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ACMG STATEMENT

Updated recommendations for *CFTR* carrier screening: A position statement of the American College of Medical Genetics and Genomics (ACMG)

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Introduction

Pathogenic variants in the *CFTR* gene are causative of cystic fibrosis (CF) as well as CF-related disorders, such as isolated congenital bilateral absence of the vas deferens (CBAVD). In 2001, several professional organizations joined in acknowledging the importance and technologic advances that would make CF amenable to population-based carrier screening.[1] However, the technology and knowledge had not advanced far enough to allow for an equitable application. Variant databases were far less advanced when compared with those that are easily and widely accessible today. Sequencing technology was also early in development. This limited screening to small sets of variants that were most commonly characterized in Ashkenazi Jewish and Northern European populations using targeted, allele-specific testing approaches rather than DNA sequencing. For this reason, recommendations at that time were that screening should be "offered" to those of

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Ashkenazi Jewish and Northern European descent and "made available" to other groups,[1] partly in recognition that the carrier frequencies are highest in those 2 ethnicities, but with the additional implication being that the identification of heterozygotes was not the same across all racial and/or ethnic groups (and indeed quite suboptimal in some). The American College of Medical Genetics and Genomics (ACMG) ultimately recommended a set of 25 pathogenic variants, later reduced to 23 pathogenic variants[2] with an allele frequency of ≥0.1% in patients with CF in the US population to represent a minimum variant set for pan-ethnic carrier screening of individuals with no family history of CF. This minimum variant set (often referred to as the "ACMG-23") has remained unchanged since then, even as molecular diagnostic technologies and genetic knowledge have dramatically advanced.

The original recommendation left open the option for laboratories to offer an expanded *CFTR* variant set beyond the recommended set, and at the time, expanded variant sets were met with some controversy on the basis of the available technologies and limited phenotypic knowledge of rare variants.[3] However, several aspects have now evolved, including the widespread availability of cost-effective, high-throughput DNA sequencing, as well as more standardized variant classification and interpretation at both the general (eg, Richards et al[4]; ClinVar [https://www.ncbi.nlm.nih.gov/clinvar/]) and gene-specific (eg, CFTR2 [http://cftr2.org]) level. In 2020, the ACMG published an updated set of technical standards for *CFTR* variant testing, which recommended that laboratories could now use either targeted or comprehensive (ie, next-generation sequencing [NGS]) methods for testing and reaffirmed the original set of 23 variants as the minimum set for CF carrier screening;[5] an overlapping workgroup subsequently convened to evaluate whether an update to the minimum *CFTR* variant set was necessary. In addition, in 2021, the ACMG published a new carrier screening clinical practice resource, which continued to recommended offering testing of *CFTR* (now along with many additional genes) to all pregnant patients, as well as those planning a pregnancy.[6]

The original ACMG-23 CF variant set was derived primarily from databases comprising individuals with well-characterized CF who were Non-Hispanic White or Ashkenazi Jewish, thereby allowing individuals from those ancestries to be more easily identified during carrier screening. However, given that CF has been reported across all races, ethnicities, and ancestries, improved equity in variant detection is both necessary and desirable. Self-reported ethnicity also has its own flaws,[7,8] and this workgroup wanted to maintain a uniform recommended screening approach that would not be subject to this bias.

Databases Considered for *CFTR* Variant Pathogenicity

ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) is a public archive of genetic variants and associated phenotypes with occasional submitted supporting evidence. ClinVar accepts submissions from multiple sources including clinical testing laboratories, research laboratories, genetics clinics, patient registries, locus-specific databases, and expert panels. *CFTR* variants that are submitted to ClinVar may have been identified in patients with CF or a CFTR–related disorder (including CBAVD and pancreatitis). Importantly, they may have also been identified in unaffected individuals undergoing carrier screening or genetic testing for other indications. ClinVar aggregates the records submitted for each variant and reports the level of review supporting the assertion of clinical significance for each variant ranging from 0 to 4 stars, with 0 stars reflecting a variant assertion that was submitted by an individual without any supportive criteria provided and 4 stars reflecting a variant assertion that is present in a practice guideline. It is important to highlight that often the details regarding the phenotype of the associated individual may be limited or unavailable at the time a genetic variant is submitted. ClinVar does not curate information (ie, determine its validity) or modify classifications once they are submitted; it instead applies the star rating described above based on the data submitted and the source of the submission.

The CFTR-France database (https://cftr.iurc.montp.inserm.fr/cftr/) is a national database focused on sharing genetic and phenotypic information of rare *CFTR* variants that have been identified by genetic testing laboratories in partnership with the French Clinical Registry of patients with CF.[9] The database was established in 2012 and includes approximately 900 different *CFTR* variants, which are retrospectively reported from 10 French diagnostic laboratories specializing in *CFTR* molecular testing. These variants were all identified in individuals with CF, CFTR-RDs, fetuses with echogenic bowel, newborns with pending or inconclusive diagnoses, and asymptomatic individuals with 2 *CFTR* variants in *trans*. CFTR-France categorizes variants as CF-causing, CFTR-RD–causing, non–disease-causing, variants of unknown clinical significance, and as variants of varying clinical consequence (VVCCs). VVCCs are either associated with CF or a CFTR-RD (when in *trans* with a known CF-causing variant), and this can vary within families and across populations.

The Clinical and Functional TRanslation of CFTR (CFTR2) database (http://cftr2.org)[10] currently includes a total of 485 *CFTR* variants with various annotations. This database includes phenotype and genotype information collected from approximately 89,000 individuals from national CF patient registries and large clinics from 43 different countries, and CFTR2 is actively trying to further increase the diversity of their collection. The CFTR2 website was established in 2012 and is generally updated on an annual basis. The disease liability of *CFTR* variants was evaluated using clinical, functional, and epidemiological data, using aggregate information on sweat chloride levels, lung function, pancreatic status, and Pseudomonas infection rates in patients harboring specific combinations of variants. CFTR2 classifies variants as either CF-causing, VVCCs,

non-CF causing, or variants of unknown significance. CFTR2 defines VVCCs as those variants that are associated with CF in some individuals but not in others when the variant is present in *trans* with a CF-causing variant (note that this is a slightly different definition than the one used for VVCCs by CFTR-France). CFTR2 also does not have a classification of "CFTR-RD–causing" as exists in CFTR-France. *CFTR* variants classified by CFTR2 are given a 3-star assertion status in ClinVar because CFTR2 has been designated as an expert panel by ClinGen.

The current workgroup ultimately decided to only use CFTR2 as a source for the pathogenicity of CF-causing variants. Although many pathogenic or likely pathogenic *CFTR* variant assertions exist in ClinVar, there is often insufficient phenotypic information provided for the individuals who are tested to conclusively associate the variant with a specific CF-related phenotype based solely on that database. As many of the submitted variants were detected during carrier screening and not diagnostic testing, the true phenotypic impact and penetrance of the variant may not yet be well established. Separately, though the information contained in CFTR-France is based on diagnostic testing in affected individuals, the evaluations are performed on a more biogeographically limited population than those used for CFTR2. Therefore, CFTR-France was only used for potentially excluding variants (see Methods) but not as a standalone pathogenicity source for including variants in the minimum set. Other smaller or commercial databases were likewise not pursued, given the barriers to access, varying degrees of curation quality, and/or the potential for bias toward specific populations.

Methods

Initial Variant List

The initial list of variants under consideration for inclusion (Figure 1) was a compilation of 2 data sets: (1) variants that were previously included in the set recommended by the ACMG for inclusion in carrier screening ($n = 23$)[2] and (2) variants that were interpreted as CF-causing by the CFTR2 project ($n = 401$, as of the April 29, 2022, data release). The combination of these 2 data sets resulted in an initial list of 416 *CFTR* variants (Supplemental Table 1). No CFTR2 VVCCs (other than R117H) were included in the initial list because they may not cause CF in some individuals (also see Future revisions of the minimum variant set). Variants interpreted as CF-causing by CFTR2 are also all classified as pathogenic or likely pathogenic variants in ClinVar, which is consistent with the previous 2020 *CFTR* technical standards.[5]

Automatic and Manual Filtering

The initial list of 416 variants underwent further revision, with variants being automatically excluded if they were part of complex alleles (2 variants known to occur in *cis* and interpreted as a single allele), if they were structural variants involving a deletion or duplication of ≥1 exons, or if they were absent from the gnomAD data set (v2.1.1 or v3.1.2) within the 6 ancestral populations specified below (see Frequency and coverage evaluation). In all excluded complex alleles, 1 of the 2 variants involved was also independently classified and included separately in the initial list. Large structural variants within *CFTR* were excluded because they are generally rare, may be technically more difficult to detect (and therefore potentially inaccurate or not reported in reference population sequencing), and often have unknown/ambiguous breakpoints. Presence in the gnomAD data set was considered a requirement for inclusion in the final recommended set of variants so that the population frequency and coverage within the United States could be evaluated. A total of 219 variants were excluded using these additional criteria.

A manual review was conducted on any included variants that were also deemed CFTR-RD–causing or non–disease-causing variants by CFTR-France because these variants are defined as leading to CFTR-RDs (such as CBAVD) instead of CF or have insufficient clinical and/or functional evidence to be disease causing, respectively. Based on these criteria, only 2 variants required manual review: c.350A>G (p.Arg117His; legacy: R117H) and c.1013C>T (p.Thr338Ile; legacy: T338I), both of which were considered to be CFTR-RD–causing variants by CFTR-France. It was determined that both variants should remain on the list for consideration because of the clinical and functional evidence in CFTR2, which was consistent with the variants causing CF.[11,12] However, the interrupting TG variants in the R117H-associated intronic polyT tract were not also included (see Considerations for laboratories). R117H was also present on the originally recommended set of 23 *CFTR* variants.

Frequency and Coverage Evaluation

Variants remaining after automatic and manual exclusion ($n = 197$) underwent further evaluation to estimate their frequencies in the US population.[13] The gnomAD data set, an aggregation of exome and genome sequencing samples, was selected as a reference database from which to obtain carrier frequency estimates for CF alleles because it is large, uniformly processed, and has samples from multiple ancestral populations. We started with the data from gnomAD v2.1.1 ($n = 125{,}748$ exomes and $n = 15{,}708$ genomes) and the non-v2 subset of gnomAD v3.1.2 genome data ($n = 56{,}456$) for a total of 197,912 nonoverlapping samples. We then extracted the allele frequencies for the 197 variants under consideration across each of 6 ancestral populations from gnomAD v2.1.1 plus gnomAD v3.1.2: African/African American ($n = 26{,}863$ total individuals), Latino/Admixed American ($n = 24{,}598$), Ashkenazi Jewish ($n = 6723$), East Asian ($n = 11{,}515$), non-Finnish European

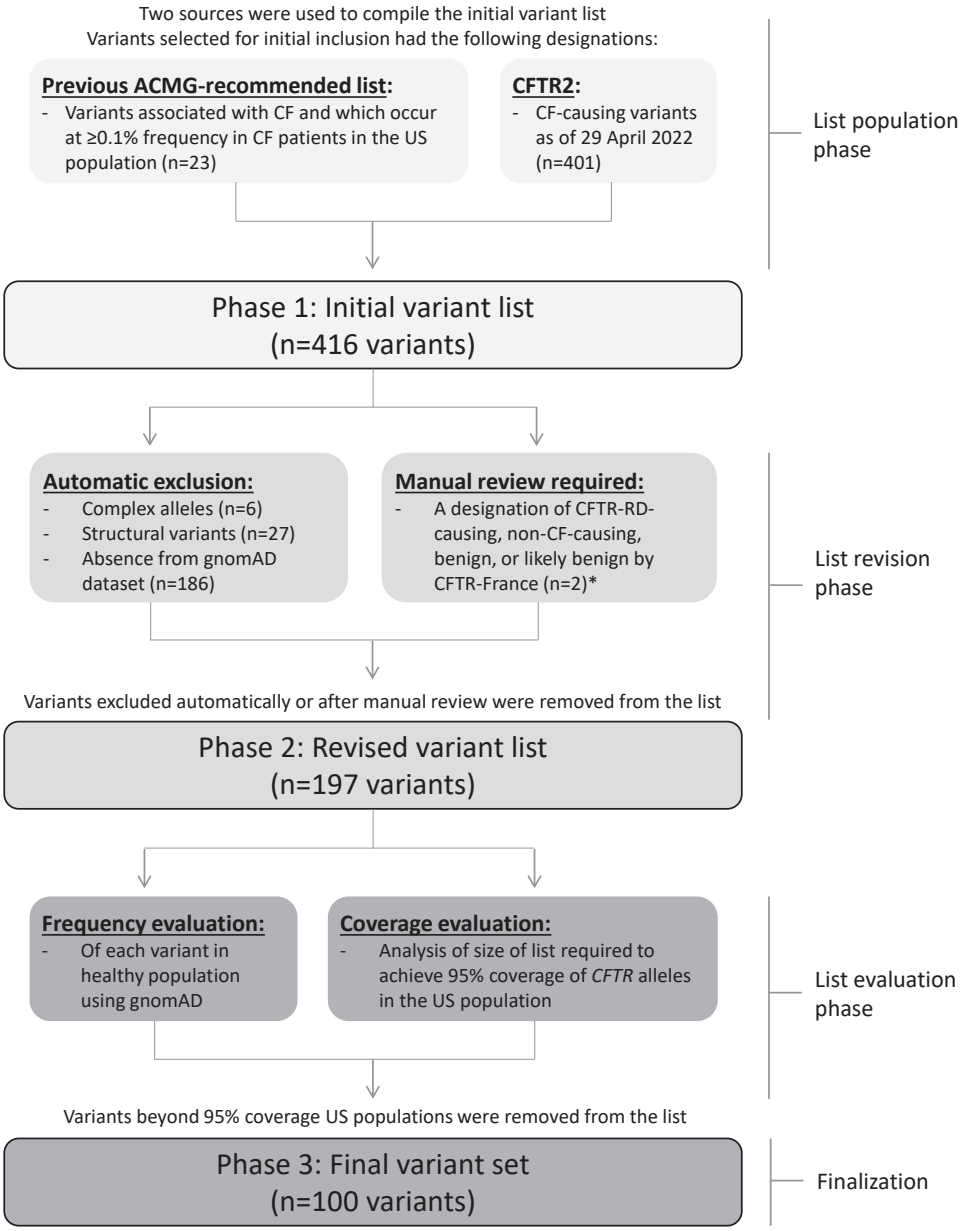

Figure 1 Flowchart depicting variants for consideration and final inclusion in the updated minimum variant set. All variant nomenclature is based on MANE Select transcript NM_000492.4. Variants for consideration were initially drawn from the previous ACMG-23 variant set and CF-causing variants available on https://cftr2.org as of April 29, 2022. The list was revised by excluding complex alleles, structural variants, and those not present in gnomAD. The remaining variants were evaluated to select those that would collectively achieve 95% coverage of *CFTR* alleles in the US population. *Two variants (c.350G>A [p.Arg117His; legacy: R117H] and c.1013C>T [p.Thr338Ile; legacy: T338I]) deemed CF-causing by CFTR2 have been interpreted as CFTR-RD-causing by CFTR-France and were manually reviewed for pathogenicity; both variants remained for inclusion after manual review. ACMG, American College of Medical Genetics and Genomics; CF, cystic fibrosis; *CFTR*, cystic fibrosis transmembrane conductance regulator.

(n = 90,591), and South Asian (n = 17,254), for a total of 177,544 individuals. We note that there are several other ancestral populations (eg, Finnish individuals) in gnomAD that were not included in the analyses because they represent a small proportion of the US population. Carrier frequency for each variant was approximated as 2 times the allele frequency. This approximation is appropriate when allele frequencies are low and because there are no individuals who are homozygous for any of these alleles. Next, for each ancestral population, we ranked the *CFTR* variants present in the population in order of decreasing frequency. We then tabulated, for each ancestral population, the minimum number of variants needed such that 95% of the total *CFTR* carrier frequency for the population is achieved; this was based on previous carrier screening practice guidelines[14] (Supplemental Figure 1). To derive the final set of *CFTR* variants, we merged the 95% variant lists from each component ancestry to achieve a nonoverlapping set of 100

variants (Supplemental Figure 2). This approach ensured that at least 95% of the total carrier frequency in each population is represented in the final variant set.

Updated Minimum *CFTR* Variant Set

The updated minimum *CFTR* variant set is presented in Table 1. Additional information about the variants is also listed in Supplemental Table 1.

Considerations for Laboratories

Current limitations of specific methodologies/platforms were not factored in when determining the updated minimum variant set because the capabilities and availabilities of specific methodologies/platforms are expected to change over time. The workgroup is also aware that there are not likely any existing targeted CF tests available that contain all of the newly recommended variants. However, some laboratories may have previously chosen to offer CF carrier screening using either Sanger or NGS of *CFTR*, and these methods should encompass all of the genomic regions containing the recommended variants.[15] Because the knowledge base in both gnomAD and CFTR2 expands, it may be easier for laboratories to continue testing for the updated minimum variant set if comprehensive testing methods (ie, NGS) are used instead of targeted testing methods.[5] Laboratories may also need to assess the financial impacts of developing, validating/verifying, and offering a new CF carrier screening method. A CPT code (81223) already exists for *CFTR* full gene sequencing, though the coverage and reimbursement for this code may need to be reassessed considering its potential recommended use for carrier screening. In addition, if targeted methods are ultimately used, it may not be possible to validate all of the variants in the updated minimum variant set, and laboratories may need to use other strategies to ensure that they can accurately detect all of these variants; however, this should be less of a concern if comprehensive methods are used for testing. Regardless of the method/platform ultimately used by a particular laboratory, the updated minimum variant set is a significant improvement compared with the previously recommended alternative.

The new set of 100 variants represents an updated minimum *CFTR* carrier screening variant set, but it does not represent a limit on the total number of variants that a laboratory can choose to assess, and it is likely that laboratories may already have many (but likely not all) of these variants included as a part of their tests. An informal analysis of the additional CF-causing variants that are present as a part of some current clinical laboratory *CFTR* tests revealed that most of them were either (1) not in gnomAD and therefore they would not have been considered for inclusion by our workgroup, or (2) they would have been included in our updated minimum variant set if we expanded our desired coverage from 95% to 99%. It is reassuring to note that none of the representative clinical laboratory *CFTR* tests that were evaluated tested for any known non-CF causing variants. However, a small number of commonly included CFTR2 VVCCs were noted to be present as a part of multiple clinical laboratory *CFTR* tests, mainly D1152H (c.3454G>C, p.Asp1152His) and F312del (c.935_937delTCT, p.Phe312del; also known as [delta]F311). Laboratories are encouraged to further review the clinical implications of these variants when deciding whether they should remain as a part of their tests, especially when used in the setting of prenatal carrier screening. All of the clinical laboratory *CFTR* tests that were evaluated were missing a number of established CF-causing variants from CFTR2 that are part of the updated minimum set of 100 variants.

Although the group recommended keeping R117H as a part of the updated minimum variant set, the group did not automatically include the associated interrupting TG variants within the intronic polyT tract even though they are typically also detectable using established methods because some of the combinations are not classified as a CF-causing variant in CFTR2 (5T;TG11 [c.1210-7_1210-6del], 5T;TG12 [c.1210-11T>G]) or are not currently present in gnomAD (5T;TG13; c.1210-11delinsGTG). The group reaffirmed the prior recommendation to reflex to polyT analysis and/or reporting for carrier screening only when R117H is also present. However, the group now recommends assessing and reporting the polyTG results whenever 5T is detected because increased numbers of polyTG repeats in *cis* with 5T are typically associated with increased severity and penetrance of CF-related symptoms compared with individuals with 5T in *cis* with fewer polyTG repeats.[16] In addition, when R117H occurs in *cis* with 5T, it is typically in association with a TG12 allele, and when it is in *cis* with 7T, it is typically in association with a TG10 allele; therefore, inferences regarding the phase can be made to further inform reproductive counseling even if familial samples are unavailable for confirmatory follow-up testing.[17]

Future Revisions of the Minimum Variant Set

The updated minimum variant set for CF carrier screening is based on (1) evidence that the variant has been established as CF causing and (2) presence of the variant in the gnomAD database. For this version, we took a conservative approach and established a framework that only incorporates well-established pathogenic and likely pathogenic variants to minimize concerns that patients would make reproductive decisions based on limited information. This version of the variant set included CF-causing variants that were annotated as of April 2022 in the CFTR2 database, and additional variants should be reassessed when new classifications are available. Other databases such as ClinVar and CFTR-France could be considered during future revisions if additional strong evidence for variant pathogenicity in affected individuals becomes available. Because *CFTR* is unique and public databases similar to CFTR2 may not exist for other

Table 1 *CFTR* Carrier Screening Variant Set (n = 100)

DNA Variant	Protein Variant	Legacy Name
c.4C>T	p.Gln2Ter	Q2X
c.178G>T	p.Glu60Ter	E60X
c.200C>T	p.Pro67Leu	P67L
c.223C>T	p.Arg75Ter	R75X
c.254G>A	p.Gly85Glu	G85E[a]
c.262_263del	p.Leu88IlefsTer22	394delTT
c.271G>A	p.Gly91Arg	G91R
c.274-1G>A	p.?	406-1G->A
c.292C>T	p.Gln98Ter	Q98X
c.293A>G	p.Gln98Arg	Q98R
c.313del	p.Ile105SerfsTer2	444delA
c.328G>C	p.Asp110His	D110H
c.349C>T	p.Arg117Cys	R117C
c.350G>A	p.Arg117His	R117H[a]
c.489+1G>T	p.?	621+1G->T[a]
c.571T>G	p.Phe191Val	F191V
c.579+1G>T	p.?	711+1G->T[a]
c.579+3A>G	p.?	711+3A->G
c.617T>G	p.Leu206Trp	L206W
c.653T>A	p.Leu218Ter	L218X
c.695T>A	p.Val232Asp	V232D
c.803del	p.Asn268IlefsTer17	935delA
c.868C>T	p.Gln290Ter	Q290X
c.988G>T	p.Gly330Ter	G330X
c.1000C>T	p.Arg334Trp	R334W[a]
c.1013C>T	p.Thr338Ile	T338I
c.1021_1022dup	p.Phe342HisfsTer28	1154insTC
c.1029del	p.Cys343Ter	1161delC
c.1040G>A	p.Arg347His	R347H
c.1040G>C	p.Arg347Pro	R347P[a]
c.1055G>A	p.Arg352Gln	R352Q
c.1155_1156dup	p.Asn386IlefsTer3	1288insTA
c.1327_1330dup	p.Ile444ArgfsTer3	1461ins4
c.1364C>A	p.Ala455Glu	A455E[a]
c.1367T>C	p.Val456Ala	V456A
c.1373del	p.Gly458AspfsTer11	1504delG
c.1393-1G>A	p.?	1525-1G->A
c.1397C>G	p.Ser466Ter	S466X
c.1400T>C	p.Leu467Pro	L467P
c.1519_1521del	p.Ile507del	I507del[a]
c.1521_1523del	p.Phe508del	F508del[a]
c.1572C>A	p.Cys524Ter	C524X
c.1584+1G>A	p.?	1716+1G->A
c.1585-1G>A	p.?	1717-1G->A[a]
c.1624G>T	p.Gly542Ter	G542X[a]
c.1646G>A	p.Ser549Asn	S549N
c.1647T>G	p.Ser549Arg	S549R
c.1651G>A	p.Gly551Ser	G551S
c.1652G>A	p.Gly551Asp	G551D[a]
c.1657C>T	p.Arg553Ter	R553X[a]
c.1673T>C	p.Leu558Ser	L558S
c.1675G>A	p.Ala559Thr	A559T
c.1679G>C	p.Arg560Thr	R560T[a]
c.1679+1G>A	p.?	1811+1G->A
c.1680-886A>G	p.?	1811+1634A->G
c.1680A>C	p.Arg560Ser	R560S
c.1682C>A	p.Ala561Glu	A561E
c.1692del	p.Asp565MetfsTer7	1824delA
c.1705T>G	p.Tyr569Asp	Y569D
c.1753G>T	p.Glu585Ter	E585X
c.1766+1G>A	p.?	1898+1G->A[a]
c.1766+5G>T	p.?	1898+5G->T
c.1837G>A	p.Ala613Thr	A613T
c.1882G>A	p.Gly628Arg	G628R
c.2052dup	p.Gln685ThrfsTer4	2184insA
c.2052del	p.Lys684AsnfsTer38	2184delA[a]
c.2125C>T	p.Arg709Ter	R709X
c.2175dup	p.Glu726ArgfsTer4	2307insA
c.2290C>T	p.Arg764Ter	R764X
c.2353C>T	p.Arg785Ter	R785X
c.2374C>T	p.Arg792Ter	R792X
c.2490+1G>A	p.?	2622+1G->A
c.2657+5G>A	p.?	2789+5G->A[a]
c.2668C>T	p.Gln890Ter	Q890X
c.2739T>A	p.Tyr913Ter	Y913X
c.2834C>T	p.Ser945Leu	S945L
c.2909G>A	p.Gly970Asp	G970D
c.2988G>A	p.Gln996=	3120G->A
c.2988+1G>A	p.?	3120+1G->A[a]
c.3067_3072del	p.Ile1023_Val1024del	3199del6
c.3107C>A	p.Thr1036Asn	T1036N
c.3140-26A>G	p.?	3272-26A->G
c.3196C>T	p.Arg1066Cys	R1066C
c.3197G>A	p.Arg1066His	R1066H
c.3266G>A	p.Trp1089Ter	W1089X
c.3294G>C	p.Trp1098Cys	W1098C
c.3353C>T	p.Ser1118Phe	S1118F
c.3472C>T	p.Arg1158Ter	R1158X
c.3484C>T	p.Arg1162Ter	R1162X[a]
c.3528del	p.Lys1177SerfsTer15	3659delC[a]
c.3612G>A	p.Trp1204Ter	W1204X
c.3659del	p.Thr1220LysfsTer8	3791delC
c.3717+5G>A	p.?	3849+5G->A
c.3718-2477C>T	p.?	3849+10kbC->T[a]
c.3744del	p.Lys1250ArgfsTer9	3876delA
c.3764C>A	p.Ser1255Ter	S1255X
c.3808del	p.Asp1270MetfsTer8	3940delG
c.3846G>A	p.Trp1282Ter	W1282X[a]
c.3889dup	p.Ser1297PhefsTer5	4016insT
c.3909C>G	p.Asn1303Lys	N1303K[a]

(continued)

Table 1 Continued

[a]Variants that were part of the previously recommended minimum 23-variant set.

conditions and their associated genes, the workgroup recognizes that an inability to use the publicly available ClinVar classifications for the selection of variants for other conditions may hamper future carrier screening standardization efforts. However, the use of 3-star review level variants in ClinVar, which have undergone review by ClinGen expert panels, will provide a growing high-quality resource over time.

Multiple factors play a role in the identification of variants associated with CF, particularly in the context of biogeographically diverse populations. For this statement, the minimum set of variants was evaluated for population frequency and coverage within 6 global ancestral populations using the gnomAD data set.

Notably, though self-reported race and/or ethnicity has been used as a proxy for genetic ancestry in clinical testing, these may inaccurately capture individuals' ancestral backgrounds.[18,19] However, these limitations are expected to be mitigated as more ancestral diversity is represented in population databases.

Future versions of this minimum variant set should reassess the feasibility and utility of incorporating additional information from other population databases, such as All of Us, TOPMed (gnomAD only contains a subset of these data), and the UK Biobank.[20-22] Although these databases were generally not used to inform this updated minimum variant set because of challenges in accessing the data and the lack of complete phenotypic/biogeographic information, future revisions should re-evaluate their inclusion to be as biogeographically diverse as possible. gnomAD was selected as part of the inclusion criteria because previous population databases were not as comprehensive for assessing the frequency of *CFTR* variants (eg, NHLBI Exome Sequencing Project); gnomAD is also expected to expand and become more biogeographically diverse over time, thereby ensuring that any CF-causing variants that are common to a specific biogeographic ancestry are appropriately represented in future revisions of the variant set. The updated minimum variant set also does not include any structural variants because of insufficient gnomAD data to support their inclusion at the time of data analysis. However, we expect that future revisions of the minimum variant set will incorporate structural variants as the detection and annotation of these variants improves.

Finally, the workgroup set a minimum 95% carrier detection rate for all biogeographic ancestries listed in gnomAD v2.1.1 plus gnomAD v3.1.2 based on precedent from previous carrier screening recommendations.[14] The group realizes that some laboratories may choose to incorporate more variants as a part of their *CFTR* tests to reach carrier detection rates approaching 99%. Future versions of this variant set may reassess the minimum detection rate and the potential harms of not including all well-established CF-causing variants annotated in population databases. In addition, because many of these variants are relatively rare, their carrier frequencies and inclusion in the current 95% threshold variant set could be susceptible to changes in the reference samples from which the carrier frequencies are estimated. However, because their pathogenicity will have already been established, any variants that are included in previous versions of the minimum recommended variant set should be included in any future versions of the variant set (eg, the previously recommended ACMG-23 variants are all included in the updated variant set).

Conclusion

The new *CFTR* variant set represents an updated minimum recommended variant set for CF carrier screening, and this new set now supersedes the previous set of 23 *CFTR* variants recommended by the ACMG. These revised recommendations apply only to carrier screening. They do not apply to *CFTR* variant testing for diagnosis or newborn screening. All other aspects of the updated 2020 ACMG *CFTR* technical standards still apply.[5]

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Conflict of Interest

The authors declare no conflicts of interest.

Additional Information

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Affiliations

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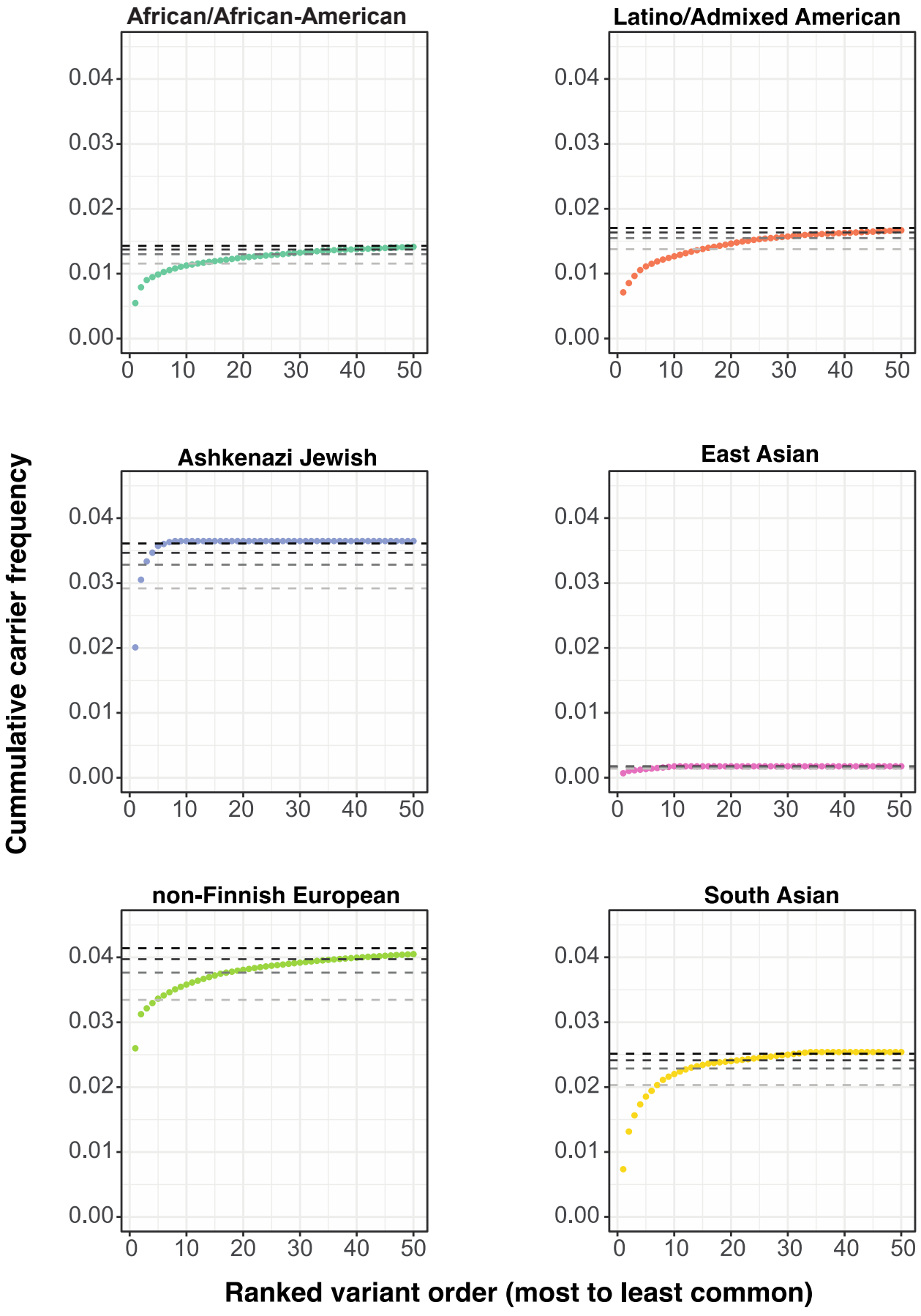
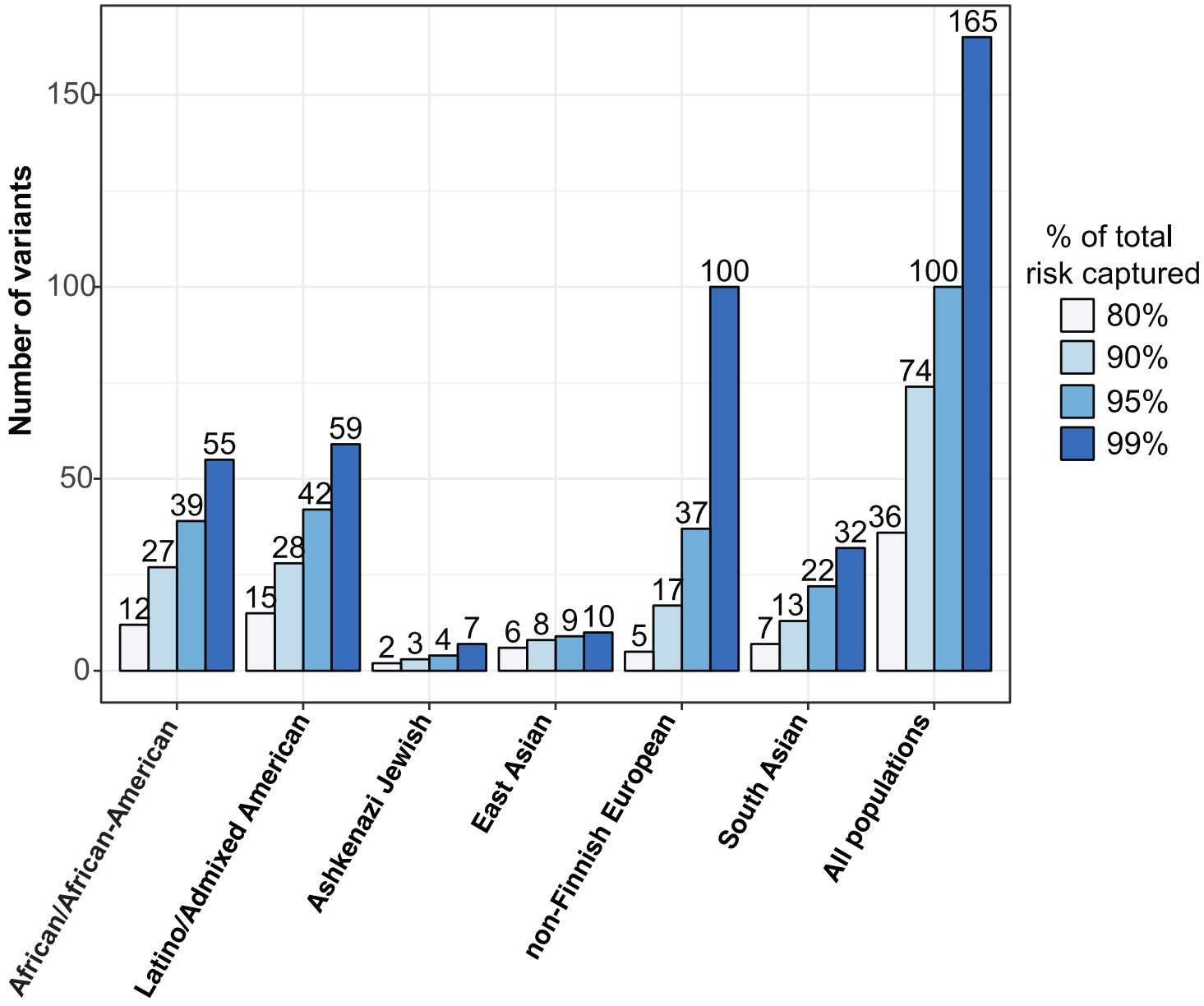

African/African-American
Latino/Admixed American
Ashkenazi Jewish
East Asian
non-Finnish European
South Asian
Cummulative carrier frequency
0.00
0.01
0.02
0.03
0.04
0
10
20
30
40
50
Ranked variant order (most to least common)
Percent of total risk
80%
90%
95%
99%

Supplementary Figure 1: Cumulative carrier frequencies detected by screening additional *CFTR* variants. For each ancestry, variants are ranked in decreasing order from highest to lowest carrier frequency based on gnomAD data. Each point represents a single variant. The cumulative carrier frequency captured by screening additional variants is plotted on the y-axis. Dotted lines show the cumulative carrier frequencies representing 80, 90, 95, and 99% of the total carrier frequency for that ancestry. Each plot represents a different biogeographic ancestry.


Number of variants
150
100
50
0
African/African-American
Latino/Admixed American
Ashkenazi Jewish
East Asian
non-Finnish European
South Asian
All populations
12
27
39
55
15
28
42
59
2
3
4
7
6
8
9
10
5
17
37
100
7
13
22
32
36
74
100
165
% of total risk captured
80%
90%
95%
99%

Supplementary Figure 2: Number of variants needed to capture proportion of total carrier frequency. For each biogeographic ancestry, the barplot shows the number of variants needed to be screened in order to capture 80, 90, 95, and 99% of the total carrier frequency for that ancestry. “All populations” represents the number of variants needed to capture a given percentage of total carrier frequency across all ancestries.

Table S1. All *CFTR* variants considered for inclusion in the updated minimum variant set.

cDNA name	Protein name	Legacy name	Final status	Reason for exclusion[a]	ACMG-23[b]	VCF position (GRCh38)[c]
c.4C>T	p.Gln2Ter	Q2X	Included in ACMG 100	NA		7:117480098:C:T
c.178G>T	p.Glu60Ter	E60X	Included in ACMG 100	NA		7:117509047:G:T
c.200C>T	p.Pro67Leu	P67L	Included in ACMG 100	NA		7:117509069:C:T
c.223C>T	p.Arg75Ter	R75X	Included in ACMG 100	NA		7:117509092:C:T
c.254G>A	p.Gly85Glu	G85E	Included in ACMG 100	NA	Yes	7:117509123:G:A
c.262_263del	p.Leu88IlefsTer22	394delTT	Included in ACMG 100	NA		7:117509127:CTT:C
c.271G>A	p.Gly91Arg	G91R	Included in ACMG 100	NA		7:117509140:G:A
c.274-1G>A	p.?	406-1G->A	Included in ACMG 100	NA		7:117530898:G:A
c.292C>T	p.Gln98Ter	Q98X	Included in ACMG 100	NA		7:117530917:C:T
c.293A>G	p.Gln98Arg	Q98R	Included in ACMG 100	NA		7:117530918:A:G
c.313del	p.Ile105SerfsTer2	444delA	Included in ACMG 100	NA		7:117530936:GA:G
c.328G>C	p.Asp110His	D110H	Included in ACMG 100	NA		7:117530953:G:C
c.349C>T	p.Arg117Cys	R117C	Included in ACMG 100	NA		7:117530974:C:T
c.350G>A	p.Arg117His	R117H	Included in ACMG 100	NA	Yes	7:117530975:G:A
c.489+1G>T	p.?	621+1G->T	Included in ACMG 100	NA	Yes	7:117531115:G:T
c.571T>G	p.Phe191Val	F191V	Included in ACMG 100	NA		7:117534357:T:G
c.579+1G>T	p.?	711+1G->T	Included in ACMG 100	NA	Yes	7:117534366:G:T
c.579+3A>G	p.?	711+3A->G	Included in ACMG 100	NA		7:117534368:A:G
c.617T>G	p.Leu206Trp	L206W	Included in ACMG 100	NA		7:117535285:T:G
c.653T>A	p.Leu218Ter	L218X	Included in ACMG 100	NA		7:117535321:T:A
c.695T>A	p.Val232Asp	V232D	Included in ACMG 100	NA		7:117535363:T:A
c.803del	p.Asn268IlefsTer17	935delA	Included in ACMG 100	NA		7:117536603:GA:G
c.868C>T	p.Gln290Ter	Q290X	Included in ACMG 100	NA		7:117536672:C:T
c.988G>T	p.Gly330Ter	G330X	Included in ACMG 100	NA		7:117540218:G:T
c.1000C>T	p.Arg334Trp	R334W	Included in ACMG 100	NA	Yes	7:117540230:C:T
c.1013C>T	p.Thr338Ile	T338I	Included in ACMG 100	NA		7:117540243:C:T
c.1021_1022dup	p.Phe342HisfsTer28	1154insTC	Included in ACMG 100	NA		7:117540248:A:ATC
c.1029del	p.Cys343Ter	1161delC	Included in ACMG 100	NA		7:117540258:GC:G
c.1040G>A	p.Arg347His	R347H	Included in ACMG 100	NA		7:117540270:G:A
c.1040G>C	p.Arg347Pro	R347P	Included in ACMG 100	NA	Yes	7:117540270:G:C
c.1055G>A	p.Arg352Gln	R352Q	Included in ACMG 100	NA		7:117540285:G:A
c.1155_1156dup	p.Asn386IlefsTer3	1288insTA	Included in ACMG 100	NA		7:117542050:A:AAT
c.1327_1330dup	p.Ile444ArgfsTer3	1461ins4	Included in ACMG 100	NA		7:117548756:A:AAGAT
c.1364C>A	p.Ala455Glu	A455E	Included in ACMG 100	NA	Yes	7:117548795:C:A
c.1367T>C	p.Val456Ala	V456A	Included in ACMG 100	NA		7:117548798:T:C
c.1373del	p.Gly458AspfsTer11	1504delG	Included in ACMG 100	NA		7:117548802:TG:T
c.1393-1G>A	p.?	1525-1G->A	Included in ACMG 100	NA		7:117559463:G:A
c.1397C>G	p.Ser466Ter	S466X	Included in ACMG 100	NA		7:117559468:C:G
c.1400T>C	p.Leu467Pro	L467P	Included in ACMG 100	NA		7:117559471:T:C
c.1519_1521del	p.Ile507del	I507del	Included in ACMG 100	NA	Yes	7:117559586:TATC:T
c.1521_1523del	p.Phe508del	F508del	Included in ACMG 100	NA	Yes	7:117559590:ATCT:A
c.1572C>A	p.Cys524Ter	C524X	Included in ACMG 100	NA		7:117559643:C:A
c.1584+1G>A	p.?	1716+1G->A	Included in ACMG 100	NA		7:117559656:G:A
c.1585-1G>A	p.?	1717-1G->A	Included in ACMG 100	NA	Yes	7:117587738:G:A
c.1624G>T	p.Gly542Ter	G542X	Included in ACMG 100	NA	Yes	7:117587778:G:T
c.1646G>A	p.Ser549Asn	S549N	Included in ACMG 100	NA		7:117587800:G:A
c.1647T>G	p.Ser549Arg	S549R	Included in ACMG 100	NA		7:117587801:T:G
c.1651G>A	p.Gly551Ser	G551S	Included in ACMG 100	NA		7:117587805:G:A
c.1652G>A	p.Gly551Asp	G551D	Included in ACMG 100	NA	Yes	7:117587806:G:A
c.1657C>T	p.Arg553Ter	R553X	Included in ACMG 100	NA	Yes	7:117587811:C:T
c.1673T>C	p.Leu558Ser	L558S	Included in ACMG 100	NA		7:117587827:T:C
c.1675G>A	p.Ala559Thr	A559T	Included in ACMG 100	NA		7:117587829:G:A
c.1679G>C	p.Arg560Thr	R560T	Included in ACMG 100	NA	Yes	7:117587833:G:C
c.1679+1G>A	p.?	1811+1G->A	Included in ACMG 100	NA		7:117587834:G:A
c.1680-886A>G	p.?	1811+1634A->G	Included in ACMG 100	NA		7:117589467:A:G
c.1680A>C	p.Arg560Ser	R560S	Included in ACMG 100	NA		7:117590353:A:C
c.1682C>A	p.Ala561Glu	A561E	Included in ACMG 100	NA		7:117590355:C:A
c.1692del	p.Asp565MetfsTer7	1824delA	Included in ACMG 100	NA		7:117590362:CA:C
c.1705T>G	p.Tyr569Asp	Y569D	Included in ACMG 100	NA		7:117590378:T:G

c.1753G>T	p.Glu585Ter	E585X	Included in ACMG 100	NA		7:117590426:G:T
c.1766+1G>A	p.?	1898+1G->A	Included in ACMG 100	NA	Yes	7:117590440:G:A
c.1766+5G>T	p.?	1898+5G->T	Included in ACMG 100	NA		7:117590444:G:T
c.1837G>A	p.Ala613Thr	A613T	Included in ACMG 100	NA		7:117592004:G:A
c.1882G>A	p.Gly628Arg	G628R	Included in ACMG 100	NA		7:117592049:G:A
c.2052dup	p.Gln685ThrfsTer4	2184insA	Included in ACMG 100	NA		7:117592212:C:CA
c.2052del	p.Lys684AsnfsTer38	2184delA	Included in ACMG 100	NA	Yes	7:117592212:CA:C
c.2125C>T	p.Arg709Ter	R709X	Included in ACMG 100	NA		7:117592292:C:T
c.2175dup	p.Glu726ArgfsTer4	2307insA	Included in ACMG 100	NA		7:117592340:G:GA
c.2290C>T	p.Arg764Ter	R764X	Included in ACMG 100	NA		7:117592457:C:T
c.2353C>T	p.Arg785Ter	R785X	Included in ACMG 100	NA		7:117592520:C:T
c.2374C>T	p.Arg792Ter	R792X	Included in ACMG 100	NA		7:117592541:C:T
c.2490+1G>A	p.?	2622+1G->A	Included in ACMG 100	NA		7:117592658:G:A
c.2657+5G>A	p.?	2789+5G->A	Included in ACMG 100	NA	Yes	7:117602868:G:A
c.2668C>T	p.Gln890Ter	Q890X	Included in ACMG 100	NA		7:117603542:C:T
c.2739T>A	p.Tyr913Ter	Y913X	Included in ACMG 100	NA		7:117603613:T:A
c.2834C>T	p.Ser945Leu	S945L	Included in ACMG 100	NA		7:117603708:C:T
c.2909G>A	p.Gly970Asp	G970D	Included in ACMG 100	NA		7:117606674:G:A
c.2988G>A	p.Gln996=	3120G->A	Included in ACMG 100	NA		7:117606753:G:A
c.2988+1G>A	p.?	3120+1G->A	Included in ACMG 100	NA	Yes	7:117606754:G:A
c.3067_3072del	p.Ile1023_Val1024del	3199del6	Included in ACMG 100	NA		7:117610592:CAGTGAT:C
c.3107C>A	p.Thr1036Asn	T1036N	Included in ACMG 100	NA		7:117610637:C:A
c.3140-26A>G	p.?	3272-26A->G	Included in ACMG 100	NA		7:117611555:A:G
c.3196C>T	p.Arg1066Cys	R1066C	Included in ACMG 100	NA		7:117611637:C:T
c.3197G>A	p.Arg1066His	R1066H	Included in ACMG 100	NA		7:117611638:G:A
c.3266G>A	p.Trp1089Ter	W1089X	Included in ACMG 100	NA		7:117611707:G:A
c.3294G>C	p.Trp1098Cys	W1098C	Included in ACMG 100	NA		7:117611735:G:C
c.3353C>T	p.Ser1118Phe	S1118F	Included in ACMG 100	NA		7:117611794:C:T
c.3472C>T	p.Arg1158Ter	R1158X	Included in ACMG 100	NA		7:117627525:C:T
c.3484C>T	p.Arg1162Ter	R1162X	Included in ACMG 100	NA	Yes	7:117627537:C:T
c.3528del	p.Lys1177SerfsTer15	3659delC	Included in ACMG 100	NA	Yes	7:117627579:AC:A
c.3612G>A	p.Trp1204Ter	W1204X	Included in ACMG 100	NA		7:117627665:G:A
c.3659del	p.Thr1220LysfsTer8	3791delC	Included in ACMG 100	NA		7:117627711:AC:A
c.3717+5G>A	p.?	3849+5G->A	Included in ACMG 100	NA		7:117627775:G:A
c.3718-2477C>T	p.?	3849+10kbC->T	Included in ACMG 100	NA	Yes	7:117639961:C:T
c.3744del	p.Lys1250ArgfsTer9	3876delA	Included in ACMG 100	NA		7:117642463:CA:C
c.3764C>A	p.Ser1255Ter	S1255X	Included in ACMG 100	NA		7:117642484:C:A
c.3808del	p.Asp1270MetfsTer8	3940delG	Included in ACMG 100	NA		7:117642527:CG:C
c.3846G>A	p.Trp1282Ter	W1282X	Included in ACMG 100	NA	Yes	7:117642566:G:A
c.3889dup	p.Ser1297PhefsTer5	4016insT	Included in ACMG 100	NA		7:117652851:A:AT
c.3909C>G	p.Asn1303Lys	N1303K	Included in ACMG 100	NA	Yes	7:117652877:C:G
c.-9_14del	p.?	124del23bp	Excluded	Outside of 95% coverage threshold		7:117480081:GCGCCCGAGAGACCATGCAGAGGT:G
c.1A>G	p.Met1?	M1V	Excluded	Outside of 95% coverage threshold		7:117480095:A:G
c.11C>A	p.Ser4Ter	S4X	Excluded	Outside of 95% coverage threshold		7:117480105:C:A
c.38C>T	p.Ser13Phe	S13F	Excluded	Absent from gnomAD		7:117480132:C:T
c.50dup	p.Ser18GlnfsTer27	175insT	Excluded	Outside of 95% coverage threshold		7:117480137:C:CT
c.50del	p.Phe17SerfsTer8	182delT	Excluded	Absent from gnomAD		7:117480137:CT:C
c.44T>C	p.Leu15Pro	L15P	Excluded	Absent from gnomAD		7:117480138:T:C
c.53+1G>T	p.?	185+1G->T	Excluded	Outside of 95% coverage threshold		7:117480148:G:T

					GCTGACCAAGTGATTACTGCTTATAAATTCACCATTTTATGGAGA AGAAGCAAACACTGCTAAATACCTTGTGGAATCAGAGGAGGGG AAATTAGTAACTTGACCCCAATACTGCGATTTTAAATTGAATTCT TGAAGCCTACAAGTTTTACACAGGACTTTAGAGAGCTGGATAGT ATCACTTTGTCAAGTCCTACTTTTACTATGATTCTTTGAGAAAAA TACATCTGACTAAATAACTCTGAATCTAAATTGGATAAAATAAA TGTGACATTCAAAATGTTATTTATGATTTTAGAAAAATATCCTTA TAGACACTAGATGAGTTTTAGTCTCAAATCAATCCTCCCTATCAT AGTCACTTATCAAAATAACTAAAGCAAAGTGGTAGAGCTGTGCT CTAGAAGTTTGGGATTTATGATCACAATCTTTTCCAATGAGTCCC CTCTTTCCTCTGCCTGTCTTCAACATTTGTTTTTTTTTTTTTTTGGT TAGGACTATCCAGATTGTGTGGCCTATTTCAAACTCATGGCAAA TACATTGGATGATCAGAAATTTTCTAATGTATTTGAATTTGTCTA CACAAACTAGAGTAATTGCTATTAATTCCTCAAGTGTTAATTATT TCATGCAAAAAGGAAAAAGGCTATTAGTCTTTAAGTGTATTAGT ATGTCAATATTTGGGAGAAGTGTCATGCAATTAGTGGTTTGAAT TTCCTATTTTATTTTATTGCATTTTATTTTATTTGCCTAGTCAAATA AAAAGTAATGTTAAATACATGGAAGCATGATTGTTTTCTACACT AAAAATCATTTTGACTTGAAAAGATCTGATATCCATGACCTTCAT CTGAAGTTTTGGCAGATGAAAATGTCAGATGCGTCTTTTGGATT AATAAAAGGCAAAAGTCAGATCGAAAAATGAGTATAAGCTTTA ATTATATGACTTTAGGAGGATATGTTATGAAAATCAAAGCTTTA ATAGTGATTATAATTGGCAAGTTCTTTTTTTATAAGGAATTACAA GTCACTCTATACAAAAATTGGAATTTTTGTCCTAAGAAATGAAA TTTACTATAGTTTCATCTGTGTGTGTGTGTGTGTGTGTGTGTGTG TGTGTTTAAAAAATCAAGTGATAGGGCTTTTCCTCAATAAAATCT GAAATCTCTTATAGTTAAGTGAACAGAACAGTGTATCTAGGATG
c.54-5940_273+10250del	p.?	CFTRdele2,3	Excluded	Structural variant	CTAGACTTTTTTTTCAAAGTTAGTTTAAAACTTATACATAGTAAA ACTTGACCCCAATACTGCGATTTTAAATTGAATTCTTGAAGCCTA CAAGTTTTACACAGGACTTTAGAGAGCTGGATAGTATCACTTTG TCAAGTCCTACTTTTACTATGATTCTTTGAGAAAAATACATCTGA CTAAATAACTCTGAATCTAAATTGGATAAAATAAATGTGACATT CAAAATGTTATTTATGATTTTAGAAAAATATCCTTATAGACACTA GATGAGTTTTAGTCTCAAATCAATCCTCCCTATCATAGTCACTTA TCAAAATAACTAAAGCAAAGTGGTAGAGCTGTGCTCTAGAAGTT TGGGATTTATGATCACAATCTTTTCCAATGAGTCCCCTCTTTCCTC TGCCTGTCTTCAACATTTGTTTTTTTTTTTTTTTGGTTAGGACTAT CCAGATTGTGTGGCCTATTTCAAACTCATGGCAAATACATTGGA TGATCAGAAATTTTCTAATGTATTTGAATTTGTCTACACAAACTA GAGTAATTGCTATTAATTCCTCAAGTGTTAATTATTTCATGCAAA AAGGAAAAAGGCTATTAGTCTTTAAGTGTATTAGTATGTCAATA TTTGGGAGAAGTGTCATGCAATTAGTGGTTTGAATTTCCTATTTT ATTTTATTGCATTTTATTTTATTTGCCTAGTCAAATAAAAAGTAAT GTTAAATACATGGAAGCATGATTGTTTTCTACACTAAAAATCATT TTGACTTGAAAAGATCTGATATCCATGACCTTCATCTGAAGTTTT GGCAGATGAAAATGTCAGATGCGTCTTTTGGATTAATAAAAGG CAAAAGTCAGATCGAAAAATGAGTATAAGCTTTAATTATATGAC TTTAGGAGGATATGTTATGAAAATCAAAGCTTTAATAGTGATTA TAATTGGCAAGTTCTTTTTTTATAAGGAATTACAAGTCACTCTAT ACAAAAATTGGAATTTTTGTCCTAAGAAATGAAATTTACTATAG TTTCATCTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTTTAAA AAATCAAGTGATAGGGCTTTTCCTCAATAAAATCTGAAATCTCTT ATAGTTAAGTGAACAGAACAGTGTATCTAGGATGCTAGACTTTT TTTTCAAAGTTAGTTTAAAACTTATACATAGTAAAATCTGTATGC CTTAGGGATCTCTGTTTGCTATCCCATAGTGAATGATTAATTAGT
c.54-5842_489+401del	p.?	IVSI-5842_IVS4+401del	Excluded	Structural variant	TTCTGTTAGAAATAGTCAGAACTAGGCTGGGTGTGGTGGTGGCT
c.57G>A	p.Trp19Ter	W19X	Excluded	Absent from gnomAD	7:117504256:G:A
c.79G>A	p.Gly27Arg	G27R	Excluded	Absent from gnomAD	7:117504278:G:A
c.79G>T	p.Gly27Ter	G27X	Excluded	Outside of 95% coverage threshold	7:117504278:G:T
c.88C>T	p.Gln30Ter	Q30X	Excluded	Absent from gnomAD	7:117504287:C:T
c.115C>T	p.Gln39Ter	Q39X	Excluded	Absent from gnomAD	7:117504314:C:T

c.137C>A	p.Ala46Asp	A46D	Excluded	Absent from gnomAD	7:117504336:C:A
c.164+1G>A	p.?	296+1G->A	Excluded	Absent from gnomAD	7:117504364:G:A
c.164+1G>T	p.?	296+1G->T	Excluded	Absent from gnomAD	7:117504364:G:T
c.164+2T>C	p.?	296+2T->C	Excluded	Absent from gnomAD	7:117504365:T:C
c.164+4dup	p.?	296+3insT	Excluded	Absent from gnomAD	7:117504366:A:AT
c.165-1G>A	p.?	297-1G->A	Excluded	Absent from gnomAD	7:117509033:G:A
c.166G>A	p.Glu56Lys	E56K	Excluded	Outside of 95% coverage threshold	7:117509035:G:A
c.168del	p.Glu56AspfsTer35	300delA	Excluded	Absent from gnomAD	7:117509035:GA:G
c.169T>G	p.Trp57Gly	W57G	Excluded	Absent from gnomAD	7:117509038:T:G
c.170G>A	p.Trp57Ter	W57X	Excluded	Absent from gnomAD	7:117509039:G:A
c.171G>A	p.Trp57Ter	W57X	Excluded	Absent from gnomAD	7:117509040:G:A
c.174_177del	p.Asp58GlufsTer32	306delTAGA	Excluded	Absent from gnomAD	7:117509040:GGATA:G
c.175dup	p.Arg59LysfsTer10	306insA	Excluded	Absent from gnomAD	7:117509043:T:TA
c.178G>A	p.Glu60Lys	E60K	Excluded	Absent from gnomAD	7:117509047:G:A
c.202A>T	p.Lys68Ter	K68X	Excluded	Absent from gnomAD	7:117509071:A:T
c.233dup	p.Trp79LeufsTer32	365-366insT	Excluded	Outside of 95% coverage threshold	7:117509096:G:GT
c.263T>A	p.Leu88Ter	L88X	Excluded	Absent from gnomAD	7:117509132:T:A
c.263T>G	p.Leu88Ter	L88X	Excluded	Outside of 95% coverage threshold	7:117509132:T:G
c.273+1G>A	p.?	405+1G->A	Excluded	Outside of 95% coverage threshold	7:117509143:G:A
c.273+3A>C	p.?	405+3A->C	Excluded	Absent from gnomAD	7:117509145:A:C
c.274-2A>G	p.?	406-2A->G	Excluded	Absent from gnomAD	7:117530897:A:G
c.274G>A	p.Glu92Lys	E92K	Excluded	Absent from gnomAD	7:117530899:G:A
c.274G>T	p.Glu92Ter	E92X	Excluded	Outside of 95% coverage threshold	7:117530899:G:T
c.296C>T	p.Pro99Leu	P99L	Excluded	Outside of 95% coverage threshold	7:117530921:C:T
c.305T>G	p.Leu102Arg	L102R	Excluded	Outside of 95% coverage threshold	7:117530930:T:G
c.310del	p.Arg104GlufsTer3	442delA	Excluded	Absent from gnomAD	7:117530933:GA:G
c.325_327delinsG	p.Tyr109GlyfsTer4	457TAT->G	Excluded	Absent from gnomAD	7:117530950:TAT:G
c.327T>A	p.Tyr109Ter	Y109X	Excluded	Absent from gnomAD	7:117530952:T:A
c.346G>A	p.Glu116Lys	E116K	Excluded	Absent from gnomAD	7:117530971:G:A
c.350G>C	p.Arg117Pro	R117P	Excluded	Absent from gnomAD	7:117530975:G:C
c.366T>A	p.Tyr122Ter	Y122X	Excluded	Absent from gnomAD	7:117530991:T:A
c.377G>A	p.Gly126Asp	G126D	Excluded	Outside of 95% coverage threshold	7:117531002:G:A
c.409del	p.Leu137SerfsTer16	541delC	Excluded	Absent from gnomAD	7:117531033:GC:G
c.413_415dup	p.Leu138dup	L138ins	Excluded	Outside of 95% coverage threshold	7:117531036:C:CCTA
c.416A>G	p.His139Arg	H139R	Excluded	Absent from gnomAD	7:117531041:A:G
c.424del	p.Ile142PhefsTer11	556delA	Excluded	Absent from gnomAD	7:117531048:CA:C
c.429del	p.Phe143LeufsTer10	557delT	Excluded	Absent from gnomAD	7:117531049:AT:A
c.442del	p.Ile148LeufsTer5	574delA	Excluded	Absent from gnomAD	7:117531066:CA:C
c.470_483del	p.Phe157Ter	602del14	Excluded	Absent from gnomAD	7:117531093:GTTTAGTTTGATTTA:G
c.481T>G	p.Tyr161Asp	Y161D	Excluded	Absent from gnomAD	7:117531106:T:G
c.494T>C	p.Leu165Ser	L165S	Excluded	Absent from gnomAD	7:117534280:T:C
c.531dup	p.Gly178TrpfsTer5	663insT	Excluded	Absent from gnomAD	7:117534315:A:AT
c.531del	p.Ile177MetfsTer12	663delT	Excluded	Absent from gnomAD	7:117534315:AT:A
c.532G>A	p.Gly178Arg	G178R	Excluded	Outside of 95% coverage threshold	7:117534318:G:A
c.543_546del	p.Leu183PhefsTer5	675del4	Excluded	Absent from gnomAD	7:117534326:TGTTA:T
c.575A>G	p.Asp192Gly	D192G	Excluded	Absent from gnomAD	7:117534361:A:G
c.577G>A	p.Glu193Lys	E193K	Excluded	Outside of 95% coverage threshold	7:117534363:G:A
c.577G>T	p.Glu193Ter	E193X	Excluded	Absent from gnomAD	7:117534363:G:T
c.579+5G>A	p.?	711+5G->A	Excluded	Absent from gnomAD	7:117534370:G:A
c.580-2A>G	p.?	712-2A->G	Excluded	Outside of 95% coverage threshold	7:117535246:A:G
c.580-1G>T	p.?	712-1G->T	Excluded	Outside of 95% coverage threshold	7:117535247:G:T
c.580G>A	p.Gly194Arg	G194R	Excluded	Absent from gnomAD	7:117535248:G:A
c.580G>T	p.Gly194Ter	G194X	Excluded	Absent from gnomAD	7:117535248:G:T
c.595C>T	p.His199Tyr	H199Y	Excluded	Outside of 95% coverage threshold	7:117535263:C:T
c.613C>T	p.Pro205Ser	P205S	Excluded	Outside of 95% coverage threshold	7:117535281:C:T
c.647G>A	p.Trp216Ter	W216X	Excluded	Outside of 95% coverage threshold	7:117535315:G:A
c.658C>T	p.Gln220Ter	Q220X	Excluded	Outside of 95% coverage threshold	7:117535326:C:T
c.675T>A	p.Cys225Ter	C225X	Excluded	Absent from gnomAD	7:117535343:T:A
c.680T>G	p.Leu227Arg	L227R	Excluded	Absent from gnomAD	7:117535348:T:G
c.717del	p.Leu240Ter	849delG	Excluded	Absent from gnomAD	7:117535382:TG:T
c.723_743+1del	p.?	852del22	Excluded	Absent from gnomAD	7:117535387:TAGGGAGAATGATGATGAAGTAC:T

c.744-2A>G	p.?	876-2A->G	Excluded	Absent from gnomAD	7:117536546:A:G
c.761del	p.Lys254ArgfsTer7	892delA	Excluded	Absent from gnomAD	7:117536563:GA:G
c.825C>G	p.Tyr275Ter	Y275X	Excluded	Outside of 95% coverage threshold	7:117536629:C:G
c.828C>A	p.Cys276Ter	C276X	Excluded	Outside of 95% coverage threshold	7:117536632:C:A
c.850dup	p.Met284AsnfsTer3	977insA	Excluded	Absent from gnomAD	7:117536648:G:GA
c.861_865del	p.Asn287LysfsTer19	991del5	Excluded	Outside of 95% coverage threshold	7:117536662:AAACTT:A
c.933C>A	p.Phe311Leu	F311L	Excluded	Absent from gnomAD	7:117540163:C:A
c.933C>G	p.Phe311Leu	F311L	Excluded	Absent from gnomAD	7:117540163:C:G
c.948del	p.Phe316LeufsTer12	1078delT	Excluded	Outside of 95% coverage threshold	7:117540175:CT:C
c.987del	p.Gly330GlufsTer39	1119delA	Excluded	Absent from gnomAD	7:117540214:CA:C
c.1001G>T	p.Arg334Leu	R334L	Excluded	Outside of 95% coverage threshold	7:117540231:G:T
c.1006_1007insG	p.Ile336SerfsTer28	1138insG	Excluded	Outside of 95% coverage threshold	7:117540236:A:AG
c.1007T>A	p.Ile336Lys	I336K	Excluded	Outside of 95% coverage threshold	7:117540237:T:A
c.1021T>C	p.Ser341Pro	S341P	Excluded	Absent from gnomAD	7:117540251:T:C
c.1037T>C	p.Leu346Pro	L346P	Excluded	Absent from gnomAD	7:117540267:T:C
c.1057C>T	p.Gln353Ter	Q353X	Excluded	Absent from gnomAD	7:117540287:C:T
c.1081del	p.Trp361GlyfsTer8	1213delT	Excluded	Outside of 95% coverage threshold	7:117540310:AT:A
c.1116+1G>A	p.?	1248+1G->A	Excluded	Outside of 95% coverage threshold	7:117540347:G:A
c.1117-1G>A	p.?	1249-1G->A	Excluded	Absent from gnomAD	7:117542015:G:A
c.1130dup	p.Gln378AlafsTer4	1259insA	Excluded	Absent from gnomAD	7:117542025:C:CA
c.1135G>T	p.Glu379Ter	E379X	Excluded	Outside of 95% coverage threshold	7:117542034:G:T
c.1202G>A	p.Trp401Ter	W401X	Excluded	Absent from gnomAD	7:117542101:G:A
c.1203G>A	p.Trp401Ter	W401X	Excluded	Outside of 95% coverage threshold	7:117542102:G:A
c.1209+1G>A	p.?	1341+1G->A	Excluded	Absent from gnomAD	7:117542109:G:A
c.1210-2A>C	p.?	1342-2A->C	Excluded	Absent from gnomAD	7:117548639:A:C
c.1211del	p.Gly404AspfsTer38	1343delG	Excluded	Absent from gnomAD	7:117548639:AG:A
c.1240C>T	p.Gln414Ter	Q414X	Excluded	Absent from gnomAD	7:117548671:C:T
c.1301_1307del	p.Ser434LeufsTer6	1429del7	Excluded	Absent from gnomAD	7:117548727:TTTCTCAC:T
c.1330_1331del	p.Ile444Ter	1460delAT	Excluded	Absent from gnomAD	7:117548758:GAT:G
c.1340del	p.Lys447ArgfsTer2	1471delA	Excluded	Outside of 95% coverage threshold	7:117548769:CA:C
c.1358T>C	p.Leu453Ser	L453S	Excluded	Absent from gnomAD	7:117548789:T:C
c.1365_1366del	p.Val456CysfsTer25	1497delGG	Excluded	Absent from gnomAD	7:117548795:CGG:C
c.1301C>A	p.Ser434Ter	S434X	Excluded	Absent from gnomAD	7:117548732:C:A
c.1301C>G	p.Ser434Ter	S434X	Excluded	Absent from gnomAD	7:117548732:C:G
c.1393-2A>G	p.?	1525-2A->G	Excluded	Outside of 95% coverage threshold	7:117559462:A:G
c.1397C>A	p.Ser466Ter	S466X	Excluded	Absent from gnomAD	7:117559468:C:A
c.1418del	p.Gly473GlufsTer54	1548delG	Excluded	Outside of 95% coverage threshold	7:117559486:TG:T
c.1420G>A	p.Glu474Lys	E474K	Excluded	Absent from gnomAD	7:117559491:G:A
c.1466C>A	p.Ser489Ter	S489X	Excluded	Outside of 95% coverage threshold	7:117559537:C:A
c.1475C>T	p.Ser492Phe	S492F	Excluded	Outside of 95% coverage threshold	7:117559546:C:T
c.1477_1478del	p.Gln493ValfsTer10	1609delCA	Excluded	Absent from gnomAD	7:117559547:TCA:T
c.1477C>T	p.Gln493Ter	Q493X	Excluded	Outside of 95% coverage threshold	7:117559548:C:T
c.1487G>A	p.Trp496Ter	W496X	Excluded	Absent from gnomAD	7:117559558:G:A
c.1505T>C	p.Ile502Thr	I502T	Excluded	Outside of 95% coverage threshold	7:117559576:T:C
c.1538A>G	p.Asp513Gly	D513G	Excluded	Outside of 95% coverage threshold	7:117559609:A:G
c.1545_1546del	p.Tyr515Ter	1677delTA	Excluded	Absent from gnomAD	7:117559612:AAT:A
c.1558G>T	p.Val520Phe	V520F	Excluded	Outside of 95% coverage threshold	7:117559629:G:T
c.1573C>T	p.Gln525Ter	Q525X	Excluded	Absent from gnomAD	7:117559644:C:T
c.1585-8G>A	p.?	1717-8G->A	Excluded	Absent from gnomAD	7:117587731:G:A
c.1585-2A>G	p.?	1717-2A->G	Excluded	Absent from gnomAD	7:117587737:A:G
c.1645A>C	p.Ser549Arg	S549R	Excluded	Outside of 95% coverage threshold	7:117587799:A:C
c.1647T>A	p.Ser549Arg	S549R	Excluded	Absent from gnomAD	7:117587801:T:A
c.1648G>T	p.Gly550Ter	G550X	Excluded	Absent from gnomAD	7:117587802:G:T
c.1650del	p.Gly551ValfsTer8	1782delA	Excluded	Absent from gnomAD	7:117587803:GA:G
c.1654C>T	p.Gln552Ter	Q552X	Excluded	Absent from gnomAD	7:117587808:C:T
c.1670del	p.Ser557PhefsTer2	1802delC	Excluded	Absent from gnomAD	7:117587823:TC:T
c.1679G>A	p.Arg560Lys	R560K	Excluded	Absent from gnomAD	7:117587833:G:A
c.1679+1G>C	p.?	1811+1G->C	Excluded	Absent from gnomAD	7:117587834:G:C
c.1680-877G>T	p.?	1811+1643G->T	Excluded	Absent from gnomAD	7:117589476:G:T
c.1680-1G>A	p.?	1812-1G->A	Excluded	Outside of 95% coverage threshold	7:117590352:G:A
c.1687T>A	p.Tyr563Asn	Y563N	Excluded	Outside of 95% coverage threshold	7:117590360:T:A

c.1687T>G	p.Tyr563Asp	Y563D	Excluded	Absent from gnomAD	7:117590360:T:G
c.1689C>A	p.Tyr563Ter	Y563X	Excluded	Absent from gnomAD	7:117590362:C:A
c.1703del	p.Leu568CysfsTer4	1833delT	Excluded	Absent from gnomAD	7:117590373:AT:A
c.1721C>A	p.Pro574His	P574H	Excluded	Outside of 95% coverage threshold	7:117590394:C:A
c.1731C>A	p.Tyr577Ter	Y577X	Excluded	Absent from gnomAD	7:117590404:C:A
c.1766+1G>C	p.?	1898+1G->C	Excluded	Outside of 95% coverage threshold	7:117590440:G:C
c.1766+1G>T	p.?	1898+1G->T	Excluded	Absent from gnomAD	7:117590440:G:T
c.1766+2T>A	p.?	1898+2T->A	Excluded	Absent from gnomAD	7:117590441:T:A
c.1766+3A>G	p.?	1898+3A->G	Excluded	Outside of 95% coverage threshold	7:117590442:A:G
c.1792_1798del	p.Lys598GlyfsTer11	1924del7	Excluded	Absent from gnomAD	7:117591958:CAAAACTA:C
c.1801A>T	p.Ile601Phe	I601F	Excluded	Outside of 95% coverage threshold	7:117591968:A:T
c.1820_1903del	p.Met607_Gln634del	1949del84	Excluded	Outside of 95% coverage threshold	7:117591983:AAAATGGAACATTTAAAGAAAGCTGACAAAATA TTAATTTTGCATGAAGGTAGCAGCTATTTTTATGGGACATTTTCA GAACTCC:A
c.1826A>G	p.His609Arg	H609R	Excluded	Outside of 95% coverage threshold	7:117591993:A:G
c.1882G>C	p.Gly628Arg	G628R	Excluded	Absent from gnomAD	7:117592049:G:C
c.1911del	p.Gln637HisfsTer26	2043delG	Excluded	Absent from gnomAD	7:117592077:AG:A
c.1920_1921dup	p.Ser641IlefsTer23	2053insTA	Excluded	Absent from gnomAD	7:117592086:T:TTA
c.1923_1931delinsA	p.Ser641ArgfsTer5	2055del9->A	Excluded	Absent from gnomAD	7:117592090:CTCAAAACT:A
c.1943del	p.Asp648ValfsTer15	2075delA	Excluded	Absent from gnomAD	7:117592109:GA:G
c.1966G>T	p.Glu656Ter	E656X	Excluded	Absent from gnomAD	7:117592133:G:T
c.1973_1985delinsAGAAA	p.Arg658LysfsTer4	2105-2117del13insAGAAA	Excluded	Absent from gnomAD	7:117592140:GAAATTCAATCCT:AGAAA
c.1986_1989del	p.Thr663ArgfsTer8	2118del4	Excluded	Absent from gnomAD	7:117592150:CCTAA:C
c.1990G>T	p.Glu664Ter	E664X	Excluded	Absent from gnomAD	7:117592157:G:T
c.2012del	p.Leu671Ter	2143delT	Excluded	Outside of 95% coverage threshold	7:117592177:AT:A
c.2017G>T	p.Gly673Ter	G673X	Excluded	Outside of 95% coverage threshold	7:117592184:G:T
c.2051_2052delinsG	p.Lys684SerfsTer38	2183AA->G	Excluded	Absent from gnomAD	7:117592218:AA:G
c.2053dup	p.Gln685ProfsTer4	2185insC	Excluded	Absent from gnomAD	7:117592219:A:AC
c.2053C>T	p.Gln685Ter	Q685X	Excluded	Absent from gnomAD	7:117592220:C:T
c.2128A>T	p.Lys710Ter	K710X	Excluded	Absent from gnomAD	7:117592295:A:T
c.2143C>T	p.Gln715Ter	Q715X	Excluded	Absent from gnomAD	7:117592310:C:T
c.2158C>T	p.Gln720Ter	Q720X	Excluded	Outside of 95% coverage threshold	7:117592325:C:T
c.2195T>G	p.Leu732Ter	L732X	Excluded	Outside of 95% coverage threshold	7:117592362:T:G
c.2215del	p.Val739TyrfsTer16	2347delG	Excluded	Outside of 95% coverage threshold	7:117592381:AG:A
c.2233G>T	p.Gly745Ter	G745X	Excluded	Absent from gnomAD	7:117592400:G:T
c.2241_2248del	p.Ile748SerfsTer28	2372del8	Excluded	Absent from gnomAD	7:117592405:GGCGATACT:G
c.2423_2424dup	p.Ser809IlefsTer13	2556insAT	Excluded	Absent from gnomAD	7:117592583:G:GAT
c.2453del	p.Leu818TrpfsTer3	2585delT	Excluded	Absent from gnomAD	7:117592618:CT:C
c.2463_2464del	p.Ser821ArgfsTer4	2594delGT	Excluded	Absent from gnomAD	7:117592628:AGT:A
c.2464G>T	p.Glu822Ter	E822X	Excluded	Outside of 95% coverage threshold	7:117592631:G:T
c.2491G>T	p.Glu831Ter	E831X	Excluded	Outside of 95% coverage threshold	7:117594930:G:T
c.2502dup	p.Asp835Ter	2634insT	Excluded	Outside of 95% coverage threshold	7:117594935:C:CT
c.2537G>A	p.Trp846Ter	W846X	Excluded	Outside of 95% coverage threshold	7:117594976:G:A
c.2538G>A	p.Trp846Ter	W846X	Excluded	Outside of 95% coverage threshold	7:117594977:G:A
c.2547C>A	p.Tyr849Ter	Y849X	Excluded	Absent from gnomAD	7:117594986:C:A
c.2551C>T	p.Arg851Ter	R851X	Excluded	Absent from gnomAD	7:117594990:C:T
c.2583del	p.Phe861LeufsTer3	2711delT	Excluded	Absent from gnomAD	7:117595017:AT:A
c.2589_2599del	p.Ile864SerfsTer28	2721del11	Excluded	Absent from gnomAD	7:117595022:TGTGCTAATTTG:T
c.2601dup	p.Val868SerfsTer28	2732insA	Excluded	Absent from gnomAD	7:117595039:T:TA
c.2645G>A	p.Trp882Ter	W882X	Excluded	Absent from gnomAD	7:117602851:G:A
c.2658-1G>C	p.?	2790-1G->C	Excluded	Outside of 95% coverage threshold	7:117603531:G:C
c.2735C>A	p.Ser912Ter	S912X	Excluded	Absent from gnomAD	7:117603609:C:A
c.2737_2738insG	p.Tyr913Ter	2869insG	Excluded	Absent from gnomAD	7:117603611:T:TG
c.2763_2764dup	p.Val922GlufsTer2	2896insAG	Excluded	Outside of 95% coverage threshold	7:117603635:G:GGA
c.2780T>C	p.Leu927Pro	L927P	Excluded	Absent from gnomAD	7:117603654:T:C
c.2810dup	p.Val938GlyfsTer37	2942insT	Excluded	Outside of 95% coverage threshold	7:117603683:C:CT
c.2822del	p.Leu941GlnfsTer27	2954delT	Excluded	Outside of 95% coverage threshold	7:117603695:CT:C
c.2825del	p.Ile942ThrfsTer26	2957delT	Excluded	Absent from gnomAD	7:117603698:AT:A
c.2859_2890del	p.Leu953PhefsTer11	2991del32	Excluded	Outside of 95% coverage threshold	7:117603732:TACATTCTGTTCTTCAAGCACCTATGTCAACCC:T
c.2875del	p.Ala959HisfsTer9	3007delG	Excluded	Outside of 95% coverage threshold	7:117603748:AG:A
c.2896del	p.Thr966ArgfsTer2	3028delA	Excluded	Absent from gnomAD	7:117603769:CA:C

c.2908G>C	p.Gly970Arg	G970R	Excluded	Absent from gnomAD	7:117603782:G:C
c.2936A>T	p.Asp979Val	D979V	Excluded	Absent from gnomAD	7:117606701:A:T
c.2989-977_3367+248del	p.?	3121-977_3499+248del2515	Excluded	Structural variant	TATTAAGTATGATTTATTTCAATGTTAAGCATGAGAAAATATGCT CCGAAAGGTTAGATAGCTTGCCTAAATGACAAGCTTGTATTTCA AGCAGAACTTTCTGAATCAAAAGACTCCAAGACGAATGCCCAGC TTTCAAAAACTGTCTAACCAAAATAAATCCTAAGATTCACCTTCA TACTAAAATTATTTAAAAATAGTTTATTTTAAATTAATATTCACTT AAAATGTATTTATCATGCAATACTTTAAAGTGTCTGGGAAATGA AAATATCCAAAGATCAAAGAACACCATGTTTTCAAACTTCAAAA ATGTTATCAGTGACCTAAACAATTTTTAAAATTTTCATAGAGCCT ATGAAAAATGTACTTGCAAATGGCTACTTTCTGACTAGGAATAG AATGGGGAGAGTATTTAGTCCAACAATGATAGACTGGATTAAG AAAATGTGGCACATATACACCATGGAACACTATGCAGCCATAAA AAATGATGAGTTCATGTCCTTTGTAGGGACATGGATGAAATTGG AAAACATCATTCTCAGTAAACTATCGCAAGAACAAAAAACCAAA CACCGCATATTCTCACTCATAGGTGGGAATTGAACAATGAGATC ACATGGACACAGGAAGGGGAATATCACACTCTGGGGACTGTTG TGGGGTGGGGGGAGGGGGGAGGGATAGCACTGGGAGATATA CCTAATGCTAGATGACGAGTTAGTGGGTGCAGTGCACCAGCAT GGCACATGTATACATATGTAACTAACCTGCACAATGTGCACATG TACCCTAAAACTTAAAGTATAATAAAAAAAATAAAAAAAAGTTT GAGGTGTTTAAAGTATGCAAAAAAAAAAAAAGAAATAAATCAC TGACACACTTTGTCCACTTTGCAATGTGAAAATGTTTACTCACCA ACATGTTTTCTTTGATCTTACAGTTGTTATTAATTGTGATTGGAG CTATAGCAGTTGTCGCAGTTTTACAACCCTACATCTTTGTTGCAA CAGTGCCAGTGATAGTGGCTTTTATTATGTTGAGAGCATATTTCC TCCAAACCTCACAGCAACTCAAACAACTGGAATCTGAAGGTATG ACAGTGAATGTGCGATACTCATCTTGTAAAAAAGCTATAAGAGC TATTTGAGATTCTTTATTGTTAATCTACTTAAAAAAAATTCTGCTT TTAAACTTTTACATCATATAACAATAATTTTTTTCTACATGCATGT
c.2989-2A>G	p.?	3121-2A->G	Excluded	Absent from gnomAD	7:117610517:A:G
c.2989-1G>A	p.?	3121-1G->A	Excluded	Outside of 95% coverage threshold	7:117610518:G:A
c.2998del	p.Ile1000LeufsTer2	3130delA	Excluded	Absent from gnomAD	7:117610526:TA:T
c.3002_3003del	p.Val1001AspfsTer45	3132delTG	Excluded	Absent from gnomAD	7:117610529:TTG:T
c.3011_3019del	p.Ala1004_Ala1006del	3143del9	Excluded	Absent from gnomAD	7:117610538:GAGCTATAGC:G
c.3017C>A	p.Ala1006Glu	A1006E	Excluded	Outside of 95% coverage threshold	7:117610547:C:A
c.3039dup	p.Tyr1014LeufsTer33	3171insC	Excluded	Absent from gnomAD	7:117610566:A:AC
c.3039del	p.Tyr1014ThrfsTer9	3171delC	Excluded	Absent from gnomAD	7:117610566:AC:A
c.3103C>T	p.Gln1035Ter	Q1035X	Excluded	Outside of 95% coverage threshold	7:117610633:C:T
c.3124C>T	p.Gln1042Ter	Q1042X	Excluded	Outside of 95% coverage threshold	7:117610654:C:T
c.3139_3139+1del	p.?	3271delGG	Excluded	Outside of 95% coverage threshold	7:117610668:AGG:A
c.3160C>G	p.His1054Asp	H1054D	Excluded	Absent from gnomAD	7:117611601:C:G
c.3181G>C	p.Gly1061Arg	G1061R	Excluded	Outside of 95% coverage threshold	7:117611622:G:C
c.3194T>C	p.Leu1065Pro	L1065P	Excluded	Absent from gnomAD	7:117611635:T:C
c.3217dup	p.Tyr1073LeufsTer3	3349insT	Excluded	Outside of 95% coverage threshold	7:117611656:C:CT
c.3230T>C	p.Leu1077Pro	L1077P	Excluded	Outside of 95% coverage threshold	7:117611671:T:C
c.3276C>A	p.Tyr1092Ter	Y1092X	Excluded	Outside of 95% coverage threshold	7:117611717:C:A
c.3276C>G	p.Tyr1092Ter	Y1092X	Excluded	Absent from gnomAD	7:117611717:C:G
c.3292T>C	p.Trp1098Arg	W1098R	Excluded	Absent from gnomAD	7:117611733:T:C
c.3293G>A	p.Trp1098Ter	W1098X	Excluded	Absent from gnomAD	7:117611734:G:A
c.3294G>A	p.Trp1098Ter	W1098X	Excluded	Absent from gnomAD	7:117611735:G:A
c.3294G>T	p.Trp1098Cys	W1098C	Excluded	Absent from gnomAD	7:117611735:G:T
c.3302T>A	p.Met1101Lys	M1101K	Excluded	Outside of 95% coverage threshold	7:117611743:T:A
c.3302T>G	p.Met1101Arg	M1101R	Excluded	Absent from gnomAD	7:117611743:T:G
c.3304A>T	p.Arg1102Ter	R1102X	Excluded	Absent from gnomAD	7:117611745:A:T
c.3310G>T	p.Glu1104Ter	E1104X	Excluded	Absent from gnomAD	7:117611751:G:T
c.3365del	p.Thr1122LysfsTer12	3497delC	Excluded	Absent from gnomAD	7:117611805:AC:A
c.3368-2A>G	p.?	3500-2A->G	Excluded	Outside of 95% coverage threshold	7:117614611:A:G
c.3382A>T	p.Arg1128Ter	R1128X	Excluded	Absent from gnomAD	7:117614627:A:T
c.3435G>A	p.Trp1145Ter	W1145X	Excluded	Absent from gnomAD	7:117614680:G:A
c.3468G>A	p.Leu1156=	3600G->A	Excluded	Outside of 95% coverage threshold	7:117614713:G:A

c.3468+2dup	p.?	3600+2insT	Excluded	Absent from gnomAD	7:117614714:G:GT
c.3468+5G>A	p.?	3600+5G->A	Excluded	Absent from gnomAD	7:117614718:G:A
c.3475T>C	p.Ser1159Pro	S1159P	Excluded	Outside of 95% coverage threshold	7:117627528:T:C
c.3476C>T	p.Ser1159Phe	S1159F	Excluded	Outside of 95% coverage threshold	7:117627529:C:T
c.3532_3535dup	p.Thr1179IlefsTer17	3667ins4	Excluded	Absent from gnomAD	7:117627584:G:GTCAA
c.3587C>G	p.Ser1196Ter	S1196X	Excluded	Outside of 95% coverage threshold	7:117627640:C:G
c.3600del	p.Asp1201MetfsTer10	3732delA	Excluded	Absent from gnomAD	7:117627650:GA:G
c.3605del	p.Asp1202AlafsTer9	3737delA	Excluded	Absent from gnomAD	7:117627657:GA:G
c.3611G>A	p.Trp1204Ter	W1204X	Excluded	Absent from gnomAD	7:117627664:G:A
c.3691del	p.Ser1231ProfsTer4	3821delT	Excluded	Absent from gnomAD	7:117627741:AT:A
c.3700A>G	p.Ile1234Val	I1234V	Excluded	Outside of 95% coverage threshold	7:117627753:A:G
c.3717G>A	p.Arg1239=	3849G->A	Excluded	Outside of 95% coverage threshold	7:117627770:G:A
c.3717+4A>G	p.?	3849+4A->G	Excluded	Absent from gnomAD	7:117627774:A:G
c.3717+40A>G	p.?	3849+40A->G	Excluded	Absent from gnomAD	7:117627810:A:G
c.3718-3T>G	p.?	3850-3T->G	Excluded	Outside of 95% coverage threshold	7:117642435:T:G
c.3718-1G>A	p.?	3850-1G->A	Excluded	Absent from gnomAD	7:117642437:G:A
c.3719T>G	p.Val1240Gly	V1240G	Excluded	Outside of 95% coverage threshold	7:117642439:T:G
c.3731G>A	p.Gly1244Glu	G1244E	Excluded	Outside of 95% coverage threshold	7:117642451:G:A
c.3747del	p.Lys1250ArgfsTer9	3878delG	Excluded	Absent from gnomAD	7:117642464:AG:A
c.3745G>A	p.Gly1249Arg	G1249R	Excluded	Absent from gnomAD	7:117642465:G:A
c.3752G>A	p.Ser1251Asn	S1251N	Excluded	Outside of 95% coverage threshold	7:117642472:G:A
c.3761T>G	p.Leu1254Ter	L1254X	Excluded	Absent from gnomAD	7:117642481:T:G
c.3763T>C	p.Ser1255Pro	S1255P	Excluded	Absent from gnomAD	7:117642483:T:C
c.3773dup	p.Leu1258PhefsTer7	3905insT	Excluded	Outside of 95% coverage threshold	7:117642487:C:CT
c.3806T>A	p.Ile1269Asn	I1269N	Excluded	Absent from gnomAD	7:117642526:T:A
c.3822G>A	p.Trp1274Ter	W1274X	Excluded	Absent from gnomAD	7:117642542:G:A
c.3848G>T	p.Arg1283Met	R1283M	Excluded	Absent from gnomAD	7:117642568:G:T
c.3873+1G>A	p.?	4005+1G->A	Excluded	Absent from gnomAD	7:117642594:G:A
c.3873+2T>C	p.?	4005+2T->C	Excluded	Outside of 95% coverage threshold	7:117642595:T:C
c.3883_3886del	p.Ile1295PhefsTer32	4010del4	Excluded	Absent from gnomAD	7:117652845:GTATT:G
c.3883del	p.Ile1295PhefsTer33	4015delA	Excluded	Absent from gnomAD	7:117652850:TA:T
c.3891dup	p.Gly1298TrpfsTer4	4022insT	Excluded	Absent from gnomAD	7:117652858:C:CT
c.3908del	p.Asn1303ThrfsTer25	4040delA	Excluded	Outside of 95% coverage threshold	7:117652870:GA:G
c.3929G>A	p.Trp1310Ter	W1310X	Excluded	Absent from gnomAD	7:117652897:G:A
c.3937C>T	p.Gln1313Ter	Q1313X	Excluded	Absent from gnomAD	7:117652905:C:T

					GAGTGTTTTTAACTCTGTGGTATCTGAACTATCTTCTCTAACTGC AGGTTGGGCTCAGATCTGTGATAGAACAGTTTCCTGGGAAGCTT GACTTTGTCCTTGTGGATGGGGGCTGTGTCCTAAGCCATGGCCA CAAGCAGTTGATGTGCTTGGCTAGATCTGTTCTCAGTAAGGCGA AGATCTTGCTGCTTGATGAACCCAGTGCTCATTTGGATCCAGTGT GAGTTTCAGATGTTCTGTTACTTAATAGCACAGTGGGAACAGAA TCATTATGCCTGCTTCATGGTGACACATATTTCTATTAGGCTGTC ATGTCTGCGTGTGGGGGTCTCCCCCAAGATATGAAATAATTGCC CAGTGGAAATGAGCATAAATGCATATTTCCTTGCTAAGAGTCTT GTGTTTTCTTCCGAAGATAGTTTTTAGTTTCATACAAACTCTTCCC CCTTGTCAACACATGATGAAGCTTTTAAATACATGGGCCTAATCT GATCCTTATGATTTGCCTTTGTATCCCATTTATACCATAAGCATGT TTATAGCCCCAAATAAAGAAGTACTGGTGATTCTACATAATGAA AAATGTACTCATTTATTAAAGTTTCTTTGAAATATTTGTCCTGTTT ATTTATGGATACTTAGAGTCTACCCCATGGTTGAAAAGCTGATT GTGGCTAACGCTATATCAACATTATGTGAAAAGAACTTAAAGAA ATAAGTAATTTAAAGAGATAATAGAACAATAGACATATTATCAA GGTAAATACAGATCATTACTGTTCTGTGATATTATGTGTGGTATT TTCTTTCTTTTCTAGAACATACCAAATAATTAGAAGAACTCTAAA ACAAGCATTTGCTGATTGCACAGTAATTCTCTGTGAACACAGGA TAGAAGCAATGCTGGAATGCCAACAATTTTTGGTGAGTCTTTAT AACTTTACTTAAGATCTCATTGCCCTTGTAATTCTTGATAACAAT CTCACATGTGATAGTTCCTGCAAATTGCAACAATGTACAAGTTCT TTTCAAAAATATGTATCATACAGCCATCCAGCTTTACTCAAAATA GCTGCACAAGTTTTTCACTTTGATCTGAGCCATGTGGTGAGGTT GAAATATAGTAAATCTAAAATGGCAGCATATTACTAAGTTATGT TTATAAATAGGATATATATACTTTTTGAGCCCTTTATTTGGGGAC
c.3964-78_4242+577del	p.?	CFTRdele22,23	Excluded	Structural variant	CAAGTCATACAAAATACTCTACTGTTTAAGATTTTAAAAAAGGT
c.3971T>C	p.Leu1324Pro	L1324P	Excluded	Absent from gnomAD	7:117664695:T:C
c.3988C>T	p.Gln1330Ter	Q1330X	Excluded	Absent from gnomAD	7:117664712:C:T
c.4004T>C	p.Leu1335Pro	L1335P	Excluded	Absent from gnomAD	7:117664728:T:C
c.4036_4042del	p.Leu1346MetfsTer6	4168delCTAAGCC	Excluded	Absent from gnomAD	7:117664758:TCCTAAGC:T
c.4046G>A	p.Gly1349Asp	G1349D	Excluded	Absent from gnomAD	7:117664770:G:A
c.4077_4080delinsAA	p.Val1360ThrfsTer3	4209TGTT->AA	Excluded	Absent from gnomAD	7:117664801:TGTT:AA
c.4086dup	p.Lys1363Ter	4218insT	Excluded	Absent from gnomAD	7:117664809:G:GT
c.4097T>A	p.Ile1366Asn	I1366N	Excluded	Outside of 95% coverage threshold	7:117664821:T:A
c.4111G>T	p.Glu1371Ter	E1371X	Excluded	Outside of 95% coverage threshold	7:117664835:G:T
c.4124A>C	p.His1375Pro	H1375P	Excluded	Absent from gnomAD	7:117664848:A:C
c.4127_4131del	p.Leu1376SerfsTer8	4259del5	Excluded	Absent from gnomAD	7:117664849:TTTGGA:T
c.4147dup	p.Ile1383AsnfsTer3	4279insA	Excluded	Absent from gnomAD	7:117665466:C:CA
c.4144C>T	p.Gln1382Ter	Q1382X	Excluded	Absent from gnomAD	7:117665466:C:T
c.4197_4198del	p.Cys1400Ter	4326delTC	Excluded	Absent from gnomAD	7:117665515:TTC:T
c.4231C>T	p.Gln1411Ter	Q1411X	Excluded	Absent from gnomAD	7:117665553:C:T
c.4234C>T	p.Gln1412Ter	Q1412X	Excluded	Outside of 95% coverage threshold	7:117665556:C:T
c.4242+1G>A	p.?	4374+1G->A	Excluded	Absent from gnomAD	7:117665565:G:A
c.4242+1G>T	p.?	4374+1G->T	Excluded	Outside of 95% coverage threshold	7:117665565:G:T
c.4251del	p.Glu1418ArgfsTer14	4382delA	Excluded	Absent from gnomAD	7:117666914:GA:G
c.4300_4301dup	p.Ser1435GlyfsTer14	4428insGA	Excluded	Outside of 95% coverage threshold	7:117666961:C:CGA
c.(?_1)_(53+1_54-1)del	p.?	CFTRdele1	Excluded	Structural variant	NA (breakpoints not determined)
c.(?_-1270)_(53+1_54-1)del	p.?	CFTRdelePr-1	Excluded	Structural variant	NA (breakpoints not determined)
c.(1392+1_1393-1)_(1584+1_1585-1)del	p.?	CFTRdele10	Excluded	Structural variant	NA (breakpoints not determined)
c.(1584+1_1585-1)_(1679+1_1680-1)del	p.?	CFTRdele11	Excluded	Structural variant	NA (breakpoints not determined)
c.(164+1_165-1)_(1584_+1_1585-1)del(2619+1_2620-1)_(2988+1_2989-1)del	p.?	CFTRdele3-10,14b-16	Excluded	Structural variant	NA (breakpoints not determined)
c.(1766+1_1767-1)_(2619+1_2620-1)del	p.?	CFTRdele13,14a	Excluded	Structural variant	NA (breakpoints not determined)
c.(2619+1_2620-1)_(3367+1_3368-1)del	p.?	CFTRdele14b-17b	Excluded	Structural variant	NA (breakpoints not determined)
c.(273+1_274-1)_(1116+1_1117-1)del	p.?	CFTRdele4-7	Excluded	Structural variant	NA (breakpoints not determined)
c.(273+1_274-1)_(1116+1_1117-1)del(1584+1_1585-1)_(3468+1_3469-1)del	p.?	CFTR50kbdel	Excluded	Structural variant	NA (breakpoints not determined)
c.(273+1_274-1)_(1584+1_1585-1)del	p.?	CFTRdele4-10	Excluded	Structural variant	NA (breakpoints not determined)
c.(273+1_274-1)_(1679+1_1680-1)del	p.?	CFTRdele4-11	Excluded	Structural variant	NA (breakpoints not determined)

c.(2908+1_2909-1)_(3367+1_3368-1)del	p.?	CFTRdele16-17b	Excluded	Structural variant	NA (breakpoints not determined)
c.(2988+1_2989-1)_(3367+1_3368-1)del	p.?	CFTRdele17a,17b	Excluded	Structural variant	NA (breakpoints not determined)
c.(2988+1_2989-1)_(3468+1_3469-1)del	p.?	CFTRdele17a-18	Excluded	Structural variant	NA (breakpoints not determined)
c.(3139+1_3140-1)_(3367+1_3368-1)del	p.?	CFTRdele17b	Excluded	Structural variant	NA (breakpoints not determined)
c.(3367+1+3368-1)_(3468+1_3469-1)del	p.?	CFTRdele18	Excluded	Structural variant	NA (breakpoints not determined)
c.(3468+1_3469-1)_(3717+1_3718-1)del	p.?	CFTRdele19	Excluded	Structural variant	NA (breakpoints not determined)
c.(3468+1_3469-1)_(3963+1_3964-1)del	p.?	CFTRdele19-21	Excluded	Structural variant	NA (breakpoints not determined)
c.(3873+1_3874-1)_(3963+1_3964-1)del	p.?	CFTRdele21	Excluded	Structural variant	NA (breakpoints not determined)
c.(3963+1_3964-1)_(*1_?)del	p.?	CFTRdele22-24	Excluded	Structural variant	NA (breakpoints not determined)
c.(53+1_54-1)_(164+1_165-1)del	p.?	CFTRdele2	Excluded	Structural variant	NA (breakpoints not determined)
c.(53+1_54-1)_(489+1_490-1)del	p.?	CFTRdele2-4	Excluded	Structural variant	NA (breakpoints not determined)
c.(743+1_744-1)_(1584+1_1585-1)dup	p.?	CFTRdup6b-10	Excluded	Structural variant	NA (breakpoints not determined)
c.[1075C>A;1079C>A]	p.[Gln359Lys;Thr360Lys]	Q359K/T360K	Excluded	Complex allele	7:117540305:C:A | 7:117540309:C:A
c.[1397C>G;3209G>A]	p.[Ser466Ter;Arg1070Gln]	S466X;R1070Q	Excluded	Complex allele	7:117559468:C:G | 7:117611650:G:A
c.[1521_1523del;3080T>C]	p.[Phe508del;Ile1027Thr]	F508del;I1027T	Excluded	Complex allele	7:117559590:ATCT:A | 7:117610610:T:C
c.[1523T>G;3752G>A]	p.[Phe508Cys;Ser1251Asn]	F508C;S1251N	Excluded	Complex allele	7:117559594:T:G | 7:117642472:G:A
c.[350G>A;1210-11T>G]	p.[Arg117His;5T]	R117H;5T	Excluded	Complex allele	7:117530975:G:A | 7:117548630:T:G
c.[3846G>A;3848G>T]	p.[Trp1282Ter;Arg1283Met]	W1282X;R1283M	Excluded	Complex allele	7:117642566:G:A | 7:117642568:G:T
c.[4C>T;7A>T]	p.[Gln2Ter;Arg3Trp]	Q2X;R3W	Excluded	Complex allele	7:117480098:C:T | 7:117480101:A:T

[a]Reasons for exclusion are aligned with **Figure 1**. Variants were excluded in the revision phase if they were complex alleles, structural variants, or not present in gnomAD. Variants excluded in the evaluation phase were those present in gnomAD but not frequent enough to be included within the goal of 95% population coverage; such variants that were excluded at this stage are noted as "Outside of 95% coverage threshold."

[b]A "Yes" in this column indicates that the variant was on the original ACMG-recommended list of 23 *CFTR* variants for carrier screening.

[c]Note that for the four structural variants below, the VCF Position cell is quite long because it includes sequence from one or more exons. Users of this list who wish to integrate it into a pipeline and convert to a different file type may need to adjust for this lengthy character count.

variant	character count
c.54-5940_273+10250del	21095
c.54-5842_489+401del	32767
c.3964-78_4242+577del	1547
c.2989-977_3367+248del	2530