sent an imminent risk to the vulnerable residents in their care. A recent Biden administration initiative that would make federal funding for nursing homes contingent on the vaccination of their employees is an important step.[2]

Certified nursing assistants work extremely hard and have an immense positive influence on the care of nursing home residents. In general, CNAs are sorely underpaid and receive inadequate benefits, including sick leave.[3] We believe low voluntary vaccination rates among CNAs suggests a failure of nursing home owners to effectively partner with their most essential workers and provides one more indication of the need to improve the pay and working conditions of this group.

Eric Ward, MD
Kenneth E. Covinsky, MD, MPH

Author Affiliations: Department of Medicine, University of California, San Francisco (Ward); Editorial Fellow, *JAMA Internal Medicine* (Ward); Division of Geriatrics, Department of Medicine, University of California, San Francisco (Covinsky); Associate Editor, *JAMA Internal Medicine* (Covinsky).

Published Online: September 16, 2021. doi:10.1001/jamainternmed.2021.5897

Corresponding Author: Eric Ward, MD, Department of Medicine, University of California, San Francisco, 505 Parnassus Ave, Room M-1480, San Francisco, CA 94143 (eric.ward@ucsf.edu).

Conflict of Interest Disclosures: Dr Covinsky reported receiving grants from the National Institute on Aging. No other disclosures were reported.

1. McGarry BE, Shen K, Barnett ML, Grabowski DC, Gandhi AD. Association of nursing home characteristics with staff and resident COVID-19 vaccination coverage. *JAMA Intern Med*. Published online September 16, 2021. doi:10.1001/jamainternmed.2021.5890

2. President Biden to announce new actions to protect Americans from COVID-19 and help state and local leaders fight the virus. News release. The White House. August 18, 2021. Accessed September 2, 2021. https://www.whitehouse.gov/briefing-room/statements-releases/2021/08/18/fact-sheet-president-biden-to-announce-new-actions-to-protect-americans-from-covid-19-and-help-state-and-local-leaders-fight-the-virus/

3. Van Houtven CH, DePasquale N, Coe NB. Essential long-term care workers commonly hold second jobs and double- or triple-duty caregiving roles. *J Am Geriatr Soc*. 2020;68(8):1657-1660. doi:10.1111/jgs.16509

HEALTH CARE POLICY AND LAW

Estimated Medicare Spending on Cancer Drug Indications With a Confirmed Lack of Clinical Benefit After US Food and Drug Administration Accelerated Approval

The accelerated approval (AA) pathway expedites the market entry of new drugs by allowing the US Food and Drug Administration (FDA) to grant approval using surrogate end points (eg, progression-free survival) that are "reasonably likely" to predict clinical benefit (eg, overall survival [OS]).[1] Drug manufacturers are required to confirm clinical benefit after approval.

Since December 2020, the FDA has reevaluated 10 AA indications with a confirmed lack of OS benefit of 4 drugs used to treat cancer: atezolizumab (breast and urothelial [cisplatin-ineligible and cisplatin-eligible] cancer), durvalumab (urothelial cancer), nivolumab (hepatocellular and lung cancer), and pembrolizumab (gastric, hepatocellular, lung, and urothelial cancer). This reevaluation resulted in voluntary manufacturer withdrawals of atezolizumab for urothelial cancer, durvalumab for urothelial cancer, and nivolumab and pembrolizumab for lung cancer.[2] In April 2021, the FDA Oncologic Drugs Advisory Committee (ODAC) considered the approval status of the 6 remaining AA indications. The ODAC members voted to withdraw 2 indications (pembrolizumab for gastric cancer and nivolumab for hepatocellular cancer), and they cited poor trial designs and the lack of other treatment options as reasons for retaining the remaining 4 indications (atezolizumab for breast and urothelial [cisplatin-ineligible] cancer and pembrolizumab for hepatocellular and urothelial cancer).[3] Although the FDA is not obliged to follow ODAC recommendations, it typically does so.

Related articles pages 1596 and 1605

Supplemental content

In this study, we estimated Medicare spending on the 10 AA cancer drug indications reevaluated by the FDA in 2021, all of which have a confirmed lack of OS benefit.[4]

Methods | We extracted aggregated annual spending for atezolizumab, durvalumab, nivolumab, and pembrolizumab from the Medicare Part B and Part D Drug Spending Dashboards for 2017 to 2019. Medicare spending data do not include information on indications. To estimate spending shares for relevant indications in each year, we extracted medical and pharmacy claims for each drug in each year among the Medicare Advantage (MA) population covered by a large US insurer from OptumInsight Clinformatics data. Medicare Advantage data include diagnosis codes with inpatient, outpatient, and pharmacy claims. We used MA claims to calculate relative annual proportions of claims with relevant indication-specific *International Statistical Classification of Diseases, Tenth Revision* codes and treatment histories after the relevant indication approval dates. We then applied annual indication shares in the MA population to annual Medicare Part B and Part D spending. We used the consumer price index for prescription drugs to adjust annual spending estimates to 2020 US dollars. See eFigures 1 and 2 and the eTable in the Supplement for details on our analytic strategy.

This exploratory study was approved by the Harvard Pilgrim Health Care Institutional Review Board. Because we used publicly available data or deidentified claims data, this study was determined to not constitute human participants research by the Harvard Pilgrim Health Care Institutional Review Board and thus did not require informed consent.

Results | Estimated monthly Medicare drug reimbursement ranged from approximately $9850 to $13 400 in 2019 based on the 2019 average sales price (**Table**). Between 2017 and 2019, Medicare spending on the 10 AA indications increased to an estimated inflation-adjusted $569 million, of which $171 million corresponded to indications voluntarily withdrawn by manufacturers and $398 million corresponded to indications reevaluated by the FDA (**Figure**). The 4 indications that ODAC voted to retain accounted for $345 million.

Discussion | Between 2017 and 2019, Medicare Parts B and D cumulatively spent at least $569 million on the 10 cancer drug indications with a confirmed lack of OS benefit after

Table. Indications, Approval Dates, Treatment Costs, and Approval Status of Cancer Drug Indication Pairs

Drug and indication (indication approval date)[a]	Dosage, mg	Monthly drug cost based on 2019 ASP, US$[b]	Indication approval status[c]
Atezolizumab			
To treat adult patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or after any platinum-containing chemotherapy or within 12 mo after receiving neoadjuvant or adjuvant chemotherapy (5/18/16)	840 Every 2 wk, 1200 every 3 wk, or 1680 every 4 wk[d]	1680 mg × 77.3/10 mg = 12 936	Voluntary withdrawal (announced 3/8/21)
To treat adult patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 or are not eligible for any platinum-containing chemotherapy, regardless of PD-L1 status (4/17/17)	840 Every 2 wk, 1200 every 3 wk, or 1680 every 4 wk[d]	1680 mg × 77.3/10 mg = 12 936	IMvigor130 trial results were discussed in September 2019. The ODAC voted to maintain indication, so the FDA is unlikely to take any further action
Combined with protein-bound paclitaxel to treat adult patients with unresectable locally advanced or metastatic triple-negative breast cancer whose tumors express PD-L1 (3/8/19)	840, Followed by 100 mg/m^2 protein-bound paclitaxel. For each 28-d cycle, atezolizumab is administered on days 1 and 15, and protein-bound paclitaxel is administered on days 1, 8, and 15[d]	1680 mg × 77.3/10 mg = 12 936	Impassion131 trial results were discussed on 9/19/20. The ODAC voted to maintain indication, so the FDA is unlikely to take any further action
Durvalumab			
To treat adult patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or after platinum-containing chemotherapy or within 12 mo after receiving neoadjuvant or adjuvant treatment with platinum-containing chemotherapy (5/1/17)	Body weight ≥30 kg: 10 mg/kg every 2 wk or 1500 every 4 wk[e] Body weight <30 kg: 10 mg/kg every 2 wk[e]	1400 mg × 70.4/10 mg = 9858	Voluntary withdrawal (announced 2/22/21)
Nivolumab			
To treat patients with hepatocellular carcinoma who were previously treated with sorafenib (9/22/17)	240 Every 2 wk or 480 every 4 wk[f]	480 mg × 27.86/mg = 13 372	CheckMate 459 trial results were posted in June 2020. The ODAC voted to withdraw
To treat patients with metastatic small cell lung cancer with progression after platinum-based chemotherapy and at least 1 other line of therapy (8/16/18)	240 Every 2 wk[f]	480 mg × 27.86/mg = 13 372	Voluntary withdrawal (announced 12/29/20)
Pembrolizumab			
To treat patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 or for patients who are not eligible for any platinum-containing chemotherapy, regardless of PD-L1 status (5/18/17)	200 Every 3 wk or 400 every 6 wk[g]	267 mg × 49.2/mg = 13 136	Results of the KEYNOTE-361 trial were released in June 2020. The ODAC voted to maintain indication, so the FDA is unlikely to take any further action
To treat patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1, with disease progression during or after 2 or more previous lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy, and, if appropriate, HER2/neu-targeted therapy (9/22/17)	200 Every 3 wk or 400 every 6 wk[g]	267 mg × 49.2/mg = 13 136	Results of the KEYNOTE-062 trial were released in June 2019. The ODAC voted to withdraw
To treat patients with hepatocellular carcinoma who were previously treated with sorafenib (11/9/18)	200 Every 3 wk or 400 every 6 wk[g]	267 mg × 49.2/mg = 13 136	Results of the KEYNOTE-240 trial were released in February 2019. The ODAC voted to maintain indication, so the FDA is unlikely to take any further action
To treat patients with metastatic small cell lung cancer with disease progression during or after platinum-based chemotherapy and at least 1 other previous line of therapy (6/17/19)	200 Every 3 wk or 400 every 6 wk[g]	267 mg × 49.2/mg = 13 136	Voluntary withdrawal (announced 3/1/21)

Abbreviations: ASP, average sales price; FDA, US Food and Drug Administration; HER2, human epidermal growth factor receptor 2 (now estrogen receptor, 1 progesterone receptor, and human epidermal growth factor receptor 2 [ERBB2]); ODAC, Oncologic Drugs Advisory Committee; PD-L1, programmed death ligand 1.

[a] As listed in Beaver and Pazdur.[4]

[b] Monthly dosage is derived from drug labels available at Drugs@FDA (https://www.accessdata.fda.gov/scripts/cder/daf/). ASP is from the Centers for Medicare & Medicaid Services Medicare Part B Drug Spending Dashboard (https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Information-on-Prescription-Drugs/MedicarePartB).

[c] As listed in Beaver and Pazdur[4] and Oakes.[5]

[d] Taken from the last 2020 label update (12/18/20).

[e] Taken from the last 2020 label update in 2020 (11/18/20).

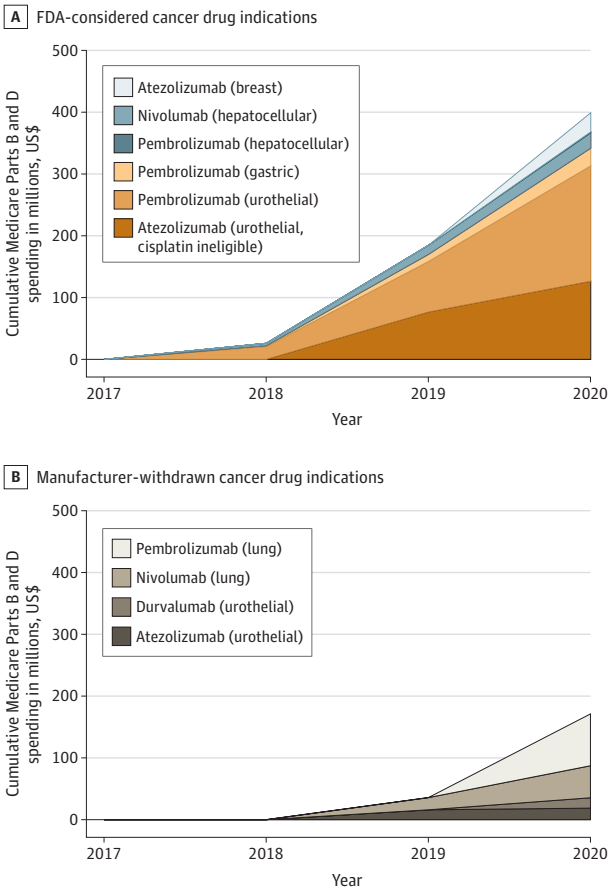
[f] Taken from the second-to-last 2020 label update (11/10/20).

[g] Taken from the last 2020 label update (11/13/20).

AA. Approximately $224 million of this spending was for indications that were either voluntarily withdrawn by the manufacturers or recommended by the ODAC for withdrawal. These results suggest that spending on the remaining 4 AA indications may continue to increase unless the FDA revokes these indications.

To fulfill its mission of protecting public health, the FDA should balance the benefits of early access to potentially effective drugs with their associated risks. Although health system efficiency is outside of the FDA's remit, spending on cancer drugs that lack OS benefit constitutes waste and risks harming health. To mitigate waste, the FDA could enforce

Figure. Estimated Cumulative Medicare Parts B and D Spending (in 2020 US Dollars) for Accelerated Approval Cancer Drug Indications With a Confirmed Lack of Overall Survival Benefit



A, Estimated spending for indications considered by the US Food and Drug Administration (FDA) Oncologic Drugs Advisory Committee in April 2021. B, Estimated spending for indications voluntarily withdrawn by manufacturers.

timely completion of confirmatory trials and accelerated withdrawal if OS benefits are not confirmed or high-quality evidence is not generated on time.[1] The FDA should also revisit the approval status of other AA drugs for which confirmatory trials show no OS benefit, for AA drugs that lack confirmatory trial data for an extended period, and for AA indications for which confirmatory trials rely on surrogate end points.

The limitations of this study are (1) its reliance on *International Statistical Classification of Diseases, Tenth Revision* codes to estimate proportions of Medicare beneficiaries with relevant cancer indications and (2) the use of a cohort of MA enrollees to estimate shares of indication-specific spending in traditional Medicare. Medicare Advantage and traditional Medicare populations may differ; however, research suggests that relative cancer prevalence would not differ by Medicare subpopulation.[6] Our spending estimate does not account for the use of these drugs for patients participating in Medicaid, individuals enrolled in other public insurance programs, or patients with commercial insurance. The magnitude of spending estimated in our study highlights the need for the FDA to withdraw approvals for drug indications with a confirmed lack of clinical benefit in a timely manner.

Mahnum Shahzad, BA
Huseyin Naci, MHS, PhD
Anita K. Wagner, PharmD, MPH, DrPH

Author Affiliations: Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, Massachusetts (Shahzad, Wagner); Department of Health Policy, London School of Economics and Political Science, London, United Kingdom (Naci).

Accepted for Publication: August 26, 2021.

Published Online: October 18, 2021. doi:10.1001/jamainternmed.2021.5989

Corresponding Author: Mahnum Shahzad, BA, Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, 401 Park Dr, Ste 401, Boston, MA 02215 (mahnum_shahzad@g.harvard.edu).

Author Contributions: Ms Shahzad had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: All authors.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Shahzad.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Shahzad.
Administrative, technical, or material support: Shahzad.
Supervision: Naci, Wagner.

Conflict of Interest Disclosures: Dr Wagner reported receiving grants from the American Cancer Society. No other disclosures were reported.

1. US Food and Drug Administration. Expedited programs for serious conditions—drugs and biologics. Published June 25, 2020. Accessed May 26, 2021. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-serious-conditions-drugs-and-biologics

2. Pazdur R. FDA in Brief: FDA Oncologic Drugs Advisory Committee to review status of six indications granted accelerated approval. Published March 15, 2021. Accessed March 23, 2021. https://www.fda.gov/news-events/fda-brief/fda-brief-fda-oncologic-drugs-advisory-committee-review-status-six-indications-granted-accelerated

3. Gyawali B, Ross JS, Kesselheim AS. Fulfilling the mandate of the US Food and Drug Administration's accelerated approval pathway: the need for reforms. *JAMA Intern Med*. 2021. doi:10.1001/jamainternmed.2021.4604

4. Beaver JA, Pazdur R. "Dangling" accelerated approvals in oncology. *N Engl J Med*. 2021;384(18):e68. doi:10.1056/NEJMp2104846

5. Oakes K. ODAC recommends pulling 2 of 6 accelerated approvals. Regulatory Focus. Published April 30, 2021. Accessed May 5, 2021. https://www.raps.org/news-and-articles/news-articles/2021/4/odac-recommends-pulling-2-of-6-accelerated-approva

6. Newhouse JP, Price M, McWilliams JM, Hsu J, McGuire TG. How much favorable selection is left in Medicare Advantage? *Am J Health Econ*. 2015;1(1):1-26. doi:10.1162/ajhe_a_00001

COMMENT & RESPONSE

Tachycardia-Dependent Paroxysmal Atrioventricular Block

To the Editor Hyman and colleagues[1] presented an interesting and well-documented case of an elderly person with intermittent confusion and falls. Results of electrocardiography and intracardiac recordings demonstrated bradycardia-dependent paroxysmal atrioventricular block (PAVB) that was localized to the His-Purkinje system. The authors provided a thorough explanation of the electrophysiologic mechanism of the bradycardia-dependent or phase 4 block.