National Society of Genetic Counselors

36th Annual Conference

September 13-16, 2017

Greater Columbus Convention Center
Columbus, OH

• GROWING OUR PROFESSION TO NEW HEIGHTS •

Incidental findings in patients referred for family variant testing

COI Disclosure

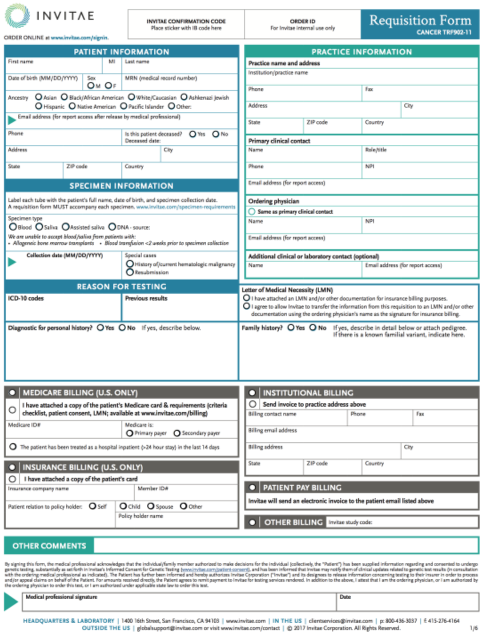
I am an employee of, and shareholder in, Invitae.

Targeted cascade testing has been the standard practice

- The yield of clinically actionable information with targeted family variant testing (FVT) is high
- Genetic testing is changing quickly
- Increased accessibility of multigene panel testing has coincided with an increase in testing family members with full panels rather than FVT
- The diagnostic yield of testing individuals with family histories of pathogenic variants for additional cancer susceptibility genes is unknown

Objective: To examine the utility of comprehensive panel testing in patients with family histories of pathogenic variants

Clinician-ordered FVT test


INVITAE

ORDER ONLINE at www.invitae.com/signin.

INVITAE CONFIRMATION CODE
Place sticker with IB code here

ORDER ID
For Invitae internal use only

Requisition Form
CANCER TRF902-11

PATIENT INFORMATION

First name | MI | Last name

Date of birth (MM/DD/YYYY) | Sex ○ M ○ F | MRN (medical record number)

Ancestry ○ Asian ○ Black/African American ○ White/Caucasian ○ Ashkenazi Jewish ○ Hispanic ○ Native American ○ Pacific Islander ○ Other:

Email address (for report access after release by medical professional)

Phone | Is this patient deceased? ○ Yes ○ No Deceased date:

Address | City

State | ZIP code | Country

SPECIMEN INFORMATION

Label each tube with the patient's full name, date of birth, and specimen collection date. A requisition form MUST accompany each specimen. www.invitae.com/specimen-requirements

Specimen type
○ Blood ○ Saliva ○ Assisted saliva ○ DNA - source:
We are unable to accept blood/saliva from patients with:
• Allogeneic bone marrow transplants • Blood transfusion <2 weeks prior to specimen collection

Collection date (MM/DD/YYYY) | Special cases ○ History of/current hematologic malignancy ○ Resubmission

REASON FOR TESTING

ICD-10 codes | Previous results

Diagnostic for personal history? ○ Yes ○ No If yes, describe below.

PRACTICE INFORMATION

Practice name and address

Institution/practice name

Phone | Fax

Address | City

State | ZIP code | Country

Primary clinical contact

Name | Role/title

Phone | NPI

Email address (for report access)

Ordering physician

○ Same as primary clinical contact

Name | NPI

Email address (for report access)

Additional clinical or laboratory contact (optional)

Name | Email address (for report access)

Letter of Medical Necessity (LMN)
○ I have attached an LMN and/or other documentation for insurance billing purposes.
○ I agree to allow Invitae to transfer the information from this requisition to an LMN and/or other documentation using the ordering physician's name as the signature for insurance billing.

Family history? ○ Yes ○ No If yes, describe in detail below or attach pedigree. If there is a known familial variant, indicate here.

MEDICARE BILLING (U.S. ONLY)
○ I have attached a copy of the patient's Medicare card & requirements (criteria checklist, patient consent, LMN; available at www.invitae.com/billing)
Medicare ID# | Medicare is: ○ Primary payer ○ Secondary payer
○ The patient has been treated as a hospital inpatient (>24 hour stay) in the last 14 days

INSURANCE BILLING (U.S. ONLY)
○ I have attached a copy of the patient's card
Insurance company name | Member ID#
Patient relation to policy holder: ○ Self ○ Child ○ Spouse ○ Other
Policy holder name

INSTITUTIONAL BILLING
○ Send invoice to practice address above
Billing contact name | Phone | Fax
Billing email address
Billing address | City
State | ZIP code | Country

PATIENT PAY BILLING
Invitae will send an electronic invoice to the patient email listed above

OTHER BILLING Invitae study code:

OTHER COMMENTS

By signing this form, the medical professional acknowledges that the individual/family member authorized to make decisions for the individual (collectively, the "Patient") has been supplied information regarding and consented to undergo genetic testing, substantially as set forth in Invitae's Informed Consent for Genetic Testing (www.invitae.com/patient-consent), and has been informed that Invitae may notify them of clinical updates related to genetic test results (in consultation with the ordering medical professional as indicated). The Patient has further been informed and hereby authorizes Invitae Corporation ("Invitae") and its designees to release information concerning testing to their insurer in order to process and/or appeal claims on behalf of the Patient. For amounts received directly, the Patient agrees to remit payment to Invitae for testing services rendered. In addition to the above, I attest that I am the ordering physician, or I am authorized by the ordering physician to order this test, or I am authorized under applicable state law to order this test.

Medical professional signature | Date

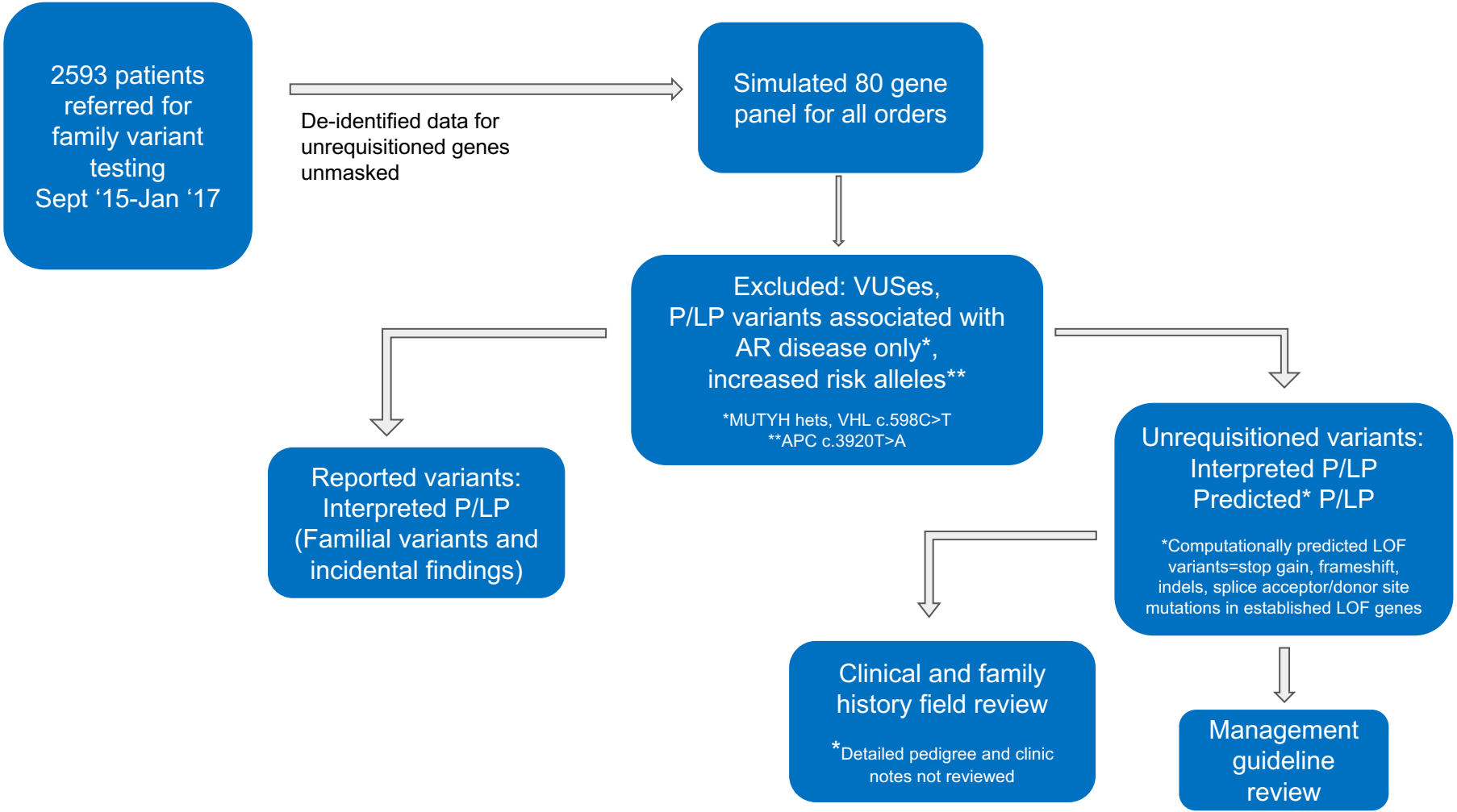
HEADQUARTERS & LABORATORY | 1400 16th Street, San Francisco, CA 94103 | www.invitae.com | IN THE US | clientservices@invitae.com | p: 800-436-3037 | f: 415-276-4164
OUTSIDE THE US | globalsupport@invitae.com or visit www.invitae.com/contact | © 2017 Invitae Corporation. All Rights Reserved. 1/6

VS.

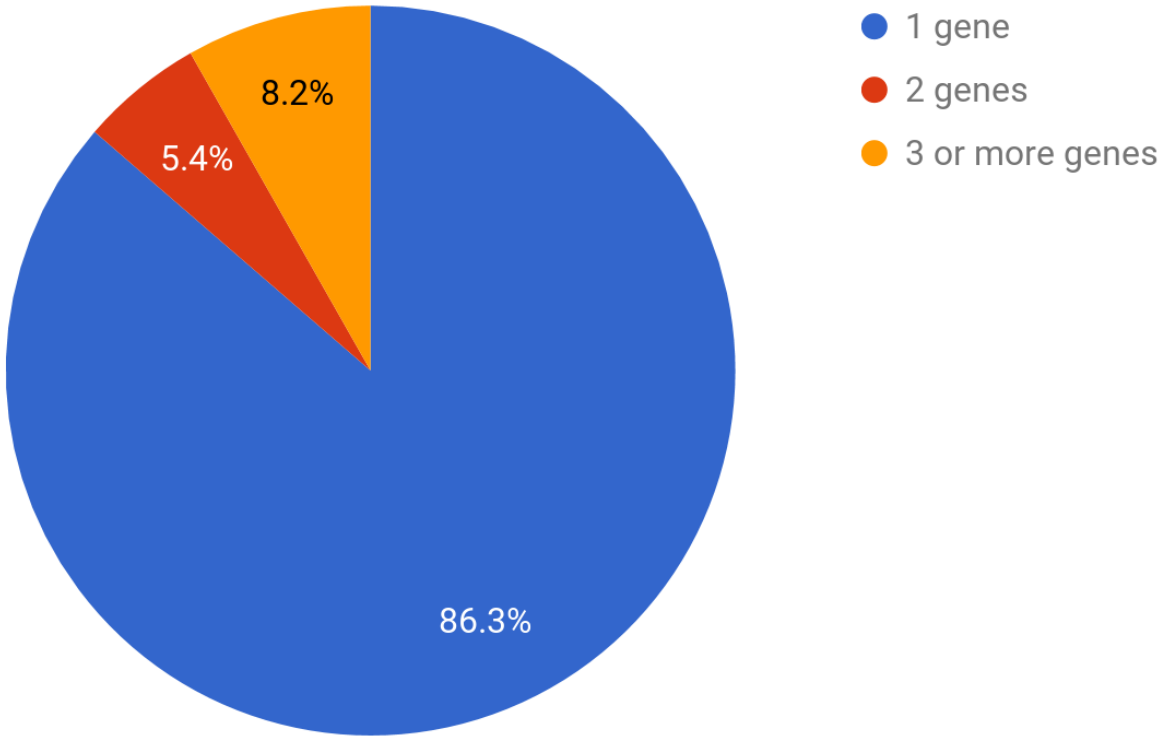
Simulated 80 gene panel

GENES TESTED:

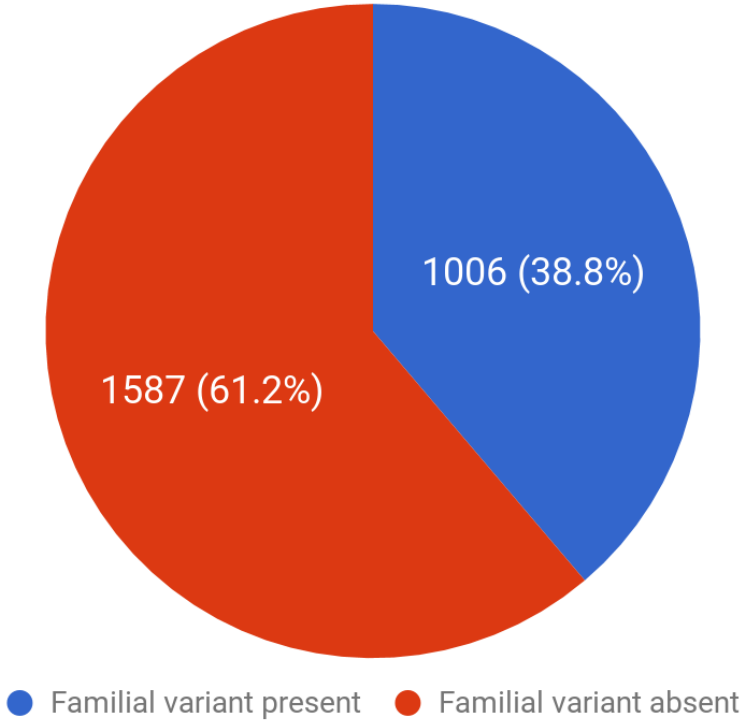
ALK	APC	ATM	AXIN2	BAP1	BARD1	BLM
BMPR1A	BRCA1	BRCA2	BRIP1	CASR	CDC73	CDH1
CDK4	CDKN1B	CDKN1C	CDKN2A	CEBPA	CHEK2	DICER1
DIS3L2	EGFR	EPCAM	FH	FLCN	GATA2	GPC3
GREM1	HOXB13	HRAS	KIT	MAX	MEN1	MET
MITF	MLH1	MSH2	MSH6	MUTYH	NBN	NF1
NF2	PALB2	PDGFRA	PHOX2B	PMS2	POLD1	POLE
POT1	PRKAR1A	PTCH1	PTEN	RAD50	RAD51C	RAD51D
RB1	RECQL4	RET	RUNX1	SDHA	SDHAF2	SDHB
SDHC	SDHD	SMAD4	SMARCA4	SMARCB1	SMARCE1	STK11
SUFU	TERC	TERT	TMEM127	TP53	TSC1	TSC2
VHL	WRN	WT1				


2593 patients referred for family variant testing Sept '15-Jan '17
De-identified data for unrequisitioned genes unmasked
Simulated 80 gene panel for all orders
Excluded: VUSes, P/LP variants associated with AR disease only*, increased risk alleles**
*MUTYH hets, VHL c.598C>T
**APC c.3920T>A
Reported variants: Interpreted P/LP (Familial variants and incidental findings)
Unrequisitioned variants: Interpreted P/LP Predicted* P/LP
*Computationally predicted LOF variants=stop gain, frameshift, indels, splice acceptor/donor site mutations in established LOF genes
Clinical and family history field review
*Detailed pedigree and clinic notes not reviewed
Management guideline review

Family variant testing ordering patterns

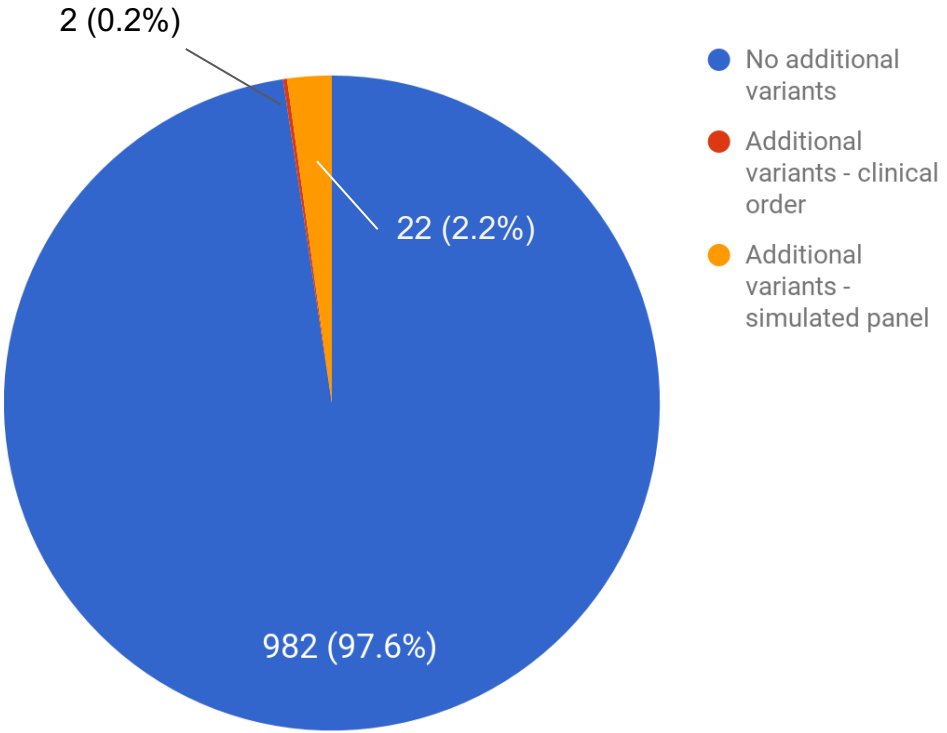


Familial variant test results matched expectations



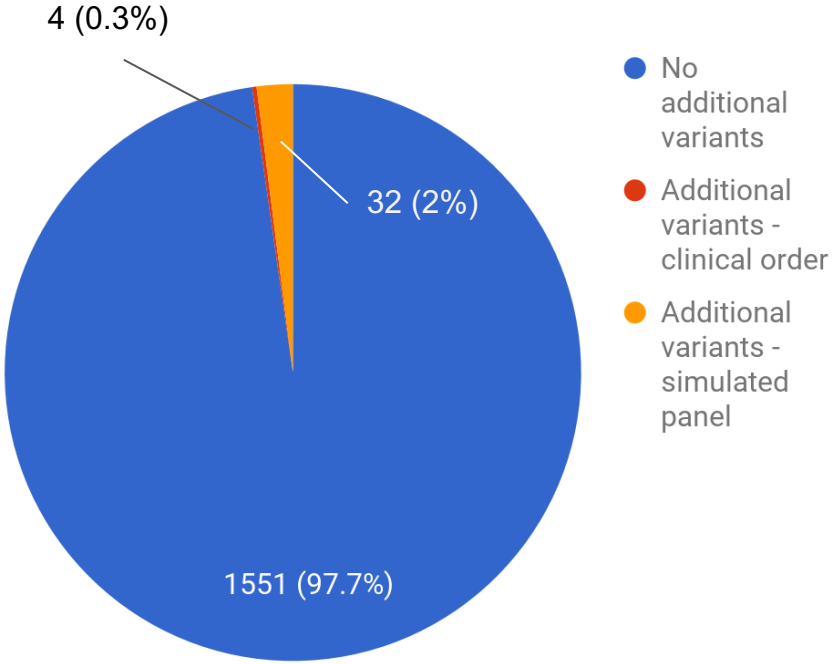
Additional variants identified when familial variant **present**

- 1006 orders were positive for the familial variant
- 24 orders (2.4%) were positive for an additional pathogenic/likely pathogenic variant in addition to the familial variant
- 22 of these were identified by the simulated 80 gene panel rather than the clinical order

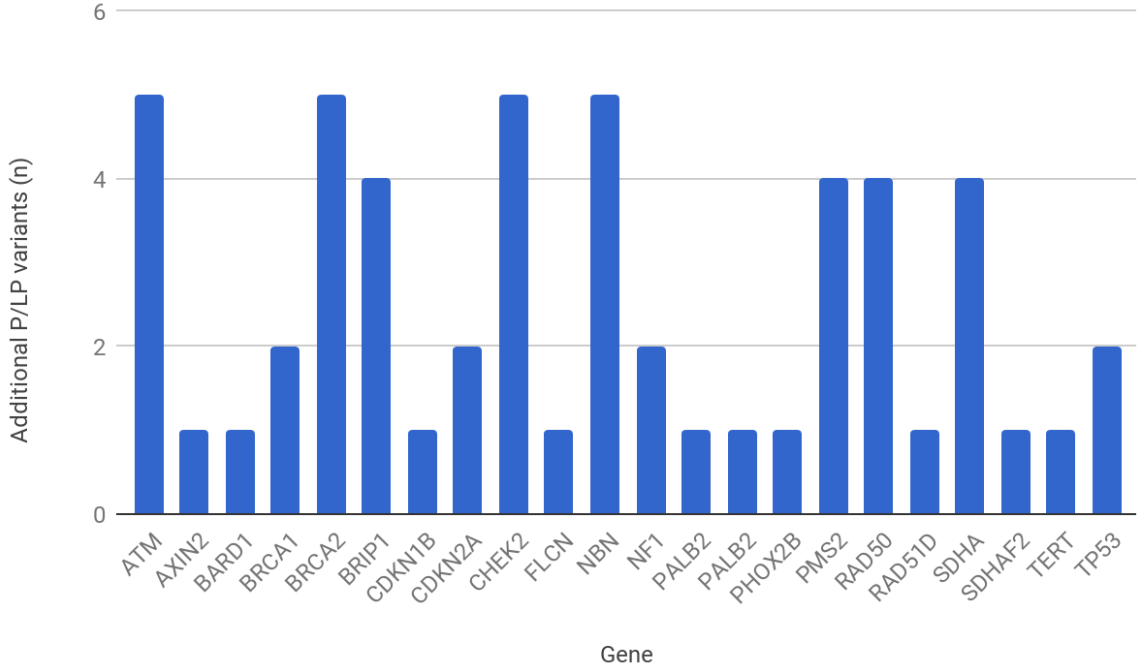


Additional variants identified when familial variant **absent**

- 1587 orders negative for the familial variant
- 36 orders (2.3%) were negative for the familial variant but positive for an additional pathogenic/likely pathogenic variant
- 32 of these were identified by the simulated 80 gene panel rather than the clinical order



Pathogenic variants identified by simulated panel



- In total 54 cases had P/LP variants which were not requisitioned (2%)
- 89% occurring in clinically actionable genes with published management recommendations

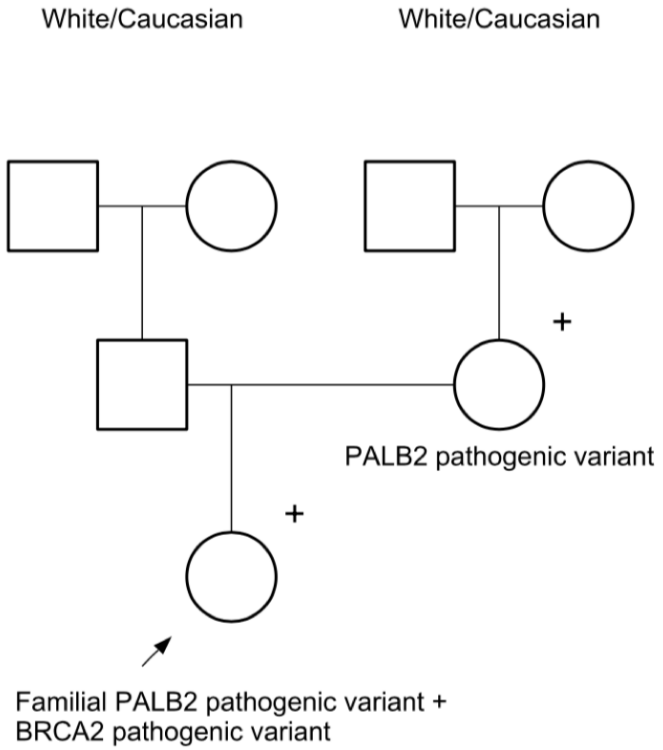
Positive for familial variant and additional finding

CASE 1:

- Caucasian female
- Mother carries pathogenic PALB2 variant
- PALB2 only was ordered

RESULTS:

- Positive for familial PALB2 variant
- Simulated panel identified pathogenic BRCA2 variant: p.Ser2022*



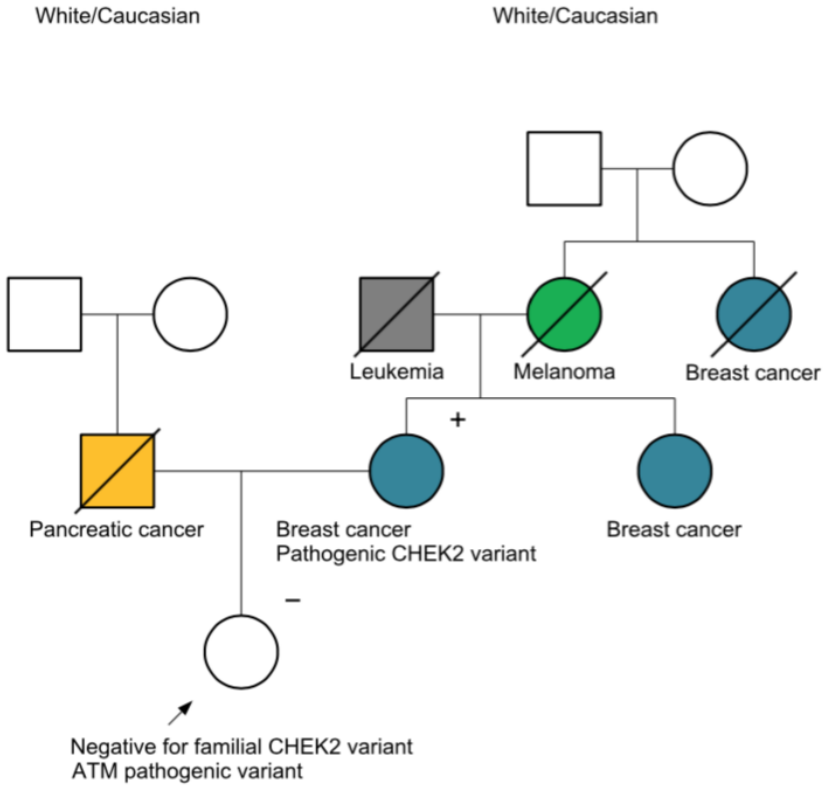
Negative for familial variant positive for additional finding

CASE 2:

- Caucasian female with family history
- Mother with pathogenic CHEK2 variant
- CHEK2 only ordered

RESULTS:

- Negative for familial CHEK2 variant
- Simulated panel identified pathogenic ATM variant: c.3G>A



Limitations

- Selection limited to cases where we were aware of a known familial variant
- Family variant documentation and clinical/family history was limited to free text fields and dependent on clinician’s documentation
- Orders for familial variants of unknown significance were excluded
- Some “second hits” were already known to the clinician and thus were not requisitioned
- Presence of management guidelines was used as a proxy for estimating clinical actionability

A small proportion of cases may have benefited from larger panels

- In 98% of cases, the pathogenic and likely pathogenic variants were detected by familial variant testing
- In 2% of cases, additional pathogenic or likely pathogenic variants were not identified by family variant testing
- The majority of unrequisitioned additional findings were in genes with medical management guidelines
- Most of the time, testing limited to the known familial variant is sufficient, but broader panels should be considered for patients with complex family histories

Acknowledgments