Returning hereditary cancer panel research results is clinically feasible and appreciated by patients

Kerry E. Kingham1, Nicolette Chun1, Marina M. Rabideau2, Allison W. Kurian1,2, Stephen E. Lincoln3 and James M. Ford4

1Stanford Health Care, 2Health Research and Policy, and 3Genetics, Stanford University Stanford, CA; 4Invitate Corporation, San Francisco, CA

Introduction

As broad multi-gene panels enter clinical use, unique genetic counseling challenges arise, particularly in cases where a result is unexpected or for which there are no established clinical guidelines. Recently, we described (Kurian et al., J. Clin Oncol 2016) results from panel testing for hereditary breast and ovarian cancer, where 14 of 141 BRCA1/2 negative patients had potentially actionable findings in other genes. Given the clinical significance of the pathway variants deemed potentially actionable, permission was obtained from the Stanford University IRB to contact patients about and counsel them on the results of their research testing. Here we describe our experience in counselling these individuals, focusing on informed consent, communication of risk, clinical management, and psychosocial issues.

Methods

Blood samples banked on an IRB-approved research protocol

• Eligibility: women tested clinically and themselves consented to research (2002-2012)
• Samples were stored frozen at -80 degrees for <1-10 years

Research multiple sequencing panel designed and performed

• 41 genes associated with cancer, DNA-repair, and cell cycle were sequenced: APC, ATM, BLM, BMPR1A, BRCA1, BRCA2, BRF1, CDH1, CDKN2A, EPCAM, FANCA, FANCC, FANCJ, FANCD2, FANC1, FANCI, FANCE, FANG1, LGMD, MEN1, MET, MSH2, MLH1, MSH6, MUTYH, NBN, PALB2, PALLD, PMS2, PRSS1, PTCH1, PTEN, RAD51C, RET, SLX4, SRCA1, SMAD4, STK11, T531, TP53, and VHL

Eligibility

• Currently available data on cancer risks were communicated to patients (including new / updated guidelines)
• 11 patients could be re-contacted 1-10 years post enrollment

• Patients were offered clinical confirmation, were informed of known cancer risks (if they had not previously received genetic counseling), and were re-consented to receive this information.
• Comments included: “I appreciate the call,” “This is certainly preferred when results may be returned. Nevertheless, findings that were not anticipated by the patient but are clinically significant can improve patient care. Reporting these results in an ethical and appropriate manner can be achieved by working closely with your IRB.
• Patients had a favorable reaction to the additional genetic information we provided despite not being initially consented for it at the time of study enrollment about possible return of results.

Results

- 198 participants tested of which 141 were BRCA1/BRCA2 negative
- 10% of BRCA-negative patients had potentially actionable findings
- 10 (7.9%) positive or high for moderate risk variants in ATM, BLM, CAV1, CYP1B1, FANCJ, FANCI, FANCE, FANG1, LGMD, MEN1, MET, MSH2, MLH1, MSH6, MUTYH, NBN, PALB2, PALLD, PMS2, PRSS1, PTCH1, PTEN, RAD51C, RET, SLX4, SRCA1, SMAD4, STK11, TP53, and VHL

Table 1. Potentially actionable findings in genes other than BRCA1/2.

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<th>Race</th>
<th>Cancer</th>
<th>Age</th>
<th>BRCA1/2</th>
<th>Gene</th>
<th>Effect</th>
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Discussion

We conclude that it is possible to ethically and successfully return panel results, even in patients not initially consented for this information. While challenging for genetic counselors, the additional management recommendations provided can improve care and outcomes.

Conclusion

Larger, population-based studies should follow to confirm and expand these results. We have expanded this study to 246 additional patients of which we plan to re-contact 23.

Table 1. Potentially actionable findings in genes other than BRCA1/2.

- 198 participants tested of which 141 were BRCA1/BRCA2 negative
- 10% of BRCA-negative patients had potentially actionable findings
- 10 (7.9%) positive or high for moderate risk variants in ATM, BLM, CAV1, CYP1B1, FANCJ, FANCI, FANCE, FANG1, LGMD, MEN1, MET, MSH2, MLH1, MSH6, MUTYH, NBN, PALB2, PALLD, PMS2, PRSS1, PTCH1, PTEN, RAD51C, RET, SLX4, SRCA1, SMAD4, STK11, TP53, and VHL

- 11 patients could be re-contacted 1-10 years post enrollment
- All 11 expressed interest in the new findings and returned to our clinic to review results.

- Patients were offered clinical confirmation, were informed of known cancer risks (if they had not previously received genetic counseling), and were re-consented to receive this information.

- Comments included: “I appreciate the call,” “This is certainly preferred when results may be returned. Nevertheless, findings that were not anticipated by the patient but are clinically significant can improve patient care. Reporting these results in an ethical and appropriate manner can be achieved by working closely with your IRB.

- Patients had a favorable reaction to the additional genetic information we provided despite not being initially consented for it at the time of study enrollment about possible return of results.

- Panel testing represents a new paradigm in clinical care. Thorough studies of patient responses to this information are critical to ensure it’s use properly.

- Genetic counselors are adapting to address the challenges of panel testing and to help patients navigate the results. Among these challenges are:
  - Lack of clinical management guidelines for some genes (although several new guidelines are forthcoming)
  - Uncertainties of risks, penetrance and disease spectrum
  - Increased VUS rates which come as the number of genes tested

- In the context of research, appropriate consent and pre-test guidance is certainly preferred when results may be returned. Nevertheless, findings that were not anticipated by the patient but are clinically significant can improve patient care. Reporting these results in an ethical and appropriate manner can be achieved by working closely with your IRB.

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