Discussion | Our findings extend prior research in other settings[1-3] to support visible, innovative actions by oncology meeting organizers, including women's networking centers and facilitation of childcare services, as steps to ensure full participation of all those who might contribute or benefit at conferences.[4]

The primary limitations of this study are that the data were self-reported and respondents (55% response rate) might not be representative of the full population. We did not measure training institution or socioeconomic status (which may vary even in this high-earning population, creating unique challenges for some). The sample contained too few single parents to analyze separately. Confounding or reverse causation is possible. However, the findings suggest the possibility that facilitating attendance at national meetings might engage physicians in ways that may improve well-being and professional satisfaction.

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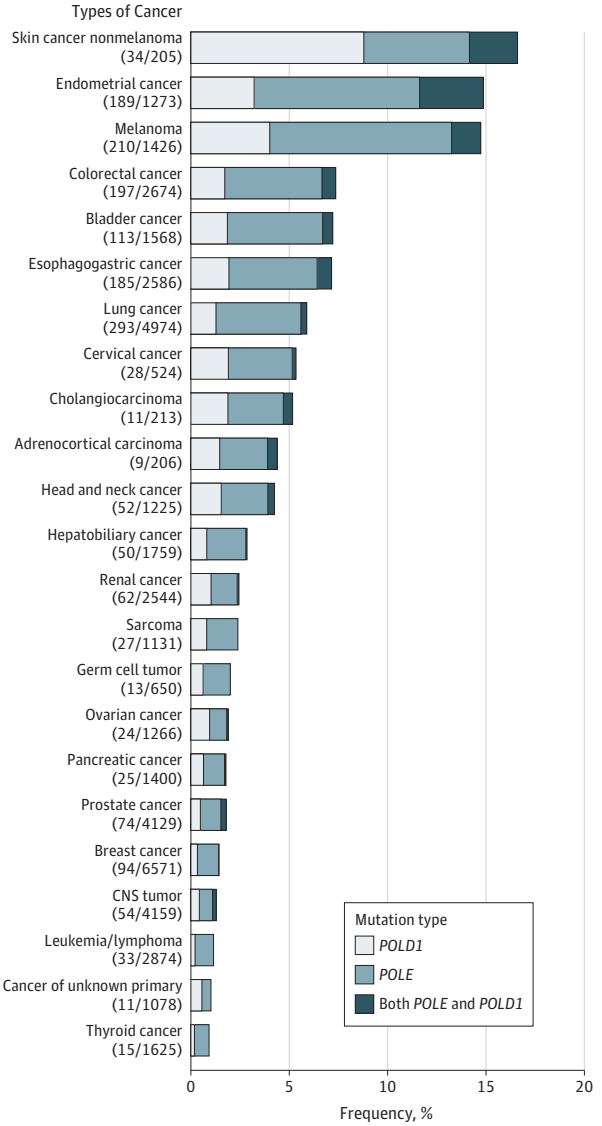
Evaluation of *POLE* and *POLD1* Mutations as Biomarkers for Immunotherapy Outcomes Across Multiple Cancer Types

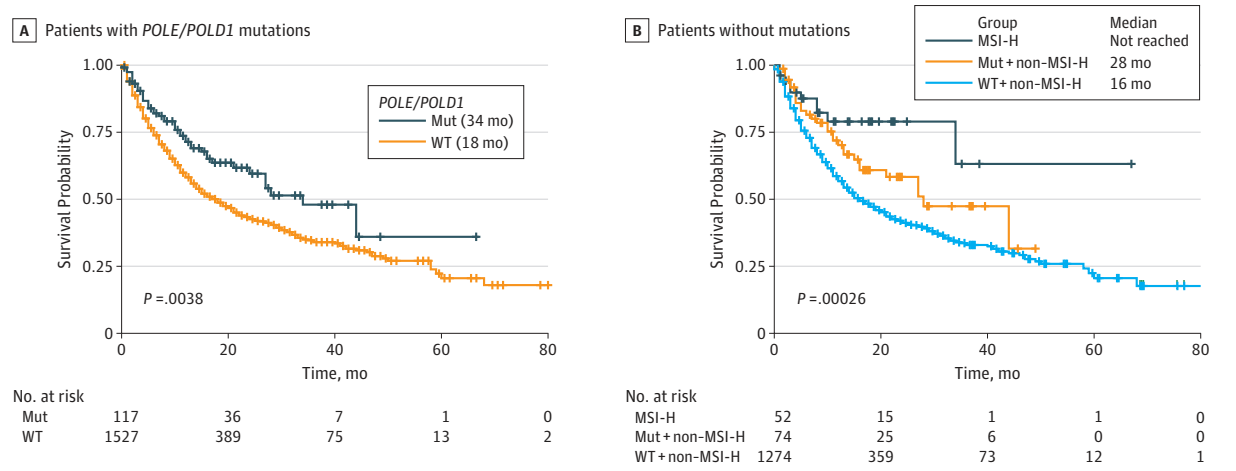
Immune-checkpoint inhibitor (ICI) therapy, including antibodies targeting programmed cell death protein 1(PD-1), programmed death-ligand 1 (PD-L1), or cytotoxic T-lymphocyte-associated protein 4 (CTLA4), has demonstrated impressive clinical efficacy in controlling advanced cancers. Recent studies have identified several positive predictive markers for ICI, including high levels of microsatellite instability (MSI-high), PD-L1 overexpression, and elevated tumor mutation burden (TMB).[1] The genes that encode DNA polymerase epsilon (*POLE*) and delta 1 (*POLD1*) are essential for proofreading and fidelity in DNA replication.[2] Their germline or somatic mutations can lead to DNA-repair deficiencies and carcinogenesis via a DNA

Figure 1. Prevalence of *POLE*/*POLD1* Mutations in 47 721 Patients With Different Cancer Types



CNS indicates central nervous system.

Figure 2. Overall Survival of Patients With *POLE*/*POLD1* Mutations vs Those Without or With MSI-H



MSI-H indicates patients who have high levels of microsatellite instability; Mut indicates patients with *POLE*/*POLD1* mutations; WT indicates patients without mutations.

hypermutated molecular phenotype.[3,4] An association between *POLE* or *POLD1* mutations and clinical benefit to ICI has been observed in several case reports.[5,6] However, to our knowledge, a comprehensive analysis of *POLE* or *POLD1* mutation frequency and their predictive value for ICI treatment outcome has not yet been reported. In this study, we conducted a combined analysis using a large data set and found that *POLE*/*POLD1* mutations are promising potential predictive biomarkers for positive ICI outcomes.

Methods | All the patients and mutation data were selected from the cBioPortal database (https://www.cbioportal.org). All nonsynonymous mutations including missense, frame-shift, nonsense, nonstop, splice site, and translation start site changes of *POLE*/*POLD1* were considered. To compare the tumor mutation burden (TMB) between different groups, a subset generated from MSK-IMPACT was selected to ensure the TMB could be comparable. The TMB was calculated with the total number of mutations divided by the number of bases in the target panel. For survival analysis, Kaplan-Meier survival curves were generated and compared using the log-rank test. All data were analyzed from December 25, 2018, to January 21, 2019. This study was deemed exempt from institutional board approval and patient informed consent was waived because all patient data were deidentified.

Results | The prevalence of *POLE*/*POLD1* mutations in 47 721 patients with different cancer types is summarized in **Figure 1**, with patients with nonmelanoma skin cancer having the highest levels of *POLE*/*POLD1* mutations (16.59%). Across all 47 721 patients, the mutational frequencies of *POLE* and *POLD1* were 2.79% and 1.37%, respectively. The TMB of patients with these mutations was substantially higher than in those without the mutations in most of the cancer types.

We further investigated the association between *POLE*/*POLD1* mutations and overall survival (OS) in the ICI treatment cohort.[1] As shown in **Figure 2**, patients with either *POLE* or *POLD1* mutations showed a significantly longer OS of 34 months vs 18 months in the wild-type population (log-rank test, $\chi^2 = 8.4$; $P = .004$). Seventy-four out of 100 patients with *POLE*/*POLD1* mutations were microsatellite stable (MSS) or had low levels of microsatellite instability (MSI-L). When cancer types and MSI status were adjusted for a multivariable Cox regression analysis, *POLE*/*POLD1* mutations were an independent risk factor for identifying patients who benefited from ICI treatment ($P = .047$; hazard ratio, 1.41; 95% CI, 1.00-1.98). Analysis of *POLE*/*POLD1* mutations could identify patients who can benefit from ICI treatment besides those with MSI-H (Figure 2). No significant differences in OS were observed between patients with MSI-H and those patients with *POLE*/*POLD1* mutations who were non-MSI-H. Notably, the patients with *POLE* exonuclease domain mutation or with other mutations showed no difference in levels TMB or OS.

Discussion | From a cohort of 47 721 patients with different types of cancer, a high frequency of *POLE*/*POLD1* mutations were observed not only in endometrial cancer and colorectal cancer, but also skin cancer, esophagogastric cancer, bladder cancer, lung cancer and others. We also observed that *POLE* or *POLD1* mutations were a negative prognostic marker and might be used to predict a survival benefit from ICI therapy across diverse cancer types. Nonsynonymous mutations in *POLE*/*POLD1* not found in the exonuclease domain had similar associations with the OS of patients receiving ICI treatment, suggesting that mutations in all exons of these 2 genes should be integrated into predictive biomarker panels for ICI therapy. Based on these data and rationale, we have initiated a phase 2 clinical trial for patients with solid cancer and *POLE*/*POLD1* mutations who are non-MSI-H to test the treatment outcomes of toripalimab, a PD1 antibody.

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Correction: This article was corrected on September 12, 2019, to fix an error in the number at risk table of Figure 2B.

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Acquisition, analysis, or interpretation of data: All authors.
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Pathogenic Germline Variants in Patients With Metastatic Breast Cancer

There is still considerable debate on the value of multigene panel testing for inherited cancer in patients with breast cancer, based on both the prevalence of pathogenic/likely pathogenic (P/LP) variants and any therapeutic implications from genetic test results. Recent studies demonstrate that the prevalence of P/LP variants is similar in patients with breast cancer whether or not they meet critera for testing by the National Comprehensive Cancer Network (NCCN) guidelines.[1,2] However, most participants in these studies were patients with early stage breast cancer and many low-risk variants were identified, raising the question of clinical actionability. The recent US Food and Drug Administration (FDA) approval of polyadenosine diphosphate–ribose polymerase (PARP) inhibitors for patients with metastatic human epidermal growth factor receptor 2 (*HER2*/*ERBB2*)-negative breast cancer with germline *BRCA1* and *BRCA2* (*BRCA*) pathogenic variants,[3,4] suggests germline testing of patients with metastatic breast cancer could have therapeutic implications. Indeed, a recent study found 11.8% of otherwise unselected patients with metastatic prostate cancer harbored a P/LP germline variant,[5] leading to a change in NCCN guidelines recommending germline testing for all patients with metastatic prostate cancer. However, to our knowledge, analogous studies to quantify the prevalence of P/LP variants among patients with metastatic breast cancer have not been performed.

Methods | In a Johns Hopkins institutional review board approved study, we prospectively enrolled 100 patients diagnosed with metastatic breast cancer and performed germline

Table 1. Demographics of Patient Cohort

Characteristic	Patients, No.
Age at time of, median (SD), y	
Consent	59 (12.0)
Initial diagnosis of breast cancer	49 (11.6)
Diagnosis of metastatic disease[a]	56 (11.9)
Race	
White	76
Black	12
Asian	6
Hispanic	3
Other	3
Receptor status	
HR-positive/*HER2*/*ERBB2*-negative[b]	66
TNBC	13
HR-positive/*HER2*/*ERBB2*-positive	13
HR-negative/*HER2*/*ERBB2*-positive	8

Abbreviations: *HER2*/*ERBB2*, Human Epidermal Growth Factor Receptor 2; HR, hormone receptor; TNBC, triple negative breast cancer.

[a] Unknown for 5 patients.

[b] Includes 2 male patients.