The Oncologist®

Uncertainty in Assessing Value of Oncology Treatments

C. Daniel Mullins,[a,b] Russ Montgomery,[a] Sean Tunis[a]

[a]Center for Medical Technology Policy (CMTP), [b]The University of Maryland School of Pharmacy, Baltimore, Maryland, USA

Key Words. Uncertainty • Cancer • Value • Pragmatic clinical trials

Disclosures: C. Daniel Mullins: *Consultant/advisory role:* AHIMA; *Honoraria:* Bristol-Myers Squibb, Pfizer, Novartis, Sanofi-Aventis; *Research funding/contracted research:* Elan, GlaxoSmithKline, Novartis, Pfizer, Sanofi-Aventis; **Russ Montgomery:** None; **Sean Tunis:** None.

The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. No financial relationships relevant to the content of this article have been disclosed by the independent peer reviewers.

Abstract

Patients, clinicians, payers, and policymakers face an environment of significant evidentiary uncertainty as they attempt to achieve maximum value, or the greatest level of benefit possible at a given level of cost in their respective health care decisions. This is particularly true in the area of oncology, for which published evidence from clinical trials is often incongruent with real-world patient care, and a substantial portion of clinical use is for off-label indications that have not been systematically evaluated. It is this uncertainty in the knowledge of the clinical harms and benefits associated with oncology treatments that prevents postregulatory decision makers from making accurate assessments of the value of these treatments. Because of the incentives inherent in the clinical research enterprise, randomized control trials (RCTs) are designed for the specific purpose of regulatory approval and maximizing market penetration. The pursuit of these goals results in RCT study designs that achieve maximal internal validity at the expense of generalizability to diverse real-world patient populations that may have significant comorbidities and other clinically mitigating factors. As such, systematic reviews for the purposes of coverage and treatment decisions often find relevant and high-quality evidence to be limited or nonexistent. For a number of reasons, including frequent off-label use of medications and the expedited approval process for cancer drugs by the U.S. Food and Drug Administration, this situation is exacerbated in the area of oncology. This paper investigates the convergence of incentives and circumstances that lead to widespread uncertainty in oncology and proposes new paradigms for clinical research, including pragmatic clinical trials, methodological guidance, and coverage with evidence development. Each of these initiatives would support the design of clinical research that is more informative for postregulatory decision makers, and would therefore reduce uncertainty and provide greater confidence in conclusions about the value of these treatments.
The Oncologist 2010;15(suppl 1):58–64

Introduction

As the costs of cancer treatments continue to increase rapidly, their value is increasingly being questioned by patients, clinicians, payers, and policy makers [1]. Assessing the value of a medical treatment requires having relevant and reliable evidence on the real-world costs

Correspondence: Sean Tunis, M.D., M.Sc., 401 E. Pratt St., Suite 631, Baltimore, Maryland 21202, USA. Telephone: 410-547-2687; Fax: 410-547-5088; e-mail: sean.tunis@cmtpnet.org Received July 22, 2009; accepted for publication November 5, 2009. 1083-7159/2010/$30.00/0 doi: 10.1634/theoncologist.2010-S1-58

and benefits of the treatment for the typical patient population. This type of real-world evidence is critical for coverage decisions by payers and treatment decisions by physicians and patients. However, in many cases, the dominant paradigms in clinical research are not congruent with the generation of this type of evidence [2]. As a result, there is considerable uncertainty surrounding the clinical benefits and harms associated with oncology treatments, which prevents postregulatory decision makers from reliably assessing the value of these treatments.

The clinical research enterprise is oriented toward designing studies—typically randomized control trials (RCTs)—to produce evidence for regulatory approval by the U.S. Food and Drug Administration (FDA). Although this regulatory process is critical to ensuring the safety and efficacy of treatments, the type of evidence generated is much less relevant to subsequent real-world decisions on coverage and treatment. As a result, these decisions are made in an environment of great uncertainty regarding the true value of the treatment. Particularly in the area of oncology, this circumstance may lead to poor clinical decisions, suboptimal outcomes, and inefficient allocation of medical resources.

Depending on the context, value has been defined in many ways. In terms of health care goods and services, the concept of value typically incorporates measures of both health-related quality of life and costs. It generally reflects clinical improvements in health outcomes and emotional, psychological, and monetary benefits, as well as productivity improvements and technological innovation. The multidimensional aspects of value in health care underscore the need for valid and reliable evidence of the impact of new technologies across a variety of domains. Unfortunately, almost every metric of value is associated with significant uncertainty because the evidence of clinical harms and benefits has not been adequately studied through properly designed clinical research. Determining the value of new oncology products is particularly challenging despite, or perhaps because of, the fact that new literature describing potential clinical benefits and outcomes of oncology agents reveals significant uncertainty surrounding the response rate across cancer patients.

After detailing the causes and consequences of uncertainty in oncology, we highlight emerging techniques and mechanisms that place an emphasis on addressing the uncertainty that is problematic for postregulatory decision makers—patients, clinicians, payers, and policy makers—while noting the requirement to adequately balance the needs of regulators at the FDA.

Limitations of RCTs

What constitutes good evidence of the value of medicines in general, and cancer therapies in particular, is a current topic of debate and concern among the medical, research, and policy communities [3]. The traditional evidentiary hierarchies proposed by organizations such as the U.S. Preventive Services Task Force, the American College of Cardiology, and others typically consider (meta-analysis of) RCTs as the "best" level of evidence [4, 5]. However, this hierarchy is designed to reflect relative internal validity, which is well suited to regulatory decisions and clinical guideline development. The approach is not as well suited to the broader evidence needs of a wide range of postregulatory decision makers.

When making value-based decisions regarding coverage and reimbursement for a new treatment option, decision makers are interested in how the new treatment compares with the prevailing treatment in terms of comparative effectiveness and perhaps cost-effectiveness. The comparative effectiveness evaluation requires data on the relative benefits of two alternative treatment options. However, RCTs generally do not compare treatments against each other, resulting in limited applicability to policy decision making [6]. There are other aspects of the very controlled environment of RCT study design for regulatory purposes that reduce their usefulness for postregulatory decision making. For instance, the inclusion and exclusion criteria of an RCT may impact reported health outcomes and limit the applicability of results to the clinical practice setting. In an effort to produce results that have low potential for confounding, researchers use study populations that have minimal comorbidities and other clinically mitigating factors. Although this may lead to results that are more statistically robust and easier to interpret, a level of pragmatism and generalizability is lost, because in real-world decisions about coverage, decision makers focus on broad patient populations with a high prevalence of comorbidities and frequency of complications [7].

Ideally, groups representing patients, clinicians, payers, and policy makers would meet in a neutral setting to provide guidance for designing more informative clinical trials. In parallel, these decision makers could deliver their views with an eye toward reaching consensus on areas of research priorities to address the most significant areas of uncertainty regarding the relative value of treatments and the need for comparative effectiveness research (CER). Although evidence from traditional RCTs has led to significant progress toward improving the quantity and quality of life for people living with cancer, addressing the major areas of uncertainty that remain will promote a more rational

approach to clinical trial design to improve cancer care and inform health care spending decisions.

Unique Aspects of Oncology That Compound Uncertainty

Off-Label Use

The ubiquitous use of oncology drugs outside their labeled indications with questionable evidence of clinically meaningful benefits further underscores the difficulty with assessing value in oncology. In many cases, there is insufficient evidence from clinical trials to determine whether off-label use of oncology treatments is likely to have any benefit at all to patients and even less evidence to determine if there is sufficient value to warrant reimbursement. Value-based decision making for oncology treatments requires having the right information at the right time so that coverage decisions and treatment plans are based upon sound research evidence and clinical judgment with appropriate consideration for patient preferences.

Attributable Costs

The uncertainty is heightened when cost considerations are added. In cancer care, clinical uncertainty leads to economic uncertainty because, for many cancers, there is no dominant treatment alternative and thus each attempt to treat incurs a separate cost [8]. Because cancer care is forever changing as new treatments and technology evolve, the attributable costs are numerous. Attributable costs for health care are defined as "the cumulative value of resources used to treat full episodes of a health condition from the time of initial diagnosis to death" [9]. As treatments become more aggressive and additional lines of therapy are used, treatment costs rise. At this point, one's willingness to initiate cancer therapy and spend additional health care resources is ultimately tied to an uncertain outcome [9].

Patient Perception of Risk

Clinicians, insurers, and policy makers are not the only ones affected by the high level of uncertainty surrounding the value of new oncology agents. Patients are impacted as well. Patients' decisions to initiate treatment and to remain involved in their health care when faced with treatment uncertainty can be influenced by how well their physicians engage them in shared decision making and how patients interpret the risk and uncertainty surrounding the survival rates and harmful effects of treatment. For example, Han et al. [10] noted that shared decision making offers to the patient information on both the benefits and harms associated with cancer preventive screening or watchful waiting. When information is uncertain or appears to be ambiguous, patients question the reliability of the cancer information. Han et al. [10] found that a person's uncertainty or ambiguity about obtaining cancer preventive screenings can be influenced by their perception of higher risk, which can be moderated by their tolerance levels for worrying about ultimately getting cancer [11]. Patients' abilities to understand probabilities of survival and adverse events are influenced by their health numeracy skills, which reflect patients' abilities to understand medical information presented with numerical or statistical data and incorporate that information into their decision-making process [11]. Health numeracy also influences risk perception among oncology patients [12]. In addition, patients update their perceptions of the benefits and harms as well as the level of uncertainty based on their individual clinical experiences and subjective assessment of treatments and treatment outcomes.

Reducing Uncertainty and the Evidence Gap

How do we create a better link between the evidence-generating enterprise and the policy makers who use that evidence to make the information delivered more responsive to existing needs or gaps? The Center for Medicare and Medicaid Services (CMS) has a lengthy history of involvement in generating better evidence for policy decision making, from the investigational device exemption for coverage of certain devices in clinical trials (1996) to coverage for routine costs for patient care in clinical trials (2000) to ad hoc efforts to work with the National Institutes of Health. These efforts and many others reflect Medicare's transition from an agency that simply paid bills in the past to one with a much more important role of informing decision makers with evidence. However, more efforts are needed to expand the information on comparative effectiveness in order to reduce uncertainty surrounding the value of oncology treatments.

The desire to synthesize evidence on the relative benefits of alternative treatments prompted the commitment of $1.1 billion for CER by the Obama administration as part of the American Recovery and Reinvestment Act of 2009. CER is defined by the Institute of Medicine 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. The purpose of CER is to assist consumers, clinicians, purchasers and policy makers to make informed decisions that will improve health care at both the individual and population levels" [13]. CER seeks to address this issue as well as the "evidence gap" surrounding "which treatment strategies work best" and the related issues surrounding the uncertainty of relative value of treatment options [14]. The ability to assimilate this knowledge so that

the appropriate alternatives are established early is critical to this process.

In the postmarketing phase, there is little incentive for practical studies to be conducted after FDA approval, a time that often coincides with when decision makers are in greatest need of evidence. The following methods and models illustrate innovative ways of reducing uncertainty in clinical practice: pragmatic clinical trials, methodological guidance documents, and coverage with evidence development.

Pragmatic Clinical Trials

An innovative, applied method of reducing uncertainty for decision makers is through the use of pragmatic clinical trials (PCTs), defined as prospective controlled studies that are specifically designed to be informative to postregulatory decision makers. In general, several major characteristics distinguish PCTs from traditional clinical trials. First, PCTs involve the deliberate comparison of clinically relevant alternative treatments, chosen based on the most common decision-making scenarios. Traditional RCTs do not include highly relevant comparisons, leaving decision makers to make comparisons across trials, for which the assumptions, research methods, patient populations, and other crucial characteristics may be different. Second, PCTs are typically designed to be generalizable to real patient populations by including patients with common comorbidities and from a variety of demographic backgrounds. Third, PCTs select clinically relevant outcomes that are intended to address the primary issues and concerns of patients, clinicians, and payers. Many RCTs include outcomes that are of primary interest to regulators, and pay less attention to the postregulatory decision makers that will also use those studies to guide their choices. These clinically relevant outcomes may include more quality-of-life information and may involve longer follow-up periods than are typical for traditional clinical trials. Importantly, the selection of the most useful and relevant outcomes requires direct consultation with decision makers during study protocol development. In fact, one of the keys to the successful design of clinical trials that are more useful for decision making is the greater engagement of decision makers in trial design to ensure that it provides answers to the critical questions affecting policy and practice [2, 15].

Methodological Guidance Documents

The most effective approach to catalyzing the increased use of PCTs is improving the link between the evidence desired by decision makers and the output of the clinical research enterprise by developing a shared understanding of the nature of the desired evidence. In accordance, an effectiveness guidance document (EGD) is analogous to the guidance documents issued by the FDA, which provide product developers and clinical researchers with guidance on the design of clinical studies intended to support regulatory approval. In contrast, EGDs provide recommendations for study designs about specific categories of technologies that are intended to provide health care decision makers with a reasonable level of confidence that the technology will improve clinical outcomes [16].

The target audience for EGDs is similar to the audience for FDA guidance documents—clinical researchers and product developers. The process for developing these documents involves integrating the perspectives of the full range of stakeholders, including consumers, payers, clinicians, product developers, regulators, researchers, and others. By setting clear prospective standards for evidence, decision makers can increase the chances that these recommendations will be incorporated into clinical studies, and that those studies will reduce uncertainty in their areas of priority.

Although EGDs have no legal or binding effect on any decision maker or stakeholder, their influence would derive from the transparency, creditability, neutrality, and technical accuracy associated with the iterative multistakeholder development process. Product developers would not be required to design studies in accordance with the relevant EGD, and payers would not be bound to those principles in making coverage decisions. Nonetheless, these documents should reduce some of the uncertainty about what sort of evidence decision makers are looking for when considering the use of new technologies.

Coverage with Evidence Development

Decision makers have long faced the problem of making coverage decisions for "promising" but unproven medical technologies. Frequently, they are torn between the demands of patients and their physicians for innovative medical techniques and the desire to have definitive evidence about the clinical and comparative effectiveness of the new technology. For most new technologies, substantial uncertainty exists about their optimal use for many years after they are initially introduced, and the incentive for these questions to be addressed is substantially reduced once payment has been secured.

In 2005, the CMS began issuing coverage decisions under a new policy called "coverage with evidence development" (CED.) Under CED, Medicare provides conditional coverage for a promising medical technology while additional clinical evidence is generated through a clinical study. Only those beneficiaries included as part of the study are provided coverage, creating an incentive for participation. These studies, which include observational patient

registries and prospective clinical trials, are intended to answer specific, real-world questions about the clinical benefit of the drug or device within the Medicare population. Once clinical data have been generated and analyzed, the CMS may issue a new coverage decision. Such decisions may include expansion or removal of coverage and a change in reimbursement level, either in the entire Medicare population or for specific subgroups [17, 18].

Currently there are about 10 CED policies in place, although CED has resulted in a coverage change only once. In September 2009, the CMS expanded coverage for fluorodeoxyglucose positron emission tomography (FDG-PET) as a diagnostic tool for various cancers as a result of positive evidence from the National Oncologic PET Registry [19]. In addition to CED projects initiated by government entities, models for CED exist in the private sector. Although CED has its share of challenges to overcome, including a long time horizon between the initiation of a CED policy and the actual analysis of data, it has the potential to be an effective approach to facilitate early coverage decisions while still generating valuable evidence for future decision making.

Paradigm Shifts for Regulators and Payers

Evidentiary uncertainty is more pervasive in oncology than in other areas of medicine. The clinical characteristics of cancer create an environment of more uncertainty, as a result of differences in survival rates and the frequency of toxic events, the fact that complex treatment regimens often involve switches and alterations and second- and third-line therapies, and other unique characteristics. Also unique to off-label indications in oncology, compendia are used as sources of evidence on off-label indications, but studies show them to be unreliable. In addition, the current regulatory pathway for oncology drugs does not fit the natural progression of drug discovery, leading to a perpetual cycle of poor evidence and off-label use. The following proposals attempt to address the issues with compendia and the regulatory pathway by incentivizing better evidence generation for off-label indications and allowing for a more adaptive regulatory process that is more congruent with oncology drug discovery.

Off-Label Use and Compendia

According to the Government Accountability Office, 33% of off-label anticancer medications were written in 1991 [20], with an increase to up to 75% according to a 2005 survey by the National Comprehensive Cancer Network [21]. This increase is not surprising because the Social Security Act within the Omnibus Budget Reconciliation Act of 1993 approved Medicare reimbursement for the off-label use of cancer drugs and biologics [22]. The CMS and other payers rely on compendia that aggregate published peer-reviewed original literature on off-label use from scientific, medical, and pharmaceutical journals [23]. As of this writing, there are four acceptable compendia approved for use by Medicare [24]. However, researchers reviewed the compendia for strength of up-to-date evidence, consensus on particular recommendations, and transparency and found quite poor results [25].

Although compendia are ostensibly a source of quality evidence for off-label use that should make value-based decisions easier for payers, they are a poor source of cogent evidence and contribute to poor decisions on coverage and reimbursement. Because there will continue to be a need for evaluating off-label use for nonlabeled indications, new incentives are needed to promote the use of pragmatic trials and other approaches to reducing uncertainty for these coverage decisions. When the clinical research enterprise generates evidence that can be applied to heterogeneous, diverse populations of real patients, favorable coverage and reimbursement decisions will serve as a compelling incentive. At the end of the day, the drug industry will not produce better evidence until it is in their financial interest. The value-based decision making and improved patient outcomes stemming from better evidence on off-label use would quickly cover the cost of higher reimbursement from the CMS and other payers and generate long-term savings.

Regulatory Process

Turning to the regulatory process for oncology drugs, some incentives in the regulatory approval process are not conducive to addressing uncertainty in oncology, though some important steps have been taken. The FDA has balanced its traditional conservative approach toward the drug approval process for new medications with an accelerated approval or "fast track" process that allows a priority review for oncology and other products that fill an unmet medical need [26]. Before a product reaches this stage in development, there remains a requirement of two animal studies [27] and time-intensive safety and toxicity studies, but the FDA remains open to new ways for accelerated approval of life-saving oncology drugs [28]. However, the process still does not allow for adaptability that would fit the natural progression of drug discovery. Pragmatic, adaptive trials that meet both regulatory requirements and the needs of postregulatory decision makers do not fit well into this framework. Moreover, although in a few instances, such as the more recent cardiovascular prevention trials, the FDA has required active comparators in approval studies, it typically does not require active comparators; this mandate has generally occurred in situations in which a placebo comparison would

be unethical. In those cases, the comparator arms were one old treatment versus the same old treatment plus the new treatment, making comparisons of the two treatments difficult to tease apart.

Proposals to revise the regulatory framework specifically for cancer drug development and to proceed with an accelerated approval process using an adaptive clinical trial design, whereby the patient population, treatment algorithms, or statistical analysis design are updated during the clinical trial, are gaining popularity. Adaptive clinical trials provide a mechanism for adjusting clinical trials midstream in response to new knowledge or changes in the standard of care. Patient accrual into newly designed trials that contain an adaptive component could be a win–win situation for both the patient and the drug industry. Research needs could be met as promising treatments would attract study patients so that subgroup analyses could be produced as the trial proceeds [29]. Part of this revision in clinical trial design would be to use surrogate endpoints, such as progression-free survival, instead of a focus on patient survival [29]. Until pharmaceutical companies and the FDA agree on a format for adaptive clinical trial design, the status quo of getting the FDA's approval in order to bring a drug to market remains a stumbling block for new cancer drug development and for better evidence on real-world outcomes for use in patient, clinician, payer, and policy maker decision making.

The Future of Uncertainty in Oncology

PCTs and CED have great potential to provide new and better evidence regarding the value of oncology drugs, devices, and other medical technologies. New and better evidence will result by providing rewards of favorable coverage and reimbursement for oncology product developers and manufacturers who provide evidence of value with greater certainty. In addition, as the value is translated and disseminated to prescribers and their patients, these decision makers will be more inclined to select those technologies with less uncertainty surrounding the clinical and patient-reported benefits and risk.

This process will be enhanced through advancements in prognostic test indicators, including the use of biomarkers to guide treatment selection. For example, for colon cancer patients, mutations in the *KRAS* gene and possibly other genes such as *BRAF* and *NRAS* may indicate that certain treatments may be ineffective [29]. It has been well documented that, for patients with a mutated *KRAS* gene, monoclonal antibodies are ineffective [30, 31]. Given these results, *KRAS* genotyping is a method of reducing uncertainty to make value-based treatment decisions at the individual level. A genomic revolution in cancer care may be closer than some have anticipated. The new paradigm is dependent on affordable biomarkers that examine the impact of gene mutations on treatment effectiveness that are highly sensitive and specific. If this paradigm emerges, then the combination of testing and treatment may significantly reduce uncertainty in cancer patients' outcomes and, thereby, improve the overall value of cancer care.

Until scientific advancements in treatment occur, significant gaps in real-world evidence will be pervasive in the area of oncology. This situation has negative consequences for a variety of players in health care, from patients and physicians to payers and policymakers. Addressing these gaps would result in better decisions that improve patient outcomes and reduce unnecessary costs. The scientific capability to address these gaps in evidence is available through pragmatic trials and other innovations, but the incentives facing actors in the health care arena make adoption unlikely. Reforming the incentive structure by offering favorable coverage to those who provide evidence of value with greater certainty will transform drug discovery and investigation, reduce evidence gaps, and benefit oncology treatment and health care decision making.

Author Contributions

Conception/Design: C. Daniel Mullins, Russ Montgomery, Sean Tunis
Manuscript writing: C. Daniel Mullins, Russ Montgomery, Sean Tunis
Final approval of manuscript: C. Daniel Mullins, Russ Montgomery, Sean Tunis

The authors wish to acknowledge Lisa Blatt, M.A., for her assistance with manuscript preparation.

References

1 Kolata G, Pollack A. The Evidence Gap: Costly Cancer Drug Offers Hope, But Also a Dilemma. The New York Times, 2008. Available at http://www.nytimes.com/2008/07/06/health/06avastin.html, accessed July 21, 2009.

2 Tunis SR, Stryer DB, Clancy CM. Practical clinical trials: Increasing the value of clinical research for decision making in clinical and health policy. JAMA 2003;290:1624–1632.

3 Garrison LP Jr, Neumann PJ, Erickson P et al. Using real-world data for coverage and payment decisions: The ISPOR Real-World Data Task Force report. Value Health 2007;10:326–335.

4 U.S. Department of Health and Human Services, Agency for Health Care Policy and Research. Acute Pain Management: Operative or Medical Procedures and Trauma. Clinical Practical Guideline No. 1. Publication no. 92–0023, 107. Rockville, MD: AHCPR, 1993.

5 American College of Cardiology Foundation. Clinical Statements/Guidelines, 2006. Available at http://www.acc.org/qualityandscience/clinical/statements.htm, accessed June 29, 2009.

6 Orszag P. Research on the Comparative Effectiveness of Medical Treatments: Options for an Expanded Federal Role. Testimony before the Subcommittee on Health, Committee on Ways and Means, U.S. House of Representatives, June 12, 2007.

7 Sørenson HT, Lash TL, Rothman KJ. Beyond randomized controlled trials: A critical comparison of trials with nonrandomized studies. Hepatology 2006;44:1075–1082.

8 Chirikos TN. Cancer economics: On variations in the costs of treating cancer. Cancer Control 2002;9:59–66.

9 Virgo KS, Vernava AM, Longo WE et al. Cost of patient follow-up after potentially curative colorectal cancer treatment. JAMA 1995;273:1837–1841.

10 Han PK, Moser RP, Klein WM. Perceived ambiguity about cancer prevention recommendations: Relationship to perceptions of cancer preventability, risk, and worry. J Health Commun 2006;11(suppl 1):51–69.

11 Ancker JS, Kaufman D. Rethinking health numeracy: A multidisciplinary literature review. J Am Med Inform Assoc 2007;14:713–721.

12 Kelly KM, Graves KD, Harper FW et al. Assessing perceptions of cancer risk: Does mode of assessment or numeracy matter? Cancer Detect Prev 2007;31:465–473.

13 Institute of Medicine of the National Academies. Initial National Priorities for Comparative Effectiveness Research. Report brief, June, 2009. Available at http://books.nap.edu/openbook.php?record_id=12648, accessed November 13, 2009.

14 Orszag PR. Letter to Honorable Pete Stark, Chairman, Subcommittee on Health, Committee on Ways and Means, U.S. House of Representatives, September 5, 2007. Available at http://www.cbo.gov/ftpdocs/85xx/doc8598/09-05-ComparativeEffectiveness.pdf, accessed June 25, 2009.

15 Roland M, Torgerson DJ. What are pragmatic trials? BMJ 1998;316:285.

16 Goodman S, Dickerson K, Wilson R. Effectiveness Guidance Document: Gene Expression Profile Tests for Early Stage Breast Cancer. Baltimore, MD: Center for Medical Technology Policy, June, 2009. Available at http://www.cmtpnet.org/documents/egd_ge.pdf, accessed June 21, 2009.

17 Tunis SR, Pearson SD. Coverage options for promising technologies: Medicare's 'coverage with evidence development.' Health Aff (Millwood) 2006;25:1218–1230.

18 Center for Medical Technology Policy. Issue Brief: Coverage for Evidence Development: A Conceptual Framework, January, 2009. Available at http://cmtpnet.org/cmtp-research/applied-policy-and-methods/coverage-with-evidence-development/20090108%20-%20CMTP%20-%20CED%20Issue%20Brief.pdf, accessed June 22, 2009.

19 Centers for Medicare and Medicaid Services. Pub 100-03 Medicare National Coverage Determinations. Available at http://www.cms.hhs.gov/transmittals/downloads/R106NCD.pdf, accessed October 1, 2009.

20 ASCO supports government report: "Off-label drugs: reimbursement policies constrain physicians in choice of cancer therapies." Oncology (Williston Park) 1991;5:29–30, 33.

21 Soares M. "Off-label" indications for oncology drug use and drug compendia: History and current status. J Oncol Practice 2005;1:102–105.

22 Social Security Administration. Compilation of the Social Security Laws. Part E—Miscellaneous Provisions: Definitions of Services, Institutions, etc. 42 U.S.C. §1395x, Sec 1861. Available at http://www.ssa.gov/OP_Home/ssact/title18/1861.htm, accessed July 11, 2009.

23 Centers for Medicare and Medicaid Services. Medicare Benefit Policy Manual Chapter 15 – Covered Medical and Other Health Services (Rev. 105, 04-24-09). Available at http://www.cms.hhs.gov/Manuals/downloads/bp102c15.pdf, accessed June 17, 2009.

24 Clinical Pharmacology. Gold Standard, Inc. Off-Label Data for Drug Information Products Policy. Available at http://www.clinicalpharmacology.com/marketing/off_label.html, accessed June 19, 2009.

25 Abernethy AP, Raman G, Balk EM et al. Systematic review: Reliability of compendia methods for off-label oncology indications. Ann Intern Med 2009;150:336–343.

26 U.S. Food and Drug Administration. Fast Track, Accelerated Approval and Priority Review. Available at http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/SpeedingAccesstoImportantNewTherapies/ucm128291.htm, accessed November 13, 2009.

27 Connors T. Anticancer drug development: The way forward. ***The Oncologist*** 1996;1:180–181.

28 Traynor K. FDA says it's open to new approaches to cancer trials. Am J Health Syst Pharm 2008;65:795–800.

29 Lambrechts D, De Roock W, Prenen H et al. The role of *KRAS*, *BRAF*, *NRAS*, and *PIK3CA* mutations as markers of resistance to cetuximab in chemorefractory metastatic colorectal cancer. J Clin Oncol 2009;27(15 Suppl): 4020.

30 Peeters M, Siena S, Van Cutsem E et al. Association of progression-free survival, overall survival, and patient-reported outcomes by skin toxicity and *KRAS* status in patients receiving panitumumab monotherapy. Cancer 2009;115:1544–1554.

31 Nevins JR, Huang ES, Dressman H et al. Towards integrated clinico-genomic models for personalized medicine: Combining gene expression signatures and clinical factors in breast cancer outcomes prediction. Hum Mol Genet 2003;12:R153–R157.