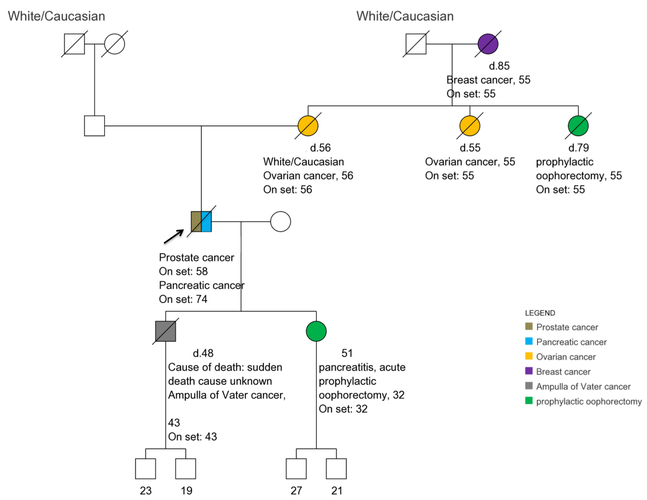
Before it's too late – broad hereditary cancer panel testing at the end of life

Marina Rabideau, Brian Vikstrom, Karen Vikstrom, Keith Nykamp, Scott Topper and Martin P. Powers.
[1]Invitae Corporation, San Francisco, CA www.invitae.com and [2]Northbay Medical Center

Introduction

- Recent publications discuss targeted testing for patients dying of ovarian cancer[1,2].
- Massively parallel sequencing allows for testing many genes for a similar cost to testing one gene using Sanger sequencing.
- New publications show the yield of broad hereditary cancer panels in patients with family histories fitting hereditary breast and ovarian cancer syndrome[3,4].
- Less is known about genetic testing at the end of life for a broad hereditary cancer panel, and providing genetic test results to family members when the results have some uncertainty associated with them.
- We present the case of a patient with a complex personal and family cancer history of cancer that did not fit guidelines for genetic testing, where the patient passed away before the positive PALB2 result was available.

Pedigree



Case Report

- The patient was a 75-year-old man diagnosed at age 58 with prostate cancer who presented with pancreatic cancer at age 74.
- His family history included a son diagnosed with an ampullary carcinoma at the age of 43 (deceased as a result of this cancer), a mother and maternal aunt who died of ovarian cancer in their 50s, and a maternal grandmother with breast cancer at age 55.
- The patient did not meet Medicare criteria for BRCA1/BRCA2 testing.
- The patient underwent a 29-gene hereditary cancer panel that included the APC, ATM, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, MEN1, MET, MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PALLD, PMS2, PTCH1, PTEN, RAD51C, RET, SMAD4, STK11, TP53, VHL genes.
- Within days of the genetic testing being ordered, the patient rapidly declined and expired before the results were available.
- The patient was found to have a pathogenic PALB2 c.1671_1676delinsCG (p.Ile558Glufs*2) mutation.
- DNA banking was not offered in time for this patient.
- This result was disclosed to the patient's wife and daughter.

Report

Summary

Positive result. Pathogenic sequence change identified in the PALB2 gene.

Clinical Summary

- A pathogenic sequence change was identified in the PALB2 gene. PALB2 gene mutations, when present in the heterozygous state, have been associated with an increased risk of breast, ovarian, and pancreatic cancer.
- As PALB2-related cancers are inherited in an autosomal dominant manner, each child of this individual has a 50% chance of inheriting the pathogenic allele. Close relatives (siblings, parents) also have a 50% chance of being a carrier.
- Biallelic mutations in PALB2 can also lead to Fanconi anemia type N (FA-N), an autosomal recessive condition. If a carrier of this pathogenic allele is considering pregnancy, carrier screening for Fanconi Anemia is recommended for his or her partner.
- Genetic counseling is advised to discuss the implications of this result. For a listing of genetic counselors, please visit www.nsgc.org.

Complete Results

Gene	Condition Group	Variant	Zygosity	Variant Classification
PALB2	Hereditary Cancers (Breast and Ovarian)	NM_024675.3:c.1671_1676delinsCG (p.Ile558Glufs*2)	heterozygous	PATHOGENIC

Discussion

- Although this was a difficult time for the family, testing provided relevant cancer risk information for the patient's daughter and grandchildren.
- Broader genetic testing can be helpful for the families of terminally ill cancer patients, because it improves risk calculation for surviving family members.
- Additional information about the risks to PALB2 carriers have been published after the patient's passing[5].
- Even if the results are in a lower penetrance gene, for which there are no management guidelines today, new guidelines and improved risk calculation models are likely to be available in the future.
- If the results have some uncertainty associated with them such as this pathogenic result in a newer gene, or Variants of Uncertain Significance, they can be followed over time.
- Working with the family of the deceased has been challenging, as this is a very sensitive time for the family, and also because the patient's daughter and grandchildren do not live nearby.
- Insurance coverage is not available for patients who do not meet current guidelines for testing.

Conclusion

- Broad hereditary panel testing can be performed at the end of life and yield information that can be useful to family members.

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