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ORIGINAL ARTICLE

# Updated estimates of eligibility for and response to genome-targeted oncology drugs among US cancer patients, 2006-2020

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**Background:** Prior studies have evaluated the percentage of cancer patients with advanced or metastatic cancer who are eligible for and respond to genome-targeted therapy, but since that publication, the number of Food and Drug Administration (FDA) approvals for drugs targeting genetic indications has grown rapidly. We sought to update the estimates of both eligibility for and response to genome-targeted and genome-informed therapies in US cancer patients for FDA-approved drugs to reflect estimates as of 2020.

**Materials and methods:** We used mortality data from the American Cancer Society to estimate eligibility for these drugs, based on prevalence statistics from the published literature. We then multiplied eligibility by the response rate in the FDA label to generate an estimate for the percentage of US cancer patients who respond.

**Results:** For genome-targeted therapy, we estimate that the eligibility increased from 5.13% in 2006 to 13.60% in 2020. For genome-targeted therapy, we estimate that the response increased from 2.73% in 2006 to 7.04% in 2020.

**Conclusions:** The percentage of US cancer patients who are eligible for and respond to genome-targeted therapy has increased over time. Most of the increase in eligibility for genome-targeted therapies was seen after 2018, whereas most of the increase in response was seen before 2018.

**Key words:** genome-targeted therapy, eligibility, response

## INTRODUCTION

Precision oncology relies upon genomic sequencing of a patient's tumor to determine optimal treatment.[1] Precision therapies typically target genetic aberrations within cancer, and this approach has widespread enthusiasm driven by high response rates. Often, genomically-targeted drugs gain Food and Drug Administration (FDA) approval in single-arm trials that lack a comparator group.[2] As such, response rates, which measure the percentage of patients who have tumor shrinkage beyond the RECIST 1.1 cut-off of 30%, are often used as a study endpoint.[3]

Prior studies have evaluated the percentage of US cancer patients with advanced or metastatic cancer who are eligible for and respond to this class of medications. Specifically, genome-targeted therapy was found to apply to 8.3% of US cancer patients as of 2018, and 4.9% might experience a partial or complete response.[4] However, since that publication, the number of FDA approvals for drugs targeting genetic indications has grown rapidly. We therefore sought to update the estimates of both eligibility for and response to genome-targeted and genome-informed therapies for drugs that have been FDA-approved to reflect estimates as of 2020.

## MATERIALS AND METHODS

We have updated the estimates for the eligibility for and response to genome-driven oncology drugs, which have been previously reported.[4] We calculated these estimates for both genome-targeted drugs and genome-informed therapies. We defined 'genome-targeted' drugs as those approved for use based on findings of a genomic test where the drug targets the aberration detected by that test, and we defined 'genome-informed' therapies as any drug given after a genomic test, including all genome-targeted drugs, regardless of whether the drug was meant to target the abnormalities found in the test or acted via an alternative mechanism of action.

### *Data*

**Drug approvals.** We searched the US FDA for all oncology drug approvals that were approved for a genomic indication

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between 1 January 2006 and 30 June 2020. Since the FDA does not report approvals before 2006, we also included five drugs for genomic indications that were approved before 2006 and were in use (four genome-targeted drugs: trastuzumab, approved in 1998, imatinib in 2001, gefitinib in 2003, and erlotinib in 2004; and one genome-informed drug: cetuximab, approved in 2004). Of note, targeted therapy approvals not linked to a genetic mutation (e.g. sunitinib for renal cell carcinoma) were not included.

For each drug approved, we abstracted the date approved, the indication, the tumor type, the genomic indication, and the response rate. For acute myelocytic leukemia (AML), we used complete response and for Philadelphia chromosome-positive acute lymphocytic leukemia and chronic myeloid leukemia, we used the complete hematologic response instead of the overall response rate. 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 conjunction with a chemotherapy backbone, we used the difference in response rate between the intervention and control arms. We also classified each drug as either a genome-targeted or a genome-informed drug. For our estimates, we assumed that all mutations of a specific gene were targetable. We also assumed that in tumors with multiple genetic mutations the different mutations were mutually exclusive.

**Eligibility and response statistics.** We used mortality statistics by cancer type from the American Cancer Society's (ACS) annual cancer statistics. Mortality statistics were used as surrogates for eligibility since eligibility data are not routinely collected at a national level and mortality data are an approximation for incident presentation of advanced or metastatic cancer. For each year there was a drug approved for a given indication, we multiplied the number of deaths for the indication by the prevalence of the genomic marker. This provided us with the total number of US cancer patients who were eligible for each indication, by year. The prevalence of the genomic marker came from the scientific literature, and sources are included in the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2021.04.003. For some cancers, we made assumptions to get more precise estimates, since the ACS reported mortality statistics broadly for certain cancer types. For example, ACS reports deaths for lung cancer, but drugs are often approved for more specific indications such as non-small-cell lung cancer (NSCLC) (85% of lung cancer deaths) and small-cell lung cancer (15% of lung cancer deaths). Sources for these assumptions are included in the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2021.04.003.

To estimate the number and percentage who responded, we multiplied the eligibility estimate by the response rate reported in the FDA label and divided by the total number of cancer cases. If no response rate was provided in the FDA label, we searched the scientific literature. We carried out this calculation for each year (2006-2020), adjusting accordingly as new drugs with higher response rates became available. All sources that we used in the eligibility and response estimations are included in the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2021.04.003. Our analysis is a best-case scenario and assumed that there was 100% market penetration of the drug for the entire year.

When multiple drugs were approved for the same genome abnormality, we used the single highest response rate (or response rate difference for drugs tested in

**Table 1. Genomic therapy drugs approved by the FDA, 2006-2020 (*N* = 71 FDA approvals)**

| 2006-2020 Genomic therapy | *N* (%) |
|---|---|
| ALL | |
| Ph+ (GT) | 3 (1.4) |
| AML | |
| FLT3 (GT) | 2 (2.8) |
| IDH1 (GT) | 1 (1.4) |
| IDH2 (GT) | 1 (1.4) |
| Breast | |
| HER2 (GT) | 7 (11.4) |
| BRCA (GI) | 2 (2.8) |
| PIK3CA (GT) | 1 (1.4) |
| Cholangiocarcinoma | |
| FGFR2 (GT) | 1 (1.4) |
| CLL | |
| 17p (GI) | 2 (2.8) |
| CML | |
| Ph+ (GT) | 5 (7.1) |
| Colorectal cancer | |
| BRAF (GT) | 1 (1.4) |
| KRAS (GI) | 2 (2.8) |
| MSI/MMR (GI) | 3 (4.3) |
| Gastric | |
| HER2 (GT) | 1 (1.4) |
| PDGFRA (GT) | 1 (1.4) |
| GIST (GT) | 1 (1.4) |
| Melanoma | |
| BRAF V600 | 6 (8.6) |
| NSCLC | |
| ALK (GT) | 5 (7.1) |
| BRAF (GT) | 1 (1.4) |
| EGFR (GR) | 7 (10.0) |
| MET (GT) | 1 (1.4) |
| RET (GT) | 1 (1.4) |
| ROS1 (GT) | 2 (1.4) |
| Ovarian | |
| BRCA (GI) | 2 (2.8) |
| HRD (GI) | 1 (1.4) |
| Pancreatic | |
| BRCA (GI) | 1 (1.4) |
| Prostate | |
| HRR (GI) | 1 (1.4) |
| BRCA (GI) | 1 (1.4) |
| Solid tumors | |
| NTRK (GT) | 2 (2.8) |
| MSK/MMR (GI) | 1 (2.8) |
| TMB H (GI) | 1 (1.4) |
| Thyroid | |
| BRAF (GT) | 1 (1.4) |
| RET (GT) | 1 (1.4) |
| Urothelial | |
| FGFR 2/3 (GT) | 1 (1.4) |
| Follicular | |
| EZH2 (GT) | 1 (1.4) |

ALL, acute lymphocytic leukemia; AML, acute myelocytic leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myelocytic leukemia; FDA, Food and Drug Administration; GI, genome informed; GT, genome targeted; NSCLC, non-small-cell lung cancer.

combination with chemotherapy backbone), thus erring on the side of the highest documented rates to give the most generous estimates for how many patients would be eligible for and respond to genome-driven therapy. When the mutational prevalence was reported as a range, we used the median. For NSCLC, gefitinib was approved for all NSCLC, regardless of the epidermal growth factor receptor (EGFR) status, and erlotinib, another tyrosine kinase inhibitor, was approved in 2013 for EGFR-specific mutations. We assumed that the response of EGFR tumors was similar for years before erlotinib's approval as before its approval.

**Duration of response.** We assessed the median duration of response (in months) for therapies that reported the highest overall response rate for indications that had approvals. For this, we abstracted the median duration of response. For drugs that did not report a median duration of response in the FDA label, we either used the time point when the percentage with a response was <50% (e.g. we used 12 months if the percentage of responders was 89% at 6 months and 19% at 12 months), or if that was not available, we used the median overall survival, which would provide a best-case estimate. If the median duration of response was not reached and therefore not reported and no other indication of duration of response was provided, we assumed that the duration of response was 80 months.

### *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 responded to genome-targeted and genome-informed therapies. As such, we provided four sets of estimates—two for eligibility and two for response. This was a descriptive study with analysis using Microsoft Excel. We calculated 95% confidence intervals (CIs) in the epiR package or R statistical software, version 3.6.2 (R core Team, 2020, https://cran.r-project.org/web/packages/epiR/index.html).

## RESULTS

We identified 72 unique approvals for 51 different drugs that were approved for 36 genomic indications for 18 cancer types from 1 January 2006 to 30 June 2020. Table 1 lists the drugs that were approved, by genomic indication.

For genome-targeted therapy, we estimate that the eligibility was 5.13% (95% CI: 5.07% to 5.19%) in 2006, increased to 8.82% (95% CI: 8.75% to 8.90%) by the end of 2018, and has since increased to 13.60% (95% CI: 13.51% to 13.68%) in 2020 (Figure 1 and Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2021.04.003). For genome-informed therapy, we estimate that the eligibility was 10.70% (95% CI: 10.62% to 10.78%) in 2006,

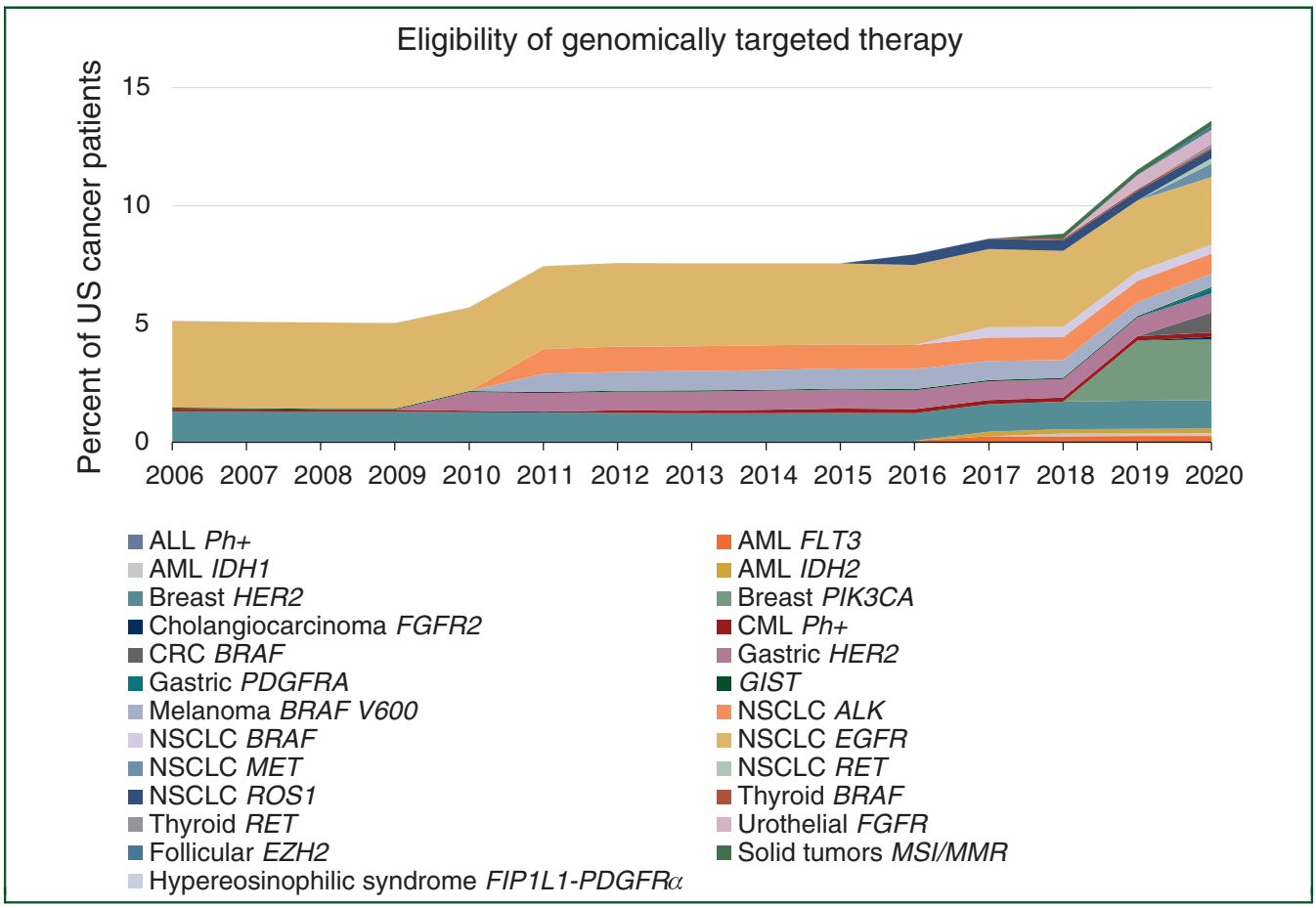


**Figure 1. Estimated eligibility of genome-targeted therapy in US cancer patients, 2006-2020.**
ALL, acute lymphocytic leukemia; AML, acute myelocytic leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myelocytic leukemia; CRC, colorectal cancer; NSCLC, non-small-cell lung cancer.

16.54% (95% CI: 16.45% to 16.63%) in 2018, and 27.30% (95% CI: 27.19% to 27.41%) in 2020 (Figure 2 and Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2021.04.003).

For genome-targeted therapy, we estimate that the response was 2.73% (95% CI: 2.69% to 2.78%) in 2006, increased to 5.48% (95% CI: 5.43% to 5.54%) by the end of 2018, and has since increased to 7.04% (95% CI: 6.98% to 7.10%) in 2020 (Figure 3). For genome-informed therapy, we estimate that the response was 3.33% (95% CI: 3.29% to 3.38%) in 2006, 7.68% (95% CI: 7.62% to 7.75%) in 2018, and 11.10% (95% CI: 11.03% to 11.19%) in 2020 (Figure 4). These estimates were based on both the prevalence of disease and the prevalence of mutation for the respective cancer type.

The median duration of response reported in the FDA approval notifications for genome-targeted therapy was 18.9 months (range: 5.7-80 months) in 2006 and 17.6 months (range: 4.6-80 months) in 2020, and the median response rate was 19.0% (range: 10.6%-95.3%) in 2006 and 63.5% (range: 12%-95.3%) in 2020.

## DISCUSSION

Since a prior study[4] that estimated the eligibility for and response to genome-driven oncology drugs in 2018, there have been an additional 21 drugs approved for an additional 10 genomic indications. The number of unique approvals increased 84% from when the original estimations were calculated, and yet, during that same time, the percentage of eligibility for and response to genome-targeted drugs increased 54% and 28%, respectively.

Of the response to drugs that had approval in 2020, almost one-third of the total response to genome-informed therapy (3.1%) was due to response from patients with NSCLC with EGFR mutations and *KRAS* wild-type colorectal cancers, whereas the remaining responses were due to the other 33 indications. In the case of EGFR NSCLC, overall survival has meaningfully improved for these patients,[5] but for many of the other oncology drugs approved for genomic indications, overall survival has yet to be demonstrated.

With an increasing number of people who are both eligible for and respond to genomic therapies, it is important to consider access to genomic testing. Initially, physicians carried out genomic testing on tumors that had not responded to standard-of-care treatments, but as testing and treatment options have become more available, the practice of testing for genetic markers has become much more common, and in some cases, has become part of initial treatment. Testing of tumor mutations at diagnosis is advantageous for certain patients who are eligible for therapies that have been shown to improve overall survival

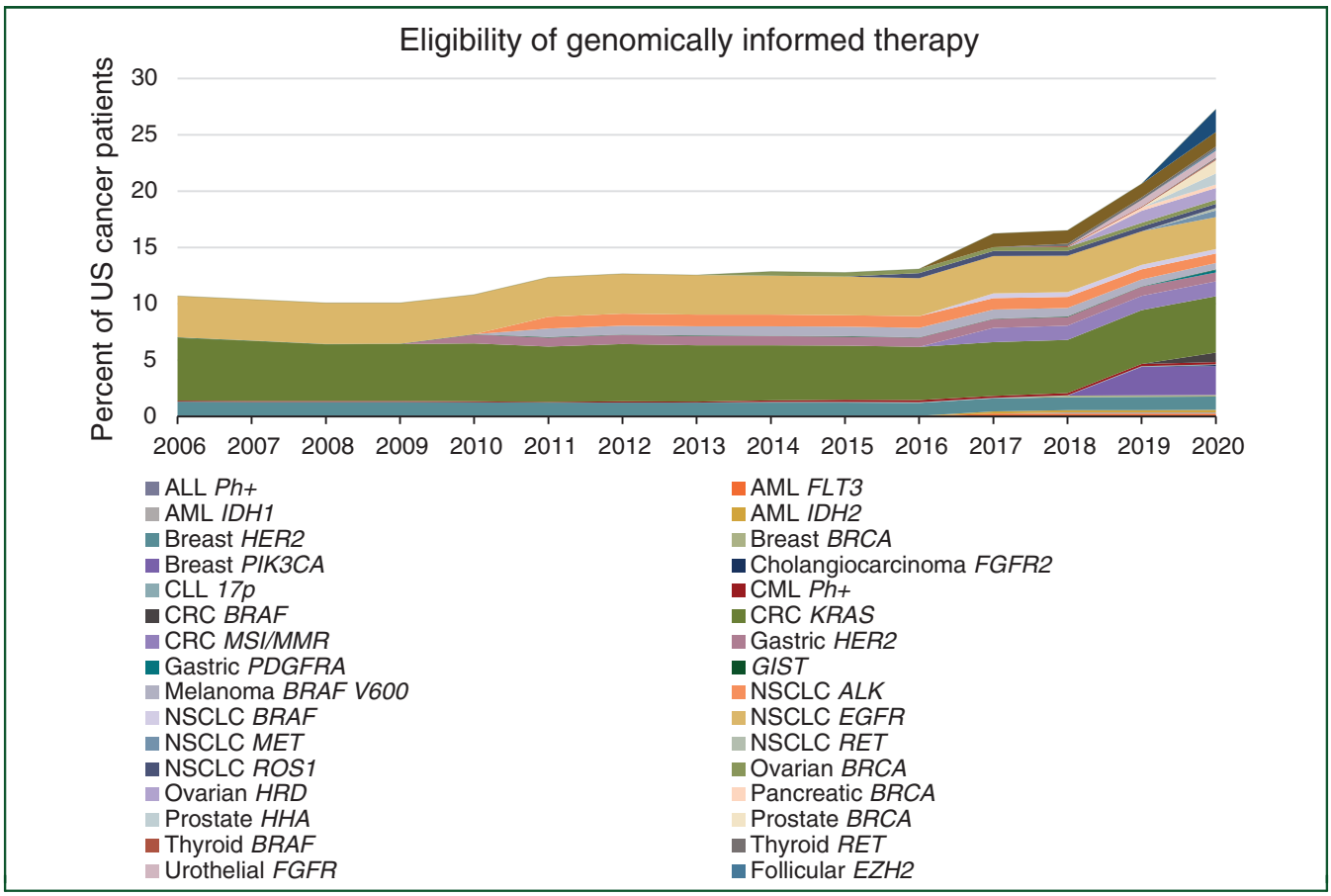


**Figure 2. Estimated eligibility of genome-informed therapy in US cancer patients, 2006-2020.**
ALL, acute lymphocytic leukemia; AML, acute myelocytic leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myelocytic leukemia; CRC, colorectal cancer; NSCLC, non-small-cell lung cancer.

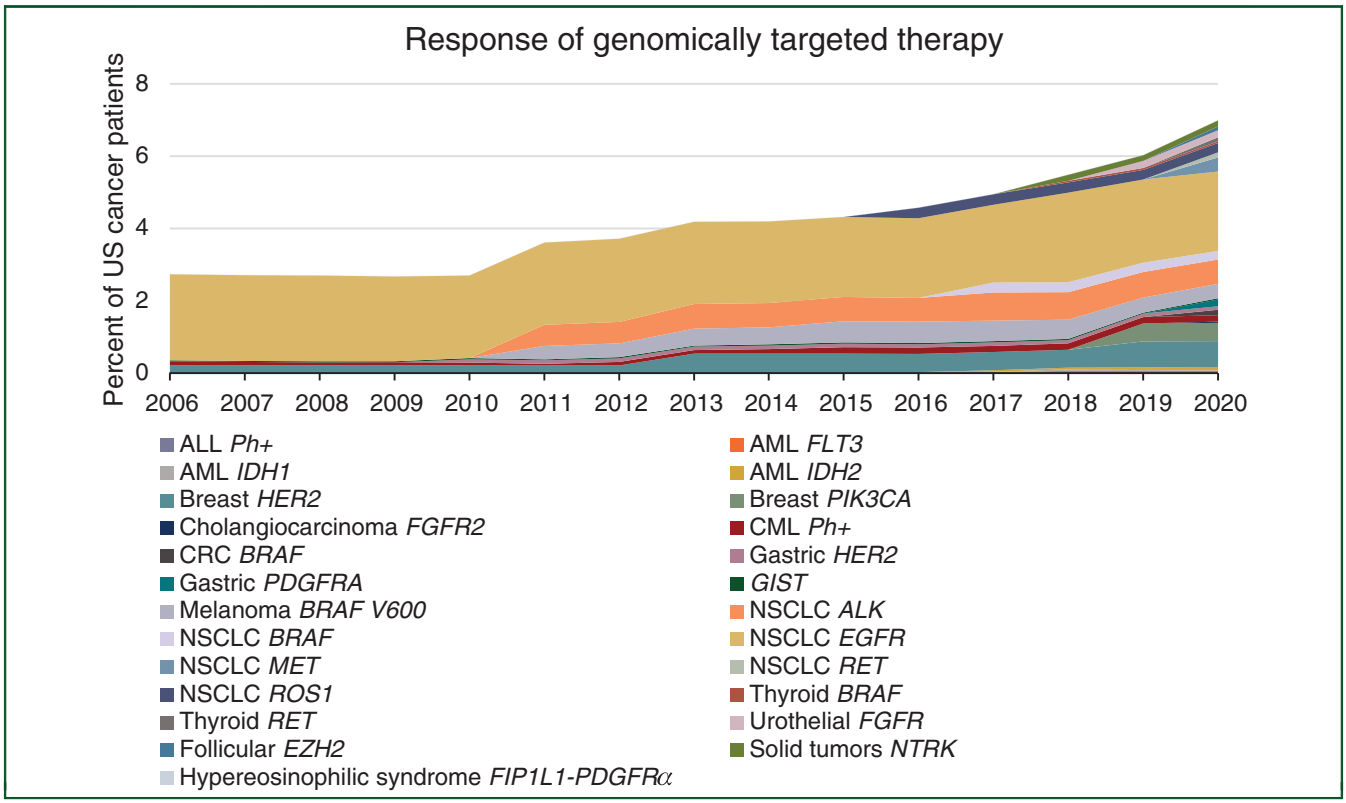


**Figure 3. Estimated response to genome-targeted therapy in US cancer patients, 2006-2020.**
ALL, acute lymphocytic leukemia; AML, acute myelocytic leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myelocytic leukemia; CRC, colorectal cancer; NSCLC, non-small-cell lung cancer.

in the front-line treatment of cancers (e.g. osimertinib for first-line treatment of EGFR-mutated NSCLC[6]). However, testing for genetic mutations in other cancers has been advocated when there is no drug approved for that genetic mutation (e.g. testing for KIT mutations in melanoma, which has low level of evidence but wide acceptance[7]), or has yet to show a benefit in overall survival (e.g. olaparib for ovarian cancer, which also has low level of evidence but wide acceptance[8]). In considering which genetic markers should be tested, we need to consider those for which there are available treatment options that have been shown to improve meaningful outcomes such as overall survival, and not just those mutations that have tests available for them.

We found that the median duration of response was 17.6 months for the year 2020, and was fairly consistent over the years that we included in our analysis. The actual duration of response for genome-targeted drugs is likely lower, considering that when these drugs are tested in randomized trials, the duration of response is often lower than in single-arm studies.[9]

### *Limitations*

We acknowledge that there are several limitations to our analysis. Firstly, we assumed that the drugs approved were available and could be used by all eligible patients for the entire year. Similarly, we assumed that all patients' tumors were genetically tested and that patients received the therapy with the highest response rate. However, in the real-world setting, genetic testing to determine appropriate therapy is $<$100%.[9-12] This may have led to higher estimates than actual real-world eligibility and response, but for these analyses, we wanted to use the most generous estimates for our estimates, thus approximating the upper boundary of eligibility and response.

Secondly, we used cancer deaths as a surrogate for advanced or metastatic cancer. National databases of cancer cases, such as Surveillance, Epidemiology, and End Results (SEER), report the stage of cancer at diagnosis, which may not reflect the stage of cancer for those who actually receive genome-targeted therapy. We felt that the number of deaths was more reflective of who actually receive these types of therapy.

Thirdly, we were not able to account for off-label use of genomic drugs. In a survey of oncologists, 17.5% of respondents used next-generation sequencing to determine therapy with off-label drug use.[13] Because of this, it is likely that our estimates for eligibility would have been higher if we had been able to use these types of data in our analysis, but it is unknown how this would have affected response since there are few studies evaluating response in these situations.

Fourthly, because the FDA does not archive drug approval announcements before 2006, there may have been genomically indicated drugs already approved at the beginning of 2006 that we missed. Nonetheless, we did include the most commonly used drugs that were approved before 2006.

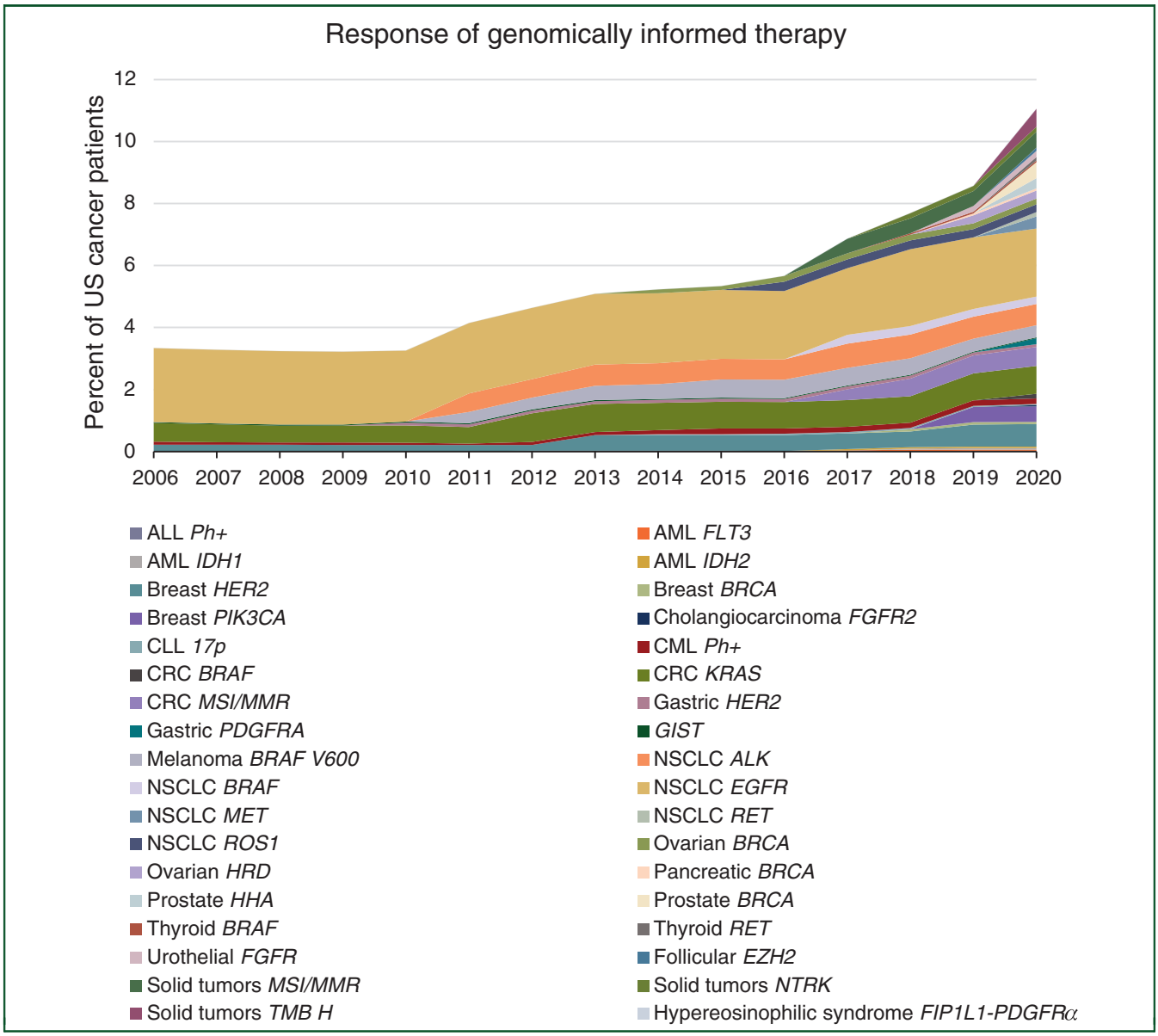


**Figure 4. Estimated response to genome-informed therapy in US cancer patients, 2006-2020.**
ALL, acute lymphocytic leukemia; AML, acute myelocytic leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myelocytic leukemia; CRC, colorectal cancer; NSCLC, non-small-cell lung cancer.

Fifthly, we did not differentiate between first-line, second-line, or third-line therapy drug approvals. For example, in AML with an *FLT3* mutation, midostaurin for newly diagnosed and gilteritinib for relapsed/refractory disease treat a different patient population; however, gilteritinib is applied to all AML patients with *FLT3* mutation from 2018 to 2020.

Finally, because there is often a lag between the diagnosis of cancer and death, and because we used deaths as a surrogate marker, our estimates may be biased. However, because we were comparing years, the bias would be similar from year to year.

### *Conclusion*

In conclusion, we found that the percentage of US cancer patients who are eligible for and respond to genome-targeted therapy has increased over time. Most of the increase in eligibility for genome-targeted therapies was seen after 2018, whereas most of the increase in response was seen before 2018.

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## DISCLOSURE

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