Genetic Information for Healthy Individuals: Developing a Medically Actionable Genetic Screening Panel

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Introduction

The ACMG policy statement surrounding secondary findings detected during diagnostic whole exome or whole genome sequencing (2016 update) recommends returning pathogenic variants in 59 genes considered medically important regardless of test indication. This list of genes has changed and will continue to change with accelerating advances and knowledge in clinical genomics. Access to this important health-related genetic information should be available to individuals and healthcare providers (HCPs) who want to incorporate it into routine healthcare. To meet this growing interest, we have developed an expanded genetic screening panel for healthy individuals that includes medically important Mendelian disorders. Proactive, health-related genetic information can identify disease risk and may lead to the earlier detection and prevention of disease.

We reviewed the 2013 ACMG secondary findings gene list, the ACMG Working Group process, and expanded gene lists published by multiple genomics groups. Our internal panel of genetic counselors and medical and clinical geneticists reviewed the clinical actionability of additional genes using criteria including disease severity, penetrance, the availability of published medical management recommendations, and the strength of gene/condition associations. Within the bounds of available clinical management guidelines, we reasoned that the potential benefit of being more inclusive outweighed the potential risk of providing expanded health-related genetic information to patients. Our list of more than 120 clinically actionable genes includes the original 56 genes selected by the ACMG and, in order to facilitate more comprehensive testing in each clinical area, 24 genes associated with increased risk for a cancer-related phenotype, 38 genes associated with increased risk for a cardiovascular-related phenotype, and six genes associated with increased risk for other medically actionable disorders. Only likely pathogenic/pathogenic variants in genes on this expanded list are considered clinically actionable and therefore reportable. Genetic variants of uncertain significance are not reported.

Health-related genetic information is of growing interest to unaffected individuals seeking to inform their long-term healthcare. Most of the data generated from whole exome or whole genome sequencing is not currently interpretable or applicable in the context of a healthy individual, but a focused gene panel presents an opportunity for these individuals to partner with their HCPs to support evidence-based personalized medical care. Given the growing interest in and decreasing costs of obtaining this type of health-related genetic information, medically actionable genetic screening represents a notable paradigm shift in clinical genomics as it begins to integrate deeper into routine medical practice, and promotes risk assessment and prevention of serious heritable diseases.

Background

- Since the 2013 ACMG guidance[1], clinical WES and WGS have reported secondary findings in healthy individuals (most commonly from the ACMG56 gene list)
  - ➢ Typically, these individuals are healthy parents or other unaffected family members sequenced in support of an affected proband
- One in 20 to 1 in 50 of these healthy individuals with no indication for WES/WGS receive a medically important result[2-5].
- There is a rapidly growing interest in broad access to genetic information
  - ➢ Decreasing DNA sequencing costs are making genetic information more accessible and pushing it further into mainstream healthcare
  - ➢ Healthy adults are beginning to proactively seek medically relevant information to inform their long-term healthcare
- Most of the data generated from WES/WGS is not interpretable or applicable for healthy individuals
  - ➢ Difficult to integrate meaningfully into routine healthcare
  - ➢ In a healthy context, the focus should be on medically actionable findings
- We focused on developing a medically actionable next generation sequencing-based gene panel for healthy individuals

Developing a medically actionable panel

- We established an internal team of ABMGG-certified clinical and medical geneticists (MDs and PhDs), genetic counselors and PhD scientists
- We evaluated multiple sources for clinically-relevant genes to consider adding:
  - ➢ Gene lists published by multiple groups since the 2013 ACMG guidance[including 6-7]
  - ➢ Private and publicly funded genomics initiatives
  - ➢ Broader expansion of already represented clinical conditions from the ACMG56
  - ➢ Additional conditions deemed medically important
- Using similar criteria to the 2013 ACMG guidance for inclusion, we considered
  - ➢ Penetrance, inheritance and management recommendations

Developing a medically actionable panel

- The ACMG56 gene list is the foundation for this medically actionable panel
  - ➢ Includes cancer and cardiovascular-related conditions
- We identified an additional 68 medically actionable genes that are within the same clinical areas as the ACMG56 gene list

ACMG56 gene list

Cancer-related genes	APC	BRCA1	BRCA2	MEN1	MLH1	MSH2	MSH6	PMS2
	MUTYH	NF2	PTEN	RB1	RET	SDHAF2	SDHB	SDHC
	SDHD	STK11	TP53	TSC1	TSC2	VHL	WT1	
Cardiovascular-related genes	ACTA2	ACTC1	APOB	COL3A1	DSC2	DSG2	DSP	FBN1
	GLA	KCNH2	KCNQ1	LDLR	LMNA	MYBPC3	MYH7	MYH11
	MYL2	MYL3	MYLK	PCSK9	PKP2	PRKAG2	RYR2	SCN5A
	SMAD3	TGFBR1	TGFBR2	TMEM43	TNNI3	TNNT2	TPM1	
Other genes	RYR1	CACNA1S						

The 56 genes identified by the ACMG in 2013 that were recommended to be returned to any individual undergoing clinical WES or WGS. The clinical areas largely fall into cancer and cardiovascular-related areas

The medically actionable panel also includes the genes below

Additional 68 genes

Cancer-related genes	ATM	BAP1	BMPR1A	BRIP1	CDC73	CDH1	CDK4	CDKN2A
	CHEK2	DICER1	EPCAM	FH	FLCN	KIT	MAX	MET
	PALB2	PDGFRA	PRKAR1A	PTCH1	SDHA	SMAD4	SMARCB1	TMEM127
Cardiovascular-related genes	ACTN2	ACVRL1	BAG3	BMPR2	CACNA1C	CACNB2	CASQ2	CAV1
	CAV3	CRYAB	CSRP3	DES	DMD	EMD	ENG	F2
	F5	F9	FHL1	GPD1L	HCN4	JUP	KCNE1	KCNE2
	KCNJ2	LDLRAP1	PLN	PRKG1	PROC	PROS1	RBM20	SERPINC1
	SMAD4	SGCD	TCAP	TGFB2	TGFB3	TNNC1	VCL	
Other genes	HAMP	HFE	HFE2	SERPINA1	SLC40A1	TRF2		

The additional 68 genes identified by Invitae to be included in a medically actionable panel. The clinical areas largely continue to encompass the cancer and cardiovascular clinical areas. All likely pathogenic (LP) and pathogenic (P) variants in the above genes will be reported (not KP or EP, as was recommended by the 2013 ACMG guidance). SMAD4 is listed twice, once in cancer and once in cardiovascular.

Considerations

- Invitae's panel-based approach to a medically actionable screening panel for healthy individuals allows:
  - ➢ A diagnostic-grade evaluation of all included genes (no gaps, full coverage, deletion/duplication analysis).
  - ➢ Patient education on a pre-defined set of genes/conditions covered by the panel
  - ➢ Genetic counseling opportunities to set expectations and discuss possible results
  - ➢ Only return results that could have medical implications
    - o Positive / Negative result only, no variants of uncertain significance (VUS) returned
- Represents a medically responsible test:
  - ➢ Offered as a provider-ordered test only (not direct-to-consumer)
  - ➢ Critical to include genetic counseling
  - ➢ Created educational materials directed towards patients and healthcare providers

References

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