EDITORIAL



Precision Medicine and Rough Justice: Wicked Problems

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Abstract

What exactly is a "wicked problem"? It is a social or economic problem that is so complex and so interconnected with other issues that it is extraordinarily difficult or impossible to resolve. This is because all proposed resolutions generate equally complex, equally wicked problems. In this essay, I argue that precision medicine, especially in the context of the U.S. healthcare system, generates numerous wicked problems related to distributive justice. Further, I argue that there are no easy solutions to these wicked problems. The need for trade-offs is inescapable. Rough justice is the best outcome we can hope for, and that outcome requires a commitment to processes of public reason that are fair and inclusive.

Keywords: Precision medicine; wicked problems; rough justice; public reason; targeted therapies

How can anyone be critical of precision medicine? It sounds as if someone would prefer imprecise medicine, or "best guess" medicine. Precision medicine is scientifically elegant, but it is ethically and economically flawed. To be ethically precise, it generates copious wicked problems.¹

What exactly is a "wicked problem"? It is a social or economic problem that is so complex and so interconnected with other issues that it is extraordinarily difficult or impossible to resolve. This is because all proposed resolutions generate equally complex, equally wicked problems.² Further, the wickedness begins with the difficulty in defining the wicked problem, that is, identifying and agreeing upon what might be called either "the shape" or the "root cause" of the problem. This is not necessarily the result of either personal or political intransigence. More often, it is the result of intransigent facts. In the case of precision medicine, those intransigent facts include the wiliness of cancer itself (only partially understood), hard economic limitations, and conflicting, relevant, legitimate ethical norms (various understandings of distributive justice and its ethical weight relative to other ethical norms).

At the core of precision medicine are "targeted" molecular therapies and immunotherapies that target specific genetic mutations that drive cancer, either directly or by provoking a specific immune response. These targeted therapies are often successful in disabling these mutations. However, tumors tend to be genetically heterogeneous, peppered with hundreds of mutations (unlike all our normal cells). Disabling one of their drivers simply leads to the emergence of another driver in its place. What is clinically observable is tumor shrinkage, which may persist for several months, followed by the reemergence of that cancer.

These targeted therapies and immunotherapies are treating mostly patients with metastatic cancer. None of these therapies is curative. These are patients with a terminal illness and no other life-prolonging options. In 2022, 610,000 Americans died of cancer, of which 360,000 were over the age of 65 and covered by Medicare.³ This is the beginning of our wicked problems. These therapies cost \$150,000 or more per year or for a course of treatment that will only yield marginal gains in life expectancy. Is this a just or prudent use of limited healthcare resources? Are there other lives or life-years that could be saved at a much lower cost? Or is that a cruel and insensitive thought? These metastatic cancer patients have no

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other options, and these targeted therapies are "effective enough" for them, given that the alternative would be an earlier death. This is our first example of a wicked problem.

There are targeted therapies for roughly 30% of cancers with specific genetic drivers. Are we, as a just and caring society, ethically obligated to fund research that will discover drugs that can attack the other 70% of those drivers, even though those drivers and related cancers may be very rare? To illustrate, uveal melanoma cancer is extremely rare. However, we now have a drug, Kimmtrak (tebentafusp), that can slow progression for \$50,000 per week.⁴ Having discovered that drug, who should pay for it? It would be surprising if more than a handful of individuals with that disease could afford that drug. Should Medicare cover those costs?

If Medicare were to cover those costs, is there any drug or intervention with any degree of therapeutic effectiveness that Medicare could refuse to cover for reasons of cost? Some might not see that as a problematic outcome, perhaps because they believe human life is priceless. However, patients outside Medicare with the very same cancers and poor, moderate, or even very good health insurance would find all these life-prolonging cancer drugs unaffordable. They would die prematurely, relative to their Medicare progenitors. Are their lives not priceless? More wickedness.

Medicare could become more parsimonious and refuse to pay for those targeted therapies or immunotherapies that yielded too little gain in life expectancy at too high a cost. To be clear, those denials would be directed at drugs where the median gain in life expectancy was less than 6 months. It would be less ethically problematic if that median were instead an absolute limit on the effectiveness of the drug. However, what that median hides would be the 10% of patients who might gain one or two extra years of life, as well as a very small number of "super-responders" who might gain 5 to 10 extra years of life. We would be sacrificing those extra life-years for economic reasons. The loss of those life-years would be invisible. No names or faces would be attached to them, which is a salve for the conscience. More wickedness.

Biomarker research could potentially help in identifying the stronger responders to one of these drugs.⁵ Should Medicare then fund their access to these drugs because of the greater degree of effectiveness? Would this be unfair to the weaker responders? Two wicked problems emerge at that point. First, where would the line be drawn for being a "strong enough" responder? This is what Daniel Callahan has dubbed the "ragged edge" problem.⁶ No ethically compelling argument can be given for drawing that line at 6, 12, or 24 months. Second, the "ragged edge" problem can be addressed. The weaker responders would argue that each month of the drug has the same \$15,000 price; therefore, they should have an equal right to the drug as the strong responders who are gaining much more benefit at a social cost. That reflects a reasonable egalitarian sentiment. However, the aggregate social cost would rapidly bloom by billions of dollars *for that one drug.* We would be ethically compelled, it seems, to offer the same option for all 150 targeted therapies and immunotherapies with additional social costs increasing to the hundreds of billions. More wickedness, certainly, from a utilitarian perspective.

These utilitarian concerns could be addressed by requiring a 30% co-pay for all these targeted therapies and immunotherapies. The general idea would be to determine whether it was "worth it" to these patients to access these therapies when their money was at stake, not someone else's. That proposal would likely reduce demand for these therapies by 75%. This is rationing by the ability to pay, which many would find violative of an egalitarian sense of justice (though utilitarians and libertarians would be comfortable with that outcome). Worse than that, the relatively wealthy who could afford the 30% co-pay would have the other 70% covered socially, that is, by those financially less well-off who contributed to the Medicare fund during their working lives. More wickedness.

The Sirens of utilitarianism call to us again in the case of CAR T-cell therapy. This is an elegant and complex form of immunotherapy. A patient's T-cells are removed and genetically reengineered over 3 weeks to fight their specific hematologic cancer. Those cells are then infused into these patients. The front-end cost of this procedure is \$475,000, plus as much as another \$200,000 for the cytokine release syndrome, which as many as 30% of these patients will experience with the re-introduction of this "foreign" material into their body. Roughly 30% of these patients will not survive a year; the rest will likely gain one to four extra years of life. Here is our wicked utilitarian challenge: if we found a biomarker that could predict with 90% confidence who would not gain an extra year of life, could we justifiably deny

them CAR T-cell therapy at social cost? That very high front-end cost makes this very different from the monthly costs of targeted therapies in general. Again, this will be offensive to the egalitarian sensibilities of many.

We can address those egalitarian concerns by refusing to accept the CAR T-cell rationing proposal. In other words, everyone who could benefit to any degree from CAR T-cell therapy for their hematologic cancer would be assured access to this therapy at their social expense. Note that roughly 60,000 cancer deaths each year are hematologic; the rest involve solid tumors. Research is going forward to find versions of CAR T-cell therapy that can successfully attack solid tumors, again with those very high front-end costs.⁷ Ethically speaking (as an egalitarian), it seems such research is obligatory and likely to be successful (to a limited degree). Would everyone with advanced or metastatic cancer have a just claim to CAR T-cell therapy, perhaps after failing one or more targeted therapies? It seems as if an affirmative answer is warranted. But this creates the ethical issue of onco-exceptionalism—the idea that cancer is ethically special and worthy of unlimited social resources (presumably at the expense of many other unmet healthcare needs that were less socially visible).⁸ Even more wickedness.

No one should draw the conclusion from this essay that precision medicine is inherently wicked. It is not! The wickedness arises from the social, political, economic, and ethical context into which precision medicine is being introduced. This essay describes only a tiny fraction of the wicked issues generated by precision medicine. I discuss many more in considerable detail in a recent book.⁹ However, no individual philosopher will be able to come up with some elegant theoretical resolution of these wicked challenges to healthcare justice. That will require a prolonged and inclusive process of painful and respectful rational democratic deliberation. Trade-offs will be inescapable because limits (ethical and economic) are inescapable. The best possible outcome will be a matter of "rough justice." However, rough justice that is a product of public reason is preferable to the random injustices inflicted upon the politically marginalized by those capable of manipulating wicked problems related to precision medicine to their advantage.

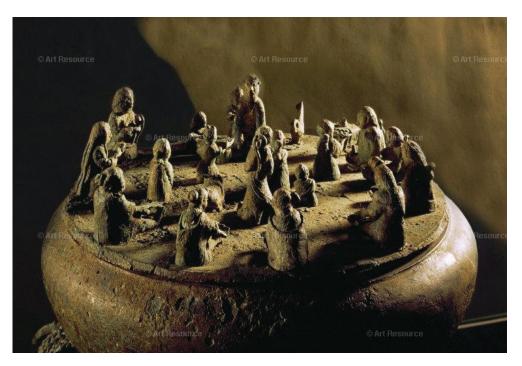
Conflict of interest. The author declares none.

Notes

- My comments in this essay refer to the healthcare system in the United States. However, these
 challenges are not country specific. I have addressed them elsewhere in a European context. See Fleck
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- 2. Rittel HW, Webber MM. Dilemmas in a general theory of planning. *Policy Sciences* 1973;4(2): 155–69. This is where the notion of wicked problems was first introduced and described.
- 3. In the European Union annual cancer deaths are roughly 1.3 million. The European Union will need to struggle with the wicked problems precipitated by precision medicine almost as much as the United States.
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Bronze cowrie container from tomb 1, decorated with peacocks and human figures in the round. Excavated 1955–1960 at Shi-Chai-Shan, Yunnan, China. Western Han Dynasty (2nd or early 1st BCE). Photo credit: Eric Lessing / Art Resource, NY. Reproduced by permission.