Multigene panel screening for hereditary disease risk in healthy individuals

Eden Haverfield,[1] Edward D. Esplin,[1] Sienna Aguilar,[1] Kelly E. Ormond,[2] Andrea Hanson-Kahn,[2] Paldeep Atwal,[3] Sarah Macklin,[3] Caron Sak,[4] Steven Bleyl,[5] Catherine Fine,[5] Peter Hulick,[6] Ora Gordon,[7] Megan McSweeney,[1] Robert L. Nussbaum,[1] Swaroop Aradhya[1]

[1]Invitae, San Francisco, CA; [2]Stanford University, Palo Alto, CA; [3]Mayo Clinic, Jacksonville, FL ; [4]Tucker Medical, Singapore; [5]Genome Medical, Monterey, CA; [6]NorthShore University HealthSystem; [7]Providence Health & Services, Southern California, Los Angeles, CA

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INTRODUCTION

Introduction: Prompted by the American College of Medical Genetics and Genomics (ACMG) policy on reporting secondary findings, health-related genetic information is becoming available to healthy individuals through their healthcare providers. This information may identify hereditary risk and allow earlier detection and prevention of certain actionable disorders, but it needs to be accompanied by appropriate educational support for clinicians and genetic counseling for patients. We report our initial findings on the frequency of pathogenic variants found in a medically actionable genetic screening panel in healthy individuals and describe several cases that highlight the clinical value of these results and how they can be incorporated into routine healthcare.

Methods: Under an IRB-approved protocol, we analyzed de-identified data from 1,300 individuals who underwent genetic screening with a panel of up to 139 genes for actionable Mendelian disorders. Clinician-documented health information, if provided, was also reviewed.

Results: Known or predicted pathogenic/likely pathogenic (P/LP) variants were observed in 16.1% (209 of 1,300) of individuals. These findings were distributed in cancer-related genes (48.2%), cardiovascular-related genes including those associated with hereditary thrombophilia (36.3%), and in genes causing other medically actionable disorders (15.5%), such as autosomal recessive alpha-1-antitrypsin deficiency and hereditary hemochromatosis. Genes with P/LP results included *BRCA1*, *BRCA2*, *APOB*, *LDLR*, *MSH6*, *MUTYH*, and *PKP2*, among others. When the evaluation was restricted to the 56 genes originally recommended by the ACMG for reporting secondary findings, the positive rate was 5.6% (73 of 1,300) or 3.2% (42 of 1,300) if heterozygous variants in *MUTYH* and other well-known moderate-risk alleles were excluded. In the 209 positive cases, up to 28% of individuals may not have met established guidelines for diagnostic genetic testing based on the provided clinical information regarding personal and family health history. No clinical information was provided for 69.8% of individuals.

Conclusions: Results from our cohort of 1,300 individuals showed that 16% may have risks for hereditary disease with established management guidelines. Identification of these variants may lead to earlier disease detection. This type of testing offers healthy individuals, who would not otherwise have met diagnostic testing criteria, based on personal or family history, the opportunity to learn more about clinically significant genetic risks for certain types of hereditary disorders. Proactive health-related genetic information represents an expanding area of personalized medicine in which healthcare providers can educate those pursuing screening for genetic risks.

BACKGROUND

There is increasing interest in broad access to genetic information that can inform genetic risk for hereditary health conditions.

- Decreasing DNA sequencing costs are making this type of genetic information more accessible and available in mainstream healthcare.
- Healthy adults are beginning to proactively seek medically relevant information to inform their long-term healthcare, including genetic information focused on medically actionable findings.
- Findings since the 2013 ACMG guidance on the return of medically important genetic information to individuals undergoing diagnostic WES or WGS, regardless of indication, has revealed at least 2-5% of individuals carry a P/LP variant in one of the 59 genes.[1-4]

These diagnostic-grade, multigene next-generation sequencing (NGS)-based panels were developed to provide access to genetic information for healthy individuals.

- The ACMG56 gene list provided the foundation for these panels.
- Expansion of clinical areas already represented within the ACMG gene list, additional publications on medically actionable genes, and gene lists developed by genomic sequencing groups and internal medical review were utilized in expanding the gene lists.
- Panels are focused on hereditary cancer, cardiovascular disorders, and other medically actionable conditions.

DESCRIPTION OF PANEL

Table 1. Multigene panels and clinical area description.

Genes included in the multigene screening panel for healthy individuals (n=139)
Cancer-related genes (n=57): ***APC***, *ATM, BAP1, BARD1, BMPR1A,* ***BRCA1***, ***BRCA2***, *BRIP1, CDC73, CDH1, CDK4, CDKN2A, CHEK2, DICER1, EPCAM, FH, FLCN, GREM1, HOXB13, KIT, MAX,* ***MEN1***, *MET, MITF,* ***MLH1***, ***MSH2***, ***MSH6***, ***MUTYH***, *NBN,* ***NF2***, *PALB2, PDGFRA,* ***PMS2***, *POLD1, POLE, PRKAR1A, PTCH1,* ***PTEN***, *RAD51C, RAD51D,* ***RB1***, ***RET***, *SDHA,* ***SDHAF2***, ***SDHB***, ***SDHC***, ***SDHD***, *SMAD4, SMARCA4, SMARCB1,* ***STK11***, *TMEM127,* ***TP53***, ***TSC1***, ***TSC2***, ***VHL***, ***WT1***
Cardiovascular-related genes (n=75): ***ACTA2***, ***ACTC1***, *ACTN2, ACVRL1,* ***APOB***, *BAG3, BMPR2, CACNA1C, CACNB2, CALM1, CALM2, CALM3, CASQ2, CAV1, CAV3,* ***COL3A1***, *CRYAB, CSRP3, DES, DMD,* ***DSC2***, ***DSG2***, ***DSP***, *EMD, ENG, F2, F5, F9,* ***FBN1***, *FHL1,* ***GLA***, *GPD1L, HCN4, JUP, KCNE1, KCNE2,* ***KCNH2***, *KCNJ2,* ***KCNQ1***, *LAMP2,* ***LDLR***, *LDLRAP1,* ***LMNA***, ***MYBPC3***, ***MYH7***, ***MYH11***, ***MYL2***, ***MYL3***, ***MYLK***, *NKX2-5,* ***PCSK9***, ***PKP2***, *PLN,* ***PRKAG2***, *PRKG1, PROC, PROS1, RBM20,* ***RYR2***, ***SCN5A***, *SERPINC1, SGCD,* ***SMAD3***, *SMAD4, TCAP, TGFB2, TGFB3,* ***TGFBR1***, *TGFBR2,* ***TMEM43***, *TNNC1,* ***TNNI3***, ***TNNT2***, ***TPM1***, *VCL*
Genes for other medically important disorders (n=8): ***CACNA1S***, *HAMP, HFE, HFE2,* ***RYR1***, *SERPINA1, SLC40A1, TFR2*

Table 1. The 139 genes present on the multigene panel for healthy individuals. The cancer-only panel contains 57 genes and the cardiovascular-only panel contains 75 genes. The bolded genes represent the original 56 genes identified by the ACMG in 2013 as medically actionable genes where variants should be returned, regardless of testing indication (including healthy individuals) in WES/WGS testing. The ACMG updated these genes to 59 in 2016.[2]

Figure 1. Multigene panel screening results in 1,300 tested individuals.

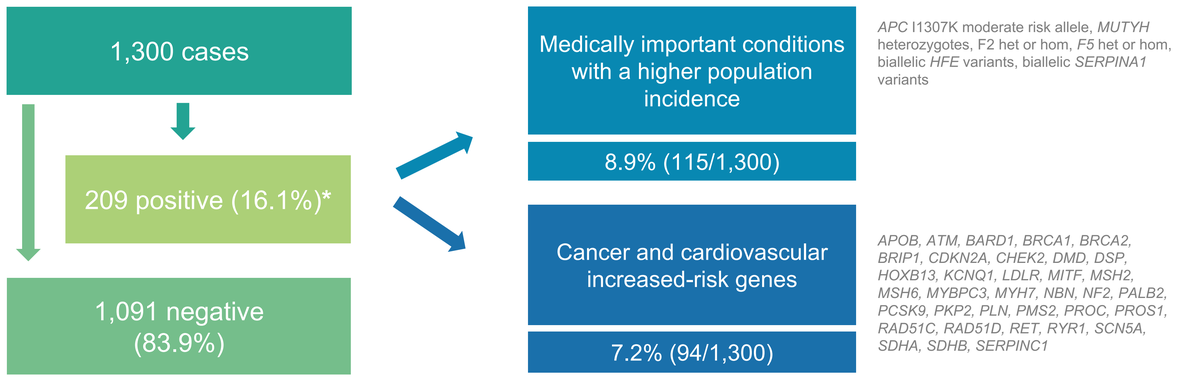

Figure 1. Positive findings detected with the multigene screening panels for healthy individuals. The 16.1% positive rate observed is broken down into two groups of findings: medically important conditions with a higher population incidence and those findings that confer a significantly increased risk of cancer and cardiovascular conditions. ***Carrier status is not included in the overall calculated positive rate.**

Figure 2. Clinical areas observed in positive cases.

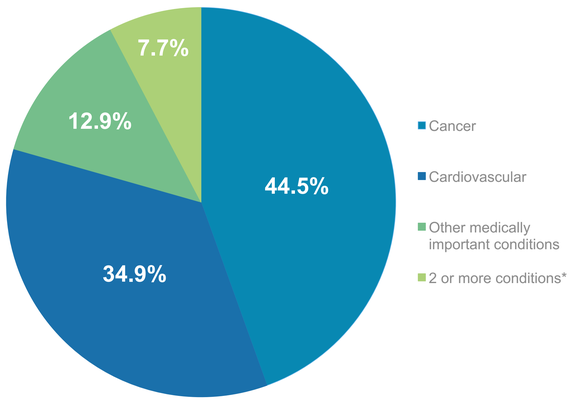

Figure 2. Positive findings broken down by clinical area. *In this data set of 1,300 individuals, 16 were found to have 2 or more positive primary findings (7.7%). A total of 226 findings were seen in 209 positive cases. Carrier status is not counted toward the positive rate of 16.1%.

Table 2. Findings in the ACMG56 genes in 1,300 individuals.

Group of genes	Findings	Positive rate
ACMG56 genes only, including: ▪ All P/LP variants, *MUTYH* hets, *APC* increased risk allele	73/1,300	5.6%
ACMG56 genes only, excluding: ▪ *MUTYH* hets, *APC* increased risk allele, or P/LP carrier status	42/1,300	3.2%

Table 2. Positive findings detected in the ACMG56 genes. All positive findings are in row 1, which includes single heterozygous *MUTYH* P/LP and *APC* increased risk allele variants. Row 2 shows the positive finding rates with strict adherence to reportable variant types per the ACMG 2013 guidance.

Table 3. Clinical information provided in 1,300 tested individuals.

Health information provided	Negative results (n = 1,091)		Positive results (n = 209)	
	Number	Percentage	Number	Percentage
Adopted / little family history known	27	2.5%	3	1.4%
No known risk factors / healthy	25	2.3%	12	5.7%
No information provided	770	70.6%	138	66.0%
Personal or family history of cancer and/or cardiovascular condition	269	24.6%	56	26.8%
Breakdown of reported personal or family history of cancer and/or cardiovascular conditions				
Personal history of cancer and/or cardiovascular condition	92 / 269	34.2%	19 / 56	33.9%
Family history of cancer and/or cardiovascular condition	177 / 269	65.8%	37 / 56	66.1%

Table 3. Clinician-documented clinical information provided for the 1,300 individuals tested. Inclusion of clinical information is not required.

EXAMPLE CASES

- **Case 1:** A 40-year-old male without significant medical or family history was positive for a pathogenic variant in *PKP2*, which is associated with arrhythmogenic right ventricular dysplasia (ARVC). Subsequent consultation with a specialist and imaging studies revealed early cardiac changes related to ARVC. Based on these findings, lifestyle and exercise modifications were recommended.
- **Case 2:** A pathogenic *BRCA2* variant was identified in a female in her 60s without personal or family history of hereditary breast and ovarian cancer. Subsequent genetic counseling reviewed established surveillance recommendations and implications for family members.
- **Case 3:** A 70-year-old healthy male screened positive for two *HFE* pathogenic variants (homozygous). Follow-up evaluation revealed a markedly elevated ferritin level. Hematology consultation recommended monitoring of ferritin and therapeutic phlebotomy, if clinically symptomatic.

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