

Cystic Fibrosis Carrier Screening Results from the Preparent™ CF 149 and 600 Mutation Panels

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Abstract

Objective: Cystic fibrosis (CF) is the most common, life-threatening genetic disease in Caucasians, with an incidence of about 1 in 2,500 people, and a carrier frequency of about 1 in 24 people. Cystic fibrosis is less common among other ethnic groups, but is still found. In 2011, the American College of Obstetricians and Gynecologists (ACOG) updated their recommendations to include prenatal and preconception CF carrier screening for all women of reproductive age regardless of ethnicity. To date, more than 1,900 variants within the *CFTR* gene have been identified (www.genet.sickkids.on.ca). While common disease-causing mutations are known for the Caucasian population, common mutations for other ethnic groups are not well characterized. To provide greater risk reduction across all ethnicities, our laboratory offers a panel of 149 disease-causing mutations, with the option to increase the panel to 600 disease-causing mutations for greater coverage of rare mutations. Here, we present data from greater than 150,000 patients.

Methods: Accepted sample types include blood, buccal swabs, and mouthwash specimens. Our test utilizes barcoded, targeted libraries, for multiplexed massively parallel sequencing on the Illumina HiSeq 2500 instrument. Sample data are then de-multiplexed, and mutations are called using a laboratory-developed bioinformatics pipeline. Positive results are confirmed by repeat sequencing.

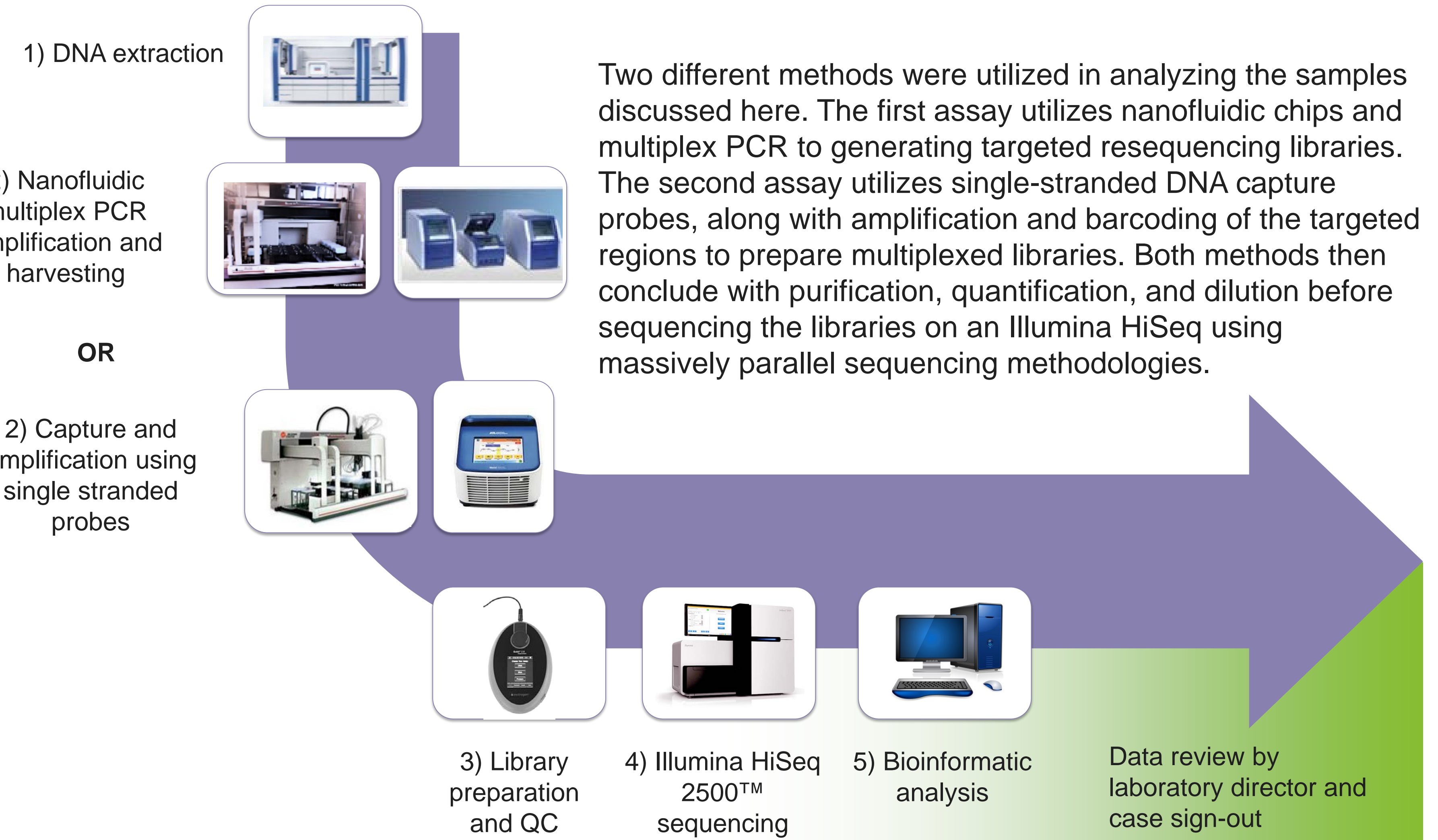
Results: A total of 4,913 (3.09%) patients were found to be carriers of *CFTR* mutations. Of those found to be carriers, 4,062 (82.6%) carried one of the 23 *CFTR* mutations recommended for testing by the American College of Medical Genetics (ACMG) and supported by the American Congress of Obstetricians and Gynecologists (ACOG). All 23 of the recommended mutations were found in our patients, and p.Phe508del was the most common in 2,848 (58.0%) of CF carriers. The remaining 851 (17.3%) CF carriers had 105 unique, non-ACMG/ACOG recommended mutations, 25 of which were each observed in only one patient. Self-reported patient ethnicity was examined to determine if the prevalence of ACMG/ACOG recommended mutations differed among ethnic groups. In Caucasians, 2,804 (88.3%) carried ACMG/ACOG recommended mutations, while 370 (11.7%) carried non-recommended mutations. In Hispanics, 484 (63.5%) carried recommended mutations, and 278 (36.5 %) carried non-recommended mutations. In African Americans, 155 (71.4%) carried recommended mutations, and 62 (28.6%) carried non-recommended mutations.

Conclusions: These data highlight the importance of offering panels consisting of more than the twenty-three recommended *CFTR* mutations, regardless of patient ethnicity, as approximately one-fifth of the carriers identified in our patient population would not have been identified without the use of an expanded panel, and non-recommended mutations were prevalent in Caucasians, Hispanics, and African Americans.

Background

Cystic Fibrosis is an autosomal recessive genetic condition caused by mutation within the *CFTR* gene. Clinical manifestations include thickened mucosal secretions, pancreatic insufficiency, intestinal blockage, and impaired fertility. CF is most prevalent within the Caucasian and Ashkenazi Jewish populations, however, it also occurs in other ethnic groups such as African, Hispanic, Asian, and Native Americans. The American College of Obstetrics and Gynecology (ACOG) and the American College of Medical Genetics (ACMG) currently recommends offering screening for cystic fibrosis (CF) carrier status to all women of reproductive age. Nearly 2000 mutations have been identified in the *CFTR* gene to date, though the overall population frequency of most of these mutations is completely unknown. While the standard 23-mutation panel recommended by ACMG covers many of the most common CF-related mutations, increasing sophistication of modern molecular biology allows for the interrogation of a far larger number of disease-causing mutations, and provides greater risk reduction for individuals screened. Increasing ethnic and racial diversity in the United States indicates the need for expanded panels. A recent publication shows that the lower coverage for minorities in CFTR screening panels place minority parents at greater risk of having a child with CF.(1) In addition, data acquired from applying expanded panels to large patient populations offers insight into the frequency of the less commonly studied mutations and these methods have revealed disparate mutation sets between Caucasian populations and racial minorities.(2-3)

Methods



Results

Table 1: Overall statistics

Total patients tested	158,879
Total patients identified with a mutation	4,913 (3.09%)
Patients with ACOG/ACMG recommended mutations	4,062 (82.6%)
Patients with non-ACOG/ACMG recommended mutations	851 (17.3%)
Number of unique, non-ACOG/ACMG recommended mutations found	105

Figure 1: Ethnicity of patients found to have a mutation

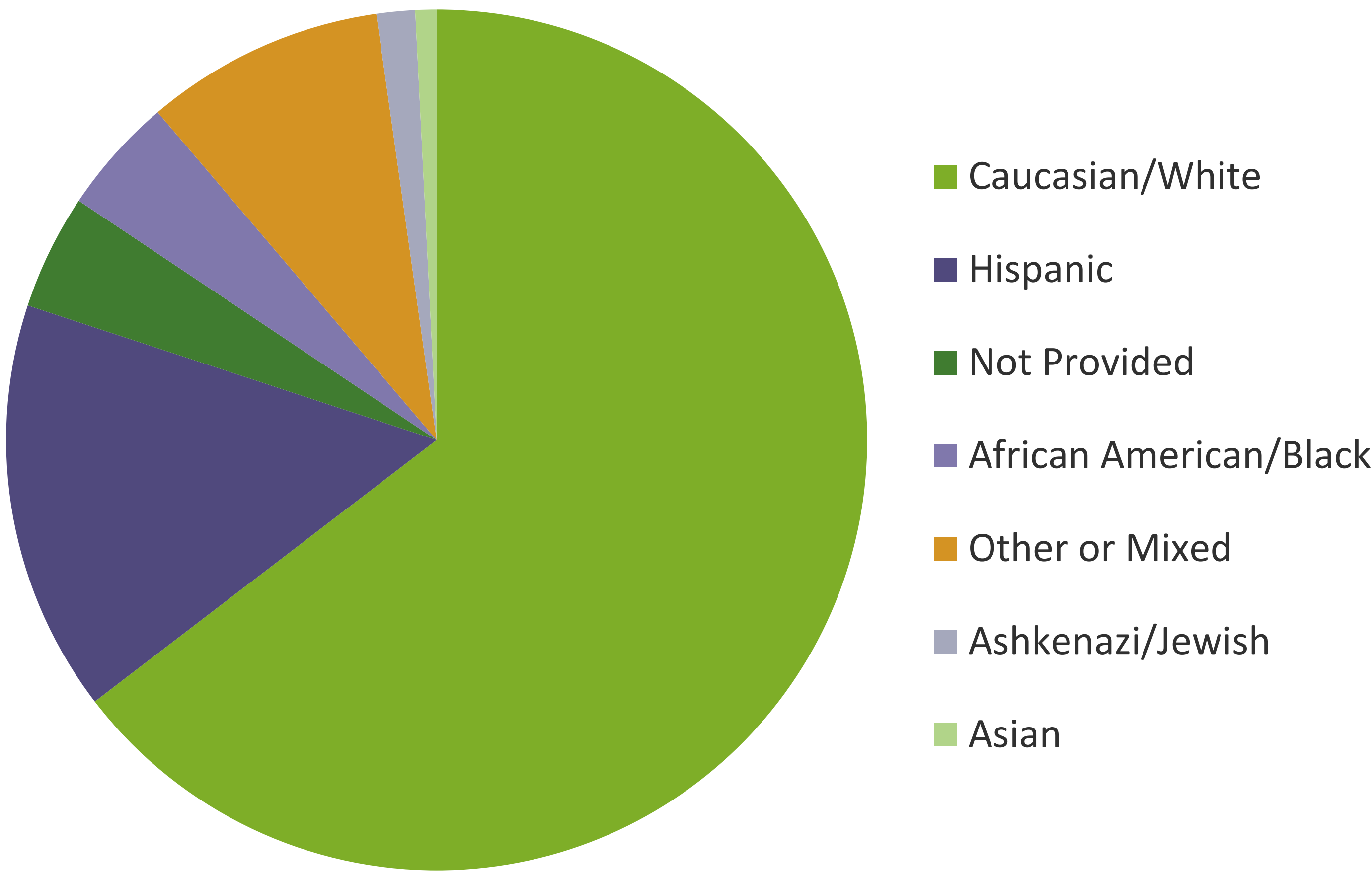
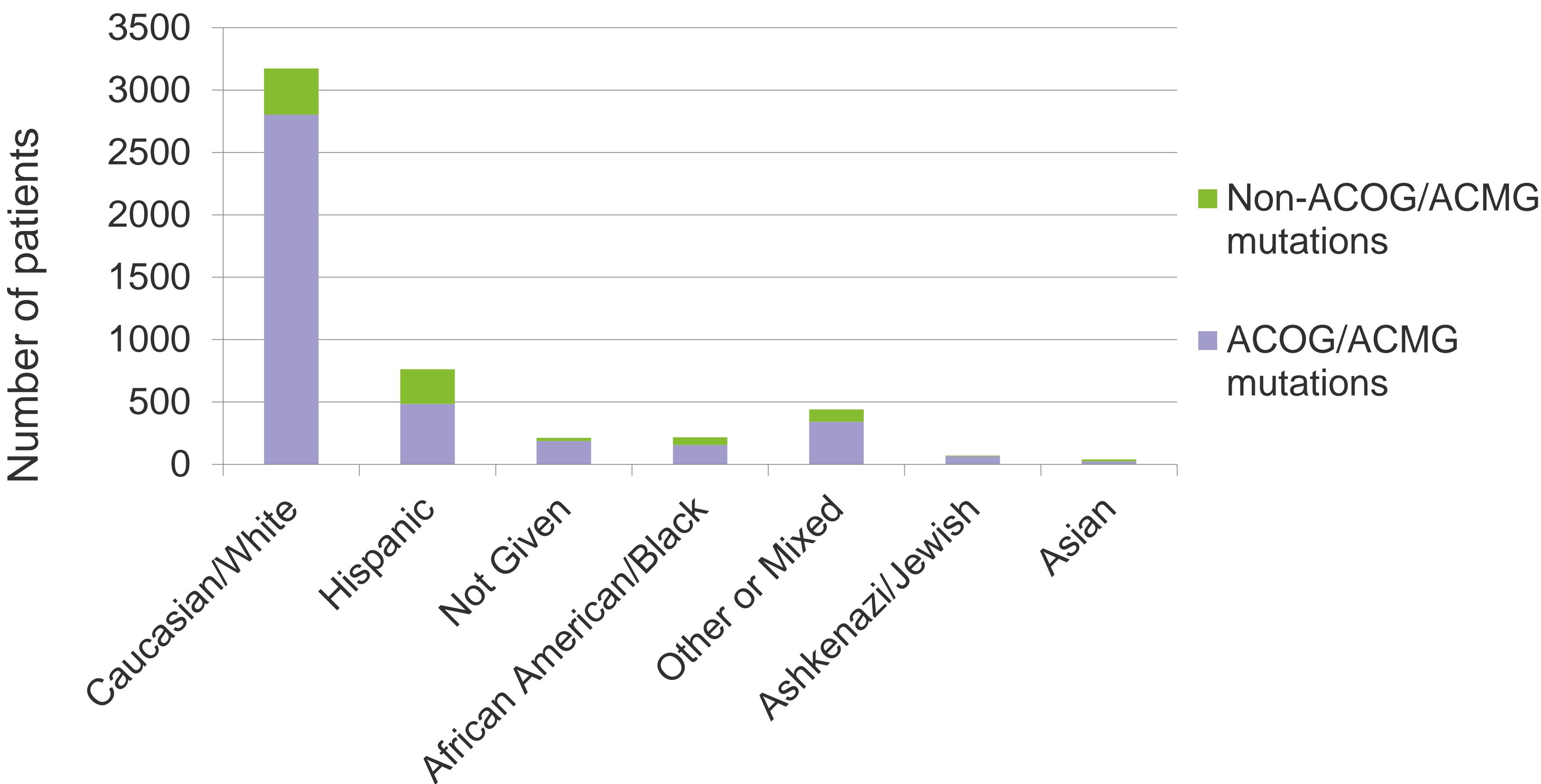


Figure 2: Number of patients with ACOG/ACMG recommended and non-recommended mutations by ethnicity



Conclusion

Screening of prenatal and preconception patient populations with expanded *CFTR* mutation panels identifies a significant number of non-ACMG/ACOG recommended, disease-causing mutations. Additionally, non-ACMG/ACOG recommended, disease-causing mutations were identified in all ethnicities included in our patient cohort. Therefore, the use of these expanded panels has clear clinical utility for patients of all ethnic backgrounds.

REFERENCES

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