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Invited Commentary

Approval and Coverage of Cancer Drugs in England, Canada, and the US

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For approval of cancer drugs, the US Food and Drug Administration (FDA) is tolerant of uncertainty and prioritizes speed over other factors.[1] Most drug approvals are based on surrogate markers, such as tumor shrinkage in a fraction of patients (response rate) or delayed tumor growth (progression-free survival). These surrogates use arbitrary percentage cutoffs and are not optimized to ensure that a drug can improve the length or quality of life.[2]

Related articles pages 499 and 490

After a cancer drug is approved, insurance coverage usually follows. As cancer drugs are a protected class of medications that typically require coverage of all drugs that are approved within a therapeutic area, Medicare reimburses for cancer drugs approved by the FDA without price negotiation. Approval by the FDA often results in billions earned by a drug company.[3]

In this issue of *JAMA Internal Medicine,* Cherla and colleagues[4] and Meyers et al[5] provide fascinating insights into the decision-making processes for cancer drug approval and coverage in England and Canada. Both studies confirm several previous observations[6] and offer new information. In contrast to the US, in England and Canada, only a fraction of approved drugs eventually are covered, and often only after price negotiations or restriction of availability to the patients most likely to benefit.

In line with prior studies documenting uncertainty in the evidence base, Cherla et al[4] found that 27 of 45 approval decisions (60%) for oncology drugs by the National Institute for Health and Care Excellence (NICE) in England were based on the same surrogate markers that are used for accelerated FDA approval. Meyers et al[5] reported that in Canada, only 39 of 78 cancer drugs (50%) that received a positive recommendation from the pan-Canadian Oncology Drug Review relied on improved overall survival. Relying on surrogate markers makes the task of calculating formal cost-effectiveness challenging. Surrogate end points result in substantial uncertainty regarding the magnitude of clinical benefit (if any exists), which is a key input to a cost-effectiveness calculation.

Both articles also show that only a fraction of cancer drugs that are approved in the US receive broad coverage in these Western countries. In England, Cherla et al[4] found that among 73 drugs that were evaluated by the European Medicines Agency, just 45 (62%) were recommended for coverage by NICE, and 39 (86%) were recommended only after a confidential price discount. In Canada, Meyers et al[5] found that the pan-Canadian Oncology Drug Review recommended for coverage only 78 of 104 submitted drugs (75%) for solid cancers. Of the 78 drugs, 72 (94%) were granted only conditional approval, meaning that use of the drugs was restricted to subpopulations of patients with cancer for whom the medication would offer greater value (ie, have more favorable cost-effectiveness).

The differences between the 3 countries raise a key policy question: does the current US system of drug approval and reimbursement speed access to better drugs and lead to better outcomes for patients with cancer? The US system of approval of drugs with uncertain clinical benefit followed by mandated coverage by Medicare without any ability to negotiate on prices ensures access. It is less clear that the US system benefits patients with cancer.

The 2 studies and previous work highlight additional considerations. First, the US reliance on surrogate end points, such as response rate and progression-free survival, does not substantively speed the time to study results. In an analysis by Chen et al,[7] the time savings of using surrogate end points in lieu of overall survival for cancer drugs resulted in just 11 months of time savings across a drug development timeline of about 7 years.

Second, because cancer drug approvals in the US do not routinely document survival or quality-of-life benefits, it is difficult to perform accurate cost-effectiveness studies. Even if the US coverage decisions do not consider survival or quality-of-life benefits or costs, these factors are quite relevant in other countries, such as England and Canada. But the limited evidence base needed for US approval means nations that do calculate cost-effectiveness are also hampered in their efforts. Put another way, the well-intentioned effort to provide drugs to patients with cancer faster has led the US to approve and cover many expensive drugs with substantial uncertainty about their clinical benefit. These choices paradoxically lead other high-income nations to delay or abandon uptake of these medications entirely because of reservations about efficacy and value. The lack of information regarding clinical end points, a consequence of the low US regulatory bar, makes it more difficult for other countries to obtain the evidence they need to justify coverage.

Third, both studies[4,5] underscore the expansive scope and influence of the FDA in drug approval, coverage, and pricing decisions in other countries. Payment for all FDA-approved cancer drugs without price negotiation in the US is in stark contrast to the multilayered decision-making processes in England and Canada. In the US, the FDA is the regulator and formulary maker. The US approach provides little downward market pressure and works to keep drug prices high. High prices make the US the most valuable market for new drugs, which in turn leads to global development of drugs with marginal or unproven benefit and little focus on cost-effectiveness.[8]

Fourth, the cancer drugs available in England, Canada, and the US are not as good as physicians would hope for patients. Only 34 of 52 drugs that were considered by NICE had shown

survival benefits at any point. In Canada, the median improvement in survival among covered drugs was just 3.7 months.

Better cancer drug policy would empower patients with cancer and speed access to affordable medications that result in meaningfully longer or better lives. It is hard to not view the entire global cancer drug ecosystem as broken. Many cancer drugs come to market in the US and, eventually, globally at unaffordable prices and with massive uncertainty about their benefits and harms. Their uptake is often delayed in high-income Western nations because of justified and persistent doubts about value.

The goal of drug policy in all nations is to maximally improve outcomes with every dollar spent. Achieving this may even involve setting higher standards for new drugs at the time of approval. Government agencies with different mandates, such as the FDA and the Centers for Medicare & Medicaid Services, should have clearly defined roles and function independently. Lastly, the US should understand and pay attention to the dynamics of drug approval in other countries. We should consider the possibility that our drug policy has negative repercussions for patients with cancer worldwide.

ARTICLE INFORMATION

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