WOMEN'S HEALTH

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Observations of Non-Ashkenazi Jewish (AJ) Individuals Testing Positive for AJ Disorders

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Introduction:

Several professional societies, including the American College of Obstetrics and Gynecology (ACOG) and the American College of Medical Genetics and Genomics (ACMG), recommend pan-ethnic carrier screening for cystic fibrosis (CF) and spinal muscular atrophy,[1,2] but ethnicity remains a driving force for the majority of reproductive carrier screening decisions. One example of ethnicity-based carrier screening are the conditions associated with AJ descent. ACOG recommends for patients reporting AJ descent to screen for 4 conditions and consideration of screening for 10 additional disorders (Table 1).[1]

Traditionally, carrier screening performed by Sanger-based technologies was primarily limited to select conditions based on a patient's reported ethnicity. However, significant advancements in genotyping and next-generation sequencing technologies have resulted in multiplex screening of a large number of conditions at a comparable or even reduced cost.

Furthermore, ethnicity is becoming increasingly difficult to ascertain, with many individuals reporting mixed ancestry or unknown descent. In 2000, the United States Census Bureau reported that 2.4% of the population reported two or more races, and this increased to 2.9% in 2010, an approximate 32% growth.[3] According to the Census, this population of mixed descent grew faster than the population of individuals reporting a single race (9.2% growth).[3]

Our goal was to utilize the commonly recommended AJ disorders to evaluate whether diseases traditionally screened for within one ethnicity are observed within other reported ancestries.

Table 1 AJ Conditions from ACOG #691

Recommended Conditions	• Canavan Disease • Cystic Fibrosis	• Familial Dysautonomia • Tay-Sachs Disease
Conditions to Consider	• Bloom Syndrome • Familial Hyperinsulinism • Fanconi Anemia • Gaucher Disease • Glycogen Storage Disease Type 1	• Joubert Syndrome • Maple Syrup Urine Disease • Mucolipidosis Type IV • Niemann-Pick Disease Types A and B, C1, and C2 • Usher Syndrome Types 1F and III

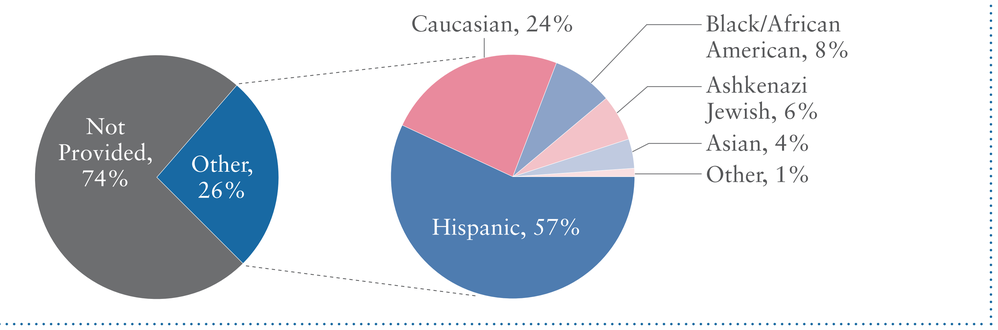
Methods:

We queried a population of patients who had a 180 disorder expanded targeted carrier screening panel at GenPath over a period of 6 years. ACOG committee opinion number 691[1] was used to identify our AJ conditions of interest. As detailed in Table 1, ACOG suggests screening for 14 AJ disorders. We removed CF from our analysis as pan-ethnic carrier screening is already widely recommended for this condition. Of note, our expanded carrier screening panel includes two subtypes of Maple Syrup Urine Disease and Usher Syndrome, thus resulting in a total of 15 distinct disorders (Table 2).

Ethnicity was obtained from the test requisition. After excluding the AJ population, the 4 most commonly reported ethnicities were Hispanic, Caucasian, African American and Asian. Cases were also excluded if ethnicity was not provided, reported to be only of non-Hispanic descent or if more than one ethnicity was reported.

The positive cases for each AJ condition within these 4 ethnicities were tallied. The frequencies of total positive cases were then calculated using the overall number of patients who underwent testing in each ethnicity.

Figure 1 Ancestry of Individuals Referred for Inherigen Panels



Results:

Expanded targeted carrier screening was performed on 16,061 Hispanic, 6,870 Caucasian, 2,165 African American, and 1,143 Asian individuals (Figure 1).

All 15 conditions were observed in the Caucasian population (n=263). The number of disorders found in the remaining ethnicities were as follows: 13/15 Hispanic (n=206), 3/15 African American (n=15), and 2/15 Asian (n=2).

Gaucher disease was the only condition that was observed in all 4 ethnicities. Three conditions (Canavan Disease, Glycogen Storage Disease Type 1A and Niemann-Pick Disease Type A/B) were observed in 3/4 ethnicities.

The frequency of positive cases within each ethnicity was calculated: 1/78 Hispanic, 1/26 Caucasian, 1/144 African American, and 1/572 Asian.

Table 2 Positive Individuals by Ethnicity

		Number of Positive Cases by Ethnicity (Total Tested)			
Condition	**Gene**	**Hispanic** (n=16,061)	**Caucasian** (n=6,870)	**African American** (n=2,165)	**Asian** (n=1,143)
Bloom Syndrome	*BLM*	8	10		
Canavan Disease	*ASPA*	3	11	1	
Familial Dysautonomia	*IKBKAP*	1	20		
Familial Hyperinsulinism	*ABCC8*	2	5		
Fanconi Anemia, Complementation Group C	*FANCC*	4	13		
Gaucher Disease	*GBA*	100	75	12	1
Glycogen Storage Disease, Type IA	*G6PC*	39	24	2	
Joubert Syndrome 2	*TMEM216*	2	4		
Maple Syrup Urine Disease, Type 1A	*BCKDHA*		5		
Maple Syrup Urine Disease, Type 1B	*BCKDHB*		17		
Mucolipidosis, Type IV	*MCOLN1*	2	2		
Niemann-Pick Disease, Type A/B	*SMPD1*	16	10		1
Tay-Sachs Disease	*HEXA*	27	55		
Usher Syndrome, Type 1F	*PCDH15*	1	8		
Usher Syndrome, Type 3	*CLRN1*	1	4		
Total N (%)		**206 (1.3%)**	**263 (3.8%)**	**15 (0.7%)**	**2 (0.2%)**
Total, 1 in..		**78**	**26**	**144**	**572**

Two subtypes of Maple Syrup Urine Disease and Usher Syndrome were reported, resulting in a total of 15 disorders.

Conclusion:

Historically, healthcare providers primarily used ethnicity to guide carrier screening options. However, with more patients reporting mixed or unknown ancestry, this approach may not be sufficient. Here we used the commonly recommended AJ disorders to evaluate whether diseases traditionally screened for within one ethnicity were observed within other ancestries. We observed that expanded carrier screening was able to identify a cohort of patients, who did not self report as AJ descent, yet tested positive for disorders that are traditionally associated with AJ ancestry. Carriers of AJ disorders were observed in self-reported Hispanic, Caucasian, African American, and Asian populations with the highest frequencies observed in the Hispanic and Caucasian populations. Furthermore, the declining cost of multiplex screening removes this as a barrier for expanded carrier screening. Using ethnicity as the main criteria to guide reproductive carrier screening may limit the detection of at-risk individuals across various ethnic backgrounds.

References:

1. ACOG Committee on Genetics. 2017. Committee Opinion #691: Carrier Screening for Genetic Conditions. Obstetrics and Gynecology 129(3).
2. Edwards, J., et al. 2015. Expanded Carrier Screening in Reproductive Medicine- Points to Consider. Obstetrics and Gyencology 125(3): 653.
3. Jones, N. and Bullock, J. 2012. The Two or More Races Population: 2010. 2010 Census Briefs.Accessed 1/29/19 from https://www.census.gov/prod/cen2010/briefs/c2010br-13.pdf.

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