Counseling healthy individuals for proactive genetic screening: A case report

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Disclosure statement: Invitae authors are employees and stockholders of Invitae Corporation.

Introduction

An estimated 2–5% of the population may have personal risk for later-onset Mendelian disease. Proponents of screening for these disorders assert that providing information to healthy individuals can save lives through increased screening and prevention. For example, half of all women with a pathogenic BRCA1 or BRCA2 variant have no family history of breast or ovarian cancer.[1] As the cost of genetic testing declines, healthy individuals are seeking genetic screening in increasing numbers, in some cases due to limited or unavailable family history. Genetic counselors (GCs) have a distinct role in educating these individuals and helping them navigate the sometimes unexpected results.

We present the case of a 43-year-old adopted woman with an incomplete biological family health history suggestive of breast cancer in her maternal lineage. Her paternal family history was unknown. She discussed with her GC the option of undergoing testing using a hereditary breast cancer panel vs. a proactive genetic screening panel, based on conditions outlined by the American College of Medical Genetics and Genomics (ACMG), and given the lack of complete family history information. She opted for the proactive genetic screening panel including more than 120 genes related to cancer, cardiovascular, and other disease risks that reports only likely pathogenic or pathogenic (LP/P) variants. The results contained two LP/P variants, one each in the BRCA2 and CHEK2 genes, indicating an increased risk for cancer. She retains at least population-level risk for the inherited cardiovascular-related conditions included on the proactive panel.

This case illustrates what is likely to occur with greater frequency as healthy individuals seek genetic screening to identify their personal risks for conditions with clinical management guidelines. Despite a limited family history, our patient received results with clear clinical implications for her health. With appropriate genetic counseling, a proactive genetic screening panel can be an integral part of a patient's long-term healthcare plan.

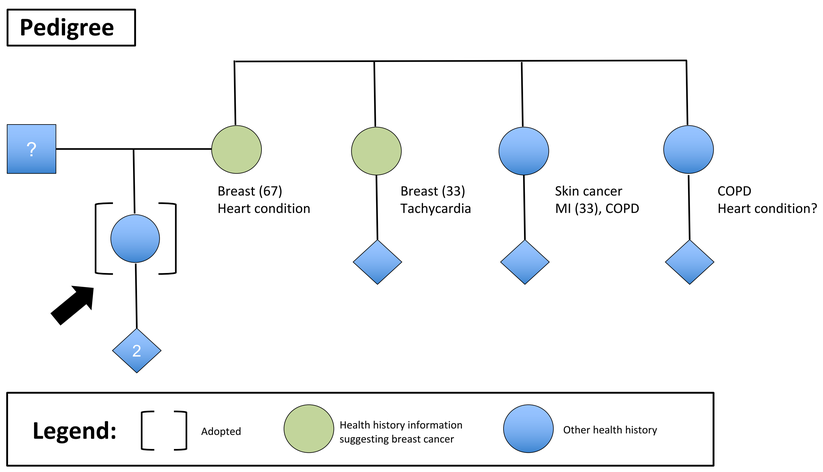
Background

- There is a rapidly growing interest in broad access to genetic information.
  - Decreasing DNA sequencing costs are making genetic information more accessible.
  - Healthy adults are beginning to proactively seek medically relevant information to inform their long-term healthcare.
  - Some individuals may have limited or no information about their family's health history.
  - Genetic information focused on medically actionable findings has the most clinical utility.

- The medically actionable next-generation sequencing (NGS)-based gene panel was developed to provide access to genetic information for healthy individuals interested in incorporating genetic information into their long-term healthcare.
  - The ACMG56 gene list is the foundation for this medically actionable panel.
  - The Invitae panel includes over 120 genes that are focused on hereditary cancer, cardiovascular disorders, and other medically actionable conditions.

- For additional information related to experiences screening healthy individuals with a medically actionable panel, see abstract B-53.

Patient information and health history



Patient information and health history (continued)

- This individual was a 43-year-old adopted female with limited information on her biological family's health history. Her past medical history was unremarkable.

- There was limited health information available on her maternal lineage, which suggested a history of breast cancer. There was no information available on her paternal lineage (see included pedigree).

Proactive panel testing result

- After discussion with her healthcare provider, this individual was offered the choice between a hereditary cancer panel or the proactive genetic screening panel. Due to her adoption history, she selected the proactive genetic screening panel. This panel provides information on genetic risk related to hereditary cancer, cardiovascular, and other disorders by evaluating for likely pathogenic and pathogenic changes in more than 120 genes (see table below for gene list).

Genes on the medically actionable genetic screening panel
Cancer-related genes: 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: 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
Other actionable disorders: CACNA1S, HAMP, HFE, HFE2, RYR1, SERPINA1, SLC40A1, TRF2

*Genes that are on the current proactive genetic screening panel but that were not included on the original proactive genetic screening panel ordered for this individual

- This individual's result came back with a pathogenic variant in the BRCA2 gene and a pathogenic variant in the CHEK2 gene (see table below), indicating a significantly increased risk to develop cancer. No other clinically significant changes were detected in the remaining genes.
- Genetic changes in the BRCA2 gene cause hereditary breast and ovarian cancer (HBOC) syndrome. Individuals with HBOC syndrome are more likely to develop one or more cancers involving the breasts (in both females and males), ovaries/fallopian tubes/peritoneum, prostate, and less frequently, the pancreas and the skin (melanoma).
- Genetic changes in the CHEK2 gene are associated with an increased risk for breast (in both females and males), colorectal, thyroid, and prostate cancers.

Gene	Variant	Classification
BRCA2	c.9891_9894dupATTT (p.Gln3299Ilefs*29)	Pathogenic
CHEK2	c.470 T>C (p.Ile157Thr)	Pathogenic (low penetrance)

- This individual plans to move forward with preventive breast and ovarian surgeries.

Conclusions

- This individual obtained health-related genetic information that has clear clinical implications and can help guide her long-term healthcare.

- Working with her GC and the rest of her healthcare team, this individual is now taking appropriate preventive measures.

- Valuable information can be obtained regarding the increased risk of developing certain Mendelian disorders with proactive genetic testing in ostensibly healthy individuals.

- This medically actionable panel for healthy individuals represents a diagnostic grade genetic evaluation that can be integrated successfully into a proactive healthcare plan.

References and acknowledgments

1. Levy-Lahad E, Lahad A, King MC. Precision medicine meets public health: population screening for BRCA1 and BRCA2. *J Natl Cancer Inst.* 2014;107(1):420.

The authors would like to thank this individual for consenting to participate in this case report.