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Which *CFTR* Variants Should be Tested by Laboratories? The ACMG Releases Updated Carrier Screening Recommendations for Cystic Fibrosis

BETHESDA, MD – June 13, 2023 | The American College of Medical Genetics and Genomics (ACMG) has released updated recommendations for *CFTR* carrier screening – Updated recommendations for *CFTR* carrier screening: A position statement of the American College of Medical Genetics and Genomics. Pathogenic variants in the *CFTR* gene can cause cystic fibrosis (CF) as well as CF-related disorders. The new updated ACMG *CFTR* variant list includes a set of 100 variants.*

The new *CFTR* variant list represents an updated minimum recommended variant set for CF carrier screening and supersedes the previous group of 23 *CFTR* variants recommended by the ACMG. These revised recommendations apply to carrier screening, a type of genetic testing used to determine whether a person possesses a genetic variant associated with a condition that typically requires the presence of two pathogenic variants in order to manifest a phenotype. These revised recommendations 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.

"When it was originally developed, the previous variant list set the standard for CF carrier screening in the country. Now that our databases and technologies have evolved, it was time to raise the bar and set a new minimum standard. This new recommended variant set should help ensure that *CFTR* variant detection is more equitable among individuals representing a variety of biogeographic ancestries," said lead author, Joshua L. Deignan, PhD, FACMG.

The updated minimum variant set for CF carrier screening is based on evidence that the variant has been established as CF-causing and is present in the Genome Aggregation Database (gnomAD), the largest and most widely used publicly available collection of population variation from harmonized sequencing data. For this 2023 version, a conservative approach was used with a framework that only incorporates well-established pathogenic and likely pathogenic variants to minimize concerns that individuals would make reproductive decisions based on limited information. Future versions of this minimum variant set should reassess the feasibility and utility of incorporating additional information from other population databases to be as biogeographically diverse as possible.

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History of ACMG's *CFTR* Carrier Screening Recommendations

The ACMG has long been involved in addressing the topic of *CFTR* carrier screening. In 2001, several professional organizations joined in acknowledging the importance and technologic advances that would make CF amenable to population-based carrier screening. However, the technology and knowledge had not advanced far enough to allow for an equitable application. Sequencing technology was also early in development. This limited screening applied to just small sets of variants that were most commonly characterized in Ashkenazi Jewish and Northern European populations. For this reason, recommendations at that time were that screening should be "offered" to those of Ashkenazi Jewish and Northern European descent and "made available" to other groups.

The ACMG ultimately recommended a set of 25 disease-causing variants, later reduced to 23 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") remained unchanged since then, even as molecular diagnostic technologies and genetic knowledge have dramatically advanced.

The original recommendation allowed 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. 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. 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 methods for testing and at the time reaffirmed the original set of 23 variants as the minimum set for CF carrier screening.

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 individuals as well as those planning a pregnancy.

*Note: The authors do not recommend use of the term "ACMG-100" when referring to the new minimum variant set.

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About the American College of Medical Genetics and Genomics (ACMG) and ACMG Foundation

Founded in 1991, the American College of Medical Genetics and Genomics (ACMG) is a prominent authority in the field of medical genetics and genomics and the only nationally recognized medical professional organization solely dedicated to improving health through the practice of medical genetics and genomics. The only medical specialty society in the US that represents the full spectrum of medical genetics disciplines in a single organization, the ACMG provides education, resources and a voice for more than 2,600 clinical and laboratory geneticists, genetic counselors and other healthcare professionals. ACMG's mission is to improve health through the clinical and laboratory practice of medical genetics as well as through advocacy, education and clinical research, and to guide the safe and effective integration of genetics and genomics into all of medicine and healthcare, resulting in improved personal and public health. *Genetics in Medicine* and the new *Genetics in Medicine Open,* a gold open access journal, are the official ACMG journals. ACMG's website, www.acmg.net, offers resources including policy statements, practice guidelines, and educational programs. The ACMG Foundation for Genetic and Genomic Medicine works to advance ACMG educational and public health programs through charitable gifts from corporations, foundations and individuals.

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