Secondary findings on multigene panels: A new frontier for clinical utility in hereditary cancer genes

Edward D. Esplin[1], Scott T. Michalski[1], Shan Yang[1], Heather Hampel[2], Joanne Jeter[2], Kevin Sweet[2], Robert Pilarski[2], Rachel Pearlman[2], Kate Shane[2], Pamela Brock[2], Judith Westman[2], Anu Chittenden[3], Jill Stopfer[3], Katherine Schneider[3], Rosalba Sacca[3], Samantha Culver[3], Lindsay Kipnis[3], Diane Koeller[3], Shraddha Gaonkar[3], Jilliane Sotelo[3], Erica Vaccari[3], Sarah Cochrane[3], Marjan Champine[4], Whitney Espinel[4], **Stephen E. Lincoln[1]**, Robert L. Nussbaum[1]

[1]Invitae, San Francisco, CA; [2]The Ohio State University, Columbus Ohio, [3]Dana Farber Cancer Institute, Boston, MA, [4]Huntsman Cancer Institute, Salt Lake City, UT

ABSTRACT

In clinical exome and genome sequencing, the current ACMG guidelines recommend that laboratories report secondary findings in genes unrelated to a patient's indication unless the patient explicitly opts-out of receiving such information. Modern multigene panels can include hundreds of genes underlying diverse conditions, from which subsets of genes are typically reported depending on the specific test ordered. Such panels could also potentially produce secondary findings, a circumstance not specifically addressed by current guidelines. We examined the potential for secondary findings in hereditary cancer genes among patients undergoing genetic evaluation for an unrelated cardiovascular condition. We found a prevalence of 1–6%, depending on the scope of findings to be considered. Moreover, findings in many of these same genes often result in a change in clinical care.

Cancer-risk secondary findings uncovered by multigene panel testing

METHODS

We analyzed de-identified data for 47 cancer-risk genes in 3679 patients who had been referred for genetic testing for a hereditary cardiovascular condition. Per our IRB-approved research protocol, these findings were not returned.

RESULTS

We observed 141 pathogenic variants in cancer-risk genes, a prevalence of 6%. Most of these findings were in genes with established management guidelines, including *BRCA1, BRCA2, ATM, CHEK2, MUTYH, PALB2, PMS2*.

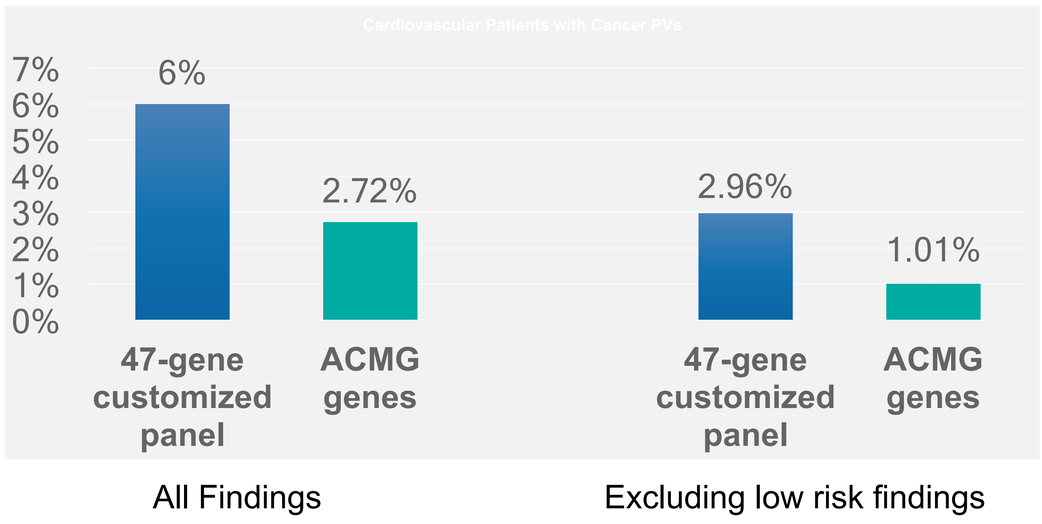

Figure 1. Prevalence of pathogenic variants in cancer-risk genes uncovered in cardiovascular patients. Low-risk findings included *MUTYH* heterozygotes and low penetrance variants in *CHEK2, MITF, and FH*.

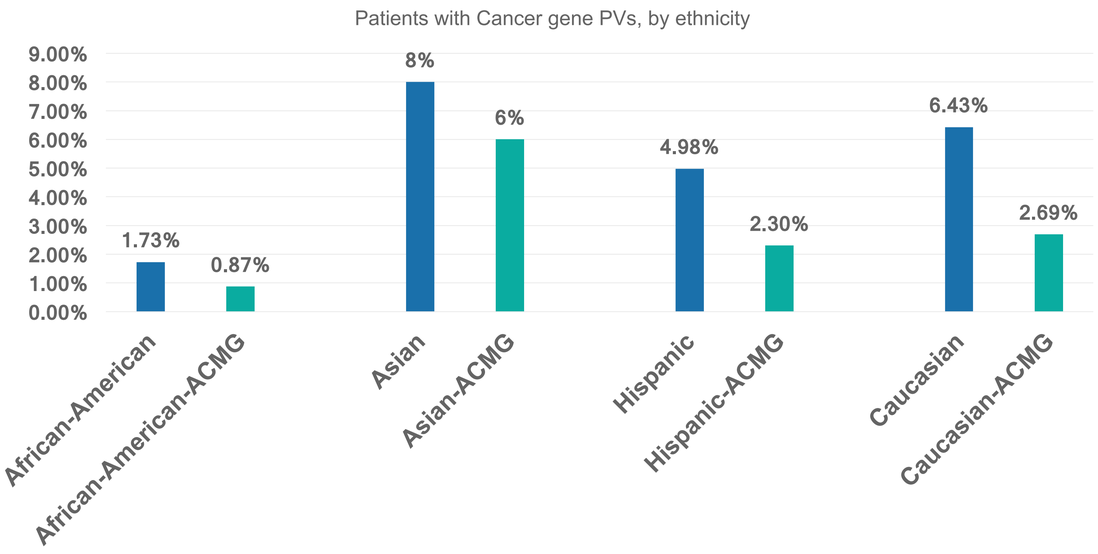

Figure 2. Prevalence of secondary findings by ethnicity. A broad spectrum of variants contributes to the high prevalence in Caucasians. By contrast, a single variant (*MUTYH:*c.934-2A>G) was responsible for many of the Asian findings.

Companion study: Clinical impact of cancer-risk findings in genes other than *BRCA1/2*

METHODS

We analyzed a separate cohort of 2184 patients undergoing medically indicated testing for hereditary breast/ovarian cancer genes at 3 academic medical centers. For the 157 patients whose clinical report included a pathogenic finding in a gene other than *BRCA1/2*, we asked clinicians to complete a case report form describing the clinical actions taken in response to the genetic test results. Results were collated both for patients and, separately, their family members.

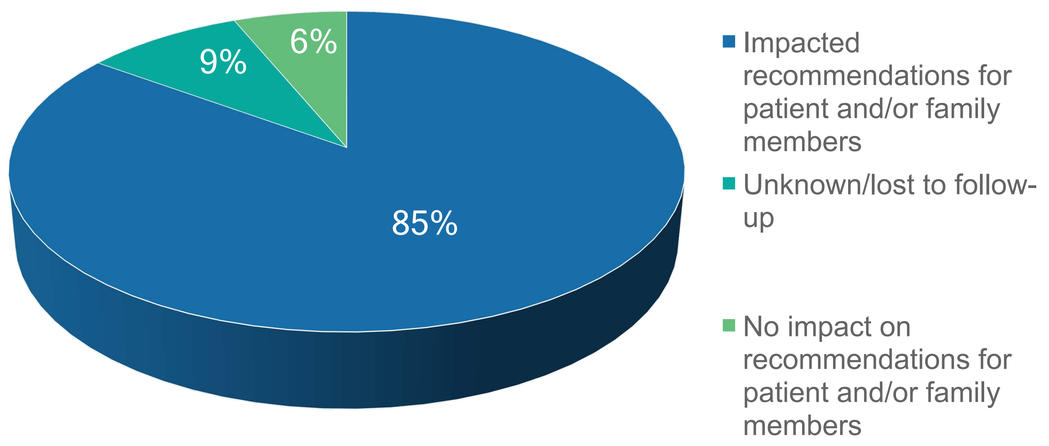

Figure 3. At this time, 80 case reports (51%) from 21 clinicians have been received. Approximately half of the test results were considered high-risk (e.g. *MSH2*) and half moderate risk (e.g. *ATM*). In 85% of cases, clinicians reported a change clinical management. Note that one individual could have multiple management changes, as listed below.

<u>For Patients</u>

- 43% – modification of imaging surveillance
- 16% – surgical prophylaxis considered/recommended
- 4% – modification of surgical intervention for existing cancer
- 3% – modification of treatment (chemotherapy, etc.)

<u>For Family members</u>

- 59% – referral for genetic counseling
- 48% – genetic testing ordered
- 22% – initiation/modification of imaging surveillance
- 5% – surgical prophylaxis considered/recommended

CONCLUSIONS

- Secondary cancer-risk findings from certain multigene panel tests are possible and could, if reported, be prevalent. The exact rate of such findings would depend on specific criteria and patient ethnicity.
- In patients undergoing medically indicated testing for cancer-risk genes, many findings result in a change in care. In a secondary finding context, the spectrum and rate of appropriate medical actions would of course be different and requires careful consideration. Nevertheless, secondary findings across a range of cancer-risk genes would likely result in medical management actions that would confer benefits.
- Taken together, these results suggest that the issue of secondary findings from panel tests should receive further study and possibly increased attention from professional societies.

Disclosures: The indicated authors are stockholders and employees of Invitae.