Secondary findings in hereditary cancer genes from multigene panel data: A new frontier unanticipated by the ACMG

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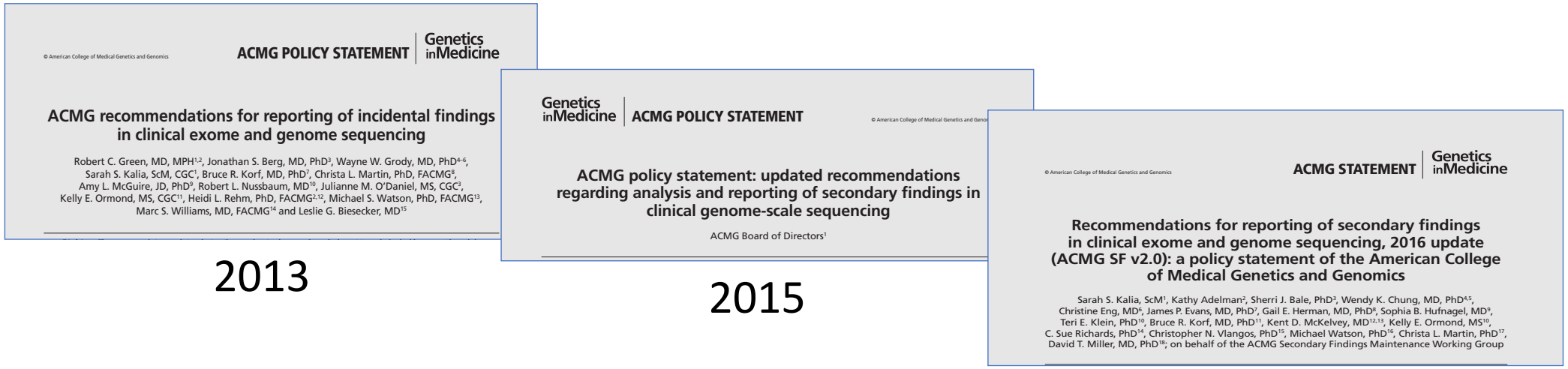
Disclosure(s): Employee and stockholder of Invitae

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

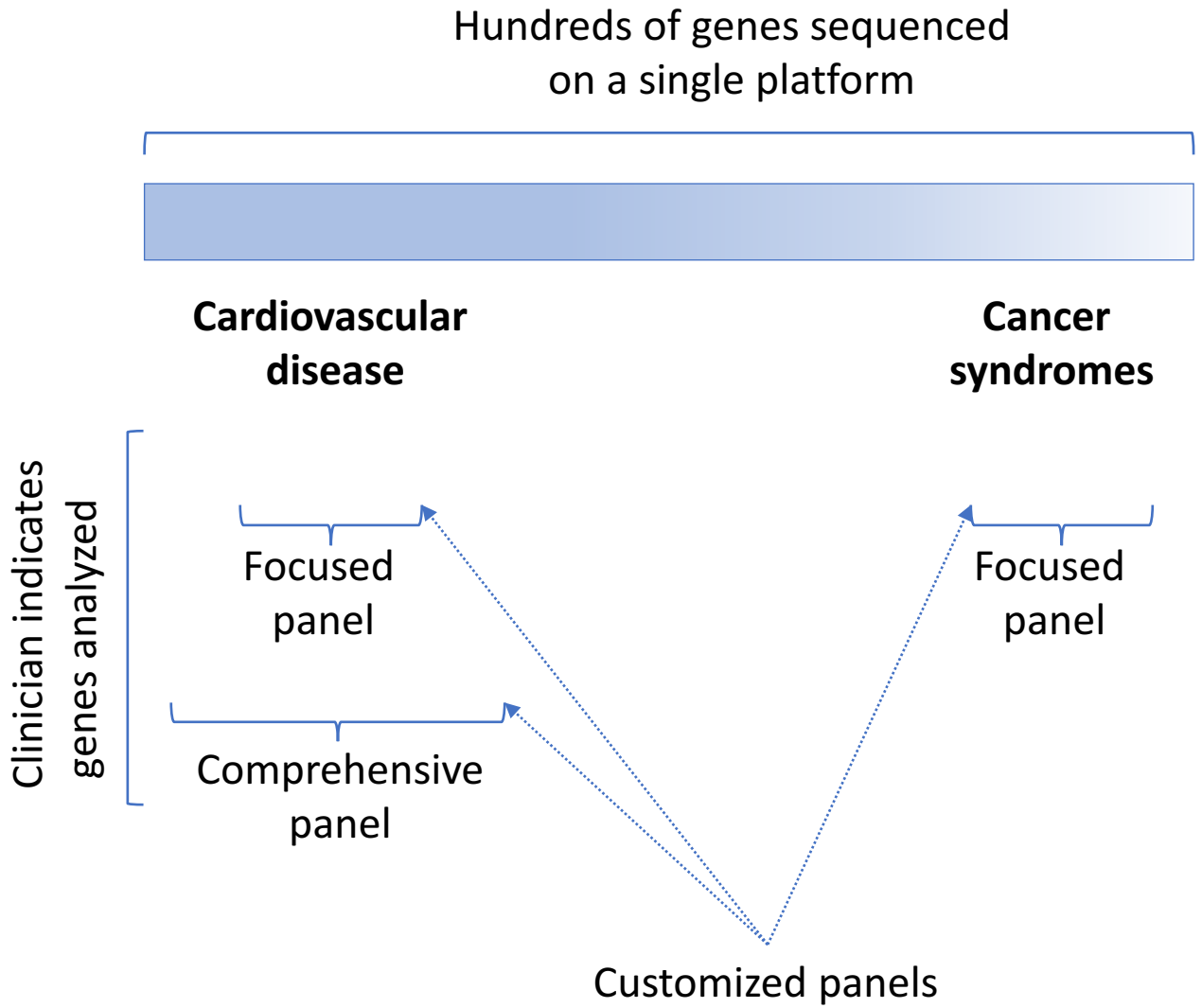
- ACMG recommendations for reporting secondary findings in diagnostic whole-exome or genome sequencing (WES/WGS), independent of indication:



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

Background

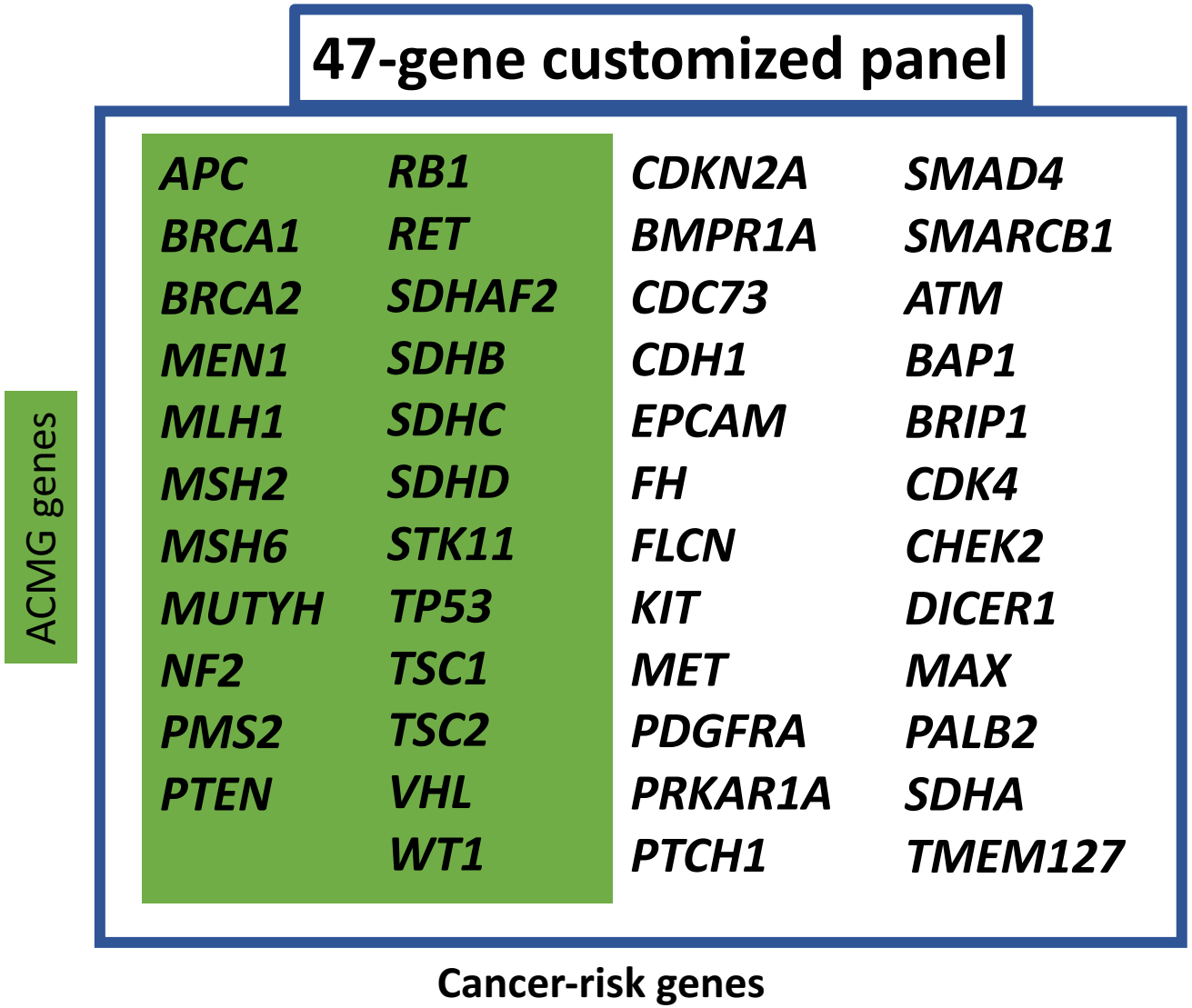
- It is now possible to perform diagnostic multigene panel testing on assay platforms that cover hundreds of genes
  - These are used to generate customized panels based on clinician indication



Study objectives

- Use a large multigene panel strategy
  - Estimate the overall prevalence of cancer gene pathogenic variants
  - In a multi-ethnic population of patients with no known cancer history
- Determine the number of secondary findings by gene
- Assess the clinical actionability of identified gene variants
- Estimate the difference in prevalence between multiple ethnic populations and Caucasians

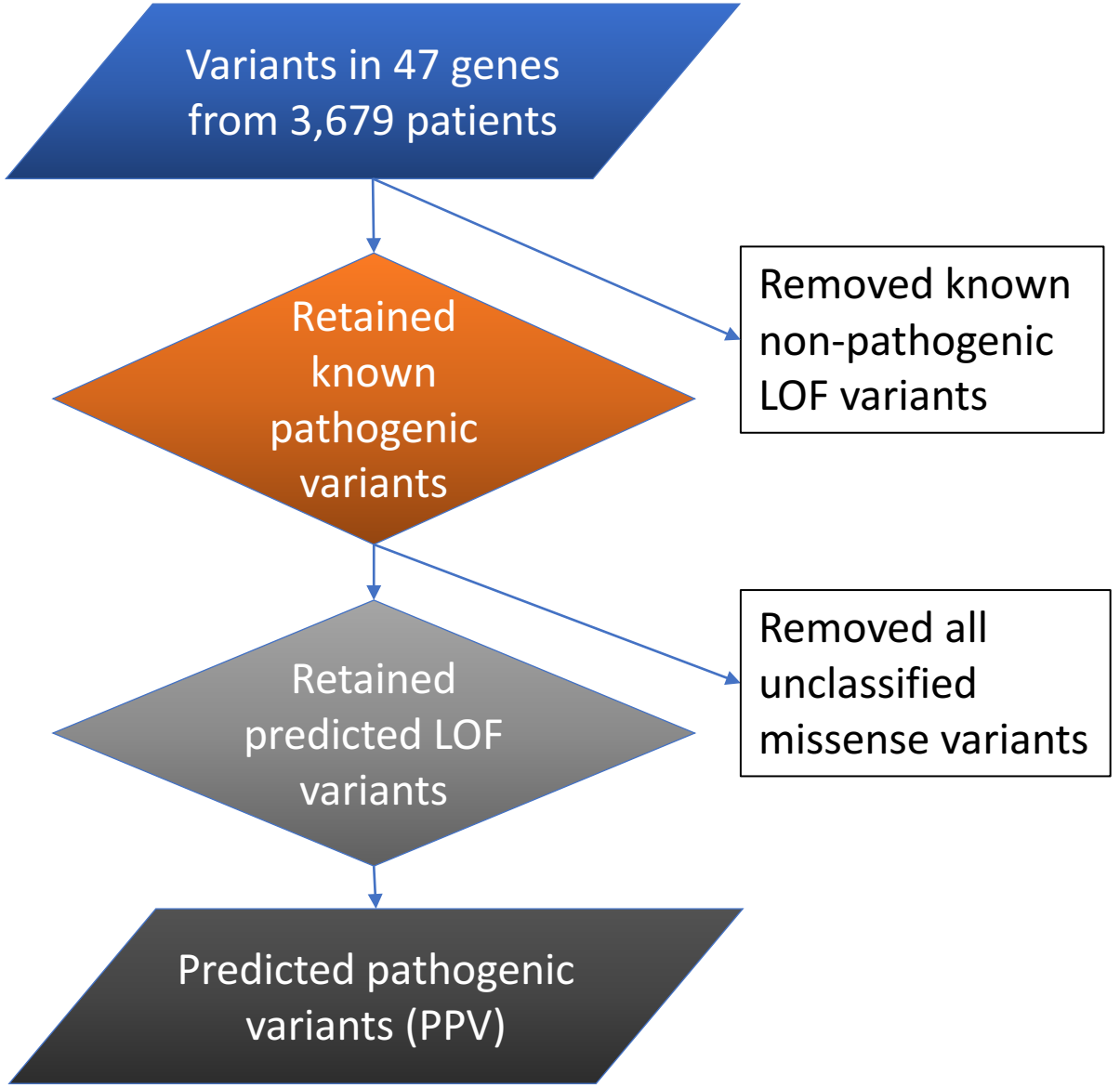
Cancer gene panel selection



- 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

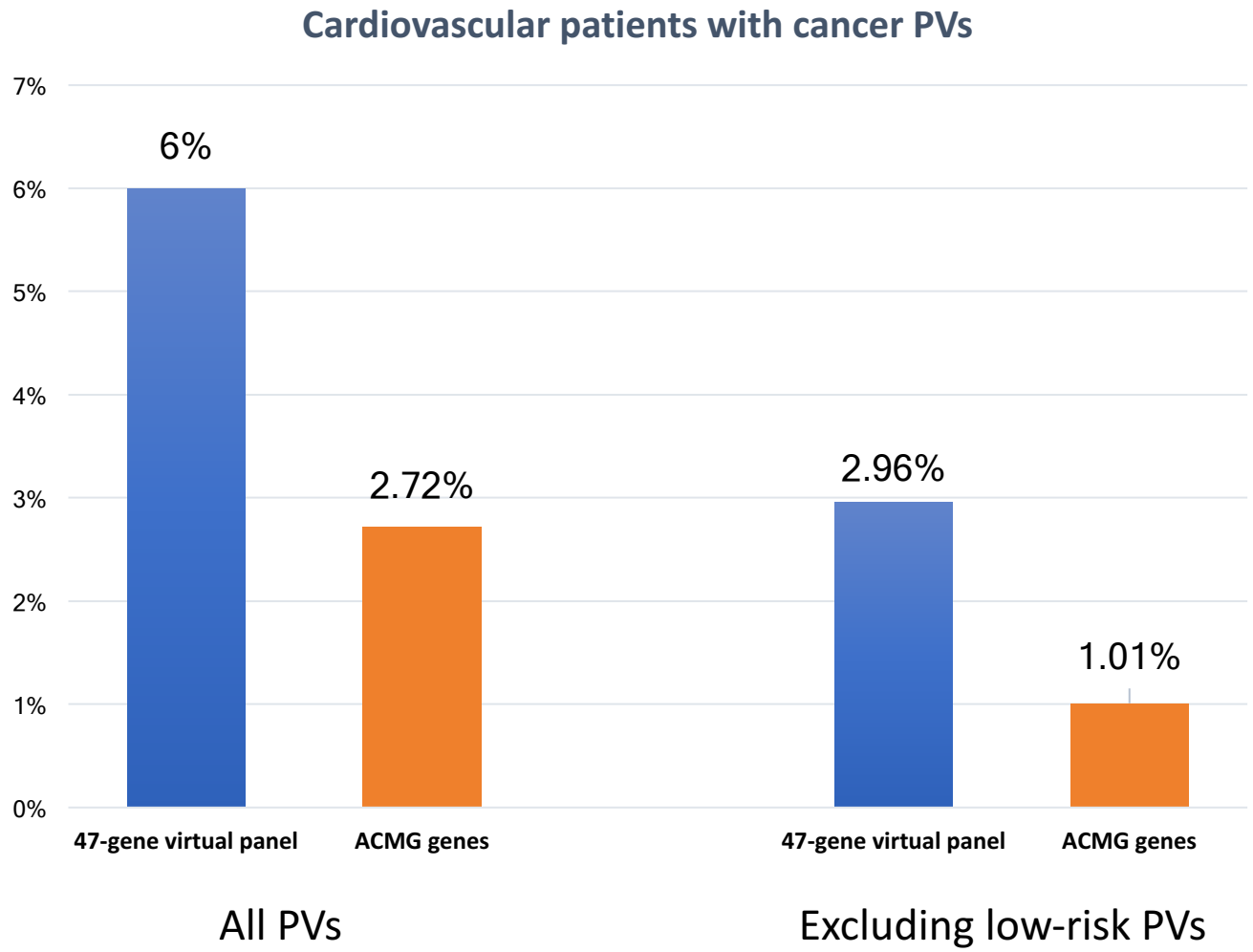
Methods

- 3,679 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 customized 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 (PVs)



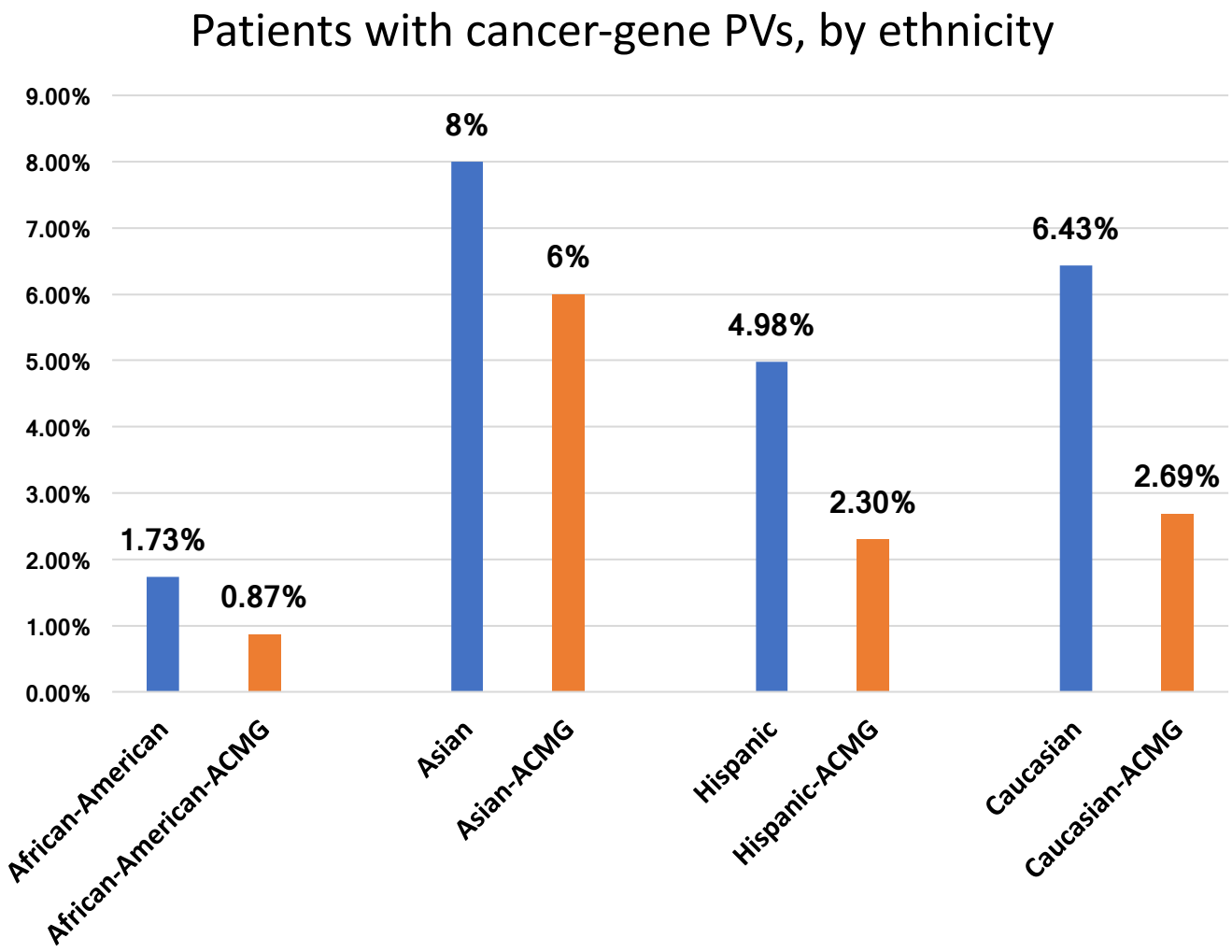
Cancer-risk gene PV prevalence

- Prevalence of ALL cancer gene PVs in 3,769 cardiovascular patients
  - 6% of patients with PV on customized panel
    - Includes 7 patients with P/LP CNVs
  - 2.7% of patients with PV when limited to ACMG cancer genes
- Positive patients after excluding lower risk variants
  - *MUTYH* heterozygotes (hets)
  - Low penetrance PVs in *CHEK2*, *MITF*, *FH*

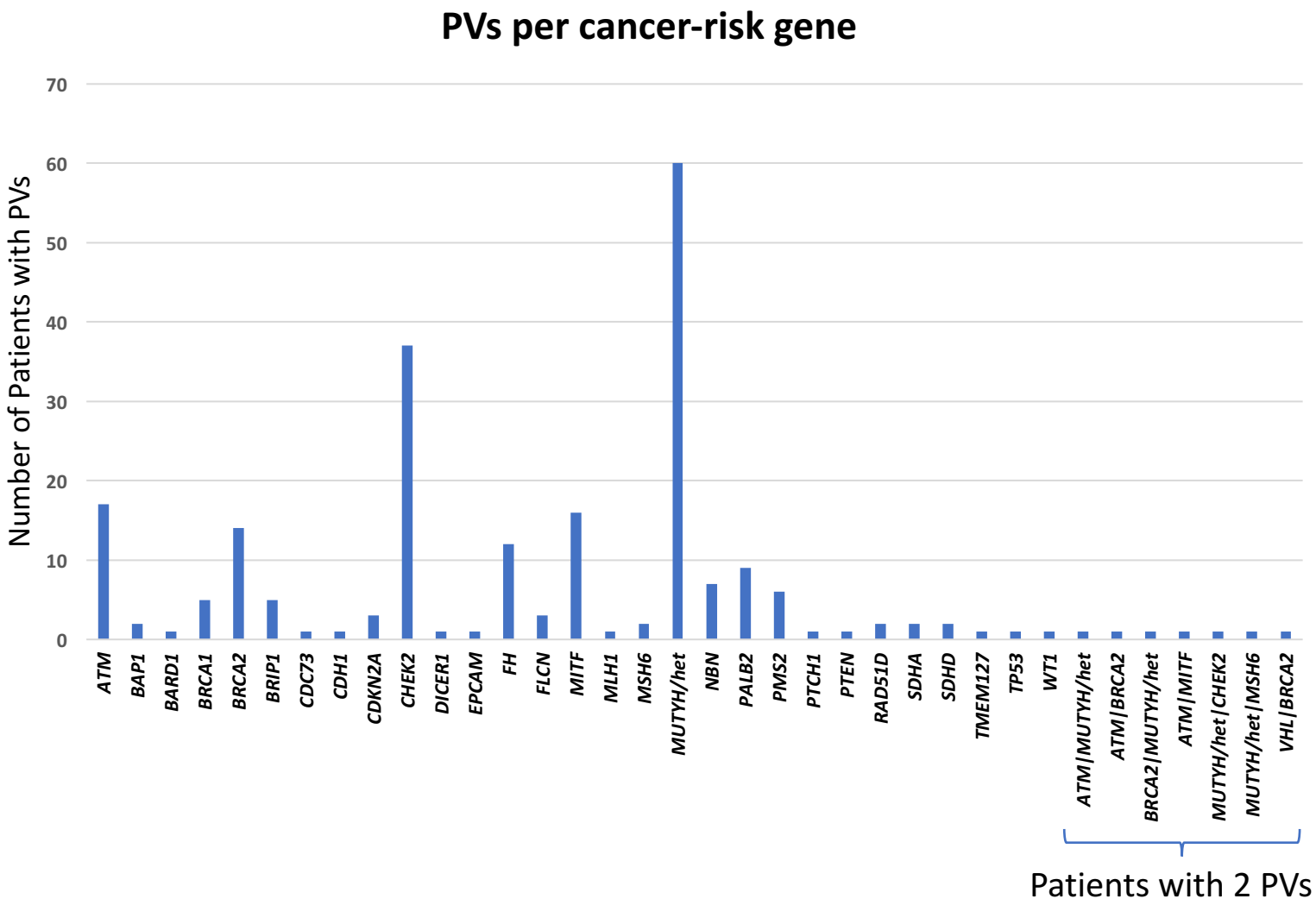


Cancer-risk gene PV prevalence by ethnicity

- Prevalence of cancer gene PVs in patients by ethnicity
  - African-American 1.73%
  - Asian 8%
  - Hispanic 4.98%
  - Caucasian 6.43%
- When limited to ACMG cancer genes
  - African-American 0.87%
  - Asian 6%
  - Hispanic 2.3%
  - Caucasian 2.69%
- Spectrum of variants by ethnicity
  - Broad variant spectrum contributes to high Caucasian prevalence
  - Asian prevalence is dominated by a single *MUTYH* variant



Positive secondary findings by gene



- 82% of the identified PVs were in
  - *ATM*
  - *BRCA1*
  - *BRCA2*
  - *CHEK2*
  - *FH*
  - *MITF*
  - *MUTYH*
  - *NBN*
  - *PALB2*
  - *PMS2*
- 7 patients (3% of positives) had PVs in two cancer-risk genes

Management guidelines for cancer genes with most PVs

Gene	Cancer risk	Management recommendations[1,2,3,4]
ATM	Breast cancer	Annual mammogram and consider breast MRI starting at 40 years
BRCA1/ BRCA2	Breast, ovarian, and prostate cancer	Breast screening, RRM, RRSO
CHEK2	Breast and colon cancer	Annual mammogram and consider breast MRI starting at 40 years old
FH	Renal cell cancer	Annual abdominal MRI
MITF	Melanoma, renal cell cancer	Monthly skin exams, renal ultrasound
MUTYH (het)	Colon cancer (moderate at most)	Colonoscopy at 40 years old for unaffected proband with colon cancer in 1st-degree relative
NBN	Breast cancer	Annual mammogram and consider breast MRI starting at 40 years old
PALB2	Breast cancer	Annual mammogram and consider breast MRI starting at 30 years old
PMS2	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. [1]Daly et al. Genetic/Familial High-Risk Assessment: Breast and Ovarian, 1.2018, nccn.org. [2]Provenzale et al. Genetic/Familial High-Risk Assessment: Colorectal, 3.2017, nccn.org. [3]Menko *et al*. Hereditary leiomyomatosis and renal cell cancer (HLRCC): renal cancer risk, surveillance and treatment. *Fam Cancer* 2014. [4]Potrony *et al*. Prevalence of MITF p.E318K in patients with melanoma independent of the presence of CKDN1A causative mutations. *JAMA Dermatology* 2016.

Factors impacting PV 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
- Lower prevalence in certain ethnicities
  - Suggests pathogenic missense variants (e.g., low penetrance founder mutations) are underrepresented in current databases

Summary

- Using a customized panel strategy, we estimate the prevalence of secondary findings for cancer risk at up to 6% in individuals undergoing hereditary cardiovascular multigene testing.
- True prevalence of secondary findings in certain ethnicities is likely underreported, highlighting the need for sequencing research in these populations.
- Each of the identified secondary finding PVs 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 customized multigene panels, a situation not currently addressed by the ACMG 2016 recommendations.

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