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

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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 2014) 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 pathogenic variants deemed potentially actionable, permission was obtained from the Stanford University IRB to contact participants again and offer them the results of their research testing. Here we describe our experience in counseling 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 for *BRCA1/2* mutations from 2002-2012
- A referral population meeting standard practice guidelines
- Samples were stored frozen at -80 degrees for <1-10 years

Research multiplex sequencing panel designed and performed
- 41 genes associated with cancer, DNA repair, and cell cycle were sequenced: APC, ATM, BLM, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4 CDKN2A, EPCAM, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, LIG4, MEN1, MET, MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PALLD, PMS2, PRSS1, PTCH1, PTEN, RAD51C, RET, SLX4, SMAD4, SPINK1, STK11, TP53, and VHL
- Del/dup analysis was performed on 90% of samples.
- Variants were classified as "Potentially pathogenic" if they caused frameshifts, affected splice donor/acceptor sites, or were reported as pathogenic in published literature.

Determined which patients should be re-contacted
- Clinician investigators reviewed pathogenicity evidence and case histories
- Genes which caused a known syndrome or which increased risk more than two fold were considered reportable in this study

Results disclosure to participants
- If variant(s) warranted a possible change in clinical care, patients were re-contacted and offered an in-person session with the genetic counselor and physician. Patients were re-consented to receive this information.
- Participants were offered clinical confirmation, were informed of known cancer risks and detailed management guidelines as well as genetic risks for relatives.
- Re-contact and re-consent procedure approved by Stanford IRB

Results

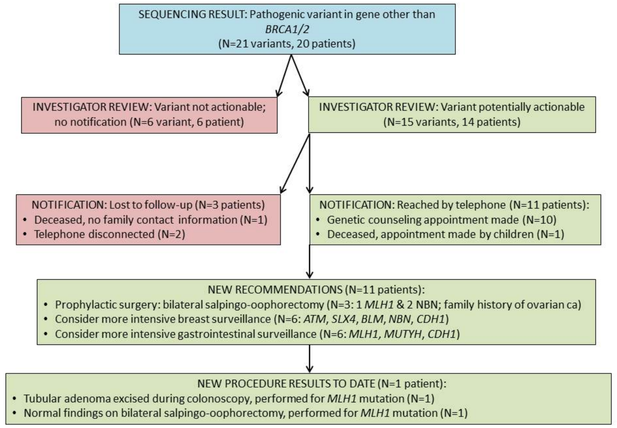

Table 1. Potentially actionable findings in genes other than *BRCA1/2*.

Race	Cancer	Age	*BRCA1/2*	Gene	Laboratory-Reported Effect	Clinician Decision
NHW	Breast, bilateral (ER/PR+,HER2-)	44, 55	None	*ATM*	Frameshift	Notify
NHW	Breast (ER-,PR-,HER2-), Endometrial	35, 46	None	*MLH1*	Frameshift	Notify
Filipina	Breast (ER/PR+,HER2-)	43	None	*PRSS1*	Missense	Notify
Chinese	Breast (ER+, PR-,HER2+)	30	None	*MLH1*	Missense	Did not notify
Filipina	Breast, bilateral (ER/PR+,HER2-)	47, 55	*BRCA1*	*MUTYH*	Spl. acceptor	Notify
NHW	None	NA	None	*SLX4*	Frameshift	Notify
NHW	Breast, bilateral (ER/PR+,HER2-)	57, 63	None	*BLM*	Spl. Donor	Notify
Chinese	Breast (ER-,PR-,HER2-)	39	None	*MLH1*	Missense	Did not notify
NHW	None	NA	None	*MUTYH*	Missense	Notify
Hispanic	Breast (Medullary, ER/PR+,HER2-)	36	None	*CDKN2A*	Missense	Did not notify
Hispanic	Breast, bilateral (ER/PR+, ER/PR-)	27, 33	None	*MUTYH*	Missense	Notify
Japanese	Breast (ER/PR+,HER2-)	48	None	*MUTYH*	Spl. acceptor	Notify
NHW	Breast (ER/PR+,HER2-)	47	None	*CDH1*	Intronic	Did not notify
NHW	Breast (ER/PR+,HER2+)	50	None	*NBN*	Missense	Notify
NHW	Breast (ER/PR+,HER2-)	61	None	*SLX4*	Frameshift	Notify
NHW	None	NA	None	*CDH1*	Intronic	Notify
NHW	None (same patient as above)	NA	None	*NBN*	Missense	Notify
Chinese	Breast (DCIS, ER-/PR-)	65	*BRCA1*	*MLH1*	Missense	Did not notify
NHW	Breast (ER/PR+,HER2-)	49	None	*ATM*	Missense	Notify
NHW	Breast (ER/PR+,HER2-)	42	None	*MUTYH*	Missense	Notify
Chinese	Breast (DCIS, ER+/PR-)	58	None	*MLH1*	Missense	Did not notify

Abbreviations: NHW, non-Hispanic white; ER/PR, estrogen/progesterone receptor; NA, not applicable; spl., splice

Results

- **198 participants tested of which 141 were BRCA1/BRCA2 negative**
  - 10% of BRCA-negatives had potentially actionable findings
  - 10 (7.1%) positive for high or moderate risk variants *in ATM, BLM, CDH1, CDKN2A, MLH1, NBN, or SLX4*
  - 5 (3.6%) were MUTYH single carriers
  - Average of 2 Variants of Unknown Significance (VUS) per patient across 41 genes; non-contributory for patient care
- **Patient notification and intervention were feasible**
  - 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.
- **Re-consent and clinical confirmation**
  - All participants provided informed consent following discussion with genetic counselor
  - 9 of 11 submitted samples for clinical confirmation
- **Risk Communication**
  - Currently available data on cancer risks were communicated
  - In some cases (ex. family with a CDH1 mutation but no family history of gastric cancer) uncertainty in risk was conveyed.
- **Clinical management was discussed with patients**
  - Positive results in ATM, BLM, CDH1, MUTYH, MLH1, NBN, PRSS1 or SLX4 were returned with appropriate recommendations for adding annual breast MRIs, escalating colonoscopy screening, adding gastroduodenoscopies (EGD) or considering bilateral salpingo-oophrectomies (BSO).
  - An MLH1 positive patient with a personal history of breast and endometrial cancer elected BSO and early colonoscopy that identified a tubular adenoma.
  - Two NBN positive patients with family histories of ovarian cancer elected to undergo BSO surgery.
  - MUTYH carriers advised to consider higher risk colonoscopy screening and informed of genetic risks for relatives.
- **Psychosocial issues**
  - Favorable responses from all subjects with only one initially concerned about the ambiguous information associated with her mutation. She subsequently embraced the added information, proceeded with clinical confirmation and testing of multiple relatives, allowing high risk screening for appropriate candidates.
  - Comments included: "I appreciate the call," "I am lucky to have this opportunity."

Discussion

- Panel testing represents a new paradigm in clinical care. Thorough studies of patient responses to this information are critical to ensure it's proper use.
- 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 increases
- In the context of research, appropriate consent and pretest guidance is certainly preferred when results may be returned. Nevertheless, findings that were not anticipated by the patient but are clinically significant findings 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.

Conclusion

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.

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.