Genetic testing for healthy individuals: A medically actionable panel finds a high positive rate for hereditary disease

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Disclosure statement

- I am an employee and stockholder of Invitae

Personal risk screening in the genomic medicine era

- There is growing interest in incorporating genomic medicine into routine medical care
  - Patients who want to understand their risks
  - Providers who want to identify risks and initiate preventive screenings

- Interest is focused on screening for actionable hereditary disorders
  - An emerging paradigm to screen healthy individuals for personal risk for actionable disorders
  - Targeted genes are similar to the ACMG59 secondary findings recommendations
  - Initiatives have shown that pathogenic changes in hereditary disease genes are far more common than we originally thought
  - These emerging data show that an expanding base of individuals may benefit from genetic testing

A multi-gene panel for elective testing

- Developed a diagnostic-grade NGS-based multi-gene panel
  - Carried out by a team of medical geneticists, GCs and PhD scientists
  - ACMG genes provide the panel foundation
  - Consistent criteria for additional gene inclusion were applied to create a panel of up to 139 genes

- A medically responsible test with appropriate support
  - Provider-ordered test (not DTC) with genetic counseling available
  - Only clinically significant findings are returned (no VUS)
  - An updated report is issued if a VUS becomes clinically significant

A multi-gene panel for elective testing

Clinical area	Clinical condition		
Cancer (n = 57)	Breast cancer Colorectal cancer Cutaneous melanoma Gastric cancer	Ovarian cancer Pancreatic cancer Prostate cancer Renal cell cancer	Thyroid cancer Uterine cancer
Cardiovascular (n = 75)	Aortopathies Arrhythmias Cardiomyopathies	Familial hypercholesterolemia Genetic forms of high blood pressure Hereditary thrombophilia	
Other medically actionable conditions (n = 8)	Alpha-1-antitrypsin deficiency Hereditary hemochromatosis Malignant hyperthermia susceptibility		

- Up to 139 genes are evaluated
  - Carrier status is reported as appropriate but is not considered a primary positive finding

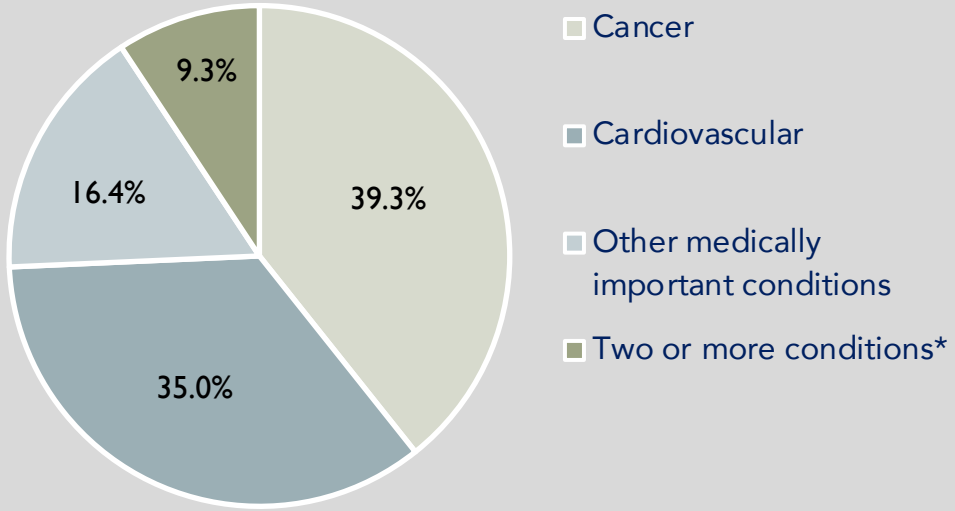
Clinically significant (LP/P) results in 2,675 individuals

Positive (LP/P)	Negative
432	2,243
16.1%	83.9%

LP/P variant in positive individuals

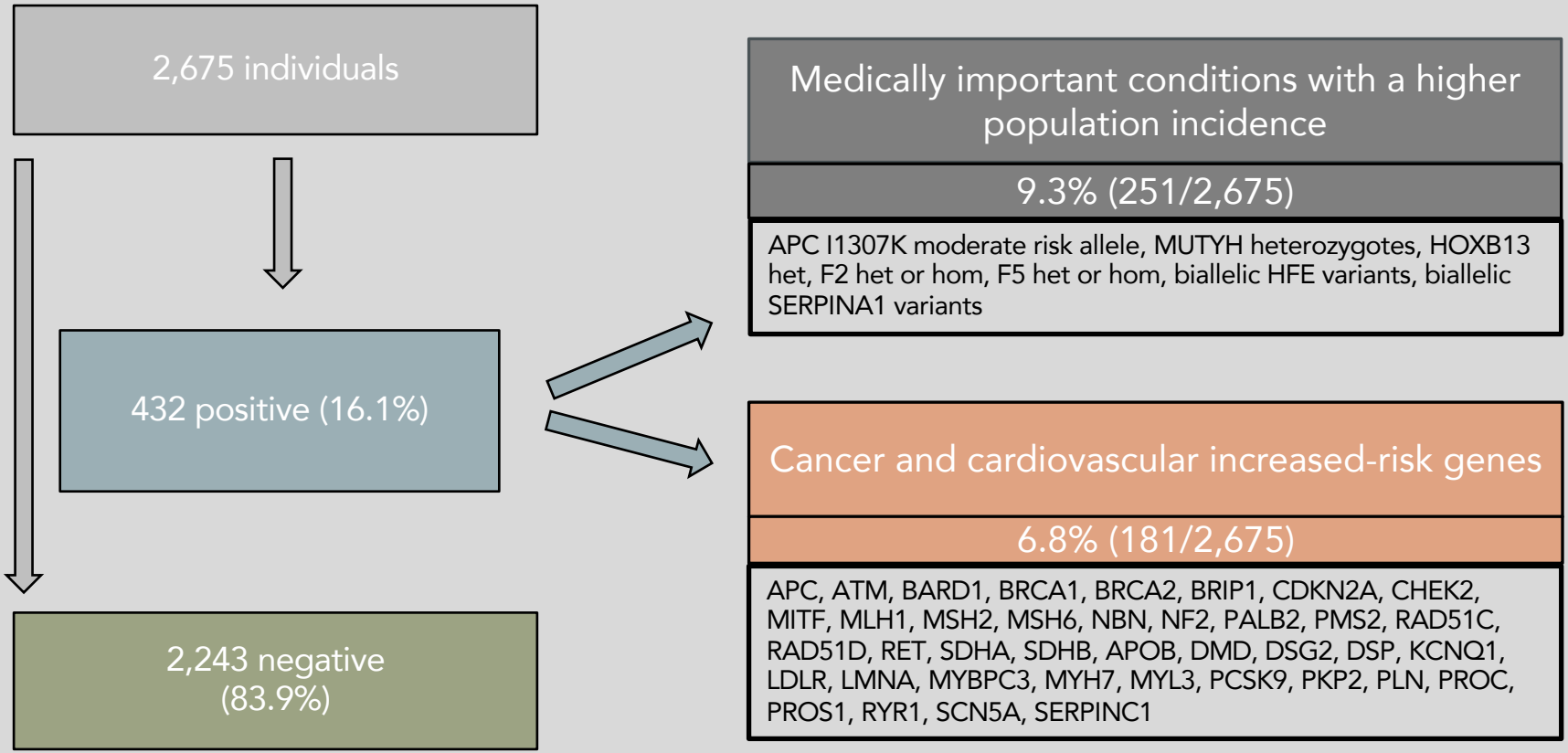
Variant type	Percentage
CNV	3.4
Missense	58.5
Frameshift	14.1
Non-coding	10.8
Splice	5.8
Nonsense	6.3
Ins/del	0.9
Initiator codon	0.2

Clinical areas for 432 positive individuals



*40/432 individuals (9.3%) had two or more positive primary

Stratification of results in 2,675 individuals



Stratified results and ACMG findings

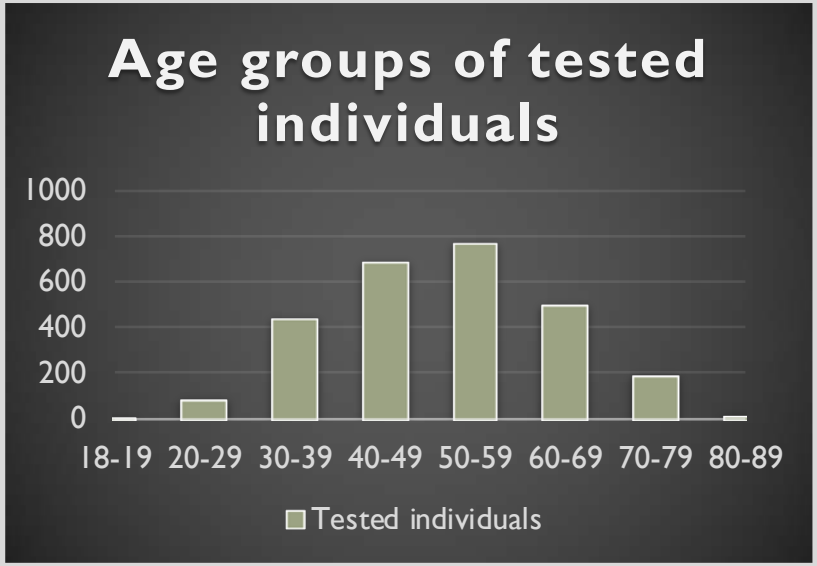
Results	#	Percentage
All reportable findings	432	16.1
Exclude hereditary hemochromatosis, alpha-1-antitrypsin deficiency, F2 (prothrombin variant), F5 (factor V Leiden)	237	8.9
Exclude APC increased-risk allele, MUTYH heterozygotes, HOXB13 increased-risk allele	181	6.8
All reportable findings in the ACMG genes	149	5.6
ACMG gene findings without MUTYH heterozygotes and moderate-risk alleles	89	3.3

- Positive findings in the ACMG genes match the range reported by clinical laboratories
  - 2–5% positive rate for LP/P variants

Demographics for 2,675 tested individuals

Sex of tested individuals	
Female	59.3%
Male	40.7%

Self-reported ancestry	Percentage
Asian	5.0
Ashkenazi Jewish	3.1
Black/African American	0.6
White/Caucasian	59.7
Hispanic	1.6
Unknown	23.1
Multiple ancestries	4.9
Other	2.0



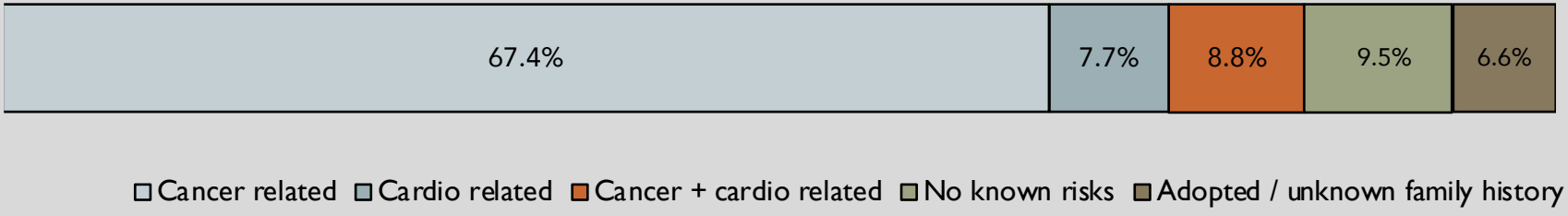
Evaluation of provided health information

Health information provided?	Number of individuals	%
Yes	895	33.5
No	1,780	66.5

- 133 of the 895 were positive (14.9%).

Positive results	#	%
Cancer finding	56	42.1
Cardio finding	49	36.8
Other important finding	19	14.3
>1 clinical area	9	6.8

Provided health information by clinical area (n = 895)



All results in samples with health information (n = 895)

Information	Number	All positive results	Percentage	High-risk positive results	Percentage
Personal and/or family history of cancer	603	86	14.3	43	7.1
Personal and/or family history of cardiovascular disease	69	16	23.2	7	10.1
Family history cancer + cardio	50	10	20.0	2	4.0
Personal history cancer +/– cardio +/– family history	29	3	10.3	2	6.9
No known risks	85	12	14.1	4	4.7
Adopted/unknown family history	59	6	10.2	3	5.1
Average			14.9		6.8

- **Similar risks across individuals with different personal and family histories**
- **The average positive finding rate of 6.8% is composed of cancer (5.1%) and cardiovascular (1.7%) results**

Reported family history of cancer is common.

Health information	Number	Percentage of cohort
Family history of cancer	451	50.4
Personal history of cancer	85	9.5
Personal + family history of cancer	67	7.5
Family history of cardio	46	5.1
Personal history of cardio	17	1.9
Personal + family history of cardio	6	0.7
Family history cancer + cardio	50	5.6
Personal history cancer +/– cardio +/– family history	29	3.2
No known risks	85	9.5
Adopted/unknown family history	59	6.6

Cancer results all/(high risk)	Percentage all/(high risk)
33/(25)	7.3/5.5
9/(5)	10.6/5.9
7/(6)	10.4/9.0

(8.1%/6.0% positive rate)

Cancer positive rate for all other groups:

4.5 (13/292)/3.4 (10/292)

- **May be identifying individuals at increased risk who likely did not meet clinical criteria for testing**

Case study 1: Cancer risk (Lynch syndrome)

- Healthy woman in her 50s who was adopted and had no information about her biological family history
- She had no personal history of cancer. She wanted to understand her personal genetic risks

A pathogenic variant was found in the PMS2 gene, which is associated with a cancer-related condition.

- Planning a TAH/BSO due to this result and other gynecologic issues
- Baseline colonoscopy identified 1 hyperplastic polyp
- Upper GI endoscopy revealed Barrett's esophagus without dysplasia

Case study 2: Cardiovascular risk

- Woman in her 40s of South Asian background
- Personal history significant for recently diagnosed breast cancer
- Appropriate diagnostic testing was uninformative. She wanted to further understand her genetic risks.

A pathogenic variant was found in the MYBPC3 gene, which is associated with a heart-related condition.

- Relief expressed for no additional cancer risks; interested in being proactive about her cardiac risk
- Referral for full cardiac workup with all assessments normal. Follow-up evaluation in five years (or sooner if symptoms arise)

Conclusions—1

- A high positive rate for hereditary disease risk in this population of individuals undergoing elective testing.

- From the health information that was provided in this cohort, we learned that family and personal health history appear to influence interest in pursuing this testing.
  - Individuals who do not meet clinical testing criteria
  - Unaffected individuals with a family health history of cancer that spurs personal interest in proactive information

Conclusions—2

- Emerging data show that an expanding base of individuals can benefit from genetic testing.
  - Individuals with clinically actionable genetic variants could be missed by current clinical testing criteria
- Providing medically actionable findings can provide the opportunity to screen for and/or detect disease at an earlier stage.
- Outcomes-focused longitudinal data is needed to determine the benefits of medically actionable risk information from elective testing.

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