10 PD events were colon and prostate cancer, which were also unrelated to earlier PD (Table 2).

Discussion | Both cancer and PD occur primarily at advanced ages and can be debilitating. Consequently, medical surveillance for cancer could be influenced by a prior PD diagnosis, which may bias the observed PD-cancer associations. Moreover, patterns of medical surveillance may differ by health care system (eg, US Medicare and Taiwan National Health Insurance Research Database). It is therefore important that in evaluating PD-cancer associations investigators adjust for medical surveillance and include negative controls.

Although we cannot rule out small risks attributable to sample size, we did not find a positive association between PD and subsequent cancer in Asian Americans in SEER-Medicare data. Although according to SEER-Medicare data Asian Americans are ethnically more diverse than the Taiwanese population, our null findings do not support the hypothesis that ethnicity is a major contributor to the elevated risk in the study by Lin et al.4 The elevated risks observed in the study by Lin et al4 could reflect various factors, including possibly more cancer surveillance after PD.

D. Michal Freedman, PhD, MPH
Ruth M. Pfeiffer, PhD

Author Affiliations: Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Rockville, Maryland.

Corresponding Author: D. Michal Freedman, PhD, MPH, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, 9609 Medical Center Dr, 7E538, Rockville, MD 20850 (freedman@mail.nih.gov).

Published Online: May 19, 2016. doi:10.1001/jamaoncol.2016.0729.

Author Contributions: Drs Freedman and Pfeiffer had full access to all the data in the study and takes responsibility for the integrity of the data and the integrity of the data analysis.

Study concept and design: Both authors.

Acquisition, analysis, or interpretation of data: Both authors.

Drafting of the manuscript: Both authors.

Critical revision of the manuscript for important intellectual content: Both authors.

Statistical analysis: Pfeiffer.

Conflict of Interest Disclosures: None reported.

Funding/Support: This work was supported by the Intramural Research Program of the National Cancer Institute, National Institutes of Health, and the US Public Health Service.


Clinical Validation of Chemotherapy Response Biomarker ERCC2 in Muscle-Invasive Urothelial Bladder Carcinoma

Neoadjuvant cisplatin-based chemotherapy (NACC) is a standard of care for muscle-invasive urothelial bladder carcinoma (MIBC), and complete responses at cystectomy are associated with improved overall survival. Somatic mutations in ERCC2, a member of the nucleotide excision repair pathway, correlated with pathologic response in a clinical discovery cohort and conferred cisplatin sensitivity in preclinical systems.3 Herein, we investigate this association in an independent validation patient cohort.

Methods | Samples were identified from patients with MIBC (at least stage T2 disease) from 2 clinical trials of NACC2,3 who completed chemotherapy and had available prechemotherapy tumor tissue. Tumor samples from this cohort previously underwent targeted gene panel sequencing2 (which did not include ERCC2). We performed whole exome sequencing of tumor and matched germline DNA. Analysis and automated variant calls were performed as previously described.1 Quality control included minimum average read coverage, DNA fingerprinting, and contamination estimation. For this validation study, only ERCC2 results were exposed from the automated data output. All putative somatic ERCC2 mutations were manually reviewed.4

A 2-sided Fisher exact test was used to test association between ERCC2 alteration and response, and P < .05 was used as the threshold for significant results. Response was defined as pT0/pTis/pTa disease at cystectomy. Overall survival from time of cystectomy was estimated using Kaplan-Meier curves and association with ERCC2 alteration tested using a log-rank test in the current validation cohort and the original discovery cohort.1

All patients were enrolled on institutional review board-approved protocols at their respective sites and provided written informed consents. They were not compensated for their participation.

Results | Of 62 patients who received all 3 cycles of chemotherapy, 55 had adequate tissue for sequencing. After quality control, 7 samples were excluded, leaving samples from 48 patients for analysis. Ten patients harbored nonsynonymous ERCC2 genetic alterations. ERCC2 was associated with response to therapy: 8 of 20 responders (40%) and 2 of 28 nonresponders (7%) had a nonsynonymous ERCC2 genetic alteration (odds ratio, 8.3; 95% CI, 1.4-91.4; P = .01). In follow-up, 17 patients had disease progression and 15 died; there was a statistically significant difference in overall survival among patients with ERCC2 alterations in both the current validation cohort (P = .03) (Figure, A) and in the discovery cohort1 (P = .049) (Figure, B).

Discussion | In this study we validate the relationship between ERCC2 alteration and response to NACC in an independent MIBC cohort. ERCC2 is the helicase that unwinds DNA for repair via the nucleotide excision repair pathway, which is important for repair of platinum-induced DNA damage. This
provides a biologically plausible mechanism for loss-of-function mutations leading to cisplatin sensitivity.

Preclinical studies have associated ERCC2 loss-of-function with cisplatin sensitivity.\(^1\) While wild-type ERCC2 cloned into an ERCC2-null cell line rescued its cisplatin-sensitive phenotype, clinically identified ERCC2 mutations introduced into the same line failed to correct the sensitivity.\(^1\) Taken together with findings from the current study, the evidence strongly suggests that alterations in ERCC2 confer vulnerability to cisplatin chemotherapy.

ERCC2 as a biomarker has limitations; while it substantially increases the odds of a complete or near-complete response and improved survival, it is not 100% specific. In non-responders, ERCC2 mutations are in the same (peri-)helicase regions as in responders. Furthermore, ERCC2 alterations are found only in 40% of responders, suggesting other factors affect NACC sensitivity. In the same cohort tested in the present study, the 3-gene signature (ATM, RB1, FANCC; all genes associated with DNA repair) predicted platinum response and survival\(^2\) and may be complementary. Further characterization of specific ERCC2 mutations to improve specificity and development of a more sensitive integrated panel of DNA repair biomarkers may inform clinical decision-making. Broadly, these findings inform the convergence of precision cancer medicine approaches with conventional chemotherapy.

David Liu, MD, MPH, MS
Elizabeth R. Plimack, MD, MS
Jean Hoffman-Censits, MD
Levi A. Garraway, MD, PhD
Joaquim Bellmunt, MD, PhD
Eliezer Van Allen, MD
Jonathan E. Rosenberg, MD

Author Affiliations: Dana-Farber Cancer Institute, Boston, Massachusetts (Liu, Garraway, Bellmunt, Van Allen), Fox Chase Cancer Center, Philadelphia, Pennsylvania (Plimack); Broad Institute of Harvard and Massachusetts Institute of Technology, Cambridge (Garraway, Van Allen); Thomas Jefferson University Hospital, Philadelphia, Pennsylvania (Hoffman-Censits); Memorial Sloan Kettering Cancer Center, New York, New York (Rosenberg).

Corresponding Author: Jonathan E. Rosenberg, MD, Sidney Kimmel Center for Prostate & Urologic Cancer, Memorial Sloan Kettering Cancer Center, 353 E 68th St, New York, NY 10065 (rosenbj1@mskcc.org).


Author Contributions: Drs Van Allen and Rosenberg had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis, and contributed equally to the research. Drs Plimack and Liu are co-first authors.

Study concept and design: Liu, Plimack, Van Allen, Rosenberg.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Liu, Plimack, Van Allen, Rosenberg.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Liu, Van Allen.

Obtained funding: Plimack, Garraway, Van Allen, Rosenberg.

Administrative, technical, or material support: Plimack, Hoffman-Censits, Bellmunt, Van Allen.

Study supervision: Bellmunt, Van Allen, Rosenberg.

Conflict of Interest Disclosures: Drs Van Allen, Garraway, and Rosenberg have ownership interest in a patent (pending) for use of ERCC2 mutational status as a clinical biomarker. Dr Plimack has ownership interest in a patent (pending) for use of an ATM-, RB1-, and FANCC-based DNA repair mutation signature as a clinical biomarker. No other disclosures are reported.

Funding/Support: This work was supported by the John R. Svenson Fellowship (Dr Liu), the Starr Cancer Consortium (Drs Garraway and Rosenberg), the Damon Runyon Clinical Investigator Award (Dr Van Allen), the Geoffrey Beene Center (Dr Rosenberg), and the National Institutes of Health/National Cancer Institute Cancer Center Support grant P30 CA08748 (Dr Rosenberg).

Role of Funder/Sponsor: The funding sources played no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Early Intervention in Lung Cancers With Rapid Plasma Genotyping for EGFR and KRAS Mutations

To the Editor Sacher and colleagues are to be congratulated on demonstrating the specificity (high) and sensitivity (not so great) of the droplet digital polymerase chain reaction technology. Of the 2 cohorts of epidermal growth factor receptor (EGFR)-mutant patients tested, the second cohort had already developed resistance (presumably diagnosed on radiological progression) and is by definition enriched for higher levels of (new) mutations. How would this test perform if patients were routinely monitored after starting first-line EGFR tyrosine kinase inhibitor treatment, before the development of resistance? Patients with chronic myeloid leukemia are tested for evidence of resistance at the molecular level at time points in their natural history, without waiting for features of overt resistance (such as alterations in peripheral blood cell counts, organomegaly, or symptoms) to appear. Early detection and intervention is arguably one of the reasons for the high survival rates achieved in this cancer. BCR-ABL translocation in chronic myeloid leukemia and EGFR mutation in a subset of lung cancers are similar in their driver functions. Regular monitoring and early intervention (without waiting for radiographic progression, by which time multiple other mutations would have developed) should be feasible in mutant lung cancers if the test is sensitive enough. Looking forward, a paradigm shift toward routine monitoring in patients with lung (and other solid) tumors carrying identifiable sensitizing mutations should encourage development of more sensitive tests and newer drugs and, with hope, to improved survival.

Ajit Venniyoor, MD, DM

Author Affiliation: National Oncology Center, Royal Hospital, Muscat, Sultanate of Oman.

Corresponding Author: Ajit Venniyoor, MD, DM, National Oncology Center, Royal Hospital, PB No. 1331, Muscat 111, Sultanate of Oman (jvenniyoor@gmail.com).


In Reply We appreciate the interest of Dr Venniyoor in monitoring plasma cell-free DNA (cfDNA) for evidence of resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in patients with EGFR-mutant lung cancer. The available data suggest that plasma genotyping can be a component of treatment selection in patients with metastatic non–small-cell lung cancer, but we also recognize the potential for serial assessment to be used to identify the emergence of acquired resistance mutations. In our recently published validation, we enrolled patients known to have clinical evidence of acquired resistance, but we have previously reported that it is often possible to detect resistance mutations weeks or months prior to objective progression during EGFR TKI treatment. Nonetheless, routine detection of tumor-derived cfDNA in plasma prior to clinical evidence of resistance may be challenging due to lower disease volume and lower metastatic potential, features that likely predict for lower tumor cfDNA shed and assay sensitivity.

For such resistance monitoring to be adopted clinically, it must also be shown that changing treatment early on the basis of the detection of a resistance mutation in plasma will improve long-term outcomes in EGFR-mutant lung cancer. In some patients with acquired resistance to EGFR TKIs, resistance emerges gradually and delaying treatment change is routine. Because resistance can be heterogeneous, early treatment of one resistance mechanism (eg, EGFR T790M) may favor the emergence of an alternate, more aggressive resistant clone, which could paradoxically produce worse clinical outcomes. We do not believe that the available data support changing therapy on the basis of resistance detected in plasma cfDNA in the absence of clinical evidence of resistance. As such, we urge careful study of this practice in patients with non–small-cell lung cancer before adoption on the basis of extrapolations from hematological neoplasms.

Adrian G. Sacher, MD
Ryan S. Alden, BA
Geoffrey R. Oxnard, MD

Author Affiliations: Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts (Sacher, Alden, Oxnard); Brigham and Women’s Hospital and Harvard Medical School, Boston, Massachusetts (Sacher, Oxnard); Columbia University/New York-Presbyterian Hospital, New York, New York (Sacher).

Corresponding Author: Geoffrey R. Oxnard, MD, Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, 450 Brookline Ave, Boston, MA 02215 (geoffrey.oxnard@dfci.harvard.edu).

Conflict of Interest Disclosures: Dr Sacher has received travel funding from AstraZeneca and Genentech-Roche. Dr Oxnard is an inventor on a pending patent related to findings described in this manuscript; is a consultant/advisory board member for Ariad, AstraZeneca, Boehringer Ingelheim, Celox Oncology, and Sysmex; and has received honoraria from AstraZeneca, Boehringer Ingelheim, and Chugai. No other disclosures are reported.

