

# Expanded carrier screening of 403,587 individuals: the case for going beyond CF

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## Introduction

Carrier testing is the current standard of care for a number of inherited conditions in the US, including cystic fibrosis. Expanded carrier screening (ECS) uses modern DNA technology to test a much larger (up to hundreds) of different conditions.

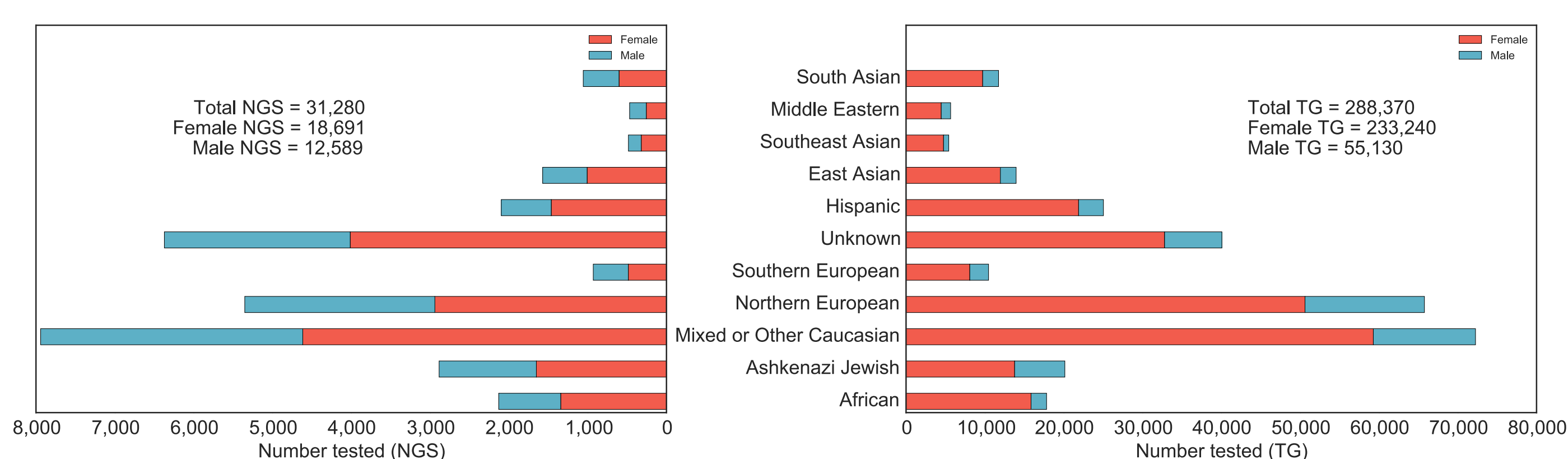
Growing clinical usage of ECS has prompted a recent joint “Points to Consider” statement by, among others, ACOG and ACMG and guidelines from the ESHG (currently in draft), but little data has been available on the true burden of “rare” recessive genetic disease.

We present data from our laboratory’s experience of providing over 400,000 expanded carrier screens to quantify the disease burden covered in expanded carrier screening panels.

## Results

### Number needed to screen is lower for severe recessive disease than for Down syndrome (T21).

The table shows the number of people needed to be tested to detect one affected pregnancy, assuming simultaneous (tandem) screening and an average fertility of 2.0/couple, by test panel and ethnicity. Smaller numbers indicate higher risk. Pink entries represent risk greater than that of trisomy 21 (Down syndrome) in mothers at age 35 (NNS=280); boldface entries indicate risk greater than that of neural tube defects (NNS=1000); italicized entries show higher risk than T21 in mothers at age 20 (NNS=1200).



	CF only	+ACOG	+ACMG	+Profound	+Severe
<b>African</b>	13029	<b>263</b>	<b>260</b>	<b>254</b>	<b>229</b>
<b>Ashkenazi Jewish</b>	2340	<b>1139</b>	<b>509</b>	<b>396</b>	<b>195</b>
<b>Mixed/Other Caucasian</b>	2008	2008	1654	<b>998</b>	<b>295</b>
<b>Northern European</b>	2137	2137	1714	<b>1030</b>	<b>319</b>
<b>Southern European</b>	3594	2617	1904	<b>1149</b>	<b>346</b>
<b>Unknown</b>	2516	2516	2026	1332	<b>345</b>
<b>Hispanic</b>	7391	7931	4628	2646	<b>630</b>
<b>East Asian</b>	392128	392128	13525	3777	<b>1114</b>
<b>Southeast Asian</b>	37560	1561	1382	1273	<b>899</b>
<b>Middle Eastern</b>	17083	17083	6001	3835	<b>451</b>
<b>South Asian</b>	6513	6513	4177	3622	<b>398</b>

In all ethnicities, the combined risk of severe or profound genetic disorders is greater than the risk of Down syndrome in the low-risk category, for which universal screening is routinely performed. In all groups other than East Asians, the risk of severe or worse genetic disorders is greater than the risk for neural tube defects.

## Conclusions

The burden of “rare” recessive disease is much larger than previously realized. A panel of 88 severe or profound recessive diseases has a smaller number needed to screen than Down syndrome or neural tube defects, motivating consideration of universal expanded carrier screening.

## Methods

Individuals were tested for carrier status in up to 108 genes by either targeted genotyping of up to 417 sites (TG) or next-generation sequencing (NGS) of the exons and selected introns of the chosen genes. SMN1 copy number was assessed by qPCR, and FMR1 CGG repeat count by PCR followed by capillary electrophoresis.

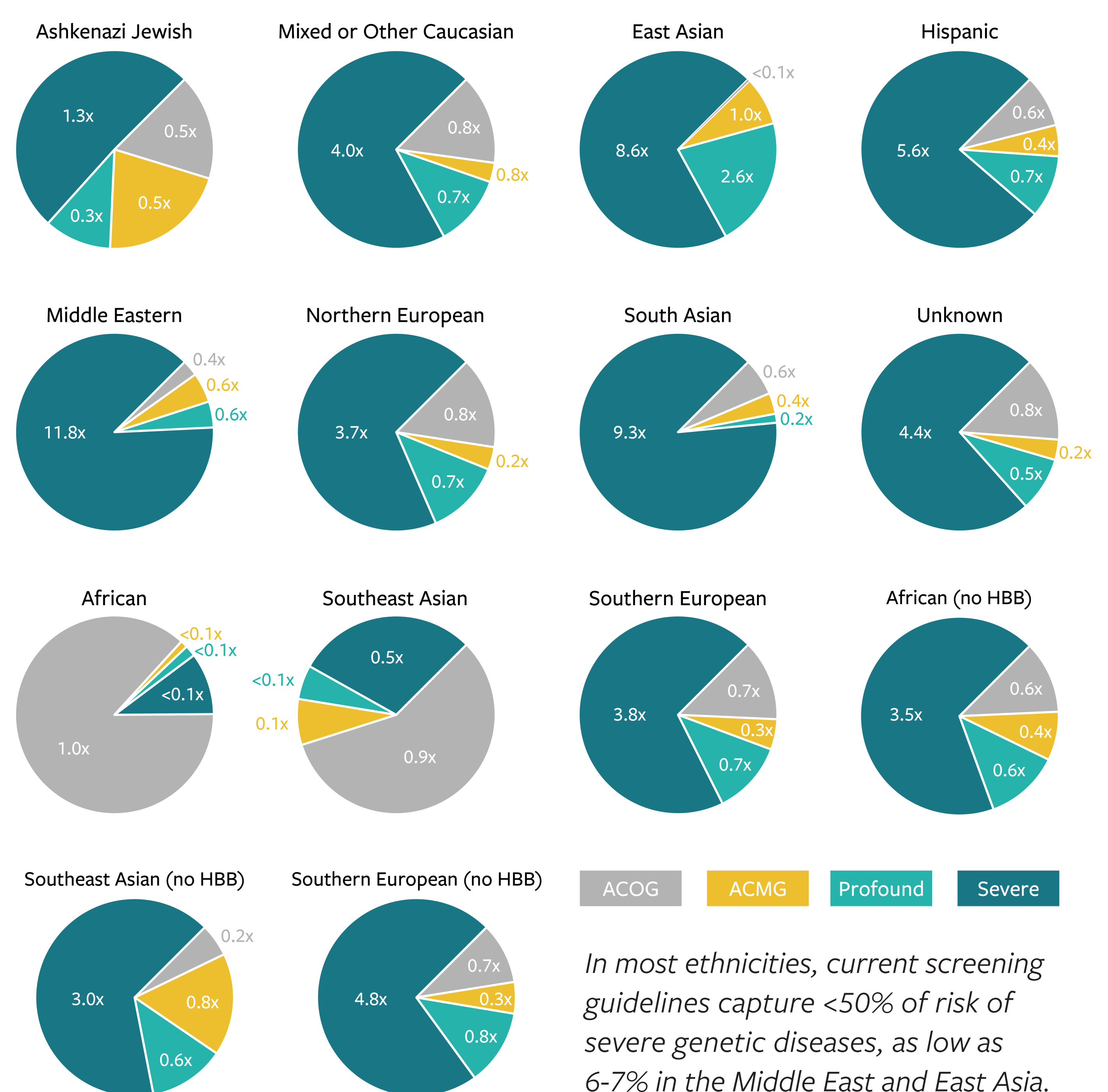
Diseases were classified as “profound”, “severe”, “moderate”, or “mild” using a recently published method [1]. Alpha-1 antitrypsin deficiency, familial Mediterranean fever, and GJB2-related nonsyndromic hearing loss and deafness were excluded from analysis because of high frequency and variable phenotype.

Carrier frequencies for each condition were calculated as the higher of TG or NGS frequencies (while NGS has a higher detection rate, fewer patients were tested by NGS). From carrier rates we computed the probability that an arbitrary pregnancy would be affected by a genetic disorder (absolute risk). Fragile X risk was weighted by allele size [2].

A subset of 319,650 patients indicating “routine carrier testing” as the reason for test were used to compute carrier frequencies to avoid bias from known carriers. Tested patients spanned a broad range of self-reported ethnicities.

### Most rare disease risk is not captured in current screening guidelines.

The plots show the total risk of severe (e.g., CF, SMA) or worse genetic diseases on the Counsyl panel by ethnicity, separated into risk covered by ACOG guidelines, ACMG guidelines, non-guideline profound, and non-guideline severe diseases. Wedge labels show the ratio of risk in the wedge to the total risk in an ACOG+ACMG panel.



In most ethnicities, current screening guidelines capture <50% of risk of severe genetic diseases, as low as 6-7% in the Middle East and East Asia.