

Estimation of the Percentage of US Patients With Cancer Who Benefit From Genome-Driven Oncology

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IMPORTANCE To date, the benefit of genome-driven cancer therapy has not been quantified.

OBJECTIVE We sought to estimate the annual percentage of patients in the United States with advanced or metastatic cancer who could be eligible for and benefit from US Food and Drug Administration (FDA)-approved genome-driven therapy from 2006 to 2018.

DESIGN, SETTING, AND PARTICIPANTS Retrospective cross-sectional study using publically available data of (1) demographic characteristics of patients with advanced or metastatic cancer; (2) FDA data on cancer drugs approved from January 2006 through January 2018; (3) measures of response and duration of response from drug labels; and (4) published reports estimating the frequency of various genomic aberrations used to estimate what percentage of patients would have been eligible for and would have benefited from genome-driven therapy during the studied period.

MAIN OUTCOMES AND MEASURES Estimated percentage of US patients with cancer eligible for and benefiting from genome-targeted and genome-informed therapy by year, response rate of genome-informed indications, and duration of response.

RESULTS A total of 31 drugs with 38 FDA-approved indications met our inclusion criteria for genome-targeted or genome-informed therapy from January 1, 2006, through January 31, 2018. The estimated number of patients eligible for genome-targeted therapy in 2006 was 28 729 of a total 564 830 patients with metastatic cancer, or 5.09% (95% CI, 5.03%-5.14%). By 2018, this number had increased to 50 811 of 609 640, or 8.33% (95% CI, 8.26%-8.40%). For genome-informed therapy in 2006, the eligible number of patients was 59 301 of 564 830, or 10.50% (95% CI, 10.42%-10.58%). In 2018, genome-informed treatment could be offered to 94 157 of 609 640, or 15.44% (95% CI, 15.35%-15.53%) of patients with metastatic cancer. The percentage of patients with cancer estimated to benefit from genome-targeted therapy in 2006 was 0.70% (95% CI, 0.68%-0.72%), and in 2018, it had increased to 4.90% (95% CI, 4.85%-4.95%). For genome-informed treatment in 2006, the percentage estimated to benefit was 1.31% (95% CI, 1.28%-1.34%), and in 2018, it had increased to 6.62% (95% CI, 6.56%-6.68%). The median overall response rate for all genome-informed drugs through January 2018 was 54%, and the median duration of response was 29.5 months.

CONCLUSIONS AND RELEVANCE Although the number of patients eligible for genome-driven treatment has increased over time, these drugs have helped a minority of patients with advanced cancer. To accelerate progress in precision oncology, novel trial designs of genomic therapies should be developed, and broad portfolios of drug development, including immunotherapeutic and cytotoxic approaches, should be pursued.

JAMA Oncol. doi:10.1001/jamaoncol.2018.1660
Published online April 17, 2018.

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Since the earliest reports of the clinical efficacy of imatinib, a potent targeted inhibitor of the *ABL* kinase, interest in the use of genome-driven therapies has grown in cancer medicine. Recently, many have sought to take stock of genomic cancer medicine.¹⁻⁵ These assessments document reasons for optimism. Clear success stories of genome-targeted medicine, such as targeting *BRAF* V600 mutations in melanoma,⁶ *ERBB2/HER2*-directed therapy in breast cancer,⁷ and targeting the *BCR-ABL* fusion gene in chronic myeloid leukemia (CML), have demonstrated the power of genomic therapy and its benefit to patients. Genomic oncology has indeed led to transformational successes.

Despite considerable excitement at the prospect of genome-driven therapy to improve oncologic care, there has been little empirical assessment of its benefit. All recent reviews have been narrative in nature. For this reason, we sought to estimate the penetrance of genome-driven oncology. We asked what percentage of US patients with cancer over the last 12 years were eligible for and benefited from genome-targeted and genome-informed therapies. In our primary analysis, we considered advanced and metastatic tumors (which account for the largest use of these therapies), and in a supplemental analysis, we broadened our review to consider incident cancers and the use of genome therapies in the adjuvant setting.

Methods

Overview

This study was not submitted for institutional review board approval because it did not involve health care records, and all data are publically available. The study was conducted between January 12, 2018, and March 20, 2018. We sought to estimate what percentage of patients in the United States with advanced or metastatic cancer annually were (1) eligible for and (2) benefited from either genome-targeted or genome-informed therapies. We defined *genome-targeted* drugs as those approved to be given based on findings of a genomic test where the drug targeted the aberration detected by that test. We defined *genome-informed* therapies more broadly, as all genome-targeted drugs and additionally any drug given after a genomic test, regardless of whether the drug was meant to target the abnormalities found in the test or acted via an alternative mechanism of action. We defined patients as *eligible* for these treatments if they had the tumor type and genomic abnormality that were the indications for the given drug; we defined *benefit from* according to available published sources on what proportion of patients could expect to experience a response; and we reported the findings on an annual basis.

Data Set

Drug Selection

We examined all US Food and Drug Administration (FDA) hematology and/or oncology approvals from January 1, 2006, through January 31, 2018, based on data available at the FDA website.⁸ While the FDA does not keep an archive website of approvals prior to 2006, our data set accounts for the 4 earlier genome-targeted therapies (trastuzumab, approved in 1998, imatinib in 2001,

Key Points

Question How many US patients with cancer are eligible for and benefit annually from genome-targeted therapies approved by the US Food and Drug Administration?

Findings In this cross-sectional study using publically available data, the estimated number of patients eligible for genome-targeted therapy in 2006 was 28 729 of a total 564 830 patients with metastatic cancer, or 5.09%; by 2018, this number had increased to 50 811 of 609 640, or 8.33%. The percentage of US patients with cancer estimated to benefit from genome-targeted therapy (ie, responders) in 2006 was 0.70%, and in 2018 it had increased to 4.90%.

Meaning Although the number of patients eligible for genome-driven treatment has increased over time, these drugs have helped a minority of patients with advanced cancer; to accelerate progress in precision oncology, novel trial designs of genomic therapies and broad portfolios of drug development, including immunotherapeutic and cytotoxic approaches, need further study.

gefitinib in 2003, and erlotinib in 2004) and the 1 earlier genome-informed drug (cetuximab, approved in 2004).

Data Extracted

For each drug approval, we catalogued the name of the drug, the date of approval, the specific treatment indication, required genomic testing for that indication, the drug's mechanism of action, relationship between the genomic aberration and drug target, and the clinical study data, specifically treatment response, per FDA drug label. For drugs that were tested against chemotherapeutic options or in single-arm studies, we used the absolute response rate of patients receiving the drug. For drugs used in concert with a chemotherapy backbone, we used the difference in response rate between the intervention and control arms.

Estimating the Number of Patients Eligible for Therapy per Year

We collected annual mortality statistics by cancer type from the American Cancer Society⁹ to ascertain the number of patients who died annually and could have benefited from genome-targeted or genome-informed therapies. For this group, we used death from cancer as a surrogate for incident presentation of advanced or metastatic cancer. In a secondary analysis we used incidence statistics of early-stage disease to estimate the proportion of patients who benefited from adjuvant molecular therapy (eAppendix 7 in the Supplement), such as trastuzumab (HER2-positive breast cancer) and imatinib (gastrointestinal stromal tumor; GIST).

For each cancer drug approval, we estimated what proportion of patients (by mortality statistics) would have been eligible for that therapy in each year from the drug approval date to the present. For instance, consider afatinib, which was approved in 2013 for the treatment of non-small cell lung cancer (NSCLC). To estimate the percentage of US patients with cancer who were eligible for this drug, we first obtained the number of deaths from lung cancer in that year, which was 159 480. We then estimated that 85% of these deaths would be due to NSCLC.¹⁰ Finally, we estimated that 15% of such patients would have an activating mutation of *EGFR*.¹¹ A full list of all assumptions, and their supporting references, for all genome-targeted and genome-informed drug approvals is provided in eAppendix 2 in the

Supplement. Using these assumptions, we estimated that 20 334 patients of a total 580 350 cancer deaths in 2013, or 3.50% of patients, would have been eligible for afatinib in that year. We performed this calculation by year in all subsequent years adjusting accordingly as newer drugs were approved. Our analysis is a best-case scenario assuming immediate and 100% market penetration of the drug following approval.

Estimating the Number of Patients Who Benefit From Therapy per Year
To estimate the percentage of US patients with cancer who could benefit each year, we performed an additional calculation. We multiplied the proportion of patients eligible for that therapy by the response rate of the drug. In the case of afatinib, the FDA label reports an overall response rate of 50.4%, which would indicate that 10 248 of 580 350 patients or 1.77% could benefit that year. We performed this calculation by year in all subsequent years adjusting accordingly as new drugs with higher response rates became available.

Many of the drugs we examined were approved on the basis of single-arm, uncontrolled studies, and prior research suggests that these studies may have response rates 10% to 20% higher than those seen in subsequent trials or real-world experience.¹² For this reason, we performed a sensitivity analysis assuming a 10% or 20% relative reduction in the response rate. In other words, if a response rate was 20%, we performed an analysis with an 18% and 16% response rate. This is reported separately.

Multiple Drugs

When the second and third drugs were approved for the same genome abnormality, we used the single highest response rate (or response rate difference for drugs tested in combination with chemotherapy backbone). In general, when there were discrepancies between sources, we erred on the side of the highest documented rates to give the most generous estimates for how many patients would be eligible and then how many would benefit from genome-driven therapy. When ranges of mutational prevalence were provided, we used the median.

Adjuvant Drugs

As a final analysis, we estimated the benefit of genome-targeted drugs in the adjuvant setting. Here we used incident cancer as the denominator. We used the increase in curative fraction or long-term disease control to define “benefit from.”

Statistical Analysis

We sought to provide a descriptive estimate of the percentage of US patients with advanced or metastatic cancer who were eligible for and benefited from genome-targeted and genome-informed therapy. Thus, we provided 4 sets of estimates. This was a descriptive study with analysis using Microsoft Excel and STATA version 13.0.

Results

We examined 31 drugs with 38 FDA approvals that met our criteria as genome-targeted or genome-informed drugs between January 1, 2006, and January 31, 2018. Of these 38

Table. Genomic Therapy Drugs Approved by the FDA, 2006-2018

2006-2018 Genomic Therapy	No. (%)
Drugs Overall	
Approved drugs, No.	31
Total indications, No.	38
GT indications	28 of 38 (73.7)
GI indications	38
Drugs per Indication	
NSCLC (GT)	
<i>EGFR</i>	4 (10.5)
<i>ALK</i>	4 (10.5)
<i>ROS1</i>	1 (2.6)
<i>BRAF</i>	1 (2.6)
Breast	
<i>ERBB2/HER2</i> (GT)	4 (10.5)
<i>BRCA</i> (GI)	1 (2.6)
Melanoma <i>BRAF</i> V600 (GT)	5 (13.2)
Colorectal <i>KRAS</i> WT (GI)	2 (5.3)
Ovarian <i>BRCA</i> (GI)	2 (5.3)
Gastroesophageal <i>ERBB2/HER2</i> (GT)	1 (2.6)
GIST (GI)	1 (2.6)
CML Ph+ (GT)	5 (13.2)
CLL 17p (GI)	2 (5.3)
AML (GT)	
<i>IDH2</i>	1 (2.6)
<i>FLT3</i>	1 (2.6)
ALL Ph+ (GT)	1 (2.6)
High-MSI solid tumor (GI)	2 (5.3)

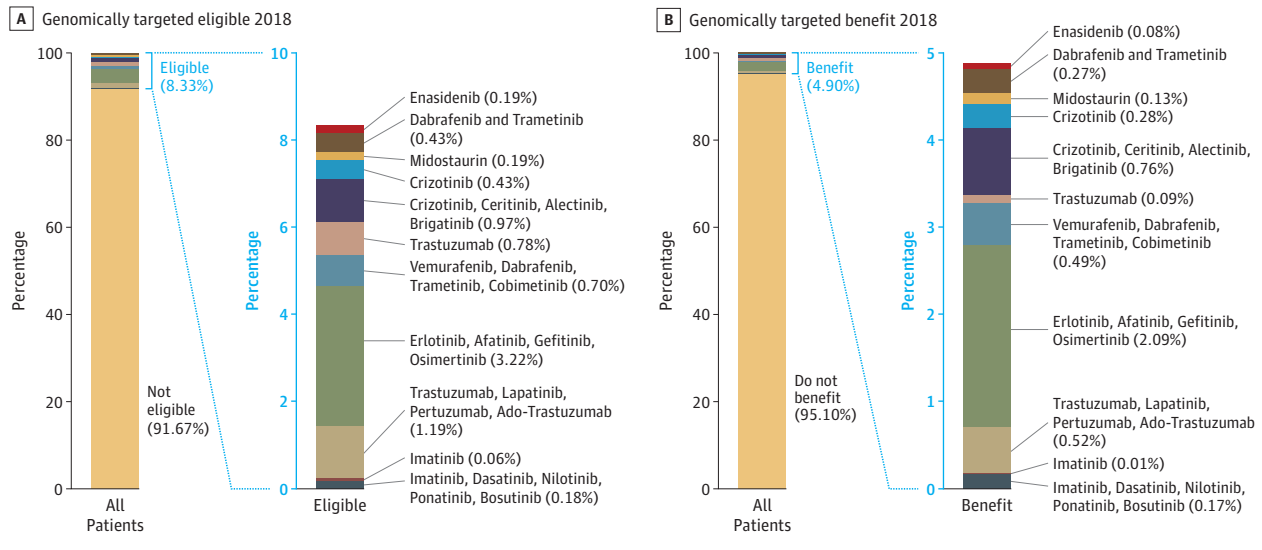
Abbreviations: *ALK*, anaplastic lymphoma kinase gene; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; *BRAF*, B-raf gene; *BRCA*, breast cancer gene; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; *EGFR*, epidermal growth factor receptor gene; FDA, US Food and Drug Administration; *FLT3*, Fms-like tyrosine kinase receptor 3 gene; GI, genome informed; GIST, gastrointestinal stromal tumor; GT, genome targeted; *ERBB2/HER2*, human epidermal growth factor receptor 2 gene; *IDH2*, isocitrate dehydrogenase 2 gene; *KRAS* WT, K-Ras wild-type gene; MSI, microsatellite instability; NSCLC, non-small cell lung cancer; Ph+, Philadelphia chromosome positive; *ROS1*, c-ros oncogene 1.

approvals, 28 (73.7%) were categorized as genome-targeted drugs, defined as those given based on the findings of a genomic test where the drug targets the aberration detected by that test. The other 10 were part of our expanded classification that includes all genome-targeted drugs plus any drug given after a genomic test, even if the drug does not directly target the abnormality detected by that test (ie, acts via an alternative mechanism of action). The Table lists genome-targeted and genome-informed as well as approved indications. Further information can be found in eAppendix 2 in the Supplement. Detailed herein are the estimated percentages of patients who were eligible for and benefited from genome-targeted and genome-informed therapy; graphic illustrations of these findings are provided in eAppendixes 3 through 6 in the Supplement with a pie chart shown for each study year.

Estimated Percentages of Eligible Patients

In 2006, we estimate that 28 729 of the total 564 830 patients, or 5.09% (95% CI, 5.03%-5.14%), were eligible for genome-targeted therapy. We found that by 2018, the number of patients eligible for genome-targeted therapy had increased to

Figure 1. Estimated US Patient Eligibility and Benefit From Genomically Targeted Benefit, 2018



50 811 of 609 640, or 8.33% (95% CI, 8.26%-8.40%) (Figure 1A). For genome-informed therapy in 2006, we estimated that 59 301 of 564 830, or 10.50% (95% CI, 10.42%-10.58%) of all patients, were eligible for treatment. This number increased to 94 157 of 609 640, or 15.44% (95% CI, 15.35%-15.53%), for genome-informed therapy in 2018 (eFigure 1 in the Supplement).

Estimated Percentages of Patients Who Benefited

Estimating the benefit of genome-targeted therapy, we found that in 2006, 3965 of 564 830 patients, or 0.70% (95% CI, 0.68%-0.72%) of all patients, would have experienced a response. By 2018, 29 899 of the 609 640, or 4.90% (95% CI, 4.85%-4.95%) of all patients, would have experienced a response (Figure 1B). For genome-informed therapy in 2006, a total of 7396 of 564 830 patients, or 1.31% (95% CI, 1.28%-1.34%) of all patients would have benefited from these drugs. By 2018, this number had increased to 40 349 of 609 640, or 6.62% (95% CI, 6.56%-6.68%) of all patients (eFigure 1 in the Supplement).

Other Factors in Measuring Genome-Driven Therapy

Overall, the estimated number of patients eligible for genome-targeted or genome-informed therapy increased from 2006 to 2018, as shown in eFigure 2 in the Supplement. A jump in 2011 is attributable to the approval of the anaplastic lymphoma kinase (ALK) inhibitor crizotinib for the treatment of NSCLC and the BRAF inhibitor vemurafenib in melanoma. The second jump in 2017 is due to the approval of dabrafenib (a BRAF inhibitor) and trametinib (a MEK inhibitor) for treatment of NSCLC, as well as enasidenib and midostaurin, respectively targeting *IDH2* and *FLT3* in acute myeloid leukemia (AML). Genome-informed therapies experienced a jump with the approval of PD-1 (programmed cell death 1) antibody drugs (nivolumab and pembrolizumab) for colorectal cancer and other solid tumors harboring high microsatellite instability.

Figure 2 illustrates the best overall response rate across the study period for genome-informed drugs per genomic aber-

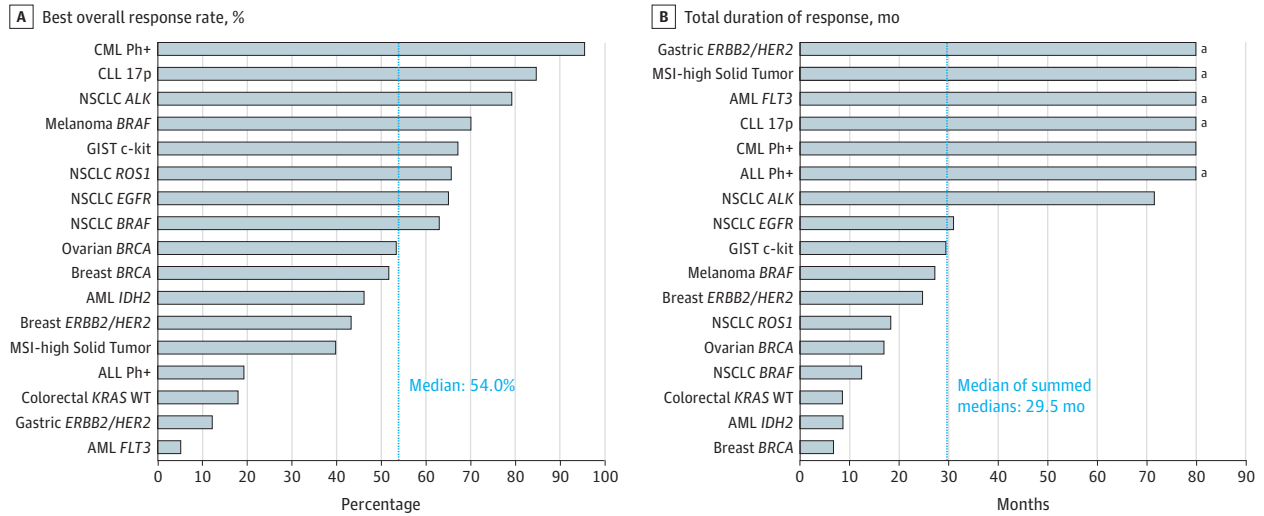
ration (Figure 2A) as well as the summed median duration of responses (ie, the duration of all sequential therapies used for the genomic aberration) (Figure 2B). Many trials have not reported data on median duration of response. The median response duration shown in Figure 2 assumes that the duration of response was more than 80 months for drugs for which the sources did not report the median or reported that the median was not reached. The median response rate for genome-informed drugs was 54%, and the median duration of response was 29.5 months.

We further explored the benefit in the treatment of localized cancer of these genome-informed drugs, such as imatinib, midostaurin, and trastuzumab in the adjuvant setting for CML, GIST, acute lymphoblastic leukemia, AML, and breast cancer. Regarding eligibility, we found that a total of 52 513 of 1 735 350 incident cancer cases, or 3.03% (95% CI, 3.00%-3.05%) of patients, would be eligible for such treatment in 2018. We then estimated that a total of 11 923 of those 1 735 350, or 0.69% (95% CI, 0.67%-0.70%) might benefit from this treatment in 2018 (eAppendix 7 in the Supplement). Finally, assuming a 10% and 20% reduction in response rates in real-world use, we found the percentage of patients benefitting from genome-targeted therapy to be 4.41% (95% CI, 4.36%-4.47%) and 3.92% (95% CI, 3.87%-3.97%) in 2018, respectively, and those benefitting from genome-informed therapies to be 5.96% (95% CI, 5.90%-6.02%) and 5.29% (95% CI, 5.24%-5.35%) in 2018, respectively.

Discussion

Cancer is, in part, a disorder of genomic regulation.¹ Accordingly, there is widespread interest in genome therapies, and genomic drugs have led to major treatment successes. The genome-informed therapies examined herein have a median response rate of 54%, with a duration of response of 29.5 months. Yet, simultaneously, our investigation reveals oppor-

Figure 2. Estimated Responses of US Patients to Genomically Informed Drug Treatment, 2006-2018



ALK indicates anaplastic lymphoma kinase gene; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BRAF, B-raf gene; BRCA, breast cancer gene; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; EGFR, epidermal growth factor receptor gene; FLT3, Fms-like tyrosine kinase receptor 3 gene; GI, genome informed; GIST, gastrointestinal stromal tumor; GT, genome targeted; ERBB2/HER2, human epidermal growth factor receptor 2

gene; IDH2, isocitrate dehydrogenase 2 gene; KRAS WT, K-Ras wild-type gene; MSI-high, high microsatellite instability; NSCLC, non-small cell lung cancer; Ph+, Philadelphia chromosome positive; ROS1, c-ros oncogene 1.

^a When median duration of response was not reported or not reached, we assumed 80 months.

tunity for improvement. Genome-informed therapies have expanded slowly over time (eFigure 2 in the Supplement). Currently, the percentage of patients who are eligible to receive these therapies and the subset who may respond are relatively small compared with the total burden of cancer deaths in America. Visual inspection of the estimates over time does not reveal clear evidence of an exponential increase in the diffusion of genomic treatments. Such a pattern would be anticipated for early adoption of new innovations.¹³ For those who hope that genome-informed therapies will lead to major improvements in treatment of the overall population, novel ways to accelerate diffusion should be considered.

One such approach is the use of next-generation sequencing efforts in broad collections of tumors, as detailed in recent coverage guidance from the Centers for Medicare and Medicaid Services to cover Foundation Medicine (F1CDx) for all patients with advanced or metastatic solid tumors.¹⁴ Yet, even this expansive effort may only incrementally advance the numbers presented in our analysis, which focus on FDA-approved therapies. Consider the recent MOSCATO-1 Trial.¹⁵ In this study of 1035 adult patients originally intended to undergo next-generation sequencing, only 199 (19%) were paired with a genome-informed therapy. This percentage is comparable to the highest reported estimates from single centers.¹⁶ However, just 22 patients, or 2.1%, of the original cohort were able to achieve an objective response.¹⁵ Thus, even adding in the estimated number of patients who may achieve a response from broad genomic sequencing, we may realistically expect this to be less than 10% of all US patients with cancer who will die annually. Many researchers have pointed to other limitations of these broad sequencing strategies, including cost, harms, and missed opportunities for conventional therapies.¹⁷⁻²²

Other researchers have anticipated that genome-informed therapies might not be able to result in benefit for most patients with cancer and have proposed a broader pursuit of functional cancer medicine.²³ Other groups also have proposed broad goals to improve population cancer statistics.²⁴ Our findings suggest that broader portfolios of research funding may be required to improve cancer statistics for the majority of Americans.

Limitations

As with any observational study, particularly one that seeks to estimate a complex phenomenon, our study has limitations. First, the decision to code a drug as *genome-targeted* or *genome-informed* requires judgment. We sought to use a transparent definition on which 2 oncologists agreed (E.Y.C. and V.P.); however, we understand that others may have different definitions. To accommodate these views, we performed a sensitivity analysis using genome-informed drugs—a broader set—yielding similar results.

Second, our analysis may be an overestimate of the benefit of these drugs. We tended to use optimistic assumptions in our estimate. First, we assumed immediate and 100% penetration of drug and molecular testing. Real-world data suggest that many mutations are poorly utilized in therapeutic decisions and predictive tests, such as EGFR testing in NSCLC,²⁵ or moderate testing, such as BRAF in melanoma.²⁶ Our analysis assumes 100% testing for all patients in the year the drug is approved. Where multiple drugs were approved for the same genomic indication (eg, ALK-rearranged NSCLC), we used the highest response rate of a targeted drug.

Third, we used deaths from a specific cancer as a surrogate for patients presenting with advanced or metastatic cancer in the year a drug was approved. We chose this measure

because cancer stage is assigned in the Surveillance, Epidemiology, and End Results (SEER) registry only at first presentation,²⁷ and the use of staging as a measure would underestimate the number of patients eligible for therapy. However, for drugs that transformed the natural history of a disease (such as CML), this method may underestimate the value of the genomic agent. To overcome this limitation, we performed a separate analysis for incident cases (detailed in eAppendix 7 in the Supplement). Moreover, we did not notice a marked change in cancer tumor death statistics by year after genomic approvals.

Fourth, we began our analysis in 2006, owing to a lack of obtainable data from the FDA website prior to this year, and could have missed genome-targeted drugs that were approved between 2000 and 2005. However, our analysis includes all molecular drugs that were approved before this date, such as *ERBB2/HER2*-directed, *BCR-ABL*-directed and *EGFR*-directed therapies.

Fifth, we did not consider the use of off-label targeted therapy. However, elsewhere our research group has performed an analysis of these drugs²⁸ and noted that drugs that appear efficacious tend to receive subsequent approval and would enter our data set. We also did not include efforts of broad next-generation sequencing.

Sixth, our analysis was intended to approximate rates in a broad fashion across a panel of different diseases with different prognoses. Because there is a time lag between actual diagnosis and death, by relying on mortality data, our

approach calculates penetration rates within a given year for cancers that were actually diagnosed in prior years. This could bias the estimates in unknown ways, although our expectation is that any bias is limited given the generally poor prognosis for the cancers we examined. Also, given the conservative assumptions we made throughout the estimation process, our estimates likely pose an upper boundary; the true underlying rates may be lower.

For these reasons, we believe that the estimates reported herein of patient eligibility for and benefit from genomic therapy is fair and optimistic.

Conclusions

Although there are clear successes of genome-informed cancer drugs, our empirical analysis suggests that fewer than 16% of patients are eligible for, and fewer than 7% benefit from, these agents, even using permissive definitions. Over time, the diffusion of genome-informed drugs has expanded linearly at a rate of 0.5% per year, with no sign of inflection or change in pace. Including the early results of broad next-generation sequencing in the treatment of all solid tumors increases our figures by approximately 2%. Therefore, we conclude that to improve cancer outcomes for most Americans, we will need to accelerate progress with genome-targeted approaches and foster other approaches to improve patient outcomes, such as drug development in immunotherapy and cytotoxic therapies, among other strategies.

ARTICLE INFORMATION

Accepted for Publication: April 2, 2018.

Published Online: April 17, 2018.
doi:10.1001/jamaoncol.2018.1660

Author Contributions: Mr Marquart and Dr Prasad 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: Prasad.

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

Drafting of the manuscript: All authors.

Critical revision of the manuscript for important intellectual content: Marquart, Chen.

Statistical analysis: Marquart, Chen.

Administrative, technical, or material support: Chen. Supervision: Prasad.

Conflict of Interest Disclosures: None reported.

Meeting Presentation: This article was presented at the American Association for Cancer Research Annual Meeting; April 17, 2018; Chicago, Illinois.

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