Family Communication (FC) of Test Results among an Unselected Pancreatic Adenocarcinoma (PC) Cohort who Underwent Germline Genetic Testing

Stobie, Lindsey[1]; Karloski, Eve[2]; Colvin, Arlene[3]; Lim Cynthia[3]; Peters, Mary Linton[1]; Krejdovsky, Jill[1]; DeLeonardis, Kimberly[1]; Luna, Melissa[1]; Moser, A James[1]; Allen, Kyle[4]; Speare, Virginia[4]; Dolinsky, Jill[4]; Borazanci, Erkut Hason[3]; Tung Nadine[1]; Brand, Randall[2]; Dudley, Beth[2].

[1]Beth Israel Deaconess Medical Center, Boston MA USA; [2]University of Pittsburgh Medical Center, Pittsburgh, PA USA; [3]Honor Health Research Institute, Scottsdale, AZ UA; [4]Ambry Genetics, Aliso Viejo, CA USA

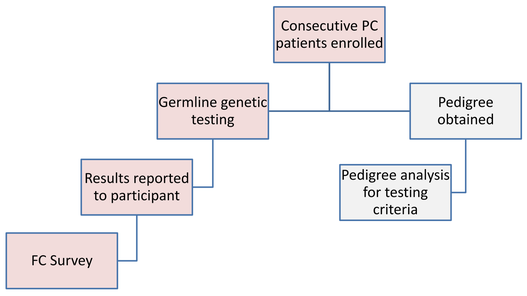
BACKGROUND

- Pancreatic cancer is the 3rd most common cause of cancer deaths in the US.
- Up to 10% of pancreatic ductal adenocarcinoma (PC) may be due to inherited cancer susceptibility.
- Germline genetic testing among individuals with PC is based on family and personal history of cancer.
- Estimates of germline pathogenic mutation prevalence in PC have largely been based on selected cohorts, such as familial cancer registries and diagnostic laboratory cohorts.
- Genes known to increase risk for PC include *APC, ATM, BRCA1, BRCA2, CDKN2A, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2, STK11,* and *TP53.*
- Communication of genetic test results to at risk relatives has been studied primarily in the setting of HBOC and Lynch syndrome.
- Identifying mutation carriers may provide targets for personalized treatment and allows for recognition of family members who may benefit from pancreatic and other cancer screening and prevention strategies.

STUDY AIMS

To assess family communication (FC) of results and determine the prevalence of germline mutations and likely pathogenic variants (VLP) in PC patients.

METHODS



- Consecutive, unselected adult patients with proven pancreatic ductal adenocarcinoma who were diagnosed within the previous 12 weeks were enrolled from May 2016 to May 2017.
- A multigene NGS panel of 32 cancer susceptibility genes consisting of genes known to be associated with hereditary PC risks (listed in the background) and genes associated with risk for other cancers (*BARD1, BMPR1A, BRIP1, CDH1, CDK4, CHEK2, GREM1, MRE11A, MUTYH, NBN, NF1, POLD1, POLE, PTEN, RAD50, RAD51C, RAD51D, SMAD4. SMARCA4)* was performed on saliva or blood samples in a CLIA approved laboratory.
- A 3-generation pedigree was obtained and the data was assessed to determine if the participant fulfilled criteria for genetic testing using the following guidelines: *BRCA1/2* (NCCN 2.2017), Familial Pancreatic Cancer (FPC), and Lynch syndrome (NCCN 2.2017).
- A subset of patients were queried through the family communication (FC) survey within several months of receiving test results as to whether they shared genetic test results with family members.

Table 1: Participant Characteristics

Characteristic	Number of participants (n=298)
Age	Mean: 68.5 years
	Range: 33-89 years
Gender	Male: 160 (53.7%)
	Female: 138 (46.3%)
Race/Ethnicity	Caucasian: 256 (85.9%)
	Ashkenazi Jewish: 26 (8.7%)
	Other/Unknown: 16 (5.4%)
PC stage	Stage I: 25 (7.6%)
	Stage II: 128 (42.9%)
	Stage III: 36 (12.1%)
	Stage IV: 87 (29.2%)
	Unknown: 24 (8.1%)
Personal history of other cancer*	Yes: 60 (20.5%)
	No: 238 (79.9%)
Family history of any cancer*	First-degree relative: 210 (70.5%)
	Only second-degree relative or higher: 56 (18.8%)
	None: 32 (10.7%)
Family history of pancreatic cancer	First degree relative: 23 (7.7%)
	Only second-degree relative or higher: 30 (10.1%)
	None: 245 (82.2%)

*Excludes cervical cancer, lung cancer, and non-melanoma skin cancer

RESULTS

- 23 mutations in genes known to increase risk for PC were identified and 13 mutations were found in genes not previously known to be associated with PC. (Table 2)
- A subset of the study population (88/298) completed the FC survey.
- Through communication within the family, 80% (60/73) at-risk first degree relatives were made aware of the positive results of 19 participants. (Table 3)
- Participants who communicated their positive result were carriers of a mutation or VLP in the following genes: *APC*(2), *ATM*(5), *BRCA1*(2), *BRCA2, CDKN2A, CHEK2*(6), *MUTYH,* and *NF1(mosaic).*
- The FC survey was completed by 42 participants with negative results and 27 participants with inconclusive results. 48% (155/326) of first degree relatives of participants whose results were uninformative (negative or inconclusive) were also informed of test results. (Table 3)
- At least one criteria for testing was met by 75% (27/36) of participants with a positive test result.

Table 3: Rate* of Result Disclosure to Family Members

Test result	Completed survey	Children	Siblings	Parents
Positive	19	80% (28/35)	84% (26/31)	86% (6/7)
Negative	42	64% (62/97)	43% (37/87)	17% (1/6)
Inconclusive	27	48% (30/63)	35% (22/63)	30% (3/10)

*Rate = disclosed to #/total # living

Table 2: Mutations/VLPs and Testing Criteria

PC genes	Pathogenic/VLP (includes moderate risk alleles)		Age at PC	Sex	Personal history other cancer* (age at diagnosis)	Fulfills genetic testing criteria
ATM	c.1027_1030delGAAA	p.E343Ifs*2	58	M	none	Yes
ATM	c.7630-2A>C	NULL	67	F	Leukemia (61), Melanoma (27)	Yes
ATM	c.7240C>T	p.Q2414*	81	F	Melanoma (<81)	Yes
ATM	c.6725DELC	p.S2242Yfs*15	50	M	none	Yes
ATM	c.3245_3247delATCinsTGAT	p.H1082Lfs*14	59	F	none	Yes
ATM	c.5932G>T	p.E1978*	59	M	none	No
ATM	c.4093delC	p.L1365Sfs*21	64	M	none	No
ATM	c.1564_1565delGA	p.E522Ifs*43	67	F	none	Yes
ATM	c.4741dupA	p.I1581Nfs*5	75	M	none	No
ATM	c.6027C>G (c.1052-2A>C)	p.Y2009* (NULL)	75	F	none	Yes
RAD50	c.1052-2A>C	NULL				
BRCA1	c.68_69delAG	p.E23Vfs*17	68	M	none	Yes
BRCA1	c.5266dupC	p.Q1756Pfs*74	70	F	Breast (55), Kidney (68)	Yes
BRCA1	c.181T>G	p.C61G	61	M	none	Yes
BRCA1	c.181T>G	p.C61G	83	M	Prostate (68), Bladder (81)	Yes
BRCA2	c.1237delC	p.L413Yfs*17	74	M	none	Yes
BRCA2	c.7341_7342delTA	p.N2447Kfs*3	63	F	none	Yes
BRCA2	5'UTR_3'UTRdel	NULL	67	M	none	Yes
BRCA2	c.1444delC	p.A483Qfs*2	89	M	none	No
CDKN2A	c.-34G>T	NULL	66	M	none	No
MSH6	c.2230dupG	p.E744Gfs*12	50	M	none	No
PALB2	c.1240C>T	p.R414*	75	M	none	Yes
PMS2	c.2174+1G>A	NULL	85	M	none	Yes
TP53 (VLP)	c.542G>A	p.R181H	50	M	Sarcoma (4)	Yes
Other Genes						
APC	c.3920T>A	p.I1307K	83	F	none	Yes
APC	c.3920T>A	p.I1307K	69	F	none	Yes
BARD1	c.1652C>G	p.S551*	77	F	none	Yes
CHEK2	c.1116dupC	p.K373Qfs*22	75	M	Melanoma (74)	Yes
CHEK2	c.1283C>T	p.S428F	67	M	none	Yes
CHEK2	c.470T>C	p.I157T	88	F	none	Yes
CHEK2	c.470T>C	p.I157T	47	M	none	Yes
CHEK2	EX8_9del	NULL	54	M	none	No
CHEK2	c.470T>C	p.I157T	62	F	none	Yes
CHEK2	c.470T>C	p.I157T	71	M	none	Yes
CHEK2	c.470T>C	p.I157T	89	M	none	No
CHEK2 (VLP)	EX13del	NULL	78	F	none	Yes
CHEK2 (VLP)	c.349A>G	p.R117G	78	F	none	No

*Excludes cervical cancer, lung cancer, and non-melanoma skin cancer

MUTYH heterozygotes (5) and mosaic results (2) were not included in this list of positive test results.

TAKE-HOME POINTS

- In this sample of recently diagnosed pancreatic cancer cases, the majority of mutation carriers shared results with their family.
- Mutations in cancer susceptibility genes may contribute to a significant proportion of PC diagnoses. Germline mutations were found in 12% of unselected PC patients. 4% of individuals had mutations in genes not previously related to PC risk.
- Timely communication of genetic test results in a population without long survival is important to allow for cascade testing for at-risk relatives.
- Further investigation of the communication of test results and cascade testing of family members are needed to ensure that at-risk relatives may take advantage of screening and risk reduction strategies.

REFERENCES

1.Grant, RC et al. Prevalence of germline mutations in cancer predisposition genes in patients with pancreatic cancer. *Gastroenterology*. 2015;148:556-564.
2. Graves, KD et al. Communication of genetic test results to family and health care providers following disclosure of research results. *Genet Med*. 2014;16(4): 294-301.
3. Holter, S et al. Germline BRCA mutations in a large clinic-based cohort of patients with pancreatic adenocarcinoma. *J Clin Oncol*. 2015;33:3124-3129.
4. Hruban ,RH et al. Familial pancreatic cancer. Annals of oncology : official journal of the European Society for Medical Oncology. 1999;10 Suppl 4:69-73.
5. Hu, C et al. Prevalence of pathogenic mutation in cancer predisposition genes among pancreatic cancer patients. *Cancer Epidemiol Biomarkers Prev*. 2015; Published OnlineFirst on October 19, 2015.
6. Montgomery, SV et al. Preparing individuals to communicate genetic test results to their relatives: Report of a randomized control trial. *Fam Cancer*. 12(3):537-546.
7. Network NCC. [cited 2017 August 14, 2017]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf.
8. Salo-Mullen, EE et al. Identification of germline genetic mutations in patients with pancreatic cancer. *Cancer*. 2015:121:4382-4388.
9. Syngal, S et al. ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. The American journal of gastroenterology. 2015;110(2):223-62; quiz 63.
10. Vasen, HFA et al. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative Group on HNPCC. Gastroenterology.116(6):1453-6.

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