



Pharmacogenomics and personalized medicine: wicked problems, ragged edges and ethical precipices

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In the age of genomic medicine we can often now do the genetic testing that will permit more accurate personal tailoring of medications to obtain the best therapeutic results. This is certainly a medically and morally desirable result. However, in other areas of medicine pharmacogenomics is generating consequences that are much less ethically benign and much less amenable to a satisfactory ethical resolution. More specifically, we will often find ourselves left with 'wicked problems,' 'ragged edges,' and well-disguised ethical precipices. This will be especially true with regard to these extraordinarily expensive cancer drugs that generally yield only extra weeks or extra months of life. Our key ethical question is this: Does every individual faced with cancer have a just claim to receive treatment with one of more of these targeted cancer therapies at social expense? If any of these drugs literally made the difference between an unlimited life expectancy (a cure) and a premature death, that would be a powerful moral consideration in favor of saying that such individuals had a strong just claim to that drug. However, what we are beginning to discover is that different individuals with different genotypes respond more or less positively to these targeted drugs with some in a cohort gaining a couple extra years of life while others gain only extra weeks or months. Should only the strongest responders have a just claim to these drugs at social expense when there is no bright line that separates strong responders from modest responders from marginal responders? This is the key ethical issue we address. We argue that no ethical theory yields a satisfactory answer to this question, that we need instead fair and respectful processes of rational democratic deliberation.

Introduction: the ethical challenges of personalized medicine

We start with the recognition that the notion of personalized medicine has a built-in positive bias (and for good reason). Many drugs have dangerous and debilitating side effects. Whether those effects would manifest themselves in any individual was often a surprise. What medical researchers know today is that genetic features of an individual often explain negative responses to a drug whose intent is therapeutic. Thus, some individuals are (for genetic reasons) fast metabolizers of drugs, which may diminish the intended therapeutic effect of a specific dosing schedule. Other

individuals are (for genetic reasons) slow metabolizers of drugs, which may negatively enhance the effect of that drug with a specific dosing schedule. Individuals with the HLA-B*1502 allele are at risk for Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS-TEN) if they take the anti-convulsant carbamazepine [1]. Patients who are candidates for simvastatin therapy and who have a variant of SLCO1B1 are at increased risk of myopathy [2]. If those same patients have two copies of the SLCO1B1 variant, they have a 20-fold increased risk of myopathy.

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medicine pharmacogenomics is generating consequences that are much less ethically benign and much less amenable to a satisfactory ethical resolution. More specifically, we will often find ourselves left with 'wicked problems' [3], 'ragged edges' [4], and well-disguised ethical precipices.

This essay will focus on problems of health care justice related to extremely costly cancer drugs, such as trastuzumab. Trastuzumab costs about \$70,000 for a course of treatment. It is a monoclonal antibody used to treat women whose breast cancer is *HER2* positive, roughly 25–30 percent of these women. About 230,000 women are diagnosed with breast cancer each year in the United States (340,000 in the European Union), which means roughly 60,000 in the U.S. (85,000 in the EU) would be candidates for trastuzumab. That represents a potential cost of \$4 billion in the US. By itself this does not represent a serious problem of health care justice. But more than 30 such drugs have received approval in the United States from the Food and Drug Administration (and its analogues in Europe) for attacking various cancers, and many more are in various stages of development. In the United States alone the potential costs for these drugs would be in the tens of billions of dollars per year. This will raise problems of health care justice, which we sketch below.

Does every individual faced with cancer have a just claim to receive treatment with one of more of these targeted cancer therapies at social expense? If any of these drugs literally made the difference between an unlimited life expectancy (a cure) and a premature death, that would be a powerful moral consideration in favor of saying that such individuals had a strong just claim to that drug. But no one can justifiably make such a claim regarding any of these drugs. What the literature currently shows for the vast majority of these drugs is that they yield gains in life expectancy measurable in weeks and months. If the cost of many of these drugs is in the vicinity of \$100,000 that will imply incremental cost effectiveness ratios [ICERs] in the hundreds of thousands of dollars [5].

These ICERs prompt another question: In the universe of all the health care needs in our society, how high a priority (speaking either ethically or economically) ought these drugs to have when they seem to yield so little good at such a high price? One response is that these are cancer patients with no other options faced with a probable terminal illness. These drugs represent a 'last chance therapy' for patients who are clearly among the 'medically least well off,' that is, patients who are most deserving of societal compassion. Further, if these drugs offer some positive benefit in terms of extending meaningful life to them, then the cost of these drugs has no moral relevance. We ought to regard human life as being priceless (the argument goes), and consequently, assuring access to these drugs ought to have the highest priority, ethically speaking. However, as I argue below, this perspective represents an ethical precipice. It presents itself as representing maximal social empathy while in practice it would precipitate widespread invisible injustices.

An alternate response would take seriously the problem of cost effectiveness associated with these targeted therapies. What is needed is fine-grained targeting of these drugs. If subsets of individuals are much stronger responders to any of these drugs, that means we need to identify biomarkers that would allow researchers to identify those individuals, who would then have the strongest just claims to those drugs, especially if they were to gain extra

years of life as opposed to extra weeks or months. Those drugs would then have more reasonable cost effectiveness ratios. But then the 'ragged edge' problem emerges. Rarely will we have a medical bright line that separates the strong responders from the non-responders or extremely poor responders. Most often patients will be arraigned along a continuum. We can imagine a future in which we have developed excellent prognostic capacities for where any given patient will most probably fall along that continuum. However, that would still leave unanswered the question of where we should draw a line that would distinguish patients who were strong enough responders, who would have a just claim to that costly drug at social expense, from patients who were not quite strong enough responders, who would justly be denied that drug at social expense.

This sort of problem is what some policy analysts refer to as 'wicked problems,' problems that are 'devilishly difficult,' usually characterized in terms of ten distinguishing features [4,6]. These are problems that are fundamentally irresolvable in the sense that any solution we choose and implement will generate more problems just as 'wicked' as the first. Some problems of health care justice can be 'wicked' in precisely that sense.

Some cancer researchers, for example, look forward to the day when cancer will be a chronic disease rather than a terminal disease [7]. What they imagine is that cancer could follow the AIDS treatment paradigm. Just as HIV+ patients are given several drugs that contain HIV for a period of time, followed by additional drugs switched in and out as the virus mutates around the earlier drugs, so also with cancer. Patients might need to be given several targeted biologics that block different pathways that a cancer needs to grow and spread, never able to entirely rid the body of that cancer, but sufficiently effective that the cancer is contained. That would mean these patients were on several very expensive drugs (perhaps with costs of a \$100,000 per year or more) for a decade or two or longer. That eliminates the problem of very marginal benefit at very high cost. But it replaces it with a much larger problem of aggregated costs for very large cohorts of cancer patients, and additional costly cohorts of such patients with each passing year. This is one dimension of a wicked problem.

Cancer, of course, is primarily a disease of older patients. These patients do not have eternal life because they have been saved from cancer. Instead, they will have their heart disease with all the additional costs that would imply for this growing cohort of patients that in the past would have already died. Further, the majority of these patients might also become costly dementia patients. This is another dimension of that wicked problem generated by converting cancer into a chronic manageable disorder. Further, how do we pay for all this growing needed care? Would the non-life-threatening health care needs of the relatively young be underfunded to meet the expanding health care needs of the hyper-elderly? How can we make fair allocations of limited health care resources in the face of these wicked problems?

The 'Just Caring' problem: fair health care rationing

How can we control overall health care costs fairly? This is the problem of health care rationing. This is the larger context within which we need to think about cancer therapies and pharmacogenomics, both in the US and EU. In my own research [8] I have characterized this as the 'Just Caring' problem: What does it mean

to be a 'just' and 'caring' society when we have only limited resources to meet virtually unlimited health care needs? The limited resources would be money, either collected as taxes or insurance premiums. The 'unlimited' health care needs are tied directly to expanding medical technology. The practical implication of the 'just caring' problem is that health care rationing is inescapable. That is, individuals with genuine health needs (not wants) will have to be denied needed health care likely to yield too little good at too high a price from some social perspective. If the need for health care rationing is inescapable, who should have the moral and political authority to make just rationing decisions? I argue that just rationing decisions need to be self-imposed, not imposed by powerful economic interests on vulnerable patients. But by the same token, individuals as individuals cannot be expected to make just rationing decisions either. Instead, such choices need to be made through a fair public process of rational democratic deliberation.

Callahan [4] first called our attention to the link between emerging health technologies and what we identify as health care needs. For example, no Americans needed bypass surgery [CABG] in 1970 because bypass surgery had barely been invented at the time. But in 2010 in the United States we did more than 400,000 bypass surgeries at a cost of about \$70,000 each and 1.2 million coronary angioplasties at a cost of about \$40,000 each [9], roughly \$76 billion in health care costs in 2010.

More recent examples would include the left ventricular assist device [LVAD] for patients in late stage heart failure (\$200,000 per patient) and the totally implantable artificial heart [TIAH] for patients at risk of complete heart failure (\$300,000 per patient). In the United States 550,000 new patients are diagnosed each year with heart failure [9]. In 2010 about 5,800,000 Americans were living with heart failure and 17,600,000 were living with coronary heart disease [9, at e56]. How many of these patients in late-stage heart failure ought a 'just' and 'caring' society to offer either the LVAD or the TIAH at social expense to prevent a 'premature' death when that society has only limited resources to meet virtually unlimited health care needs? These are patients in their late seventies or beyond, which ought to precipitate reflection on what ought to count as a premature death for purposes of allocating costly life-prolonging resources.

In 2011 the United States spent \$2.7 trillion on health care, roughly 17.9% of our GDP. In 1960 total health expenditures were just \$26 billion or 5.2% of GDP. Projections to 2019 along this same trend line put expenditures at \$4.5 trillion, or about 19.8% of projected GDP [10]. Health care expenditures have been increasing over the past 40 years at about 7% per year, roughly 2.5 times the core rate of inflation in the US economy. This is not a growth path that is sustainable into the indefinite future, which is why health care cost containment has emerged as a top priority policy issue in the United States. Although countries in Europe spend much less on health care as a fraction of GDP (6–11.4%) all are facing the same moral and economic pressures for controlling health costs. Further, the wicked problems precipitated by emerging medical technologies and associated escalating costs seem no more amenable to resolution by appeals to solidarity as a moral norm than appeals to justice or equal rights.

Although new medical technologies have been the primary driver of escalating health care costs, the aging of the population

in both the U.S. and the EU has also been a major contributor to this trend. In the United States about 35% of all health expenditures are attributable to the 13% of the population in 2011 over the age of sixty-five. Consequently the Medicare program is expected to increase in cost from \$530 billion in 2010 to almost \$1 trillion in 2019 [10]. Also, our past medical successes have contributed to an increasing burden of chronic illness within the population as a whole, especially among the elderly. Roughly 23% of the Medicare population is burdened with five or more chronic illnesses [11]. Over the past 30 years our successes in cardiology have reduced by 50% expected deaths from cardiac disease. That means more people are living with cardiac disease, along with their cancer or stroke or COPD and arthritis and Alzheimer's disease. Again, this is as true in Europe as in the U.S.

In all Western countries cancer needs more effective interventions. Since 1999 cancer has actually been the leading cause of death in most Western countries for those under age eighty-five [12, at 222]. In the United States there were about 580,000 deaths from cancer in 2010 [12] while in the European Union there were about 1.3 million cancer deaths [13, at 948]. Targeted biologics are extraordinarily costly drugs that represent a novel approach to attacking various cancers. Their primary medical virtue is that they are precisely targeted to interrupt pathways necessary for cancers to sustain themselves, thereby minimizing the collateral damage that has generally been associated with chemotherapeutic agents. The primary medical vice of these drugs is that they are extraordinarily expensive with costs in the range of \$50,000 to \$130,000 for a course of treatment.

Such costs would be reasonable, if, for example, these drugs were curative or if they yielded many extra years of high quality of life. But these drugs generally yield only extra weeks or extra months of life. Thus, Fojo and Parkinson [14] point out that bevacizumab for non-small cell lung cancer yields an average gain in overall survival of about ten days at a cost per Quality Adjusted Life Year [QALY] of about \$1.2 million; erlotinib for pancreatic cancer yields a gain in overall survival of 11 days at a cost per QALY of about \$660,000; bevacizumab for breast cancer yields a gain in overall survival of six weeks at a cost per QALY of about \$496,000 and cetuximab for non-small cell lung cancer yields a gain in overall survival of about five weeks at a cost per QALY of about \$401,000. They conclude, 'Increasingly, the advances observed in clinical trials that form the basis of approval do not translate into a *statistical or meaningful* overall survival (OS) benefit' [14, at 5972, *author italics*]. Certainly this seems like a reasonable medical scientific conclusion to draw. But cancer patients faced with a terminal prognosis do not draw this conclusion. These drugs represent for them a 'last chance' for a meaningful prolongation of survival. Ethically speaking, who has the right perspective?

Fojo and Parkinson also write, 'It is a truism that many cancer therapeutics provide marginal benefits to the majority of patients to whom they are administered' [14, at 5972]. The notion of 'marginal benefits' can be interpreted in two quite disparate ways, the one economic, the other medical. The economic interpretation calls attention to the unreasonableness of paying a very high cost for a very small benefit. But this is a point of considerable controversy. Many health economists will say that \$50,000 per QALY should be seen as the reasonable limit for any social health care expenditure. This number is typically linked to the cost of

dialysis for a year. Historically, this is linked to the United States putting in place the End-Stage Renal Disease [ESRD] amendments to the Medicare program in 1972. The British use £30,000 per QALY as a comparable limit.

The ESRD program provided public payment for either dialysis or kidney transplant for any patient with end-stage renal failure, no matter their employment status or insurance status or age. It was a sort of national health insurance *for these patients*. The implicit (moral and economic) argument of appealing to this patient group as a reference point was that if we were willing to spend \$50,000 per year to sustain the life of a dialysis patient we ought to be willing to spend an equal amount for any other patient faced with a life-threatening medical disorder for which there is an effective medical intervention. We can amend this argument a bit by noting that in 2010 the cost of a year of dialysis on average was about \$67,000. Critics, however, will add that patients on dialysis have a diminished quality of life and that the correct QALY figure in 2007 for a year on dialysis would be about \$123,000 [7]. Those same critics also note that the \$50,000 figure started to be used in the early 1980s; and consequently, if we adjust for inflation and the development of medical technology we ought to be willing to pay about \$197,000 per QALY [7]. Nadler *et al.* [15] found in a survey of oncologists that roughly half of them believed \$300,000 per QALY was not an unreasonable price for society to pay for these newer targeted cancer drugs. Lichtenberg, an economist, has been an ardent defender of the economic reasonableness of these drugs despite their extraordinarily high costs [16,17]. For now I am passing over this debate.

Although Fojo and Parkinson call attention to the high costs per QALY of these cancer drugs, their ultimate argument is a moral argument that rests on the substantially less controversial facts of marginal *medical* benefits for these patients and significant toxicity attached to these drugs. Granted, the toxic side effects of these more recent cancer drugs are generally significantly diminished compared to the side effects of older chemotherapeutic regimens, still the side effects can hardly be described as 'minor.' What Fojo and Parkinson conclude is that for the vast majority of patients currently receiving these drugs the marginal benefits associated with these drugs are outweighed by the toxic side effects. Consequently, if the prime moral imperative that ought to govern medicine is to 'do no harm,' then good doctors ought to refrain from offering these drugs to their cancer patients. This is not a conclusion that I imagine most oncologists would embrace with enthusiasm.

How could these drugs have become so widely disseminated if they represent a net harm for most patients? The answer that Fojo and Parkinson provide is that medical researchers have been too uncritically liberal in identifying biomarkers related to cancers that *might be* responsive to cetuximab or bevacizumab or other targeted drugs. Thus, they write: 'Yet in the FLEX trial, 85% of tumors were positive because positive was defined as 'immunohistochemical evidence of EGFR expression *in at least one positively stained tumor cell.*' They add: 'A marker found in 85% of patients in the FLEX study [18] and in 89% in a second cetuximab lung cancer trial [19] is hardly a paragon of personalized medicine' [14, at 5978]. Their ultimate conclusion is that '*the time has come for the era of personalized medicine to become a reality*' [14, at 5973]. In other words, despite all the rhetoric about personalized medicine having arrived, we are still very far from the goal of strong evidence-based

personalized medicine. To achieve that goal, they argue, we need to have a much more sophisticated understanding of the biology of various tumors that would then allow us to develop clinically useful and accurate diagnostic tests closely linked to medically appropriate targeted drugs. We could then identify patient subgroups likely to substantially benefit at an affordable social cost.

A recurrent theme in oncology journal editorials is that the cost of these targeted cancer therapies is not socially economically sustainable [20–28]. Further, this is not simply an economic problem; rather, it is a profound moral problem, a problem of health care justice [29]. These targeted cancer therapies have the potential to add tens of billions of dollars per year to the cost of health care in both the United States and Europe. Individuals in the U.S. with very good private health insurance would have virtually unlimited access to these drugs, although the cost of that insurance to both employers and employees would increase significantly each year. Employees are expected to bear more of these costs, and it feels like an imposed tax. But they also feel that they are potential beneficiaries. However, if these targeted therapies are supposed to be provided to the Medicare and Medicaid population, taxes would have to be increased to cover those costs. The well insured will increasingly resist paying such taxes (by punishing politicians who would raise those taxes) because they would not see themselves as beneficiaries of those programs. In addition health reform efforts elicit more intense resistance because this adds to the tax burden of the well insured without any perceived added benefits for them. The net effect is that access to needed and effective health care becomes even more unfairly distributed than is presently the case in the United States [15, at 2112; 30]. If increased taxes to the presently well insured are to be avoided, however, politically visible decisions would have to be made to deny the uninsured, the poor and the elderly access to these targeted therapies. That is, we would have explicit and politically divisive rationing decisions being made that were *prima facie* unjust from the perspective of medical egalitarianism.

Given the above scenario, the practical implication of the argument and analysis of Fojo and Parkinson is that if we successfully develop the scientific understanding and corresponding technology for precisely personalized medicine, then the politically divisive problem of health care rationing and the morally challenging issues of health care justice related to health care rationing would be minimized or dissipated. In other words, we would be spared having to make these morally and politically painful choices. We would have solved these otherwise irresolvable 'wicked' problems through diligent scientific research and innovative medical technological developments that reduced overall demand for these now very precisely targeted therapies. However, I deeply disagree with this excessively optimistic conclusion. We can achieve the technological breakthroughs that Fojo and Parkinson hope for, but we will still be left with the moral and political challenges associated with the 'Just Caring' problem, the need to do health care rationing fairly. One major reason for this conclusion will be the 'ragged edge' problem. But there will also be the problems of 'pricing human life' and denying desperate patients 'last chance' therapies. European nations with national health plans will not have the same political dynamic as in the U.S. but their commitment to a medical egalitarianism will be equally threatened by the 'ragged edge' issue.

Ragged edges, rising costs and rough justice

Targeted cancer therapies have had one major success that occurred more than ten years ago and that may have created excessively optimistic expectations. This was the drug imatinib used to treat chronic myelogenous leukemia [CML] [14]. The success occurred because CML was precipitated by a single 'driver' mutation whose cancerous effects (abnormal proteins) were effectively suppressed by imatinib for years [31,32]. *TIME* magazine put this drug on its cover in May of 2001, hailing the drug as a 'silver bullet' that was going to cure cancer. But it did not cure any cancers. Other mutations in the target of imatinib generated resistance to imatinib, usually after several years. More recently, two other BCR-ABL kinase inhibitors have been developed, dasatinib and nilotinib, that overcome that resistance. But they too will probably fail because of another mutation, T3151, although there is a third-generation drug that might inhibit T3151 [32]. If that proves true, then the ultimate hope is that a combination of these drugs would completely defeat or keep in check CML. What should we conclude from this, ethically speaking?

Do we have good reason to believe that with enough research persistence we can ultimately expect the same sort of success with regard to other targeted therapies for other kinds of cancer? Again, Fojo and Parkinson point out that what researchers are discovering regarding the complexity of the biology of various cancers would warrant more pessimism than optimism. 'Studies suggest extensive biological complexity within the historical classifications of colon, breast and pancreatic cancer as well as high-grade glioblastoma, a complexity far greater than our most pessimistic original expectations' [14, at 5972]. Should we (health care policymakers) conclude from this that we are making a serious ethical mistake by allowing unlimited clinical dissemination of all these other very costly targeted cancer drugs (ICERs of several hundred thousand dollars per QALY) that yield only extra weeks or extra months of life? Should we insist that before any of these other targeted cancer therapies can move outside limited clinical trials they must achieve a comparable level of success (multiple years of high quality life at reasonable cost) as with imatinib or dasatinib?

About 65% of CML patients given imatinib will achieve a complete cytogenetic response by 12 months, which predicts an average gain of five years before progressing to the accelerated phase of CML. That figure for a complete cytogenetic response at 12 months rises to 80% for dasatinib [33]. Is this too ambitious, too unreasonable, a norm of success to be ethically acceptable for determining who and when patients with other cancers would have a just claim to access other targeted cancer therapies outside clinical trials at social expense? Should we settle instead for a gain of three years of additional life expectancy of acceptable quality? Or two years? Or is one year enough? This is one illustration of what we (and Callahan) have referred to as the 'ragged edge.' These are crucial ethical challenges for both the U.S. and the EU.

We might say that ragged edges are ubiquitous in medicine. Patients with the same medical problem often respond in radically different ways to the same therapy. This is true and usually ethically uninteresting. But when we are talking about therapies that might make 'some difference' between a 'premature' death and 'some' gain in life expectancy an ethical assessment seems necessary. We should ask ourselves this question: What would justify a physician or health care policymaker saying to a patient

with lung cancer that the two extra months of life they *might* gain from bevacizumab or cetuximab for \$100,000 is just not worth it (as far as some private or public insurance plan is concerned)? We could ask the same question, except substitute four months or six months or one year. Anywhere we try to draw a bright line to eliminate the ragged edge will seem arbitrary and uncaring and unjust and incongruent with norms of solidarity.

One response to the ragged edge problem would be to follow the apparent pattern in the United States and allow any novel drug on the market that is safe and effective (no matter how marginal the degree of effectiveness), ignoring altogether the cost of achieving very minor benefits. Doing that, we could convince ourselves that we had dodged the ragged edge problem. If everyone with a specific cancer gets the relevant targeted therapy, then there is no ragged edge to be the focus of ethical concern. Of course the 'everyone' referenced here refers to individuals who are well-insured. All of them were treated equally, fairly, without any form of arbitrary discrimination. But the ragged edge (and the 'wicked problem' it represents) was not eliminated; it was simply displaced to another patient population less likely to attract ethical concern. In a cynical moment we could even say that all of the uninsured and underinsured are treated equally and fairly as well, not threatened by any arbitrary ragged edges, because they will all equally be denied access to any of these targeted therapies.

In a country such as the United Kingdom where all are covered by the National Health Service [NHS] ragged edges cannot be displaced in the same way. But the distinctive feature of the NHS is that it does have a fixed budget, as do the hospital trusts and Primary Care Trusts funded by the NHS. Thus, in 2006 the NHS was confronted with the question of whether to include trastuzumab [Herceptin] as a covered drug for women with metastatic breast cancer. The National Institute of Clinical Excellence [NICE] was charged with deciding this question. Their initial judgment recommended that the NHS not provide coverage because the medical research at the time showed a median gain of 5.5 months in life expectancy. But a 'grass roots' response was orchestrated by the manufacturer of the drug that resulted in a reversal of that recommendation. That meant that the hospital trusts had to provide trastuzumab to these women, but the NHS did not provide any extra funding to accomplish this due to budgetary limits.

No clinical judgments were made as to whether any individual woman would be a better or worse responder to the drug. (Roughly half these women are poor responders to this drug.) That avoids a morally perilous ragged edge among *these* patients. Instead, as reported by the Norfolk and Norwich University Hospital Trust, they expected to treat 75 women during the year with that drug. To cover those costs they expected to deny palliative chemotherapy to 208 other patients during the year [34]. This is where the ragged edge was displaced. Did that solve the ethical problem? Should we be morally confident that the additional suffering that had to be endured by the 208 patients denied palliative care was morally acceptable because extra months of life were provided to these women faced with a terminal prognosis? Should we always believe that it is ethically preferable to prolong life, no matter what the cost, no matter how marginal the gain, rather than spend money to relieve suffering that is not life-threatening? These questions can be considered in the light of the following example.

We saw earlier that Fojo and Parkinson hope to see the development of *very precisely* targeted therapies. That would control costs and reduce pressures for having to make morally perilous rationing decisions. A recent trial of patients with advanced breast cancer compared their being treated with paclitaxel alone to paclitaxel plus bevacizumab [35]. Median survival in those two arms was virtually indistinguishable: 25.2 months vs. 26.7 months. Bevacizumab increased median overall survival by six weeks. However, when specific genotypes were analyzed there were very marked median differences in survival.

The median overall survival times for the subgroup with the VEGF-2578AA genotype was 37.0 months and for the subgroup with the VEGF-1154AA genotype 46.5 months. In addition, if the VEGF genotype of an individual was AA/AA, median survival was 49.7 months. But if their VEGF genotype was AA/GA, median survival dropped to 30.2 months. And individuals with a VEGF genotype of CC/GG had a median survival of only 21.7 months. Finally, the AA/AA subgroup represented 7.6% of the cohort; AA/GA represented 11.4%; and CC/GG represented 32.9%.

About 44,000 women die of breast cancer each year in the US. Roughly 35,000 of these women would be HER-2 negative, which means they would be candidates for the following treatment. If all those women received paclitaxel plus bevacizumab, that would represent a cost of about \$3.5 billion for the bevacizumab. So how should we decide who among all these women would have a just claim to the therapy that included bevacizumab? What considerations of health care justice ought to determine our judgment? Should the fact that this is a 'last chance' therapy be determinative, or that all these patients are among the 'medically least well off,' or that human life is 'priceless'? If any of these factors are determinative, then no distinctions will be made among these patients so far as access to bevacizumab is concerned. All of these women are doomed to die because of the advanced nature of their cancer. Bevacizumab will not cure any of them, no matter what their genotype. But if we consider cost-effectiveness alone, then the AA/AA genotype subgroup has the strongest just claim. Each QALY achieved there would cost about \$50,000, and aggregate costs would be reduced to about \$350 million. Would the AA/GA subgroup have just cause to complain if their access to bevacizumab were not socially underwritten? They would only gain five months in additional life expectancy, which would yield a cost per QALY of about \$240,000. Aggregate costs for bevacizumab would then rise to about \$1 billion. This concession will hardly break the bank, given that in 2011 we in the US spent \$2.7 trillion on health care, or about 17.9% of GDP.

However, the next genotype subgroup on the list, CA/GA, would achieve a median survival of 27.1 months. This group represented 20.9% of that patient cohort and an additional \$1 billion in costs. This group would gain *on average* only two extra months of life above median survival in the paclitaxel alone treatment group, which yields a cost per QALY of \$600,000.

To many it might seem reasonable and fair to deny these individuals access to bevacizumab at social expense. However, we can imagine an egalitarian-based argument from those with this last genotype. In brief, if society is willing to spend \$100,000 to prolong the lives of each of those AA/GA individuals (same disease as me) for a very modest gain in life expectancy (five months), then society ought to be willing to spend that same \$100,000 for each of

us with the CA/GA genotype. We too want as much life as possible of acceptable quality, even if it is a bit shorter than someone else's. John Harris would make this argument against advocates for the use of cost-effectiveness to determine which lives to save. He writes, 'So long as people want to live out the rest of their lives, however long this may be, or looks like being, then they should be given the best chance we can give them of doing so and we should not choose between such people on any other grounds, but treat each as an equal' [36, at 110]. We could add (in the spirit of John Harris) that the \$600,000 figure is just a theoretical mathematical calculation. The *actual* amount of money spent on any of these patients would be the same \$100,000, whether the gain is two months, five months or two years.

If the work of Schneider *et al.* [35] is accurate, then we would have some very precise information regarding the effectiveness of bevacizumab for some seemingly sharply defined sub-groups of patients with advanced breast cancer. This is exactly the sort of information that Fojo and Parkinson would like to see developed to advance the field of personalized medicine. However, this work hardly eliminated any ragged edges. If anything, it multiplied them and created an even more complex ethical problem.

We might be inclined to say there is an obvious bright line/sharp edge between the 7% of these patients where the median gain in survival was more than two years compared to the next group (11%) where the median gain in survival was only five months. The implication is that Medicare and other health insurance companies (European health plans) ought to fund access to bevacizumab for these most genetically responsive breast cancer patients and deny it to all the others. However, the medical reality might be more complicated than that. The comparisons among the sub-groups are about *median* survival. So it might well be the case that some number of individuals in that 11% cohort, even if only a relatively small number, also survived for that additional two years or very close to that. It might also be the case that in the 7% cohort some number of individuals below the median survived for only an additional year or less. This would suggest some degree of actual overlap between the two groups, something best characterized as a ragged edge, morally speaking, rather than a bright line. Of course, we do not know with regard to any particular individual that that individual with metastatic breast cancer might have achieved those additional survival gains even if they did not receive bevacizumab. What then ought a just and caring society with limited resources and virtually unlimited health care needs do by way of underwriting the costs of this drug for these women?

In late 2011 the Food and Drug Administration [FDA] in the US withdrew approval of bevacizumab for metastatic breast cancer. The FDA Commissioner, Margaret Hamburg, wrote in her opinion that there might well be some 'super responders' to the drug but that the scientific evidence needed to identify them confidently was not strong enough to warrant continued approval for bevacizumab. This decision elicited an angry anonymous editorial in the *Wall Street Journal* [37] denouncing this decision and concluding that 'there's no denying that Dr. Hamburg's decision is an awful turn for anticancer progress and innovation, and especially for the women who may lose a treatment option in the time they have left to live.' The author goes on to decry the decision as 'another way of imposing a blanket government abstraction over the individual choices of a patient and her physicians.'

One of the perplexing responses to the Hamburg decision by Medicare and several private insurers was to say that they would continue to fund access to bevacizumab for these patients on a case by case basis. (In the UK the Cameron government created a £200 million cancer drug fund to accomplish essentially the same goal.) The obvious question to raise would be: What would be the objective, reasonable, fair basis for making such individual decisions? The FDA has a large number of leading experts in the field who endorsed the original decision. What would justify ignoring and overriding this expertise? Would this be a matter of an insurance company respecting the 'individual choices of a patient and her physician'? What basis would we have for believing those choices were suitably scientifically informed, reasonable and fair? Would we find in practice that women who were more assertive, better educated, and more willing to call upon a lawyer also more successful at gaining access to this drug at social expense while women who were less assertive, less educated, and less financially able to hire a lawyer were denied access to this drug? An outcome such as that would be neither fair nor reasonable.

Joe Nocera, another opinion writer, notes that bevacizumab is an enormously expensive drug that largely does not work in this clinical context and has serious side effects. He concludes, 'If we're not willing to say no to a drug like Avastin, then what drug will we say no to?' [38] What gets in the way of saying no? The short answer is that the ragged edge gets in the way. If we were to use a legal analogy, we could say that because life itself is at stake (a last chance therapy) we ought to make a negative decision only when we were 'beyond a reasonable doubt,' knew with near certainty that this drug was much more likely to yield a net harm rather than a net benefit for a particular patient in particular clinical circumstances. If we take this perspective seriously, then the practical implication will be that there will be no effective health care cost control, at least for patients who are well insured in the United States. Costs, of course, will be controlled. But if we cannot find just ways of addressing the ragged edge problem, we can be virtually certain that the methods by which costs will be controlled will be neither just nor caring.

If the ragged edge problem were confined to these patients with metastatic breast cancer and what was at stake were several billion dollars in additional health care costs, we could certainly afford to offer these patients this 'last chance' therapy. But the problem of the ragged edge is ubiquitous in medicine. The European Medical Agency recently approved panitumumab (Vectibix) and cetuximab (Erbix) as first line therapies with chemotherapy for patients with metastatic colorectal cancer 'with no mutations in the codon 12 and 13 of the KRAS gene' [39]. Both these drugs are extraordinarily expensive: more than \$100,000 for a course of treatment. Neither drug will effect a cure for the cancer. If these drugs are given to everyone with metastatic colon cancer, then the average gain in life expectancy will be a few weeks. If these drugs are given only to patients lacking the specified mutations, some of those patients might gain two extra years of life [40]. About 40% of these patients have a KRAS mutation predictive of non-response to these drugs. Another 35–40% with wild-type KRAS will have an objective response to these drugs. More recently, to further complicate matters, Blanke *et al.* called attention to 'a pooled data analysis suggesting that patients whose tumors harbor a codon 13, as opposed to codon 12 or 60 KRAS, mutation *might have at least*

some potential to benefit from cetuximab treatment' (my italics) [41]. What practical conclusion should we draw? Do these patients now have a just claim to cetuximab because they 'might have some potential to benefit'? May codon 12 patients demand that researchers must work harder to determine *for certain* that they have *no opportunity* to benefit from cetuximab? Further, until that *certainty* has been achieved, may codon 12 patients claim that they too have a presumptive just claim to cetuximab?

To put all of this in context, about 55,000 patients in the US died of colorectal cancer in 2010 (143,000 in the EU). If all these American patients had access to these drugs at \$100,000 for a course of treatment, that would add about \$5.5 billion per year to caring for these patients. In theory, several billion dollars could be saved if access to these drugs was restricted to individuals with a genotype that was most likely to be responsive to these drugs (the 35–40% with wild-type KRAS). Such a limited choice would be both morally and economically reasonable. However, future research will make this more morally complicated. Individuals with wild-type KRAS do not all show the same 'objective response.' Only some will achieve maximal gains in life expectancy [42]. Others will only gain extra months or a bit more than a year. We do not know whether additional genetic factors identified through future research will yield a picture of enhanced median survival comparable to what we described above in connection with advanced breast cancer. Would it be unjust to do the further research that will yield more restrictive access to these expensive drugs for patients with marginally responsive genotypes?

Would it be unjust to deny the whole cohort of patients access to these drugs at social expense who would only gain extra months of life (less than a year), especially when current practice often provides aggressive and expensive therapies to many sorts of end-stage patients who will gain only weeks or months of additional life? [43,44] But there are alternative scenarios that cannot be ignored as well. Thus, a recent article in the *Chicago Tribune* called attention to Mary Cipolla who, at age 89, underwent radical surgery for a rare type of pancreatic cancer. She is 101 years old today. Another woman received a balloon angioplasty at age 96 and celebrated her 100th birthday. At Northwestern University a 101-year-old woman received a new heart valve; she is now 102 [45]. Again, what should we conclude, morally speaking? The recommendation of one cardiologist is the following: 'Similarly, rationale for stents, devices, and surgery must be reconsidered in terms of their value with respect to the personalized clinical goals of each patient' [46, at 1805]. It is easy to imagine any oncologist saying the same thing. And, if the issue were a pure medical issue requiring *only* an assessment of medical risks and benefits from an informed patient's perspective, this would clearly be the correct response. But those patient choices also involve a claim on social resources, which may be just or unjust. This cannot be fairly resolved through a conversation between the patient and a clinician. A social choice and a social conversation are necessary, what I refer to as a process of rational democratic deliberation. Ragged edges mean 'rough justice.' The complexity and uncertainty associated with the science and clinical judgment will allow us to achieve no more than 'rough justice.' That in turn raises the question of how rough 'rough justice' can be and still be 'just enough'.

To summarize, our key question is this: What are the just claims of cancer patients to these expensive cancer drugs when they have

a genotype that would predict only a very modest gain in life expectancy? Alternatively, what are their just claims when they have a genotype that would predict a substantial gain in life expectancy (more than one year)? More specifically, is there a 'just enough' way of establishing limits regarding accessing these drugs when there is a seamless continuum of responses from very strong to relatively weak? I will argue that 'rough justice' (with its ragged edges) can be achieved and legitimated through suitably managed processes of rational democratic deliberation.

Just health care rationing and rational democratic deliberation

We begin with the claim that every patient faced with a potentially deadly cancer has a just claim to any targeted therapy that offers some promise of benefit, primarily extended life expectancy. The moral justification for this claim might take several forms. One would be that these targeted therapies represent 'last chance' therapies, that these patients are faced with a terminal prognosis, and they have no other options. An implicit premise in this line of argument is that it would be indecent and unjust to deny such desperate patients the only medical intervention that offered hope of prolonged life. Another rationale would be that these patients are clearly among the 'medically least well off,' and consequently, they ought to have very high priority for whatever medical interventions might benefit them [47,48]. Of course the major problem with these interventions is that they are so extraordinarily costly. But the response will be that human life is priceless. That is, if we have the medical or technological capacity to save or prolong a human life, then no amount of money should stand in the way. The practical embodiment of that perspective is the 'rule of rescue,' acted on whenever individuals are stranded at sea or on a mountain and so on.

I have bundled all these apparently disparate rationales together because they all have the same practical consequence. Specifically, they would distort our health care priorities in ways that would be unjust, imprudent and unaffordable. If all end-stage cancer patients had a just claim to these expensive targeted cancer therapies, the annual cost to our health care system in the US would be \$50–\$60 billion. This is affordable. However, no persuasive moral argument can be offered for restricting such social largesse to cancer patients. Virtually all end-stage patients would have the same moral right to whatever medical interventions could offer them any additional life expectancy. If this were really a strong moral obligation, we would have little ability to provide somewhat expensive health care that 'merely' improved quality of life, not length of life, such as somewhat expensive pain medications or various technologies that restored functional abilities otherwise lost to disease or accident. This outcome would be neither just nor compassionate.

To be clear, I am not arguing that considerations of health care justice would *never* warrant providing patients with terminal diseases 'last chance' therapies. Morally important distinctions must be made. Effectiveness matters. AIDS patients in 1995 were doomed to die within two years once they were faced with opportunistic infections. But protease inhibitors were discovered in 1996, and, more recently, fusion inhibitors. The cost of four-drug combination therapy is now about \$35,000 per patient per year, but these drugs are very effective in restoring a reasonable quality

of life for an additional ten to twenty years. The targeted cancer therapies we have been discussing offer nothing comparable in terms of effectiveness, and, as we have seen, their ICERs tend to be in the hundreds of thousands of dollars.

The logic of our moral argument does not put at risk the lives of persons with various disabilities, such as vent-dependent quadriplegics. Those individuals will often incur medical expenses approaching one million dollars for the first year after an accident. But again substantial functional restoration is usually possible through intense rehabilitation and reliance upon assistive technologies. If one reasonable basis for determining fair allocation of health care resources is a fair equality of opportunity principle, as Daniels has argued [49], then persons with these sorts of disabilities will have strong just claims to the services and technologies that will protect access to many functional opportunities for years. That range of opportunities (regrettably) is no longer available to individuals with end-stage cancers. What these individuals do have a strong just claim to is high quality palliative care that will ease their dying, and often prolong their lives as well [50].

This brings us to a second type of moral argument that might be invoked by these end-stage cancer patients with a genotype predictive of marginal benefits at best. They might say, 'I do not want high quality palliative care to ease my dying; I want these drugs that might prolong my living.' This plea is certainly understandable. However, respect for patient autonomy is often justifiably constrained by considerations of health care justice. That a patient desperately wants some scarce or expensive form of life-prolonging medical care does not justify a claim to that care. To be clear, in the case of non-scarce health care resources, such as these cancer drugs, justice will not absolutely deny access to these drugs. What justice denies is access *at social expense*. If individuals have the personal resources to purchase these drugs (without any type of social subsidy, such as tax deductions), no weighty moral considerations would justify denial of these drugs. This is because no other patients would have their just claims to these drugs (or other high priority health care) compromised by allowing the financially well off to buy these drugs. This issue is especially important in the United States in 2012 because we must define an 'essential benefit package' guaranteed to all as part of health reform. This package must be affordable for both government and individuals.

This brings us to an egalitarian argument for denying individuals these expensive cancer drugs because they have a genotype predicting only marginal responsiveness. We earlier called attention to Harris [36] who argued (in effect) that the size of the gain in life expectancy from these drugs was irrelevant to determining who would have a just claim. His view is that if anyone has a just claim to access these cancer drugs at social expense, then everyone who might benefit with only a few extra days of life would have an equally just claim. He sees himself as defending a principle of equal concern and respect.

What Harris is really defending is a radical egalitarianism, which is not rationally defensible, given the explosion of costly life-prolonging medical technologies. We need a more moderate egalitarianism. If we consider one medical condition at a time and ask whether we (in the U.S. or the EU) can afford to provide medical interventions to treat that condition for all who have that condition with any degree of effectiveness for whatever it might cost, we will almost always have to answer in the affirmative. But

in the real world there are endless health needs and a correspondingly enormous range of health care interventions that *might* positively effect a therapeutic outcome. Making no discriminations among those needs and interventions to protect the integrity of an ideological egalitarianism is neither rational nor just nor affordable.

When Harris advocates that everyone with an advanced cancer have access to these expensive cancer drugs, no matter how minimal the gain in life expectancy, he is in effect saying that he has gotten rid of the morally troubling (potentially discriminatory) ragged edges because all are being treated equally. Viewed in a perfectly abstract way, this claim will be true enough. In the real world, however, individuals will often have a cancer and some other life-threatening co-morbid conditions. An individual may be at risk of dying from his cancer in two years, but what is immediately threatening to end his life in three months is an advanced heart condition requiring a \$300,000 artificial heart transplant. If we are committed to Harris' strict egalitarianism, then we would be morally obligated to treat both the cancer and the heart disease (or the kidney failure, or the COPD or the end-stage liver disease, among others). This is another ragged edge. It is also an ethical precipice so far as health care justice is concerned. If human life is priceless and all must be treated in accord with a strict egalitarian framework, there is no rational moral basis for denying anyone life-prolonging medical care, no matter how little the gain, no matter how enormous the cost.

I have argued elsewhere [8, chap. 4] that our moral theories (given their generality) have only limited utility for addressing the very complex problems of fair health care rationing and priority-setting, such as we are discussing here. Our theories are simply too general to address all the morally relevant complexities and uncertainties associated with health care in the real world. This is what the philosopher, John Rawls, refers to as the 'burdens of judgment' [51, at 54–58]. This is the primary reason why in these complex medical moral circumstances we will often have several morally reasonable 'just enough' (or roughly just) options that we (collectively) could choose. Our norms of justice are necessarily a *social* construct. These are not matters that can be left to individual choice. We need very specific shared social understandings of what will be 'just enough' when we are faced with the need to make rationing decisions. To accomplish that, we need to utilize fair processes of rational democratic deliberation.

Our general theories of health care justice demarcate the moral space within which these deliberative discussions need to occur. They function very much like constitutional principles reasonably balanced in relation to one another and always subject to future modification in the light of future experience. These principles constrain the democratic deliberative process and would de-legitimate deliberative proposals that violated these boundaries. Considerable moral space exists within these boundaries, and consequently, for any particular health care rationing problem there will often be multiple possible resolutions that could be deliberatively endorsed and that will be 'just enough.' This will be true for our genotype and cancer problem.

Consider the following scenario. We (currently very healthy Americans or Europeans who have little knowledge of what future serious health vulnerabilities might afflict us) want to control overall health care costs and maximize the health good we accomplish

with the dollars or euros we spend on health care. We think of ourselves as moderate egalitarians and moderate utilitarians. We are increasingly aware of what personalized genomic medicine in relation to cancer (and other life-threatening medical disorders) might mean for us, both personally and collectively. We are reflective enough that we can say to ourselves (as individuals) that we would not want to pay \$100,000 of our own money for a cancer drug that promised us only an extra two months or five months of life. We see that money as being better spent on a university education for our grandchildren. But we understand the logic of the 'tragedy of the commons.' Our health insurance, whether public or private, is a shared resource. If others feel free to use \$100,000 to gain five extra months of life for a cancer treatment, then we might be tempted to do the same (because the perception is that it is 'someone else's money'). That, of course, is a mistake. So we must talk to one another for purposes of identifying reasonable restraints on the uses of those common funds. This is the beginning of the deliberative process.

We are certain that five extra months of life is not worth \$100,000, but two or three years of extra life of reasonable quality would be worth that. Should we then agree with one another that the 7% of individuals with a particular cancer and a particular genotype who are likely to get two or three extra years of life from a particular targeted cancer drug should have access to that drug at social expense? I realize that there is only a small chance that I might have the favored genotype for that cancer. But, then again, the chance that I would have that cancer and need that drug is very small as well. We can imagine that we now have available a \$1000 genome test. That is, my complete genome can be read for that reasonable sum. I find out that I am not among the favored 7% who might have access to this drug for this type of cancer at social expense. What would I see as the practical implication of that knowledge for my currently healthy self trying to determine with my fellow citizens whether public resources ought to cover the cost of that drug for that favored 7%?

I might be tempted to be stingy because I would now know that I cannot be a beneficiary of having access to that drug. Of course, the same will be true of 93% of my fellow citizens. I would know at least several thousand such facts, all of which will have only a tiny chance of having any practical medical relevance for me in the future. That would suggest I would vote down the vast majority of genetically linked funding for specific medical interventions, as would every one of my fellow citizens. Nothing would be funded related to personalized genomic medicine. That result might satisfy the radical egalitarian predilections of John Harris. But this would be neither a fair nor reasonable outcome. Thoughtful citizens would come to this realization through the deliberative process.

What do we imagine this deliberative process might look like? We start by emphasizing that this would be a 'rational' deliberative process. That means two things. First, these public conversations would be informed by the best medical evidence available at present. This evidence would be presented in a way that was intelligible to most lay people and as unbiased as reasonably possible (free of language likely to precipitate common cognitive errors). Second, the core of the deliberative process would be the giving of 'public reasons' [51] to one another for the particular health care justice judgments we as individuals would be inclined to defend with respect to a particular rationing issue. Public

reasons are the sorts of reasons citizens in a liberal pluralistic democratic society can reasonably give to one another as justifications for a public policy. These are reasons that are separable from what Rawls [51] would refer to as comprehensive religious or philosophic visions of what would count as a good life, such as the views of an ardent Right to Life activist. These reasons are also public in the sense that they must be broader than considerations of personal self-interest.

What do we hope to accomplish through this deliberative process with regard to our cancer and pharmacogenomics problem? We would have to create some 'bright lines' in place of the 'ragged edges' that are the clinical reality. Then we would have to judge how high a priority these targeted cancer therapies ought to have relative to all the other health needs we have in our society for which there are effective and costworthy medical interventions. We can briefly work through an example.

Consider our earlier paclitaxel/bevacizumab example in connection with advanced breast cancer. Perhaps we could agree that the minimal predicted gain in life expectancy ought to be one year at a cost of less than \$100,000 per QALY. The 'gain' would be over and above whatever the next best treatment reliably offered. If we did come to such an agreement, only 7% of women with advanced breast cancer would have a just claim to this cancer therapy at social expense. Would any of the other 93% have a just complaint in being denied access to this treatment at social expense, especially if during the deliberative process they vigorously objected to this rationing protocol? The short answer is negative. We have to keep in mind that the deliberative process is occurring among individuals who are mostly healthy and largely ignorant of what their future possible health needs might be. We are behind what Rawls refers to as a 'veil of ignorance,' which is what assures an adequate degree of impartiality in these public deliberations. Even those with an active and serious disease process are going to be rationally (prudentially) constrained with regard to the vigor of their advocacy for their own current health needs. Let me offer an illustrative example.

Imagine a 67-year old individual who has had a serious heart attack. He might be inclined to be an excessively vigorous advocate for every somewhat promising form of cardiac treatment no matter what the cost. But this would be imprudent and unjust and unreasonable. It would be imprudent because he would be vulnerable to many other medical problems associated with advancing age for which there are some costly but very effective therapies available that ought to be funded. And, being thoughtful, he would want them adequately funded for reasons of prudence and justice. Further, if he demanded that some number of very expensive marginally beneficial cardiac interventions be funded, such as LVADs at \$200,000 each for Stage IV heart failure, then millions of others could make precisely the same demands for comparable kinds of therapies whatever their specific medical problems might be. Further, we imagine that he would not be willing to pay the increased taxes or insurance premiums that would be necessary to fund such an expansion of the medical armamentarium. So there is a consistency requirement, both moral and practical, that prevents his justly demanding that all these marginally beneficial cardiac treatments be funded at social expense.

Another prudential consideration must be noted. If we collectively send a signal to pharmaceutical companies that we are willing

to pay exorbitant sums for marginal benefits, then these are the drugs they will be economically motivated to deliver. Prudence and justice would dictate that we send two other sorts of signals instead. One of them would be that there will be no market for drugs connected to end-stage disease processes if those drugs cannot deliver more than an additional year of reasonable quality life for less than \$100,000 [52,53]. The second signal would be that we want medical interventions that are costworthy and very effective in much earlier stages of chronic degenerative disease processes so that patients gain more high quality life years at a reasonable cost. In the context of targeted cancer drugs, that means we are not satisfied with reports of 'progression free survival' that fail to translate into anything more than very marginal gains in overall survival. The trade-off is that we shorten low quality end-stages of these degenerative diseases. This is not an abandonment of patients because we make instead investments in affordable palliative care.

If we achieve these sorts of agreements through a fair and reasonable democratic deliberative process, then individuals who disagree with a particular outcome will not necessarily have a just claim for their future possible self with a minimally responsive genotype to some expensive cancer drug. They have certainly not been discriminated against for morally corrupt reasons. Their fate may be unfortunate but it is not unjust. Again, to illustrate the point, we can imagine Mr. Smith at age 82 with this end-stage cancer demanding access to these drugs at social expense. However, at age 71 Mr. Smith developed life-threatening cardiac problems which were very effectively responded to with some costly interventions developed and funded through the funds we were no longer spending on very marginally beneficial end-stage cancer interventions. In other words, he has gained additional years of life at social expense that he otherwise would have been denied if we had a less just and less prudent approach to making these rationing and resource allocation decisions. The collective agreement that emerges from a fair and reasonable democratic deliberative process is what yields judgments that are both 'just enough' and 'legitimate enough.'

We can imagine yet another argument that might be offered by those in the 11% metastatic breast cancer group, just below our 7% group. The median gain in life expectancy for that group was five months. Again, however, there might be wide variation. Perhaps a small number in that group would be capable of achieving an extra year of life or more if they had access to bevacizumab at social expense. Would knowing this as a statistical fact (no capacity to identify ahead of time who those individuals might be) morally require that we fund access to bevacizumab for the group as a whole? No. An actual deliberative process might yield the exact opposite answer (and there might be no compelling moral argument to show that this was morally unjustified). What explains the possibility of such radically different judgments? We are at another 'ragged edge.' Those who advocate for either view need to explain to the others what they see as the most compelling justice-relevant considerations supportive of their view. One obvious response from my critic would be that we had agreed to a one-year-of-life-gained rule. That was what required providing funding for bevacizumab for the 11% cohort. Otherwise, we would be treating unjustly those in the cohort who might gain that year, even if only a tiny fraction of the cohort. My response would be that the rule applied when we had a high degree of medical

confidence (not certainty) that individuals would achieve that extra year of survival. We do not know that about *any specific individual* in that cohort. Should we concede that there is something 'less than just' in the view I am defending? I concede that. This is what it means to say that 'rough justice' is the best we can hope to achieve in these complex circumstances. Space does not permit delineating all the complex options and trade-offs that might also have been 'just enough' outcomes around cancer and pharmacogenomics. But a quick example of an unjust outcome might be helpful. Compromise is often seen as a fair and reasonable way of addressing complex moral and political problems. We might be tempted to suggest that we should not simply fund that 7% with the most favorable genotype and do nothing for the other 93%. So someone might argue for 50% social funding of these drugs for individuals with genotypes that are only marginally responsive. In that way no individual would feel 'abandoned.' However, this approach would create serious injustices because we would be providing social funding for these drugs for wealthier portions of our population. The lower three quintiles of our population would be very unlikely beneficiaries of such a policy because they could not afford the 50% co-pay. But if the social/

economic/moral judgment has been made that these drugs yield too little benefit at too high a cost in specific clinical circumstances, there should be no social subsidy at all for patients in those circumstances for all the reasons given above. There may be scientific reasons for believing some drugs currently yielding only marginal benefits could be tweaked with more research and clinical testing to yield a costworthy version of that drug. If so, clinical trials could be publicly funded and individuals in the relevant clinical circumstances from all socio-economic strata would have to be assured access to those trials, if they met the relevant clinical criteria. This policy would be 'just enough.'

The rational democratic deliberative process for which I advocate will not eliminate morally problematic ragged edges when it comes to health care rationing and the moral challenges associated with these targeted therapies. But, if done fairly, the ragged edges will be justly trimmed, the ethical precipices fairly fenced, and the wicked problems hewn to a roughly just texture. From a European perspective and the norms of solidarity the deliberative process will protect those norms from the moral and political fragmentation that is otherwise a probable consequence of the dissemination of personalized genomic medicine.

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