prices online so that patients could plan for costs. As treatment may span months and unexpected costs have been reported to be associated with decreased willingness to pay, high parking costs may be a source of financial toxicity to patients and caregivers and ultimately interfere with cancer care.

Previous research has found that transportation was the single highest out-of-pocket nonmedical cost for patients with cancer receiving treatment. The negative economic and psychological consequences of parking fees have been consistently noted in qualitative studies of patients with cancer and families. Because travel costs including parking may become a barrier to patients receiving optimal care, a 2017 study has specifically suggested subsidized parking as a way to ameliorate economic burden.

Study limitations include the potential inaccuracy of costs collected via telephone, as the center staff contacted may not have had the full information or costs may have since changed. Estimated costs were conservative and did not incorporate extra trips for consultation, imaging procedures, or laboratory tests.

This study found high variability in costs with the potential for patients to pay hundreds of dollars in parking to receive cancer care. Efforts to minimize financial toxicity may benefit from a focus on this potentially underreported patient concern.

Anna Lee, MD, MPH
Kanan Shah, BS
Fumiko Chino, MD

Author Affiliations: Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, New York (Lee, Chino); New York University Grossman School of Medicine, New York, New York (Shah).

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Corresponding Author: Fumiko Chino, MD, Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, 1275 York Ave, PO Box 33, New York, NY 10065 (chinof@mskcc.org).

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Association of Impaired Spermatogenesis With the Use of Immune Checkpoint Inhibitors in Patients With Metastatic Melanoma

The emergence of immune checkpoint inhibitors (ICIs) has provided previously unachievable curative therapy for many patients, particularly those with metastatic melanoma. However, the long-term outcomes for patients using ICIs are only beginning to be investigated. One important potential unexplored adverse effect is impaired male fertility. The current American Society of Clinical Oncology guidelines (July 2018) state that “sperm cryopreservation is effective, and health care providers should discuss sperm banking with postpubertal males receiving cancer treatment.” The direct association of ICI treatment with spermatogenesis has not been explored, to our knowledge. It will be critical to determine the risk to future male fertility for patients undergoing ICI therapy to accurately guide pretreatment counseling. To address the association between the potential gonadotoxic effect of ICIs and spermatogenesis, to our knowledge, we performed the first retrospective review of an index patient who became infertile after ICI therapy and subsequently died, and we performed a retrospective cohort cadaver study of patients with metastatic melanoma.

Methods | We queried the Johns Hopkins Pathology database (January 1, 1985, through December 31, 2016) for untreated patients and the Johns Hopkins Legacy Gift Rapid Autopsy database (January 1, 2013, through December 31, 2016) for patients with a history of metastatic melanoma treated using immunotherapy for more than 1 month (ipilimumab, nivolumab, or pembrolizumab). Tissue specimens of the testes were retrospectively examined from deceased patients for whom autopsies were performed. Patients who had received systemic chemotherapy or radiotherapy to the thorax, abdomen, pelvis, or lower extremities were excluded. We obtained approval from the Johns Hopkins Hospital institutional review board for review of pathologic samples under a consent waiver.

A proportioned control cohort was matched for age at tissue acquisition. Control samples came from men with a history of metastatic melanoma who had never undergone immunotherapy, chemotherapy, or radiotherapy to the thorax, abdomen, pelvis, or lower extremities between January
1, 1986, and December 31, 2016. For each patient, data on demographic characteristics, time from death to autopsy, treatment history, type of immunotherapy, and duration of therapy were recorded.

Autopsy and biopsy tissues were fixed in 10% buffered formalin within 24 hours after death. The testicular pathology slides were stained with hematoxylin-eosin and observed under light microscopy by a blinded independent genitourinary

### Table. Characteristics and Testicular Morphologic Conditions of Patients With Metastatic Melanoma With or Without Immunotherapy Treatment

<table>
<thead>
<tr>
<th>Age at diagnosis, y</th>
<th>Age at death, y</th>
<th>Postmortem interval, h</th>
<th>Immunotherapy</th>
<th>Duration of immunotherapy, mo</th>
<th>Other agents</th>
<th>Spermatogenesis pathological diagnosis</th>
<th>Johnsen scoring*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late 20s</td>
<td>Early 30s</td>
<td>2</td>
<td>Ipilimumab and pembrolizumab</td>
<td>4</td>
<td>BRAF and MEK inhibitors</td>
<td>Sertoli cell only</td>
<td>2</td>
</tr>
<tr>
<td>60s</td>
<td>60s</td>
<td>15</td>
<td>Ipilimumab and nivolumab</td>
<td>18</td>
<td>Cyberknife radiotherapy and vemurafenib</td>
<td>Sertoli cell only</td>
<td>2</td>
</tr>
<tr>
<td>Early 30s*</td>
<td>30s</td>
<td>NA</td>
<td>Ipilimumab and nivolumab</td>
<td>Unknown</td>
<td>None</td>
<td>Sertoli cell only</td>
<td>2</td>
</tr>
<tr>
<td>50s</td>
<td>Late 50s</td>
<td>5</td>
<td>Ipilimumab and pembrolizumab</td>
<td>8</td>
<td>Interleukin 2</td>
<td>Hypospermatogenesis</td>
<td>8</td>
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<td>60s</td>
<td>60s</td>
<td>17</td>
<td>Ipilimumab and nivolumab</td>
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<td>None</td>
<td>Hypospermatogenesis</td>
<td>8</td>
</tr>
<tr>
<td>Early 60s</td>
<td>60s</td>
<td>6</td>
<td>Ipilimumab and nivolumab</td>
<td>5</td>
<td>None</td>
<td>Focal active spermatogenesis</td>
<td>9</td>
</tr>
<tr>
<td>50s</td>
<td>Late 50s</td>
<td>4</td>
<td>Ipilimumab and nivolumab</td>
<td>11</td>
<td>Dabrafenib and trametinib</td>
<td>Normal spermatogenesis</td>
<td>10</td>
</tr>
<tr>
<td>Early 50s</td>
<td>Early 50s</td>
<td>24</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Sertoli cell only</td>
<td>2</td>
</tr>
<tr>
<td>Late 70s</td>
<td>80s</td>
<td>6</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Sertoli cell only</td>
<td>2</td>
</tr>
<tr>
<td>20s</td>
<td>20s</td>
<td>5</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Normal spermatogenesis</td>
<td>10</td>
</tr>
<tr>
<td>40s</td>
<td>Early 50s</td>
<td>5</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Normal spermatogenesis</td>
<td>10</td>
</tr>
<tr>
<td>40s</td>
<td>50s</td>
<td>24</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Normal spermatogenesis</td>
<td>10</td>
</tr>
<tr>
<td>Late 60s</td>
<td>Late 60s</td>
<td>6</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Normal spermatogenesis</td>
<td>10</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.

* Index patient.
pathologist (A.M.). Testicular histopathologic conditions were diagnosed for each individual, and the degree of spermatogenesis was quantified using the约翰sen scoring system.4 Owing to the restrictive sample size, we present descriptive data on testicular pathologic conditions. Statistical analysis was performed from February 21, 2018, to December 12, 2019. Comparisons between cohorts for age at diagnosis, age at death, and time to autopsy were performed using a Mann-Whitney test using Prism, version 8 (GraphPad Software, Inc).

Results | We queried more than 10 000 potential participants and identified a total of 13 men (median age, 54 years [range, 23-78 years]) with metastatic melanoma who had testicular autopsy tissue specimens available. Of these, 7 underwent immunotherapy and 6 were treatment naive. There was no difference between groups for age at diagnosis, age at death, and time to autopsy (Table). Six of the 7 men (86%) with metastatic melanoma who received ICI therapy had impaired spermatogenesis, including focal active spermatogenesis (n = 1), hypospermatogenesis (n = 2), and Sertoli-cell-only syndrome (n = 3). Two of the 6 men (33%) who were untreated had impaired spermatogenesis (Figure). We did not identify any increased peritubular hyalinization or fibrosis in the treated group, and there were no Leydig cell abnormalities noted in any patients.

Discussion | Fertility preservation is an important facet in the care of men with cancer who are within their reproductive years.5,6 One key to improving cancer survivorship and quality of life is to anticipate potential treatment-associated sequelae. Identifying the association of ICIs with future fertility will be an important step in determining whether male fertility preservation is an essential component to pretreatment counseling. A limitation of our study was the small sample size. To our knowledge, the data herein are the first to evaluate the association of ICIs with testicular function, but prospective evaluations will be essential to determining the gonadotoxic effect of ICIs.

Jason M. Scovell, MD, PhD
Karl Benz, MD
Iryna Samarska, MD, PhD
Taylor P. Kohn, MD
Jody E. Hooper, MD
Andres Matoso, MD
Amin S. Herati, MD

Author Affiliations: Scott Department of Urology, Baylor College of Medicine, Houston, Texas (Scovell); Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, Ohio (Scovell); James Buchanan Brady Urological Institutions, The Johns Hopkins Medical Institutions, Baltimore, Maryland (Benz, Kohn, Herati); Department of Pathology, The Johns Hopkins Medical Institutions, Baltimore, Maryland (Samarska, Hooper, Matoso).

Corresponding Author: Amin S. Herati, MD, James Buchanan Brady Urological Institutions, The Johns Hopkins University School of Medicine, 4940 Eastern Ave, 301 Bldg, Ste 3100, Baltimore, MD 21224 (herati@jhmi.edu).

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Author Contributions: Dr Herati had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Scovell, Benz, Matoso, Herati. Acquisition, analysis, or interpretation of data: Scovell, Benz, Samarska, Kohn, Hooper, Herati. Drafting of the manuscript: Scovell, Benz, Samarska, Kohn, Herati. Critical revision of the manuscript for important intellectual content: Benz, Hooper, Matoso, Herati. Statistical analysis: Scovell, Benz, Samarska, Kohn, Herati. Administrative, technical, or material support: Samarska, Hooper. Supervision: Matoso, Herati.

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COMMENT & RESPONSE

High-Dose Chemotherapy With Hematopoietic Stem Cell Transplant in Patients With High-Risk Breast Cancer

To the Editor Steenbruggen et al1 shared a 20-year follow-up of a phase 3 randomized clinical trial of high-dose chemotherapy (HDCT) with hematopoietic stem cell transplant in patients with high-risk breast cancer and 4 or more involved axillary lymph nodes. The authors’ conclusion suggests that selected subgroups may benefit from this treatment, highlighting a 14.6% improvement in 20-year overall survival estimates with HDCT in the predefined subgroup for patients with 10 or more involved axillary lymph nodes. The authors are to be commended for their efforts in reporting the long-term results of this trial. However, the conclusions generate questions in both statistical interpretation and generalized application.

First, the use of subgroup analysis in an isolated trial best represents a snapshot of the heterogeneity of a study and means to examine if the intervention effect differs between subgroups, rather than the magnitude of the intervention within the subgroup, which requires higher statistical power. Challenges of subgroup analysis, especially in a single clinical trial rather than a meta-analysis, introduce misleading, underpowered results and should always be interpreted with

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