Role of NCCN in Integrating Cancer Clinical Practice Guidelines into the Healthcare Debate

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Many new drugs and drugs in the pipeline are referred to as targeted therapy*. Targeted therapies have revolutionized the care of certain cancers, such as chronic myelogenous leukemia, but for other common malignancies, such as colon cancer, the impact on survival has been more modest. These seemingly incremental improvements coupled with the high cost of targeted therapy have focused the debate about the cost of healthcare squarely on oncology. Clinical practice guidelines are a common baseline starting point for this debate. Guidelines reflect clinical evidence and expert judgment, which is necessary to fill in the gaps when clinical evidence is not yet available or is evolving quickly. In addition, clinical guidelines inform other key aspects of oncology care, such as establishing a standard of care, which can then be translated into quality measures. Guidelines can also be reformatted to create an oncology drug compendium or rewritten to provide patient information.*

The data regarding healthcare costs are clear, persistent, troubling at the least, and truly frightening at worst. It is estimated that by 2014, nearly 20% of the nation's economy will be consumed by healthcare, and the growth in healthcare spending will outpace economic growth through the next decade.[1] The National Institutes of Health estimated that the overall cost of cancer in 2006 was $206.3 billion. Of this total figure, $78.5 billion represents direct medical costs, including inpatient and outpatient care, drugs, and devices.[2]

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The Cost of Improving Care

The rising cost of cancer care is in part related to many new and expensive antineoplastic drugs that have reached the market in the past 7 years, including those that specifically target tumor cells. These drugs are collectively known as *targeted therapy*, and include such drugs as imatinib (Gleevec®), erlotinib (Tarceva®), rituximab (Rituxan®), bevacizumab (Avastin®), cetuximab (Erbitux®), and trastuzumab (Herceptin®). Many others are in the pipeline. Some of these drugs are targeted to specific proteins only expressed on tumor cells, and thus their application is limited to those tumors expressing these proteins. For example, trastuzumab is targeted to a tyrosine kinase overexpressed in 25% to 30% of early-stage breast cancer cells. As an adjuvant therapy, trastuzumab reduces the risk of recurrence by 50% in women with surgically treated breast cancer. A full course of trastuzumab treatment costs approximately $50,000.[3] Another example is imatinib, a monoclonal antibody directed at another tyrosine kinase, but one specific to chronic myelogenous leukemia (CML) and stromal tumors of the gastrointestinal (GI) tract. Imatinib has revolutionized the treatment of CML and GI stromal tumors, essentially turning these malignancies into treatable diseases requiring lifelong maintenance imatinib therapy. The impact on GI stromal tumors is particularly noteworthy, since prior to imatinib, there were no effective chemotherapy options. The annual cost for imatinib is in the range of $30,000,[4] but the

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total population of patients who are candidates for imatinib is small compared with the large population of patients with breast cancer.

The effectiveness of imatinib has somewhat stifled the debate surrounding its high cost. Other targeted therapies have not been as clearly effective, in part because the multiple biologic pathways underlying other malignancies are not as well defined. For example, many targeted therapies are directed at biologic pathways that may play a part in a wide variety of malignancies, such as epidermal or vascular endothelial growth factors. Elegant preclinical work has defined these pathways, but there are still gaps in understanding how these pathways may interact in individual tumors and individual patients. For common epithelial tumors, such as colon cancer, it is quite likely that effective biologic therapy will require targeting multiple underlying pathways. Further refinement of patient selection criteria will be needed to ensure that these costly drugs are optimally used. This necessary phase of development requires research linking the biologic profile to treatment response. For example, molecular analysis of resected tumor specimens has now been routinely integrated into clinical trial protocols.

Another unique aspect of imatinib is that this drug is effective as a single therapy because the underlying tyrosine kinase target dominates the tumor biology of CML and GI stromal malignancies. In contrast, other targeted therapies are typically used with conventional chemotherapy. For example, in 2006, the U.S. Food and Drug Administration (FDA) approved the drug bevacizumab as an option for second-line therapy of colorectal cancer in 5-FU–based chemotherapy regimens. This FDA approval was based in part on a randomized study comparing the survival outcomes of patients treated with a regimen known as FOLFOX (the combination of oxaliplatin, leucovorin, and 5-FU) with or without additional bevacizumab.[5] The median duration of survival for the group treated with FOLFOX and bevacizumab was 12.9 months compared with 10.8 months for the group treated with FOLFOX alone, a statistically significant difference (P = .0011). It is estimated that bevacizumab adds about $10,000 to the FOLFOX regimen per every 8-week cycle.[6]

Similarly, cetuximab, another monoclonal antibody directed at epithelial growth-factor receptors, has been FDA approved as a second-line therapy for metastatic colon cancer. This approval was based on a randomized trial that showed the combination treatment of cetuximab and irinotecan (Camptosar®) delayed tumor growth by approximately 4.1 months compared to 1.5 months in patients who received cetuximab alone.[7] It is estimated that an 8-week course of the irinotecan-cetuximab combination would cost about $30,790.[6]

Oncology—Focus of Debate on the Cost of Healthcare

These examples of seemingly incremental improvements at high cost have focused the debate about the cost of healthcare squarely on oncology. As Schrag noted, this debate puts individual oncologists caring for individual patients in an increasingly difficult position; the oncologist's first responsibility is to be an advocate for their patients, and not the arbiter of what is considered cost-effective from a societal perspective.[6] During the consultation with the patient, the oncologist must evaluate and recommend those therapies that best meet the patient's goals, whether it be in terms of cure, survival, or palliation, and dismiss, albeit temporarily, the cost issue.

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Outside the individual physician/patient relationship, the oncology community as a whole takes a leadership role as one of the many stakeholders in the political debate regarding the pricing of drugs and the complex issue of cost-effectiveness and what a society may be willing to pay; however, all stakeholders recognize that the debate must first be grounded in clinical data and expert judgment. From the payor's perspective, a technology assessment is typically used to analyze the clinical data. These technology assessments are focused on a single technology, such as a new drug, device, or procedure, and their many potential clinical indications. Although this approach fits the need to develop technology-specific coverage policies, it does not reflect the way cancer care is delivered across a continuum. For example, what the oncologist sees is not that a single drug may add a median of 2 to 6 months of survival, but rather the incremental gains of multiple different drugs and other supportive therapies that can collectively result in a significant impact on the patient's duration

and quality of life. Furthermore, a debate that merely focuses on median survival as the key outcome may obscure the fact that some patients respond to novel therapies remarkably well, although others do not, a perspective that only an oncologist can provide.

Clinical Practice Guidelines—Function Before Form

Clinical practice guidelines function to review and synthesize the data across the entire continuum of cancer care, and thus are a better reflection of how cancer care is delivered. There is probably no field of medicine that is evolving more rapidly than oncology, thus practicing oncologists must always recommend therapies to their patients in a setting of therapeutic uncertainty. Although technology assessments typically do not incorporate expert judgment, this is a key element of clinical guidelines necessary for providing real-world and timely guidance to practicing oncologists. Chronic lymphocytic leukemia (CLL) has been traditionally thought of as an indolent disease where the treatment goals are primarily palliative in nature, and thus past research has focused on drug toxicities and quality of life. Management of CLL, however, is rapidly evolving based on 3 converging factors: (1) the availability of specific monoclonal antibodies like rituximab and others in the pipeline; (2) the emergence of novel prognostic factors that will enable risk-adapted therapy; and (3) the ability to more closely monitor the presence of residual disease. Controlled studies are the basis of many technology assessments, but such studies integrating all of these advancements will always lag behind their clinical availability, particularly given the lengthy natural history of CLL. Clinical practice guidelines integrating both the available clinical data and expert judgment provide a flexible, nonprescriptive approach that best serves the needs of practicing oncologists and their patients.

It is important to clearly define the guideline development process, and to indicate to what extent the guideline recommendations are based on clinical data versus expert judgment.

Standardizing Care

Clinical guidelines can also provide important guidance in standardizing care to ensure that clinical advances that are developed in academic settings will translate to community settings. As previously mentioned, trastuzumab therapy has emerged as a standard adjuvant therapy for early-stage breast cancer that overexpresses a tyrosine kinase protein called human epidermal growth factor receptor 2 (HER-2); however, the effectiveness of this new treatment option is absolutely dependent on the accurate assessment of HER-2 in tumor cells. As the therapy moved from the academic settings to the community setting, it became apparent that different laboratory techniques and interpretations resulted in patients being variably categorized as candidates for trastuzumab therapy depending on where or how their HER-2 status was evaluated. In 2007, the American Society of Clinical Oncologists (ASCO) published clinical guidelines to establish standards for optimal testing performance.[8] This example illustrates one of the assumptions underlying the development of clinical guidelines; guidelines have the potential to identify unnecessary tests and services, leading to improved patient quality of care.

Identifying Relevant Outcomes

The initial starting point for a clinical guideline is similar to a technology assessment (ie, a review of the available evidence). A key element of this initial step is identification of the most relevant outcomes—the yardsticks by which a therapy will be measured. Although the primary outcome of interest is often overall survival, disease-free survival may be the key outcome in some situations, reflecting the flexible approach of clinical guidelines. Evaluation of diagnostic technologies is often challenging because the final health outcome is based on how the diagnostic information, such as serum tumor markers or prognostic indicators, might influence patient management, which could be many years and many therapeutic interventions down the road. The initial review establishes the state of the evidence, which is then interwoven with expert judgment to address the literature gaps and incorporate real-world clinical experience. Throughout this process, it is important to clearly define the guideline development process, and to indicate to what extent the guideline recommendations are based on clinical data versus expert judgment.

The Development Process

A variety of different oncology organizations have developed clinical practice guidelines. In the United

States the 2 leading organizations are the National Comprehensive Cancer Network (NCCN), a group of 21 preeminent cancer care centers, and ASCO. ASCO has been publishing clinical guidelines since 1994. The guideline process is initiated with a systematic literature review, which is then reviewed by a panel of experts followed by development of specific recommendations. As of January 2007, 33 guidelines had been published by ASCO, of these 19 were considered active, and 14 were considered inactive. In addition, 19 new guidelines or updates to existing guidelines were in progress. ASCO guidelines are specifically focused on emerging technologies, interpretation of major clinical trial results, common clinical management problems, and perceived misuse or overuse of technologies. The guidelines are not designed to address the entire spectrum of cancer care.

In contrast, the NCCN guidelines address the entire continuum of cancer care. The NCCN has developed 110 different guidelines that cover 98% of all cancers. Additional guidelines focus on screening, early detection, and supportive care. The NCCN process is designed to be both multidisciplinary and comprehensive across all stages of cancer including all modalities of treatment. Guideline development incorporates an evidence-based approach when evidence is available, and evidence-based expert consensus when high-level evidence is lacking.[9]

The NCCN guidelines are unique in that the recommendations are not presented in a tabular list, but comprise a series of algorithms that address the entire continuum of cancer care, ranging from initial diagnosis to end-of-life care. Extensive footnotes and a manuscript accompany the algorithms, both of which provide supporting references, background information, and discussion of ongoing controversies. A level of evidence/consensus is assigned to each recommendation (**Table 1**).

It is interesting to note that the majority of recommendations in the NCCN guidelines are considered Category 2A, illustrating that the minority of cancer treatments are based on the results of high-level evidence, such as randomized controlled trials.

Updating Guidelines

Every guideline is updated yearly. Before the panel meeting, the existing guidelines are distributed to panel members for broader review in their institutions and for identifying specific areas that require discussion and potential revision. The panel meets face-to-face or by

Table 1. NCCN Levels of Evidence/Consensus

- Category 1: Uniform consensus of the NCCN panelists based on high-level evidence
- Category 2A: Uniform NCCN consensus, based on lower-level evidence
- Category 2B: Nonuniform NCCN consensus (but no major disagreement), based on lower-level evidence
- Category 3: Major NCCN disagreement that the recommendation is appropriate

NCCN indicates National Comprehensive Cancer Network.

Table 2. Medicare Coverage Advisory Committee: Desirable Characteristics for a Drug Compendium

- Extensive breadth of listing
- Quick throughput from application for inclusion to listing
- Detailed description of the evidence reviewed for every individual listing
- Use of prespecified published criteria for weighing evidence
- Use of prescribed published process for making recommendations
- Publicly transparent process for evaluating therapies
- Explicit "not recommended" listing when validated evidence is appropriate
- Explicit listing and recommendations regarding therapies, including sequential use or combination in relation to other therapies
- Explicit "equivocal" listing when validated evidence is equivocal
- Process for public identification and notification of potential conflicts of interest of the compendia's parent and sibling organizations, reviewers, and committee members, with an established procedure to manage recognized conflicts

3/30/2006–Compendia for coverage of off-label uses of drugs and biologicals in an anti-cancer chemotherapeutic regimen. http://www.cms.hhs.gov/mcd/viewmcac.asp?where=whatsnew&mid=33#agenda.

teleconference on alternate years. Each panel member is asked to disclose any potential conflict of interest, which typically consists of pharmaceutical research support or participation in a pharmaceutical advisory board. It should be recognized that most panel members are likely to have conflicts. The conflicts of interest are disclosed in aggregate in every guideline. The guidelines are then discussed at the meeting and revised accordingly.

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One of the strengths of the NCCN guideline process is that the guidelines can also be updated on an ad hoc basis to respond to particularly important trial results or new drug approvals by the FDA. Initial results of influential, high-profile phase 3 studies are often presented at the annual meetings of either ASCO or the American Society of Hematology. The NCCN guidelines can rapidly incorporate these important clinical data into their guidelines, giving it high visibility to both practicing oncologists and payors, who increasingly depend on the NCCN guidelines as a resource for their own coverage policy development process. Aspects of cancer care that cut across multiple different malignancies are not well addressed by cancer-specific guidelines. These topics have been addressed by separate NCCN task forces that bring together members of different NCCN guideline panels and other experts as necessary. Recent task force reports have included bone health, focusing on the prevention and management of osteoporosis in patients with cancer, PET scans in a variety of malignancies, and oral mucositis as a complication of either chemotherapy and radiation therapy in a variety of malignancies. The multidisciplinary approach is another distinguishing feature of the NCCN guidelines.

Leveraging Guidelines

The guidelines and task force reports are publicly available on the NCCN Web site (www.nccn.org), and in collaboration with the American Cancer Society, the NCCN guidelines have been reformatted into patient versions for the most common malignancies. The NCCN has also sought other ways to leverage the clinical guidelines to improve cancer care and quality of care. For example, based on the clinical guidelines for breast cancer, colorectal cancer, and non-Hodgkin's lymphoma, the NCCN initiated the NCCN Oncology Outcomes Database Project. The project is designed to identify the most efficacious and cost-effective strategies for the management of these common cancers, and monitor and benchmark the member institution's concordance with the guideline recommendations. The database will be able to describe patterns and outcomes of care, and will serve as the basis of a feedback loop to physicians and their member institutions. Breast cancer was the initial focus of the database project and has now accrued some 30,000 patients.

Drug Compendium

The clinical guidelines have also served as the basis for the development of the *NCCN Drugs & Biologics Compendium*. Although the parent clinical guidelines look at the treatment of the patient across the continuum of care, the drug compendium reformats this information to list all the indications for a given drug and cancer type in a tabular format. Users seeking additional information are referred to the clinical guidelines. Every NCCN clinical guideline now has a corresponding entry in the *NCCN Drugs & Biologics Compendium*, and the compendium is revised at the same time as the guidelines. The Medicare Coverage Advisory Committee (MCAC) has evaluated different compendia for cancer care and identified desirable characteristics for an optimal compendium (**Table 2**).[10] The criteria describe a comprehensive compendium based on a well-defined and transparent evidence-based process. Drugs can be categorized as recommended, not recommended, or equivocal, based on the evidence.

The MCAC reviewed and scored 6 different compendia, including NCCN, the American Hospital Formulary Service Drug Information, and the United States Pharmacopeia. The NCCN scored highest of any of the 6 compendia on each criterion. Increasingly, the NCCN clinical guidelines and drug compendium are used by many payors as the basis for their coverage policies. A 2006 survey by the Blue Cross Blue Shield Association of 49 senior medical directors reported that 78% indicated that the NCCN guidelines should be the standard for clinical policy in centers of excellence.[11]

The original impetus for the development of oncology clinical guidelines was simple—to provide guidance to practicing oncologists to improve the care of their patients; however, the above examples illustrate that the synthesis of data and expert opinion that is the backbone of clinical guidelines can be leveraged in many ways to inform the larger debate regarding healthcare costs and access to healthcare. From third-party payors' coverage policies, pharmacy formularies, quality measures, pay for performance, to the debate surrounding the cost of new biologic therapy—all of these initiatives will be grounded in clinical guidelines. ■

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AHDB Stakeholder Perspective

Cancer therapy is experiencing an astonishing rate of new breakthrough therapies that succeed in both prolonging life and improving the health-related quality of life. This amounts to a society-wide paradigm shift involving all stakeholders in the process of care. The principal drivers are the high quality of new drugs and the correspondingly high costs, requiring new tactics to balance quality with cost and access to care. The sequence of events is as follows:

- Growth in number and quality of new cancer agents =
- Increases in healthcare resource consumption ($$) =
- Call for new efficiency measures
  - Preventive medicine
  - Personalized medicine
    - **STRATEGIES:** predetermine responders, eliminate waste usage of expensive biologic drugs
    - **METHODS:** molecular mapping and imaging
  - NCCN guidelines: updated continually, directing providers and payors to best practices, especially needed in the complex field of oncology
- **PUBLIC:** must decide if it wants the new *personalized medicine* model and if so, whether they will finance it by paying more of their income into healthcare; this requires a major educational initiative so that lay persons will understand the issues to make an informed strategic public policy shift
- **GOVERNMENT:** must find new systems for financing
  - Coverage for new cancer drugs, molecular mapping, and imaging
  - Equitable reimbursement models for providers and provide appropriate income and incentives to administer optimal care
- **MANUFACTURERS:** must align research closely with provider organizations, FDA, and CMS
- **PAYORS:** must pursue efficiency measures appropriate to cancer care, not simplistic cost-containment measures, which have not been shown to reduce costs or otherwise take effective advantage of the new breakthroughs in cancer drug therapy