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ETHICS CASE

How Should Therapeutic Decisions about Expensive Drugs Be Made in Imperfect Environments?

Commentary by Leonard M. Fleck, PhD, and Marion Danis, MD

Abstract

Clinicians must inevitably make therapeutic decisions under nonideal conditions. They practice in circumstances that involve incomplete evidence. They deliver care in health care systems that are complex and poorly coordinated. Each of the patients that they take care of is unique while research offers evidence regarding relatively homogeneous populations of patients. Under these circumstances, many parties—medical scientists, reviewing agencies, insurers, and accountable care organizations—can and should contribute to optimizing the development, approval, funding, and prescription of therapies—particularly expensive and marginally beneficial therapies. In aggregate, they should aspire to achieve a pattern of fair, cost-effective therapeutic decisions to ensure a sustainable health care system. Here we offer some suggestions regarding decisions that physicians might pursue to facilitate fair and cost-effective patient care.

Case

Dr. C sits on a committee as part of his tertiary care center's accountable care organization (ACO) that is considering whether a new biologic, Expensivimab, should be included in the organization's bundled treatment plan for its patients. Expensivimab is a new humanized antibody that targets an apoptotic receptor. One study suggests that it increases tumor-free survival in late stage non-small cell lung cancer (NSCLC) by a median of six months relative to a drug approved several years ago. Another suggests that it increases overall survival by a month-and-a half relative to the same drug. Yet no research on the comparative effectiveness of Expensivimab relative to other interventions for NSCLC exists, and even data on the risks of Expensivimab relative to the older drug is scant.

Furthermore, assessing Expensivimab's cost-benefit ratio is difficult. Although Expensivimab costs $750,000 per patient, the United States Food and Drug Administration (FDA) did not request any data on trial participants' perceptions of their quality of life. Hence, no assessment of quality-adjusted life years (QALYs) or disability-

adjusted life years (DALYs) is available to assess the cost-benefit ratio of Expensivimab—either on its own or relative to other interventions.

Dr. C has grown worried about the increasing costs of drug coverage—especially relative to the potential benefits. Containing such costs is especially difficult because the Centers for Medicare and Medicaid Services (CMS), which determine whether Medicare will cover a drug and whose decisions many other insurers follow, are legally prohibited from negotiating the prices of such drugs. He worries that unless providers and insurers start to demand evidence regarding quality of life and benefits relative to other available drugs, pharmaceutical companies will have no incentive to investigate Expensivimab. In consequence, assessments of benefit will be only informed by standard clinical parameters such as time-to-mortality and tumor-free survival.

A similar committee at a nearby tertiary center's ACO decided that the drug was not part of its coverage. Dr. C fears that this only makes his ACO's decision more politically controversial. A decision to cover the drug would be seen as a disagreement with fellow experts, a message that may be particularly problematic when the precedent for covering oncologic agents has been to cover agents with similar benefits.

While considering how to vote, Dr. C's thoughts turn to two patients that he recently met. Ms. G is a 68-year-old woman who was just diagnosed with NSCLC. She could benefit from Expensivimab. Mr. J is 71-year-old patient with colorectal cancer who recently started a similar agent that has recently been approved for colorectal cancer and has a benefit profile similar to that of Expensivimab. Mr. J's drug is very expensive but costs slightly less than Expensivimab. Dr. C worries how he might feel the next time he sees Ms. G or Mr. J, knowing how his vote might affect patients like them. Dr. C considers what to say and how to vote at the upcoming meeting.

Commentary

As this case illustrates, clinicians must inevitably make therapeutic decisions under nonideal conditions. The health care systems they work in are administratively and economically fractured. Each of their patients is unique and incommensurable while clinical research offers evidence and guidelines based on relatively homogeneous populations. In commenting on this case, we will focus on policies that might facilitate cost-effective and fair therapeutic decisions for cancer patients generally.

The core ethical challenge for Dr. C is to be both a loyal advocate for the best interests of his cancer patients and a prudent steward of social resources with which he is entrusted. Ethicists disagree about the extent to which a physician must be an uncompromising advocate for the best interests of her patients [1-3]. In this essay, we argue that there are ethically acceptable ways of meeting this challenge, either by working through professional organizations to effect policy changes more protective of patient financial

interests related to cancer care or by holding sensitive conversations with individual patients aimed at helping them make more prudent financial choices regarding their own cancer care.

Patient-Centered Drug Coverage Policies

Physicians are responsible for a substantial fraction of health care expenditures. They authorize prescription drugs, surgery, home health care, diagnostic tests, and so on. They ultimately play an inescapable role in the distribution of medical resources. In the United States, for example, they are responsible for 60-70 percent of health care expenditures [4], which reached $3.2 trillion in 2015 [5]. Physicians would be ethically irresponsible if they simply acquiesced to cost restraints imposed by policymakers (in organizations or governments, for example), which means physicians are professionally obligated to engage with those policymakers, perhaps by questioning application of guidelines in particular cases. What policies, then, should Dr. C endorse?

First, whatever policies are endorsed ought to be patient-centered. That is, physicians must take account of the best interests of their patients as determined in part by the values of those patients. This does not mean that patients have a moral right to commandeer unlimited social resources. Given limited budgets, considerations of fairness and justice will limit what any patient can demand in the way of cancer care, especially with metastatic disease and a predictable terminal outcome. Hence, patient-centered care must be fair and cost effective.

Patient-centeredness is challenged by demands for evidence-based medical practice in accord with clinical guidelines generated with cost effectiveness in mind. Care that yields too little benefit at too high a cost is not cost effective. This is usually described as "low-value" care. Clinical guidelines are always based on patient populations and thus may poorly fit individual cancer patients with their unique medical histories, comorbidities, and genetic vulnerabilities. Still, ignoring such guidelines would often be medically, ethically, and economically irresponsible. So what should complex patient-centered care look like?

Given et al. [6] suggest a strategy of dynamic assessment of value in the context of high-cost cancer treatment. In particular, they discuss oral molecular agents similar to Expensivimab in the context of metastatic disease. They start by following the recommendations of the American Society of Clinical Oncology (ASCO) [7] to calculate the net health benefit (NHB) for a patient using these molecular agents. Their working assumption is that value for that individual patient changes as treatment unfolds. They write: "The value of treatment may hang on modest reductions in progression, tolerable adverse effects, and out-of-pocket costs that are not ruinous. Each dimension can change quickly as treatment progresses" [8]. In other words, the NHB can change significantly from the patient's perspective—for better or worse, depending on the

patient's values—as treatment proceeds. Patient-centeredness means that such changes will be looked for and responded to appropriately.

Perhaps there should be minimal concerns about costs for those oral molecular agents that yield years of gain in overall survival with tolerable side effects. Imatinib for chronic myeloid leukemia (CML) would be a good example, certainly for patients with minimal comorbid conditions. But imatinib is not curative and would need to be taken for years (at least eight years for first-line treatment to prevent disease progression), and it is very expensive. More precisely, the current list price of imatinib is over $120,000 per year, although its list price had been only $26,400 per year when it was introduced in 2001 [9]. Nothing has changed about that drug since 2001 to justify that price increase [10]. What does this mean from a patient-centered perspective?

Trade-Offs: Policies for Drug Coverage in the Real World

As reported in the *Washington Post*, Dianne Dale Watson, 77 years old, has been on imatinib for nine years watching her savings erode at the rate of $500 per month for that drug [9]. Research by Dusetzina et al. found that monthly copayments for imatinib ranged from $0 to $4,792 from plan-to-plan [11]. Obviously, such differences in cost have variable consequences for individual patients. Dusetzina et al. also found a 70 percent increase in the risk of discontinuing imatinib (or other tyrosine kinase inhibitors) for patients whose copayments were in the upper 75th percentile [11]. Surely these findings should be regarded as ethically problematic, given the sustained effectiveness of this drug for CML patients.

Accordingly, we suggest removing economic barriers—such as copayments and deductibles imposed by insurers or ACOs with an insurance role—for very effective cancer drugs. Individual physicians may have little ability to effect changes such as these, but physician professional organizations may have that ability if sufficient political courage can be mustered. What individual physicians can do is have conversations with their patients about costs that are aimed at helping patients make decisions that better accord with their values [12]. We also suggest that pharmaceutical manufacturers be held responsible for what is justly regarded as price gouging, as illustrated by media coverage of Valeant [13]. Many other pharmaceutical companies are open to the same criticism. For example, ARIAD Pharmaceuticals was challenged by lawmakers for raising the price of its leukemia drug, ponatinib, in one year from $114,960 to $198,732 [14]. We agree with lawmakers that such price increases are unconscionable.

If Dr. C endorsed the strategy of ignoring costs in the care of cancer patients, it would spare the consciences of physicians caring for individual patients with otherwise different capacities to pay, but it would be ethically and economically irresponsible since those costs would still be passed on either to taxpayers or to other insured individuals. To emphasize that point, ipilimumab, another drug that has proven quite effective in

treating advanced melanoma, in combination with nivolumab, costs about $300,000 for a course of treatment [15]. Saltz [15] proposes this mental experiment: in the United States, 589,430 cancer deaths were expected to occur in 2015 [16], presumably all from metastatic disease. If all these patients had available to them an ipilimumab-like drug (or drug combination) for their specific cancer, it would add $174 billion per year to health care budgets in the United States. Given limits on health budgets (established by willingness to pay taxes and insurance premiums), increased expenditures of this magnitude would likely prohibit the feasibility of addressing other health needs that lack the political visibility and social anxiety associated with cancer. That would not be an ethically defensible position.

Returning to the real world, the vast majority of new targeted cancer therapies have nothing like the efficacy hypothesized in that mental experiment. As Saltz [15] and others [17] have concluded, there is no rational relationship between the price of these drugs and their actual efficacy. Further, the efficacy of the vast majority of these cancer drugs is far below that of imatinib. Fojo and colleagues [18] examined 71 cancer drugs approved by the FDA for solid tumors between 2002 and 2014 and found that the median gains in progression-free survival and overall survival were respectively a very modest 2.5 months and 2.1 months. These drugs cost $100,000 or more per year. This is the world in which Dr. C must make some decisions.

Some Policy Options, Some Practice Options

Both of Dr. C's patients have Medicare coverage; the price of these drugs is the core problem. Medicare, with its more than 55 million covered lives in 2015 [19], should be able to extract large discounts from pharmaceutical companies. However, both Medicare and the FDA are forbidden by law from considering the price of these drugs in making coverage decisions [20]. Congress put these laws in place in 2004 as a result of heavy lobbying by Big Pharma that was aimed at preventing Medicare from bargaining for large discounts, as most European countries have been able to do [20]. No doubt those laws should be repealed, but Dr. C must make his decisions under current law.

The ACO and Dr. C do have options. Considerations of fairness (i.e., all patients with CML should have equal access to drugs like imatinib), just allocation, and maximizing patient welfare all speak in favor of making cost-effective decisions regarding these cancer drugs. The ACO should insist on adequate scientific evidence of a certain level of cost-effective benefit. For example, the ACO board could require a six-month median gain in life expectancy for a $100,000 drug for a certain indication. In our opinion, this might be regarded as a minimum benchmark for high-value care regarding these cancer drugs. It would send a signal to drug developers regarding what is acceptable. Few such signals exist now.

The ACO board members are few in number, which is to say, only minimally representative of a diversity of perspectives. Perhaps the necessary choices should be the focus of well-informed rational democratic deliberation [21], in this case, by all ACO members willing to invest the time. If a majority of members are willing to pay the additional costs associated with reducing the survival norm for coverage to four months and to accept the trade-off in either reduced benefits or higher costs that would be required, then few obvious ethical considerations would speak against such a choice. Likewise, while ethical norms advise treating like cases equally, there may be reasons to approve Expensivimab for some indications and not others. If adequate evidence suggests greater than a six-month median overall survival for colorectal cancer but only six-week median survival for NSCLC, then approving coverage for one indication but not the other would be ethically permissible. Note that the range around that median will also make things more ethically complicated. If the range of overall survival is two to eight months around a five-month median, not very much is ethically at stake. But if the range is from two months to four years around a five-month median, the ethical stakes are significant. Achieving sufficient agreement on some uniform policy for all these indications through a democratic deliberative process in these latter circumstances might be virtually impossible. What, then, might be ethically acceptable options for that ACO and Dr. C?

American political cultural is highly individualistic. Ethically acceptable options can be constructed congruent with that cultural background. For all those $100,000 cancer drugs that yield only very marginal benefits in terms of progression-free survival or overall survival, one option, in our opinion, would be an add-on insurance rider. Individuals would have to purchase such riders while disease-free with a disease-free family history, and insurance companies or ACOs could accept or reject individuals as they wished and price accordingly. These riders could be very expensive, which would underscore that this option was not cost effective, both for individuals and society. Financially well-off individuals could afford such riders. This outcome is not unjust since the likely benefits are marginal and uncertain. The riders could be embraced by individual ACOs and provide a competitive advantage if presented effectively and honestly ("working to save you money").

Alternatively, financial risk and responsibility could be shifted to drug companies in the form of value-based pricing or performance-based reimbursement [22-25]. As a hypothetical example, if a drug company's research showed a six-month median gain in overall survival for its drug, then it would receive only 10 percent of the drug price for patients whose survival gain was less than three months, 20 percent for less than six months, and full price for those who exceeded that six-month gain. The same percentages would apply if patients experienced intolerable toxicities within that six-month window and withdrew from using the drug. This approach is congruent with the dynamic value, patient-centered approach discussed earlier [8]. That is, patients would

be at dramatically reduced risk of financial toxicity if the drugs were too medically toxic or failed to yield predicted gains in life expectancy. Furthermore, these same value-based pricing rules would apply for all cancer drugs. Such a policy would not be disadvantageous to either Mr. J or Ms. G. Dr. C would be fulfilling his responsibilities as a physician, both as a patient advocate (or patient educator) and as a prudent user of social resources. This approach is essentially a form of consumer protectionism by government, which physicians can embrace in good conscience.

Finally, Dr. C should not endorse a policy that put in place high copays or coinsurance for targeted cancer therapies that are very costly and yield only marginal gains in life expectancy. Assume a required 30 percent copay by patients that would be affordable by the financially well- off exclusively. Further assume the benefits of the drug are marginal, so it might not seem to be unjust. However, it *is* unjust because the other 70 percent of those costs are being financed through a common insurance pool financed in part by the less well-off. Some drug companies provide coupons to the relatively poor to cover that copay. However, that practice only encourages the costly over-consumption of these marginally beneficial targeted therapies to the benefit of the bottom line of these drug companies but to the detriment of the just and cost-effective allocation of social resources.

Conclusion

In summary, we have argued that physicians have moral obligations to protect their patients from both unnecessary medical harms as well as financial harms associated with very expensive drugs that are likely to provide little benefit. At times, fulfilling this obligation will require that physicians work through professional organizations to effect policy changes at the state or national level that will provide necessary patient protections as well as a more just and prudent allocation of social resources. At other times, their obligations in this regard will require that physicians spend time with individual patients to help them make more informed choices regarding worthwhile care, as judged from both a social perspective and the perspective of that individual patient.

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Leonard M. Fleck, PhD, is a professor of philosophy and medical ethics in the Center for Ethics and Humanities in the Life Sciences in the College of Human Medicine at Michigan State University in East Lansing, Michigan. He is the author of *Just Caring: Health Care Rationing and Democratic Deliberation* (Oxford University Press, 2009). His research focuses on the role of rational democratic deliberation in addressing issues related to

health care cost containment and allocation, and more recently, he has explored a number of ethical and policy issues related to cancer, genetics, and precision medicine.

Marion Danis, MD, is head of the Section on Ethics and Health Policy in the Department of Bioethics at the National Institutes of Health (NIH) in Bethesda, Maryland, and is also chief of the ethics consultation service at the NIH Clinical Center. She holds BA and MD degrees from the University of Chicago and trained in internal medicine at the University of North Carolina. Her research focuses on reducing health disparities by addressing the social determinants of health and on finding strategies for fairly rationing limited health care resources by involving the public.

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