

Reproductive Carrier Screening: Benefits for Reproduction and for Maternal Health

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Introduction

- The American College of Medical Genetics and Genomics (ACMG) recommends offering all pregnant individuals and those planning pregnancy a pan-ethnic, 113-gene (‘Tier 3’) carrier screening panel.
- We reviewed our experience with this panel.

Methods

- Retrospective study
- Cohort: women aged 18–55 with samples submitted to a commercial lab (01/2023–08/2024) for carrier screening including ACMG-Tier 3 genes
- The Tier 3 panel comprises 113 genes (97 autosomal recessive, 16 X-linked conditions).
- Pathogenic or likely pathogenic (P/LP) variants were identified primarily via next-generation sequencing.
- We calculated carrier frequencies, and estimated at-risk and affected pregnancy rates.
- Carrier frequencies for genes relevant to maternal health and reproductive risk were also analyzed.

Reproductive carrier screening can benefit a racially and ethnically diverse population.

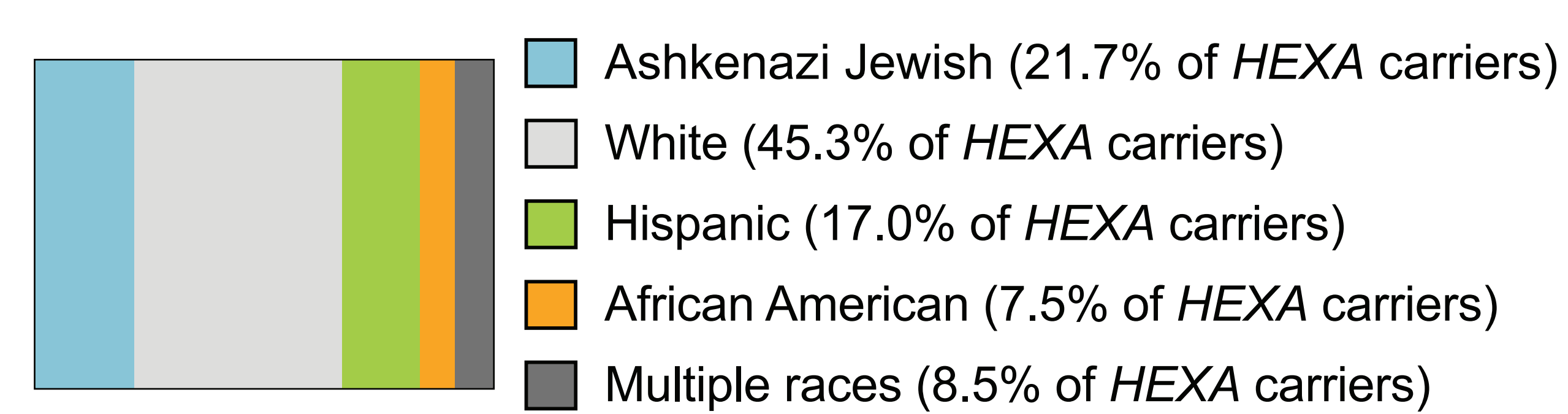
Table 1. Demographics and clinical characteristics (n=62,687)	
Ethnicity	
African American	2,356 (3.8%)
East Asian	2,658 (4.2%)
South Asian	1,180 (1.9%)
Southeast Asian	919 (1.5%)
Hispanic	4,107 (6.6%)
White	10,875 (17%)
Ashkenazi Jewish	797 (1.3%)
Multiple Races	2,151 (3.4%)
Other	9,264 (15%)
Unknown	28,380 (45%)
Test Ordering Clinic Type	
IVF Clinic	25,272 (40%)
Ob/Gyn Clinic	15,001 (24%)
MFM Clinic	10,446 (17%)
Other or Unknown	11,968 (19%)

Results

- 62,687 samples were evaluated.
- Median maternal age was 33 years; 43% of patients were not pregnant, 34% were pregnant, and 24% were of unknown pregnancy status.
- Carrier frequency was highest for the following conditions: alpha thalassemia (1 in 13), cystic fibrosis (1 in 25), beta-hemoglobinopathies (predominantly sickle cell disease) (1 in 33), and spinal muscular atrophy (1 in 60).

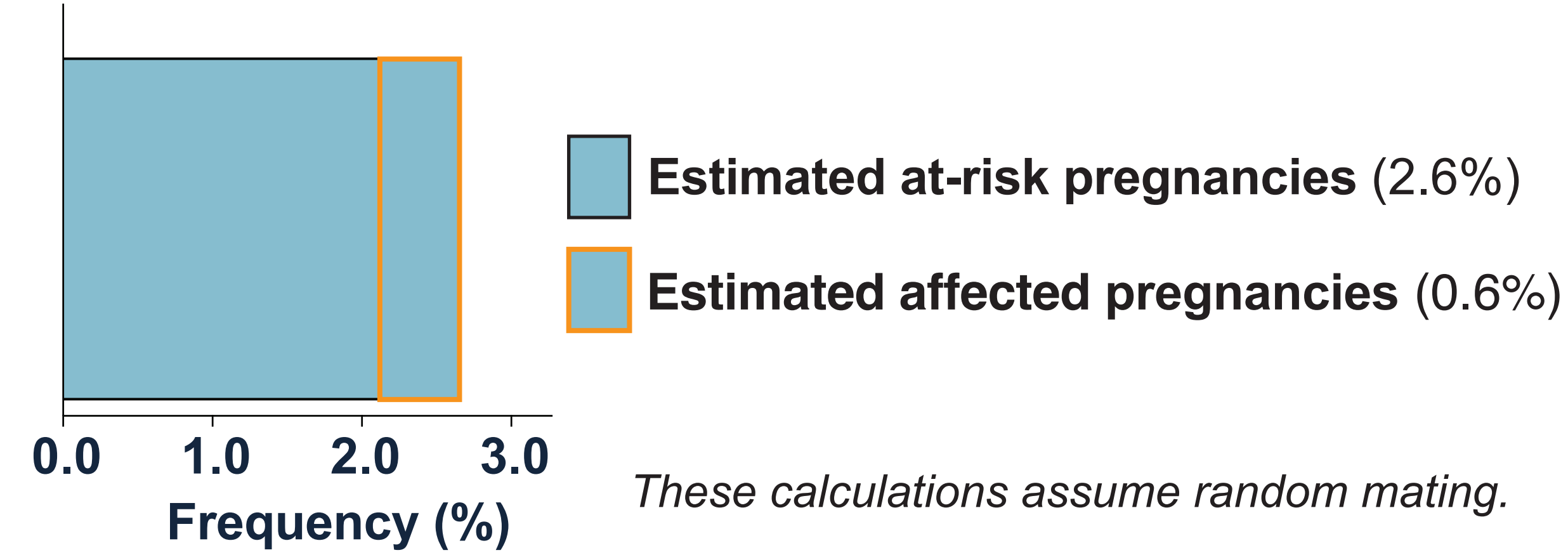
Table 2. Screen positive rates for the Tier 3 panel: approximately half or more of patients had a positive screen result regardless of race or ethnicity.								
	Overall	African American	East Asian	South Asian	Southeast Asian	Hispanic	White	Ashkenazi Jewish
Any Tier 3 gene	56.2%	63.5%	49.1%	53.4%	54.2%	52.4%	58.7%	73.1%
Any Autosomal Recessive gene	55.8%	63.3%	48.9%	52.8%	53.9%	52.0%	58.2%	72.6%
Any X-Linked gene	1.0%	0.9%	0.3%	1.5%	0.8%	1.0%	1.3%	1.8%

Figure 1. Of 103 patients identified as carriers for Tay-Sachs (1 in 646), approximately 20% self-identified as of Ashkenazi Jewish ethnicity only.



Patients with missing race and ethnicity data are excluded from this calculation.

Figure 3. As many as 2.6 % of pregnancies in the cohort could be at-risk, and 0.6% affected, by one of the Tier 3 panel conditions.



These calculations assume random mating.

Figure 2. Select conditions with potential pregnancy risks for carriers.

OTC (Ornithine transcarbamylase deficiency)
Carrier Frequency: 1 in 6965
Hyperammonemic crisis during or after pregnancy

F8 (Hemophilia A)
Carrier Frequency: 1 in 536
Bleeding; implications for mode of delivery with an affected fetus

DMD (Duchenne/Becker muscular dystrophy)
Carrier Frequency: 1 in 847
Cardiomyopathy

F9 (Factor IX deficiency)
Carrier Frequency: 1 in 5699
Bleeding; implications for mode of delivery with an affected fetus

Conclusions

- 56% of women screened were carriers for at least one condition on the panel.
- 1 in 153 pregnancies would be expected to be affected by a condition on the panel.
- 1.5% of women were at increased risk for pregnancy complications due to their carrier status.
- The results demonstrate the potential benefits of carrier screening in a racially and ethnically diverse population.