OUTCOMES OF CLINICAL TESTING FOR 76,000 PATIENTS UTILIZING A PANEL OF 25 GENES ASSOCIATED WITH INCREASED RISK FOR BREAST, OVARIAN, COLORECTAL, ENDOMETRIAL, GASTRIC, PANCREATIC, MELANOMA AND PROSTATE CANCERS

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BACKGROUND

Genetic assessment for inherited risk is now an established tool for cancer prevention, but genetic testing strategies are evolving due to the availability of new technologies for cost-effective analysis of large numbers of genes, as well as new information about gene associations.

In order to evaluate the clinical utility of expanded multi-gene panels for identifying inherited cancer risk, we analyzed data from a diverse cohort of over 76,000 US individuals for whom clinical testing was performed with a panel of 25 genes known to be associated with an increased risk for 8 common cancers with known genetic associations.

METHODS

- Results are included from 76,574 consecutive individuals tested with the 25-gene panel in a CLIA certified laboratory.
- All clinical information was obtained from test requisition forms completed by ordering healthcare providers. During the time-frame for this study, the majority of individuals were ascertained for testing based on suspicion of either Hereditary Breast and Ovarian Cancer (HBOC) or Lynch Syndrome (LS).
- Only results for testing with the full 25-gene panel were included. Specifically excluded were all single-site tests for individual mutations in genes, and all tests for Ashkenazi Jewish individuals that were ordered as a 2-step process beginning with targeted testing for the 3 common founder mutations in *BRCA1* and *BRCA2*.
- The panel included the genes listed in Table 1. Sequence alterations and large rearrangements were identified with an NGS platform, with confirmation of large rearrangements using additional technologies, such as qPCR and array CGH.
- Variants were considered to be pathogenic variants (PVs) if they had a laboratory classification of Deleterious or Suspected Deleterious.

Table 1. Panel Gene Summary

Gene	Syndrome	Associated Cancers								
		BR	OV	CO	EN	ME	PA	GA	PR	OC
BRCA1	Hereditary Breast and Ovarian Cancer Syndrome (HBOC)	✓	✓				✓		✓	
BRCA2		✓	✓			✓	✓		✓	
MLH1	Lynch Syndrome (LS)		✓	✓	✓		✓	✓		✓
MSH2			✓	✓	✓		✓	✓		✓
MSH6			✓	✓	✓		✓	✓		✓
PMS2			✓	✓	✓		✓	✓		✓
EPCAM			✓	✓	✓		✓	✓		✓
APC	Familial Adenomatous Polyposis (FAP)			✓			✓	✓		✓
MUTYH	MUTYH-Associated Polyposis (MAP)			✓						✓
TP53	Li-Fraumeni Syndrome (LFS)	✓	✓	✓	✓	✓	✓	✓	✓	✓
PTEN	PTEN Hamartoma Tumor Syndrome (PHTS)	✓		✓	✓	✓				✓
CDH1	Hereditary Diffuse Gastric Cancer (HDGC)	✓		✓				✓		
BMPR1A	Juvenile Polyposis Syndrome (JPS)			✓			✓	✓		✓
SMAD4	Juvenile Polyposis Syndrome (JPS) & Hereditary Hemorrhagic Telangiectasia (HHT)			✓			✓	✓		✓
STK11	Peutz-Jeghers Syndrome (PJS)	✓	✓	✓	✓		✓	✓		✓
CDKN2A	Melanoma-Pancreatic Cancer Syndrome (M-PCS)					✓	✓			
CDK4	Melanoma Cancer Syndrome (MCS)					✓	✓			
ATM	ATM-Associated Cancer Risk	✓					✓			
CHEK2	CHEK2-Associated Cancer Risk	✓		✓					✓	
PALB2	PALB2-Associated Cancer Risk	✓					✓			
BARD1	BARD1-Associated Cancer Risk	✓								
BRIP1	BRIP1-Associated Cancer Risk	✓	✓							
NBN	NBN-Associated Cancer Risk	✓							✓	
RAD51C	RAD51C-Associated Cancer Risk	✓	✓							
RAD51D	RAD51D-Associated Cancer Risk		✓							

BR - Breast / **OV** - Ovarian / **CO** - Colorectal / **EN** - Endometrial / **ME** - Melanoma / **PA** - Pancreatic / **GA** - Gastric / **PR** - Prostate / **OC** - Other Cancer

RESULTS

- The vast majority of individuals tested to date are female, about half of whom had no reported diagnosis of cancer or colorectal polyps at the time of testing (Table 2).
  - The most common diagnoses among women tested were breast cancer (35.1%) and ovarian cancer (6.2%).
  - 9.8% of affected women had at least one PV identified, compared to 4.6% of unaffected women.
- Close to 3/4 of men tested were affected at the time of testing (Table 2).
  - The most common diagnosis among men was colorectal cancer (38.6%).
  - 16.5% of affected men were identified as having at least one PV, compared to 8.4% of unaffected individuals.

Table 2. Personal Cancer Histories of Individuals with Pathogenic Variants (PVs)

	Female				Male			
	N	% of Tested Individuals	Individuals with PVs Identified	% of Individuals with a PV	N	% of Tested Individuals	Individuals with PVs Identified	% of Individuals with a PV
Total	**74,095**	**96.8%**	**5,320**	**7.2%**	**2,479**	**3.2%**	**356**	**14.4%**
Personal Cancer History								
Breast	26,003	35.1%	2,546	9.8%	300	12.1%	52	17.3%
Ovarian	4,598	6.2%	650	14.1%	-	-	-	-
Colorectal	2,182	2.9%	247	11.3%	956	38.6%	162	16.9%
Endometrial	2,041	2.8%	237	11.6%	-	-	-	-
Gastric	76	0.1%	8	10.5%	44	1.8%	6	13.6%
Pancreatic	199	0.3%	24	12.1%	66	2.7%	12	18.2%
Melanoma	1,014	1.4%	92	9.1%	51	2.1%	7	13.7%
Prostate	-	-	-	-	137	5.5%	33	24.1%
C. Adenomas (>5)	713	1.0%	90	12.6%	293	11.8%	55	18.8%
Other	5,645	7.6%	455	8.1%	515	20.8%	87	16.9%
Unspecified	70	0.1%	3	4.3%	4	0.2%	0	0%
Total Affected	**36,407**	**49.1%**	**3,584**	**9.8%**	**1,828**	**73.7%**	**301**	**16.5%**
Unaffected	37,688	50.9%	1,736	4.6%	651	26.3%	55	8.4%

- 5,805 PVs linked to an increased risk for cancer were found in 5,676 individuals.
- PVs in most genes were found in individuals of all ancestries.
- PVs were most often identified in the genes *BRCA1* and *BRCA2* (43.7%), consistent with the majority of individuals being ascertained for testing for Hereditary Breast Ovarian Cancer (HBOC), as evidenced by the fact that 86.6% of all tested individuals met current NCCN criteria for *BRCA1* and *BRCA2* testing.
- The second highest percentage of PVs (26.4%) were detected in 3 genes (*ATM*, *CHEK2* and *PALB2*) associated with a >20% lifetime breast cancer risk, as well as an increased risk for other cancers .
- 10.1% of PVs were identified in one of the 5 genes associated with Lynch syndrome.
- 0.2% of all individuals tested, and 2.0% of all individuals with a PV, were found to have PVs in two genes -- this excludes individuals with biallelic *MUTYH* PVs. For more information on individuals with 2 PVs, see Poster #337.
- PVs are often detected in individuals with no personal or family history of a gene-related cancer (Table 3).
  - This is relatively rare for genes associated with very high cancer risks, i.e. *TP53* and *PTEN*, and more common for genes associated with lower cancer risks, i.e. *MSH6* and *PMS2*.
  - This is also less likely for genes associated with risks for cancers that are prevalent in our testing population, i.e. breast and colorectal, as opposed to genes associated only with risks for cancers that are less common, i.e. ovarian (*RAD51D*) and melanoma/pancreatic (*CDKN2A*).

Table 3. Distribution of Pathogenic Variants and Clinical Features of 76,574 Tested Individuals

Gene	Individuals with Pathogenic Variant (PV)	No Cancer in Individual	No Gene Related Cancer in Individual*	No Gene Related Cancer in Individual, FDR or SDR*
*BRCA2***	1,311	411 (31.4%)	471 (35.9%)	24 (1.8%)
BRCA1	1,228	323 (26.3%)	386 (31.4%)	15 (1.2%)
CHEK2	641	240 (37.4%)	284 (44.3%)	32 (5.0%)
ATM	503	173 (34.4%)	243 (48.3%)	52 (10.3%)
PALB2	392	111 (28.3%)	149 (38.0%)	16 (4.1%)
PMS2	246	94 (38.2%)	161 (65.4%)	45 (18.3%)
BRIP1	216	96 (44.4%)	107 (49.5%)	7 (3.2%)
MSH6	194	60 (30.9%)	98 (50.5%)	18 (9.3%)
MSH2	176	35 (19.9%)	46 (26.1%)	1 (0.6%)
MLH1	141	35 (24.8%)	44 (31.2%)	6 (4.3%)
NBN	140	72 (51.4%)	97 (69.3%)	33 (23.6%)
RAD51C	116	40 (34.5%)	50 (43.1%)	6 (5.2%)
BARD1	109	42 (38.5%)	58 (53.2%)	16 (14.7%)
APC†	96	16 (16.7%)	23 (24.0%)	8 (8.3%)
TP53	76	5 (6.6%)	5 (6.6%)	0 (0%)
CDKN2A (p16INK4a)	60	25 (41.7%)	50 (83.3%)	37 (61.7%)
RAD51D	47	23 (48.9%)	41 (87.2%)	29 (61.7%)
CDH1	36	10 (27.8%)	16 (44.4%)	2 (5.6%)
MUTYH (Biallelic)‡	25	2 (8.0%)	6 (24.0%)	5 (20.0%)
PTEN	21	2 (9.5%)	2 (9.5%)	0 (0%)
STK11	10	1 (10%)	1 (10%)	0 (0%)
EPCAM	9	2 (22.2%)	2 (22.2%)	0 (0%)
BMPR1A	5	1 (20.0%)	1 (20.0%)	0 (0%)
SMAD4	5	0 (0%)	1 (20.0%)	0 (0%)
CDKN2A (p14ARF)	2	2 (100%)	2 (100%)	2 (100%)
CDK4	0	-	-	-
Total All Genes	**5,805**			

*All cancers listed in Table 1 are considered "gene related" in this analysis.

**Individuals with two PVs in *BRCA2* (n=3)and *NBN* (n=2) were counted once.

†*APC* I1307K variant is not included as a PV.

‡Individuals with biallelic *MUTYH* PVs are counted as having a single *MUTYH* PV.

CONCLUSIONS

- PVs are detected in close to 10% of all affected individuals as an outcome of clinical testing using this 25 gene panel.
  - The positive rate in unaffected individuals is close to 5%, consistent with these individuals having at least one first-degree relative with a 10% or higher likelihood of carrying a PV in one of the panel genes.
  - The positive rate is significantly higher in men compared to women, probably due to the higher proportion of affected men and adherence to inclusive professional society guidelines for testing women at risk for hereditary breast and ovarian cancer.
  - The overall positive rate with panel testing is similar in individuals of all ancestries.
- Close to 90% of all PVs identified in this cohort are in genes for which there are explicit professional society recommendations for medical management.
- Compared with testing for *BRCA1* and *BRCA2*, the panel resulted in a 2.3-fold increase in the percentage of individuals identified with an increased risk for cancer.
- The 2% of PV carriers with findings in two different genes would probably not have been identified without panel testing.
- The significant fraction of PVs identified in individuals with no personal history or family history of a gene associated cancer suggests that one advantage of panel testing may be the identification of inherited cancer risks not apparent from evaluation of clinical history.

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