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Comparison of pan-ethnic and ethnic-based carrier screening panels for individuals of Ashkenazi Jewish descent

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I. Introduction

The intent of carrier screening is to identify individuals at risk for a child with a genetic disease. ACMG guidelines currently recommend that individuals of Ashkenazi Jewish descent be screened for carrier status for nine diseases[1]. A joint statement from ACMG, ACOG, NSGC, SMFM, and the Perinatal Quality Foundation acknowledges benefits of screening for more than nine diseases (expanded carrier screening)[2]. Here we analyze detection rates for Ashkenazi Jewish individuals screened by panels with different numbers of diseases, to assess the benefit of disease panels targeted to the Ashkenazi Jewish population.

II. Materials and Methods

Array-based hybridization and allele-specific primer extension with a custom Illumina Infinium ™ array (IGv1.1) were used to detect 434 mutations in 87 genes that cause 87 diseases or a subset of 147 mutations in 18 genes that cause 18 diseases. Mutations were confirmed by Sanger sequencing. The 87-gene panel was intended for pan-ethnic carrier screening (pan-ethnic panel, Table 1), and the 18-gene panel was intended for Ashkenazi Jewish carrier screening (AJ panel).

The study sample comprised individuals self-identified as Ashkenazi Jewish and their indication for testing was carrier screening with no personal or family history of a genetic disorder. A total of 1150 individuals were tested in the pan-ethnic panel and 1248 individuals were tested in the AJ panel.

To compare pan-ethnic and AJ-based panels, positive findings for the AJ individuals tested in the pan-ethnic panel were re-analyzed with the 18 genes in the AJ panel and with the 9 genes recommended by ACMG. Similarly, positive findings for the AJ individuals tested in the AJ panel were re-analyzed with the 9 genes recommended by ACMG.

Table 1. The 87 genes and diseases included in the pan-ethnic panel.

Gene	Disease	Gene	Disease	Gene	Disease
ABCC8	Familial Hyperinsulinism, ABCC8-Related	*DPYD*	Dihydropyrimidine Dehydrogenase Deficiency	*MEFV*	Familial Mediterranean Fever
ACADM	MCAD Deficiency	*ETHE1*	Ethylmalonic Encephalopathy	*MMAA*	Methylmalonic Acidemia, MMAA-Related
ADA	Adenosine Deaminase Deficiency	*FAH*	Tyrosinemia Type 1	*MMAB*	Methylmalonic Acidemia, MMAB-Related
AGA	Aspartylglucosaminuria	*FANCC*	Fanconi Anemia Group C	*MMACHC*	Cobalamin C Disease (Methylmalonic Aciduria and Homocystinuria Type cblC)
AGL	Glycogen Storage Disease Type IIIa and IIIb	*FKTN*	Walker-Warburg Syndrome, FKTN-Related	*MUT*	Methylmalonic Acidemia, MUT-Related
AGXT	Primary Hyperoxaluria Type 1	*G6PC*	Glycogen Storage Disease Type Ia	*NBN*	Nijmegen Breakage Syndrome
ALDH3A2	Sjogren-Larsson Syndrome	*GAA*	Pompe Disease (Glycogen Storage Disease Type II)	*NEB*	Nemaline Myopathy, NEB-Related
ALDOB	Hereditary Fructose Intolerance	*GALC*	Krabbe Disease	*NPC1*	Niemann-Pick Disease Type C, NPC1-Related
ARSA	Metachromatic Leukodystrophy	*GALT*	Galactosemia, GALT-Related	*NPC2*	Niemann-Pick Disease Type C, NPC2-Related
ASL	Argininosuccinic Aciduria	*GBA*	Gaucher Disease	*NPHS1*	Nephrotic Syndrome, NPHS1-Related (Congenital Finnish Nephrosis)
ASPA	Canavan Disease	*GCDH*	Glutaric Acidemia Type 1	*NPHS2*	Nephrotic Syndrome, NPHS2-Related
ASS1	Citrullinemia Type I	*GLDC*	Glycine Encephalopathy, GLDC-Related (Non-Ketotic Hyperglycinemia, GLDC-Related)	*PAH*	Phenylalanine Hydroxylase Deficiency (including PKU)
ATM	Ataxia-Telangiectasia	*GRHPR*	Primary Hyperoxaluria Type 2 (Hyperoxaluria Type 2)	*PCCA*	Propionic Acidemia, PCCA-Related
ATP7B	Wilson Disease	*GSS*	Glutathione Synthetase Deficiency	*PCCB*	Propionic Acidemia, PCCB-Related
BBS1	Bardet-Biedl Syndrome, BBS1 Related	*HADHA*	LCHAD Deficiency	*PCDH15*	Usher Syndrome Type IF
BBS10	Bardet-Biedl Syndrome, BBS10 Related	*HBB*	Beta Hemoglobinopathy, including Sickle Cell Disease	*PEX1*	Zellweger Syndrome Spectrum, PEX1-Related
BCKDHA	Maple Syrup Urine Disease Type 1A	*HEXA*	Tay-Sachs Disease	*PEX7*	Rhizomelic Chondrodysplasia Punctata Type 1
BCKDHB	Maple Syrup Urine Disease Type 1B	*HEXB*	Sandhoff Disease	*PKHD1*	Polycystic Kidney Disease, Autosomal Recessive
BCS1	GRACILE Syndrome	*HMGCL*	HMG-CoA Lyase Deficiency	*PMM2*	Congenital Disorder of Glycosylation Type 1a
BLM	Bloom Syndrome	*HLCS*	Holocarboxylase Synthetase Deficiency	*PPT1*	Neuronal Ceroid-Lipofuscinosis, PPT1-Related
CBS	Homocystinuria, CBS-Related	*HSD17B4*	D-Bifunctional Protein Deficiency	*RMRP*	Cartilage-Hair Hypoplasia
CFTR	Cystic Fibrosis	*IDUA*	Mucopolysaccharidosis Type I (Hurler Syndrome)	*SACS*	Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (ARSACS)
CLN3	Neuronal Ceroid-Lipofuscinosis, CLN3-Related	*IKBKAP*	Familial Dysautonomia	*SLC12A6*	Andermann Syndrome
CLN5	Neuronal Ceroid-Lipofuscinosis, CLN5-Related	*LAMA3*	Junctional Epidermolysis Bullosa, LAMA3-Related	*SLC17A5*	Salla Disease
CLN8	Neuronal Ceroid-Lipofuscinosis, CLN8-Related	*LAMB3*	Junctional Epidermolysis Bullosa, LAMB3-Related	*SLC26A2*	Sulfate Transporter-Related Osteochondrodysplasias
CLRN1	Usher Syndrome Type III	*LAMC2*	Junctional Epidermolysis Bullosa, LAMC2-Related	*SLC37A4*	Glycogen Storage Disease Type Ib
CTNS	Cystinosis	*LRPPRC*	Leigh Syndrome, French-Canadian Type	*SMPD1*	Niemann-Pick Disease Type A/B
DHCR7	Smith-Lemli-Opitz Syndrome	*MAN2B1*	Alpha-Mannosidosis	*TMEM216*	Joubert Syndrome 2
DLD	Dihydrolipoamide Dehydrogenase Deficiency (MSUD Type 3)	*MCOLN1*	Mucolipidosis Type IV	*TTP1*	Neuronal Ceroid-Lipofuscinosis, TTP1-Related

Legend:
Blue: the pan-ethnic panel genes that are not also AJ or ACMG
Green plus yellow: the subset of 18 AJ panel genes
Yellow: the subset of 9 ACMG recommended AJ genes

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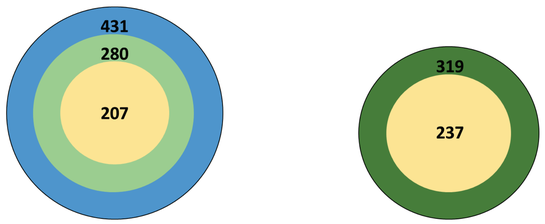
III. Results and Discussion

Table 2. Comparison of positive results for Ashkenazi Jewish individuals tested in the pan-ethnic and AJ panels.

Test	Number of genes assessed	Number of individuals tested	Number of individuals positive: 1 gene	2 genes	3 genes	4 genes	Total number positive	% Positive
Pan-ethnic panel	87	1150	344	72	13	2	431	37.5
	18		246	30	4	0	280	24.3
	9		186	19	2	0	207	18.0
AJ panel	18	1248	259	53	5	2	319	25.5
	9		203	33	1	0	237	18.9

Figure 1. Companion diagram for Table 2.



Pan-ethnic panel
N = 1150 AJ individuals tested
- Individuals who were positive for at least one of the 87 pan-ethnic genes
- Individuals who would have been positive if screening was limited to the 18 AJ genes
- Individuals who would have been positive if screening was limited to the 9 ACMG recommended genes

AJ panel
N=1248 AJ individuals tested
- Individuals who were positive for at least one of the 18 AJ genes
- Individuals who would have been positive if screening was limited to the 9 ACMG recommended genes

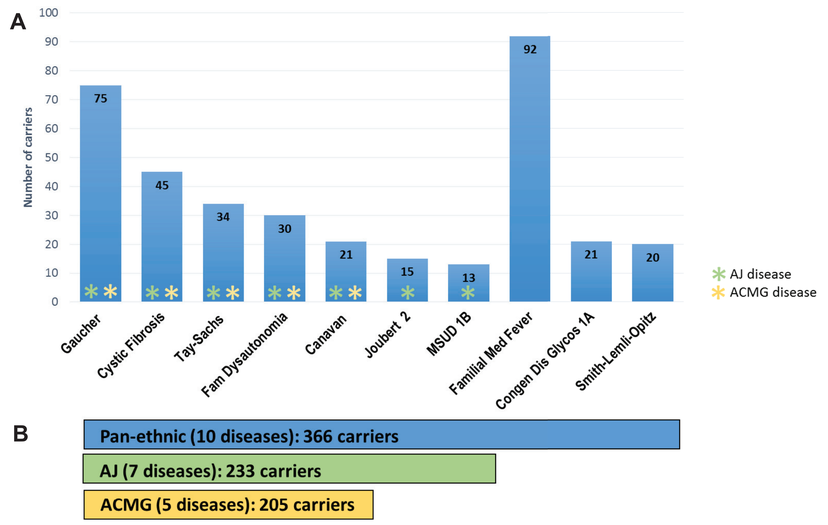
DISCUSSION: In the pan-ethnic panel 431/1150 (37.5%) AJ individuals were carriers of at least one disease. If these individuals were tested in the AJ panel, the detection rate would be 280/1150 (24.3%). If these individuals were tested for the nine ACMG recommended diseases, the detection rate would be 207/1150 (18.0%). The validity of this extrapolation is demonstrated by the equivalent findings that the detection rate is 25.5% for AJ individuals tested with the AJ panel and 18.9% for the ACMG recommended diseases. (Table 2 and Figure 1)

Table 3. Twenty-one diseases not included in the ethnic-specific AJ panel, but identified in Ashkenazi Jewish carriers tested in the pan-ethnic panel.

Disease	Gene	Disease	Gene
Beta Hemoglobinopathy, including Sickle Cell Disease	*HBB*	Neuronal Ceroid-Lipofuscinosis, TTP1-Related	*TTP1*
Cobalamin C Disease (Methylmalonic Aciduria and Homocystinuria Type cblC)	*MMACHC*	Niemann-Pick Disease Type C, NPC1-Related	*NPC1*
Congenital Disorder of Glycosylation Type 1a	*PMM2*	Niemann-Pick Disease Type C, NPC2-Related	*NPC2*
Cystinosis	*CTNS*	Pompe Disease (Glycogen Storage Disease Type II)	*GAA*
Dihydropyrimidine Dehydrogenase Deficiency	*DPYD*	Primary Hyperoxaluria Type 1	*AGXT*
Familial Mediterranean Fever	*MEFV*	Smith-Lemli-Opitz Syndrome	*DHCR7*
Galactosemia, GALT-Related	*GALT*	Sulfate Transporter-Related Osteochondrodysplasias	*SLC26A2*
Glycogen Storage Disease Type Ib	*SLC37A4*	Tyrosinemia Type 1	*FAH*
Hereditary Fructose Intolerance	*ALDOB*	Wilson Disease	*ATP7B*
Homocystinuria, CBS-Related	*CBS*	Neuronal Ceroid-Lipofuscinosis, TTP1-Related	*TTP1*
Mucopolysaccharidosis Type I (Hurler Syndrome)	*IDUA*		

DISCUSSION: The pan-ethnic panel identified carriers for 38 diseases among Ashkenazi Jews; however, carrier status for only 17 of these diseases could be assessed using the AJ panel. Therefore, 21 “non-AJ” diseases accounted for the difference in carrier rates between the pan-ethnic and AJ panels (Table 3)

Figure 2.
A. The ten diseases with the largest number of carriers among Ashkenazi Jewish individuals screened in the pan-ethnic panel.
B. Comparison showing the subset of these ten diseases and carriers that would be identified if only the 18 AJ panel genes or 9 ACMG recommended genes were assessed.



DISCUSSION: Of the ten diseases with the largest number of carriers among Ashkenazi Jewish individuals screened in the pan-ethnic panel, three diseases would have been missed if the AJ panel had been used: familial Mediterranean fever (92 carriers), congenital disease of glycosylation type 1a (21 carriers), and Smith-Lemli-Opitz syndrome (20 carriers). With the ACMG-recommended panel, two more of the most commonly identified diseases would have been missed: Joubert syndrome type 2 (15 carriers) and maple syrup urine disease type 1B (13 carriers). (Figure 2)

IV. Conclusions

- A pan-ethnic expanded carrier screening panel of 87 genes increased the carrier detection rate in Ashkenazi Jewish individuals by approximately 50%, compared with a panel of 18 genes considered to be relevant to the Ashkenazi Jewish population.
- The detection rate would have increased by approximately 100% if the pan-ethnic panel were compared to just the ACMG recommended genes in this data set.
- These data show that a pan-ethnic panel is more effective than targeted AJ panels in carrier detection among individuals of Ashkenazi Jewish descent.

V. References

1. Gross SJ, Pletcher BA, for the Professional Practice and Guidelines Committee KG. Carrier screening in individuals of Ashkenazi Jewish descent. Genetics in Medicine. 2008;10(1):54-56.

2. Edwards JG, Feldman G, Goldberg J, et al. Expanded carrier screening in reproductive medicine-points to consider: a joint statement of the American College of Medical Genetics and Genomics, American College of Obstetricians and Gynecologists, National Society of Genetic Counselors, Perinatal Quality Foundation, and Society for Maternal-Fetal Medicine. Obstet Gynecol. 2015; 125(3): 653–662.