Payment for Cancer Biomarker Testing

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Simply put, chemotherapy is poison that kills dividing cells. Medicare and other payers pay for it because, as cancers display unrestricted growth, frequently dividing cancer cells are killed by the poison—along with some normal cells, hence hair loss and other unpleasant but generally survivable side effects. All that payers traditionally have required in order to authorize payment for chemotherapy has been (1) an understanding the patient actually has cancer (diagnosis); (2) assurance that the poison is not so strong it would kill or otherwise unreasonably harm the patient (safety); (3) and some indication that the poison actually kills dividing cells, such as demonstration of increased survival rates or cure rates (efficacy). Chemotherapy is a “one-size-fits-all” treatment and is not usually cost prohibitive, so payers have generally paid for it without much fuss.

With an increasing understanding of the molecular basis of cancers, medicine is shifting from one-size-fits-all cancer treatment to personalized medicine, in which certain subsets of cancers qualify for molecular-based therapies. Molecular-based therapies are not chemotherapy, indiscriminately killing cells by physically obstructing their division. Instead, cancers—defined by their broken genes—are treated with drugs that stop cancer by interfering with specific molecules involved in tumor growth and progression. Molecular-based therapy requires the testing of cancer tissue with predictive biomarkers to identify cancer subsets for reliably determining which patients should—and just as importantly, should not—be given molecular-based therapies. Efficient use of a specific molecular-based therapy absolutely requires an appropriate cancer biomarker to define subsets of patients who have a prognosis or response to a particular type of therapy that differs from the mean. Successful cancer biomarkers “provide a reliable, predictive correlation to differential patient responses” and address direct anticancer efficacy.

Molecular-based cancer therapy has shown benefit with certain subsets of cancer patients, such as patients with colon, breast, and lung cancer. The lung cancer biomarker testing guidelines provide an evidence-based strategy for selecting lung cancer patients for targeted therapy with first-generation EGFR and ALK tyrosine kinase inhibitors. The guidelines, vetted by experts from multiple disciplines and multiple nations, help ensure that patient selection for biomarker testing is properly performed, tissue is appropriately managed, and costs are minimized. The lung cancer guideline’s evidence-based strategy—and the evidence-based, peer-reviewed literature upon which it is based showing efficacy—should be a powerful tool for persuading skeptical government payers and private insurers to pay for lung cancer biomarker tests. And the federal government’s promotion of the expansion of personalized medicine is congruent with the goal of increased biomarker testing. Because cost-effective prescription of new molecular cancer therapies requires that their use be limited to biomarker-positive subgroups, the cost of detecting biomarker-positive tumors—including the cost of screening biomarker-negative tumors—is a legitimate consideration in determining therapeutic cost-effectiveness. But payment for biomarker testing is a growing concern in the emerging world of personalized medicine. And the concern is legitimate; although personalized cancer therapy is successfully tackling biological, technical, and pharmacologic challenges, payment is emerging as the challenge most difficult to overcome, and the one that puts the ultimate success of personalized cancer therapy at greatest risk.

CANCER BIOMARKER PAYMENT TODAY

At a time when payers, struggling to thrive in the current dynamic health care environment, must clearly understand the cost of patient care, they “are definitely on board with biomarker tests, particularly when it means that they are paying for drugs that patients will likely respond to—and conversely are not paying for several months of drugs or chemotherapy that will have little positive effect.” But it has been difficult to “get a handle” on biomarker test payment because payment requirements evolve and change over time, payers approach payment in different ways for different technologies, and the majority of payers pay for diagnostic molecular tests separately from the associated therapy. In fact, payment for cancer biomarker tests may be a more difficult issue than payment for new oncology treatments themselves.

Biomarker testing has yet to be specifically recognized in the reimbursement system, and “there are relatively few standard coverage policies for biomarker tests . . . [so] as a result, coverage for many is still determined on a case-by-case basis.” “Because of a lack of codes tied to testing for different genes or mutations, laboratories often must build insurance claims using a strategy called code ‘stacking,’ employing a series of codes for methodology-based steps...
that add up to a molecular test.”10 But stacking existing codes often yields significantly lower reimbursement, emphasizing the critical need for accurate codes as a means to identify biomarker tests for appropriate payment.5,10 At the same time, more payers are instituting bundled payments, based on the average cost of care, “to decrease overall expenditures and shift financial risk from the payer to the provider.”11

Fortunately, recent Medicare coverage determinations have become more timely and open; however, they continue to lack the degree of predictability that biomarker test and molecular therapy manufacturers prefer in order to predictably and optimally plan and innovate.12 This lack of predictability is accentuated by the fact that biomarker tests lag behind the development of molecular-based therapeutic drugs, possibly because “drug companies are stalling on companion diagnostics because they don’t want to run the risk of delaying drug development or having to share royalties with a diagnostic partner. Moreover it is pointed out that drugs in general are only 30–60% effective so it might expose the weak efficacy of some drugs.”13

And recently, Medicare has sharply changed the way it pays for diagnostic tests, cutting payment rates across the board by an average of about 20% from 2012 levels, and curtailing coverage for some new tests altogether.14 “Most of the new rates are being based on the work of one Medicare contractor, Palmetto GBA [Columbia, South Carolina].”14 So-called tier 2 tests—not yet a part of routine practice, or suitable alternative, the new scheme will thwart the introduction of novel diagnostics and limit bets on new therapies.2 If they determine it is, they are likely to require evidence of a tumor’s biomarker positivity before agreeing to pay for the associated molecular-based therapy.2 Because of the cost, some payers, before approving payment, may require patients to sign waivers acknowledging they are not required to pay for these services.15

But the reasonable counterargument is that in many cases the value of these biomarker tests has not been substantiated.

Most of these [biomarker] tests . . . are now speculative at best. Not that years down the road some of them may prove of some value, but not today. To make things worse they are very expensive. Why is it that these labs don’t provide more information to Medicare on what the heck these tests are for? They don’t know. At best they are just guessing. Today when a simple blood test is billed out at a thousand dollars a pop you can only start guessing what some of these boutique medical tests which their conclusions are questionable at best cost.15

**PAYER REQUIREMENTS**

Payers are becoming increasingly sophisticated about biomarker testing, and many determine whether biomarker testing is necessary before they cover new molecular therapies.2 If they determine it is, they are likely to require evidence of a tumor’s biomarker positivity before agreeing to pay for the associated molecular-based therapy.2 Because of the cost, some payers, before approving payment, may require patients to sign waivers acknowledging they are not candidates for the corresponding molecular therapy if the test result is negative.2

Payers view cancer biomarker tests “as medical advances with potential to add value” and are increasingly demanding strong evidence of value—linking biomarker testing and patient outcomes—to make increasingly value-based coverage and payment decisions.4 “[T]he cost-effectiveness of a [cancer biomarker] screening test will be dependent upon the cost of the future events avoided as well as the cost of resources and infrastructure required to set up the test within a healthcare setting.”4 “Economic considerations include but are not limited to test and treatment costs, impatient and outpatient resource utilization, insurance coverage, and provider reimbursement.”4 Ultimately, “[t]he cost of the test is not as important as the impact that the test has on the longer-term health outcomes.”4

The decisive question is whether outcome improvement is attained at a “reasonable” additional cost compared with existing technology.4 Without evidence of clinical utility in improving patient outcomes, payers will consider such tests “financially wasteful at a time when it has become critical to control increasing health care costs.”10 “[I]t is [therefore]
vital to assess their incremental and full economic impact, including the costs and outcomes of the downstream decisions that ensue, to ensure that scarce healthcare resources are put to their most efficient use.\textsuperscript{4,16} What is required are “large observational studies that can link the outcome of the biomarker to a longer-term health outcome, and are able to show a cost benefit.”\textsuperscript{4}

**INDUSTRY CONCERNS**

Developing new drugs has long been expensive and risky. But with the development of targeted molecular therapies, there is a new risk that a therapy—unsuccesful in a general nontargeted cancer population, and a seeming financial loss for the company—might be discontinued from research or production because its legitimate value to a subgroup of patients goes unrecognized.\textsuperscript{4} As such, accurate assessment of biomarker test efficiency depends upon its utility in identifying patient subsets for whom treatment provides a substantial benefit. And because new molecular-based cancer therapies will therefore not be marketed with emphasis on “demand generation” but instead on “identification of appropriate high-risk patients,”\textsuperscript{2} relatively sophisticated marketing issues also come into play.

Beyond these therapeutic and [marketing] issues, biomarkers represent a significant drug-pricing hurdle for manufacturers. A biomarker can identify a subpopulation for whom the therapy is ideal, while simultaneously excluding a large part of the potential market. Market size is one of the factors that goes into pricing decisionmaking, and when the market is significantly contracted, the pricing analysis breaks down.\textsuperscript{8}

And regarding cancer biomarker test payment, the catch-22 is that although clinical utility studies for cancer biomarker tests—complicated, expensive, time-consuming, and not directly required by the United States Food and Drug Administration for their approval—are often not performed, to gain wide payer acceptance, cancer biomarker tests “must be accompanied by a demonstration of cost-effectiveness.”\textsuperscript{10}

Developers understand that the provision of robust clinical evidence provides the best chance for insurer coverage, yet biomarker test developers do not have clear expectations for the level of evidence that is necessary for reimbursement.”\textsuperscript{10} “At the core of this is a more central debate: What level of evidence should a test demonstrate before Medicare will pay [for it]?”\textsuperscript{14}

**COST-EFFECTIVENESS, COST-EFFECTIVENESS ANALYSIS, AND QUALITY-ADJUSTED LIFE-YEARS**

Traditionally, payers have required evidence of test efficacy—that the test the laboratory performed and reported, and is being billed for, actually works—to authorize laboratory test payment. But now, payers are increasingly demanding evidence not only of efficacy but also analysis of the test’s cost-effectiveness. Cost-effective does not merely mean inexpensive. If the clinical benefits are substantial, expensive tests and therapies deliver good value, providing efficient use of health care resources compared with their available alternatives.\textsuperscript{16} And cost-effectiveness analysis (CEA) is not a substitute for traditional efficacy analysis; “cost-effectiveness” is meaningless for a test that is not efficacious. Cost-effectiveness analysis is increasingly being used to assess the clinical and economic impact of medical interventions, and has become the most important tool for the quantitative assessment of biomarkers’ economic value.\textsuperscript{4} Judicious use of CEA allows for the assessment of the comparative impact of 2 or more interventions to ensure that scarce resources are allocated to the uses most likely to maximize clinical outcome, aiding in “decision-making by offering tools to quantitatively assess different clinical scenarios and synthesize existing evidence.”\textsuperscript{4,16} “By providing a comprehensive estimate of both costs and outcomes, CEA illustrates the trade-offs involved in deciding among all the options under investigation.”\textsuperscript{4}

Cost-effectiveness analysis is expected to provide significant guidance for ensuring that health care value is delivered by a quantitative weighing of costs and benefits across a range of potential interventions.\textsuperscript{16} It is already being required of some therapies, and in the laboratory, cost-effectiveness has developed particular significance with respect to cancer biomarker testing because the associated molecular-based cancer therapies so far only provide incremental survival benefit beyond that provided by standard, much less expensive cancer therapeutic regimens. And because prescription of these molecular-based cancer therapies will be limited to only those patients with maximal potential benefit from a drug, CEA must address aspects of screening as well.\textsuperscript{5} Payment for cancer biomarker testing depends on whether the improvement in patient outcomes can be attained at reasonable cost when compared with current cancer treatments, and CEA—evaluating both the clinical and economic effect of a test or treatment—may be the best method for assessing cancer biomarkers’ and subsequent treatments’ value.

Cost-effectiveness also involves patient quality of life, but quality of life has not been extensively studied in patients receiving molecular-based therapies.\textsuperscript{5} And showing quality-of-life cost-effectiveness is not something that pathologists are used to doing, or that is easily or inexpensively done. Patient quality-of-life measurements are being performed, though; CEA has been used to help ascertain an estimated cost per quality-adjusted life-year (QALY) gained by the use of a test or a treatment.\textsuperscript{16} Quality-adjusted life-years extensively influence the National Institute for Health and Care Excellence recommendations that inform the United Kingdom’s National Health Service national payment policy. Generally, in the United Kingdom, approval of a targeted therapy or biomarker test requires that the new treatment or test deliver enhanced patient outcomes at a reasonable cost per QALY.\textsuperscript{15} The generally accepted threshold for an acceptable cost per QALY is unclear, but currently amounts between $33,000 and $100,000 have been used.\textsuperscript{4,8,37} In the United States, the political debate regarding health care reform’s proposed comparative effectiveness research emphasizes the growing significance of efficient resource allocation in medicine, and QALY determinations can reasonably be expected to play an increasingly prominent role in determining those allocations.\textsuperscript{1,18} Although CEA and QALY are currently legally problematic in the United States,\textsuperscript{49} they or measurements similar to them will likely soon play a key role in US health care payment policy, and it behooves the pathology community to work to develop evidence-based cost-effectiveness analyses for cancer biomarker tests.

Comparative effectiveness research may also play a future role in health care payment policy in the United States. Comparative effectiveness research “is defined as ‘the
generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care.” 16 “Comparative effectiveness research . . . is a broader concept than cost-effectiveness analyses, and care must be taken to distinguish between them, especially in regards to the current discussions around healthcare reform.” 16 “Comparative effectiveness research can play a key role in elucidating the relative effectiveness of competing approaches to diagnosis or therapy by transparently defining and quantifying comparative clinical (and economic) outcomes including survival, quality of life, resource utilization (and costs).” 16

“Recent political debates over the merits of comparative effectiveness research as part of health reform initiatives suggest the rising importance of this approach to the efficient allocation of health care resources.” 3,14 The continuing technological developments in genomics, proteomics, and metabolomics and the corresponding increased scope, breadth, and number of future biomarkers; the growing concern with cost containment; and the dearth of cost-effectiveness and comparative effectiveness studies have prompted payers to demand better evidence regarding economic impact of both new therapies and their associated biomarker tests.4 Properly designed comparative-effectiveness research initiatives might facilitate efficient research and drug development models, including biomarker testing models. 15

**CONCLUSION**

“Historically, a common effect of medical innovation has been improved quality of health care but with a corresponding increase in cost of delivery.” 20 But today, payer coverage decisions are strongly affected by whether a technology is cost raising or cost reducing. Concerns about limited resources, appropriate patient selection, and cost-effectiveness of cancer biomarkers is not new 21; however, the current economic climate has added rigor and urgency to these concerns. 3,17

Cost-effectiveness and cost-utility studies are commonly used to make payment decisions for new drugs and expensive interventions . . . [but] such studies are relatively rare for evaluating the cost-utility of clinical laboratory tests. As medical costs continue to increase in the setting of decreased resources it is likely that new biomarkers may increasingly be examined with respect to their economic benefits in addition to clinical utility. This will represent an additional hurdle for routine use of new biomarkers. 17

In the future, merely showing the traditionally required safety and efficacy of a new laboratory test is unlikely to ensure payment for its use. Test developers are increasingly being required to show that a proposed test is cost-effective. But there is little guidance on how to proceed in determining cost-effectiveness—a new, subjective, and likely expensive requirement with which test developers have little familiarity. Ultimately, test developers, particularly cancer biomarker test developers—whether large companies producing kits or individual laboratories producing laboratory-developed tests—will have to prove not only the traditionally required efficaciousness of a test, but also cost-effectiveness to best ensure payment. Cost-effectiveness—no longer ignored or assumed—will require pathologists, in concert with treating physician colleagues, to provide robust evidence of economic value. “Until the clinical utility of personalized cancer therapy can be demonstrated broadly, it will not be considered standard of practice and thus not billable, which will restrict access to a privileged few. Research efforts should be directed at generating the level of evidence required to make comprehensive testing reimbursable. Until that time, partnerships between academia and industry as well as significant philanthropic support are needed to facilitate comprehensive molecular characterization to demonstrate that it benefits patients. 7

Pathologists are far from powerless in helping to determine whether there will be appropriate payment for cancer biomarker tests. Clinical guidelines, prepared by pathologists with their nonpathologist colleagues, will increasingly be used by payers in determining whether to pay for a biomarker test. 10 Pathologists have a central role in the production of evidence-based health policy literature that is now required to answer questions of cancer biomarker test utility so that payers can correctly determine payment structures for these tests and the resulting treatments. 22 And ultimately, when cancer biomarker utility has been demonstrated, “personalized cancer therapy will become the financially preferred model, by treating the [right] patient with the right therapy, the first time, achieving prolonged responses, and, ultimately leading to cures.” 7

**References**


Submissions Now Accepted for CAP ‘15 Abstract Program

Abstract and case study submissions are now being accepted for the College of American Pathologists (CAP) 2015 meeting, which will be held October 4th through the 7th in Nashville, Tennessee. Submissions for the CAP ‘15 Abstract Program will be accepted from:

Monday, February 9, 2015 through 6 p.m. CT Friday, April 10, 2015

Accepted submissions will be published as a Web-only supplement to the October 2015 issue of the Archives of Pathology & Laboratory Medicine and will be posted on the Archives Web site. Visit the CAP ‘15 Web site at www.cap.org/cap15 to access the abstract submission site and additional abstract program information as it becomes available.