PHARMACOGENETIC INTERVENTIONS, ORPHAN DRUGS, AND DISTRIBUTIVE JUSTICE: THE ROLE OF COST-BENEFIT ANALYSIS*

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I. Introduction

With the human genome mapped, and with the mapping of more than one hundred animal genomes in progress,[1] the amount of genetic data available is increasing exponentially.[2] This exponential increase in data is having an immediate impact on the process of drug development. By using techniques of information technology to manipulate data regarding the genes, proteins, and biochemical pathways associated with various diseases, scientists are beginning to be able to design drugs in a systematic fashion. In the context of any given disease, scientists look to see whether a gene, a protein for which the gene codes, or another protein in the relevant biochemical pathway could be the "target" biological molecule, the "knocking out" of which would halt or slow the disease's progression. Once a target molecule has been identified and characterized structurally, drug therapies that would be likely to knock out this target can be identified and tested systematically. The merger of information technology and genetic technology has changed the process of pharmaceutical development so much that a new term—bioinformatics—has been coined to describe this new approach to such development.

One of the more compelling features of pharmaceutical development based on bioinformatics will be the ability to identify gene-level variations that cause individuals who present with similar disease symptoms to have different responses to drugs for those symptoms. As matters currently stand, when a drug is developed for a particular set of symptoms, or phenotype,[3] many people with that phenotype are either not helped by the drug or actually suffer adverse effects from taking it. In many of these cases of either no response or adverse response, the indi-

[1] David J. Lockhart and Elizabeth A. Winzeler, "Genomics, Gene Expression, and DNA Arrays," *Nature* 405, no. 6788 (2000): 827–36.
[2] The amount of genetic data available has been increasing tenfold every five years. See Jon Cohen, "The Genomics Gamble," *Science* 767, no. 5303 (1997): 767–68.
[3] An individual's phenotype is the physical profile he or she presents to the external world. Thus, for example, one might say that an individual's phenotype includes asthmatic breathing.

viduals in question have a complement of small genetic variations (known as single-nucleotide polymorphisms, or "SNPs") that renders their DNA complement, or genotype,[4] different from that of those who respond to the drug favorably.[5] In the past, it was not possible to segregate the favorable responders who exhibit a given phenotype from the unfavorable responders who also exhibit that phenotype; this is still true to a large extent today. However, our knowledge of SNPs is advancing rapidly. As a consequence, we should, in the relatively near term, be able to use SNP-based tests to segregate those individuals with a particular disease phenotype who are likely to respond well to a particular drug from those with that phenotype who are not.

The segregation of disease populations based on SNP variation—segregation known in the literature as pharmacogenomics—is likely to promote efficiency in both research and health-care delivery. From the standpoint of research, if only those who have a high probability of responding favorably to a given drug are included in its clinical trials, then the drug's efficacy will be proved faster and more cheaply than is currently the case.[6] In the context of health-care delivery, if drugs are prescribed only to individuals with SNP complements that suggest a favorable response, unnecessary and/or dangerous prescriptions will be avoided.

By the same token, once genotypic subgroups are segregated through SNP testing, there will arise situations in which a subgroup with a particular genotype is insufficiently large to provide the requisite market incentive for private pharmaceutical companies to develop a separate drug for that group. In the parlance of U.S. food and drug law, because the group does not provide a sufficiently large market, the group will be "orphaned."[7] Thus far, orphan groups have shared a rare phenotype,

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[4] An individual's genotype comprises the genetic information contained in his or her chromosomes.

[5] Lucid discussions of the use of SNPs in medicine include Allen Roses, "Pharmacogenetics and the Practice of Medicine," *Nature* 405, no. 6788 (2000): 857–65; and Jeanette J. McCarthy and Rolf Hilfiker, "The Use of Single-Nucleotide Polymorphism Maps in Pharmacogenomics," *Nature Biotechnology* 18, no. 5 (2000): 505–9.

[6] Indeed, in "The Information Revolution Reaches Pharmaceuticals: Balancing Innovation Incentives, Cost, and Access in the Post-Genomics Era," *Illinois Law Review* 2001, no. 1 (2001): 173–210, I argue that one of the chief benefits of making drug development an information science involves the possibility of reduced preclinical and clinical development costs.

[7] To be sure, an orphan group created through SNP testing is not necessarily worse off than it would have been in the days before SNP testing. In the days before SNP testing, the group would have been prescribed either a drug that had adverse effects, an ineffective drug (that is, a drug that worked only for other genotypic groups), or no drug at all (if the population with the relevant phenotype was so fragmented into separate genotypic groups that no single drug for the phenotype could have passed the Food and Drug Administration's efficacy standards). Nonetheless, in the past, the orphan group would have been difficult, if not impossible, to identify. In the same way that ordinary diagnostic techniques have given us the ability to identify groups with rare phenotypic diseases, SNP testing will give us the ability to identify, and perform further study on, groups orphaned by their SNP inheritance.

such as Gaucher's disease or hypopituitary dwarfism.[8] In the future, there will emerge a parallel, and possibly much larger, group of discrete orphan genotypes.[9] Policymakers will need to consider the extent to which existing federal subsidies that provide incentives for pharmaceutical companies to develop drugs for orphan phenotypes should also apply to drugs aimed at these new, genotypic orphans. Indeed, because the existing system of subsidies for so-called orphan drugs does not acknowledge the problem of scarce resources, the likely emergence of a significant number of new orphan groups will, in all probability, compel reconsideration of this system.[10]

This essay begins such a reconsideration. Specifically, it addresses the question of how, as a matter of distributive justice, we should treat claims to public resources made by those in orphan groups (including, but not limited to, the large number of orphan groups that SNP testing is likely to create). After establishing that diverse substantive views of distributive justice counsel in favor of using cost-benefit analysis as an evaluative tool, the essay specifies a cost-benefit framework that could be used as one means of assessing claims that the federal government should subsidize the development of particular orphan drugs. A key issue that will determine the number of orphan drugs found to be cost-effective is the so-called discount rate. As discussed further below, the discount rate is the rate at which future benefits—whether monetary or health-related—are determined to be of diminished importance simply because they occur in the future. The essay argues that even if the discount rate for health benefits is the same as that for monetary benefits, some percentage of orphan-drug development is likely to be cost-effective. Notably, this subset of orphan drugs will be cost-effective even though these drugs will, by definition, not be able recoup their research and development (R&D) costs in the marketplace under the ordinary system of patent protection

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[8] In some cases, drugs developed to treat a particular orphan phenotype have emerged as treatments for more common diseases. Thus, for example, the human growth hormone developed to treat hypopituitary dwarfism ended up being useful in treating other growth deficiencies; see Robert A. Bohrer and John T. Prince, "A Tale of Two Proteins: The FDA's Uncertain Interpretation of the Orphan Drug Act," *Harvard Journal of Law and Technology* 12, no. 1 (1999): 381. For this reason, the designation of human growth hormone (and other drugs that have ended up being useful for relatively large populations, such as the anti-AIDS drug AZT) as orphan drugs that deserve protection under the Orphan Drug Act (discussed below) has proved controversial. Ibid., 332. This possible problem with orphan-drug protection is but one example of the general difficulty biomedical-research regulators face when the implications of the research they are considering are not fully known. A discussion of this general problem is beyond the scope of this essay.

[9] In addition, if a particular phenotype has no genotypic subgroup that is sufficiently large to provide an appropriate market, then the entire phenotype could be considered orphaned. The analysis in this essay would apply to each of the orphan genotypes within the orphan phenotype.

[10] In addition, even if pharmacogenomics does not ultimately yield many new orphan genotypes, the number of orphan phenotypes that are emerging may be sufficiently large such that reconsideration of the current system is warranted.

for drugs. To the extent that particular orphan drugs are found to be cost-effective, the essay considers whether these drugs should be subsidized through the granting of longer patent terms or through direct funding.

The essay's analysis divides into five parts. Section II outlines the science behind SNPs and discusses the reasons why SNP testing is likely to create a significant number of orphan groups. Section III outlines the Orphan Drug Act of 1983, the central regulatory structure within the United States for subsidizing research on orphan diseases. Section IV critiques the failure of the Orphan Drug Act to assess systematically claims for federal subsidy, and argues that diverse substantive views of distributive justice counsel in favor of cost-benefit analysis as one mechanism for such systematic assessment. Section V discusses the basic principles of cost-benefit analysis and how these principles apply to the economic structure of drug development. It then discusses how cost-benefit analysis could be applied to drugs that are likely to be orphan drugs. Section VI considers whether the framework outlined in Section V should be used to assess claims for federal funding of pharmacological research more generally.

II. SNP Testing and Orphan-Group Creation

It is no exaggeration to say that pharmacogenomics is taking the drug industry by storm. A consortium of drug and digital-technology firms, working in conjunction with Great Britain's Wellcome Institute, has identified about 1.3 million SNPs; the biotechnology firm Celera claims to have identified over 2 million.[11] Some SNPs reflect individual variations, such as variations in hair or eye color, that have no particular medical significance. Researchers have, however, begun to identify circumstances in which SNPs can be used to predict individuals' responses to particular drugs.

In order to understand how SNPs can give information about drug response, it is necessary first to understand the different ways in which SNPs are associated with such response. SNPs found in so-called coding DNA—that is, the 3 to 5 percent of DNA that actually contains genes that express proteins—can affect drug response directly.[12] For example, if a SNP is found in a gene that produces a protein associated with a particular disease, the SNP may affect the structure of the protein. To the extent

[11] See SNP Consortium, "SNP Data Release: September 2001," available on-line at http://snp.cshl.org/data; and Celera Corporation, "Academic and Non-Profit Offerings: From Data to Discovery," available on-line at http://www.celera.com/genomics/academic/home.cfm?ppage=cpage=snps.

[12] These so-called coding SNPs (or "cSNPs") may be more common than was previously thought: a recent study of 313 human genes found an average of fourteen SNP variations per gene. See Geeta Anand, "Genaissance Publishes a Study Outlining Variations in 313 Genes," *Wall Street Journal*, July 13, 2001, C1.

that the given protein is the target for drug therapy, changes in its structure will often affect the relevant individuals' drug response. Alternatively, if a SNP is found in a gene that codes for a protein responsible for metabolizing a particular drug, the SNP may determine whether an individual is likely to metabolize that drug properly. SNPs that are found in noncoding, or "junk," DNA can also be relevant for predicting drug response. These noncoding SNPs may have predictive value to the extent that they tend to be found in conjunction with particular disease-gene variations.

Not all SNPs associated with drug response will create orphan groups. For example, coding SNPs that affect drug metabolism in a relatively straightforward manner may not create such groups. Consider the case of SNPs in the CYP2D6 gene locus, which codes for the drug-metabolizing enzyme cytochrome P450 2136. For approximately 15 to 25 percent of people, these SNPs can interfere with proper metabolism of certain drugs, including many pain medications, antidepressants, and antipsychotics.[13] At the ordinary dose of these drugs, those who metabolize them abnormally do not receive the expected benefit. Once the dose is adjusted, however—downward for slow metabolizers and upward for ultrarapid metabolizers—these patients may be able to respond properly. Moreover, where a disease is affected by multiple genes, information about SNPs in a single gene locus is generally not a perfect predictor of drug response. Hence, such information will not necessarily, in and of itself, create orphan groups. Thus, for example, information about variants in the APOE gene, which is associated with susceptibility to Alzheimer's disease, can only suggest that a patient is less likely to respond to the Alzheimer's drug tacrine; such information does not provide a definitive prediction.[14] As a consequence, the division between the group that should get tacrine and the group that should not is hardly crystal clear. In the case of Alzheimer's, a more accurate prediction of drug response will require more information about susceptibility genes for Alzheimer's and about SNPs within those susceptibility genes. Relatedly, in cases in which noncoding SNPs do not affect response to a given drug directly, but are simply found in conjunction with particular disease-gene variants, information about multiple noncoding SNPs will often be necessary if we are to predict response to the drug accurately.

On the other hand, researchers have already identified a variety of situations in which SNPs do appear to predict drug response in a manner that can create orphan groups. For example, in individuals with asthma,

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[13] See Urs A. Meyer, "Pharmacogenetics and Adverse Drug Reactions," *Lancet* 356, no. 9242 (2000): 1667–82; and John Weinstein, "Pharmacogenomics—Teaching Old Drugs New Tricks," *New England Journal of Medicine* 343, no. 19 (2000): 1408–9.

[14] Judes Poirier et al., "Apolipoprotein E4 Allele as a Predictor of Cholinergic Deficits and Treatment Outcome in Alzheimer Disease," *Proceedings of the National Academy of Sciences* 92, no. 26 (1995): 12260–61.

the presence of a particular type of promoter[15] (the ALOX5 promoter) is a perfect predictor for a lack of response to conventional antiasthma treatment.[16] To the extent that other treatments for asthma are not available, individuals with the ALOX5-promoter genotype may represent an orphan group. Similarly, to the extent that alternative treatments are not available, the approximately 5 percent of AIDS patients who have genetically identifiable predispositions to develop dangerous and potentially fatal reactions to certain anti-AIDS drugs[17] may represent an orphan group. Indeed, as a general matter, as more information is generated about SNPs that either cause, or are linked to, variation in disease-susceptibility genes, more orphan groups are likely to emerge. Given scarce resources, it may no longer be possible to fund all subsidy applications for drugs whose R&D costs will not be recovered through sales in the marketplace. As a consequence, we need to think proactively about how to address the issue of orphan groups. In the next two sections, I discuss, and critique, the existing regulatory structure for dealing with orphan drugs.

III. The Orphan Drug Act

In the United States, the major regulatory scheme that addresses orphan groups is the Orphan Drug Act of 1983.[18] This act amends the Food, Drug, and Cosmetics Act[19] to promote the development of drugs for people with "rare diseases or conditions."[20] In enacting the Orphan Drug Act, Congress determined that "because so few individuals are affected by any one rare disease or condition, a pharmaceutical company which develops an orphan drug may reasonably expect the drug to generate relatively small sales in comparison to the cost of developing the drug and consequently to incur a financial loss."[21]

Under the Orphan Drug Act, drugs are considered orphan drugs under either of two circumstances: first, if they treat conditions that affect fewer than 200,000 patients; or second, if there is no reasonable expectation that the cost of developing the drug will be recovered from U.S. sales.[22] The

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[15] A promoter is a DNA sequence that is responsible for regulating the expression of a particular gene.

[16] J. M. Drazen et al., "Pharmacogenetic Association between ALOX5 Promoter Genotype and the Response to Anti-Asthma Treatment," *Nature Genetics* 22, no. 2 (1999): 168–70.

[17] On such patients, see Marc Wortman, "Medicine Gets Personal," *MIT Tech Review* 104, no. 1 (2001): 72–78.

[18] Orphan Drug Act of 1983, Pub. L. No. 97–414, 96 Stat. 2049 (1983) (codified as amended in scattered sections of 21 U.S.C. and 42 U.S.C.).

[19] Food, Drug, and Cosmetics Act, 21 U.S.C. § 301 (1994).

[20] 21 U.S.C. § 360bb (1994).

[21] Orphan Drug Act § 1, 96 Stat. 2049 (1983).

[22] 21 U.S.C. § 360ee(b)(2) (1994). Because the United States represents the only major market in which drug prices are not tightly regulated (and hence is the major market in which profits from drug sales are realized), the Orphan Drug Act focuses on U.S. sales. Similarly, in this essay, I will focus on the U.S. market for drugs.

second category of drugs encompasses the first—in effect, Congress determined that if a condition affects fewer than 200,000 individuals, that fact, in and of itself, is enough to show that there is no reasonable expectation that a pharmaceutical company can recover costs incurred to develop a drug for the condition. By the same token, the second category is not limited to situations meeting the first category's criterion: even if a disease does affect more than 200,000 individuals, a pharmaceutical manufacturer may seek orphan-drug status for a drug used to treat that disease. Manufacturers may seek such status for a drug at any point during the preclinical or clinical R&D process.[23]

The Orphan Drug Act requires that the Food and Drug Administration (FDA) assist companies developing orphan drugs in negotiating the agency's drug-approval process.[24] In many cases, the FDA also funds the clinical testing necessary for approval of an orphan drug.[25] In addition, the Internal Revenue Service provides tax breaks for expenses related to orphan-drug development. Indeed, an orphan-drug developer can claim up to 50 percent of relevant clinical trial costs as a credit against taxes owed.[26] Finally, even if an orphan drug is not truly novel, and thus does not meet the ordinary requirements for patentability,[27] it can benefit from a seven-year period of market exclusivity after FDA approval. As of 1998,

[23] See 21 C.F.R. § 316.23 (1999):

    (a) A sponsor may request orphan-drug designation at any time in the drug development process prior to the submission of a marketing application for the drug product for the orphan indication.

    (b) A sponsor may request orphan-drug designation of an already approved drug product for an unapproved use without regard to whether the prior marketing approval was for an orphan-drug indication.

One difficulty with the current system is that it appears to require the manufacturer to identify a particular drug candidate before Orphan Drug Act protections are triggered. Because even initial identification of a candidate drug can be costly, this requirement may place too great a burden on the would-be researcher into an orphan disease. This difficulty could be alleviated by altering the language of the relevant regulations so that Orphan Drug Act protections are available to manufacturers with a research plan for work on a particular orphan disease.

[24] See 21 U.S.C. § 360aa(a) (1994) (specifying that an orphan-drug manufacturer may request from the FDA written recommendations for clinical and nonclinical tests that must be conducted for a drug's approval).

[25] See 21 U.S.C. § 360ee(a) (1994) (providing that "The Secretary may make grants to and enter into contracts with public and private entities and individuals to assist in (1) defraying the costs of qualified testing expenses incurred in connection with the development of drugs for rare diseases and conditions . . . .").

[26] 26 U.S.C. § 45C (1994). By contrast, most firms that engage in costly R&D receive a tax credit equal to only 20 percent of R&D spending that exceeds a certain base amount (typically defined by a firm's spending patterns in the previous three years).

[27] Under the patent statute, an invention must not only be new (see 35 U.S.C. § 102 [1994]), but it must also be something that would not have been obvious, at the time it was made, to a person of ordinary skill in the relevant field. See 35 U.S.C. § 103 (1994).

99 orphan drugs had been approved by the FDA, and another 189 were undergoing clinical testing.[28]

In giving a series of special subsidies to all drugs whose development costs may not be recovered through ordinary sales, the Orphan Drug Act makes no attempt to distinguish between different applications for subsidy. Rather, all applicants that can make a colorable claim to being a producer of an orphan drug are granted subsidies. To the extent that the number of orphan groups has been relatively small, this liberal approach may not have strained resources unduly. Indeed, a liberal approach may have been justified by the substantial administrative costs of coming up with, and applying, a more restrictive approach. As the number of orphan-drug applications increases, however, a liberal approach may strain government resources. Thus, it will probably be necessary to come up with more parsimonious criteria for the granting of orphan-drug subsidies.

IV. Evaluating Orphan Drugs: Why Cost-Benefit Analysis?

In one sense, any analysis of how scarce resources for orphan-drug research should be allocated is simply a subset of the much larger inquiry into how scarce health-care resources should be allocated. Many moral philosophers have engaged this larger question. Some libertarian analysts who reject compelled redistribution of social goods generally have concluded that there is no social obligation to redistribute health-care resources.[29] For the most part, however, even scholars who operate from otherwise divergent theoretical perspectives agree that society has an obligation to redistribute resources in a manner that guarantees to each of its citizens a "basic" or "decent" minimum of health-care resources.[30] Theorists who stress obligations of beneficence argue that redistribution is necessary to ensure that we discharge our moral duty to relieve the acute suffering caused by lack of basic care.[31] Liberal egalitarians assert that basic health care is part of the "social minimum" of goods to which

[28] See Jean O. Lanjouw, "The Introduction of Pharmaceutical Product Patents: Heartless Exploitation of the Poor and Suffering?" (NBER working paper, 1998).

[29] See, e.g., Richard Epstein, "Rationing Access to Medical Care: Some Sober Second Thoughts," *Stanford Law and Policy Review* 3 (1991): 81–89; and Loren E. Lomasky, "Medical Progress and National Health Care," in Marshall Cohen, Thomas Nagel, and Thomas Scanlon, eds., *Medicine and Moral Philosophy* (Princeton, NJ: Princeton University Press, 1981), 115.

[30] See President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, *Securing Access to Health Care: A Report on the Ethical Implications of Differences in the Availability of Health Services* (Washington, DC: U.S. Government Printing Office, 1983), 1:3–6, 1:18–47; and also Tom L. Beauchamp and James F. Childress, *Principles of Biomedical Ethics*, 4th ed. (New York: Oxford University Press, 1994), 356 (developing the argument for an individual right to basic health care and noting that such a right holds out the potential for "compromise among libertarians, utilitarians, communitarians, and egalitarians").

[31] See generally Allen E. Buchanan, "The Right to a Decent Minimum of Health Care," *Philosophy and Public Affairs* 13, no. 1 (1984): 55–78.

citizens must have access in order to be afforded basic opportunity.[32] Some egalitarians make the more ambitious claim that health-care redistribution can secure equality of opportunity.[33] Utilitarians observe that redistribution of health-care resources is desirable as a mechanism for promoting overall social welfare. For at least some utilitarians, theirs is more than a simple argument for redistribution of income on the traditional ground that because income has declining marginal utility (i.e., the millionth dollar one acquires enhances one's welfare less than the thousandth, and the thousandth enhances it less than the hundredth), redistribution of income from rich to poor will increase overall social welfare. Rather, the claim is that redistributing health care is likely to be more welfare-enhancing than merely redistributing money.[34]

The virtue of the decent-minimum position is that it brings together philosophers from a variety of different theoretical perspectives. Perhaps not surprisingly, however, these theorists disagree substantially on the details of how the decent minimum should be defined. Utilitarians tend to argue that the content of the decent minimum should be determined by some type of cost-benefit analysis:[35] the government should encourage only those interventions that provide sufficient aggregate health benefits to justify the interventions' costs. For example, in the late 1980s, the state of Oregon famously attempted to apply a version of cost-benefit analysis in determining what interventions would be covered under the Medicaid plan that the state was prepared to make available to all indigent individuals.[36] As applied to orphan drugs, the utilitarian position would

[32] See, e.g., Amy Gutmann and Dennis Thompson, *Democracy and Disagreement* (Cambridge, MA: Harvard University Press, 1996), 213–23. Gutmann and Thompson discuss not only health care but also the full range of social goods that are, in their estimation, necessary to protect basic opportunity. These include food, shelter, education, and health care.

[33] See Norman Daniels, *Just Health Care* (Cambridge: Cambridge University Press, 1985), 36–58.

[34] See, e.g., Einer Elhauge, "Allocating Health Care Morally," *California Law Review* 82, no. 6 (1994): 1493–96.

[35] In order to comport fully with utilitarianism, cost-benefit analysis should not assume (as it often does) that the benefit an individual derives from a particular item is equivalent to his or her willingness to pay for that item. While an individual's willingness to pay is clearly income-dependent, utilitarians reject the idea that utility is necessarily income-dependent. See Donald Hubin, "The Moral Justification of Cost-Benefit Analysis," *Economics and Philosophy* 10, no. 2 (1994): 187–88 (noting that because cost-benefit analysis often measures benefit in terms that reflect ability to pay, it tends to discount the utility of poor individuals). As discussed further below, the calculation of benefit that is used in medical cost-benefit analysis is not dependent on willingness to pay. Thus, medical cost-benefit analysis is not subject to the critique that it favors wealthy individuals over poor ones.

[36] Oregon subsequently revised its initial application of cost-benefit methodology, primarily in response to criticism that that application of the methodology undervalued the saving of identifiable lives. See Arti K. Rai, "Rationing through Choice: A New Approach to Cost-Effectiveness Analysis in Health Care," *Indiana Law Journal* 72, no. 4 (1997): 1054. Although Oregon's revised methodology placed greater emphasis on saving identifiable lives, it placed much less emphasis on overall medical benefits. Ibid., 1073–74. The focus on health benefits was further diluted by the federal government's determination that efforts to assess quality of life in measuring medical benefits violate the Americans with Disabilities

suggest that the government encourage production of orphan drugs whose aggregate health benefits exceed the drugs' aggregate costs. In contrast with utilitarians, egalitarians such as philosopher Norman Daniels argue in favor of public provision of medical interventions that are necessary to secure "normal" life opportunities.[37] To the extent that scarcity may prevent the government from providing all such interventions, it should provide those interventions aimed at treating diseases that are particularly injurious to one's life prospects (presumably irrespective of whether the interventions in question are especially effective in alleviating those diseases).[38] Alternately, the government might provide interventions aimed at groups that are particularly young.[39] In the specific context of orphan drugs, then, Daniels might argue in favor of government subsidies for drugs that treat diseases that are unusually severe or that disproportionately affect the young.

It is difficult to reconcile these competing specifications of the decent minimum. Indeed, while the concept of the decent minimum enjoys substantial acceptance, each specification of the concept is highly controversial. Utilitarian maximization of aggregate welfare is vulnerable to the criticism that it pays insufficient attention to liberty concerns and that it fails to take into account how welfare is distributed.[40] By the same token, strongly egalitarian conceptions of the decent minimum fail to the extent that they suggest that medical resources should continue to be directed toward individuals with intractable disabilities who will never be able to secure normal life opportunities.[41]

In recent years, a number of commentators have stressed that while moral theory provides us with some principles to guide thinking about how to redistribute health care, it does not (at least within the limits of current knowledge) define the decent-minimum concept in any deter-

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Act. As a consequence of this determination, Oregon was forced to ignore quality-of-life improvements when it assessed medical interventions. When the Oregon plan was finally implemented in February 1994, it did not incorporate cost-benefit methodology to any significant degree.

[37] See generally Daniels, *Just Health Care*, 36–58.

[38] Ibid., 35.

[39] Ibid., 103–5. While Daniels argues for preferring the young from a liberal egalitarian standpoint, Daniel Callahan reaches a similar conclusion from a communitarian standpoint. Callahan asserts that once an individual has achieved her "natural life span," society's goal should be to relieve suffering rather than to pursue life-extending care. Daniel Callahan, *What Kind of Life: The Limits on Medical Progress* (New York: Simon and Schuster, 1990), 141.

[40] Gutmann and Thompson, *Democracy and Disagreement*, 192–94. Utilitarianism is also controversial to the extent that it focuses on the informed preferences of individuals and not on the deliberative process by which groups of individuals might come to a collective understanding of their preferences. Ibid., 173–77. However, as I will argue below, even though utilitarian philosophy may not stress deliberation, utilitarian methodologies like cost-benefit analysis can significantly enhance the deliberative process.

[41] See, e.g., Rai, "Rationing through Choice," 1024 (discussing this sort of "bottomless pit" problem).

minate fashion.[42] This recognition of the limits of moral theory in prescribing rules for health-care redistribution parallels a more general recognition of moral theory's limits in resolving distributive-justice dilemmas. Thus, for example, the later work of John Rawls embraces an approach that emphasizes the importance of political procedure in mediating conflicts between divergent substantive views of justice.[43] Similarly, in recent writing, health-care theorists like Daniels who previously emphasized comprehensive moral views have called attention to the importance of political procedure.[44]

   The work of the political philosophers Amy Gutmann and Dennis Thompson presents a particularly detailed sketch of how political, or "democratic," deliberation can guide the elaboration of such substantive moral concepts as liberty and basic opportunity.[45] Gutmann and Thompson's account of democratic deliberation stresses the importance of three procedural values, which they call reciprocity, publicity, and accountability. Appropriate respect for these values requires a transparent deliberative forum in which both citizens and government officials justify their substantive positions by giving reasons "that can be accepted by others."[46] Similarly, a recent article by Daniels and ethicist James Sabin argues that institutions that allocate medical care must give clear, publicly accessible reasons for their decisions.[47] According to Daniels and Sabin, these reasons must be "accepted as relevant by people who are disposed to finding terms of cooperation that are mutually justifiable."[48] Invoking the writings of legal theorist Frederick Schauer, Daniels and Sabin note that a procedural requirement as simple as transparent reason-giving can improve the substantive quality of decision-making by counteracting "bias, self-interest, insufficient reflection, or simply excess haste."[49]

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[42] See ibid., 1021–30; Einer Elhauge, "Allocating Health Care Morally," 1465–72; and Ezekiel Emanuel, *The Ends of Human Life* (Cambridge, MA: Harvard University Press, 1991), 114–45.

[43] See John Rawls, *Political Liberalism* (New York: Columbia University Press, 1993), 9: "The aim of justice as fairness, then, is practical: it presents itself as a conception of justice that may be shared by citizens as a basis of a *reasoned, informed, and willing political judgment*" (emphasis added).

[44] See generally Norman Daniels and James Sabin, "Limits to Health Care: Fair Procedures, Democratic Deliberation, and the Legitimacy Problem for Insurers," *Philosophy and Public Affairs* 26, no. 4 (1997): 303–50.

[45] Gutmann and Thompson, *Democracy and Disagreement*. As Gutmann and Thompson emphasize, they diverge from some advocates of deliberation in believing that political deliberation cannot itself be the "sovereign guide" to resolving moral disagreements. Rather, Gutmann and Thompson contend that liberty and basic opportunity must operate as substantive concepts that guide the content of deliberation. Ibid., 17–18.

[46] Ibid., 53.

[47] Daniels and Sabin, "Limits to Health Care."

[48] Ibid., 323. In their essay, Daniels and Sabin are focusing on allocation decisions made by private health-insurance organizations. However, their arguments are equally applicable to public institutions.

[49] Ibid., 326 n. 24, citing Frederick Schauer, "Giving Reasons," *Stanford Law Review* 47, no. 4 (1995): 657.

The deliberative goals proposed by Gutmann/Thompson and Daniels/ Sabin suggest a robust role for cost-benefit analysis in just resource allocation. As its name might suggest, cost-benefit analysis requires that policymakers enunciate with some specificity and rigor the predicted costs and benefits of any proposal that they seek to implement. Cost-benefit analysis's clear methodology can promote many of the deliberative goals emphasized by Gutmann/Thompson and Daniels/Sabin. Most obviously, cost-benefit analysis is transparent to outside monitoring groups[50] and can correct for misguided arguments based on cognitive errors in reasoning.[51] Cost-benefit analysis also has advantages beyond its links to deliberative goals. For instance, it is relatively easy for policymakers with limited resources and abilities to implement.[52] Furthermore, as a substantive matter, the social-welfare goals emphasized by cost-benefit analysis—particularly by medical cost-benefit analysis, which, as discussed further below, measures benefits in terms that are independent of an individual's ability to pay for those benefits—are recognized as morally relevant not only in utilitarian theory but also in many other moral and political theories.[53] For these reasons, even commentators who are skeptical about cost-benefit analysis endorse its importance as one mechanism by which to assess government action.[54] In addition, policymakers in ideologically diverse regimes ranging from the Reagan administration to the Clinton administration have adopted cost-benefit analysis as a mechanism for assessing regulatory proposals.[55]

Environmental-risk regulation has been a particularly fruitful area for the application of cost-benefit analysis. Many scholars of risk have employed a cost-per-life-saved methodology to evaluate systematically an

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[50] Matthew D. Adler and Eric A. Posner, "Implementing Cost-Benefit Analysis When Preferences Are Distorted," *Journal of Legal Studies* 29 (2000): 1106.

[51] For example, individuals often do a very poor job of assessing the probability of uncertain events. See generally Cass S. Sunstein, "Cognition and Cost-Benefit Analysis," *Journal of Legal Studies* 29, no. 2 (2000): 1059–97; see also Rai, "Rationing through Choice," 1069.

[52] Adler and Posner, "Implementing Cost-Benefit Analysis," 1106.

[53] Ibid. (observing that many moral and political theories hold that "a policy's effect on people's welfare is a relevant, though not necessarily conclusive, consideration").

[54] See generally Adler and Posner, "Implementing Cost-Benefit Analysis"; and Sunstein, "Cognition and Cost-Benefit Analysis." Even Gutmann and Thompson, who offer a vigorous critique of cost-benefit analysis and of utilitarianism more generally, note that utilitarian analysis "deserves a place in deliberative democracy." Gutmann and Thompson, *Democracy and Disagreement*, 196. Similarly, Daniels and Sabin suggest that private insurance companies should use cost-effectiveness criteria and should be forthcoming about such use. See Daniels and Sabin, "Limits to Health Care," 335: "If people share the goal of meeting the varied medical needs of a population covered by limited resources, and they share a commitment to justifying limitations by reference to reasons all can consider appropriate and relevant, then they will be interested in a reason that says a particular technology falls below some defensible threshold of cost-effectiveness or relative cost-worthiness."

[55] By executive order, Presidents Reagan, George H. W. Bush, Clinton, and George W. Bush have all required cost-benefit analysis of major regulations.

impressive variety of environmental regulation.[56] In the area of federal funding for biomedical research, particularly early-stage research (in other words, research that is far removed from commercial application), concerns about the uncertainty associated with calculating future costs and benefits have given regulators pause with respect to applying the methodology. However, even in this context, the idea of cost-benefit accounting is hardly novel. Indeed, in the late 1990s, the National Institutes of Health (NIH) responded to claims that it had failed to allocate research funds in a systematic and transparent manner by stating that it intended to begin relying in part on utilitarian calculations of "disease burden." The current NIH criteria for calculating disease burden include the number of people who have a particular disease; the number of deaths the disease causes; the degree of disability the disease produces; the degree to which the disease cuts short a normal, productive, comfortable lifetime; the economic and social costs of the disease; and the need to act rapidly to control the disease's spread.[57]

In the spirit of these various commentators and policymakers, this essay proposes a framework by which cost-benefit analysis could be used as one means of evaluating claims that the government should subsidize the development of particular orphan drugs. To the extent that policymakers want to supplement the results of cost-benefit analysis with an assessment of whether particular disease groups deserve consideration over and above the consideration they receive under cost-benefit analysis, they can do this after the analysis is performed. For example, young or severely disabled individuals whose diseases cannot be ameliorated to any significant extent through medical intervention will not fare well under cost-benefit analysis, but might deserve special attention on non-utilitarian grounds.

V. A Framework for Cost-Benefit Analysis of Orphan Drugs

A. The economic structure of drug development

In order to understand how cost-benefit analysis would apply to orphan drugs, it is first necessary to understand the economic structure of drug development and the manner in which intellectual property rights—specifically, patent rights—provide incentives for such development. Drug

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[56] See generally Stephen Breyer, *Breaking the Vicious Circle: Toward Effective Risk Regulation* (Cambridge, MA: Harvard University Press, 1993); and W. Kip Viscusi, *Fatal Tradeoffs: Public and Private Responsibilities for Risk* (New York: Oxford University Press, 1992).

[57] NIH Working Group on Priority Setting, "Setting Research Priorities and the National Institutes of Health" (NIH publication number 97–4265, September 1997). As Rebecca Dresser has pointed out, current levels of NIH funding for particular diseases are strongly correlated with the welfare losses that the diseases cause. Rebecca Dresser, *When Science Offers Salvation* (New York: Oxford University Press, 2001), 83. As discussed further below, these welfare losses are typically calculated in units called quality-adjusted life-years, or QALYs.

development in the United States is a long, expensive, and risky process comprising two stages: the preclinical research stage, in which a likely drug candidate is identified; and a FDA-mandated clinical testing stage, in which the drug candidate is put through three sets of human testing and a final FDA review. Only a very small percentage of drug candidates succeeds in passing through both preclinical and clinical testing. As a consequence, the process of discovering and developing a successful drug (i.e., one that makes it to market) typically takes ten to fifteen years and costs approximately $500 million.[58]

Once a successful drug has been developed, however, its marginal cost of production—that is, the cost of producing each additional drug unit—is effectively zero.[59] Thus, a competitor to the original innovator that wants to copy and market the drug can make a profit even if it sells the drug at a negligible cost. By contrast, if the original innovator is forced to sell the drug at a negligible cost, it will not recover its R&D expenditures. Absent the ability to recover R&D expenditures, the innovators will presumably (at least in the long term) stop innovating.

In order to avoid this market failure, the U.S. intellectual property regime provides a fairly robust—albeit time-limited—system of protection against copying. Inventions that are truly new, and also meet other statutory criteria for patentability, are granted a twenty-year term of patent protection that starts at the time the relevant patent application is filed. Pharmaceutical inventions also receive certain special protections over and above the ordinary patent term. The most important of these protections compensates drug manufacturers for the reduction in marketing exclusivity that results from the mandatory FDA approval process for drugs. This reduction occurs because drug manufacturers typically file patent applications—and thereby trigger the start of patent terms—before their drugs enter the clinical-testing stages.[60] The time spent in clinical testing and in the final review stages thus reduces the period of marketing exclusivity. The Drug Price Competition and Restoration Act of 1984 (the so-called Hatch-Waxman Act)[61] compensates for this reduction by allowing drug manufacturers to extend their patent term by the sum of two periods of time: the time taken by the final FDA review and half the time spent in clinical testing after the patent is granted.[62]

[58] See Rai, "The Information Revolution Reaches Pharmaceuticals," 181. This $500 million figure includes the cost of drugs that fail preclinical or clinical testing.

[59] The marginal cost is effectively zero because the cost of the chemical(s) that make up the drug is generally negligible.

[60] See Alfred Engelberg, "Special Provisions for Pharmaceuticals: Have They Outlived Their Usefulness?" *IDEA* 39, no. 3 (1999): 420 (noting that it is common practice to file patent applications before human testing has begun, because waiting might result in the information relevant to the invention becoming generally known and therefore unpatentable).

[61] The Drug Price Competition and Restoration Act of 1984, Pub. L. No. 98–417, 98 Stat. 1585 (1984) (codified as amended throughout 21 U.S.C. [1994]).

[62] 35 U.S.C. § 156 (1994). Hatch-Waxman imposes a five-year cap on the extension term that can be granted.

In recent years, most new drugs have received extensions that result in a total of fourteen years of patent life post–FDA approval, the maximum time allowed if a manufacturer avails itself of Hatch-Waxman protection.[63] During the extended patent term that they receive by virtue of Hatch-Waxman, drug manufacturers recover their R&D costs by charging prices well above the drugs' marginal production cost of zero.

B. Applying medical cost-benefit analysis to orphan drug development

In many respects, cost-benefit analysis (including medical cost-benefit analysis) is supposed to mimic the workings of the market. In the market, purchasers are not willing to pay for products whose costs exceed the benefits the products provide.[64] Similarly, the policymaker who uses cost-benefit analysis will not endorse policies that have costs in excess of their benefits. Given the similarity between cost-benefit analysis and market analysis, one might suppose that any drug that could not be produced through ordinary market mechanisms—or, more accurately, market mechanisms fortified against failure by the robust system of patent protection for drugs discussed above—could not, on balance, be cost-beneficial. From this perspective, the application of cost-benefit analysis to drug development would seem irrelevant.

I contend, however, that such analysis is relevant. In this subsection, I argue that despite their limited markets, orphan drugs may well produce health benefits commensurate with their costs. In brief, the argument runs as follows: Although a drug manufacturer can capture the dollar value of the health benefits produced by its drug only during the period of patent protection, drugs do not stop producing health benefits once manufacturers' patents expire. As a consequence of this economic reality, a careful application of cost-benefit arguments may provide a sufficient basis for developing treatments for at least some orphan groups. In any given case, the extent to which cost-benefit arguments provide such a basis will

[63] See Engelberg, "Special Provisions for Pharmaceuticals," 420 (citing analysis issued by the Patent and Trademark Office). Indeed, with respect to particularly lucrative drugs, drug manufacturers sometimes manage to gain patent protection for more than fourteen years after FDA approval. They obtain this additional protection by strategically seeking additional patents on a drug several years before the basic patent that received the Hatch-Waxman extension is set to expire. Ibid., 415, 420. Although these additional patents are often somewhat marginal in that they claim uses for the drug that have not previously been approved, specific drug formulations, or even tablet shape (see ibid.), they can succeed in delaying competition by generic drugs. Such delay results because the Hatch-Waxman Act contains a provision requiring the FDA to stay the approval process for a generic drug for thirty months if a brand-name manufacturer claims that one of its patents, no matter how marginal, is being infringed by the generic. I discuss these problems with the Hatch-Waxman Act in Rai, "The Information Revolution Reaches Pharmaceuticals," 183–85.

[64] To be sure, the widespread presence of insurance in health-care markets may lead purchasers to consume health care whose costs exceed its benefits. For the purposes of this essay, however, I assume that health-care markets function efficiently because insurers have implemented mechanisms for curbing this insurance-induced tendency to overspend.

depend on whether the health benefits produced by orphan drugs are discounted over time, and, if they are, on the rate at which discounting is done. Even with relatively high discount rates for health benefits, however, a substantial number of orphan drugs may produce health benefits commensurate with the drugs' costs.

1. Principles of medical cost-benefit analysis. In order to apply cost-benefit analysis to orphan drugs, it is first necessary to understand the basic framework of such analysis in the medical arena. Assuming that a decision-maker is adopting a societal perspective (as contrasted with that of a single hospital or physician), the costs of a medical intervention are calculated by determining the sum of the following items: the direct medical costs of the intervention; the costs of adverse side effects associated with the intervention; and any future costs related to the treatment of the relevant disease. Any savings that might be associated with prevention or alleviation of the disease are subtracted from the cost figure.[65]

In many forms of cost-benefit analysis, benefits are also calculated in dollars, with analysts using an individual's willingness to pay for a particular outcome as a measure of the utility associated with that outcome. Because willingness to pay is a function of income, forms of cost-benefit analysis that rely upon willingness to pay have often been criticized on the ground that they undervalue the utility of poor individuals. The standard version of medical cost-benefit analysis is not subject to this criticism. In medical cost-benefit analysis, benefits are typically calculated not in dollars but in income-neutral units known as quality-adjusted life-years, or QALYs.[66] QALYs are a measure of the life-years available to an individual, as adjusted by the quality of health (usually measured on a scale of 0 to 1) that the individual will enjoy during those years. Quality-adjustment ratings for particular states of health are derived from questions posed to interviewees. The simplest approach to such questioning is the ratings-scale approach, in which interviewees are asked to rate a particular state of health on a scale of 0 to 1, where being dead is valued at 0 and perfect health is valued at 1. Other approaches are generally seen as being more complicated but more accurate: these include the standard-gamble approach (which asks what chance of death the interviewee would

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[65] See, e.g., Milton C. Weinstein and William B. Stason, "Foundations of Cost-Effectiveness Analysis for Health and Medical Practices," *New England Journal of Medicine* 296, no. 13 (1977): 718. There is some debate about whether future medical costs *unrelated* to the relevant disease and/or future nonmedical costs should be included in the cost calculation. See ibid. (arguing that future unrelated medical costs should be included); and David Meltzer, "Accounting for Future Costs in Medical Cost-Effectiveness Analysis," *Journal of Health Economics* 16, no. 1 (1997): 33–64 (arguing that future nonmedical costs should also be included). See also U.S. Department of Health and Human Services, Office of Public Health and Science, Office of Disease Prevention and Health Promotion, Panel on Cost-Effectiveness in Health and Medicine, *Cost-Effectiveness in Health and Medicine* (Washington, DC: U.S. Government Printing Office, 1996) (arguing that future nonmedical costs should *not* be included). Resolving these debates is not essential for the purposes of this essay.

[66] Weinstein and Stason, "Foundations of Cost-Effectiveness Analysis."

risk to avoid living in a particular diminished state of health) and the time trade-off approach (which asks what percentage of the interviewee's life-span she would give up to avoid living in a diminished health state). For example, if an interviewee would risk a 20 percent chance of death (or would give up 20 percent of her life-span) to avoid living in a particular health state, then that state would have a rating of 20 percent less than perfect health, or 0.8 on the 0 to 1 scale.

The QALY benefit associated with a given intervention is calculated as the difference between the number of QALYs available if the intervention is made and the number of QALYs available if it is not. Interventions that increase life expectancy, improve quality of life, or reduce the risk of mortality thus yield positive QALY benefits. For example, assume that a particular drug extends an individual's life-span from 70 years to 72 years. Assume further that during that extra time, the individual's health is perfect—in other words, it has a quality of 1. In this case, the QALY benefit is two years multiplied by a quality-adjustment of 1, or 2 QALYs. Alternatively, suppose the drug does not extend the individual's life— with or without the drug, she will live to the age of 70. However, if she takes the drug when she is between the ages of 50 and 70, the drug will relieve her chronic nausea and thus improve her quality of life during those years by 0.2 on the quality-of-life scale (say, by taking her from 0.7 to 0.9). In this case, the drug yields a QALY improvement of 0.2 multiplied by twenty years, or 4 QALYs. For particular life-saving interventions, this sort of basic assessment of QALY benefit may need to be supplemented so as to capture the symbolic utility that many individuals derive from saving identifiable lives.[67] For example, consider the aforementioned pair of hypothetical drugs. Although the drug that extends one's life by two years yields only 2 QALYs, some people might on reflection think that "saving" an identifiable life, even if only for two years, is just as valuable as improving quality of life by 4 QALYs over twenty years. While traditional methods of eliciting quality-of-life valuations do not usually question interviewees directly about potential trade-offs between saving identifiable lives and achieving other health benefits, such questions may need to be used to incorporate the symbolic utility that people attach to life-saving.[68]

Most health economists would agree that a medical intervention is cost-justified if it has a cost-per-QALY-gained ratio of $50,000 or lower. Some would even argue that interventions with a cost-per-QALY-gained ratio of up to $100,000 are cost-justified. These estimates are based on

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[67] See, e.g., Paul Menzel, "How Should What Economists Call 'Social Values' Be Measured?" *Journal of Ethics* 3, no. 3 (1999): 249–73; and Rai, "Rationing through Choice," 1070–77.

[68] See David Eddy, "Oregon's Methods: Did Cost-Effectiveness Fail?" *Journal of the American Medical Association* 266, no. 15 (1991): 2140. For a similar suggestion, see Menzel, "How Should 'Social Values' Be Measured?" 261–65.

surveys of individuals' willingness to pay for health improvements and on the average efficacy of a range of common medical interventions.[69]

With the possible exception of symbolic-utility measurement, the aforementioned observations on medical cost-benefit analysis are not deeply contested. Two significant methodological controversies do persist, however. The first controversy involves charges that the quality-of-life ratings used to determine quality-adjustments may discriminate unfairly against individuals with disabilities, particularly if the ratings used are drawn not from individuals affected by a particular disability but from the population at large. Consider the following example: Suppose that the general population rates the quality of life of an individual with quadriplegia at 0.5 on the 0 to 1 scale. Suppose further that we have a drug that can treat otherwise-fatal kidney failure, but that we only have enough of the drug to give it to one of two individuals with kidney disease—one with quadriplegia, the other fully mobile. The drug would extend the first person's life by ten years, and the second person's life by six. Giving the drug to the individual with quadriplegia would yield 5 QALYs (ten years multiplied by a quality-adjustment of 0.5). By contrast, giving the drug to the fully mobile individual would yield 6 QALYs (six years multiplied by a quality-adjustment of 1). In this situation, then, QALY-maximization requires that we give the drug to the fully mobile individual. Such allocation might be considered quite unfair, particularly if the individual with quadriplegia assigns her life a quality-of-life rating that is much higher than 0.5.

The question of discrimination posed by situations like this has been discussed at length by many commentators.[70] For present purposes, it suffices to say that under both moral analysis and existing antidiscrimination law (specifically, the Americans with Disabilities Act),[71] it is probably permissible to use quality-of-life ratings—even quality-of-life ratings drawn from the population at large—to make allocation decisions, so long as the disability assessed in those ratings is itself at issue in the relevant medical interventions. In the case of the kidney patient with quadriplegia, the disability is unrelated to the intervention being considered: the quadriplegia does not occasion the need for the kidney drug and does not interfere with the efficacy of the drug in treating the kidney ailment. Thus, the quality of life associated with quadriplegia itself should not count in the QALY calculus used to determine how to allocate the drug.

Although the discrimination issue has received quite a bit of critical attention in discussions of medical cost-benefit analysis generally, the

[69] See David M. Cutler and Mark McClellan, "Is Technological Change in Medicine Worth It?" *Health Affairs* 20, no. 5 (2001): 1129–45.

[70] I analyze the arguments put forward by some of these commentators in Rai, "Rationing through Choice," 1076–97. A recent interesting treatment of the discrimination issue is found in Menzel, "How Should 'Social Values' Be Measured?" 259–73.

[71] The Americans with Disabilities Act, 42 U.S.C. §§ 12101 et seq. (1994).

more relevant methodological difficulty for pharmaceutical cost-benefit analysis involves discounting—specifically, the discounting of health benefits. The concept of discounting emerges from the intuition that even independent of inflation, it is better to have money now than to have that money later. This intuition is in turn rooted in at least three independent concepts: pure time-preference, time-preference associated with economic growth, and opportunity cost.[72] Pure time-preference refers to the fact that people prefer present pleasure over the same kind and intensity of pleasure in the future. Time-preference associated with economic growth refers to the idea that because the declining marginal utility of money causes richer people to value each unit of wealth less than poorer people do, economic growth—which makes us richer overall—will cause a given amount of money to be less valuable in the future than it is now. Finally, the concept of opportunity cost alludes to the fact that consuming or giving away resources now means not having those resources available when investing for the future.

With respect to money, discounting is not controversial. Indeed, pure time-preference, time-preference based on economic growth, and opportunity cost are all reflected in the ordinary institution of interest. If a lender L gives a borrower B $100 to use today and asks that the money be repaid at some point in the future, L will expect back more than $100. Assuming a 5 percent "real" annual rate of interest—that is, a rate of interest of 5 percent after inflation is factored out—L will expect $105 if she is paid back in one year, $110.25 if she is paid back in two years, and so on.[73] Conversely, at a 5 percent real discount rate, a promise of $105 in one year is worth $100 today, as is a promise of $110.25 in two years.

Similarly, in the context of medical cost-benefit analysis, discounting costs that will be incurred in the future is not controversial. Thus, for example, if a particular medical intervention requires that $100 be spent immediately and an additional $105 be spent in a year, all economists would agree that the total present cost of the project is $200 (again assuming a 5 percent annual discount rate). By contrast, discounting health benefits is quite controversial. For one who discounts health benefits, lives saved in the future matter less than lives saved today: for example, at a discount rate of 5 percent, a life saved in twenty years is worth only about .38 lives today. Noting implications like this, some analysts have argued that health benefits should be discounted at a low rate or not at all.[74] These analysts have questioned the extent to which concepts of

[72] See Alan L. Hillman, "Economic Decision Making in Healthcare: A Standard Approach to Discounting Health Outcomes," *Pharmacoeconomics* 7, no. 3 (1995): 199.

[73] In this essay, I make the simplifying assumption that interest is compounded annually. On this assumption, the value of a sum D invested for t years at a rate of interest r would be $D (1 + t)^r$. By contrast, in a more formal mathematical treatment, interest might be calculated instantaneously.

[74] See Michael Parsonage and Henry Neuberger, "Discounting and Health Benefits," *Health Economics* 1, no. 1 (1992): 71–79.

time-preference and opportunity cost apply to health. First, they argue that the available data does not provide clear empirical support for the claim that people actually exhibit pure time-preference with respect to health.[75] As for time-preference based on economic growth, they contend that economic growth is likely to make a healthy life-year in the future more enjoyable, and therefore worth more, than a healthy life-year in the present.[76] Finally, with respect to opportunity cost, these analysts suggest that deferring expenditures on current health does not necessarily mean that one will obtain greater health with those resources in the future.[77] Proponents of discounting health benefits concede that discounting future health benefits may be different in important respects from discounting future monetary benefits. Nonetheless, they emphasize that the available evidence suggests that there exists a pure time-preference of about 2 to 3 percent with respect to health.[78] Given this pure time-preference, health benefits should be discounted.

Thus far I have confined my discussion to the dispute over what discount rate should be used *intra*generationally—that is, within ranges of twenty to thirty years. The literature on cost-benefit analysis also contains vigorous discussion of what (if any) discount rate should be used *inter*generationally. This discussion is important because the benefits associated with many regulations, particularly regulations of environmental risk, may not accrue for many generations. Discounting across generations is particularly vexing because it poses the very difficult ethical question of what justice requires across generations. Fortunately for my purposes in this essay, the intergenerational discounting question does not have to be addressed in most cases of pharmaceutical cost-benefit analysis. In sharp contrast with environmental regulations, pharmaceutical innovations typically yield their most significant benefits within the first twenty to thirty years after their development. After that time, the innovations are often superseded by, or are at least in competition with, other, newer innovations. Thus, for purposes of this essay, I consider a time horizon of only twenty to thirty years.[79]

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[75] Ibid., 73. See also Lisa Heinzerling, "Regulatory Costs of Mythic Proportions," *Yale Law Journal* 107, no. 7 (1998): 2046–49; and Hillman and Kim, "Economic Decision Making in Healthcare," 200. The available data here has generally been gathered from experimental studies of subjects who are asked questions about how they value future harms and from evidence on workers' willingness to accept wage premiums in exchange for future health risks.

[76] Hillman and Kim, "Economic Decision Making in Healthcare," 200.

[77] Ibid.

[78] See Richard Revesz, "Environmental Regulation, Cost-Benefit Analysis, and the Discounting of Human Lives," *Columbia Law Review* 99, no. 4 (1999): 975–79; and Daniel Farber and Paul A. Hemmersbaugh, "The Shadow of the Future: Discount Rates, Later Generations, and the Environment," *Vanderbilt Law Review* 46, no. 2 (1993): 283–85.

[79] To the extent that the time horizon is extended because particular drugs yield appreciable benefits even after one generation, considerations of intergenerational justice might require using a somewhat lower discount rate for future generations than is used for the

In this essay, I do not attempt to resolve the debate over whether health benefits should be discounted intragenerationally and, if so, whether they should be discounted at the same rate as costs. Rather, I will illustrate what the cost-benefit analysis of orphan-drug production would look like under various different intragenerational discounting scenarios. Significantly, even under the conservative assumption that costs and health benefits should be discounted at the same rate, certain orphan drugs will still produce benefits commensurate with their costs. Of course, the number of orphan drugs whose production can be justified on cost-benefit grounds will increase as the rate at which health benefits are discounted drops.

2. An illustration of the analysis. Consider the following simplified example, in which I assume a discount rate of 3 percent for both costs and health benefits. A particular disease (call it disease X) affects two hundred new individuals a year and has an average age of onset of 40. A drug that treats the disease can be developed at a cost of $500 million (with this cost estimate made at the time the drug is put on the market);[80] its marginal cost of production is then zero. Without the drug, the affected individuals die at age 40. With the drug (which the patient takes on a one-time basis at age 40), the average member of the disease X population can live to age 44 in a state of good health. Under conventional analyses of medical benefits, the health benefit of the drug would be quantified as four years, adjusted by the quality of life during those four years. If quality of life is measured on a scale of 0 to 1, with 1 representing good health, the health benefit conferred by the drug would be 4 QALYs per treated person. Thus, the drug would, on an annual basis, confer 800 QALYs of health benefit (two hundred persons multiplied by 4 QALYs per person). Over the course of twenty years, as a total of four thousand affected individuals emerged, the drug would confer a total of 16,000 QALYs. Assuming that each QALY is worth $50,000, the drug would, over the course of the twenty years, generate an undiscounted health benefit of $800 million. Even at an annual discount rate of 3 percent, moreover, the total health benefit over the course of the twenty years would be about $595 million.[81]

If a private firm could appropriate most of this gain in health benefit, it might be willing to produce the drug. However, given that the patent system gives only about fourteen years of patent exclusivity post–FDA

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current generation. The lower the discount rate for future generations, the greater the weight attached to their interests.

[80] For ease of explication, this example calculates costs and benefits at the time that the drug is placed on the market. By contrast, in standard analyses of drug-development costs, the relevant time of calculation (T_0) is generally about ten years earlier, when a manufacturer is deciding whether to commit research dollars to a particular drug-development effort. For purposes of my example, which assumes the same discount rate for costs and health benefits, the choice of T_0 does not affect the analysis. What is important is that costs and benefits are measured at the same T_0.

[81] For purposes of this essay, I make the simplifying assumption that benefits accrue, and are discounted at, the end of each year.

approval, the private company would have only about fourteen years to appropriate a welfare gain that emerges over the course of twenty years. Over the course of fourteen years, the drug would produce a discounted health benefit of only $452 million; even if the manufacturer could appropriate all of this, it would not recoup the $500 million cost of developing the drug. Hence, the drug would qualify as an orphan. The central intuition here is that because the marginal costs of producing a drug are negligible, some orphan drugs could, over the long term, produce health benefits that may justify their cost. However, given an effective patent term of only fourteen years, private firms may not be able to capture fully the value of these health benefits.

It is perhaps obvious that if we assume that the discount rate for health benefits is lower than 3 percent, the health benefit produced by the drug that targets disease X would be even greater than it was under the 3 percent rate. Indeed, at a discount rate of 0 percent, the health benefit produced in a period of fourteen years would be $560 million, more than enough to compensate for the drug's development cost. It is important to emphasize, however, that the drug manufacturer *itself* never has a discount rate of 0 percent. To the contrary, because a rational drug manufacturer sees future health benefits as a source of future income flow that will compensate for R&D costs, it necessarily discounts health benefits at least at the same rate as the prevailing real interest rate for money.[82] To put the point another way, a policymaker's decision to use a discount rate for health benefits that is lower than the prevailing real interest rate will not change the actions of private parties. A lowered discount rate for health benefits merely means that there are even more drugs that are cost-effective from a social-policy standpoint that private drug manufacturers nonetheless will not want to develop.

To the extent that a policymaker assumes a discount rate for health benefits that is the same as the discount rate for costs, an indirect subsidy in the form of patent-term extension might be a sufficient response to the problem of insufficient drug development. For example, if the patent term in the hypothetical case of disease X lasted for twenty years rather than fourteen—in other words, for the effective life of most drugs, given the rapid progress of technology—the drug manufacturer would be able to recoup its investment: it would recover a discounted sum of $595 million over the course of twenty years, and it would thus have an incentive to develop the drug.

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[82] In fact, there is reason to believe that the pharmaceutical industry uses a discount rate significantly higher than the real interest rate for money. To the extent that the pharmaceutical industry demands rates of return higher than those found in other industries (in order to compensate for the high level of risk involved in pharmaceutical development), it may discount future income flow more steeply than other industries do. For purposes of this essay, however, I will make the conservative assumption of a 3 percent real discount rate for money, even in the pharmaceutical industry.

There are, however, problems with patent-term extensions. One difficulty arises from the fact that patent-term extensions rely on the implicit cost-benefit analysis of the health-care marketplace. As contrasted with the medical cost-benefit analysis used by policymakers, the health-care market's version of cost-benefit analysis measures health benefit in a manner that reflects ability to pay. As a consequence, if a disease were to affect individuals who were, for the most part, poor and uninsured, even a patent-term extension might not motivate private firms to produce that drug. In addition, patent-term extensions exacerbate the problems posed by patents generally. Under standard economic theory, patents are, almost by definition, an inefficient mechanism for stimulating innovation. Although the monopoly power that is often conveyed by patent rights[83] may be necessary to provide incentives to innovate, a producer with monopoly power will generally charge more and produce less than a producer in a competitive market.[84] To put the point another way, in a monopolistic situation, certain sales that would be beneficial to both the producer and the purchaser are simply not made.[85] Not only is stimulating innovation by allowing for intellectual property rights inefficient, but the supracompetitive pricing upon which this approach relies inevitably raises difficult questions regarding access. When one is discussing health-care products, access questions have a particularly compelling moral basis.[86]

An alternative to the indirect subsidy of a patent-term extension might be some sort of direct research subsidy for orphan drugs that are likely to be cost-effective (from a societal perspective) over, say, a twenty-year term. The subsidy would be calculated as the present discounted value of the additional profits that the relevant drug's developer would make over a term that lasted twenty years rather than fourteen. The discount rate for the profits would be the rate at which the policymaker thinks health

[83] The precise nature of a drug manufacturer's monopoly power will depend on the scope of its patent, the possible availability of substitutes for the relevant drug, the price-sensitivity of consumers, and the amount of price discrimination that health insurers can secure in virtue of their bargaining power. In the case of pharmaceutical products, patents are often broad and consumers (particularly insured consumers) are quite price-insensitive. Thus, even though competitors to a patented drug generally emerge after a few years, their potential impact on price competition is softened by the fact that they are imperfect substitutes that price-insensitive consumers will not readily embrace. Rai, "The Information Revolution Reaches Pharmaceuticals," 206.

[84] Hal Varian, *Intermediate Microeconomics: A Modern Approach*, 5th ed. (New York: W. W. Norton, 1999), 420–24. Unlike the competitive producer, who produces to the point where price equals marginal cost, the monopolistic producer typically operates only at prices well above marginal cost. Ibid., 420. This is particularly true in industries like the prescription-drug industry, where the marginal costs of production are virtually zero.

[85] Ibid., 422–24.

[86] See William Sage, "Funding Fairness: Public Investment, Proprietary Rights, and Access to Health Care Technology," *Virginia Law Review* 82, no. 8 (1996): 1741–42: "[A]n obvious side-effect of patent monopolies—like other monopolies—is to increase price and decrease output. As a result, patented inventions may not be affordable to those who need them. If equity is a concern in the provision of health care services, awarding patents, especially for breakthrough therapies, tends in the opposite direction."

benefits should be discounted. The lower the discount rate, the higher the subsidy. As contrasted with the cost-benefit analysis embodied in patent-term extensions, the direct-subsidy alternative measures health benefit independently of ability to pay. It also has the advantage of allowing a discount rate for health benefits at variance with the market rate. Finally, while the cost-benefit analysis embodied in patent-term extensions is not transparent and open to public criticism, a program of publicly justified direct subsidies could use cost-benefit analysis in a transparent manner that promotes the deliberative goals discussed in Section IV.

The central difficulty with a direct-subsidy approach is that it assumes that the government will be in a position to know which drugs are likely to be cost-effective and which are not. By contrast, a patent-term-extension approach relies upon market incentives to stimulate the production of orphan drugs whose utility may be limited but is nevertheless sufficiently large to make the drugs cost-effective from a societal standpoint. Another way of making the same point is to note that direct subsidies rely upon the government to pick winners and losers. Indirect subsidies in the form of patent-term extensions (or, indeed, in the form of patents generally) rely upon the market. With respect to applied research, such as research on particular drugs, the market generally has better information than the government does. For this reason, the government has, at least in the United States, tended to focus its direct funding on basic research. Applied research has been the province of the market, as fortified against market failure by the patent system.

In this essay, I do not resolve the question of whether patent-term extensions or direct subsidies are a superior mechanism for addressing the orphan-drug issue. If patent-term extensions are implemented, however, they should be coupled with initiatives to ensure that those who cannot pay the ordinary monopoly price for the relevant drugs still have access to them. Such initiatives might include subsidies for purchasing the drugs directly or for insurance that would cover the drugs.[87]

VI. Application of the Cost-Benefit Framework to Non-Orphan Drugs?

It might be thought that this suggested framework for thinking about the subsidization of orphan-drug development should be used to assess federal subsidies of pharmacological research more generally. On this view, either direct financial aid or longer patent terms (of, say, twenty years post–FDA approval) would be useful for all drugs, not simply orphan drugs. After all, the average patent term of fourteen years is

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[87] For an extended discussion of how subsidies for the purchase of insurance could be used to secure access to drugs, see Rai, "The Information Revolution Reaches Pharmaceuticals," 198–210.

simply not long enough for most drugs to capture fully for their manu-
facturers the value of the health benefits that the drugs produce. This
argument misconceives, however, the goal that this essay's cost-benefit
framework is intended to achieve. That goal is to ensure that drugs that
would not otherwise be developed, but which are in fact cost-beneficial,
do get developed. The goal is not to secure to all drug manufacturers all
the profits that might be generated by the health benefits that the man-
ufacturers' drugs provide. Nonorphan drugs will, by definition, be de-
veloped without additional subsidies, whether given in the form of direct
financial aid or a longer patent term. Thus, there is no reason to have
these additional subsidies. Indeed, longer patent terms (or patent terms of
any sort) have sufficient negative consequences with respect to efficiency
and access that they should be advocated only to the minimal extent
necessary to stimulate cost-beneficial innovation.

VII. Conclusion

In the not-too-distant future, pharmacogenomic research will yield a
plethora of information about the manner in which individual genotype
affects drug response. This information will, in turn, create orphan geno-
types parallel to the orphan phenotypes currently addressed by the Or-
phan Drug Act. Because the number of orphan genotypes is likely to be
quite large, pharmacogenomics will force government policymakers to
consider seriously (as they have not in the past) the question of how
scarce resources for orphan-drug research should be allocated. Moral
theory does not provide a definitive answer to this question of distribu-
tive justice. In order to resolve the question, we must supplement moral
theory with transparent and well-reasoned political debate. This essay
has advocated cost-benefit analysis as an important contribution to such
debate. Specifically, this essay has argued that some orphan drugs that
would not be profitable for private firms to develop under the current
system of marketplace patent protection may in fact be cost-beneficial. In
any future system of research subsidies for orphan drugs, these cost-
beneficial drugs should receive some preference.

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