

Genetic screening for healthy individuals:
Preliminary results from a medically
actionable genetic screening panel

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Disclosure Statement

- I am an employee and stockholder of Invitae Corporation

Increasing access to genetic information

- Decreasing DNA sequencing costs make genetic information more accessible
- There are expanding options and increased availability of genetic information
 - Diagnostic testing
 - Carrier testing
 - Pharmacogenomic testing
 - Genomic screening tests

Increasing access to genetic information

Genomic medicine is moving into the clinic

Healthcare providers

are expressing increasing interest in integrating genetics into a patient's personalized healthcare plan

Patients

are proactively seeking genetic information to understand potential genetic risks that could guide long-term healthcare

Frequency of ACMG medically actionable secondary findings

- Since the 2013 ACMG guidance on reporting secondary findings in clinical WES and WGS, medically actionable results from the ACMG56 / ACMG59 have been returned to:

Affected probands

Healthy parents
from diagnostic
trio analysis

Healthy
WES/WGS

- 2-5% receive a medically important result

Developing a medically actionable panel

- Carried out by a team of clinical geneticists, GCs, and PhD scientists
- ACMG56 used as the foundation of the panel
- Sources evaluated:
 - Gene lists recently published by multiple groups
 - Additional genes for already represented clinical conditions
 - Critical medical review of additional relevant clinical conditions
- Consistent criteria for inclusion, including:
 - Strength of gene/condition association, disease severity, penetrance, and availability of published medical management recommendations

Developing a medically actionable panel

- 139 genes

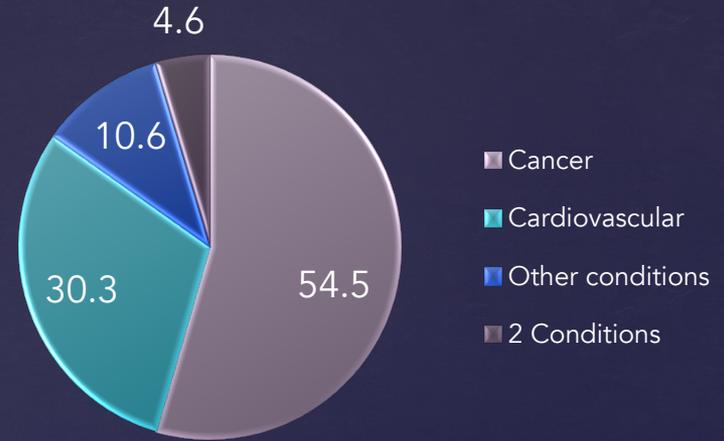
| Clinical area | Genes |
|---|---|
| Cancer (n=57) | APC, BRCA1, BRCA2, MEN1, MLH1, MSH2, MSH6, MUTYH, NF2, PMS2, PTEN, RB1, RET, SDHAF2, SDHB, SDHC, SDHD, STK11, TP53, TSC1, TSC2, VHL, WT1 ATM, BAP1, BARD1, BMPR1A, BRIP1, CDC73, CDH1, CDK4, CDKN2A, CHEK2, DICER1, EPCAM, FH, FLCN, GREM1, HOXB13, KIT, MAX, MET, MITF, NBN, PALB2, PDGFRA, POLD1, POLE, PRKAR1A, PTCH1, RAD51C, RAD51D, SDHA, SMAD4, SMARCA4, SMARCB1, TMEM127 |
| Cardiovascular (n=75) | ACTA2, ACTC1, APOB, COL3A1, DSC2, DSG2, DSP, FBN1, GLA, KCNH2, KCNQ1, LDLR, LMNA, MYBPC3, MYH7, MYH11, MYL2, MYL3, PCSK9, PKP2, PRKAG2, RYR2, SCN5A, SMAD3, TGFB1, TGFB2, TMEM43, TNNT3, TNNT2, TPM1 ACTN2, ACVRL1, BAG3, BMPR2, CACNA1C, CACNB2, CALM1, CALM2, CALM3, CASQ2, CAV1, CAV3, CRYAB, CSRP3, DES, DMD, EMD, ENG, F2, F5, F9, FHL1, GPD1L, HCN4, JUP, KCNE1, KCNE2, KCNJ2, LAMP2, LDLRAP1, MYLK, NKX2-5, PLN, PRKG1, PROC, PROS1, RBM20, SERPINC1, SGCD, SMAD4, TCAP, TGFB2, TGFB3, TNNC1, VCL |
| Other medically actionable conditions (n=8) | CACNA1S, RYR1 HAMP, HFE, HFE2, SERPINA1, SLC40A1, TFR2 |

Developing a medically actionable panel

- A panel-based approach to allow
 - Diagnostic-grade evaluation of genes
 - Patient education for genes/conditions evaluated
- A medically responsible test with appropriate support
 - Provider-ordered test (not DTC) with opportunity for genetic counseling
 - Educational materials for patients and healthcare providers
 - Only clinically significant findings are returned – No VUS
 - An update report issued if a VUS become clinically significant

Results in first 440 patients

| Positive (LP/P) | Negative |
|-----------------|----------|
| 66 | 378 |
| 14.9% | 85.1% |



- Larger gene list
- Report some types of variants that are not included in the ACMG guidelines
 - Heterozygosity for MUTYH, moderate risk (increased risk) alleles

Results in first 440 Patients in the ACMG56

| Results | # | Percentage |
|---|----|------------|
| All reportable findings in the ACMG56 | 29 | 6.5% |
| ACMG56 findings without MUTYH heterozygotes and moderate risk alleles | 15 | 3.4% |

- The observed positive rate is within the range reported in the literature for the ACMG56 / ACMG59 secondary findings

Positive test results by gene

| Genes with positive findings identified | | |
|--|------|---|
| Cancer-related genes | N=41 | APC, ATM, BRCA1, BRCA2, BRIP1, CHEK2, FH, HOXB13, MITF, MSH2, MSH6, MUTYH, NF2, RAD51D, RET, SDHB |
| Cardiovascular-related genes | N=20 | APOB, F2 (het and/or hom), F5 (het and/or hom), PKP2 |
| Genes related to other clinical conditions | N=8 | HFE (biallelic LP/P variants) |

- Hereditary thrombophilia (n=17), MUTYH heterozygotes (n=10), hereditary hemochromatosis (n=8), APC increased risk allele (n=6)

Provided health information

- Inclusion of personal or family health history not required
- Of those with a positive finding:

| Clinical information provided | Percentage of cases |
|---|---------------------|
| Limited or unknown family history | 3.0% |
| No known risk factors | 15.2% |
| Some personal or family history of one or more conditions | 39.4% |
| No information included | 42.4% |

Carrier frequencies

- Of those tests where carrier status was reportable, about 30% of individuals were found to carry a recessive condition

| Condition | Percentage of cases |
|--------------------------------|---------------------|
| Hereditary hemochromatosis | 80.0% |
| Alpha-1-antitrypsin deficiency | 15.6% |
| More than 1 condition | 4.4% |

Carrier status is not considered a primary positive finding

Example cases 1 & 2

Case 1: Cancer-related

- A healthy, unaffected male in his 40s was interested in understanding personal genetic risk for hereditary conditions.
- A heterozygous ATM pathogenic variant was identified.
- The healthcare provider is using this genetic risk information to develop a personalized screening plan that includes a baseline colonoscopy.

Case 2: Cardiovascular-related

- Healthy, athletic male in his 40s without significant family or personal medical history desired genetic testing to be proactive about his health.
- 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 were recommended.

Example cases 3 & 4

Case 3: Cardiovascular-related

- An unaffected male in his 60s without indication for genetic testing wanted to learn genetic risk information to be proactive about his health.
- A heterozygous F2 pathogenic variant (prothrombin G20210A) was identified.
- The healthcare provider counseled the individual on his thrombophilia, and plans to review any change of management with the 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 was interested in genetic risk information.
- A homozygous change, H63D, was identified in the HFE gene.
- The healthcare provider 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 considering phlebotomy if ferritin remains high or clinical symptoms arise.

Conclusions

- A higher than expected positive rate from these preliminary data
- Shows that actionable findings can provide the opportunity to proactively screen for and/or detect disease at an earlier stage
- Outcomes-focused longitudinal data is needed to determine if there is any benefit to knowing medically actionable risk information

Challenges of healthy testing

- Ensuring individuals receive targeted genetic testing when there is a diagnostic indication
 - Need a family / personal history evaluation to assess risk
- Ensuring understanding of a genetic screening test
- Incomplete understanding of the penetrance of conditions when no personal or family history

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