Carrier screening of 346,790 individuals reveals greater risk of severe recessive disease than of Down syndrome or NTDs

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Introduction

Current U.S. medical guidelines recommend universal ultrasound and serum screening in pregnancy for Down syndrome (T21, MIM 190685) and neural tube defects (NTDs, MIM 182940). Genetics guidelines recommend offering screening for cystic fibrosis (MIM 219700) and spinal muscular atrophy (MIM 253300) to all prospective parents and additional screens on an ethnicity-specific basis.

Growing clinical usage of expanded carrier screening, testing many more (up to hundreds) conditions, has prompted a recent "Points to Consider" statement by ACOG and ACMG (among others), but the population risk for expanded panels of rare recessive diseases is an open question.

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 110 genes by either targeted genotyping (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.

We interpreted novel variants using literature curation with ACMG guidelines and considered pathogenic those curated as known or likely deleterious [1]. We assigned diseases profound, severe, moderate, or mild severity by review of their symptoms [2]. Alpha-1 antitryspin deficiency, familial Mediterranean fever, and *GJB2*-related nonsyndromic hearing loss and deafness were excluded from analysis because of high frequency and variable phenotype.

From carrier frequencies we computed the probability that a random birth would be affected by a disease (absolute risk). Fragile X syndrome risk was weighted by allele size distribution [3].

Results

346,790 patients indicating "routine carrier testing" as the reason for testing were selected from a total population of 430,584 (all indications). From this subset, 308,668 (89%) received the genotyping (TG) test and 38,122 (11%) received the next-generation sequencing (NGS) test. Males comprised 18.8% and 39.7% of TG and NGS tests respectively. 173,081 individuals (49.9%) indicated European, other Caucasian, or mixed ancestry; 29,405 (8.5%) were Hispanic; 24,471 (7.1%) were Ashkenazi Jewish; 23,004 (6.6%) were East or Southeast Asian; 21,674 (6.3%) were African-American; 20,083 (5.8%) were South Asian or Middle Eastern.

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

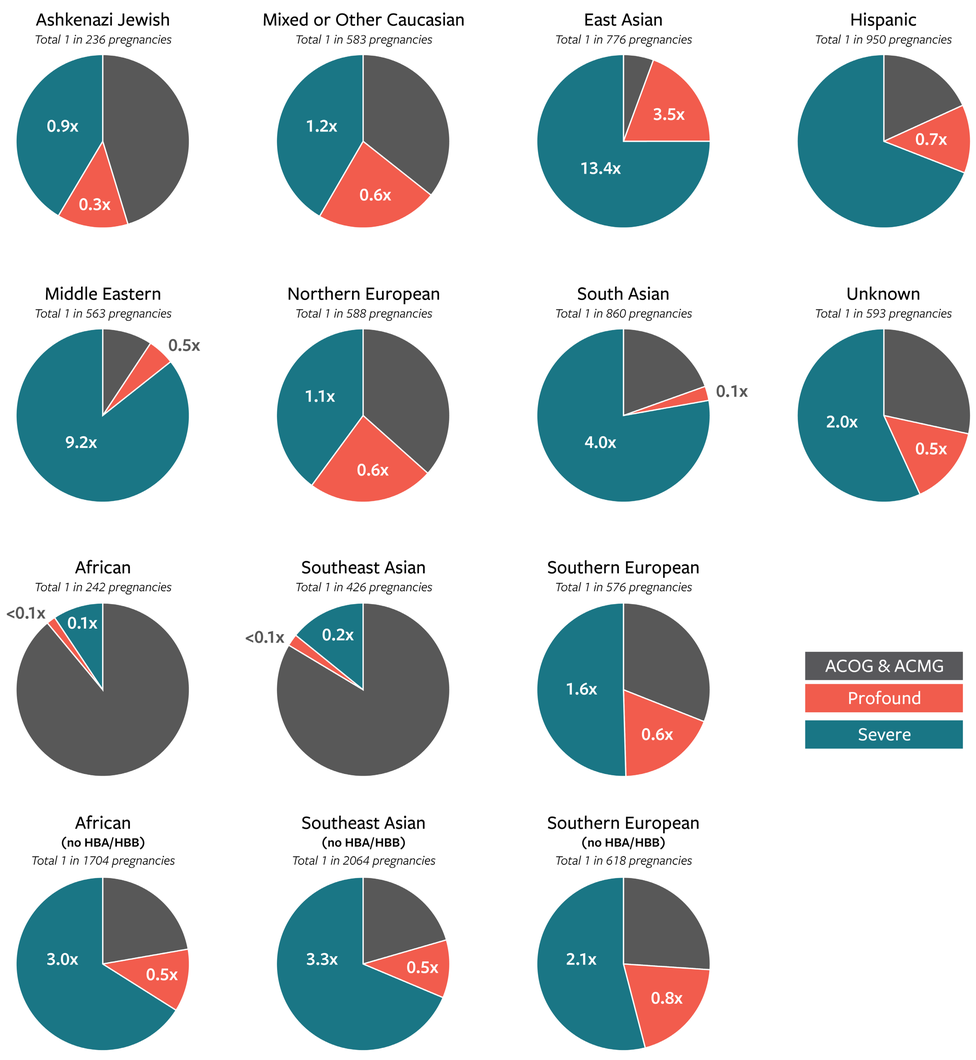
In all ethnicities, the combined risk of severe or profound genetic disorders is greater than the risk of Down syndrome in the low-risk category, for which universal screening is routinely performed. In all groups, the risk of severe or worse genetic disorders is greater than the risk for neural tube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

	ACOG	+ACMG	+Profound	+Severe
African	275	271	266	242
Ashkenazi Jewish	*1110*	**520**	**403**	263
Mixed/Other Caucasian	1981	1635	**999**	**583**
Northern European	1969	1607	**979**	**588**
Southern European	2581	1859	*1162*	**576**
Unknown	2602	2088	1374	**593**
Hispanic	8195	4977	2926	**905**
East Asian	326041	13815	3105	**776**
Southeast Asian	**534**	**510**	**496**	**426**
Middle Eastern	17060	6051	3928	**563**
South Asian	7040	4401	3873	**860**

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. Red 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) [4,5].

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) recessive genetic diseases on the Counsyl panel, separated into risk covered by ACOG/ACMG guidelines, non-guideline profound, and non-guideline severe diseases. Wedge labels show the ratio of risk in the wedge to the risk in the ACOG+ACMG wedge.

Conclusion

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.

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