Retrospective analysis of preliminary results from a medically actionable genetic screening panel for healthy individuals

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Abstract

Introduction

Motivated by the American College of Medical Genetics and Genomics (ACMG) policy statement on secondary findings, health-related genetic information is increasingly available to healthy individuals through their healthcare professionals. This information can identify disease risk and may lead to earlier detection and prevention. However, it must be accompanied by adequate educational support for clinicians and genetic counseling for patients. We report the frequency of medically important variants found in a medically actionable genetic screening panel in healthy individuals and present several cases that highlight the need for genetic counseling when incorporating such results into routine healthcare.

Methods

Under an IRB-approved protocol, we analyzed de-identified data from 120 healthy individuals who had genetic screening with an expanded panel of up to 139 medically actionable genes. Clinician-documented health information, if provided, was also reviewed.

Results

Pathogenic/likely pathogenic (P/LP) results were observed in 18% (22 of 120) of cases, with findings in cancer-related genes (45.5%), cardiovascular-related genes including those associated with hereditary thrombophilia (36.4%), and genes causing other medically actionable disorders (18.1%), such as hereditary hemochromatosis and alpha-1-antitrypsin deficiency. When we restricted our evaluation to the 56 genes originally recommended by the ACMG, the positive rate was 7.5% (9 of 120) or 5.8% (7 of 120) depending on whether MUTYH heterozygosity was reported. Several cases related to increased hereditary cancer, cardiovascular, and bleeding risks are highlighted.

Conclusions

Health-related germline genetic information is of increasing interest to healthy individuals and represents a unique and expanding area in which genetic counselors can educate those pursuing screening for genetic risks. Genetic counselors can play a significant role in this type of testing in healthy individuals who would not otherwise meet diagnostic testing criteria based on personal or family history.

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.
  - Genetic information focused on medically actionable findings has the most clinical utility.
  - 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 medically actionable next generation sequencing (NGS)-based gene panels were 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.
  - Expansion of clinical areas already represented within the ACMG gene list, additional publications on medically actionable genes, gene lists developed by genomic sequencing groups and internal medical review were components to expanding the gene list.
  - Over 130 genes are included that are focused on hereditary cancer, cardiovascular disorders and other medically actionable conditions.
- Growth of medically relevant genetic tests to a broader audience should continue to involve healthcare providers.
  - Genetic counselors are important stakeholders.
  - Genetic counselors can play a significant role in patient education, test selection, post-test counseling and follow-up clinical management needs.

Panel and clinical area description

Table 1: Genes on the medically actionable genetic screening panel (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
Other actionable disorders (n=8): **CACNA1S**, HAMP, HFE, HFE2, **RYR1**, SERPINA1, SLC40A1, TFR2

Table 1: The 139 genes present on the medically actionable panel. 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 if available, regardless of testing indication (including healthy individuals). The ACMG updated these genes to 59 in 2016.

Preliminary findings and positive rates

Table 2

Group of genes	Findings	Positive rate
Medically Actionable Genetic Screening Panel	22/120	18.3%
ACMG56 genes only (All P/LP variants, including increased risk alleles)	9/120	7.5%
ACMG56 genes only (MUTYH het P/LP variants and increased risk alleles excluded)	4/120	3.3%

Table 2: Positive findings detected with the medically actionable panels. This table is broken down into three categories. All positive findings are in row 1, which includes single heterozygous MUTYH P/LP and APC increased risk allele variants. Carrier status for a single heterozygous change in HFE or SERPINA1 are not counted as positive results here. Row 2 shows the positive findings just within the ACMG56 genes, and row 3 shows conservatively what was detected if MUTYH heterozygotes and APC increased risk alleles are not included.

Figure 1: Grouping of Positive Findings by Clinical Area

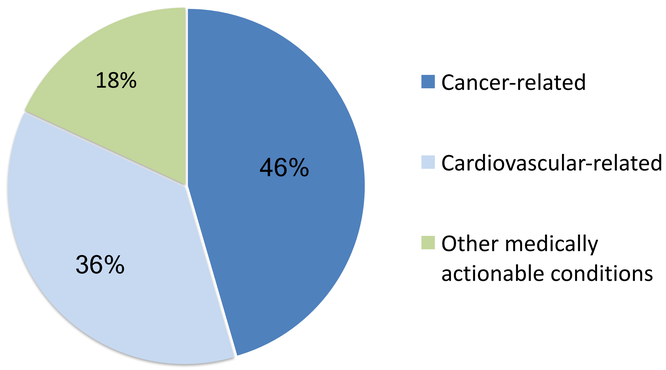

Figure 1: Breakdown of findings in the medically actionable panels by clinical area. Carrier status for an autosomal recessive condition is not counted towards the positive findings rate.

Table 3

Genes with positive findings		
Cancer-related genes	N=10	APC, ATM, BRCA2, CHEK2, FH, MUTYH, NF2
Cardiovascular-related genes	N=8	F2 (het and/or hom), F5 (het and/or hom), PKP2
Genes related to other clinical conditions	N=4	HFE (biallelic P/LP variants), SERPINA1 (biallelic P/LP variants)

Table 3: The genes where P/LP variants were observed in tested samples. HFE and SERPINA1 heterozygous carrier results are not counted towards the positive rate.

Figure 2: Demographic information on ordering clinics

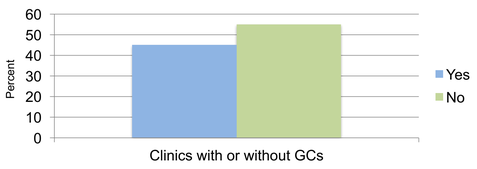

Figure 2: Of the 22 clinics that ordered the medically actionable gene panel in this initial retrospective cohort, 10 had GCs on staff (45%) and 12 did not (55%).

Example cases

Case 1: Cancer-related

- Healthy unaffected male individual interested in understanding personal genetic risk for hereditary conditions underwent testing with the medically actionable genetic screening panel.
- A heterozygous ATM pathogenic variant was identified.
- Healthcare provider is using this genetic risk information to develop a personalized screening plan, including surveillance and biochemical assessments. This includes baseline colonoscopy, MRI of the abdomen and pelvis (including prostate), and monitoring PSA levels.

Case 2: Cardiovascular-related

- Healthy male in his 40s without significant family or medical history desired genetic testing to be proactive about his health. The medically actionable genetic screening panel was ordered.
- A pathogenic PKP2 variant was identified.
- Review of history uncovered no concerning cardiovascular symptoms. Referral for evaluation with a cardiologist uncovered no arrhythmia on Holter monitor, but cardiac imaging identified early changes related to ARVC.
- Lifestyle and exercise modification recommended.

Case 3: Cardiovascular-related

- Unaffected male in his 60s without indication for genetic testing, who wanted to learn genetic risk information to be proactive about his health, underwent testing with the medically actionable genetic screening panel.
- A heterozygous F2 pathogenic variant (prothrombin G20210A) was identified.
- Healthcare provider counseled individual of his increased risk to develop a blood clot, and plans to review any change of management with primary care provider. Implications of this finding were discussed with respect to this individual's siblings and children.

Case 4: Other medically actionable condition

- A healthy male in his 70s who was interested in genetic risk information was tested with the medically actionable genetic screening panel.
- A homozygous change, H63D, was identified in the HFE gene.
- The GC counseled the patient that this change is considered a mild variant with low likelihood of penetrance. In follow-up evaluation, patient was noted to have an extremely elevated ferritin level, with iron level, total iron binding capacity and transferrin saturation all wnl.
- Follow-up hematology evaluation recommended monitoring ferritin levels for 1 year and consider phlebotomy if ferritin remains high or clinical symptoms arise.

Conclusions

- Germline genetic information is of increasing interest to healthy individuals and represents a unique and expanding area in healthcare.
- Proactive testing for hereditary disease risk can uncover medically important genetic information in individuals who would not otherwise meet diagnostic testing criteria.
  - Identification of potential disease risk may lead to earlier detection and prevention of disease.
- As availability of this type of testing grows, genetic counselors can play a very important and significant role.
  - It is important to ensure that patients and their families have appropriate education and counseling to understand testing risks and limitations, and know how to incorporate this information into their long-term healthcare plan.

References

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