# Expanded carrier screening of 322,484 individuals: the case for going beyond CF

IS Haque, GA Lazarin, M Raia, H Bellerose, EA Evans, J Goldberg

Counsyl

@Counsyl
@ImranSHaque

*South San Francisco, California*

## 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 many more conditions (up to hundreds).

Growing clinical usage of ECS has prompted a recent "Points to Consider" statement by ACOG and ACMG (among others), as well as 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.

## 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 syndrome risk was weighted by allele size [2].

## Results

322,484 patients indicating "routine carrier testing" as the reason for testing were selected from a total population of 403,587 (all indications). From this subset, 290,996 (90%) received the genotyping (TG) test and 31,488 (10%) received the next-generation sequencing (NGS) test. Males comprised 19.1% and 40.3% of TG and NGS tests, respectively. 162,716 individuals (50.5%) indicated European, other Caucasian, or mixed ancestry; 27,140 (8.4%) were Hispanic; 23,033 (7.1%) were Ashkenazi Jewish; 21,438 (6.6%) were East or Southeast Asian; 19,960 (6.2%) were African-American; 18,917 (5.9%) were South Asian or Middle Eastern.

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

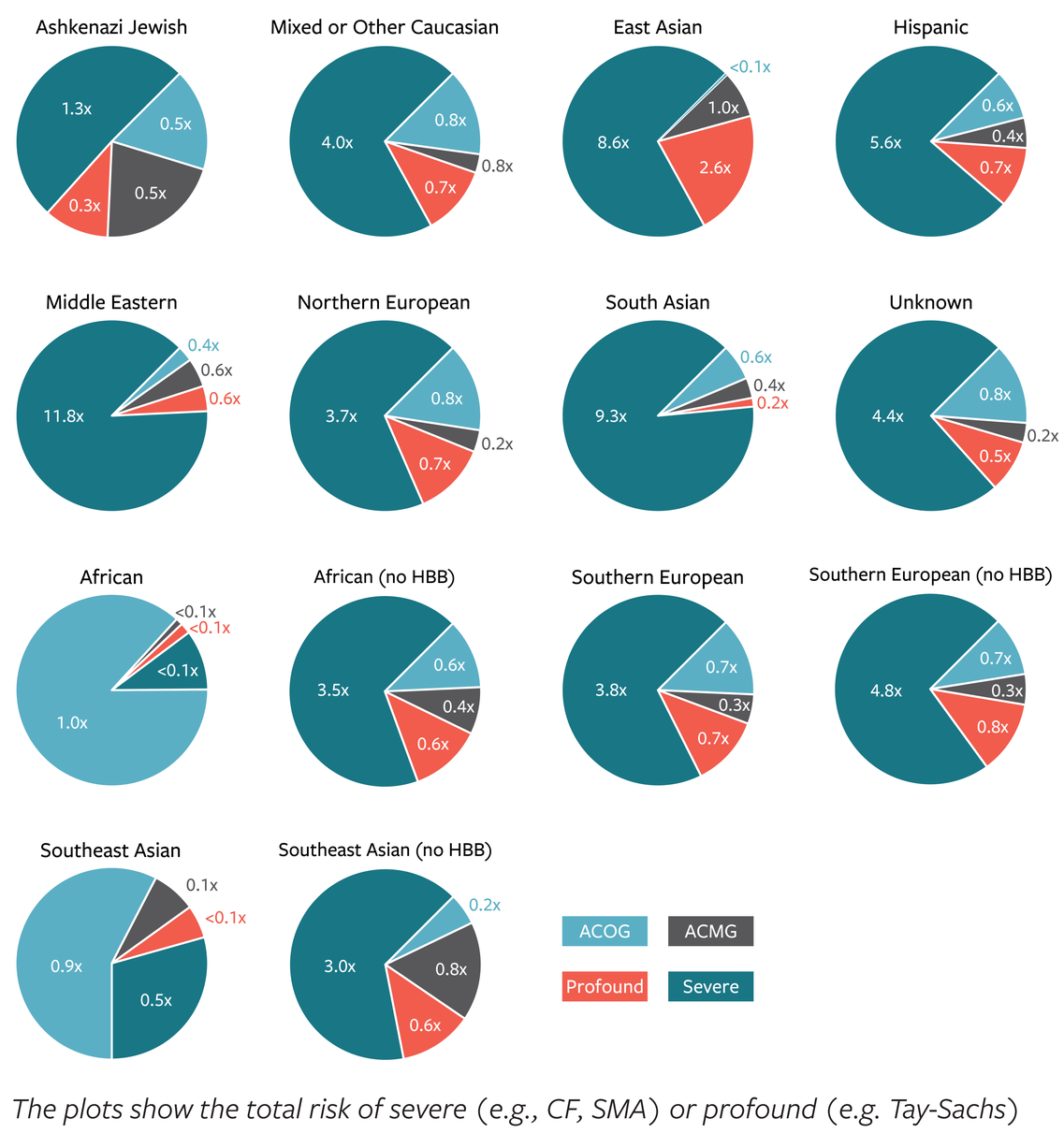
In all ethnicities, the combined risk of severe or profound genetic disorders is greater than the risk of Down syndrome in the low-risk category, for which universal screening is routinely performed. In all groups other than East Asians, the risk of severe or worse genetic disorders is greater than the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

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

*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, grouped 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) [3,4].*

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

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.




*The plots show the total risk of severe (e.g., CF, SMA) or profound (e.g. Tay-Sachs) 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.*

## Conclusions

**The burden of "rare" recessive disease is much larger than previously realized and much more uniform across ethnicities than indicated in guidelines. 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.**

**REFERENCES** 1. Lazarin GA et al. PLoS One, 2014. | 2. Yrigollen CM et al., Genet Med 14(8), 2012. | 3. Snijders et al. Ultrasound Obstet Gynecol, 13(3) 1999. | 4 Cragan et al. MMWR CDC Surveillance Summaries, 44(4) 1995

**DISCLOSURE** All authors are employed by Counsyl, a laboratory offering expanded carrier screening.