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RAD51B Harbors Germline Mutations Associated With Pancreatic Ductal Adenocarcinoma

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abstract

PURPOSE Genetic alterations in many components of the homologous recombination, DNA damage response, and repair (HR-DDR) pathway are involved in the hereditary cancer syndromes, including familial pancreatic cancer. HR-DDR genes beyond *BRCA1*, *BRCA2*, *ATM*, and *PALB2* may also mutate and confer the HR-DDR deficiency in pancreatic ductal adenocarcinoma (PDAC).

METHODS We conducted a study to examine the genetic alterations using a companion diagnostic 15-gene HR-DDR panel in PDACs. HR-DDR gene mutations were identified and characterized by whole-exome sequencing and whole-genome sequencing. Different HR-DDR gene mutations are associated with variable homologous recombination deficiency (HRD) scores.

RESULTS Eight of 50 PDACs with at least one HR-DDR gene mutation were identified. One tumor with *BRCA2* mutations is associated with a high HRD score. However, another tumor with a *CHEK2* mutation is associated with a zero HRD score. Notably, four of eight PDACs in this study harbor a *RAD51B* gene mutation. All four *RAD51B* gene mutations were germline mutations. However, currently, *RAD51B* is not the gene panel for germline tests.

CONCLUSION The finding in this study thus supports including *RAD51B* in the germline test of HR-DDR pathway genes.

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is a malignant disease with a dismal 5-year overall survival rate of 9%.[1] The poor prognosis of PDAC is primarily because of the drug-resistant nature of PDAC and a lack of effective treatment strategies. Therefore, new treatment choices are urgently needed, especially for patients with metastatic disease.

Numerous studies have demonstrated that the homologous recombination, DNA damage response, and repair (HR-DDR) pathway is essential for DNA double-strand break repair.[2-4] Accumulated studies have delineated the components in the HR-DDR pathway.[5-7] Genetic alterations in many of the components in this repair pathway are involved in the hereditary cancer syndromes, including familial pancreatic cancer. *BRCA1*, *BRCA2*, *PALB2*, and *ATM* mutations are among the most studied germline mutations in familial pancreatic cancer.[8-11] PDACs with *BRCA1/2* mutations are more sensitive to platinum-based chemotherapy than those without HR-DDR mutations.[12-14] Breast and prostate cancers with *BRCA1/2* mutations and ovarian cancers in general demonstrated the response to poly-ADP ribose polymerase (PARP) inhibitor, which inhibits the alternative repair pathway and leads to the synthetic lethality in the tumor cells that have suffered a homologous recombination repair deficiency. In PDAC patients with germline *BRCA1/2* mutations, the overall survival of patients with platinum chemotherapy was much longer than those without platinum chemotherapy (22 months *v* 9 months).[12] In patients with metastatic PDAC who had no progression after a minimum of 4-month first-line platinum-based chemotherapy, the maintenance therapy with a PARP inhibitor, olaparib, compared with a chemotherapy break, prolonged the progression-free survival from 3.8 months to 7.4 months ($P = .004$).[15]

More recently, a 15-gene panel including *BRCA1*, *BRCA2*, *ATM*, *BRIP1*, *BARD1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, and

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CONTEXT

Key Objective

Pancreatic ductal adenocarcinoma (PDAC) has a dismal prognosis, and homologous recombination, DNA damage response, and repair (HR-DDR) genes may mutate and confer the HR-DDR deficiency in PDAC. This study used a 15-gene HR-DDR panel beyond *BRCA1*, *BRCA2*, *ATM*, and *PALB2* to examine the genetic alterations in PDAC patients. It identified eight patients with at least one HR-DDR gene mutation with homologous recombination deficiency scores calculated.

Knowledge Generated

Eight of 50 PDACs with at least one HR-DDR gene mutation were identified. *RAD51B* germline mutations were found in four out of the eight patients, while *RAD51B* currently is not a gene listed on germline test panel.

Relevance

Including the *RAD51B* in germline test panel could allow more PDAC patients with HR-DDR pathway deficiency being identified, and these patients may benefit from HR-DDR pathway related therapies.

RAD54L was chosen as a companion diagnostic HR-DDR gene panel for the US Food and Drug Administration–approved olaparib indication in prostate cancer.[16] However, genetic alterations in most of these 15 HR-DDR genes were not characterized in depth in PDACs. Therefore, we conducted a study to examine genetic alterations in these 15 HR-DDR genes in PDACs in our database.

METHODS

Patients and Specimens

Genomic variants of 15 genes in the FoundationOne companion diagnostic HR-DDR gene panel,[16] including *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*, were used in our study. Eight deidentified PDAC patients with one or more HR-DDR gene variants in the tumors were identified from 50 consecutive patients from the Pancreatic Cancer Precision Medicine Center of Excellence registry database. Patient consent was waived by John Hopkins Medicine Institutional Review Board. These patients were treated at the Johns Hopkins Hospital between March 2016 and February 2018. Tumor samples were obtained from the primary tumor through surgery or endoscopic ultrasound-guided fine-needle aspiration biopsy. Normal samples for controlling were obtained from adjacent normal tissues of the primary tumor.

DNA Extraction, Library Preparation, and Sequencing

Genomic DNA was extracted by using the AllPrep DNA/RNA Kit (Qiagen, Germantown, MD) according to the manufacturer's instructions. To construct whole-exome capture libraries, genomic DNA was randomly fragmented into 200 approximately 250 bp fragments, and the fragments were purified and ligated by specific adaptors according to instructions of the MGIEasy Universal DNA Library Prep Set, and then captured with the MGIEasy Exome Capture V4 Probe Set (approximately 59 Mb; MGI, Shenzhen, China). The whole-genome sequencing (WGS) libraries were constructed according to instructions of the MGIEasy Universal DNA Library Prep Set. All constructed libraries were sequenced on a DIPSEQ platform (BGI). We performed both whole-exome sequencing (WES) and WGS if there was sufficient DNA. WES achieved an average coverage of 268× (90-420) in normal samples and 665× (83-1,251) in tumor samples. For WGS data sets, the normal samples achieved an average coverage of 46× (34-80), and the tumor samples achieved an average coverage of 49× (36-72).

Sequencing Data Analysis

The raw sequencing data were processed by SOAPnuke v 2.0.7[17] to filter low-quality reads and adaptor contaminations. The clean reads were processed on the basis of the UCSC human reference genome (hg19) using Sentieon pipeline[18] with the Sentieon driver. The Sentieon DNA Software package is a speed-up software program that rebuilt the phasing algorithms following Genome Analysis Toolkit (GATK) best practices: read alignment, mark duplication reads, indel realignment, base quality score recalibration, and variant calling.

Germline Variant Calling

For patients with family history of PDAC, the germline variants including single-nucleotide polymorphism (SNP) and short insertion and deletions (indels) were identified using Sentieon's Haplotyper algorithm on WES data. The raw SNPs were then filtered by GATK Variant Quality Score Recalibration. Raw indels were filtered using the GATK VariantFiltration module with the parameter QD $<$ 2.0 || FS $>$ 200.0 || ReadPosRankSum $<$ –20.0 || SOR $>$ 10.0 || InbreedingCoeff $<$ –0.8.

Somatic Variant Calling

First, single-nucleotide variations (SNVs) and indels were detected using WES and WGS data. There were six widely used somatic mutation callers: Lancet v1.0.7,[19] Strelka2 v2.9.2,[20] Muse v1.0,[21] Mutect2 (GATK4.0.6),[22] Somticsniper v1.0.5.0,[23] and Svaba v0.2.1.[24] The variant calls were refined by intersecting the callings from Mutect2, Strelka2,

TABLE 1. Homologous Recombination, DNA Damage Response, and Repair Gene Variants in Pancreatic Ductal Adenocarcinoma

Patient ID	Sex	Age (year)	Gene Name	Genome Change	Protein Change Position	Amino Acid Change	Clinical Significance Category	Variant Allele Frequency	Germline *v* Somatic
1	Male	74	*BRIP1*	21:g.30699137A>G	331	Q/R	Potentially clinically significant_b	0.38	Germline
			RAD51B	14:g.68352672A>G	180	Y/C	Potentially clinically significant_b	0.52	Germline
			RAD54L	1:g.46714242A>G	21	D/G	Potentially clinically significant_b	0.52	Germline
2	Female	64	*ATM*	11:g.108216545C>T	2,832	R/C	Clinically significant	0.61	Germline
			RAD51B	14:g.68290267A>G	3	S/G	Potentially clinically significant_b	0.47	Germline
3	Female	71	*RAD51B*	14:g.68331815_68331819del	137-139	AVV/AX	Potentially clinically significant_a	0.45	Germline
4	Female	72	*BRIP1*	21:g.30699557G>C	471	G/A	Potentially clinically significant_b	0.50	Germline
5	Male	61	*CHEK2*	22:g.29121087A>G	200	I/T	Clinically significant	0.52	Germline
6	Male	55	*RAD54L*	1:g.46739120T>C	490	L/P	Potentially clinically significant_b	0.48	Germline
7	Male	67	*BRCA2*	13:g.32920968_32920971del	2,314-2,315	TI/X	Clinically significant	0.48	Germline
			BRCA2	13:g.32931983G>A	2,574	W/*	Clinically significant	0.06	Somatic
8	Male	69	*RAD51B*	14:g.68353893A>G	243	K/R	Potentially clinically significant_b	0.61	Germline

Lancet, Muse, and Somticsniper for SNVs, and Strelka2, Lancet, Mutect2, and Svaba v0.2.1 for indels. The high confident variants were identified by at least two variant callers.

The following criteria eliminated possible germline-induced artifacts: (1) For variants deposited in the dbSNP database, < 19 supporting reads in the paired-normal sample or not presented in the COSMIC[25] database. For variants that did not deposit in dbSNP, less than eight supporting reads in the normal sample; (2) more than 0.1% minor allele frequency in the 1000 Genomes Project; and (3) more than 0.1% minor allele frequency in the EXAC and the annotation of the ClinVar is not pathogenic.

FACETS v0.5.11,[26] an allele-specific copy-number algorithm, was used to identify the copy-number variation for the WES and WGS data with default parameter setting. The structural variants (SVs) were called for WGS data by Manta v1.5.0[26] with default parameters. Moreover, a simple reciprocal inversion format was transformed to single inverted sequence junctions by a supplement script provided with Manta.

Determining the Clinical Significance of Genomic Variants

All SNVs and indels, germline or somatic, of HR-DDR genes were categorized into four groups: (1) clinically significant; (2) potentially clinically significant_a; (3) potentially clinically significant_b; and (4) not clinically significant. First, clinically significant variants were defined as SNV/indel variants with annotations of pathogenic or likely pathogenic in ClinVar[27] (GRCh37, database date December 10,

TABLE 2. SV in Pancreatic Ductal Adenocarcinoma Tumors With Homologous Recombination, DNA Damage Response, and Repair Gene Variants

Patient ID	Gene Name	Genome Change	SV Translocation, No. (%)	SV Inversion, No. (%)	SV Deletion, No. (%)	SV Tandem Duplication, No. (%)	SV Insertion, No. (%)	SV Total
1	*BRIP1*	21:g.30699137A>G	138 (47.9)	58 (20.1)	64 (22.2)	27 (9.4)	1 (0.4)	288
	RAD51B	14:g.68352672A>G						
	RAD54L	1:g.46714242A>G						
2	*ATM*	11:g.108216545C>T	96 (46.6)	35 (17.0)	58 (28.2)	17 (8.2)	0	206
	RAD51B	14:g.68290267A>G						
3	*RAD51B*	14:g.68331815_68331819del	60 (53.1)	32 (28.3)	15 (13.3)	6 (5.3)	0	113
4	*BRIP1*	21:g.30699557G>C	21 (31.8)	5 (7.5)	27 (41.0)	12 (18.2)	1 (1.5)	66
8	*RAD51B*	14:g.68353893A>G	92 (60.5)	28 (18.4)	20 (13.2)	12 (7.9)	0	152

Abbreviation: SV, structure variation.

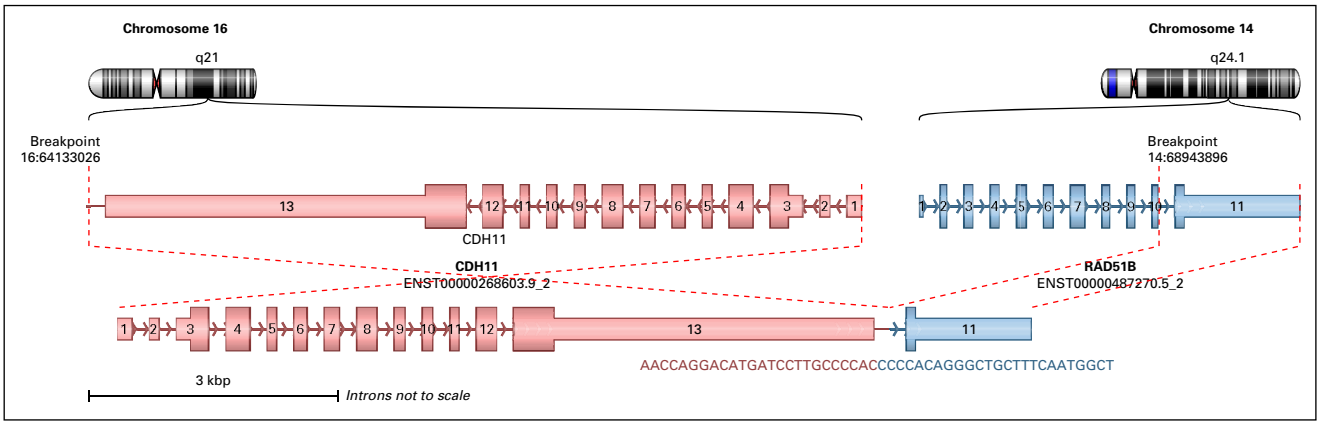

FIG 1. The structural variant of the *RAD51B* translocation identified in one patient. PDAC according the WGS result. The schema depicts the location, the fusion partner, the orientation, and the breakpoint junction fragment. One breakpoint on chr16:64133026 is located at a distance of 844631 bp from the *CDH11* gene; and a second breakpoint on chr14:68943896 is located in intron 10 of the *RAD51B* gene and anticipated to truncate RAD51B at the 346th amino acid (alanine). The breakpoint junction fragments on chromosome 14 and chromosome 16 are labeled in blue and pink, respectively. PDAC, pancreatic ductal adenocarcinoma; WGS, whole genome sequencing.

2020). Second, potentially clinically significant_a variants were defined as truncated variants (nonsense, frameshift, or splice intervening sequence ± 1 or 2) with annotations of the variant of unknown significance (VUS) or without an entry in ClinVar. Third, the pathogenicity of missense variants with annotations of VUS or with no entry in ClinVar was predicted with MetaSVM,[28] MetaLR,[28] and FATHMM-MKL.[29] The missense variants were categorized as potentially clinically significant_b if any of these three algorithms had an outcome of deleterious. Pathogenicity of indels with annotations of VUS or had no entry in ClinVar were predicted with SIFT.[30] The indel variants were categorized as potentially clinically significant_b if the outcomes of SIFT were deleterious. Fourth, not clinically significant variants were defined as SNV/indel variants annotated as benign or likely benign in ClinVar.

Homologous Recombination Deficiency Score

The scar-based homologous recombination deficiency (scarHRD) R package,[31] a genomic scar-based algorithm, was performed to calculate the homologous recombination deficiency (HRD) score. The score was the sum of the loss of heterozygosity (LOH), telomeric allelic imbalance, and large-scale state transitions. In our study, a reliable estimation of ploidy and purity was estimated and manually confirmed on the basis of three tools (FACETS, PyLOH v1.1,[32] and ABSOLUTE v1.2[33]). A combination of ploidy, purity, and allele-specific copy-number profile was used as the scarHRD input to measure the HRD score. scarHRD scores were estimated separately using WES and WGS data.

For the whole-genome sequenced tumors, we also estimated the HRD scores by classifier of homologous recombination deficiency (CHORD),[34] which was independent

TABLE 3. Homologous Recombination, DNA Damage Response, and Repair Gene Variants and Corresponding HRD Scores

Patient ID	Gene Name	Genome Change	scarHRD (WES)	scarHRD (WGS)	CHORD (WGS)
1	*BRIP1*	21:g.30699137A>G	19	22	0
	RAD51B	14:g.68352672A>G			
	RAD54L	1:g.46714242A>G			
2	*ATM*	11:g.108216545C>T	20	21	0
	RAD51B	14:g.68290267A>G			
3	*RAD51B*	14:g.68331815_68331819del	20	36	0.18
4	*BRIP1*	21:g.30699557G>C	20	15	0.63
5	*CHEK2*	22:g.29121087A>G	8	NA	NA
6	*RAD54L*	1:g.46739120T>C	19	NA	NA
7	*BRCA2*	13:g.32920968_32920971del	54	NA	NA
	BRCA2	13:g.32931983G>A			
8	*RAD51B*	14:g.68353893A>G	10	17	0

Abbreviations: CHORD, classifier of homologous recombination deficiency; HRD, homologous recombination deficiency; NA, not available; scarHRD, scar-based homologous recombination deficiency; WES, whole-exome sequencing; WGS, whole-genome sequencing.

TABLE 4. Neoantigen Load and Tumor Mutation Burden of Pancreatic Ductal Adenocarcinoma Tumors With Homologous Recombination, DNA Damage Response, and Repair Gene Variants

Patient ID	Gene Name	Genome Change	Neoantigen Load (all neoepitopes)	Neoantigen Load (neoepitopes 9-11 mer)	Tumor Mutation Burden
1	*BRIP1*	21:g.30699137A>G	94	42	1.24
	RAD51B	14:g.68352672A>G			
	RAD54L	1:g.46714242A>G			
2	*ATM*	11:g.108216545C>T	48	24	1.27
	RAD51B	14:g.68290267A>G			
3	*RAD51B*	14:g.68331815_68331819del	275	132	2.27
4	*BRIP1*	21:g.30699557G>C	59	42	0.61
5	*CHEK2*	22:g.29121087A>G	0	0	0.03
6	*RAD54L*	1:g.46739120T>C	78	33	0.91
7	*BRCA2*	13:g.32920968_32920971del	151	100	2.21
	BRCA2	13:g.32931983G>A			
8	*RAD51B*	14:g.68353893A>G	132	51	2.21

of genomic scar information. Briefly, CHORD used a random forest-based classifier and involved the counts of three types of mutation contexts as input features for the model: (1) SNVs subdivided by base substitution type; (2) indels stratified by the presence of sequence homology, tandem repeats, or the absence of either; and (3) SV, stratified by type and length. A sample was considered HRD if the HRD probability (sum of the probability of belonging to the BRCA1 and BRCA2 classes) was ≥ 0.5.

Calculation of Tumor Mutation Burden and Neoantigen Prediction

The tumor mutation burden (TMB) was calculated by the total number of nonsynonymous SNV and INDEL per megabase in the coding region. HLA-allele typing was predicted by OptiType v1.3.1[35] using the WES results. Nonsynonymous SNVs and INDEL were translated into 9 approximately 11 amino acids with a sliding window method as the candidate mutated peptides. NetMHC v4.0[36] and NetMHCpan v4.1[37] were applied to predict the HLA-binding peptides. The final neoantigens were retained with binding affinity < 500 nM predicted by at least one method. Neoantigen burden was estimated as the number of peptides that bind to the HLA-A allele.

RESULTS

Whole-Exome Sequencing of the HR-DDR Genes

Twelve HR-DDR gene variants according to WES were found in eight PDACs (Table 1). The average age of these eight patients was 67 years (range, 61-74 years). All eight patients had a family history of PDAC. One PDAC had three variants of the HR-DDR genes; two PDACs had two HR-DDR gene variants, and all other five PDACs had only one HR-DDR pathway variant. Within these 12 gene variants, the majority were missense (n = 9, 75%), followed by two frameshifts (17%) and one missense (13%). Both of the two frameshift variants were predicted to be prematurely truncated variants, which are anticipated to result in a loss of function in *BRCA2* and *RAD51B*, respectively, as previously described.[38] One PDAC carried a somatic mutation in *BRCA2* with a variant allele frequency (VAF) of 0.06. The highest variant frequency was found in *RAD51B* (n = 4, 50%), followed by *BRIP1* (n = 2, 25%) and *RAD54L* (n = 2, 25%). LOH was only found in *BRIP1* 21:g.30699137A>G and *ATM* 11:g.108216545C>T in PDAC from patient 1. The clinical significance of the HR-DDR gene variants was determined by using the algorithm as described above. Three variants were clinically significant, one was potentially clinically significant_a, and the remaining eight were potentially clinically significant_b (Table 1).

Structure Variation Analysis Via WGS

Structure variation was analyzed in five PDACs whose WGS results are available. The median number of total structure variations in the five PDACs was 165. The tumor (patient 1) with three HR-DDR gene variants had the highest SVs (No. = 286), followed by the tumor (patient 2) with two HR-DDR pathway variants (No. = 206). The SVs and subtype results were summarized in Table 2. One tumor (patient 1) has a breakpoint in intron 11 of the *RAD51B* gene, resulting in the translocation of the *RAD51B* gene (Fig 1).

HRD Score of PDACs With HR-DDR Gene Variants

HRD scores of all eight patients were assessed by using the scarHRD analysis of the WES results (Table 3). The median scarHRD score of the eight PDACs was 21.3. The highest score was detected in the PDAC (patient 7) with two clinically significant *BRCA2* variants, whereas the lowest score was detected in the PDAC (patient 5) with one clinically significant *CHEK2* variant. HRD scores were also

calculated by using both scarHRD and CHORD analyses of the WGS results that are available with five PDACs. The median scarHRD (WGS) and CHORD score of PDAC with HR-DDR pathway variants were 22 and 0, respectively. The PDAC tumor (patient 3) with the highest scarHRD score (WGS) had a *RAD51B*, a potentially clinically significant_a variant. The highest CHORD score was found in the PDAC tumor (patient 4) with a *BRIP1* potentially clinically significant_b variant (Table 3).

Neoantigen and TMB Analysis Via WES

Neoantigen load and TMB were assessed in all eight PDACs with HR-DDR gene variants. The average tumor neoantigen load predicted by netMHC according to neoepitopes in length from 9 to 11 amino acids was 53. The average TMB was 1.34. Both the highest tumor neoantigen level and TMB were associated with the PDAC from patient 3 that carried a *RAD51B* frameshift variant. The tumor (patient 5) that carried a *CHEK2* missense variant had no predicted neoantigen and also demonstrated the lowest TMB (0.03/Mb; Table 4). Four tumors with the *RAD51B* variants had an average neoantigen load of 62.3 and an average TMB of 1.75. Therefore, HR-DDR–deficient PDACs also have a low TMB and neoantigen load.

DISCUSSION

This comprehensive analysis of HR-DDR–deficient PDAC showed the *BRCA2* mutation was associated with a high HRD score, as anticipated. However, *CHEK2* mutation was associated with a zero HRD score. The ranges of TMB and neoantigen load in HR-DDR–deficient PDACs were lower than those of the high-TMB or microsatellite instability-high tumors, suggesting that HR-DDR deficiency does not increase the rate of missense mutations. Thus, HR-DDR–deficient PDACs are unlikely to respond to the single-agent immune checkpoint inhibitors. In addition, as different HR-DDR gene mutations were associated with variable HRD scores, their sensitivity to the PARP inhibitors would be anticipated to be different.

Interestingly, *RAD51B* alterations were present in four of eight PDACs in this study. *RAD51B* is a member of the RAD51 protein family. RAD51 family members are evolutionarily conserved proteins essential for DNA repair by homologous recombination. The RAD51B protein has been shown to form a stable heterodimer with the family member RAD51C. The *RAD51B* gene mutations have been reported to be associated with leiomyoma[39,40] and hereditary breast ovarian cancer syndrome.[41-43] Two patients with somatic *RAD51B* variants in the tumors were previously identified in a combined data set of 3,584 patients.[34] In this study, all four *RAD51B* gene mutations appear to be germline mutations. However, currently, *RAD51B* is not the gene panel for germline tests. The finding in this study thus supports including *RAD51B* in the germline test of HR-DDR pathway genes.

Nevertheless, this study is limited by its small sample size and descriptive nature. A larger study is warranted in the future.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Stock and Other Ownership Interests: Seattle Genetics
Honoraria: Merck
Consulting or Advisory Role: Merck, Bristol Myers Squibb, Janssen, Nouscom, HalioDX
Research Funding: Merck, Bristol Myers Squibb, Aduro Biotech, Curegenix, Medivir, Nouscom (Inst), AbbVie (Inst)
Patents, Royalties, Other Intellectual Property: Inventor of technology, "Microsatellite Instability as a Pharmacogenomic Marker of Therapeutic Response to Immune Checkpoint Inhibition"

Michael Pishvaian
Stock and Other Ownership Interests: Perthera
Consulting or Advisory Role: AstraZeneca/MedImmune, Merck, Pfizer, Novartis, TriSalus Life Sciences
Research Funding: Tesaro (Inst), Seattle Genetics (Inst), Pfizer (Inst), Arcus Biosciences (Inst), IDEAYA Biosciences (Inst), Repare Therapeutics (Inst), Merck (Inst), Tizona Therapeutics, Inc (Inst), Novartis (Inst), Takeda (Inst), Hutchison MediPharma (Inst), BioMed Valley Discoveries (Inst), Amgen (Inst), Ambrx (Inst)
Patents, Royalties, Other Intellectual Property: Perthera patient matching algorithm, Use patent for veliparib and FOLFOX
Uncompensated Relationships: RenovoRx

Eun Ji Shin
Consulting or Advisory Role: Boston Scientific

Anne Marie Lennon
Patents, Royalties, Other Intellectual Property: Patent for CancerSEEK

Mouen Khashab
Honoraria: Boston Scientific, Medtronic, Apollo Endosurgery
Research Funding: Boston Scientific

Vikesh Singh
Leadership: Kyttaro
Stock and Other Ownership Interests: Kyttaro
Consulting or Advisory Role: AbbVie, Ariel Precision Medicine
Research Funding: AbbVie, Orgenesis, Theraly

Alison P. Klein
Consulting or Advisory Role: OptumInsight, Merck
Research Funding: OptumLabs

Amol Narang
Research Funding: Boston Scientific

Elliot K. Fishman
Honoraria: GE Healthcare, Siemens Healthineers (Inst), HipGraphics
Research Funding: GE Healthcare (Inst), Siemens Healthcare Diagnostics (Inst)

Robert Anders
Employment: Johns Hopkins Hospital
Honoraria: Peerview
Consulting or Advisory Role: AstraZeneca/MedImmune, Merck, Bristol Myers Squibb/Medarex
Research Funding: Stand up to Cancer, Bristol Myers Squibb/Medarex, RAPT Therapeutics

Christopher L. Wolfgang
Leadership: Catalio HealthCor
Stock and Other Ownership Interests: Catalio HealthCor

Lei Zheng
Stock and Other Ownership Interests: Z and L International Medical, Alphamab, Mingruizhiyao
Consulting or Advisory Role: Merrimack, Merck, AstraZeneca, NovaRock, Biosynergies, Foundation Medicine, Alphamab, Mingruizhiyao, DataRevive, Ambrx, NovaGenesis, Coherent, Johnson & Johnson/Janssen, Snow Lake Capital, BioArdis, Xilio Therapeutics
Research Funding: Bristol Myers Squibb, Amgen, ITeos Therapeutics, Gradalis, Merck, Halozyme, NovaRock, InxMed, AstraZeneca (Inst)
Patents, Royalties, Other Intellectual Property: GVAX, licensed to Aduro Biotech
Other Relationship: QED Therapeutics

No other potential conflicts of interest were reported.

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