Three Steps Toward a More Sustainable Path for Targeted Cancer Drugs

Spending on cancer drugs in the United States has increased substantially over the past 5 years, from $26 billion in 2012 to more than $45 billion in 2016. Targeted cancer drugs, including small molecules, monoclonal antibodies, and other therapies based on genomic and related analyses, contributed 60% of this spending growth. One estimate suggests that by 2021, cancer drugs will comprise one-quarter of the US late-stage pharmaceutical research and development pipeline, and 87% of these products will be targeted agents.

Imatinib, the small-molecule oral tyrosine kinase inhibitor for chronic myeloid leukemia (CML), is often cited as the model targeted cancer drug; imatinib is highly effective and has reduced toxicity vs previous therapies. For patients with CML treated with imatinib, overall 10-year survival is 84%. Introduction of imatinib was associated with a reduction in US age-adjusted CML deaths per 100,000 persons from 0.9 in 1996 to 0.4 in 2006. In 2015, the Medicare estimated monthly price for imatinib was $9299.

Yet most targeted cancer drugs do not extend life to nearly the same degree. Even though many cancer drugs show improvement in surrogate measures, such as progression-free survival, substantial improvements in overall life expectancy have been rare. For example, in 2017, neratinib was approved for patients with early-stage breast cancer after improving invasive disease-free survival by 2% (from 92% to 94%) after 2 years of follow-up, without published survival data. The estimated monthly price of neratinib is $10 500.

Neratinib exemplifies the promise of targeted therapy, whereas neratinib exemplifies the concern: marginally effective treatments that, in aggregate, strain US health care spending. The distorted pricing of marginally effective drugs risks crowding out the capacity of the US health system to pay for highly effective cancer drugs or other therapies of public health importance, potentially jeopardizing valuable innovation and escalating out-of-pocket expenses. The combination of high prices and marginal effectiveness is unsustainable.

We propose 3 steps to promote targeted cancer drugs that yield meaningful clinical benefits while reducing overall price growth. The recommendations are informed by discussions of a group of experts from health care economics, policy, law, and regulation; cancer research and medicine; patient advocacy; and the pharmaceutical and insurance industries.

The FDA Should Define Minimum Clinically Meaningful Effect Sizes

The FDA has 2 pathways to approve new drug applications. The regular approval pathway is based on demonstration of “clinical benefit,” which is defined as prolongation of life, a better life, or “an established surrogate.” The accelerated approval pathway, in contrast, is based on a surrogate measure reasonably likely to predict clinical benefit. In 2007, the FDA issued guidance on cancer trial endpoints to support claims of benefit. The guidance referenced approval as being “highly dependent on ... effect size” but did not specify minimum effect sizes.

An essential question thus remains unanswered: what minimum effect size defines meaningful benefit? This ambiguity is particularly problematic in increasingly common scenarios, such as when new targeted cancer drugs demonstrate statistically significant but clinically questionable improvements in surrogate measures.

The FDA should develop guidance on minimum clinically meaningful effect sizes for cancer drugs. This would clarify prior FDA guidance and move from the current uncertain concept of meaningful clinical benefit to a consensus-driven definition. The agency could empanel multidisciplinary advisory councils of scientists, oncologists, patient advocates, and industry representatives to achieve this aim.

Clinical experts already support the principle. After convening work groups to define clinically meaningful outcomes for 4 malignancies, the American Society for Clinical Oncology (ASCO) endorsed a minimum absolute improvement of 3 to 6 months in overall survival over best available treatment for drug trials among patients with metastatic disease. Guidance could separately address cases in which, despite little or no change in median overall survival or hazard ratios, small proportions of patients experience large gains and the challenge of estimating benefits when pivotal trials involve head-to-head comparisons against active controls, thereby potentially underestimating the overall efficacy of novel agents.

By defining norms, the FDA would encourage manufacturers to design trials that demonstrate clinically meaningful benefits. The FDA could consider these thresholds in weighing benefits and risks for the purpose of approval decisions, payers could use them to better bargain on price and formulary with drug makers, guideline writers could use them to prioritize among drugs with similar indications, and clinicians and patients could use them to improve shared decision making.

Medicare Should Negotiate for Targeted Cancer Drugs

Medicare is the largest purchaser of cancer drugs. Medicare pays for targeted cancer drugs through Part B, which covers infused drugs, and Part D, which covers prescription drugs. The law, however, prevents Medicare from directly negotiating with manufacturers on drug prices. Instead, in Part B, Medicare pays for drugs under the buy-and-bill system, in which hospitals and physician offices purchase drugs and bill Medicare at 6% above the average sales price. In Part D, Medicare plan sponsors, typically...
insurance companies or pharmacy benefit managers, manage pricing negotiations. The law also effectively ensures that Medicare Parts B and D cover all FDA-approved cancer drugs for on-label indications as well as off-label indications listed in approved compendia, provided they are not a "protective class". Consequently, Medicare cannot exercise price leverage through coverage determinations or formulary design.

Congress could direct the Centers for Medicare & Medicaid Services (CMS) to conduct a demonstration project in which Medicare negotiates the prices of targeted cancer drugs paid for by Parts B and D. The demonstration also should authorize Medicare to apply limited formulary tools, such as coverage restrictions or tiering, to marginally effective targeted cancer drugs or targeted cancer drugs with therapeutic alternatives. Alternative drugs should include not only biosimilars but also chemically or biologically different drugs with overlapping indications and benefit-risk profiles. Protected classes could be narrowed to permit exclusion of drugs with overlapping indications or mechanisms of action. An appeals process could address special cases. Advisory panels with diverse and relevant expertise, including patient advocates, could inform pricing discussions and formulary design.

Granting Medicare the ability to negotiate on price and use a formulary is politically challenging. The National Academies, the Medicare Payment Advisory Commission, and others have recommended that the federal government use its bargaining power to negotiate drug prices. This step could be operationalized either by Congress granting CMS authority as a single entity to negotiate with pharmaceutical companies or through competitive bidding. The program could phase in over multiple years, starting with clinical settings where therapeutic alternatives exist. This approach could foster evaluation and refinement based on lessons learned.

Guidelines Should Prioritize Drugs by Benefit and Price

Physicians and patients should be able to consider the prices of targeted cancer drugs along with their benefits and harms when selecting treatments. Evidence-based guidelines are best positioned to meet this need. Such guidelines should demarcate marginally effective from highly effective drugs. In addition, for cases in which 2 or more drugs or regimens have comparable benefit-harm profiles for an indication, guidelines should prioritize the lower-priced alternative.

Although organizations that produce practice guidelines have taken steps to incorporate costs, they should go further. ASCO could extend its value framework, which displays cost alongside net health benefit, to prioritize treatment regimens in its clinical practice guidelines. The National Comprehensive Cancer Network could rank-order treatment regimens in its practice guidelines, informed by its Evidence Blocks, which already evaluate affordability alongside other measures. In addition, other groups have developed reports on pricing, effectiveness, and value for cancer treatments and drugs more broadly that merit the attention of guideline writers.

Guidelines should also promote price transparency. To do so, they could report the estimated monthly price of cancer drugs, perhaps by using the amount reimbursed by Medicare. Although estimates of out-of-pocket expenses would be most useful to patients, and prices vary by payer, the Medicare payment amount correlates with patient co-insurance expenses and has the advantage of being a reference standard. Practice guidelines that rank-order targeted cancer drugs by clinical benefit and price and deprioritize marginally effective drugs could be influential, informing insurer value-based reimbursement programs and clinical pathways.

Conclusions

Successfully implementing steps to limit the use of high-priced, marginally effective drugs will be difficult; patients with life-threatening diseases may expect access to drugs despite their high costs and limited benefits. Nevertheless, the ultimate beneficiaries of these changes will be patients, who deserve the substantial efficacy, reduced toxicity and enhanced value that were the original promise of targeted cancer drugs.

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REFERENCES


