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

Edward D. Esplin1, Scott T. Michalski1, Shan Yang1, Heather Hampel2, Joanne Jeter2, Kevin Sweet2, Robert Pilarski2, Rachel Pearlman2, Kate Shane3, Pamela Brock4, Judith Westman4, Anu Chittenden3, Jill Stopfer3, Katherine Schneider1, Rosalba Sacca3, Samantha Culver3, Lindsay Kipnis3, Diane Koeller1, Shradhha Gaonkar3, Jilliane Sotelo3, Erica Vaccari3, Sarah Cochrane3, Marjan Champine4, Whitney Espinel1, Stephen E. Lincoln1, Robert L. Nussbaum1

1Invitae, San Francisco, CA; 2The Ohio State University, Columbus Ohio, 3Dana Farber Cancer Institute, Boston, MA, 4Huntsman 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 in cancer-risk 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, MIF, 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.

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.

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, MIF, 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.

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 shareholders and employees of Invitae.