Controlling Healthcare Costs

Just Cost Effectiveness or "Just" Cost Effectiveness?

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Abstract: Meeting healthcare needs is a matter of social justice. Healthcare needs are virtually limitless; however, resources, such as money, for meeting those needs, are limited. How then should we (just and caring citizens and policymakers in such a society) decide which needs must be met as a matter of justice with those limited resources? One reasonable response would be that we should use cost effectiveness as our primary criterion for making those choices. This article argues instead that cost-effectiveness considerations must be constrained by considerations of healthcare justice. The goal of this article will be to provide a preliminary account of how we might distinguish just from unjust or insufficiently just applications of cost-effectiveness analysis to some healthcare rationing problems; specifically, problems related to extraordinarily expensive targeted cancer therapies. Unconstrained compassionate appeals for resources for the medically least well-off cancer patients will be neither just nor cost effective.

Keywords: cost-effectiveness; healthcare justice; QALYs; equity; targeted cancer therapies; National Institute for Health and Clinical Effectiveness (NICE); rule of rescue; medically least well-off; invisible rationing; bedside rationing

Introduction

Virtually no one denies the need to control healthcare costs, both for the benefit of society and for the benefit of individuals (whether healthy or ill).[1] Even advocates for the view that human life is priceless (no limits on spending to save or prolong a life) will concede that waste and inefficiency in health spending undermine their primary commitment, although Uwe E. Reinhardt, as well as all other economists, dismisses the pricelessness view as "silly" and "utterly romantic."[2] The basic problem is that healthcare needs (in a morally significant sense) exceed the financial capacity of even very wealthy societies to meet those needs. Over the past 50 years, numerous emerging medical technologies have dramatically expanded what generally would be identified as healthcare needs. There was no "need" for cardiac bypass surgery until bypass surgery had been invented and disseminated. If we assume that meeting healthcare needs is a matter of social justice, and if we accept that healthcare needs are virtually limitless but that resources, such as money, for meeting those needs are limited, then how should we (just and caring citizens and policymakers in that society) decide which needs must be met as a matter of justice with those limited resources? One reasonable response would be that we should use cost effectiveness as our primary criterion for making those choices. The goal would be the utilitarian goal of maximizing the number of quality-adjusted life years (QALYs) saved at the lowest possible cost (the key background assumption being that we need to accomplish this within a fixed budget).

Peter Ubel is a strong defender of the value of cost-effectiveness analysis for purposes of making reasonable and rational (unavoidable) rationing decisions. However, his ultimate conclusion is that cost-effectiveness measurement "can and

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should be improved, but it will still be an imperfect moral guide for rationing health care."[3] It will be imperfect because it will not take into account relevant considerations of healthcare justice. Cost-effectiveness analysis applied to healthcare distribution essentially reflects a utilitarian view of healthcare justice. In some range of circumstances, that will yield a just analysis of some distributive outcome; however, in other cases, it will not yield an adequately just result. The goal of this article will be to provide at least a preliminary account of how we might distinguish just from unjust or insufficiently just applications of cost-effectiveness analysis to some healthcare rationing problems, specifically, problems related to extraordinarily expensive targeted cancer therapies.[4]

Some Cases for Consideration

Consider the case of Mr. Krieger. The last 10 days of his life cost $323,000. He was 88 years old, had late-stage Alzheimer's disease, cardiac problems, brittle bones, and a broken hip, as well as necrotizing fasciitis, which had brought him to the emergency room.[5] From a cost-effectiveness perspective, those last 10 days would have been assigned a value of $116,280,000 per QALY (assuming 0.1 as the quality value of his life before treatment). Would it have been unjust if, on this basis alone, Mr. Krieger had been provided comfort care only and had been allowed to die? I think a negative answer to this question is obvious because there was no reasonable medical basis for expecting a good outcome.

David Eddy is a physician and health economist who is a strong advocate for using cost-effectiveness analysis to make allocation decisions. He imagines a scenario in which 1,000 women are working in a factory. They are concerned about their risk for breast cancer. The factory owner offers them $1,500,000 over 10 years to be used either to purchase annual screening mammograms or (at the time in 1991) autologous bone marrow transplants (ABMT) at a cost of $150,000 for women with metastatic breast cancer (believed at the time to offer a 10 percent chance of 3 year survival). If nothing were done, 36 of those women would die of breast cancer over 10 years. If ABMT were chosen, one additional life might be saved for 3 years. If screening mammograms were chosen, 29 women would still die of breast cancer over those 10 years but 7 lives would be saved. If each of those lives were extended for 20 years, then the cost per QALY would be approximately $10,000, whereas the ABMT option would yield a cost per QALY of $500,000.[6] If 80 percent of these women chose the mammogram option (which would be for everyone), that would seem to be rational, reasonable, and just. It is the most cost-effective option; it maximizes the number of lives and life-years saved; it has been freely chosen by the vast majority of these women; it is not a product of some ethical or cognitive bias. Do the 20 percent who did not chose this option have any just cause for complaint? No, because statistically, some of them will have their lives saved as a result of the annual screening mammograms that they voted against. Likewise, some of the women who voted against the ABMT option will die of breast cancer and not have available ABMT as a "last chance" option. The only conclusion I would draw at this point is that justifying this choice on the basis of cost effectiveness is not unjust *in this specific context*.

Controversy continues among health policy researchers regarding what should be regarded as a reasonable cost-effectiveness number per QALY. Space does not permit getting into those details. A widely used number is $100,000 per QALY.

This is related to the cost of renal dialysis in the United States, roughly $89,000 per year (in 2013 dollars), largely paid for through the end-stage renal disease amendments to the Medicare program.[7] The implicit ethical argument for this number is that if public resources can be used to prolong the lives of dialysis patients at this level, then fairness requires an equal level of commitment for non-dialysis patients faced with life-threatening problems and a costly but effective medical treatment option. The flip side of this argument might be construed to imply that individuals would not have a just claim to life-prolonging treatment options that had costs greater than $100,000 per QALY. However, that conclusion will often elicit strong public resistance.

Hemophiliacs used to have a life expectancy of approximately 20 years. With the development of clotting Factor VIII, hemophiliacs can now expect to live beyond the age of 50. Hemophilia has more severe and less severe variants. For patients with more severe variants, the mean annual direct medical costs for "on demand" treatment will be $184, 518. If those same patients receive instead "prophylactic" treatment, the mean annual medical costs will be $292,525.[8] Both these figures exceed that $100,000 cost-effectiveness threshold; however, I doubt that many people would conclude that it was ethically acceptable to allow these individuals to die prematurely and unnecessarily. Perhaps some ethical disagreement would exist in support of prophylactic treatment. This treatment does reduce the incidence of bleeding episodes and the need for emergency room visits, but it is costlier than "on demand" treatment; that is, waiting for a bleeding episode to occur. Still, many would argue that a just and caring society ought to support such prophylactic care for patients with more severe forms of hemophilia.

Gaucher disease is a lysosomal storage disease with a prevalence of approximately 1 in 70,000. Untreated, it will cause liver enlargement and severely debilitating bone disease. Today it can be treated with enzyme replacement therapy, either imiglucerase or eligustat. Both of these drugs have annual costs in excess of $300,000. If treatment begins with the emergence of symptoms, lifetime costs of treatment will be in excess of $6,000,000.[9] Pompe disease is a type 2 glycogen storage disease affecting 1 in 20,000 births, and treated with enzyme replacement therapy; specifically, the drug alglucosidase alfa. If treating an infant, this drug has costs of $300,000 per year; the annual cost for a 70 kg patient would be approximately $584,640. Idursulfate is used to treat Hunter syndrome, another enzyme deficiency disorder, at a cost of $375,000 per year. It has an incidence of 1 in 130,000. Galsulfase is another enzyme replacement therapy used to treat Maroteaux–Lamy syndrome at a cost of $365,000 per year.[10] None of these diseases is cured by any of these drugs. None of these drugs would meet current norms for cost effectiveness. However, these drugs are clearly very effective for most patients (because they replace a critical enzyme), and this allows both improved length of life and quality of life. Further, these patients have no effective alternative therapies. These latter facts would seem to warrant the conclusion that these patients have a just claim to these therapies.[11]

This is the moral logic that justified the federal government's putting in place, in 1972, the end stage renal disease amendments to the Medicare program, which would pay for renal dialysis or renal transplants for anyone having that medical need (regardless of insurance status). Dialysis represented a costly but effective intervention that prevented premature death. Interventions such as that, the argument goes, should not be denied to individuals for lack of ability to pay. Likewise,

interventions such as enzyme replacement therapy should not be denied to individuals simply because those interventions failed to meet some standard of cost effectiveness. Stated succinctly, sometimes equity trumps utility as expressed in cost-effectiveness assessments.

Being NICE: Just and Unjust Cost-Effectiveness Analysis

As noted, Peter Ubel is a strong advocate for the use of cost effectiveness in making rationing decisions and setting healthcare priorities. He has conducted a considerable amount of empirical survey research aimed at eliciting the sort of rationing decisions that ordinary individuals would endorse when there was an obvious conflict between equity considerations and cost-effectiveness considerations. He put the following scenario before a sampling of ordinary individuals as well as a sampling of bioethicists. He asked both groups to imagine two tests (test 1 and test 2), which were designed to identify individuals on Medicaid who were at low risk for colon cancer, but who might have an early treatable version of the disease. Test 1 was only half as expensive as test 2. However, test 2 was much better at identifying early colon cancer in a low risk population. The budget was such that test 1 could be offered to the entire Medicaid population and result in saving 1,000 lives. Test 2 could only be offered to half the Medicaid population (randomly determined) because of its greater cost, but it would save 1,100 lives. Which should be judged the morally preferable option? A total of 56 percent of the ordinary individuals and 53 percent of the bioethicists endorsed choosing test 1, despite the fact that fewer lives would be saved. Pressed for justification for their choice, a common refrain was that equity was more important than efficiency; all had a chance to have their lives saved with test 1.[12] This is certainly an interesting result, though what might have been more interesting would have been the results from an actual Medicaid population.

Ubel offers another scenario. Imagine that there are 200 patients needing a liver transplant in the next year, but there are only 100 livers available. There is a simple blood test that will distinguish the two groups based on the probability of surviving the transplant. In one version, the group is divided equally between an 80 percent chance of survival and a 70 percent chance of survival. In other versions, the ratio is 80/50 and 80/20. The results of the survey were that only 13 percent of respondents would give all 100 organs to the 80 percent group in the 80/70 version; 33 percent of respondents would give all 100 organs to the 80 percent group in the 80/50 scenario; and 24 percent would give all 100 organs to the 80 percent group in the 80/20 scenario.[13] Ubel concluded that three values ultimately constrain the application of cost-effectiveness/maximization assessments to various rationing/priority-setting decisions: (1) people want to give priority to severely ill patients, even when their treatments are not cost effective; (2) people want to give priority to patients who are chronically ill or disabled when it comes to life-prolonging interventions rather than apply strict QALY standards that would value less those life-years saved that were diminished by some disability; (3) people want health services and health outcomes distributed fairly, the intent being that all should at least have some chance to have their lives prolonged, which is why in the 80/20 transplantation scenario only 24 percent would give all 100 organs to the group with an 80 percent chance of survival.[14]

Ubel's ultimate conclusion is that cost-effectiveness assessment must be adjusted so that it can include these other widely endorsed value commitments. However, I wish to argue that this conclusion needs to be flipped. Our complex pluralistic sense of healthcare justice needs to be fundamental, then qualified in various circumstances by considerations of cost effectiveness. Equity must constrain utility and maximizing impulses. Equity must also constrain misplaced compassion.

I noted previously several examples of extraordinarily expensive enzyme replacement therapies that would clearly fail the cost-effectiveness threshold. Still, it would be unjust and unconscionable to deny those drugs to individuals who would otherwise suffer unnecessarily and die prematurely were they denied those drugs. The ethically relevant considerations that justify overriding cost-effectiveness norms are that these drugs are very effective in restoring individuals to something much closer to a healthy state. They are not curative, because these individuals need to be on these drugs for the remainder of their lives. However, they yield a reasonable quality of life with manageable side effects. Moreover, it is ethically relevant that the number of individuals who would be the beneficiaries of these drugs is very small. Hence, even though lifetime costs for each individual might be several million dollars, relative to the wealth of the United States or most countries in Europe the aggregate costs are still miniscule. The key conclusion here is that cost-effectiveness considerations are overridden justly in this case.

I will next call attention, for comparative purposes, to a change in policy enacted by the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom. NICE is responsible for judging whether new drugs or other diagnostic or therapeutic interventions yield sufficient benefit to justify their cost for purposes of inclusion or exclusion in the National Health Service (NHS). In general, interventions that yield a cost per QALY of less than £20,000 will be included, whereas interventions with a cost per QALY greater than £30,000 will be excluded. NICE's methodology for making these judgments is not a matter of pure cost effectiveness. NICE takes into account various social values well. An enormous amount of political and public attention has been given to these targeted cancer therapies, often collectively referred to under the rubric of "precision medicine."

In the United States, more than 70 of these drugs have received approval from the Food and Drug Administration (FDA) as being "safe and effective." However, these drugs are extraordinarily expensive and the median gains in life expectancy or progression-free survival tend to be marginal. More precisely, very few of these drugs in the United States cost less than $100,000 for a course of treatment (and the cost of many is closer to $200,000), and median gains in life expectancy tend to be measurable in weeks or months, not years. Keith D. Eaton et al. write, "Between 2002 and 2014, a total of 71 therapies for cancer were approved by the FDA. The median survival benefit of these drugs in the trials that led to their approval was 2.1 months."[15] Leonard Saltz, a physician researcher, calls attention to the CheckMate 067 Trial in which a combination of nivolumab plus ipilimumab was used to treat metastatic melanoma. That trial yielded a median gain in progression free survival of 11.5 months at a cost of $295,000 per patient (not including the cost of treating side effects). Saltz goes on, however, to draw out the economic and ethical implications of these trial results. With 600,000 annual cancer deaths in the United States, if one assumes that all these patients would have a just claim to other cancer drugs that might be equally efficacious and equally costly, the annual cost would be $174 billion.[16]

In the United States, Medicare, Medicaid, and private insurance companies do not operate with hard budgets. These payers guess at what their outlays might be for healthcare needed by patients covered by these programs; however, they are obligated to pay whatever needs to be paid no matter how far off their guess might have been. In contrast, the NHS in the United Kingdom operates with a hard budget, which, as will be discussed, has different consequences when NICE approves any of these targeted cancer therapies. NICE has approved some of these drugs for limited use and declined to approve others. This has generated some public pushback, often instigated by pharmaceutical companies concerned about constrained profits. Consequently, in 2009, NICE approved a deviation from its normal cost-effectiveness practices. They would give special additional weight to health gains from life-extending end-of-life treatments. Three conditions were attached to any justified invoking of this exception: (1) the treatment had to be indicated for patients with a life expectancy of less than 24 months; (2) there had to be adequate evidence that the treatment would yield a gain of 3 months over any alternative NHS treatment; and (3) the patient population expected to benefit had to be small. No specification was given of how small "small" had to be. Moreover, although the policy was general, in practice, its application was to these targeted cancer therapies.

The obvious normative question to raise is whether this deviation from prior practice was either just or justified. One of the arguments made in defense of the policy was that cancer was especially dreaded. However, this argument seems to be irrelevant or misleading at best. None of these targeted cancer therapies are curative of metastatic disease. Consequently, the "dread" is neither dissipated nor defeated. At best, it is simply postponed briefly. Might some argument be made that this deviation from the standard cost-effectiveness assessment practices is warranted for reasons similar to what would warrant funding the enzyme replacement therapies discussed previously? This seems to be an especially irrelevant comparison. The enzyme replacement therapies generally yield indefinitely large gains in life expectancy, as does Factor VIII for hemophiliacs. Both restore most individuals to something close to normal health. In contrast, these cancer patients have metastatic disease, which might be held at bay for some number of months. However, metastatic disease is a terminal condition; these drugs will not restore individuals to something close to normal health. Further, the vast majority of cancers occur in individuals of advanced age who are close to achieving or have exceeded a normal life expectancy. This point might bring to mind concerns about some form of discriminatory ageism. Such concerns would be legitimate if resources were unlimited and if there were no serious unmet health needs among the non-elderly in the United Kingdom. However, neither of these conditions would be satisfied by the NHS as things are now.

Richard Cookson raises the question of whether providing access to these drugs should be seen as ethically obligatory under the "duty to rescue" rubric.[17] That is, we clearly spend resources very inefficiently when we rescue young individuals who foolishly try to sail the Pacific in a 17 foot boat. As Cookson observes, however, such rescues give an individual the rest of a long life. This is precisely what is not true of individuals with metastatic cancer. A cure would be a rescue in an ethically relevant sense. Further, from the perspective of the use of societal resources, typical costly rescues are rare events; hence, total societal resources required are very tiny in relative terms. However, rescuing metastatic cancer

patients, as Saltz noted for the United States, could require as much as $174 billion per year. That would clearly have serious healthcare justice implications for the NHS.

Cookson also raises the question of whether "severity of illness" might justify NICE's deviation from its usual use of cost-effectiveness criteria.[18] Other language that might be used would invoke the special claims of needed care by those who are "medically least well off." However, this language yields an extraordinarily expansive range of patients whose healthcare needs would have to be covered at extraordinary cost-ineffective expense. Not only cancer patients are among the medically least well off. Patients in end-stage heart failure would also belong in this category, because they would generally have less than a 2 year life expectancy. However, they would have the option of a left ventricular heart device (LVAD) at a cost of approximately $250,000 in the United States. With this device, 30 percent of these patients might only survive an additional year; however, 30 percent might survive as long as 4 years. In theory, 200,000 such patients would be candidates for this device each year in the United States, which would suggest 40,000 in the United Kingdom. This would not be judged cost effective in the United Kingdom; however, these patients would clearly gain more life and a better quality of life than the cancer patients for whom this exemption has been made. That outcome for these heart failure patients would seem to be unjust for both utilitarian and egalitarian reasons.

We noted previously that the NHS must work within a hard budget, a budget that has been severely constrained for the past 5 years. This is especially relevant for assessing the justness of their end-of-life exemption. Two researchers, Marissa Collins and Nicholas Latimer, assessed the actual impact of this exemption in the period 2009–11. They calculated that the cost of the exemption for each of those years was £549,000,000.[19] This represented the loss of 15,098 QALYs in each of those years, because resources had to be taken from other portions of the NHS budget (where they would have produced more QALYs) in order to fund these cancer drugs. These authors put it another way as well: these costs represented the annual cost of dialysis in the United Kingdom for 21,544 kidney patients.[20] I will note that these authors are not saying that any dialysis patients were denied dialysis in order to pay for these targeted cancer therapies. However, what can be said is that no one knows precisely what healthcare needs were unmet because of this shift of resources.

One might imagine that the necessary savings were achieved through pure efficiency gains, which is to say that no actual health needs were ignored or unmet. However, that would be pure imagining. It could just as easily (and more likely) have been the case that some unknown number of patients were given less expensive and less effective drugs for their medical problems instead of more expensive and more effective drugs, in order to achieve the necessary savings. That would represent a portion of the loss of QALYs suggested by Collins and Latimer. The fact of the matter is that no one has any idea what trade-offs were actually made to achieve the savings needed to pay for those cancer drugs. This is invisible rationing. It is presumptively unjust because it is not possible to critically assess any of these trade-offs from the perspective of healthcare justice. They are effectively hidden from ethical assessment by virtue of their dispersion throughout the NHS. Affected patients would be unaware of the fact that they were less well off than they could have been and should have been.[21] Just policy decisions must satisfy what John Rawls refers to as the "publicity condition."[22] Just policy decisions,

along with their rationale and consequences, must be visible and transparent. Nothing should be hidden. This is precisely what is not satisfied by NICE's end-of-life exemption.

It is important to note that NICE is formally outside the control of the British government. That is, Parliament does not have the right to override any of NICE's decisions. This is actually a good thing, because it avoids having NICE's decisions corrupted by political meddling for partisan political gain. Still, the British government felt obligated to be responsive to the perceived public outcry that the needs of desperate patients with metastatic cancer were being ignored in order to save money, when there were these "promising" cancer drugs that had been approved in other nations. Consequently, the British government created a special Cancer Drug Fund (CDF), initially with £50,000,000, that cancer patients could access if they were denied access to these drugs by the NHS, perhaps because NICE had not approved these drugs. Few criteria determined who was eligible for these funds. As the reader might readily guess, the fund was quickly exhausted, and £1.27 billion had to be infused into the fund to keep it viable from 2010 until 2016. Researchers who assessed this fund came to the following conclusion: "The majority of cancer medicines funded through the CDF were found wanting with respect to what patients, clinicians, and NICE would count as clinically meaningful benefit. In addition, no data on the outcome of patients who used drugs accessed through the fund were collected."[23] That is a very telling conclusion, which permits obscuring any likely injustices brought about as a result of this effort.

The key conclusion I would draw from this analysis is that most of the decisions made by NICE in accord with their cost-effectiveness methodology are just or "just enough" (given that in these policy contexts we must usually settle for non-ideally just outcomes). However, NICE's deviation from their normal practice to create this special end-of-life cancer exemption was neither just nor justified. In this respect, cost-effectiveness analysis can be a valuable tool in the service of just allocation and rationing practices.

Just Cost-Effectiveness: More Ethical Challenges

In this concluding section, I will identify several ongoing or emerging ethical challenges related to just cost effectiveness. I will start with this. Context matters when it comes to interpreting and applying cost-effectiveness assessments. In the case of these targeted cancer drugs, cost-effectiveness judgments are typically made based on median progression-free survival or overall survival. The practical implication of this is that for half of the patients, the cost-effectiveness outcome will overstate the value of the gain achieved, whereas for the other half, it will understate the value of the gain achieved. As things are now, most of the time these facts can be ignored, because the results of cost-effectiveness analysis average out, as it is not known which individual patient falls on which side of the line. However, ongoing research is getting better and better at identifying various biomarkers that can predict before the fact which patients are likely to be poor responders and which patients are likely to be superior or super responders.[24] The obvious ethical question is whether that information ought to be used to justly provide or deny access to these very expensive drugs, at least at social expense.

A strict application of cost-effectiveness analysis would affirm the ethical legitimacy of denying these drugs to those likely to be poor responders. An ethical

concern, however, is that there is, in practice, no bright lines that separate poor responders from somewhat better responders, and that separate somewhat better responders from superior responders. Instead, the clinical reality will be a continuum. The ethical risk is that a predicted (moderately) poor responder would be unjustly denied access to a drug that might have yielded a barely cost-effective benefit. Alternatively, as things are now, some of these drugs, as in the United Kingdom with NICE assessment, might be judged not to be cost effective for some specific cancer. The practical implication of that judgment is that some individuals who would still have been superior responders will be denied access to that drug at social expense. Is this an injustice in current practice? Perhaps these sorts of outcomes represent "rough justice," and this might be the best that can be reasonably expected. Perhaps a fair process of rational democratic deliberation could yield a "just enough" policy decision, as in the David Eddy example. Such a process might be guided by cost-effectiveness considerations or might choose to override such considerations in light of other ethical values.[25]

Context matters; the fact that each of several interventions needed by a patient are each judged to be cost-effective does not necessarily yield a just claim to all those interventions if the aggregation of all the medical problems of that patient are likely to yield only a very small gain in either length of life or quality of life. Making such judgments would have to be the responsibility of a clinician caring for that patient, perhaps in an environment with strong pressures for cost control. Such circumstances are fraught with ethical pitfalls. This is what is often referred to as the problem of bedside rationing. Physicians may be excessively loyal to the interests of their patients, refuse to consider anything related to cost effectiveness in these contexts, and, consequently, command healthcare resources unjustly. Physicians can also be excessively loyal to the economic interests of the institution to which they are attached, with adverse consequences for the just interests of their patients. Marion Danis and Samia Hurst have identified some practical strategies for finding a just and reasonable balance among these competing pressures.[26] In the final analysis, however, nothing can substitute for ethical sensitivity and ethical integrity on the part of physicians in circumstances requiring astute clinical and ethical judgment.

Another challenge is: How should a commitment to patient-centered care be seen in relation to the use of cost-effectiveness analysis as a tool for the more just distribution of healthcare resources? Patient-centered care is supposed to be about physicians incorporating patient preferences and values as part of shared decisionmaking. This can be seen as part of what respect for patient autonomy means. However, respect for patient autonomy does not include the right of patients to command healthcare resources to which they have no just claim. In some cases, patients might have a just claim to care that is not judged cost effective, as in the hemophilia and enzyme replacement examples. In other cases, patients might have no such just claim.

Consider proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, evolocumab or alirocumab. These are new drugs that dramatically lower low-density lipoprotein (LDL), so-called "bad cholesterol." For patients with very high LDL levels (patients with familial hypercholesterolemia) these drugs significantly reduce the risk of heart attack or stroke. They have an annual cost of $14,500, and generally would have to be taken for the rest of one's life. Still, research shows that these drugs are not cost effective for this patient cohort, although no other patient

cohort would come close to benefitting as much from access to these drugs. To be precise, even though 316,300 major adverse cardiac events could be prevented in this cohort, the cost of achieving this would be $503,000 per QALY gained over much less expensive alternative interventions.[27] People could argue about whether or not some justice-relevant considerations would warrant funding this drug in the United States, but it is extremely difficult to imagine what would justify funding these drugs in the context of the fixed budgets of the NHS in the United Kingdom.

What I want to make a point about, however, is the anxious individual patient with LDL of 105 mg/dL. Patients with LDL above 130 mg/dL would be strongly advised to start taking a statin. There are 12,000,000 such individuals in the United States. Patients with LDL above 100 mg/dL would be offered a statin, which they could freely accept or reject. There are 70,000,000 such individuals in the United States. If those 12,000,000 individuals had a just claim to a PCSK9 inhibitor, which could reduce their LDL by 60–70 percent (compared with 17 percent with a statin), the aggregate annual cost for that drug would be $150 billion in the United States. It is impossible to justify this expenditure, even in the United States, given that all these individuals would be at lower risk than any individual with familial hypercholesterolemia (and that the cost per QALY would be somewhere far in excess of $1,000,000). Hence, neither justice nor a commitment to patient-centered care would justify giving the anxious patient with LDL of 105 mg/dL access, at social expense, to a PCSK9 inhibitor.

This brings me to a third justice-relevant challenge regarding cost effectiveness: price matters. If the price of PCSK9 inhibitors were reduced from $14,500 per year to $4,536 per year, then the cost per QALY gained for patients with familial hypercholesterolemia would just meet the $100,000 threshold.[28] However, that would still say nothing about whether that was a just price, nor would that justify the claim that this represented just cost effectiveness for that drug. In Europe, most countries are able to extract large discounts for many drugs because they bargain over price with pharmaceutical companies, with their entire population as a single buyer. In the United States, the Medicare program has 55,000,000 covered lives, but is forbidden by law from bargaining with pharmaceutical companies for comparable discounts. Congress passed that law at the behest of pharmaceutical lobbyists. Likewise, Medicare and the FDA are forbidden by law from using cost-effectiveness considerations in determining that a particular drug will be approved for coverage by Medicare.

To illustrate the effects of this law, the drug imatinib (GLEEVEC®) was introduced in 2001 to treat chronic myeloid leukemia. It is a very effective drug that has kept 70 percent of these patients alive for 15 or more years. Its initial cost was $26,000 per year. In 2016, the drug was priced at $146,000 per year, although nothing about the drug had changed during those 15 years.[29] An even more outrageous example is ponatinib (Iclusig®), also used to treat chronic myeloid leukemia. At the end of 2015, its annual price was approximately $120,000 in the United States; at the end of 2016 the price had been raised to $199,000.[30] Again, nothing had changed with regard to the drug itself or the cost of producing it that would have justified this price increase. Obviously, this alters what is judged to be the cost effectiveness of these drugs. Imatinib, a drug that some patients have been taking for 15 years as a life-sustaining drug, was cost effective in 2001, but would not be judged to be cost effective today. Still, it would be unconscionable for

Medicare, Medicaid, or any insurance company to refuse to fund the drug any longer because the drug had "become" cost ineffective, thereby condemning most of these patients to a premature death. However, continuing to fund the drug at these exaggerated and unjust prices means other that health needs would go unfunded, even though other interventions for those needs were more cost effective and made clearly just claims on social resources.

Finally, there is the challenge of fuzzy, ethically disingenuous, self-serving variants of cost-effectiveness analysis. A number of prominent academic economists have become paid consultants for pharmaceutical companies. Their job has been to construct cost–value assessments that would justify unconscionably high drug prices. Darius Lakdawalla is one such individual. He argues for his version of "value-based pricing" that essentially allows pharmaceutical companies to charge whatever the market will bear, often invoking the language of ethics disingenuously. He writes: "Payers often estimate the value of rare disease therapy by calculating the gains to treated patients alone. However, the value of a rare disease therapy does not only accrue to patients who consume therapy but to *all* premium-paying beneficiaries who are *at risk*, albeit low, of developing a given rare disease."[31] He also contends in that same essay that higher prices need to reflect "significantly greater altruism toward patients suffering from uncommon diseases with limited treatment options."[32] The reader might think of the enzyme replacement examples given previously, but this "rare disease" category would now include relatively small clusters of genetically defined cancer patients who might marginally benefit from those very expensive targeted cancer therapies. For pharmaceutical companies, altruism is priceless (and very profitable). Dana Goldman is another principal (with Lakdawalla) in a firm that they founded called Precision Health Economics. In another essay Goldman justifies the potential $150 billion annual cost for PCSK9 inhibitors in the United States by claiming that their net social value over 20 years would be between $3.4 trillion and $5.1 trillion. Given numbers such as that, any concerns about healthcare justice would seem trivial and distracting![33]

In conclusion, given limited resources and unlimited healthcare needs, cost-effectiveness analysis can be a useful tool in making just and reasonable healthcare rationing and priority-setting decisions at the societal level. However, its use needs to be constrained by considerations of healthcare justice endorsed through fair processes of rational democratic deliberation.

Notes

1. Dan Brock writes: "It is not possible, nor would it be rational or just, to provide all potentially beneficial care to everyone, no matter how small the benefits or how great the cost." Priority to the worse off in health-care resource prioritization. In: Rhodes R, Battin MP, Silvers A, eds. *Medicine and Social Justice: Essays on the Distribution of Health Care*. New York: Oxford University Press; 2002, at 362.
2. Reinhardt writes: "The second group among the opponents of cost-effectiveness analysis includes individuals who sincerely believe that health and life are 'priceless'—for them, cost should never be allowed to enter clinical decisions. It is an utterly romantic notion and, if I may say so, also an utterly silly one. No society could ever act consistently on such a credo." Reinhardt UE. "Cost-effectiveness analysis" and U.S. health care. *New York Times*, March 13, 2009; available at https://economix.blogs.nytimes.com/2009/03/13/cost-effectiveness-analysis-and-us-health-care/?_r=0 (last accessed 18 May 2017). See also Ubel PA. *Pricing Life: Why It's Time for Health Care Rationing*. Cambridge, MA: MIT Press; 2000.

3. See note 2, Ubel 2000, at 156–7.
4. There are numerous ethical and methodological issues that might be addressed with respect to cost-effectiveness and the use of QALYs. Among the more prominent are risk of age discrimination or discrimination against persons with disabilities. Several volumes would be required to address these issues. Good overviews of these issues may be found in: Menzel P, Gold MR, Nord E, Pinto-Prades JL, Richardson J, Ubel P. Toward a broader view of values in cost-effectiveness analysis of health. *Hastings Center Report* 1999;29(3):7–15. See also: Menzel PT. Can cost-effectiveness analysis accommodate the equal value of life? *APA Newsletter on Philosophy and Medicine* 2013;13(Fall):23–6; Schwappach DLB. Resource allocation, social values and the QALY: A review of the debate and empirical evidence. *Health Expectations* 2002;5:210–22.
5. Krieger L. The cost of dying: it's hard to reject care even as costs soar. San Diego: *The Mercury News*, February 5, 2012; available at http://www.mercurynews.com/2012/02/05/the-cost-of-dying-its-hard-to-reject-care-even-as-costs-soar/ (last accessed 19 May 2017). The author of this piece is Mr. Krieger's daughter who authorized all this care, thinking at the time that she could not choose death for the man who had given her life.
6. If ABMT offered a 10 percent chance of 3 year survival, then the cost per QALY is obtained by dividing $150,000 by 3, then multiplying by 10. Eddy DM. *Clinical Decision Making: From Theory to Practice*. Boston: Jones and Bartlett; 1996:110–20. Originally published as The individual vs. society: Resolving the conflict. *JAMA* 1991;265:2399–401, 2405–6.
7. See the University of California-San Francisco summary of renal disease statistics related to their "Kidney Project," n.d.; available at https://pharm.ucsf.edu/kidney/need/statistics (last accessed 19 May 2017). U.S. Renal Data System. *USRDS 2013 Annual Data Report: Atlas of End-Stage Renal Disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2014.
8. Chen S. Economic costs of hemophilia and the impact of prophylactic treatment on patient management. *American Journal of Managed Care* 2016; 22(4) (5 suppl):S126–S33.
9. Dussen L, Biegstraaten M, Hollak CEM, Dijkgraaf MGW. Cost-effectiveness of enzyme replacement therapy for type 1 Gaucher disease. *Orphan Journal of Rare Diseases*, 2014; available at https://ojrd.biomedcentral.com/articles/10.1186/1750-1172-9-51 (last accessed 19 May 2017). See also Weisman R. New Genzyme pill will cost patients $310,250 a year. *Boston Globe*, September 2, 2014; available at https://www.bostonglobe.com/business/2014/09/02/new-genzyme-pill-treat-rare-gaucher-disease-will-cost-patients-year/5thkIb587nKi7zRAb9GgxM/story.html (last accessed 19 May 2017).
10. Harrison R. 5 very expensive rare disease treatments. *Rare Disease Report*, February 23, 2016; available at http://www.raredr.com/news/5-very-expensive-rare-disease-treatments (last accessed 19 May 2017).
11. Niklas Juth would not agree with this conclusion. He rejects the claim that these rare diseases have some special just claim to resources compared with the claims of more common diseases. He is especially concerned that the number of rare diseases is increasing rapidly because of the way in which cancer subgroups are being carved out on the basis of the genetic character of a cancer and its responsiveness to these very expensive targeted cancer therapies. I address that concern subsequently in the article. See Juth N. For the sake of justice: Should we prioritize rare diseases? *Health Care Analysis* 2017;25:1–20.
12. See note 2, Ubel 2000, at 78–80.
13. See note 2, Ubel 2000, at 82–5.
14. See note 2, Ubel 2000, at 156–7.
15. Eaton KD, Jagels B, Martins RG. Value-based care in lung cancer. *The Oncologist* 2016;21:903–6. These researchers are citing the work of Fojo T, Mailinkody S, Lo A. Unintended consequences of expensive cancer therapeutics—the pursuit of marginal indications and a me-too mentality that stifles innovation and creativity. The John Conley Lecture. *JAMA Otolaryngology Head and Neck Surgery* 2014;140:1225–36.
16. Saltz LB. Perspectives on cost and value in cancer care. *JAMA Oncology* 2016;2:19–21. The CheckMate 067 Trial he references is reported in: Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *New England Journal of Medicine* 2015;373:23–34.
17. Cookson R. Can the NICE "end of life premium" be given a coherent ethical justification? *Journal of Health Politics, Policy, and Law* 2013;38:1131–50, at 1135–7.
18. See note 17, Cookson 2013, at 1146–7.

19. Collins M, Latimer N. NICE's end of life decision making scheme: Impact on population health. *BMJ* 2013;346.
20. See note 19, Collins 2013.
21. I have written extensively about the injustices associated with invisible rationing. Interested readers may consult: Fleck LM. *Just Caring: Health Care Rationing and Democratic Deliberation*. Oxford: Oxford University Press; 2009, at 88–95.
22. Rawls J. *A Theory of Justice*. Cambridge, MA: Harvard University Press; 1971, at 133.
23. Cohen D. Most drugs paid for by £1.27bn Cancer Drugs Fund had no "meaningful benefit." *BMJ* 2017;357.
24. Blanshard A, Stroud R. *Cancer Biomarkers: Ethics, Economics, and Society*. Kokstad: Megaloceros Press; 2017.
25. I have explicated in great detail what such a fair process of rational democratic deliberation ought to look like. See note 21, Fleck 2009, chap. five.
26. Hurst SA, Danis M. Rationing by clinical judgment. In: Danis M, Hurst SA, Fleck LM, Forde R, Slowther A, eds. *Fair Resource Allocation and Rationing at the Bedside*. Oxford: Oxford University Press; 2015:284–300.
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28. See note 27, Kazi et al. 2016, at 743.
29. Kantarjian H. The arrival of generic imatinib into the U.S. market: An educational event. *The ASCO Post*, May 25, 2016; available at http://www.ascopost.com/issues/may-25-2016/the-arrival-of-generic-imatinib-into-the-us-market-an-educational-event/ (last accessed 21 May 2017).
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31. Jena A, Lakdawalla D. Value frameworks for rare diseases: Should they be different? *Health Affairs Blog*, April 12, 2017; available at http://healthaffairs.org/blog/2017/04/12/value-frameworks-for-rare-diseases-should-they-be-different/ (last accessed 23 May 2017).
32. See note 31, Jena, Lakdawalla 2017.
33. Jena A, Blumenthal DM, Stevens W, Chou JW, Ton TG, Goldman DP. Value of improved lipid control in patients at high risk for adverse cardiac events. *American Journal of Managed Care* 2016;22(6):E199–207. For a critical assessment of Precision Health Economics and its principals, see Waldman A. Big Pharma quietly enlists leading professors to justify $1,000-per-day drugs. *ProPublica*, February 23, 2017; available at https://www.propublica.org/article/big-pharma-quietly-enlists-leading-professors-to-justify-1000-per-day-drugs (last accessed 23 May, 2017).