Creating A Medically Actionable Genetic Screening Panel For Healthy Individuals

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Introduction

The 2013 ACMG policy statement recommended 56 genes for the return of incidental findings but noted that this list will, and should, evolve. Catalyzed by accelerating advances in clinical genomics, we generated an expanded gene list where pathogenic variants would be considered clinically actionable.

We reviewed the ACMG56 list, the ACMG Working Group process, and expanded gene lists published by multiple genomics groups. An expert panel of genetic counselors and medical and clinical geneticists reviewed the clinical actionability of individual genes beyond the ACMG56 using criteria such as penetrance, mode of inheritance, and the availability of published medical management recommendations.

Our novel list of 124 clinically actionable genes includes the ACMG56 plus 17 conditions (24 genes) with increased risk for a cancer-related phenotype, three conditions (38 genes) with increased risk for a cardiovascular-related phenotype, and two conditions (6 genes) with increased risk for other medically actionable disorders, all of which have published guidelines for medical management.

The ACMG policy statement addresses pathogenic variants discovered by diagnostic whole-exome or whole-genome sequencing (WES or WGS). WES/WGS is increasingly available to healthy individuals seeking to proactively inform their healthcare. The high cost and mostly uninterpretable results of these broad tests are obstacles for integration into routine healthcare. A focused gene panel restricted to clinically actionable variants presents an opportunity for healthy patients to partner with their healthcare providers for preventive genetic testing with significant potential to inform personalized medical care. This can significantly impact current clinical genetics practices and necessitate the development of new models for clinical genetic counseling. With decreasing costs of and growing interest in this type of information, the transition from what are considered incidental findings to primary findings represents a novel opportunity for genetic information to be introduced into routine medical practice, which in turn can lead to increased clinical utilization for the preventive care of patients.

Background

- Since the 2013 ACMG guidance[1], clinical WES and WGS have reported incidental findings in healthy individuals (typically from the ACMG56 gene list)
  - Typically, these are healthy parents or other family members sequenced as a trio in support of an affected proband
- 1 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

- Established an internal team of ABMGG-certified clinical and medical geneticists (MDs and PhDs), genetic counselors and PhD scientists
- 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
- Used similar criteria to the 2013 ACMG guidance for inclusion considered
  - Penetrance, inheritance, management recommendations

Developing a medically actionable panel

- The ACMG56 gene list is the foundation for this medically actionable panel
- The ACMG56 gene list 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						

Table above: the 56 genes identified by the American College of Medical Genetics and Genomics 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 MUTYH gene follows an autosomal recessive mode of inheritance; the ACMG recommended reporting only if 2 known pathogenic (KP) or expected pathogenic (EP) variants are present.

The medically actionable panel also includes the below genes

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		

Table above: 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). Any gene that follows an autosomal recessive mode of inheritance, per the 2013 ACMG guidelines, will not be reported (with the exception of ATM). 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 of results that could have medical implications
    - Positive / Negative result only, no variant 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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