Swiss (17)	43.2	3.2	0.0	1.1	0.0	0.0	24.2	2.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-
Caucasian	Ukrainian (17)	80.4	0.0	1.8	0.0	0.0	0.0	3.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-
Caucasian	Ukrainian (46)	50.0	-	0.3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	170
Caucasian	Welsh (47)	72.6	2.4	3.0	0.5	0.0	0.5	1.1	0.5	5.1	-	-	-	1.4	-	0.5	-	-	0.0	0.3	-	-	-	-	184
Caucasian	Yugoslavian (48)	70.4	3.7	0.0	-	-	-	0.0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	54
Average Caucasian		**65.69**	**2.27**	**2.07**	**1.17**	**0.88**	**1.58**	**1.22**	**0.75**	**0.63**	**0.21**	**0.29**	**0.46**	**0.23**	**0.29**	**0.31**	**0.14**	**0.44**	**0.35**	**0.33**	**0.15**	**0.26**	**0.13**	**0.19**	-
Mexican	American (49)	47.9	2.1	2.1	6.3	0.0	0.0	2.1	-	-	-	0.0	-	-	-	-	-	-	-	-	6.3	-	-	-	24
Mexican	American (11)	30.0	20.0	0.0	0.0	0.0	-	0.0	10.0	-	-	-	0.0	-	-	-	-	-	-	-	-	-	-	-	5
Mexican	American (8)	37.1	3.5	0.3	0.0	0.0	0.3	0.3	0.3	0.3	0.6	0.9	0.6	0.6	2.2	0.3	0.0	0.3	0.0	0.0	3.5	0.0	0.0	0.6	159
Mexican	Mexican (50)	40.7	6.2	0.5	2.1	0.0	0.5	0.5	-	-	-	0.5	0.0	0.5	0.0	2.6	-	-	-	-	-	-	-	-	97
Mexican	American (51)	45.7	5.4	0.0	-	0.8	0.0	0.8	0.0	0.0	-	2.3	1.6	-	-	0.0	-	0.0	0.0	0.0	1.6	-	-	-	-
Mexican	American (2)	54.4	5.1	0.6	1.7	0.6	0.1	2.8	0.3	0.3	0.2	1.6	0.6	0.2	0.2	0.7	0.1	0.1	0.2	0.0	1.8	0.1	0.2	0.2	-
Mexican	Mexican (52)	47.8	4.4	0.0	1.1	0.0	-	0.0	-	1.1	-	2.2	-	-	-	-	-	-	-	-	-	-	-	-	45
Mexican	Mexican (53)	45.0	5.0	0.0	1.3	0.0	-	0.0	0.0	1.3	-	2.5	-	-	-	0.0	-	-	0.0	0.0	0.0	0.0	-	-	40
Average Mexican		**43.58**	**6.46**	**0.43**	**1.76**	**0.18**	**0.19**	**0.81**	**2.12**	**0.59**	**0.39**	**1.44**	**0.55**	**0.46**	**0.79**	**0.71**	**0.03**	**0.15**	**0.04**	**0.00**	**2.61**	**0.02**	**0.08**	**0.43**	-
Mediterranean	Greek (17)	52.3	3.9	0.4	3.3	0.4	1.2	0.2	0.0	4.5	1.8	0.2	0.0	1.0	0.6	0.4	0.4	0.0	0.2	0.0	1.2	0.0	0.0	0.0	--
Mediterranean	Greek (54)	52.7	4.3	0.5	3.8	0.0	1.1	0.3	-	4.6	-	-	-	-	-	-	-	-	-	-	1.1	-	-	-	184
Mediterranean	Greek (55)	52.2	4.0	0.4	3.2	0.4	1.2	0.2	-	4.6	1.8	0.2	-	1.0	0.6	0.4	0.4	-	0.2	-	1.2	-	-	-	250
Mediterranean	Italian (56)	47.6	2.7	0.4	4.0	0.9	-	1.3	2.2	0.9	1.3	0.4	9.8	1.3	-	-	-	-	0.4	-	-	-	-	-	133
Mediterranean	Italian (57)	56.4	5.7	0.0	6.8	3.8	0.0	1.1	2.3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	132
Mediterranean	Italian (58)	51.5	5.9	0.0	7.3	2.2	-	1.5	1.8	0.0	0.7	0.9	0.0	0.3	-	0.0	-	0.0	0.5	-	0.1	-	-	0.7	371
Mediterranean	Italian (17)	50.9	4.4	0.0	4.4	1.2	0.0	0.9	1.7	0.3	0.0	0.0	2.0	0.3	0.0	0.1	0.0	0.0	0.4	0.0	0.2	0.0	0.0	0.0	-
Mediterranean	Italian (59)	51.1	4.8	0.1	4.8	1.2	-	1.2	2.1	0.4	-	0.1	2.4	0.4	-	0.1	-	-	0.6	-	0.3	-	-	-	1746

Mediterranean	Moroccan (60)	72.7	0.0	0.0	0.0	0.0	-	-	0.0	-	-	0.0	-	0.0	-	-	-	-	-	-	-	-	-	-	-
Mediterranean	S European (61)	-	12.0	0.5	6.5	1.1	-	0.2	-	-	-	-	7.2	-	-	0.0	-	-	0.3	-	0.9	-	-	-	-
Mediterranean	Spanish (62)	53.2	8.4	0.3	2.7	0.8	0.2	0.3	0.1	0.5	0.9	0.4	1.6	0.9	-	0.8	-	-	0.2	-	1.6	-	-	1.7	640
Mediterranean	Spanish (63)	50.6	8.0	0.4	2.4	0.6	-	0.0	0.1	0.3	0.7	-	1.9	0.8	-	0.5	-	-	0.0	0.0	1.1	-	0.4	1.2	486
Mediterranean	Spanish (17)	54.4	7.7	0.4	2.5	0.5	0.2	0.4	0.1	0.4	0.7	0.1	1.3	0.7	0.0	0.3	0.0	0.0	0.0	0.0	0.9	0.0	0.3	1.0	-
Mediterranean	Spanish (64)	43.5	11.4	0.0	0.0	1.0	1.0	0.0	0.0	0.0	2.3	0.0	3.0	0.0	-	1.0	0.0	0.0	0.0	0.0	5.0	0.0	0.0	0.0	-
Mediterranean	Turkish (17)	34.8	2.8	0.0	6.4	0.0	0.0	0.0	0.0	0.0	1.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-
Mediterranean	Turkish (65)	23.5	3.6	0.0	2.4	3.0	-	-	0.6	0.6	-	-	-	-	-	-	-	-	0.6	-	-	-	-	-	83
Mediterranean	Turkish (66)	28.4	0.0	0.0	3.7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	67
Average Mediterranean		**48.49**	**5.28**	**0.20**	**3.78**	**1.07**	**0.54**	**0.54**	**0.85**	**1.31**	**1.16**	**0.21**	**2.66**	**0.56**	**0.24**	**0.32**	**0.13**	**0.00**	**0.27**	**0.00**	**1.13**	**0.00**	**0.12**	**0.58**	-
Middle Eastern	Algerian (67)	16.7	1.4	0.0	8.3	4.2	-	0.0	0.0	1.4	-	-	-	-	-	-	-	-	-	-	-	-	4.2	8.3	36
Middle Eastern	Arab-American (68)	15.1	0.0	0.0	5.4	4.3	0.0	0.5	0.0	0.0	0.5	0.0	0.0	0.0	11.3	0.0	-	0.0	0.0	0.0	0.0	0.0	0.0	1.6	93
Middle Eastern	Iranian (69)	18.1	3.6	0.0	4.3	-	-	0.0	0.0	0.0	4.3	0.0	1.4	-	3.6	0.0	1.4	-	-	0.0	2.9	-	6.5	-	69
Middle Eastern	Iranian (70)	21.7	0.0	0.0	0.0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	30
Middle Eastern	Iranian (71)	15.8	0.8	0.0	5.8	-	-	-	-	-	-	-	-	0.8	-	-	-	-	-	-	0.8	-	-	-	60
Middle Eastern	Iranian (72)	16.2	2.7	0.0	0.0	4.1	1.4	-	0.0	0.0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	37
Middle Eastern	Israeli (Arab) (73)	23.5	1.2	0.0	21.2	10.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Middle Eastern	Lebanese (74)	36.3	1.3	0.0	20.0	13.8	2.5	-	-	-	2.5	-	-	-	-	-	-	-	-	-	-	-	-	-	40
Middle Eastern	N African (17)	32.0	4.8	1.4	10.2	8.2	0.0	0.0	0.0	0.0	0.0	0.0	2.7	0.0	0.0	0.0	0.0	0.7	0.0	0.0	0.0	0.0	0.7	7.5	-
Middle Eastern	Pakistani (75)	12.7	0.0	0.0	0.0	-	-	0.0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	150
Average Middle Eastern		**20.80**	**1.58**	**0.14**	**7.53**	**7.51**	**0.96**	**0.11**	**0.00**	**0.28**	**1.85**	**0.00**	**1.39**	**0.28**	**4.97**	**0.00**	**0.72**	**0.34**	**0.00**	**0.00**	**0.93**	**0.00**	**2.84**	**5.81**	-
South American	Argentine (76)	57.5	3.9	0.0	1.8	3.1	-	0.4	0.9	-	-	-	0.4	-	-	0.0	-	-	-	-	-	-	-	-	114
South American	Argentine (77)	58.6	4.1	0.0	2.7	2.7	-	0.2	1.1	0.7	0.7	0.9	0.5	0.7	-	0.7	-	0.5	-	-	1.1	-	0.5	-	220
South American	Brazilian (78)	22.7	0.0	3.0	-	-	-	0.0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	33

South American	Brazilian (79)	30.7	2.3	1.1	0.0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	44
South American	Brazilian (80)	31.7	8.3	0.0	2.5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
South American	Brazilian (81)	48.2	4.5	0.0	0.5	0.5	-	-	-	-	-	-	5.4	3.6	4.1	-	-	-	-	-	-	-	-	0.9	111
South American	Brazilian (82)	48.7	3.2	0.0	0.0	0.6	-	0.6	-	-	-	-	-	-	-	-	-	-	0.0	-	1.3	-	-	-	77
South American	Chilean (83)	30.6	2.4	0.0	0.0	0.2	0.2	1.2	0.0	0.0	0.0	1.7	0.9	0.5	0.2	0.0	0.0	0.0	0.0	0.0	3.1	0.2	0.0	0.2	289
South American	Chilean (84)	27.8	0.0	0.0	0.0	-	-	4.2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	36
South American	Columbian (52)	35.4	6.3	0.0	2.1	2.1	-	-	-	2.1	-	0.0	-	-	-	-	-	-	-	-	-	-	-	-	24
South American	Columbian (85)	41.8	3.8	0.0	0.5	1.1	-	-	-	-	0.5	-	1.1	-	0.5	-	-	-	-	-	0.5	-	-	-	92
South American	Venezuelan (52)	29.6	3.7	0.0	0.0	0.0	-	-	-	0.0	-	0.0	-	-	-	-	-	-	-	-	-	-	-	-	27
Average South American		**38.61**	**3.54**	**0.35**	**0.91**	**1.28**	**0.20**	**1.11**	**0.67**	**0.69**	**0.41**	**0.65**	**1.66**	**1.60**	**1.60**	**0.23**	**0.00**	**0.23**	**0.00**	**0.00**	**1.52**	**0.20**	**0.23**	**0.55**	-

Supplemental Table S4. Evidence linking *CFTR* genotype with Ivacaftor efficacy

Type of experimental model (*in vitro*, *in vivo* preclinical, or clinical)	**Major findings**	**References**	**Level of evidence[1]**
In vitro	Ivacaftor stimulates CFTR gating activity in cells expressing *G551D-CFTR* compared to untreated cells.	Van Goor *et al*. (2009) (86) Yu *et al*. (2012) (87) Jih *et al*.(2013) (88) Vachel *et al*. (2013) (89) Van Goor *et al*. (2013) (90)	Moderate
Clinical	Ivacaftor is associated with improvements in CFTR and lung function in CF patients with at least one *G551D-CFTR* allele.	Accurso *et al*. (2010) (91) Ramsey *et al*. (2011) (92) Seliger *et al*. (2013) (93) Harrison *et al.* (2013)(94)	High
Clinical	Ivacaftor is associated with substantial improvements in the risk of pulmonary exacerbations, patient-reported respiratory symptoms, weight and concentration of sweat chloride in CF patients with at least one *G551D-CFTR* allele.	Ramsey *et al*. (2011) (92) Seliger *et al*. (2013) (93) Harrison *et al.* (2013) (94)	High
Clinical	Ivacaftor is associated with significant improvements in lung function in CF patients (6 – 11 years old) with at least on *G551D-CFTR* allele.	Davies et al. (2013) (95) Seliger *et al*. (2013) (93)	High
Clinical	On average, ivacaftor is associated with significant improvements in lung function (FEV_1) and weight loss in patients with severe CF (FEV_1 <40% predicted) or excerbations, and a *G551D-CFTR* variant; however, this response was variable.	Hebestreit *et al*. (2013) (96) Polenakovik and Sanville (2013) (97) Harrison *et al.* (2013) (94)	Strong

In vitro	Ivacaftor may be effective on other *CFTR* variants.	Yu *et al*. (2012)(87) Yarlagadda *et al*. (2012)(98) Van Goor *et al*. (2013)(90)	Moderate
In vitro	Ivacaftor potentiates F508del-CFTR expressing cells, however this seems to be minimal without temperature treatment, a cell-free system, or a correcting mutation.	Van Goor *et al*. (2009)(86) Yu *et al*. (2011)(99) Eckford *et al*. (2012)(100) Namkung *et al*. (2013)(101) Yu *et al*. (2012)(87) Van Goor *et al*. (2013)(90)	Moderate
In vitro	In half the samples from F508del/F508del patients, ivacaftor significantly augments CFTR activity of human bronchial epithelial cells, and increases chloride transport of stable FRT cell lines expressing F508del-CFTR.	Van Goor *et al*. (2009)(86) Van Goor *et al*. (2013)(90)	Moderate
Clinical	Clinical efficacy (improvement in CFTR and lung function) not observed in patients homozygous for *F508del-CFTR* variant treated with ivacaftor (study not powered to detect difference in efficacy).	Flume *et al*. (2012) (102)	Weak

[1]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.

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