

Secondary findings after virtual panels: A new frontier in incidental findings

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Disclosure statement

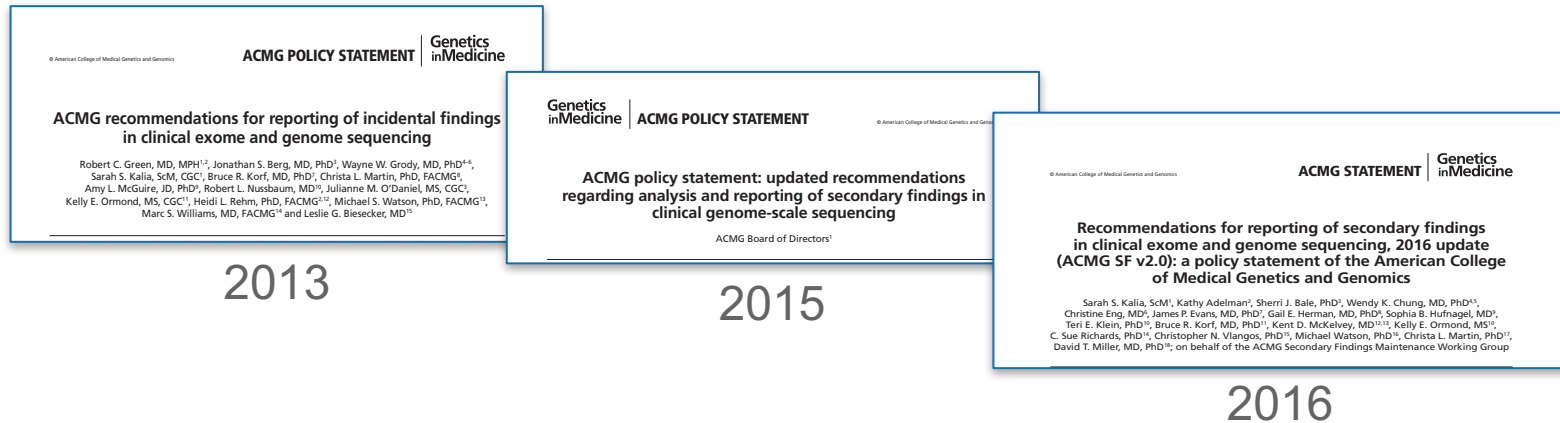
- I am an employee and stockholder of Invitae

Overview

- 1) Background on Incidental/Secondary findings
- 2) Utilization of virtual panels
- 3) Objectives of this study
- 4) Prevalence of secondary findings on a virtual panel
- 5) Summary

Background

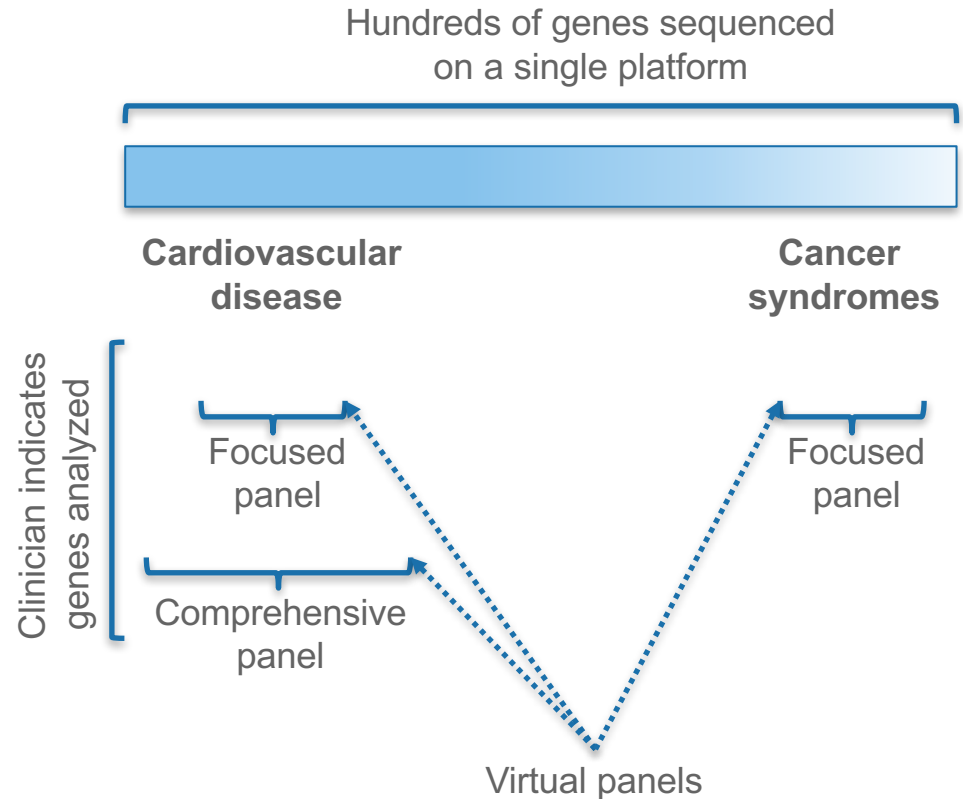
- ACMG recommendations for reporting secondary findings in diagnostic whole exome or genome sequencing (WES/WGS), independent of indication



- Various studies have estimated the prevalence of secondary findings in apparently unaffected individuals using WES/WGS
 - Published estimates range between 1.0%-6%

Background

- It is now possible to perform diagnostic multigene panel testing on assay platforms that cover hundreds of genes
 - These are used to generate “virtual panels” based on clinician indication



Study Objectives

- Use a virtual multigene panel strategy
 - Estimate the overall prevalence of cancer gene pathogenic variants
 - In a population of patients with no known cancer history
- Determine the number of secondary findings by gene
- Assess the clinical actionability of identified gene variants

Cancer gene panel selection

47 gene virtual panel

ACMG genes

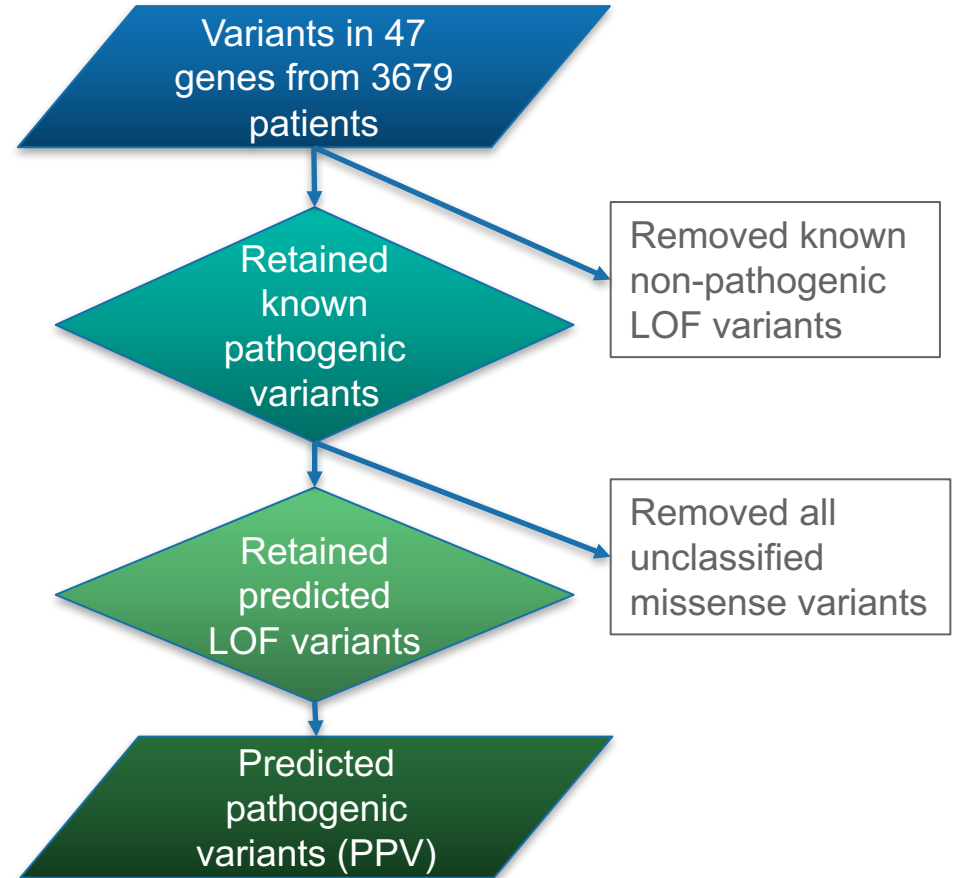
<i>APC</i>	<i>RB1</i>	<i>CDKN2A</i>	<i>SMAD4</i>
<i>BRCA1</i>	<i>RET</i>	<i>BMPR1A</i>	<i>SMARCB1</i>
<i>BRCA2</i>	<i>SDHAF2</i>	<i>CDC73</i>	<i>ATM</i>
<i>MEN1</i>	<i>SDHB</i>	<i>CDH1</i>	<i>BAP1</i>
<i>MLH1</i>	<i>SDHC</i>	<i>EPCAM</i>	<i>BRIP1</i>
<i>MSH2</i>	<i>SDHD</i>	<i>FH</i>	<i>CDK4</i>
<i>MSH6</i>	<i>STK11</i>	<i>FLCN</i>	<i>CHEK2</i>
<i>MUTYH</i>	<i>TP53</i>	<i>KIT</i>	<i>DICER1</i>
<i>NF2</i>	<i>TSC1</i>	<i>MET</i>	<i>MAX</i>
<i>PMS2</i>	<i>TSC2</i>	<i>PDGFRA</i>	<i>PALB2</i>
<i>PTEN</i>	<i>VHL</i>	<i>PRKAR1A</i>	<i>SDHA</i>
	<i>WT1</i>	<i>PTCH1</i>	<i>TMEM127</i>

Cancer-risk genes

- Inclusive cancer gene selection strategy (benefit>risk for gene-variant clinical management)
 - ACMG56 cancer-risk genes (23)
 - Reviewed literature for cancer-risk genes with:
 - Strong evidence of gene-condition association
 - Clinical management recommendations
 - Surveillance
 - Family cascade testing
 - Circumstances to avoid
 - 24 additional genes deemed clinically actionable by a panel of Clinical Geneticists, Genetic Counselors & PhD Scientists

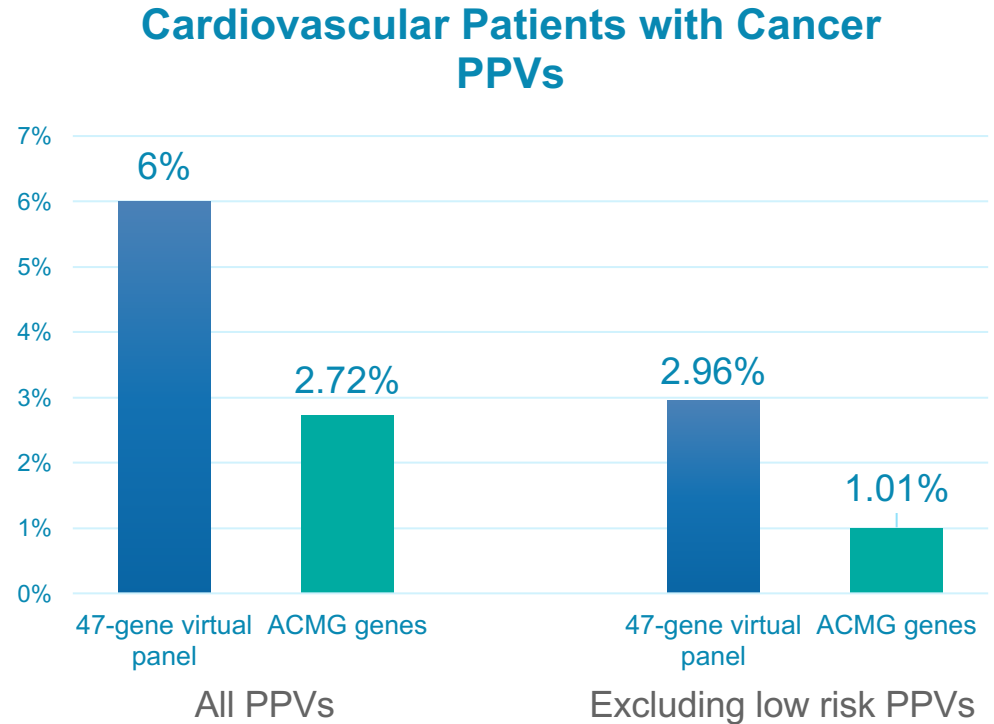
Methods

- 3679 patients referred for hereditary cardiovascular multigene panel testing
 - No known personal/family history of cancer
- Reviewed de-identified sequence data, under an IRB-approved protocol, for the 47-gene virtual cancer-risk panel
- Classification of variants from these 47 cancer-risk genes
 - Pathogenic if previously classified at Invitae as pathogenic
 - Novel variants predicted to be pathogenic if variant resulted in a frameshift, nonsense or splice-site disruption predicted to cause loss of function (LOF)
 - Removed known non-pathogenic LOF variants
- Predicted pathogenic variants (PPVs)



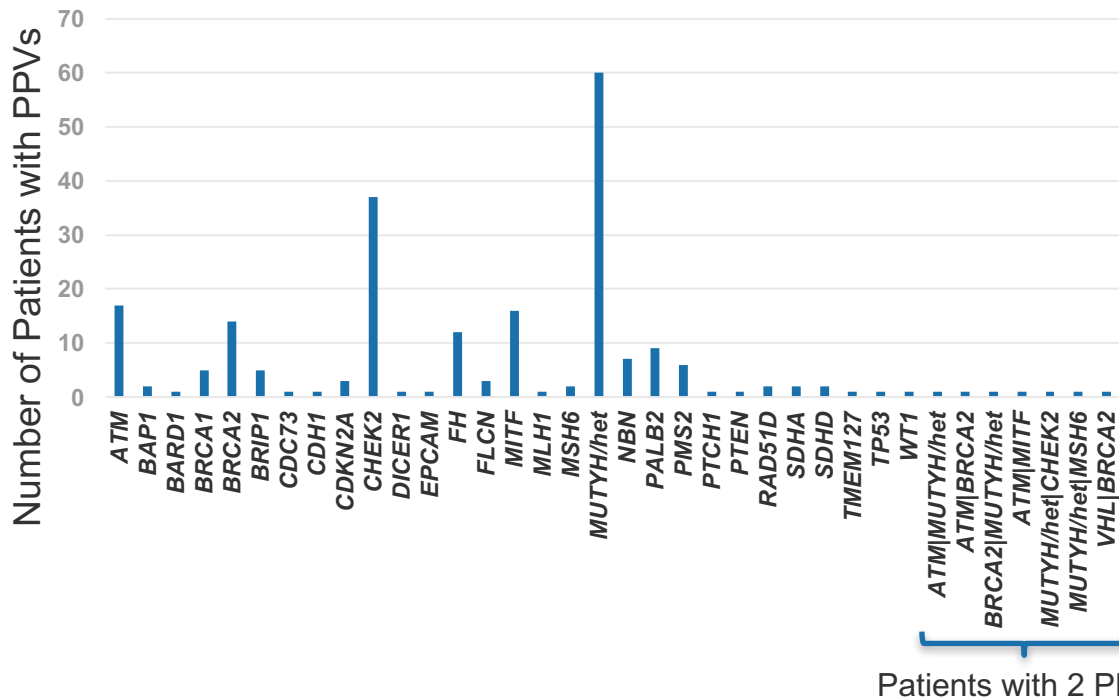
Cancer-risk gene PPV prevalence

- Prevalence of ALL cancer gene PPVs in 3769 cardiovascular patients
 - 6% of patients with PPV on virtual panel
 - 2.7% of patients with PPV when limited to ACMG cancer genes
- Positive patients after excluding lower risk variants
 - MUTYH heterozygotes (hets)
 - Low penetrance PPVs in CHEK2, MITF, FH



Positive secondary findings by gene

PPVs per cancer-risk gene



- 82% of the identified PPVs were in
 - ATM
 - BRCA1
 - BRCA2
 - CHEK2
 - FH
 - MITF
 - MUTYH
 - NBN
 - PALB2
 - PMS2

- 7 patients (3% of positives) had PPVs in two cancer-risk genes

Management guidelines for cancer genes with most PPVs

Gene	Cancer risk	Management recommendations ^{1,2,3,4}
<i>ATM</i>	Breast cancer	Annual mammogram and consider breast MRI starting at 40 years
<i>BRCA1/BRCA2</i>	Breast, ovarian and prostate cancer	Breast screening, RRM, RRSO
<i>CHEK2</i>	Breast and colon cancer	Annual mammogram and consider breast MRI starting at 40 years old
<i>FH</i>	Renal cell cancer	Annual abdominal MRI
<i>MITF</i>	Melanoma, Renal cell cancer	Monthly skin exams, renal ultrasound
<i>MUTYH</i> (het)	Colon cancer (moderate at most)	Colonoscopy at 40 years old for unaffected proband with colon cancer in 1 st degree relative
<i>NBN</i>	Breast cancer	Annual mammogram and consider breast MRI starting at 40 years old
<i>PALB2</i>	Breast cancer	Annual mammogram and consider breast MRI starting at 30 years old
<i>PMS2</i>	Colon and ovarian cancer	Colonoscopy every 1-2 years starting at 20-25 years of age

RRM – risk reducing mastectomy; RRSO – risk reducing salpingo-oophorectomy; het – heterozygote. ¹Daly et al. Genetic/Familial High-Risk Assessment: Breast and Ovarian, 1.2018, nccn.org, ²Provenzale et al. Genetic/Familial High-Risk Assessment: Colorectal, 3.2017, nccn.org, ³Menko et al. Hereditary leiomyomatosis and renal cell cancer (HLRCC): renal cancer risk, surveillance and treatment. Fam Cancer 2014, ⁴Potrony et al. Prevalence of MITF p.E318K in patients with melanoma independent of the presence of CKDN1A causative mutations. JAMA Dermatology 2016

Factors impacting PPV prevalence estimate

- Secondary findings in only cancer-risk genes estimated at up to 6%
 - Possibly impacted by analyzing larger number of cancer-risk genes
 - Inclusion of variants conferring moderate risk (e.g. MUTYH heterozygotes)
- Prevalence is likely underestimated
 - We did not include novel missense or copy number variants

Summary

- Using a virtual panel strategy we estimate the prevalence of secondary findings for cancer-risk at up to 6% in individuals undergoing hereditary cardiovascular multigene testing
- Each of the identified secondary finding PPVs is associated with published management guidelines with the potential to impact the clinical care of patients and their family members
- This study suggests that secondary findings of potential clinical utility could be gleaned from virtual multi-gene panels, a situation not currently addressed by the ACMG 2016 recommendations

Acknowledgements

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- Poster 2617 – Shan Yang, Cardiovascular risk PPVs in hereditary cancer patients
- Thursday 11am session – Emilie Zoltick, PeopleSeq Consortium early findings
- Friday 9am session – Eden Haverfield, Genetic screening for healthy individuals