original reports

Therapeutic Implications of Germline Testing in Patients With Advanced Cancers

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abstract

PURPOSE Tumor mutational profiling is increasingly performed in patients with advanced cancer. We determined the extent to which germline mutation profiling guides therapy selection in patients with advanced cancer.

METHODS Patients with cancer undergoing tumor genomic profiling were prospectively consented for germline cancer predisposition gene analysis (2015-2019). In patients harboring germline likely pathogenic or pathogenic (LP/P) alterations, therapeutic actionability was classified using a precision oncology knowledge base. Patients with metastatic or recurrent cancer receiving germline genotype–directed therapy were determined.

RESULTS Among 11,947 patients across > 50 malignancies, 17% (n = 2,037) harbored a germline LP/P variant. By oncology knowledge base classification, 9% (n = 1042) had an LP/P variant in a gene with therapeutic implications (4% level 1; 4% level 3B; < 1% level 4). *BRCA1/2* variants accounted for 42% of therapeutically actionable findings, followed by *CHEK2* (13%), *ATM* (12%), mismatch repair genes (11%), and *PALB2* (5%). When limited to the 9,079 patients with metastatic or recurrent cancer, 8% (n = 710) harbored level 1 or 3B genetic findings and 3.2% (n = 289) received germline genotype–directed therapy. Germline genotype–directed therapy was received by 61% and 18% of metastatic cancer patients with level 1 and level 3B findings, respectively, and by 54% of *BRCA1/2*, 75% of mismatch repair, 43% of *PALB2*, 35% of *RAD51C/D*, 24% of *BRIP1*, and 19% of *ATM* carriers. Of *BRCA1/2* patients receiving a poly(ADP-ribose) polymerase inhibitor, 45% (84 of 188) had tumors other than breast or ovarian cancer, wherein the drug, at time of delivery, was delivered in an investigational setting.

CONCLUSION In a pan-cancer analysis, 8% of patients with advanced cancer harbored a germline variant with therapeutic actionability with 40% of these patients receiving germline genotype–directed treatment. Germline sequence analysis is additive to tumor sequence analysis for therapy selection and should be considered for all patients with advanced cancer.

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INTRODUCTION

Tumor mutational profiling is increasingly performed in patients with advanced cancer to identify clinically actionable somatic alterations as a guide to systemic therapy selection.[1-5] Recently, the National Cancer Institute's Molecular Analysis for Therapy Choice trial demonstrated the feasibility of identifying actionable somatic genetic alterations through large-scale sequencing efforts and delivering targeted treatments for underexplored advanced tumor types.[6] In contrast, historically, germline genetic testing has focused more on early-stage cancers aimed at identifying cancer predisposition syndromes in patients who would benefit from risk-reducing surgery, chemoprevention, and enhanced cancer surveillance. In 2014, the first poly(ADP-ribose) polymerase inhibitor (PARP-I) was approved by the US Food and Drug Administration (FDA) for advanced ovarian cancer patients with germline *BRCA1/2* alterations.[7,8] Since then, additional drugs have gained approval on the basis of pathogenic germline alterations in various cancer susceptibility genes.[9-19] Wider utilization of multigene germline panels and whole-exome analysis has further demonstrated that pathogenic germline alterations are quite common in patients with cancer.[5,20-22] A pan-cancer analysis demonstrated that approximately 17% of patients with advanced cancer harbored a pathogenic (P) or likely pathogenic (LP) germline variant in a cancer susceptibility gene, with 55% not meeting genetic testing criteria on the basis of historical clinical guidelines.[20] In response, clinical practice guidelines now incorporate germline analysis for broader cancer populations. Universal germline analysis for all patients with ovarian, pancreas, advanced prostate, and metastatic breast cancers is now endorsed by the National Comprehensive Cancer Network.[23,24] Tumor

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

What is the impact of germline genetic testing on germline-directed therapy selection in a pan-cancer patient population?

Knowledge Generated

Among cancer patients with metastatic or recurrent cancer, 8% had a germline alteration with therapeutic actionability. Overall, 3.2% of all patients with advanced cancer received germline-directed treatment.

Relevance

Our study findings suggest that multigene germline genetic analysis should be considered for all patients with metastatic or recurrent cancer to guide treatment selection.

testing for markers of Lynch syndrome (LS) is also recommended for all colorectal and endometrial cancers.[25]

As many oncologists have limited training in cancer genomics, precision oncology knowledge bases (OncoKB, CIViC, and others)[26-31] have been developed to better communicate the strength of evidence supporting the clinical actionability of somatic mutations. These knowledge bases stratify mutations and/or genes on the basis of the level of clinical and/or biologic data supporting their use as predictive biomarkers of drug response. For germline alterations, interpretation of variant pathogenicity for cancer risk has been well-established; however, there has been less focus on determining therapeutic actionability at the gene or gene variant level.[32]

Using a prospective pan-cancer cohort, the current study was designed to assess the utility of broad germline panel testing for germline-directed therapy selection and to determine the frequency with which germline genotype–directed treatment is given in patients with metastatic or recurrent cancer.

METHODS

Patient Population and Germline Genetics Analysis

Patients (N = 11,947) consented to an institutional review board–approved research protocol (ClinicalTrials.gov identifier: NCT01775072) between January 2015 and May 2019. Paired tumor-normal sequencing was performed using Memorial Sloan Kettering-IMPACT, a next-generation sequencing assay that identifies mutations, fusions, and copy number alterations in up to 468 cancer-associated genes and assesses microsatellite instability and tumor mutation burden.[2] All patients provided additional consent for germline analysis in our CLIA-approved laboratory using the normal blood-derived DNA.[20] Germline analysis was restricted to a subset of 76-88 genes in the Memorial Sloan Kettering-IMPACT panel (Data Supplement, online only), inclusive of all cancer-predisposing genes in the American College of Medical Genetics and Genomics guidelines.[33] Likely pathogenic or pathogenic (LP/P) variants were interpreted and clinically reported as previously described; variants of unknown significance were not reported.[20] Individuals with P/LP variants were offered genetic counseling.

Gene Classification on the Basis of Therapeutic Actionability

Genes with germline LP/P alterations were classified using the OncoKB knowledge base according to the level of evidence for the gene as a predictor of drug sensitivity.[26] Pertinent OncoKB levels of evidence for gene classifications for this study included *Level 1*, an FDA-recognized biomarker predictive of response to an FDA-approved drug in this indication (tumor type–specific); *Level 3B*, biomarker predictive of response to an FDA-approved or investigational drug in another indication; and *Level 4*, compelling biologic evidence of the biomarker as being predictive of response to a drug (Data Supplement; Table 1). Level of evidence assignment for an implicated gene was based on the last OncoKB update issued on September 17, 2020 and may be different from assignment level at the time of drug delivery. One exception to the existing OncoKB classification was that patients with LS-associated LP/P germline variants (*MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*), who also harbored tumors exhibiting high-frequency microsatellite instability (MSI-H) and/or DNA mismatch repair deficiency (dMMR) on immunohistochemistry, were given a special classification as level 1-MSI-H, as this genotype-treatment association is based on the tumor agnostic FDA authorization of pembrolizumab for MSI-H/dMMR tumors.[34,35] Patients with multiple LP/P alterations were classified according to the gene with the highest OncoKB level of evidence. Medical records of patients with level 1 or 3B alterations were reviewed to identify germline genotype–directed treatment received in a clinical or investigational setting. This analysis was limited to patients with metastatic or recurrent cancer at the time of review, where the utilization of germline genotype–directed systemic therapies is currently most pertinent.

RESULTS

Cohort Characteristics and Germline Variant Detection

Between 2015 and 2019, 30 patients with 479 solid tumor underwent combined germline and somatic mutation analysis,

TABLE 1. Classification of Germline Susceptibility Genes With Therapeutic Actionability

OncoKB Level of Evidence[a]	Gene(s)	Drug Class	Examples of Implicated Therapies	Clinical Implications
1	*BRCA1* and *BRCA2*	PARP-I	Olaparib Rucaparib Talazoparib Niraparib	FDA approval: advanced ovarian, breast, pancreas, and prostate cancers[8-15,36]
1	*RET*	Tyrosine kinase inhibitor	Selpercatinib	FDA approval (RET-associated)[b]: medullary thyroid cancer[37]
1	*PTCH1*	Hedgehog-signaling inhibitor	Vismodegib	FDA approval (PTCH1-associated): locally advanced basal cell carcinoma[19]
1	*TSC1*, *TSC2*	mTOR inhibitor	Everolimus	FDA approval (TSC-associated): subependymal giant cell astrocytoma (S EGA) and renal angiomyolipoma[16]
1	*ALK*	ALK kinase inhibitor	Brigatinib Lorlatinib	FDA approval[b]: NSCLCs with *ALK* oncogenic alterations[38,39]
1	*EGFR*	EGFR inhibitor	Osimertinib	FDA approval (EGFR-mutated)[b]: advanced lung cancer[40-42]
1	*KIT*	Tyrosine kinase inhibitor	Imatinib	FDA approval (cKIT-mutated)[b]: gastrointestinal stromal tumors[43,44]
1	*NF1*	MEK 1/2 inhibitor	Selumetinib	FDA approval (NF1-associated): inoperable plexiform neurofibromas[17,18]
1	*ATM*	PARP-I	Olaparib	FDA approval: advanced prostate cancer[15]
1	*PALB2*	PARP-I	Olaparib	FDA approval: advanced prostate cancer[15]
1	*RAD51C* and *RAD51D*	PARP-I	Olaparib	FDA approval: advanced prostate cancer[15]
1	*BRIP1*	PARP-I	Olaparib	FDA approval: advanced prostate cancer[15]
1	*BARD1*	PARP-I	Olaparib	FDA approval: advanced prostate cancer[15]
1	*CHEK2*	PARP-I	Olaparib	FDA approval: advanced prostate cancer[15]
1	*RAD51B*	PARP-I	Olaparib	FDA approval: advanced prostate cancer[15]
1-MSI-H	Lynch syndrome (*MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*)	Checkpoint inhibitors	Pembrolizumab	FDA approval[b]: advanced MSI-H/dMMR solid tumors (not Lynch syndrome specifically)[34,35]
3B	All level 1 genes	See level 1	See level 1	Drug class has FDA approval (level 1) in a different cancer type
3B	*MET*	MET kinase inhibitor	Cabozantinib	Renal cell carcinoma[45,46]
4	*POLE* and *POLD1*	Checkpoint inhibitors	Durvalumab	Under clinical investigation[47]
4	*CDKN2A* and *CDK4*	CDK4/6 inhibition	Abemaciclib Palbociclib Ribociclib	Under clinical investigation[48-52]
4	*SDHB*	Alkylating agent	Temozolomide	Under clinical investigation[53]
4	*FH*	EGFR inhibitor and anti-VEGF	Erlotinib Bevacizumab	Under clinical investigation[54]
4	*VHL*	HIF-2α inhibitor	MK-6482	Under clinical investigation[55]

Abbreviations: dMMR, defective DNA mismatch repair; FDA, US Food and Drug Administration; MSI-H, high-frequency microsatellite instability; NSCLC, non–small-cell lung cancer; PARP-I, poly(ADP-ribose) polymerase inhibitor.

[a]Further data supporting the current OncoKB level of evidence can be found at OncoKB website.[56]

[b]Designates that FDA approval is not specific to the germline alteration.

with 11,947 consenting to germline analysis of cancer susceptibility genes. The most prevalent malignancies were breast (14%), prostate (14%), pancreas (12%), and colorectal cancers (11%) (Table 2). The 10 most common cancers in the germline cohort were similar to the distribution of tumor types among patients undergoing tumor analysis only, with the exception that lung cancer was under-represented in the germline analysis (Data Supplement Fig 1).

Among 11,947 patients, 4,593 underwent germline analysis using a 76-gene panel, whereas 7,354 had an updated 88-

TABLE 2. Baseline Characteristics and Overall Prevalence of Germline Variants (N = 11,947)

Characteristic	Overall (N = 11,947)	Germline-Negative (n = 9,910)	Positive for Any Germline LP/P Variant (n = 2,037)
Sex (male), No. (%)	5,590 (46.8)	4,645 (46.9)	945 (46.4)
Ancestry, No. (%)			
White	7,143 (60)	6,037 (61)	1,106 (54)
AJ	1,956 (16.3)	1,413 (14.3)	543 (26.6)
Non-White	2,332 (19.5)	2,015 (20.3)	317 (15.5)
Unknown	516 (4.3)	445 (4.5)	71 (3.4)
Age at diagnosis, years: mean/median			
Mean	54.9	55.2	53.4
Median	57	58	56
Stage			
Metastatic or recurrent	9,079 (76%)	7,573	1,506
Cancer types (percentage of all cancers) and stage (percentage of metastatic cancer among that type)			
Breast cancer, No. (%)	1,711 (14.3)	1,413	298 (17.4)
	Metastatic: 1,256 of 1,711 (73.4)		
Prostate cancer, No. (%)	1,653 (13.8)	1,387	266 (16)
	Metastatic: 1,285 of 1,653 (77.7)		
Pancreas cancer, No. (%)	1,446 (12.1)	1,162	284 (19.6)
	Metastatic: 1,280 of 1,446 (88.5)		
Colorectal cancer, No. (%)	1,259 (10.5)	1,065	194 (15.4)
	Metastatic: 912 of 1,259 (72.4)		
Uterus cancer, No. (%)	871 (7.3)	750	121 (13.9)
	Metastatic: 522 of 871 (59.9)		
Ovary cancer,[a] No. (%)	721 (6.0)	526	184 (25.5)
	Metastatic: 684 of 721 (94.9)		
Kidney cancer, No. (%)	493 (4.1)	416	77 (15.6)
	Metastatic: 349 of 493 (70.8)		
Bladder cancer, No. (%)	388 (3.3)	324	64 (16.5)
	Metastatic: 264 of 388 (68)		
Brain or CNS cancer, No. (%)	384 (3.2)	327	57 (14.8)
	Metastatic: 111 of 384 (28.9)		
Sarcoma, No. (%)	357 (3.0)	292	65 (18.2)
	Metastatic: 265 of 357 (74.2)		
Others, No. (%)	2,664 (22.3)	2,239	425 (15.9)
	Metastatic: 2,151 of 2,664 (80.7)		

Abbreviations: AJ, Ashkenazi Jewish; LP/P, likely pathogenic or pathogenic.
[a]Ovarian cancer classification also includes patients with fallopian tube or primary peritoneal cancer.

gene panel (Data Supplement). The LP/P germline variant prevalence was 17% (n = 2,037), similar to the variant detection rate previously reported by our group for the first 1,040 patients on this prospective protocol.[20] By cancer penetrance (Data Supplement), 10% of patients harbored an LP/P variant in a high- or moderate-penetrance gene with the most frequent alterations identified in *BRCA1/2* (4%) and LS-associated genes (1%).

Therapeutic Actionability of Pathogenic Germline Alterations

To determine how often a germline variant with therapeutic implications was detected in this pan-cancer cohort, we classified all 2,037 LP/P variants identified using the OncoKB classification system (Data Supplement). Overall, 9% of patients (n = 1,042/11,947) harbored an LP/P germline variant in a potentially therapeutically

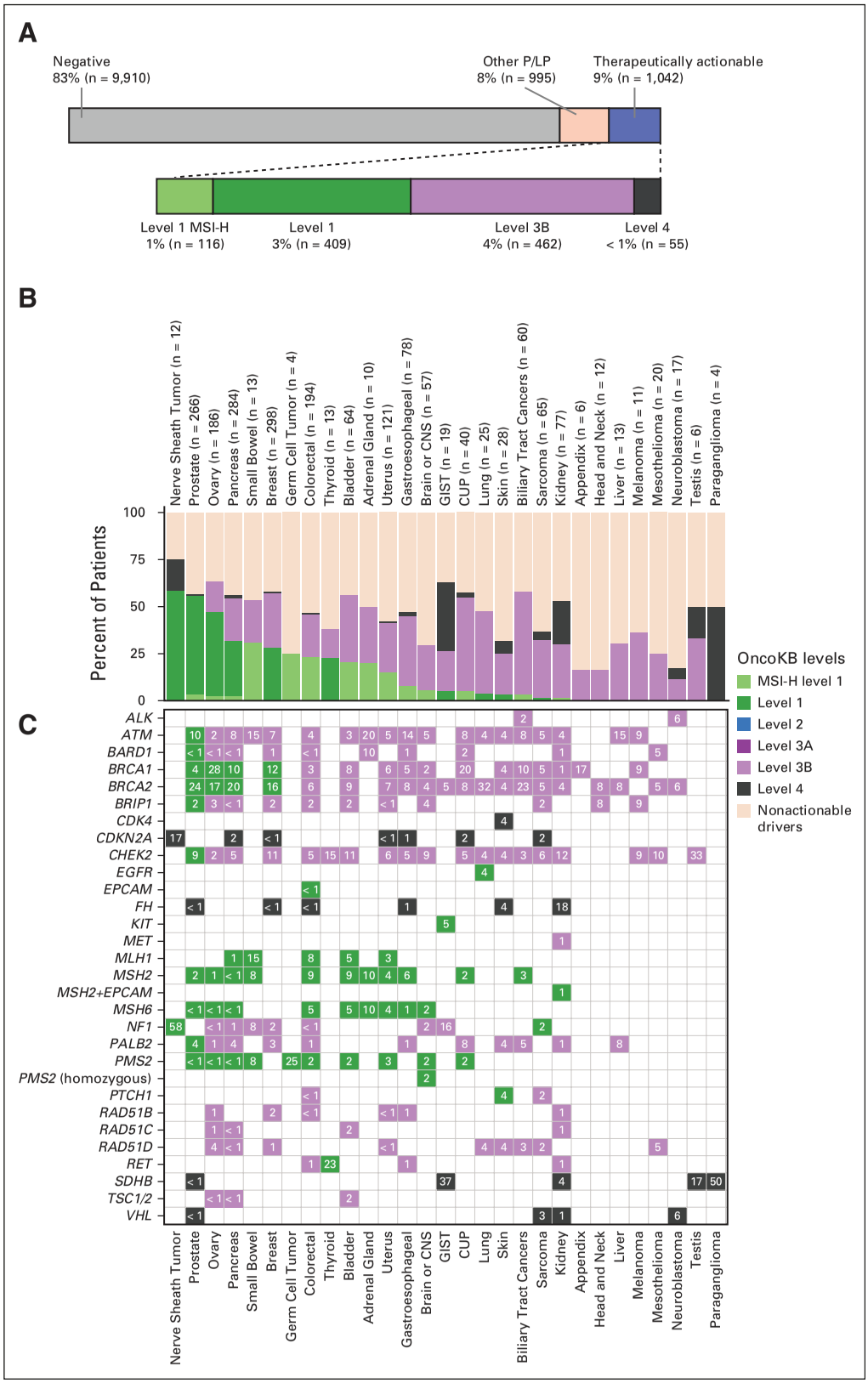

FIG 1. (continued on following page).

FIG 1. (Continued). Prevalence of germline variants with therapeutic actionability as classified by OncoKB. (A) Top panel, percent of 11,947 cancer patients with LP/P germline alterations considered therapeutically actionable by OncoKB (blue). Lower panel, breakdown of therapeutically actionable germline alterations by OncoKB level of evidence. Level 1 MSI-H (light green) indicates patients with germline LP/P alterations in the DNA mismatch repair genes whose tumors also exhibit MSI-H/dMMR. In (B and C), highest OncoKB level of evidence by cancer type and gene is shown (28 cancer types shown). (B) In the stacked bar graph, columns indicate tumor type. Number of patients with LP/P alterations per cancer type specified in labels on top *x*-axis. Each bar is broken down by percentage of patients harboring a germline alteration with color-indicated level of evidence or nonactionable P/LP alteration (light orange). (C) In the frequency map, rows indicate germline gene alteration present in patients and numbers indicate the percentage of patients per cancer type that harbors an alteration in each gene. CUP, cancer of unknown primary; dMMR, defective DNA mismatch repair; GIST, gastrointestinal stromal tumor; LP/P, likely pathogenic or pathogenic, MSI-H, high-frequency microsatellite instability.

actionable gene. More specifically, 4%, 4%, and < 1% of patients had level 1 (inclusive of level 1-MSI-H), level 3B, or level 4 findings, respectively (Fig 1A). LP/P variants in *BRCA1/2* were the most common therapeutically actionable germline variants (43%, n = 441) followed by *CHEK2* (13%, n = 133), *ATM* (12%, n = 127), and *PALB2* (4%, n = 47). Notably, 159 patients harbored an LP/P variant diagnostic of LS, including one patient with constitutional MMR deficiency syndrome (CMMRD). However, of these patients, only the 116 patients with corresponding MSI-H/dMMR tumors were designated as level 1-MSI-H (Fig 1A).

The distribution of therapeutically actionable germline alterations as classified by OncoKB by tumor type is shown in Figures 1B and 1C. Of all patients harboring a germline LP/P alteration (n = 2037), the cancer types with the highest percentage of level 1 (inclusive of level 1-MSI-H) germline alterations were nerve sheath tumors followed by prostate, ovarian, pancreas, and small bowel cancers (Fig 1B). Notably, the majority of *BRCA1* and *BRCA2* germline variants were classified as level 1, on the basis of the recent expansion of FDA approval of PARP-I(s) to include patients with prostate[15,36] and pancreas cancers.[57] Since PARP-I therapy, specifically olaparib, is currently FDA-approved in only prostate cancer patients with *ATM*, *PALB2*, *BRIP1*, *RAD51B/C/D*, *CHEK2*, and *BARD1*,[15] the majority of germline variants in these genes were classified by OncoKB as level 3B (Fig 1C).

We also assessed the fraction of patients who were known to have an LP/P germline variant from prior standard of care or family-directed cascade testing. Among the 1,042 patients with LP/P germline variants classified by OncoKB as having potential therapeutic actionability, 29% (n = 298) had prior knowledge of their LP/P germline alteration with 80% of these being patients with *BRCA1/2* or LS. Among *BRCA1/2* carriers, 75% of patients with ovarian, 69% of patients with breast, 40% of patients with pancreas, and 18% of patients with prostate cancers had prior knowledge of their LP/P genetic alteration. For *ATM*, *PALB2*, *RAD51C/D*, and *BRIP1*, only 20%, 19%, 4%, and 4% had prior knowledge of the LP/P genetic alteration, respectively.

Utilization of Germline Genotype–Directed Therapies in Clinical Practice

We next assessed the clinical utilization of germline genotype–directed treatment in patients with level 1 and level 3B OncoKB variants. Only patients with metastatic or recurrent cancer (stage IV) were included for this analysis, with the exception that stage IIIC ovarian cancer and inoperable nerve sheath tumors were included, as such patients require systemic therapy. Of 9,079 patients with metastatic or recurrent cancer (Table 2), 8% (n = 710) harbored a level 1 or level 3B OncoKB variant and 3.2% (n = 289) of all patients with metastatic cancer received germline-directed therapy. Of advanced cancer patients with a therapeutically actionable LP/P germline variant, 41% (n = 289) received a germline genotype–directed therapy (Table 3). As expected, germline-directed treatment was more commonly received by patients with a level 1 (61%, n = 227/371) germline alterations as opposed to patients with level 3B alterations (18%, n = 62/339) (Fig 2A; Table 3).

Of the 188 patients receiving a PARP-I in the setting of an LP/P *BRCA1/2* mutation, 55% had ovarian (n = 72) or breast (n = 32) cancer. However, 45% had other tumor types, including pancreas (n = 39), prostate (n = 24), bile duct, gastric, and other cancer types, wherein the drug, at the time of delivery, was administered in a research context. The likelihood of receiving a PARP-I was highly tumor type–dependent with 89% of ovarian, 59% of breast, 53% of pancreas, and 42% of prostate cancer patients with *BRCA1/2* alterations receiving such therapy (Fig 2B). The lower frequency of PARP-Is received by patients with pancreas and prostate cancers is likely attributable to the fact that these agents had not yet been FDA-approved for these indications during the timeframe of the study.

Among patients with level 1 or 3B LP/P germline alterations in a gene involved in homologous-recombination repair (HRR), 59% (184 of 313) of level 1 and 19% (60 of 317) of level 3B patients received a PARP-I. After *BRCA1/2*, PARP-I for an HRR-associated germline variant was most

TABLE 3. Distribution of Level 1 and Level 3B Germline Findings and Germline-Directed Therapy Received by Patients With Advanced Cancer

Targetable Gene	Patients With LP/P Germline Alterations With Level 1 or 3B OncoKB Classification	Percentage of Advanced Cancer Patients With Level 1 or 3B Germline Alterations Receiving Germline Genotype–Directed Therapy (n = 710)	Percentage of Patients With Advanced Cancer Receiving Germline Genotype–Directed Therapy by OncoKB Level
Overall	987 (levels 1 and 3B)[a]	40.7% (289 of 710)	Level 1: 61.2% (227 of 371)
	Metastatic or recurrent: 710 (levels 1 and 3B)[a]		Level 3B: 18.3% (62 of 339)
BRCA1/BRCA2	441	54.0% (188 of 348)	Level 1: 62.8% (167 of 266)
			Level 3B: 25.6% (21 of 82)
Lynch syndrome (*MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*) and MSI-H/dMMR tumor[b]	116[c]	74.5% (35 of 47)	Level 1: 74.5% (35 of 47)
ATM	127	18.9% (17 of 90)	Level 1: 41.2% (7 of 17)
			Level 3B: 13.7% (10 of 73)
PALB2	47	43.2% (16 of 37)	Level 1: 42.9% (3 of 7)
			Level 3B: 43.3% (13 of 30)
NF1	28	5.9% (1 of 17)	Level 1: 20% (1 of 5)
			Level 3B: 0% (0 of 12)
RAD51C/D	25	35% (7 of 20)	Level 1: 0% (0 of 0)
			Level 3B: 35% (7 of 20)
RET	7	60% (3 of 5)	Level 1: 100% (3 of 3)
			Level 3B: 0% (0 of 2)
TSC1/2	4	0% (0 of 3)	Level 1: 0% (0 of 0)
			Level 3B: 0% (0 of 3)
PTCH1	3	66.7% (2 of 3)	Level 1: 100% (1 of 1)
			Level 3B: 50% (1 of 2)
ALK	2	0% (0 of 2)	Level 1: 0% (0 of 0)
			Level 3B: 0% (0 of 2)
EGFR	1	100% (1 of 1)	Level 1: 100% (1 of 1)
			Level 3B: 0% (0 of 0)
MET	1	100% (1 of 1)	Level 1: 0% (0 of 0)
			Level 3B: 100% (1 of 1)
KIT	1	100% (1 of 1)	Level 1: 100% (1 of 1)
			Level 3B: 0% (0 of 0)
BRIP1	27	23.8% (5 of 21)	Level 1: 50% (2 of 4)
			Level 3B: 17.6% (3 of 17)
BARD1	13	8.3% (1 of 12)	Level 1: 100% (1 of 1)
			Level 3B: 0% (0 of 11)
CHEK2	133	10.5% (10 of 95)	Level 1: 27.8% (5 of 18)
			Level 3B: 6.5% (5 of 77)
RAD51B	11	14.3% (1 of 7)	Level 1: 0% (0 of 0)
			Level 3B: 14.3% (1 of 7)

Abbreviations: CMMRD, constitutional mismatch repair deficiency; dMMR, DNA mismatch repair deficiency; LP/P, likely pathogenic or pathogenic; MSI-H, high-frequency microsatellite instability.

[a]An additional 55 patients harbored level 4 germline alterations. When limited to only patients with metastatic or recurrent cancer, 39 level 4 germline alterations were identified.

[b]This only includes patients with Lynch syndrome who also harbored a tumor exhibiting MSI-H and/or dMMR on immunohistochemical analysis, referred to as level 1 MSI-H.

[c]One patient had CMMRD syndrome with biallelic germline *PMS2* alterations.

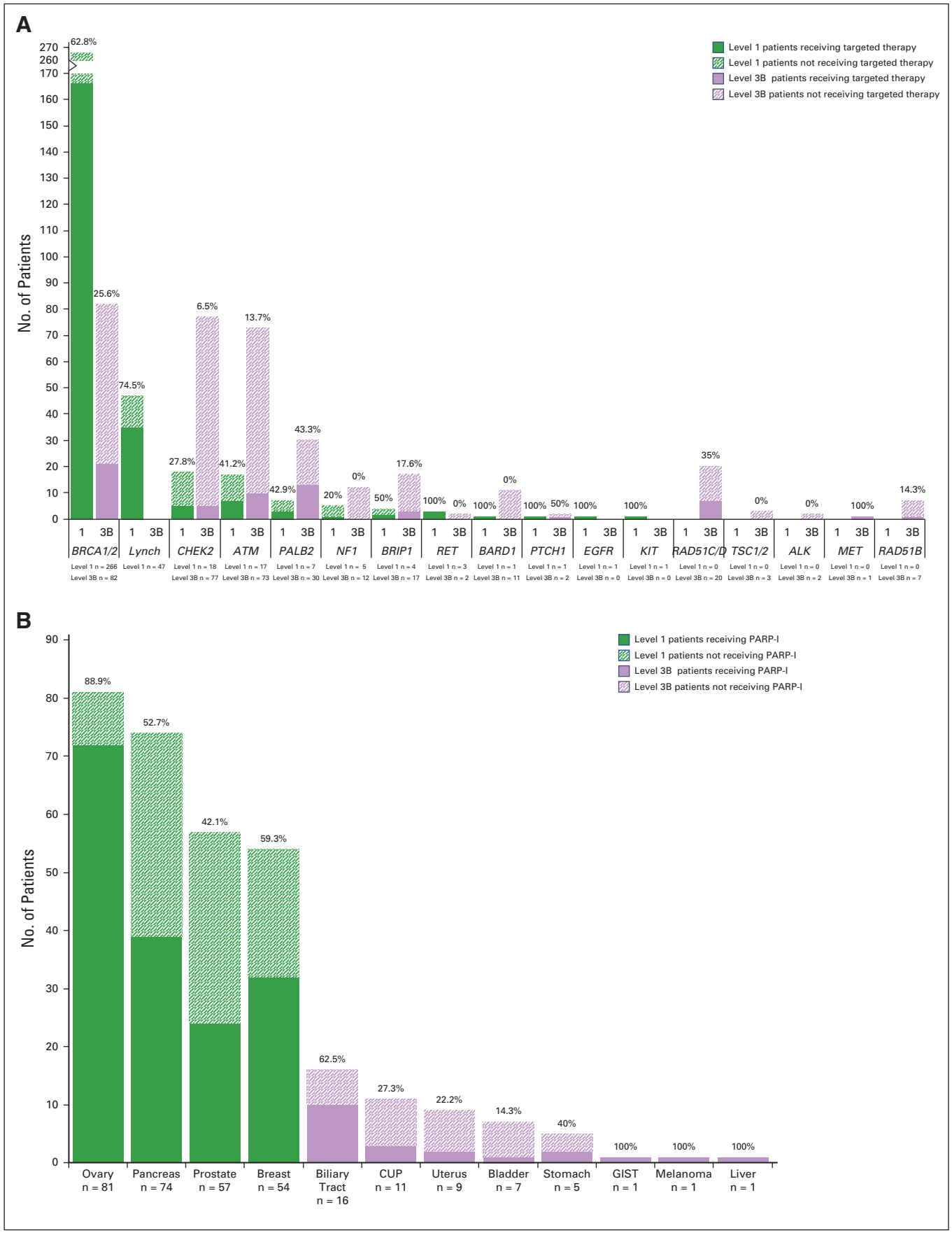

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FIG 2. (Continued). Patients with advanced cancer receiving germline genotype–directed therapy. (A) Bar graph demonstrates the 710 patients with metastatic or recurrent cancer harboring level 1 and level 3B LP/P germline variants and the percentage of these patients who received germline genotype–directed therapy by gene(s) and according to OncoKB level of evidence. (B) Bar graph demonstrates the 348 patients with advanced cancer that harbors an LP/P germline alteration in *BRCA1* or *BRCA2* and the percentage of these patients receiving a PARP-I by tumor type and according to the OncoKB level of evidence assigned for that tumor type. An additional 31 advanced cancer patients with LP/P *BRCA1/2* germline alterations with colorectal (12), lung (5), esophagus and gastroesophageal junction (4), sarcoma (3), kidney (2), appendix (1), brain (1), neuroblastoma (1), head and neck (1), and skin (1) cancers were also identified, with none of them receiving a PARP-I. CUP, cancer of unknown primary; GIST, gastrointestinal stromal tumor; LP/P, likely pathogenic or pathogenic; PARP-I, poly(ADP-ribose) polymerase inhibitor.

often administered to patients with LP/P *PALB2*, *RAD51C/D*, and *BRIP1* variants where 43%, 35%, and 24% of patients received a PARP-I, respectively. Although 49% of *PALB2* LP/P carriers had breast or pancreas cancer, the remaining patients had other cancer types including prostate, ovary, or an unknown primary. PARP-I was received by 47% of these patients.

In patients with LS, at risk for the development of MSI-H/dMMR tumors,[58] 75% received immune checkpoint blockade (Fig 2A; Table 3) inclusive of one patient with CMMRD. Beyond colorectal cancer, patients with LS-associated prostate, bladder, pancreas, and ovarian cancers received immunotherapy.

Of 244 patients with cancer of unknown primary, 22 had an LP/P germline variant with therapeutic actionability including 11 *BRCA1/2*, 2 MMR-associated genes, 3 *ATM*, 3 *PALB2*, 2 *CHEK2*, and 1 *BARD1* carriers. Among these patients, six (27%) received germline genotype–directed treatment. A proportion of patients with level 1 or 3B genetic alterations in *RET*, *PTCH1*, *KIT*, and *NF1* also received a germline genotype–directed treatment (Fig 2A). In patients with LP/P variants in these genes, the targeted therapy was usually delivered for a level 1 indication (ie, selumetinib in *NF1*-associated neurofibroma) with some exceptions, including a colorectal cancer patient with germline *PTCH1* alterations who received a hedgehog signal inhibitor.

DISCUSSION

Our study highlights the clinical utility of germline sequence analysis for therapeutic decision making in patients with advanced cancer. Specifically, among patients with metastatic or recurrent cancer, 8% harbored OncoKB level 1 or level 3B therapeutically actionable germline alterations, with an overall 3.2% of all patients with metastatic cancer receiving germline genotype–directed treatment. Importantly, we anticipate that over time, the fraction of patients receiving germline-directed treatment will increase as newer therapies are developed or as current agents are approved for additional tumor types. For example, as this study only analyzed patients sequenced before mid-2019, patients with *BRCA*-associated pancreatic and prostate cancer received PARP-I in a research setting. However, given the recent FDA approval of PARP-Is for advanced pancreatic and prostate cancer,[15,36,57] we anticipate an increase in germline genotype–directed treatment in these cancers. In fact, the delivery of the germline genotype–directed treatments correlated with FDA regulatory approval timelines; the highest frequency of PARP-I use was observed in patients with *BRCA*-associated ovarian cancer (nearly 90%), the tumor type for which PARP-I therapy was first approved in 2014. As germline-directed treatments are now being evaluated in early-stage cancers (ClinicalTrials.gov.identifier: NCT03499353, NCT02032823, etc), an increasing number of patients with cancer will receive genotype-directed therapies on the basis of the identification of potentially actionable germline alterations.

Our study also demonstrates that germline analysis may identify novel, previously unrecognized, genomically directed treatment opportunities for patients with advanced cancer. For example, although *PALB2* germline alterations are associated with increased susceptibility to pancreas and breast cancers, 47% of patients with LP/P *PALB2* germline variants who received a PARP-I had other cancers including prostate, ovary, and cancer of unknown primary. As more than half of patients with LP/P germline variants do not meet standard clinical criteria for genetic testing,[20] patients with advanced cancer may inadvertently be excluded from receiving germline-directed treatments if they are not evaluated for germline alterations. Indeed, in our group, $>$ 80% of *PALB2* carriers had no prior knowledge of their heritable and potentially actionable genetic alteration.

As the identification of a pathogenic germline alteration, even if unexpected, may have important treatment implications for patients with advanced cancer, a multigene approach to genetic analysis with incorporation of at least level 1 and 3B therapeutically actionable genes in this patient population seems reasonable. Further research into level 4 genes will be necessary to define the benefit of testing for such genes in patients with advanced cancer in need of systemic therapies. Although herein we focus on direct germline analysis, if tumor-only sequencing is performed, an alternative approach may be to perform reflex germline analysis of any tumor finding with potential germline relevance.

To our knowledge, our study is the first to use a precision oncology evidence-based knowledge base, OncoKB, and apply it in a systematic manner to categorize the therapeutic actionability of genes with germline alterations. There were unique challenges to this. We included

germline alterations in the DNA MMR genes, diagnostic of LS, as having targeted therapeutic actionability if, and only if, the tumor also exhibited an MSI-H/dMMR phenotype. The FDA has approved pembrolizumab for tumors with evidence of MSI-H or dMMR, and the presence of LS predicts for the development of such tumors, but not all cancers in patients with LP/P variants in LS genes are MSI-H tumors.[58] The special designation of variants such as level 1-MSI-H emphasizes that if a germline MMR gene alteration is identified in a patient with advanced cancer, tumor testing for MSI/dMMR must be undertaken before checkpoint inhibitor administration.

The distinction between genotype and phenotype in patients with Lynch syndrome also underscores the importance of integrating tumor and germline genomic information to fully understand the clinical implications of pathogenic germline variants. Further research is necessary to determine whether a germline variant alone is sufficient to induce response to germline genotype–directed treatments or if the tumor is driven by pathways unrelated to the variant, as suggested by the absence of biallelic inactivation and/or associated mutational signature. This is especially important for those genes involved in HRR, which are one of the most frequent germline findings in patients with cancer. Our study did not evaluate treatment response, inclusive of possible somatic genomic biomarkers of response; however, such studies are currently being conducted in specific cancer types and were previously assessed by our group in *BRCA*-associated tumors.[59]

Importantly, the predictive role of germline alterations in certain HRR genes remains an area of controversy. Although response to PARP-Is in *BRCA*-associated cancers has been demonstrated across many different cancer types, the efficacy of PARP-Is may be more modest in patients harboring other HRR gene alterations. For example, although both *CHEK2* and *ATM* alterations received a level 1 designation in metastatic prostate cancer because of the FDA approval of olaparib[15] and, thus, a level 3B designation in other cancer types, PARP-I response because of *ATM* and *CHEK2* alterations was not observed in other studies of patients with advanced prostate and breast cancer.[60,61] This highlights the need for precision OncoKBs to start to formally incorporate genes with germline alterations into their classification schemas with careful ongoing reassessment of evidence level assignments on the basis of research findings in specific cancer types.

This study has certain limitations. Although the sample size was large and included patients with a broad spectrum of cancer types, patients with lung cancer were underrepresented. If 15% of our ascertainment were lung cancer cases, on the basis of our somatic profiling of > 30,000 tumors (Data Supplement Fig 1A), and the prevalence of germline alterations in lung cancer is approximately 8%,[62] one may conservatively estimate that one half (approximately 4%) of these patients would have had OncoKB level 3B germline alterations. In this case, the prevalence of a germline variant with targeted therapeutic actionability would decrease in the entire somatic testing cohort from 9% to just over 8%. As expected, on the basis of population frequencies, the majority (53%) of germline alterations with therapeutic actionability were either in *BRCA1/2* or in the Lynch syndrome genes, suggesting that the impact of these results may be most pertinent to patients with these two more common cancer predisposition syndromes. As some patients in the cohort received treatment outside of our institution, it is possible that more patients actually received germline-directed treatment. Previously identified predictive associations of chemotherapy response with certain germline alterations were not considered in the total, such as platinum response in *BRCA1/2*-positive patients or in other genes associated with DNA damage repair pathways.[63] Although this study focused on patients with advanced cancer who usually receive multiple lines of therapy, germline-directed chemotherapy selection may be more pertinent in patients with early-stage cancer.

We demonstrate that germline genetic analysis has important implications for the management of patients with cancer beyond the risk reduction strategies most relevant to early-stage patients. With the increasing number of genes with germline alterations predictive of drug response and the proliferation of tumor agnostic basket trials assessing germline genotype–directed treatments, the tumor agnostic evaluation of patients with metastatic or recurrent cancer for potentially actionable germline alterations should be considered. On the basis of our study findings, using a multigene panel that incorporates *BRCA1/2* and other HRR genes, as well as the MMR genes, appears a reasonable undertaking for patients with metastatic or recurrent cancers. Future endeavors including standardized classification of the increasing number of germline alterations with therapeutic actionability and the impact of germline-directed therapies in patients with early-stage cancer are needed.

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Therapeutic Implications of Germline Testing in Patients with Advanced Cancers

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