Coverage Policy Development for Personalized Medicine: Private Payer Perspectives on Developing Policy for the 21-Gene Assay

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Abstract

Purpose: Personalized medicine is changing oncology practice and challenging decision making. A key challenge is the limited clinical evidence for many personalized medicine technologies. We describe the strategies private payers employed to develop coverage policy for personalized medicine using the example of the 21-gene assay in breast cancer.

Methods: We examined the coverage policies of six private payers for the 21-gene assay. We then interviewed senior executives (n = 7) from these payers to elucidate factors informing coverage decisions. We additionally focused on the timing of payer decisions compared with the timing of evidence development, measured by publication of primary studies and relevant clinical guidelines.

Results: The 21-gene assay became commercially available in 2004. The interviewed payers granted coverage between 2005 and 2008. Their policies varied in structure (eg, whether prior authorization was required). All payers reported clinical evidence as the most important factor in decision making, but all used some health care system factors (eg, physician adoption or medical society endorsement) to inform decision making as well. Payers had different perceptions about the strength of clinical evidence at the time of the coverage decision.

Conclusion: Coverage of the 21-gene assay is currently widespread, but policies differ in timing and structure. A key approach private payers use to develop coverage policies for novel technologies is considering both clinical evidence and health care system factors. Policy variation may emerge from the range of factors used and perception of the evidence. Future research should examine the role of health care system factors in policy development and related policy variations.

Introduction

Personalized medicine, here referring to the use of genetics or genomics to guide health care decisions, is changing clinical practice and challenging policy decision making.[1,2] Personalized medicine is particularly relevant in oncology, where a number of these technologies have been pioneered. A key challenge to decision makers is that the clinical evidence is limited for many personalized medicine technologies,[3,4] in part because of the inherent characteristics of the US diagnostic regulatory system, and because these technologies are less likely to be studied in randomized clinical trials.[5] Yet there are now several examples of personalized medicine that have been adopted in care and covered by health insurance.[6,7]

This study examines the overarching issue of what strategies private payers use to develop policy for personalized medicine.[8] Private payers insure more than two thirds of the US population. Their policy decisions are critical factors in access to new technologies and their use in practice.[9,10] The topic of how payers make decisions is important to examine, because it identifies the evidence needed for payer decisions and helps clinicians understand payer policies and their impact on clinical practice.[11,12] Our objective is to describe the strategies private payers used to develop coverage policy for Onco*type* DX (Genomic Health, Redwood City, CA), a novel 21-gene assay.

Methods

Onco*type* DX Test

Onco*type* DX is a gene expression profiling test that helps determine the probability of breast cancer recurrence and potential benefit from chemotherapy in estrogen receptor–positive node-negative breast cancers. The test categorizes recurrence risk as low, intermediate, or high. Patients with low recurrence scores are less likely to relapse and less likely to benefit from chemotherapy; high recurrence scores indicate higher probability of relapse and higher likelihood of chemotherapy benefit.[13,14] Although it had been known that some patients with breast cancer would not benefit from chemotherapy, decision methods were limited before Onco*type* DX. Onco*type* DX is relatively expensive (approximately $3,500) compared with many diagnostic tests, and for patients with intermediate recurrence scores, Onco*type* DX may not change treatment decisions. As a laboratory-developed test, Onco*type* DX did not require approval by the US Food and Drug Administration (FDA). Evidence on clinical effectiveness of Onco*type* DX is still developing in at least one current large study, TAILORx [Trial Assigning IndividuaLized Options for Treatment (Rx)].[15] Onco*type* DX has now gained broad use, coverage, and reimbursement. We examined this test rather than those of competitors (eg, MammaPrint; Agendia, Amsterdam, the Netherlands), because it is most commonly used.

Study Data and Methods

We used mixed methods research, including literature review and focused interviews. The literature review was developed to describe selected payer policies for Onco*type* DX as well as to identify relevant clinical guidelines and original clinical studies. We examined Onco*type* DX coverage policies for date of establishment and policy content. We examined clinical guidelines

and clinical studies for publication date. We then used the literature review findings to construct a timeline of evidence development and payer coverage decisions for Oncotype DX and to inform our interviews.

We conducted focused interviews with seven representatives of six private US health plans in December 2008. The interviewed payers were major national insurers, including Aetna (Hartford, CT), Kaiser Permanente (Oakland, CA), Humana (Louisville, KY), UnitedHealth Group (Minneapolis, MN), and WellPoint (Indianapolis, IN); one insurer declined to be identified. Together they represent more than 113 million enrollees.[16] Interviewees were senior executives actively engaged in coverage policy decision making for their organizations, including decisions on Oncotype DX. Interviewees were asked about:

- Factors considered in coverage decision making on Oncotype DX.
- Perception of the strength of evidence for Oncotype DX at the time of coverage decision and how it affected policy.
- Features of resulting policies for Oncotype DX.

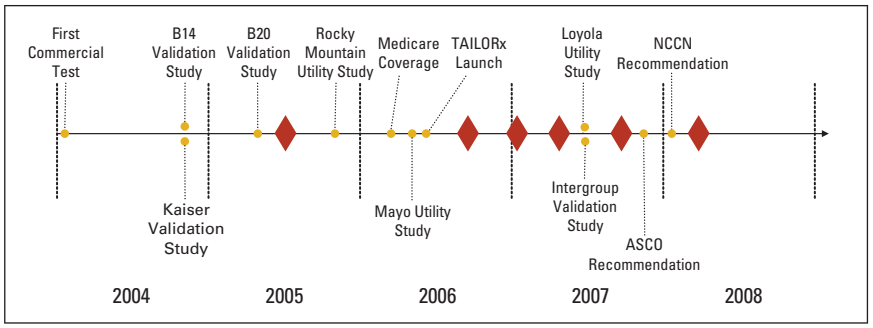

Figure 1. Timeline of clinical evidence (gold circles) and payer coverage decisions (red diamonds) for Oncotype DX. Exact dates of payer coverage decisions are not provided to protect payer anonymity. TAILORx, Trial Assigning IndividuaLized Options for Treatment (Rx); NCCN, National Comprehensive Cancer Network.

Results

Timing of Coverage Decisions, Clinical Studies, and Guidelines

Oncotype DX became commercially available in January 2004. Public payer coverage began with a local Medicare decision in California in January 2006.[17] By the time of our interviews, all interviewed payers covered Oncotype DX, but the timing of coverage decisions spanned from 2005 to 2008. We identified seven clinical studies of Oncotype DX in the adjuvant setting published between January 2004 and May 2008. The timing of clinical study publication and when coverage decisions were made varied: one payer granted coverage when three published studies were available, three payers made coverage decisions after five clinical studies were available, and two payers made coverage decisions after at least seven clinical studies were available. One interviewed payer made a coverage decision after ASCO and the National Comprehensive Cancer Network issued recommendations on Oncotype DX (in November 2007[18] and January 2008,[19] respectively). Only one interviewed payer covered Oncotype DX before the California Medicare coverage decision. Figure 1 and Table 1 illustrate timing of coverage decisions for the interviewed payers relative to evidence development and other events.

Factors Used to Develop Policy

All payers reported clinical effectiveness as the most important factor in their coverage decisions, and our review of Oncotype DX policies suggested that the clinical literature was well cited. Payers noted their preference for health outcomes evidence (ie, the impact on patient disease and survival), but they acknowledged that for Oncotype DX, this evidence would evolve over 10 to 15 years as the TAILORx trial progressed. For Oncotype DX, four payers expressed willingness to base their decisions on the intermediate end point of clinical utility, which they defined as evidence that the test affects clinical decisions. One example of an intermediate end point was demonstrated in a study conducted at the Rocky Mountain Cancer Centers (Greenwood Village, CO), which showed that Oncotype DX recurrence scores changed physician recommendations for adjuvant chemotherapy.[28]

Payers also reported using factors arising from the health care system, in conjunction with clinical evidence, to make coverage policy decisions. Payers stated that these factors helped them overcome the uncertainties caused by a lack of clinical effectiveness evidence. For Oncotype DX, payers reported that the following health care system factors informed their coverage decisions: patient and physician adoption, coverage by a local Medicare provider in California, endorsement of medical societies, and the fact that the test did not undergo the FDA approval process (in contrast, MammaPrint received FDA approval). Table 2 provides examples of the health care factors payers considered.

Payer Perceptions of Evidence at Time of Policy Decisions

Although all payers used clinical evidence as a primary decision factor, they reported different interpretations of its strength. Payers described the clinical evidence on Oncotype Dx at the time of their decisions as reasonably persuasive (n = 2), evolving (n = 2), or insufficient (n = 2). Of interest, payers who issued decisions approximately at the same time varied in this assessment. One of the two payers granting coverage in early 2007 noted the evidence available then as sufficient, whereas another payer reported it as insufficient but still covered Oncotype DX based on other factors.

Similarly, payers perceived health care system factors differently. Three payers reported patient and provider adoption as an important factor, whereas the other three noted them as unimportant. Where adoption was a factor, payers reported that signs of broader adoption, such as increased number of

Table 1. Selected Oncotype DX Clinical Studies[10] and Other Events in Figure 1

Study or Guideline	Description	Date of Announcement or Publication
Kaiser validation study[20]	Validation study among 4,964 Kaiser patients	December 2004, 27th San Antonio Breast Cancer Symposium
B14 validation study[21]	Validation study of 668 patients in NSABP B-14 trial	December 2004, *New England Journal of Medicine*
B20 validation study[22]	Validation study of 651 patients in NSABP B-20 trial	May 2005, 41st ASCO Annual Meeting
Local Medicare coverage decision[17]	Contractor in California grants coverage of Oncotype DX	January 2006
Rocky Mountain utility study[23]	Retrospective analysis of clinical utility of Oncotype DX affecting chemotherapy decisions for 68 patients	December 2005, 28th San Antonio Breast Cancer Symposium
Intergroup E2197 validation study[24]	Validation study of 776 patients in Intergroup E2197 trial	June 2007, 43rd ASCO Annual Meeting
Mayo utility study[25]	Analysis of clinical utility of Oncotype DX affecting chemotherapy decisions for 31 Mayo patients	June 2007, 43rd ASCO Annual Meeting
TAILORx study[15]	Large prospective study of clinical validity, utility, and health outcomes of Oncotype DX	Launched May 2006
Loyola study[26,27] of clinical utility	Prospective study of clinical utility of Oncotype Dx in 89 patients	June 2007, 43rd ASCO Annual Meeting
Inclusion in ASCO recommendations[18]	ASCO update recommends Oncotype Dx	November 2007
Inclusion in NCCN guidelines[19]	NCCN clinical guidelines include Oncotype DX	January 2008

Abbreviations: NSABP, National Surgical Adjuvant Breast and Bowel Project; TAILORx, Trial Assigning IndividuaLized Options for Treatment (Rx); NCCN, National Comprehensive Cancer Network.

Table 2. Health Care System Factors Considered by Payers to Inform Coverage Policy

Factor	Effect	Payer Comments
Patient and provider adoption	Patients and/or providers start to ask for or use test and file claims for test; prompts closer test review for coverage	"There was demand for the test and that did influence us . . . . If there is pressure from the community and providers, we will do a review sooner. The other thing that influenced us was the test was ordered, and the patient didn't have much say in it, and if we don't approve that test, the member is suddenly left with a $3,000 bill, on top of dealing with cancer. That put an influence in terms of not necessarily making a decision to cover, but making a decision: Do we need to review the test?"
Coverage by local Medicare contractor in California	Decision creates status quo for other insurers; may tip decision toward coverage	"We reviewed the studies of clinical utility and said, 'There is clinical utility data on it, and Medicare covers it . . . .' So these two things ultimately played a role for us."
Endorsement by medical societies	Inclusion in clinical guidelines suggests standard of care; tips decision toward coverage	"What we found with Oncotype was that it wasn't the new information that came out but rather a broadening sense of consensus about how it may be used in terms of patient preferences . . . . Our committee reviewed the data and reviewed the NCCN recommendations and largely reflected the use based on the NCCN recommendations with some minor changes."
Regulation	Test is not FDA approved; potentially tips decision away from coverage; some insurers believe evidence would be better with FDA regulation	"It certainly gives a test some credibility that the evidence was re-looked at [by the FDA], although the FDA looks at safety and efficacy and not clinical utility."

Abbreviations: NCCN, National Comprehensive Cancer Network; FDA, US Food and Drug Administration.

claims, served as triggers for a closer policy review. One payer took into account medical society (ASCO and the National Comprehensive Cancer Network) recommendations, whereas the other five granted coverage before these recommendations. Only one payer reported the local Medicare coverage decision in California as a key factor. Payers were unconcerned that Oncotype DX did not go through the FDA approval process. However, some suggested that FDA review may have improved the evidence base for Oncotype DX. All payers stated explicitly that cost-effectiveness analyses do not influence coverage decisions and did not affect decisions for Oncotype DX.

Oncotype DX Policy Features

Our review found salient differences among Oncotype DX coverage policy features for interviewed payers. They varied in whether prior authorization was required, attestation that there were no predetermined factors for chemotherapy, attestation that a discussion about use of test results was held with patient, requirement that surgery and pathology were

completed before test order, requirement that the test be ordered by the physician administering chemotherapy, and retrospective review by the payer of chemotherapy use based on Onco*type* DX results.

The payers stated that their coverage policy features for Onco*type* DX reflected the clinical evidence. Payers varied in their specific concerns about the appropriate use of the test. Two payers felt that the available evidence was sufficient and did not have concerns about improper test use. These payers did not have prior authorization policies in place. The other payers were concerned about inappropriate test ordering and not using test results in decisions; these payers developed policies to mitigate these concerns.

Discussion

Decisions Varied in Timing and Structure Despite Widespread Coverage

Personalized medicine is changing clinical practice, and payers are being challenged to develop strategies to manage technologies emerging in this field. This study suggests that major US private payers are able to develop policies for new technologies like Onco*type* Dx. However, the timing and structure of policies differ among payers. Some private payers developed Onco*type* Dx policies earlier than their counterparts, and some payers have stricter utilization policies. Whether policy variation is warranted is not elucidated by this study. Elsewhere, studies have examined the variability among health plan coverage policies. Steiner et al[29] found variability in health plan coverage for laser therapies, indicating that variation in policy led to variation in patient access to these therapies. Klabunde et al[30] examined variation in colorectal screening policies, suggesting that they may be a factor in colorectal cancer screening rates. We suggest that additional studies on variability among coverage policies for cutting-edge technologies such as personalized medicine will help explain and potentially mitigate the impact of policy variation on physicians and patients.

Different Perceptions of Clinical Evidence and Application of Health Care System Factors May Produce Coverage Variation

Our research suggests that coverage decisions are informed by both clinical evidence and health care system factors, and when clinical evidence is less certain, other factors may play more important roles. For example, one payer believed that the clinical evidence for Onco*type* DX was weak but granted coverage based on its adoption by oncologists, which indicated to the payer that Onco*type* DX was becoming a standard of care. We identify only the health care system factor categories that influenced decisions, but we did not examine how to measure their contribution. Research has similarly suggested that in addition to clinical evidence, other factors inform coverage decisions. Steiner et al[29] found that for laser therapy coverage decisions, payers considered competition factors (ie, coverage provided by other payers), legal factors (eg, whether denial of coverage could be legally challenged), and economic and other factors (eg, severity of condition).[22] Meckley et al[31] suggested that clinical society recommendations strongly influence reimbursement of personalized medicine technologies and—as found in our study—that cost effectiveness and type of regulatory oversight do not. Future research might continue to examine how health care system factors are used in decisions. We suggest that improving both the clinical evidence and our understanding of how health care system factors are applied by payers is important.

Policy Development and Clinical Practice

Our findings suggest that in the case of novel technologies, not only policy features but also timing of coverage by various payers may have implications for clinical practice. For oncology practices that accept multiple insurance plans, variation may be particularly challenging. In the case of Onco*type* Dx, private payers in this study implemented coverage differently over a 4-year span, which potentially created challenges in use of Onco*type* Dx in practice. However, payers also described that clinical practice similarly affects policy development for new technologies via the level of adoption by clinicians and patients, which can trigger a technology review or policy development. Additional research of the mutual impacts of policy development and clinical practice may be important as more technologies enter the oncology market.

This report describes how payers are developing strategies for coverage policy decisions for personalized medicine, a field often characterized by promising interventions with uncertain clinical evidence and high cost. In making coverage policy decisions, a key approach for payers seems to be the integration of health care system factors and clinical evidence. Our study found that coverage policies vary by payer organization, suggesting that variation may be a result of both type of evidence used and perceptions of that evidence. Future studies should elucidate more specifically what factors contribute to policy decisions when clinical evidence is uncertain and should examine the implications of policy variation for clinical use of novel technologies.

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