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Cost Sharing in Insurance Coverage for Precision Medicine

Mark V. Pauly

6.1 Introduction

Many medicines (and other treatments) work well for some apparently similar patients but not others. One of the factors known to determine effectiveness of a treatment is the genetic makeup of the patient or the disease. While physicians for centuries have honed the skill of determining which patients are good candidates for which treatments, the advent of "precision medicine" adds a tool in the form of a genetic test to predict effectiveness (or its absence) of a treatment regimen. The main advantages of such a test are avoiding the cost, side effects, and false hope for those for whom the treatment is unlikely to work, while at the same time reassuring those willing to go through the treatment that they will ultimately benefit. The widely touted promise is that testing will both lower total spending (on the specific treatment whose effectiveness can now be predicted) and improve health outcomes by avoiding specific treatment side effects for those for whom it would have been ineffective (Aspinall and Hamermesh 2007). But are cost reduction and outcome improvements sufficient reasons for or necessary outcomes of generous insurance coverage of precision medicine-tested treatments? More specifically, what is the optimal pattern of insurance coverage for tests and related treatments? It may well be efficient to have some cost sharing to discourage low value uses of testing and treatment, but such potentially improved incentives trade-off against less protection from finan-

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cial risk. The economic theory of optimal insurance coverage (Pauly 1968; Zeckhauser 1970) shows how to characterize the ideal trade-off in simple cases, but what is ideal in this more complex case?

Some insurance coverage is now near universal in the United States, but insurance appropriately does not fully cover everything a physician or patient might think useful. Coverage is incomplete, with sometimes substantial patient cost sharing (as high deductibles, coinsurance, or copayments), both to avoid insurer administrative cost and to inhibit inefficient stimulation to low- or no-value use. Coverage may also wholly exclude some products and services judged experimental or overpriced. In this chapter, I will outline some theoretical models of the ideal role of insurance in such settings with genetic testing and a specific treatment whose effectiveness is predicted by the test. I will contrast those theoretical prescriptions with what appears to be current practice in public and private insurance coverage.

Coverage of the specific treatment will not usually be a major issue in this chapter, though proportional cost sharing of the cost of specialty drugs can add up, and high deductibles usually apply to all tests and treatments. However, coverage of testing will be an interesting question, in part because some testing is still experimental, some insurances do not cover purely diagnostic tests at all, and many insurance deductibles (including the most popular plans on exchanges) will leave tests uncovered until the deductible is exceeded. Coverage decisions by insurers involve both the binary decision of whether to cover a test and/or treatment at all (presumably, in part, as a function of evidence on effectiveness and cost effectiveness), and the continuous question of what level of positive cost sharing to impose, given that there is to be some coverage some of the time. The pricing of tests, the alternatives to testing, and the effect of testing on the pricing of treatment will all be important.

6.1.1 An Important Digression

We will explore later in the chapter the pricing of tests and treatment when either or both markets are not competitive (as opposed to prices resulting in $P = MC$). However, we should note here that it is very likely that the price of the treatment, especially if it is a drug treatment under patent protection and/or Food and Drug Administration (FDA) exclusion, is likely to exceed marginal cost by a wide margin. This means that if we use price rather than marginal cost in the benchmark model, we are much more likely to find the test is "efficiently" improving from an insurer or consumer perspective because it helps to avoid a treatment which, in addition to possible side effects, carries a very high *price* offset. However, this saving may not be true saving from a societal welfare perspective because (at least in the short run and without more complexity) the financial benefit from reduced spending on precision medicines to the insurer or the patient substantially overstates

the benefit to society since the avoided price is well above the value of the resources saved. Pricing of drugs above marginal cost can engender a significant overuse of precision medicine tests even for treatments with small side effects, while overpricing of proprietary genetic tests can lead to underuse. Finally, prospective insurance coverage can influence decisions to invest in the R&D costs needed to develop a test-treatment package.

6.2 Heterogeneity

In the general theory of optimal coinsurance, the key determinant of the level of cost sharing for a product or service, if it is to take on a value between zero and one, is the shape of distribution of marginal benefits (otherwise known as the demand curve). If patients are identical, with identical marginal benefits from care and identical disutility from side effects of testing (so there are perfectly horizontal demand curves for testing and treatment for everyone at risk), and if the population at risk can be defined and limited precisely, optimal coverage is either 100 percent or zero (Pauly 2015).

Next, we assume that physicians provide the insurer with all the clinical information they know, while patients retain private information on the value they place on health outcomes (e.g., as measured by QALYs). With that assumption, it is variation in the monetary value attached to expected outcomes that can generate negatively sloped demand curves. These values are known by the patient-consumer, but not by the insurer. The conventional quality-adjusted life years (QALYs) measure already assumes away differences across subjects in the value of length of life (from successful treatment) versus quality of life (from treatment side effects), but there is considerable reason to believe that the monetary valuation of a QALY varies across people, based on both income and tastes. It is this variation that will be our primary focus as a rationale for insurance to contain partial cost sharing.

The cases just discussed furnish the primary and most consequential reason for "interior" cost sharing of tests or treatments in precision medicine, but there are some other possible rationales. If the cost of either test or treatment is very low, the administrative expense of paying claims may not justify the benefit of a tiny reduction in risk. If the plan has standard coinsurance rates that it applies across the board to categories of clinical services in the interest of administrative simplicity, it may choose to do so for precision medicine tests and treatment rather than make coverage even more complex than it really is. We also abstract from the problems raised by Filipova-Neumann and Hoy (2014) that a test may change subsequent incentives to engage in preventive behaviors (like monitoring through other tests). Finally, if patients misestimate the benefits of tests or treatment, there may be a case for value-based cost sharing (Pauly and Blavin 2008) to encourage the use of undervalued services.

6.2.1 Situations and Solutions

While positive cost sharing can improve efficiency by reducing moral hazard in the heterogeneous-hidden information case, the extent to which it will do so depends on how responsive demand is to such charges. The classic optimal insurance proposition is that the more responsive use is to insurance coverage, the higher the ideal level of cost sharing. We will show that this proposition still applies to genetic and genomic testing, but it is more complicated than usual.

This proposition becomes more complex because of interrelated demands in this case—insurance design needs to take into account both price responsiveness of demand for tests and price responsiveness of demand for treatment. But one baseline finding is that if neither testing nor treatment responded to cost sharing and the combination always has net benefit greater than the threshold value, there would be no point in any cost sharing—just make care free. Later we will see what empirical evidence we have on this question.

6.2.2 Insurance and Pricing

Often the seller of a test or treatment has patent protection or some other source of market exclusivity and is inclined to charge the monopoly price (which of course can much exceed marginal cost). What are the issues in optimal insurance design when either or both markets are not competitive?

There are three possible (noncompetitive) situations here with respect to IP protection: (a) both test and treatment are patented, (b) testing is competitive but treatment is monopolized, and (c) testing is monopolized but treatment is competitive. In case (a) there is also the issue of whether the same firm holds both patents.

If either the test or the treatment is monopolized alone, the equilibrium total price will be the same since the monopoly rent can be collected at either stage of the production process, ignoring game theory issues. Adding monopoly control of one component when the firm already controls the other component will not add to profits since the monopoly price can only be collected once. If the firms are separate, but each has market power, the outcome is ambiguous and depends on bargaining.

The profit-maximizing combination price for test and treatment when sold by a single firm is thus different from that if the two monopoly firms are separate. Compared to the absence of a test, the price of a treatment will increase when the test becomes available because its marginal effectiveness will increase. For example, if there is a fifty-fifty chance the treatment will work, but the test picks out the half of the population where it will work, the treatment price will at least double (Pauly 2009). This increase in markup will also increase the bias in favor of testing. While a drug firm may not increase its drug price to fully match increased effectiveness if a test becomes newly

available, its price for the specific treatment when a companion diagnostic already exists will reflect that value. There will also be an addition to the total price to reflect the ability to avoid side effects of useless treatment for those who test negative. Compared to the price of a single firm monopolizing both test and treatment, the price under bilateral monopoly will be higher unless the seller of the treatment subsidizes the price of the test.

How do these pricing considerations feed back into the design of cost sharing in insurance, especially if prices sometimes vary?

The most important consideration here is the proof by Gaynor, Haas-Wilson, and Vogt (2000) that consumers cannot be made better off by monopoly pricing of insured services if insurance markets are competitive. While prices higher than marginal cost will discourage the use of care under a given level of proportional coinsurance, insurance firms will set coinsurance rates with competitive pricing of products and services that always improve welfare compared to that under "ideal" coinsurance with monopoly pricing (and higher benefit payouts). As a general conclusion, the dollar amount of cost sharing will be higher under monopoly and may discourage both test and treatment. Some private insurance markets for some parts of the US population may not be competitive. While large group coverage is often self-insured, high insurance market shares, perhaps aided by preferential treatment of some "Blue" plans, may confront small group and individual buyers with premiums that yield higher than normal payouts or administrative costs. In this chapter we will, nevertheless, assume that the pricing of insurance for increments to coverage for new precision medicine tests and treatments is competitive, and briefly discuss implications of removing this assumption in the conclusion.

The other issue is whether monopoly pricing may make the entire therapeutic approach not cost effective from the perspective of an insurer with customers who attach lower value to outcomes (and who must pay the price charged, not the marginal cost). The answer seems clearly affirmative and it is unclear if there is an obvious work-around to this overpricing.

6.2.3 Current Patterns of Insurance Coverage for Genetic Tests and Related Treatments

There is considerable variation across clinical conditions and types of insurance coverage—both the gross prices paid for genetic tests and genetic counseling, and for the prices of treatments whose selection depends on test results. In this discussion, we will focus primarily on tests and treatments for cancer, but will also comment on some broader patterns.

Prices of common genetic tests have generally been dropping as the technology for genetic tests has become faster and more accurate (though new expensive tests are also being introduced). The price of a test obviously depends both on what genetic variation is being explored and how extensive a description of the genome in terms of genetic variants is sought. Simpler

genetic tests can now be obtained for as little as $200–$500 for common tests targeted at common parts of the genome, into thousands of dollars for tests for all variants and all modifications, but prices rise.

In addition to tests per se, often genetic counseling is either required or useful. The cost of counseling has not been falling and generally exceeds $200 for a single test for a single treatment. The prices of treatments also vary greatly, depending on type and payer. The more restrictive intellectual property protection and the fewer close substitutes available, the higher the price.

Both the maximum reimbursement and the willingness to restrict use vary across insurers. Private-sector insurers have the ability both to negotiate the prices for tests, counseling, and treatments, and (less commonly) to refuse to cover or only partially cover tests except on favorable terms. Some Medicaid managed care carriers also have this process. Traditional Medicare, in contrast, cannot negotiate prices for Part D drugs for which there are no therapeutic equivalents, can only set administrative prices for Part B drugs, and is required to cover all classes of FDA-approved drugs when they are clinically appropriate. It has somewhat more flexibility in coverage of genetic tests, and different Medicare carriers seem to have different policies as to which tests they will cover and how. Part D (oral drugs) are subject to Part D cost sharing. Part B specialty drugs in medicine can be subject to coinsurance (and in Medicare Advantage plans as well), usually at 20–30 percent, if it is required. Most beneficiaries buy Medigap coverage to offset patient cost sharing.

Private insurers usually cover genetic tests under the same cost-sharing provisions (deductibles and coinsurance) as they apply to other tests. Thus cost sharing can vary across carriers and across employer customers within insurers. If genetic tests are designated clinical laboratory tests, they are often covered in full. Full coverage is not required for screening or prevention.

There is some consistency in coverage patterns. The Affordable Care Act (ACA) requires zero coinsurance for BRCA tests (two genes only) for women with breast cancer for testing and counseling. The more common genetic tests (e.g., for Lynch syndrome in colon cancer) are generally covered, though cost sharing may still vary based on overall cost-sharing provisions in a policy. More rare and more experimental tests are subject to enormous variation, from full coverage (e.g., as part of a trial) to no coverage at all for a test deemed experimental by insurers. Beyond these obvious cases, there has been considerable variation in coverage of testing across insurers and over time.

There have been a few surveys of insurers asking about their testing coverage policy. Results generally show that in 2000–2010, coverage generally became more available for tests that entered routine clinical use. A survey by Graf et al. (2013) found that 77 percent of large insurers indicated coverage of at least one genetic test. A review sponsored by the Commonwealth Fund (2016) of tests for women found only 15 percent (of 109 insurers) excluded

Table 6.1 **Website coverage information: thirty large private insurers[a]**

	Genetic testing	Genetic counseling	BRCA 1/2	Oncotype Dx	Lynch syndrome
Covered	30	26	27	25	24
Not covered	0	0	0	2	0
Not mentioned	0	4	3	3	6

[a] Enrollment ≥ two million persons.

coverage of common genetic tests, even when they were not required by law. We examined more recent website data from large insurers (table 6.1) and found similar patterns of coverage in principle for tests accepted as clinically useful. As indicated there, all large insurers (except for Medicare) cover genetic testing in general. But as the table shows, coverage for specific tests is irregular. In addition, websites tell us that the amount of cost sharing for those tests and treatments varies with policy cost-sharing provisions (deductibles and coinsurance), which themselves vary widely; for this reason they do not give an average amount of cost sharing.

We requested internal analysis of a large claims database from a nationwide commercial insurer in order to describe cost sharing for genetic test codes over calendar year 2016 linked to the drugs Erbitux (for colon cancer), Keytruda (for lung and other cancers), and Herceptin (for breast and ovarian cancer). (The tests were KRAS [for Erbitux and Keytruda], PD-L1 and eGFR [for Keytruda], and HER2 via FISH [for Herceptin]. The claims data also includes these tests used for purposes other than as companion diagnostics.) The claims data indicated that usually tests were fully covered by insurance (65 percent of claims) and that, among those claims where cost sharing was positive, its average level ranged between $100 and $200 depending on the test, with the median likely below the mean. Thus high cost sharing for tests in precision medicine is not typical, but cost sharing still may matter because there is other evidence that relatively low levels of cost sharing for drugs can still have a decided impact on quantity compared to free care (Hillman et al. 1999).

Over time, as more genetic tests have been clinically linked to therapy with specific drugs, Medicare coverage has become more extensive (Medicare .gov 2016). There is apparently still some variation across carriers, but most carriers now follow the "Palmetto" list of approved genetic and genomic tests. Medicaid coverage is more variable across state programs, with explicit coverage specification often not publically accessible. The ACA required that BRCA-1 and BRCA-2 tests and counseling be covered in full, but that is virtually the only regulatory constant (Kaiser Foundation 2015).

Insurers explain their determination of coverage by appeal to the concept of "medical necessity." One large insurer (CIGNA 2017) defines "medical necessity" in the context of genetic tests as having three requirements:

1. The test is FDA approved and/or performed in a Clinical Laboratory Improvement Amendments (CLIA)-approved lab.
2. The test is medically necessary for the diagnoses indicated.
3. Results of the test will directly impact clinical decision-making.

However, different insurers have different interpretations of these criteria (especially the second one). In some cases, as in the case of testing for BRCA, there is "a clear algorithm for whether or not to test (for BRCA mutations)," and sometimes testing is recommended by the FDA for proved use of a treatment, but in other cases pathways and protocols are unclear.

As genetic test prices have fallen, the willingness of insurers to cover them has risen—an example yet again of the vacuity of the concept of medical necessity (Ho 2017). In addition to tests per se, often genetic counseling is either required or useful. The price of counseling has not been falling. Some insurers require genetic counseling before approving testing or treatment (CIGNA 2017).

The prices of cancer treatments also vary greatly, depending on type and payer. Generally a treatment whose selection and use might be determined to be a test is in the (wide) range of $50,000 to $500,000, although some oral and generic treatments sell for less depending on patents and FDA exclusions. The more restrictive intellectual property protection and the fewer close substitutes available, the higher the price.

There is no information on the demand elasticity for genetic tests or counseling. The demand elasticity for drugs in general is said to range from 0.2 to 0.6. Coinsurance for specialized cancer drugs is common in Medicare Advantage and Part B plans, unless the person has purchased Medigap insurance.

Estimates of demand elasticity for specialty drugs cover the range from 0.01 to 0.2—a wide range, but one consistent with low-demand elasticity. The theory of optimal coinsurance suggests strongly that in such cases, high cost sharing is not optimal. Explanations of insurer behavior in imposing high cost sharing as a desire for higher profits or lower premiums are quite unsatisfactory, because such provisions make insurance unattractive and thus reduce demand. Higher cost sharing may be a risk-selection device, implemented (say) to discourage cancer patients from enrolling because their higher risk is not adequately offset by providing risk-adjustment payments. Medigap insurance may also play a role in offsetting the effects of Medicare cost sharing, and diminishing any cost-containment effects of Medicare cost sharing in curtailing moral hazard.

6.3 Relationship to Our Analysis

Our theoretical analysis generally supports the view that cost sharing for current genetic tests, many of which appear to be cost effective, should be

low. The ultimate argument in favor of coverage with lower cost sharing for tests and treatment, in either the private or public sectors, must be based on cost and effectiveness results. If the treatment, and therefore coverage of them, can be shown to generate high net value, employers can ensure profits by offering better benefits, and Medicare and Medicaid can enhance social value. The empirical work needed to document demand elasticity and marginal clinical effectiveness relative to cost of much of precision medicine remains to be done, as does analysis of the pricing choices in the face of government-enforced market power through the patent system and FDA grants of exclusivity. But these goals can in principle be accomplished and result in some lives saved for moderate spending.

6.4 Some Simple Theories

We now provide a brief sketch of the theoretical possibilities for cost and health outcomes with and without genetic testing being possible. This discussion will characterize situations in which the use of testing is or is not undertaken in an efficient end-state outcome. It will also describe the potential changes in patient behavior from a setting when no testing is available. Many scenarios are possible in theory, but some of them will be ruled out for institutional reasons. For example, in many situations FDA regulations rule out the use of an approved drug treatment unless testing is first done.

6.4.1 Notation and Description

Let:

p = probability of successful treatment with a genetic mutation, given a person is high risk

B = value of increase in marginal health benefits from successful treatment $T = ((\Delta \text{QALYS}_M)(\text{VQALY}))/\Delta T$.
(where VQALY is the assumed uniform monetary value of a quality-adjusted life year and (ΔQALYS_M) is in the increase in QALYS from successful treatment).
This increase in benefit occurs with probability p.

L = value of marginal side effects of treatment = $((\Delta \text{QALYS}_S)(\text{VQALY}))/\Delta T$
(where (ΔQALYS_S) is the decrease in QALYS from the treatment side effects).
This reduction in benefit occurs with probability one for all those treated.

$P_t = C_t$ = price or marginal cost of specific treatment

$P_g = C_g$ = price or marginal cost of genetic test plus counseling

C_f = marginal cost of avoided treatment for future illness if the patient is treated successfully (present discounted value).

For those treated unsuccessfully, future costs are the same whether treated or not. Avoiding future costs is one of the benefits from successful treatment.

Before the test exists, two behaviors are possible (in the world of homogeneous personal risk):

Case A

(1) $p(B + C_f) - L > P_t \rightarrow$ cover treatment and expect all to be treated.

Case B

(2) $p(B + C_f) - L < P_t \rightarrow$ do not cover treatment and expect none to be treated.

That is, either expected benefits from treatment minus side effects for all exceed cost and all should be treated, or they fall short and none should be treated. The benefit from successful treatment is the sum of health benefits and avoided future treatment cost for those successfully treated. All those treated bear the negative side effects L, whether they benefit from the treatment or not.

6.4.2 When the Test Becomes Available

The marginal conditions become:

Cover test and treatment if

$$p(B + C_f - L) > P_g + pP_t \tag{3}$$

and

$$(1 - p)(P_t + L) > P_g \tag{4}$$

That is, the test and treatment should be covered if the net expected benefit from testing and treating those who should be treated exceeds the sum of the cost of the test *and* the value of expected cost of treatment and the expected avoided cost and side effects for them, while for those for whom the treatment would be ineffective, avoiding the treatment cost side effects is greater than the cost of the test.

Equation (3) is the condition for the cost effectiveness of the combined test and subsequent treatment regimen, while equation (4) is the condition for cost effectiveness of the test.

In Case A, if condition (4) holds, condition (3) will hold as well. Since the treatment was preferred even when there is a "cost" of treating and causing side effects for those who are not positive, it must be optimal to treat if it becomes optimal to test; that is, if the avoided cost and side effects for those who do not test positive are greater than the price of the test.

In Case B, it is optimal to cover test and treatment if conditions (3) and (4) hold. However, condition (4) may hold (given treatment, it is optimal to test) but condition (3) may not. This can either happen because the treatment does not provide net benefit for those who test positive or the treatment does

provide net benefit, but that benefit is not large enough to cover the cost of the test for those who test positive.

What is the impact of availability of the test on treatment volume and total cost? In Case A, treatment volume falls as the test winnows out those who do not test positive and otherwise would incur treatment cost. Total cost will fall if the expected cost savings from avoiding the treatment of those who do not test positive exceeds the cost of the test, but costs need not fall even if treatment volume falls if the value of avoided side effects is large and the test is expensive.

Treatment volume rises in case of risks in Case B, if the two conditions hold, because the test avoids the unnecessary disutility and treatment cost for those who would not benefit and that will clear the way for those who would benefit to use the treatment. However, if either of the marginal conditions does not hold (the treatment is not worth it to those who test positive or the test costs more than the avoided adverse consequences for those who would not test positive), then the availability of the test will not affect the optimal outcome: the optimal choice should still be no treatment along with no testing.

In these cases, what should be the optimal level of insurance coverage?

1. If (a) testing provides benefits (in terms of avoided cost of treatment and the value of avoided side effects of treatment) greater than its price and (b) the combination of testing and treatment provides more benefits (in terms of net QALYs gained and avoided future treatment cost) than the sum of the price of testing and the expected price of treating those who are positive, then both testing and treatment should be fully covered. Those for whom the expected side effects of treatment are aggressive (e.g., prophylactic colectomy) outweigh the benefits, and should not receive testing and treatment even at a zero user price for both.

2. Treatment should be fully covered, but not testing, if condition (a) does not hold but the benefits from treatment in terms of expected net QALYs gained from treating all—expected value of QALYs gained from treatment plus avoided future treatment costs from those who would have tested positive minus QALYs lost from side effect of treating all—is greater than the price of treatment.

If both (a) and (b) do not hold, neither test nor treatment should be covered.

6.5 Going from Homogeneity to Heterogeneity

If consumers differ in the values they place on QALYs, but are identical in terms of expected clinical outcomes, there can be variation in the cost effectiveness of treatment and testing, or treatment alone, around a mean measure of net benefits per person (value of net QALYs gained minus incremental spending on treatment and testing). The mean cost-effectiveness

Box 6.1

Example 1: Rare Condition

Probability test is positive: 0.1

Price of test: $4,000

Price of specific treatment: $50,000

Present discounted value of future treatment costs without treatment: $10,000

Case A: **Treat all**
Total cost/person (in $ thousands): 50 + 0.9(10) = 59

Case B: **Treat none**
Total cost/person: 10

Test and treat

Total cost/person: 4 + (0.1)(50) + 0.9(10) = 18

Incremental costs: TT versus treat all: –41

Incremental costs: TT versus treat none: +8

Implications for efficiency and insurance coverage

If initial state is treat all (most likely), do testing since it is a dominant strategy: lower cost and the same outcome unless there is very high disutility to treatment. Insurance coverage of testing should be 100 percent if treatment is cost effective. If initial state is treat none (the more likely), the efficient strategy depends on the value of net benefit from treatment compared to incremental cost of $8,000 per person at risk. Either cover the test 100 percent or not at all.

ratio for alternative strategies combined with the shape of the distribution of these values will determine whether there should be insurance with partial cost sharing, assuming uniform financial-risk aversion. In what follows, we provide some illustrative hypothetical examples of different possible scenarios and insurance coverages and then discuss ideal insurance coverage from some examples of genomic testing to determine the effectiveness of treatment. To focus on the effect of testing, we assume that insurance coverage of the specific and expected future treatments is either 100 percent or zero, and consider positive cost sharing for testing and counseling. We first present two polar case examples of the cost impact of that availability (boxes 6.1 and 6.2). (The figures in these boxes are not chosen for realism, but rather to illustrate these cases.)

Box 6.2

Example 2: Common Condition

Price of test: $4,000

Probability test is positive: 0.95

Price of specific treatment conditional on a positive test: $50,000

Present discounted value of future treatment costs without specific treatment: $10,000

Case A: **Treat all**
Total cost per person: 50 – (0.05)(10) = 55

Case B: **Treat none**
Total cost/person: = 10

Test and treat

Total cost per person: 4 + (0.95)(50) + .05(10) = 52

Incremental cost: TT versus treat all = –3

Incremental cost: TT versus treat none = 42

Then cost of treating all (55) is greater than cost of test and treat (52); test and treatment is a dominant strategy unless disability from treatment is very high. There is large incremental cost of testing with treatment compared to treating none, but a large gain in outcomes.

These two numerical examples indicate that the potential for genetic testing to lower cost depends on the frequency in the population at risk of the condition the test will detect and on the initial treatment strategy. If the condition is rare, but take-up of the treatment is high, the test will reduce total costs by a large amount because it will eliminate expensive treatment of no benefit, but in the more likely case where the initial status is no treatment, using testing and treatment will raise cost. Conversely, if the condition is common but the take-up of the treatment is low (because of fear of side effects), testing may encourage treatment by reducing the fear of unnecessary side effects that treatment may have, but will add to cost. If initially all are treated, testing will lower the cost level. In both dominance cases, testing will be cost reducing and full coverage is optimal.

But there can be cases in which testing adds to cost, yet improves outcomes. Then the issue is the magnitude of the improvement in outcomes

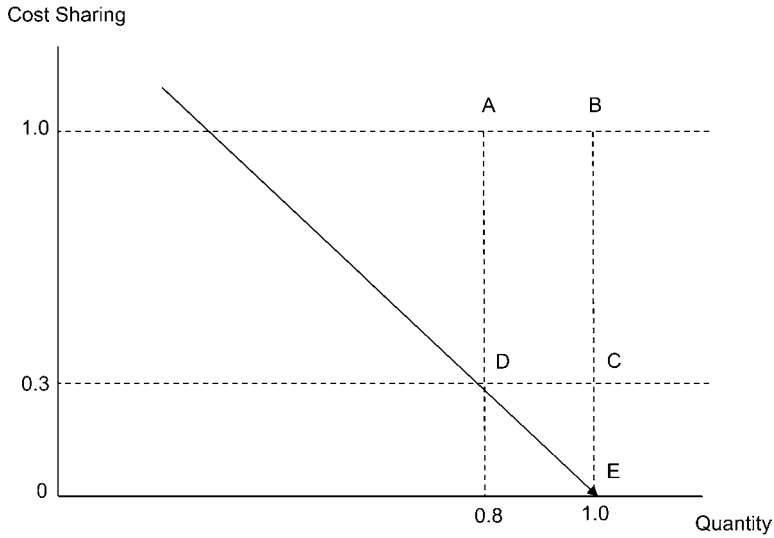

Fig. 6.1 Reduction in the marginal welfare cost of moral hazards

(net of any side effects) and the value attached to that improvement. Cost-effectiveness results depend as well on the threshold value attached to health outcomes. If it is high, full coverage for testing may be optimal, while if it is uniformly low, coverage should be zero. However, if it varies across the population at risk, partial cost sharing will be ideal.

To estimate the net change in utility from raising cost sharing in such "interior" cases from zero to some positive fraction, we need to calculate two effects of the change. One effect is that consumers are exposed to greater financial risk because their out-of-pocket payment now becomes positive. The monetary amount of that out-of-pocket payment for this high-risk population is the volume of test cost (compared to zero cost sharing) times the out-of-pocket percentage. The risk premium that comes from the risk of incurring this part of the cost of the test is assumed to be some proportion of the incremental expected out-of-pocket cost. One way to approximate that additional willingness to pay to avoid the risk of having to pay the designated amount out of pocket is to observe the marginal loading on insurance at which many are willing to buy coverage. We assume that the marginal insurance buyer will purchase individual insurance with a loading of 33 percent or less.

The other component is the marginal reduction in the welfare cost of moral hazard associated with this change in insurance coverage. In terms of figure 6.1, where the demand curve is the (net) marginal value of testing, it is the rectangle ABCD plus the triangle DCE, which (in the case of 0.3

Box 6.3

Incremental cost with testing and determination of welfare cost and risk premium of partial cost sharing.

Effect of cost sharing at 30 percent of test and 0 percent of treatments (vs. test and treat all).

Assume that cost sharing for testing reduces quantity of testing by 20 percent, that marginal risk premium (MRP) is 33 percent of out-of-pocket cost, and that probability of positive test is 0.95.

Computing Optimal Insurance Coverage:

Initial State: Full Coverage of Test and Treatment.

Cost sharing when alternative is treat all:

$$\text{MWC} = (0.7(4 - (0.05(50))(0.2) + 0.5((0.3)(4 - (0.05)(50))(0.2) = 210 + 45 = 255$$

$$\text{MRP} = .3\ (.8)\ (4)(.33) = 320$$

This implies that cost sharing of 30 percent is only a little higher than optimal.

coinsurance) equals [0.7 (net change in expected cost)(change in volume) + ½(0.3)(Net change in cost)(change in volume)].

Box 6.3 presents an example of optimal and partial cost sharing.

6.6 Imperfect Test Predictability

The model discussed so far of testing with a companion diagnosis to predict effectiveness of a treatment assumes that a given value of the test is associated with a single known probability of effectiveness of a given magnitude. For example, the probability that the treatment will provide benefit is p if the test is above a certain threshold and is zero if it is below.

But there is an interesting and more general case: when the value of the test is positively correlated with the probability the treatment will produce the benefit B—when the expected value of the benefit pB increases as the test value indicates increased p (chapter 4, this volume). When is coverage for such a test optimal? Even more interesting, we can in this case answer the question of how a firm with market power selling the treatment sets its price and how insurers would respond by varying cost sharing.

Suppose the price of the treatment is C. At any given threshold, expected benefits are $p(R)B$-C, where p is a function of the test reading R. What is the optimal threshold for R from an insurer's perspective, and the associated price charged by the monopoly seller of the treatment? What is the inefficiency that arises from the seller's pricing?

The relevant comparison is the value of the change in expected total benefit when the threshold is lowered relative to increase in treatment cost per person. That level depends both on the distribution of persons by threshold value and how different values map into probabilities of effectiveness.

Assume that all persons with given risk characteristics are to be tested. If you know the ideal threshold, you can enforce it by making coverage for the treatment conditional on evidence showing the person exceeding the threshold. However, beyond recommendations and FDA approvals for treatment conditional on some threshold, it does appear that sellers of treatments with companion diagnostics let insurers set the levels at which they will cover the treatment.

A perhaps surprising implication is that the behavior of the treatable population at various levels of the threshold and its associated treatment effectiveness define a demand curve for the treatment (even if subjective values of health outcomes are uniform). A small number of people with "high" test results are willing to pay a high price, but as the price is reduced more people with lower test results are willing to buy. Then we can determine the price a seller of the treatment with market power will choose by using the usual monopoly pricing rule—comparing marginal revenue (along this demand curve) with marginal cost of production and distribution.

As already noted, how quantity demanded changes as price was reduced depends on two parameters: the number of people at each test value and the relationship of that test value to the effectiveness of treatment. Beginning at the highest price at which anyone will buy, with a bell-shaped curve on test values, the numbers of customers brought in by lower prices at first increases rapidly and then falls off. It is not clear what assumption is plausible about how test values are related to effectiveness. What is clear is that, as usual, use of the treatment will be suboptimal if the seller has market power. We provide some numerical examples of different elasticities of effectiveness with respect to test value.

Box 6.4 provides a numerical example to illustrate these points.

6.7 Some Current Examples of Genetic Testing and Treatment

The data on test and treatment cost and outcomes for three prominent examples of the use of genomic testing is displayed in table 6.2. All of these cases were "no testing and treatment" (usual case) as the comparator; we could find no cases where "treat all" is the comparator. (References for the data used in those case studies are in the Appendix.) Here we discuss what

Box 6.4

Optimal and Profit Maximizing Use of Treatments With Imperfect Companion Diagnostics: Numerical Example

Parameters: distribution of test results per 100 persons at risk: high 25, medium 50, low 25

Proportion of users at each threshold who obtain benefit B: high 0.8, medium 0.4, low 0.2. This implies total number benefitting in each increment is 20, 20, and 5 with cumulative totals of 20, 40, 45.

Suppose the marginal cost of treatment $C = 1$. Suppose that the 50 people who have medium test levels would at most be willing to pay $3C = 3$. That implies that $B = 7.5$ and the maximum price that will bring in the first 25 is 6, and that which will bring in the last 25 is 1.5.

Revenues and profits at each "threshold":

High: 25 (6–1) = 125; medium 75 (3–1) = 150; low 100(1.5–1) = 50. Hence the profit-maximizing threshold is "medium" with price of 3 and demand of 75.

However, in this example, the socially optimal quantity is 100 since 45(7.5)–100, or 237.5, is greater than 40 (7.5)–75, or 225, or 20(7.5)—25, or 125.

As is usually the case in economics, profit maximization by a seller with market power leads to an equilibrium with a smaller than socially optimal rate of use of the product being sold. The reason is that the incremental social benefit of treating the lowest threshold group is (5 × 7.5), which is more than the marginal cost of 25, even though the marginal revenue from bringing in those 25 new buyers (by cutting the price from 3 to 1.5) is negative since the price halves, but the quantity increases only by 25/75 or 33 percent.

is known about those cases and speculate about what it implies for insurance coverage.

BRCA 1/2: Women who test positive for a particular set of genes (BRCA-1 and BRCA-2) are much more likely than average to develop breast and ovarian cancer at an early age and to die from cancer. The medical costs incurred by a designated high-risk population (definitions vary but include

Table 6.2 **Illustrative example of cost sharing for a rare condition**

Test/treatment	BRCA—prophylactic surgery	BRCA—tamoxifen prophylaxis	PD-L1—Keytruda versus carboplatin + pemetrexed	KRAS test—Erbitux + FOLFIRI versus FOLFIRI alone	KRAS test—Erbitux + FOLFIRI versus Avastin + FOLFIRI
Price of test and counseling ($)	2,933	2,933	790	247	1,467
Price of specific treatment for those who test positive	15,925	623	82,201	105,216	300,018
Avoided future costs for those who test positive and have treatment (per person tested)	13,343	1,396	n/a	n/a	n/a
Proportion testing positive	0.25	0.25	0.255	0.67	0.67
Total spending per person with testing and treatment	12,389	18,379	36,031	83,668	283,489
Total spending per person with no testing or treatment (usual care)	16,686	16,686	19,168	37,939	245,485
Gain in QALYs with avoiding illness (overall per person tested)	Cost saving	0.30	1.05	0.51	0.5
Comparator (test all or test none)	Test none, cancer costs as normal	Test none, costs from mammograms and cancer	Test none, chemo-therapy for all	Test none, FOLFIRI for all	Test none, FOLFIRI + Avastin for all
Change in total cost from test and treatment relative to comparator	4,297 saved per patient	1,693 increase per patient	16,863 increase per patient	45,729 increase per patient	38,004 increase per patient
Cost-effectiveness ratio if change is positive	Cost saving	2,609/QALY	62,982/QALY	133,827/QALY	113,445 /QALY

Notes: The general formula for computing the change in cost for the test and treatment innovation relative to the comparator is: (new cost per person tested)—(comparator cost per person tested) = (cost per person per genetic test) + (proportion testing positive) * (cost per treatment)—(net long-term cost reduction per person tested). The last term includes both reduced treatment cost for those who test positive and are successfully treated and any cost savings from avoiding further screening for those who test positive. For example, for tamoxifen treatment after testing for the BRCA gene for breast cancer, this difference in cost is the sum of the cost of genetic testing and 0.25 times the cost of tamoxifen minus the expected net reduced future treatment cost (relative to comparator) for cancer for those who test positive. The last component includes both lower costs for avoided cases of breast and ovarian cancer for those who test positive. Treatment costs are unaffected for the 75 percent who test negative, and mammogram rates are assumed unchanged. Cost values in the last column are lifetime costs.

those with breast cancer at an early age and those with first-degree relatives who contracted breast cancer at an early age) have been studied under the alternative scenario of no genetic testing versus genetic testing and then prophylactic surgery if the test is positive. Testing and counseling of the high-risk population has been recommended (with a "B" recommendation) by the US Preventive Services Task Force and consequently all insurers are currently required to cover both testing and counseling for this population. The alternative to surgery is a plan of more frequent mammograms and preventive cancer chemotherapy such as tamoxifen.

In what follows, we assume that the alternative to testing and a treatment with large negative side effects is no treatment and no testing. We assume that surgery has negative effects on short-term and long-term quality of life, but avoids future lifetime costs for this type of cancer.

Looking only at medical care costs, studies have compared the cost of testing and counseling all members of the high-risk population and the cost of surgery for those with positive findings with the future costs for screening for, biopsying, and future surgery and treatment for these cancers. The cost offset from prophylactic surgery in terms of the present discounted value of related future medical costs is larger than the cost of testing and treatment. Unless a high value is attached to reduction in quality of life from surgery, the net change in QALY is usually estimated to be positive.

Hence, compared to no testing and no treatment, use of genetic testing followed by prophylactic surgery for positive test results is a dominant strategy. It saves money and leads to outcomes that are better. It follows that testing and treatment should be fully covered by insurance to protect against the risk of becoming at high risk for this condition.

In the case of a nonsurgical alternative (tamoxifen) after testing, there is an increase in cost per subject but also a much more modest addition to QALYs (because tamoxifen is not very effective as prevention). Despite being cost effective compared to usual care, this alternative is dominated by surgery.

Erbitux and testing for metastatic colon cancer. The FDA currently approves cetuximab (Erbitux) for treatment of colon cancer following a test to determine whether the person's genetic makeup has an abnormality in KRAS or is "wild type" with no abnormality. Erbitux is only effective for wild-type genetic profiles, and about two-thirds of those with colon cancer have this profile. Though one might suppose that a strategy of universal treatment might be reasonable, the FDA currently recommends Erbitux only after testing and a finding of no genetic defects. The alternative to testing and treatment with Erbitux is a colectomy (surgical removal of the colon) or more frequent colonoscopies.

Studies find that, compared to a strategy of treating everyone at high risk with Erbitux without testing, testing, and then Erbitux treating based on test results is cost reducing. However, compared with usual care (no testing,

no Erbitux), testing and then treating with Erbitux adds to total cost but improves health outcomes. If FDA guidelines are followed, it is the second case that is more relevant.

Because testing is a mandatory gateway to Erbitux treatment, we can consider cost sharing for testing as effectively an increase in cost sharing for treatment with probability *p*. There is no benefit to those who test negative. The average $/QALY for Erbitux is $113,000 to 138,000 per QALY, representing higher cost for the test-treatment combination than the conventional threshold of $100,000 per QALY.

Keytruda and testing for non-small cell lung cancer (NSCLC). Keytruda is a new and expensive drug that has shown efficacy against non-small cell lung cancer and other tumors. In the NSCLC case, the drug is effective only if the patient tests positive for PD-L1 and negative for the genes eGFR and ALK. In some cases, the drug is used if eGFR and ALK inhibitors have failed, as has platinum-based chemotherapy.

About 80 percent of NSCLC patients would pass both of the genetic screens just described. The test and counseling to determine the status of a patient costs about $1,000. Compared to a strategy of no testing and no treatment, there is a positive cost and positive health benefits from adding both testing and Keytruda. There has been no analysis of the costs and benefits from testing if all NSCLC patients were using Keytruda. Hence the case is similar to Erbitux, but with a more cost-effective treatment. The mean estimated incremental cost per QALY is $63,000 per QALY, below the conventional threshold.

Coverage. As already noted, testing and surgical treatment is cost reducing for breast cancer, so it should be fully covered. Testing and treatment with tamoxifen is dominated so it should only be covered for populations that attach low value to the quality of life after prophylactic mastectomy.

The average cost per QALY for Erbitux would often be regarded as above the threshold for efficient use of the testing and treatment program, but if there is variation across consumers around the mean ratio because of variation in the values attached to increments in health or side effects, there may still be demand for and optimal provision of coverage for the combination for those with high values. However, mandatory coverage by private insurance is not warranted nor is universal coverage for all Medicare beneficiaries. Medigap insurance will also not cover costs of care that is experimental or not deemed medically necessary.

The FDA requirement for testing before treatment effectively rules out the "treat all/no test" option for consumers, so the value of testing per se is irrelevant. Private insurers may or may not choose to cover the Erbitux program, without additional conditions or restrictions. Medicare coverage is uncertain; if Medicare determines that testing for Erbitux responsiveness is not medically necessary, coverage is unlikely to be provided by private insurers. One response of Medicare when clinical evidence is not conclusive (as in

the case of genetic testing to predict responsiveness to warfarin) is to limit coverage to those participating in clinical trials of effectiveness, so-called "coverage with evidence determination." Private insurers generally restrict their coverage until the clinical evidence is generated.

Optimal coinsurance when no treatment is the alternative to testing and treatment. In both the cases of Erbitux and Keytruda, if there is variation in the value attached to net QALYs added by test and treatment (additional years of survival minus reduction in quality of life due to treatment side effects), there will be a demand curve for a test-treatment combination that will be affected by any cost sharing for the test. In effect, cost sharing on either test or treatment raises the user price of the combination package. The distribution of these values determines the response to test cost sharing. It is possible that the key assumption behind the QALY measure is violated—for example, if the person attaches no value to a few more months of survival but wants to avoid the side effects of an aggressive treatment—but in that case there will be no demand for testing, even a zero price and no value to insurance coverage of either test or treatment.

The relevant price here is, as before, the price of the test plus p times the price of treatment less any cost offset from avoided illness. The latter savings can be "taken off the top" so the percentage cost sharing depends on whether we analyzed the gross price or the price net of cost offsets; cost sharing as a proportion of net cost will be larger than cost sharing as a proportion of gross price.

Summary. These cases show some of the range of practical considerations that would govern specification of insurance coverage for testing and treatment. In the case of BRCA testing leading to prophylactic surgery, the evidence that total cost is reduced by testing while the health levels of those who opt for testing and this treatment is improved implies that coverage should be complete for both testing and treatment. In the two examples where testing is required for treatment, but one drug has a higher cost-effectiveness ratio than the other, the ideal pattern of insurance depends on the extent and form of variation in values attached to health improvements. If it is small, and if the threshold value for the great majority of the population is equal to or greater than $100,000 (say), then coverage should be nearly complete for Keytruda but lower for Erbitux. If there are few people with values per QALY above the mean value for Erbitux, it may be (second best) efficient to have high cost sharing for testing and, if feasible, for treatment. If health plans can sort consumers by their personal values of health improvements, plans with full coverage of testing and treatment for Keytruda should be more common than plans with full coverage for Erbitux.

Other companion diagnostics. We also examined the Tufts registry of cost effectiveness studies, a comprehensive listing of all such studies. We searched using the key words "precision medicine," "personalized medicine," "genetic," or "genomic." We found forty-four articles that matched. Fol-

Table 6.3 Illustrative impact of cost sharing for a common condition

Cost-effectiveness range	Study estimate count (38 total)
Dominant (cost-saving)	4
$0–50,000/QALY	12
$50–100,000/QALY	14
>$100,000/QALY	8

Note: Taken from twenty-three articles, some with multiple comparisons.

lowing the procedure in Glick et al. (2015), we deleted studies before 2002, performed outside the United States, and those that did not use QALYs as a measure of outcome; the resulting sample had twenty-three studies (including the ones used in our case studies above). Table 6.3 shows the overall pattern of results in terms of incremental cost and incremental benefits measured in QALYs.

About 11 percent of the studies found the test and treatment to be cost saving, relative to the comparator, implying full coverage of test and treatment is optimal; this was a smaller fraction than the 28 percent of cost-saving studies found in the sample of all studies investigated by Glick et al. Most of the studies showed cost-effectiveness ratios below the conventional $100,000 per QALY cutoff, but eight did not. As noted earlier, these studies do not show the distribution of values around the mean estimate, but those studies with favorable values considerably below the $100,000 threshold would probably be good candidates for complete or nearly complete coverage of both treatment and companion diagnostics. However, the case for full coverage or even any coverage of the 21 percent of cases above that cutoff is questionable.

6.8 Conclusion

Our review of coverage for genetic testing reveals a trend toward a more general acceptance of such tests as having clinical utility, and therefore in principle appropriate candidates for insurance coverage. There is still a reluctance to cover tests deemed experimental, and there are relatively high bars for the evidence that can make coverage routine—though in most cases the coverage usually follows rather than facilitates clinical practice.

Insurers with market power seem to adopt similar coverage policies for new technology as those in more competitive markets. If monopolistic insurers do retain the savings, the increase in affected denials from coverage of precision medicine may lead to lower than optimal rates of use. There may, however, be a disconnect between what happens to net societal benefits (additional health benefits, rather than lower premiums, minus additional marginal resource costs) versus net benefits to consumers (additional benefits—change in cost)

because prices do not equal cost. However, there is also a substantial tax subsidy to employment-based group insurance, which implies that excessively generous coverage will be chosen. Market power and tax subsidies obviously raise much larger questions than coverage of precision medicine, and determining their net impact on the marginal after-tax premium for coverage of precision medicine would be needed for definitive welfare evaluation in cases where they are present.

Genetic testing to determine the effectiveness of treatment is still relatively new, though growing rapidly. There does seem to be a common cycle in which three trends compete: evidence for and use of genetic testing increase over time, insurance coverage (though present) initially imposes higher cost sharing, then test prices fall and coverage improves and out-of-pocket cost falls.

In principle, cost-effectiveness studies could provide the basis for determining those tests so efficient that coverage should be 100 percent, but this determination may vary across consumers depending on their willingness to pay for health outcomes and avoiding side effects of treatment. So coverage may become broader but shallower.

The other conflicting influence is that new but initially expensive tests appear that do impose a financial burden but, with dubious evidence for their effectiveness or cost effectiveness, are generally not covered. Thus there is likely to be continued debate on how insurance should deal with both the testing and treatment associated with personalized medicine.

Appendix

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