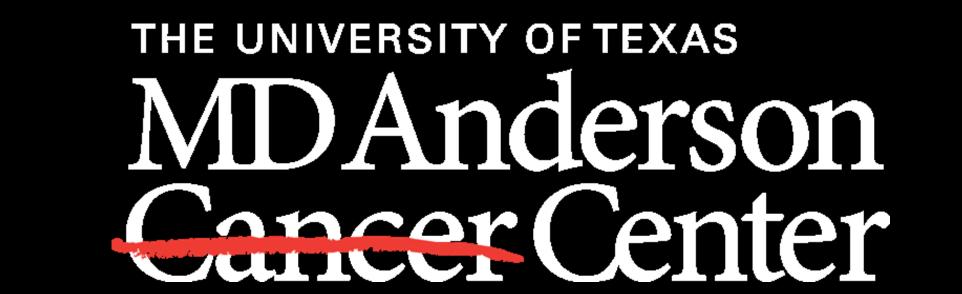


Multi-Gene Panel Testing in an Unselected Endometrial Cancer Cohort

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BACKGROUND

- Endometrial carcinoma (EC) is associated with multiple hereditary cancer genes, including the mismatch repair (MMR) genes associated with Lynch syndrome (LS).
 - MLH1, MSH2, MSH6, PMS2, EPCAM
- LS mutations are thought to account for 2-6% of all EC¹. In women diagnosed at ages <50 years, the mutation prevalence is greater (~9%)².
- The role of other genetic mutations in hereditary EC is unclear.
- Evaluation of a hereditary cancer panel of 25 genes known to be associated with a variety of hereditary cancers and cancer syndromes, including LS, could provide knowledge on the possible influence of genes other than MMR genes in hereditary EC.
- This 25 gene panel includes the following:
 - APC, ATM, BARD1, BMPR1A, BRIP1, BRCA1, BRCA2, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, PTEN, RAD51C, RAD51D, SMAD4, STK11, TP53

OBJECTIVE

 Determine the prevalence of germline mutations in LS and other cancer predisposition genes in an unselected EC cohort.

METHODS

- Mutations in 25 cancer genes were identified using a next generation sequencing based panel for 381 EC patients unselected for age of diagnosis with banked blood samples available for testing.
- Germline sequence variation and large rearrangements were classified for pathogenicity.
- Patient's clinical data, tumor testing with immunohistochemistry (IHC) for MMR proteins, microsatellite instability (MSI), and MLH1 methylation were abstracted from the medical record.

Table 1. Patient clinical characteristics.

N (%)

Clinical Characteristic

(N=381)	N (%)		
Age at Diagnosis, mean (SD)	60.8 (11.0)		
Age at Diagnosis <50			
Yes	50 (13.1)		
No	331 (86.9)		
Race			
Caucasian	265 (69.6)		
African-American	34 (8.9)		
Hispanic	66 (17.3)		
Asian	14 (3.7)		
Native American	2 (0.5)		
BMI			
Underweight	3 (0.8)		
Normal Weight	58 (15.2)		
Overweight	79 (20.7)		
Obese	241 (63.3)		
Stage			
	266 (69.8)		
II	25 (6.6)		
III	55 (14.4)		
IV	34 (8.9)		
Unknown	1 (0.3)		
Grade			
1	35 (9.2)		
2	215 (56.4)		
3	131 (34.4)		
Histology			
Endometrioid	289 (75.9)		
Serous	26 (6.8)		
Clear Cell	10 (2.6)		
N 4:	11 (11 F)		

44 (11.5)

(1.8)

Mixed

Carcinosarcoma

Undifferentiated

Table 2. Overview of germline mutations in 25 gene cancer panel.

Gene (N=381)	No. of Patient with DM	% of Patient with DM (95% CI)		
Any Deleterious Mutation	35	9.19 (6.48-12.54)		
Lynch Syndrome Genes	22	5.77 (3.65-8.61)		
MLH1	3	0.79 (0.16-2.28)		
MSH2	5	1.31 (0.43-3.04)		
EPCAM	2	0.52 (0.06-1.88)		
MSH6	6	1.57 (0.58-3.40)		
PMS2	6	1.57 (0.58-3.40)		
Non-Lynch Syndrome Genes	13	3.41 (1.83-5.76)		
PTEN	1	0.26 (0.01-1.45)		
BRCA1	1	0.26 (0.01-1.45)		
BRCA2	1	0.26 (0.01-1.45)		
APC	1	0.26 (0.01-1.45)		
ATM	1	0.26 (0.01-1.45)		
BARD1	1	0.26 (0.01-1.45)		
BRIP1	1	0.26 (0.01-1.45)		
NBN	1	0.26 (0.01-1.45)		
RAD51C	1	0.26 (0.01-1.45)		
CHEK2	4	1.05 (0.29-2.67)		

Table 3. Type of deleterious mutation by clinical characteristics.

Clinical Characteristic	No DM N (%)	LS DM N (%)	Other DM N (%)	p-value None v LS	p-value None v Other
Age at Diagnosis, mean (SD)	61.5 (10.7)	51.7 (9.1)	57.7 (14.7)	p<0.01	p=0.21
Age at Diagnosis <50					
Yes	38 (11.0)	10 (45.5)	2 (15.4)	p<0.01	p=0.62
No	308 (89.0)	12 (54.5)	11 (84.6)		
BMI					
Not Overweight	50 (14.5)	8 (36.4)	3 (23.1)	p<0.01	p=0.39
Overweight	296 (85.5)	14 (63.6)	10 (76.9)		
Tumor Location					
Corpus	310 (92.5)	14 (70.0)	12 (92.3)	p<0.01	p=0.98
Lower Uterine Segment	25 (7.5)	6 (30.0)	1 (7.7)		
MSI or IHC Screen Positive					
Yes	31 (9.3)	19 (90.5)	1 (8.3)	m <0 01	p=0.91
No	301 (90.7)	2 (9.5)	11 (91.7)	p<0.01	
SGO 5-10% Criteria					
Yes	84 (24.3)	13 (59.1)	4 (30.8)		p=0.59
No	262 (75.7)	9 (40.9)	9 (69.2)	p<0.01	
Serous Histology					
Serous	22 (6.4)	1 (4.5)	3 (23.1)	0.70	p=0.02
Other	324 (93.6)	21 (95.5)	10 (76.9)	p=0.73	

RESULTS

- 35 patients had a deleterious mutation (DM).
- 22 patients had a DM in LS genes and 13 patients had a DM in non-LS genes (Table 2).
- Compared to patients with no DM, Table 3 shows that patients with DM in LS genes were:
 - Younger at diagnosis (mean 51.7 v 61.5, p<0.01)
 - Less likely to be overweight (63.6% v 85.5%, p=0.01)
 - More likely to have a tumor in the lower uterine segment (30.0% v 7.5%, p<0.01)
 - More likely to meet SGO guidelines for genetic assessment referral (59.1% v 24.3%, p<0.01)
- 3 patients (13.6%) with DM in LS genes were diagnosed >60 years.
- Of 21 patients with DM in LS genes and available tumor results, 2 (9.5%) had a DM (1 *PMS2*, 1 *MSH6*) and IHC results suggestive of sporadic cancer (Table 3).
- Patients with DM in non-LS genes were more likely to have serous histology (23.1% v 6.4%, p=0.02) than those with no DM.
- 3 patients with non-LS DM and serous histology had mutations in BRCA2, BRIP1, and RAD51C, genes previously linked to hereditary ovarian cancer (Table 4).

Table 4. Patients with non-Lynch syndrome mutations.

Gene	Age at Diagnosis	Histology	Family History
APC	28	Endometrioid	Bladder Cancer – FDR unknown age CRC – FDR 47
ATM	76	Endometrioid	Breast Cancer – SDR unknown age Renal Cancer – SDR unknown age
BARD1	59	Mixed Serous and Clear Cell	Breast Cancer – SDR unknown age
BRCA1	55	Endometrioid	None
BRCA2	58	Serous	Breast Cancer – FDR 79
BRIP1	58	Serous	Pancreatic Cancer – FDR 61 CRC – SDR unknown age
CHEK2	60	Endometrioid	None
CHEK2	52	Endometrioid	Breast Cancer – SDR 35
CHEK2	56	Endometrioid	Breast Cancer – SDR 60 Breast Cancer – TDR 60 Gastric Cancer – SDR 50
CHEK2	57	Clear Cell	None
NBN	78	Endometrioid	Breast Cancer – FDR 55
PTEN	35	Endometrioid	Breast Cancer – SDR 70 CRC – SDR unknown age
RAD51C	78	Serous	Pancreatic Cancer – FDR 62

Abbr: FDR = first degree relative, SDR = second degree relative, TDR = third degree relative

CONCLUSIONS

- A panel testing approach to EC identifies alternative genes (especially CHEK2) with clinical implications for multiple cancers.
- Panel testing to include non-LS genes allowed for the identification of possibly novel genes that may be associated with serous-type EC, the most clinically aggressive form of this cancer.

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Abstract #1533. For additional information, please contact Russell Broaddus at rbroaddus@mdanderson.org

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