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**The “NCCN Comparative Therapeutic Index™” as a
Paradigm for Near Term Comparative Effectiveness Analyses
of Existing Data in Oncology**

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NCCN Oncology Comparative Effectiveness Work Group Members

Co-Chairs:

Al Benson III, MD, Associate Director for Clinical Investigations, Professor of Medicine, Robert H. Lurie Comprehensive Cancer Center of Northwestern University
Bill McGivney, PhD, CEO, NCCN

Work Group Members:

From NCCN Institutions

Robert Carlson, MD, Professor, Division of Medical Oncology, Stanford Comprehensive Cancer Center
Thomas D'Amico, MD, Director of Clinical Oncology, Associate Professor, Department of Surgery, Program Director, Thoracic Surgery, Duke Comprehensive Cancer Center
David Ettinger, MD, Alex Grass Professor of Oncology, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
David Pfister, MD, Chief, Head and Neck Medical Oncology Service, Memorial Sloan-Kettering Cancer Center
Lori Pierce, MD, Professor, University of Michigan Comprehensive Cancer Center
Michael Wong, MD, PhD, Medical Director, Clinical Drug Development, Roswell Park Cancer Institute
Andrew Zelenetz, MD, PhD, Chief, Lymphoma Service, Memorial Sloan-Kettering Cancer Center

From Non-NCCN Organizations

Jeff M. Allen, PharmD, BCOP, Clinical Oncology Pharmacy Advisor, Humana Pharmacy Solutions
John Cox, DO, Texas Oncology – Methodist Charlton Cancer Center
James Cross, MD, National Medical Policy and Operations, Aetna
Nancy Davenport-Ennis, Chief Executive Officer, National Patient Advocate Foundation
Scott Gottlieb, MD, Resident Fellow, American Enterprise Institute for Public Policy Research
Kimary Kulig, PhD, MPH, Outcomes Research, Oncology, Pfizer Global Pharmaceuticals
Len Lichtenfeld, MD, Deputy Chief Medical Officer, American Cancer Society
Ellen V. Sigal, PhD, Chair and Founder, Friends of Cancer Research

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EXECUTIVE SUMMARY

The increasing availability of innovative health care technologies for the treatment of cancer and the substantial expense of some of these technologies are driving the need for more explicit comparison of therapeutic options for specific clinical indications. Major constituencies, including legislators and policy makers, are calling for the application of comparative effectiveness analysis in developing clinical policy.

The NCCN Clinical Practice Guidelines in Oncology™ are widely recognized and applied as the standard for clinical cancer care in the United States. The NCCN Guidelines and the NCCN Drugs & Biologics Compendium™ also are recognized and used by the Medicare program and by private payers to set coverage policy. In this document, NCCN considers the application and implementation of a process that is particularly suited to the comparative evaluation of therapeutics in cancer care through integration into the NCCN Guidelines development process.

To address the translation and adoption of comparative effectiveness research, NCCN introduces a clinical evaluative paradigm labeled, “the NCCN Comparative Therapeutic Index,” to gradually be incorporated into the NCCN Clinical Practice Guidelines. The NCCN Comparative Therapeutic Index™ (CTI) will be an evidence-based, systematic, comprehensive, and transparent process using explicit criteria for evaluating and then comparing the risk-versus-benefits of different treatment options recommended in the Clinical Practice Guidelines. The effectiveness, toxicity, and resource utilization variables used in the CTI model are based upon the evaluation of available scientific data (including comparative effectiveness research studies) integrated with the expert judgment of leading oncologists.

The CTI will be implemented in three phases. In the first phase, one Guideline Panel will serve as the pilot program and implement the CTI on a limited scale for one particular setting within their disease guidelines. The second phase will enlist more Guidelines Panels in the process, followed by system-wide adoption in the third phase. At each phase and at regular intervals after system-wide adoption, the scoring tool and recommendations based on the CTI will be assessed for reliability (inter- and intra-rater) and validity. The CTI tool will be improved as necessary based on those findings.

As identified by the Federal Coordinating Council for Comparative Effectiveness Research, the NCCN CTI paradigm addresses one critical activity of CER, its translation and adoption specific for the specialty of hematology/oncology. The other investments and activities identified by the Council such as Research, Human and Scientific Capital, and CER Data Infrastructure could also be addressed by NCCN through the NCCN Oncology Research Program, continuing medical education initiatives sponsored by NCCN, and the NCCN Oncology Outcomes Database Project.

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Further, as emphasized in the Friends of Cancer Research White Paper, randomized controlled clinical trials remain the gold standard for the development of scientific data that will serve to advance the safety and effectiveness of care for patients with cancer. Other methodologies, such as outcomes databases, registries, and practical clinical trials can contribute substantially. Development of new models integrating the advantages of available methods also must be sought.

The NCCN model will use scientific data made available from all reputable resources. The NCCN CTI paradigm seeks to address near term needs for comparative effectiveness analyses in high priority areas in order to improve care for patients whom we serve.

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INTRODUCTION

Comparative Effectiveness Research (CER) has emerged as a priority concept as part of the larger health care reform agenda. The need for the attainment of optimal value for the dollars spent on health care has become acute. National health expenditures are approaching \$2.5 trillion and 17% of the Gross Domestic Product.[1-2] The pressure on the United States Health Care System will only become greater as health care reform likely will add substantial numbers of uninsured individuals to the rolls of those insured for the receipt of health services.

The need for better use of existing research methods, for the development of innovative research paradigms, and for the more formal and effective use of existing data has been recognized by many national committees and organizations. Indeed, in early 2009, the federal government allocated \$1.1 billion in funding in the American Recovery and Reinvestment Act (ARRA) for CER.[3] These dollars are directed to government agencies such as the Agency for Healthcare Research and Quality (AHRQ), the National Institutes of Health (NIH), and the Department of Health and Human Services (HHS) for programmatic administration. As part of this legislation, a Federal Coordinating Council for Comparative Effectiveness Research (FCCER) was established to “coordinate and guide research investments in comparative effectiveness research funded by the Recovery Act.” Additionally, a proposed health care reform bill, “America’s Healthy Future Act of 2009,” would increase provisions for CER by increasing funding and by establishing a private, non-profit entity known as the “Patient-Centered Outcomes Research Institute” (the “Institute”) to oversee the conduct of federally-funded research by coordinating with the FCCER to develop the methodologic principles for the conduct of CER and disseminate the findings of CER results.[4]

The proposed and enacted legislation underscore the importance of CER in current and future U.S. health policy. In discussions about the rapid pace of scientific advancement coupled with expensive health care technologies, no area of medicine is afforded more emphasis than oncology. As payers and other constituencies of the health care community focus on cancer care, it is critical that the world’s leaders in oncologic research and clinical practice be actively involved in the development and implementation of processes at all levels.

The National Comprehensive Cancer Network (NCCN) seeks to continue its leadership role in developing and communicating scientific, evaluative information to inform and improve decision-making to assure that patients have available the safest and most effective options for their cancer care. The NCCN has the distinct advantage of having ready access to the world’s thought leaders in oncology cutting across all relevant specialty lines.

This paper will review other reports and recommendations on the future of CER, with special emphasis on the White Paper developed by Friends of Cancer Research, in

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collaboration with multiple organizations.[5] The present NCCN paper will focus on ways in which the extensive NCCN infrastructure and process of guideline development might further evaluate existing data integrated with expert judgment into comparative analyses to optimize the use of drugs, biologics, procedures and techniques in cancer care. As with all NCCN scientific programs, such CER analyses would be broadly communicated to all stakeholders.

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COMPARATIVE EFFECTIVENESS RESEARCH BACKGROUND

Definition

Increasingly, there has been recognition of “knowledge gaps” regarding the most effective intervention or treatment for a given indication. Because of the current regulatory and approval process, newly introduced technologies are not always compared head-to-head against the other available options, particularly the leading available intervention. The resultant uncertainty about the most effective and appropriate therapy most likely factors into the occurrence of inconsistent care and variable outcomes within our current health care system.[6]

CER seeks to address these issues by obtaining additional information regarding the relative effectiveness of different treatment options. The definition of CER has previously been described by various organizations. For example, the Institute of Medicine (IOM) defines CER 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.”[7]

Additionally, the FCCCER defines CER as:

“...the conduct and synthesis of systematic research comparing different interventions and strategies to prevent, diagnose, treat and monitor health conditions. The purpose of this research is to inform patients, providers, and decision-makers, responding to their expressed needs, about which interventions are most effective for which patients under specific circumstances. To provide this information, comparative effectiveness research must assess a comprehensive array of health-related outcomes for diverse patient populations. Defined interventions compared may include medications, procedures, medical and assistive devices and technologies, behavioral change strategies, and delivery system interventions. This research necessitates the development, expansion, and use of a variety of data sources and methods to assess comparative effectiveness.”[8]

The similarities between the two definitions highlight the concept that CER should be the genesis of new information or synthesis and analysis of existing data that

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can comparatively evaluate all facets of health care, from diagnosis to treatment, for the purpose of allowing relevant stakeholders (such as providers and patients) to make the best decision about what is effective and efficient care. While the definition of CER can be readily determined, the strategies surrounding the proper conduct of CER projects and the implementation of these results into routine clinical practice is the current focus of discussion.

Strategies and Challenges

To address the knowledge gap problem with CER, one must consider the current challenges of transforming CER ideas into improved patient outcomes and develop a strategy for overcoming these challenges. The Friends of Cancer Research White Paper (FWP) emphasized the preeminence of randomized controlled clinical trials as the standard for the development of scientific data that defines the safety and effectiveness of a health care technology.[5] Additionally, the FWP affirmed the value of large outcomes databases or registries in serving to address important clinical issues and provide scientific data for comparative analyses.

There is much discussion around the use of randomized clinical trials (RCTs) for carrying out CER studies. It is recognized that while RCTs are the gold standard for determining safety and efficacy, there can be drawbacks to their use in determining safety and effectiveness for the general patient population. First, RCTs usually focus on a narrowly selected population in a controlled setting and may utilize surrogate endpoints.[9] Selectively enrolling patients allows for robust internal validity, but the results cannot always be readily generalized and extrapolated to the entire patient population likely to receive the treatment. Additionally, RCTs may not be the most practical approach to CER, as they are expensive and require a significant time investment. One alternative to the RCT is the use of “practical clinical trials,” wherein the patient population being studied is reflective of those most likely to receive the treatment in routine clinical practice, and the outcomes studied are those that are most relevant to clinical decision-making.[10] Other alternatives to the RCT include nonrandomized observational and/or retrospective analyses of registries, claims data, or other types of databases (i.e., “secondary data sources”).[11] It is important to note that nonrandomized studies of secondary data sources have different strengths and limitations compared to RCTs, and it is with these studies that there is concern with methodologic conduct and interpretation.

Reports, such as that from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), emphasize the value of data from retrospective database analysis based upon good research practices. In the three-part ISPOR report, guidance is given on how to design a CER study from secondary data sources that minimizes bias and confounding variables and utilizes analytic techniques to infer causality.[12-14] Furthermore, guidance is provided on how to interpret the results derived from these

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types of studies. To carry out CER from secondary data sources would require a significant investment in the current data collection infrastructure to ensure quality of data. Secondary data sources would likely be derived from registries, claims databases, or electronic health records currently used in the day-to-day practice of caring for patients.

Specific to cancer, the NCCN has created and maintains databases for quality assessment and outcomes research purposes in a variety of cancer diseases. The NCCN Oncology Outcomes Database Project is a network-based data collection, reporting, and analytic system that describes the patterns and outcomes of care delivered in the management of patients with cancer. The concept for the Project was established in 1996, and the operation of the first database in breast cancer was initiated in July of 1997. Presently, the NCCN Oncology Outcomes Database Project has five active database components: breast, colon/rectal, non-Hodgkin's lymphomas, non-small cell lung, and ovarian cancers. The Project follows more than 60,000 patients with approximately 300 data elements collected on each patient in areas of sociodemographics, clinical interventions, and clinical and non-clinical outcomes. The data is high-quality and research-worthy as on-site audits of data occur within three months of a site joining the database and on an annual basis thereafter.

In addition to the above challenges with methodology and different data sources, with emphasis on the use of existing data, the literature has further expanded on some of the challenges of establishing formal CER programs in oncology:

- Standards for taxonomy and methodology for CER have not yet been clearly defined or established within the context of oncology.[2, 11, 15]
- Given the vast number of “information gaps” in current medical literature pertaining to cancer, prioritization of research questions specific to cancer is necessary.[2, 16]
- Comparative effectiveness programs should be continuously evaluated to measure their impact on policies and practices and to identify means of improving dissemination of information.[2,17]
- CER in oncology is not necessarily limited to comparisons of active treatment of cancer. The implementation of different health strategies could also be compared.[17]
- “Individualized (or personalized) medicine” is a growing field in oncology and could be advanced through CER by analyzing different subgroups of patients receiving a specific treatment.[18, 19]
- Translation, adoption, and dissemination of results from available comparative effectiveness studies have been limited. An ideal strategy for disseminating such research in a manner that can influence clinical decision-making must combine valid evidence and appropriate interpretation of data.[2, 8]
- A systematic framework for incorporating the existing body of evidence to comparatively evaluate treatment strategies should be developed to facilitate the

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selection of appropriate interventions while accounting for patient-specific comorbidities and situations.[2, 8]

The NCCN agrees with these conclusions with particular emphasis on the last two bullets. Our nation's great biomedical research enterprise that is based upon the RCT will continue to generate data critical to advance all areas of medicine. However, there is a need to better address decision-making processes today with improved use of the data, information, and expert judgment that currently exist and are available. The NCCN Guideline development process is based upon such formal, critical evaluation of scientific data by multidisciplinary experts. The NCCN will seek to integrate a systematic process to apply comparative effectiveness analysis to high priority issue areas in the NCCN Guideline Development Schema.

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**NCCN RECOMMENDATIONS FOR ADDRESSING THE CHALLENGES OF
ONCOLOGY COMPARATIVE EFFECTIVENESS RESEARCH**

The authoring committee of this white paper presents the following recommendations to further the use of comparative effectiveness research in the field of oncology to benefit both physicians and patients.

Recommendation: The NCCN should incorporate a paradigm entitled “The NCCN Comparative Therapeutic Index” to translate comparative effectiveness analyses into clinical recommendations to inform and improve decision-making for patients.

Because the NCCN Clinical Practice Guidelines in Oncology™ are widely recognized and used as the standard of care in oncology in both the academic and community settings and significantly influence appropriate practice patterns, prescribing behavior and coverage policy, they serve as the perfect vector for the dissemination of CER results for adoption into practice. To a certain extent, the Guidelines already provide comparative recommendations based on a clinical evaluation of the available data, but in a way that is not completely explicit. To competently translate CER results from existing raw data from clinical trials, meta-analyses, observational reports, or other types of studies into concrete clinical guideline recommendations, a paradigm utilizing a systematic, explicit, and transparent approach must be created for use within the guideline development process. Additionally, toxic effects of an intervention must be considered, as they are likely to influence practice decisions along with effectiveness considerations. Therefore, any such paradigm must incorporate this risk-benefit calculation when considering the evidence.

The NCCN paradigm will be termed the *NCCN Comparative Therapeutic Index (CTI)*. Evaluations initially will be focused on treatments. Clinical decision-making, as a risk/benefit analysis, evaluates the effectiveness and the toxicity of treatments across the continuum of patient stage, the variability of patient characteristics, and the specific objectives of treatments.

Ideally, CER studies would be carried out in such a fashion that every possible treatment option is directly compared to each other, where the study is designed such that clinical endpoints are standardized. The clinical application of such studies could considerably aid the clinical decision making process which currently judges and evaluates the available data via indirect comparisons. Unfortunately, such CER studies are unlikely to be available in the foreseeable future. The rapidity of knowledge advancement, especially in oncology, and problems with data infrastructure and availability render the reliance on such ideal studies as impractical. The clinical decision-making realm, as NCCN is attuned to, acknowledges the limitations of using available studies and their corresponding data for direct comparison. However, if patient care is to

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advance, a judgment must be made utilizing such evidence and synthesizing an appraisal as best directed by these clinical comparisons.

The NCCN CTI is a clinical evaluative process that utilizes existing data to clinically appraise the risk-versus-benefits of treatment options using explicitly stated criteria. Utilized data would include, among other types of studies, scientific comparative effectiveness analyses from credible organizations and authors and would continually integrate new data as it becomes available. These appraisals can then be compared to each other for the purpose of discerning on a global scale what options are preferred, appropriate, or acceptable. This general appraisal does not factor in specific patient co-morbidities, preferences or nuances that are apparent during the physician-patient consultation that affects specific treatment decisions.

This evaluative process already occurs whenever treatment decisions are made. Clinicians, in their own minds, have made judgments on the therapeutic indices of available options based on available data and personal clinical experience and have compiled a comparative list to be applied for their patients. The final selection of a specific treatment is then made based on patient-specific parameters. The NCCN CTI paradigm seeks to systematize the above judgment in an explicitly stated manner utilizing the expert opinion of oncology thought leaders from NCI-designated cancer centers. The final selection of the specific treatment is the responsibility of the individual physician based on patient-specific parameters elucidated during the course of the physician-patient relationship.

In the risk/benefit analysis of clinical decision-making, the CTI communicates the ratio of the likelihood of effectiveness of the proposed treatments versus the potential toxicity. The explicit consideration of toxicity is critical in oncology decision-making. The NCCN proposes an incremental integration of the CTI into the NCCN Guidelines process on a pilot basis with select NCCN Guidelines panels. In the early stages, it is proposed that:

1. Select NCCN panels will focus on the chemotherapeutic/biologic regimens available for the treatment of metastatic disease.
2. Panel members apply the CTI evaluative schema to identified treatments (i.e., regimens) for specified indications (e.g., first-line, second-line) for the treatment of metastatic disease.
3. During the in-person panel meetings or in select teleconferences, the panel evaluative scores will be discussed and result in the categorization of treatment regimens as “preferred,” “appropriate,” “acceptable,” or “not acceptable.”
4. These categories will be communicated (similar to what the Breast Cancer Panel has started to do) in a tabular format that is consistent and recognizable across guidelines yet allows flexibility for individual panel needs.

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5. The complete analysis will be reviewed on an “as needed” basis as determined by the panel chair and panel members with assistance from NCCN staff.

The CTI Process

The CTI process would start by assigning separate scores for a treatment’s effectiveness and toxicity. These scores will be developed through a matrix that explicitly translates effectiveness and toxicity variables into a numeric value. These variables will ultimately be finalized by the CTI pilot exercise (see Appendix D), but the general concept is to allow individual panels to weigh the importance of each variable in reference to each other, depending upon what oncologic condition and stage/setting is currently being evaluated. The proposed effectiveness and toxicity variables are the following:

Effectiveness:

- Survival: overall, disease-free, progression-free
- Response rates
- Impact on health-related subjective outcomes: performance status improvement, disease-related pain improvement, etc.

Toxicity:

- Probability of fatal event (Grade 5)
- Probability of severe, life-threatening or disabling side effects (Grades 3 – 4)
- Probability of mild or moderate side effects (Grades 1 – 2)
- Duration of adverse effects (chronic vs. acute)
- Impact on Health-Related Quality of Life (HR-QOL)

Proposed effectiveness and toxicity matrices can be found in **Appendix A**. Using these variables, the Panel will consider the relevant body of literature (CER results, RCTs, case reports) and data from other reputable sources (such as the NCCN Oncology Outcomes Database Project) as well as utilize their clinical acumen to judge the effectiveness and toxicity scores for a given treatment option. New data will be incorporated into appraisals as it becomes available. The result is a CTI score of two dimensions (toxicity, effectiveness) which can be represented by x,y coordinates on a Cartesian graph and further translated into a descriptive category as shown in Figure 1. The toxicity score is represented on the x -axis while the effectiveness score is represented on the y -axis. Plotting the treatment option’s toxicity and effectiveness scores as a point on the Cartesian graph would result in it falling into one of four possible sections that determines the descriptive category. A table listing each therapeutic option with the corresponding category would be displayed, similar to what is currently listed in the NCCN Breast Cancer Guidelines.

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A Model for Translating the CTI into a Descriptive Category

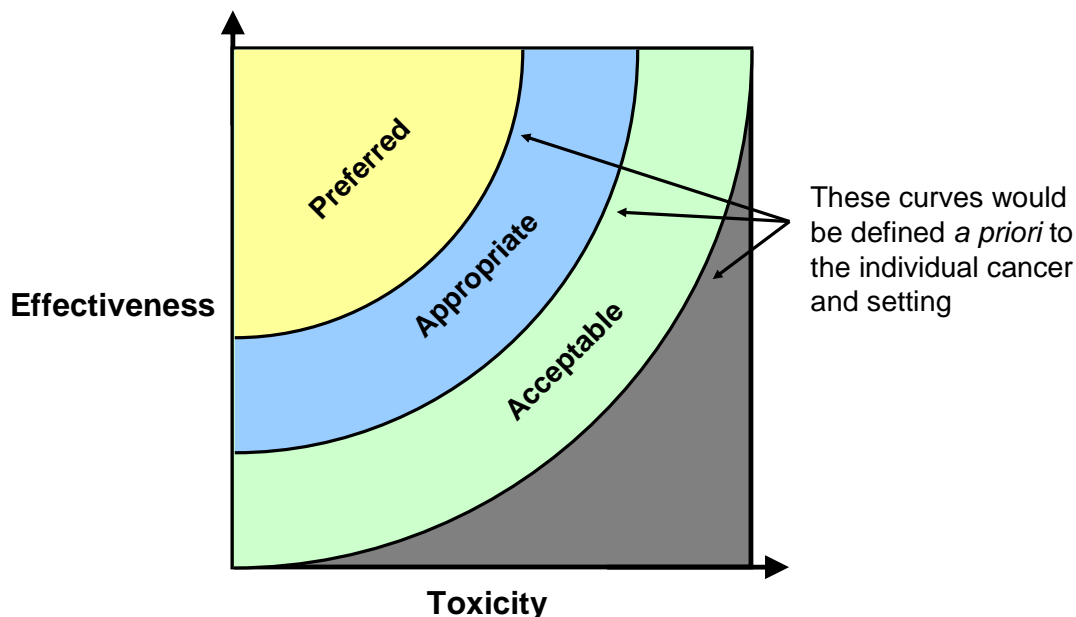


Figure 1. A proposed decision model for categorization of CTI scores with preliminary labels for the specific categories. For a complete description of this model, please see Appendix B.

To aid in clinical decision-making on the individual physician-patient level to meet the needs of patients with differing co-morbidities, the above categories would be further described to communicate the complicated nature of patient co-morbidities, the tradeoff of highly-toxic therapies with curative intent, and other characteristics.

Resource Utilization

In addition to the effectiveness and toxicity, a therapeutic option's resource utilization is an increasingly important factor when deciding on therapy. It is obvious that resource utilization alone should not be a factor in choosing therapy, as it may be appropriate to utilize more resources for a more effective, less toxic therapy. Conversely, given a case of diminishing returns with an option that exhibits a modest favorable effectiveness/toxicity profile but consumes an excessive amount of resources, the option may not be practical or appropriate. The challenge with considering the resource utilization of different options lies with the fact that there is no agreed upon definition of what constitutes "excessive resource utilization" and "modest benefit." Taking this point into consideration, NCCN's resource utilization comparison does **not** seek to define this

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concept. Rather, we will present the facts surrounding the resource utilization of our different recommendations. It would then be left to the deciding party how to integrate information on resource utilization or consumption into their specific circumstances.

It is important to maintain a practical approach when creating a paradigm to compare resource utilization of different options. The challenge is in creating a system that allows the interested party to quickly compare the resource utilization of each option. A practical approach to comparing resource utilization could utilize icons or symbols to visually compare resource utilization parameters of different options recommended by the NCCN Guidelines. These parameters might be: 1) price of therapy; 2) administration setting; 3) monitoring intensity; and 4) any other special needs. Visually comparing all these parameters using a tabular format presents an advantage over summarizing them further into a “social impact score” because a single-dimension score would not be able to discriminate the differences in the above parameters, where subtle differences may be important for treatment decisions. A suggested draft example of this system for first-line metastatic colon cancer is listed in **Appendix C**.

In the example provided, Average Sales Price (ASP) for a duration of therapy is used as the price or cost parameter. While NCCN recognizes there are flaws with using ASP in calculating the price of therapy, the purpose of this parameter is not to precisely state the costs for a particular patient. Rather, this parameter is intended to be a comparative frame of reference when considering the price of one option versus another. It is expected that the end-user (provider or patient) will gain value from the relative differences observed between the options, and not necessarily from their absolute values. In the future, the associated costs to administer each regimen could be determined through mapping reimbursement of services associated with the billing of each regimen as an estimation of cost. Additionally, costs associated with the use of supportive care medications and therapies (e.g., myeloid growth factors) may be listed.

CTI Application in the NCCN Clinical Practice Guidelines

The CTI paradigm is an extension of the recommendations already provided in the NCCN Clinical Practice Guidelines. For a more detailed description of the NCCN Clinical Practice Guidelines and the development process, please visit our website at www.nccn.org. The CTI process will be initially applied and updated during the individual guideline update meeting process. The NCCN guidelines meet regularly to update the guidelines based on the most current data and practice considerations, and the CTI evaluations for new and existing interventions will be added or updated accordingly. As data from actual CER studies become available, they will be integrated into the CTI clinical evaluative process.

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It is important to note that the CTI evaluation is not appropriate for every recommendation listed in the NCCN Clinical Practice Guidelines. Certainly, there are situations that call for the application of the NCCN CTI. These situations are those that have multiple recommendations for a particular setting, such as the example of adjuvant chemotherapy regimens for invasive Breast Cancer. However, it may not be appropriate to apply this paradigm in situations where there are very few options. Furthermore, in situations where there are multiple treatment options, but each will be used in a sequential manner (as in the case of stage IV, unresectable Kidney Cancer), the CTI does not necessarily apply. As experts, the NCCN Panels will decide the most appropriate application for the CTI paradigm within their guideline.

The NCCN CTI process will not be in conflict with “personalized medicine” as it pertains to the care of cancer patients. Based on available data, the NCCN guidelines already identify and in some cases, segregate patient groups based on genetics, biomarkers, or other criteria to direct treatment based on these considerations. If necessary, the CTI would be applied to the various options *within* a specific patient population, not across different patient populations.

Implementation of the Paradigm

The implementation of the CTI paradigm as detailed in **Appendix D** will encompass three phases, in a gradual, progressive approach with the goal of system-wide adoption into all Guidelines. The first phase will be a pilot exercise utilizing 6 – 8 physicians each from 1 – 2 Guideline Panels, with the primary purpose of improving the process, testing for reliability and validity (see below) of the CTI, and collecting feedback regarding workload and practical issues. This pilot exercise is not related to the usual Guideline Panel meeting process and any categorization developed at this point would not be incorporated into the next iteration of the Guideline. Phase Two will be a pilot utilizing one to three Panels, collecting the same types of feedback for improvement. Once the issues have been sufficiently addressed, the phase three system-wide release to all Guidelines will be recommended. It is important to note that the individual Panels will be encouraged to take small steps in implementing the CTI scoring. That is, one specific situation (e.g., adjuvant chemotherapy regimens) could be assessed using the CTI initially, adding additional situations with future updates.

Because external credibility of the paradigm is critical, the reliability will be tested and used for the paradigm’s quality improvement. Inter-rater reliability will be measured by examining the agreement in CTI scores among panel members using kappa statistics. A subset of individual Guidelines Panel members will also independently complete CTI scoring on two separate occasions. Intra-rater reliability will be examined by correlating the two CTI scores for each panel member.

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Construct validity of the CTI process will also be assessed by comparing CTI-based therapy recommendations with practice patterns at NCCN institutions. If the recommendations produced by the CTI process are consistent with the practice patterns of oncologists practicing at NCI-designated cancer centers, then we can be confident that the CTI paradigm is a valid clinical evaluative process. Practice patterns will be assessed using two methods: 1) as the relative frequency of therapy utilization measured using the NCCN Oncology Outcomes Database Project; and 2) using a survey of practicing oncologists at NCCN institutions wherein they will be asked to select the most effective therapy for the majority of patients from a list of Guideline recommended therapy options. Since the patients seen at NCI-designated cancer centers may exhibit different characteristics than the general population of cancer patients in the United States, data obtained from the NCCN Oncology Outcomes Database Project will be controlled for differences by stratifying the data by patient characteristics such as age, stage, and severity of disease. Construct validity and reliability will be measured in cancer types and for indications where the current standard of practice is well established.

Based on the findings from the reliability and construct validity tests, the CTI scoring may be modified, improved upon, and re-evaluated until an acceptable level of reliability and validity is reached. Because this is a continual improvement process, it is likely that these analyses will need to be performed at regular intervals to ensure a robust product. As with all recommendations in the NCCN Clinical Practice Guidelines, these CTI categorizations reflect the expert consensus of clinicians at NCI-designated cancer centers. Individuals or other entities must decide whether these guidelines (and the corresponding CTI categories) are appropriate for use within their respective community. In the future, clinical recommendations in the Guidelines could be validated to different patient groups using real-world data (such as those from the NCCN Oncology Outcomes Database Project) through outcomes research studies.

Recommendation: The NCCN should be an active leader in the dissemination of comparative effectiveness research results.

Once the validity of the CTI is established and panels are utilizing the CTI, NCCN has the capability to influence practice patterns of oncologists and hematologists worldwide. CTI results will be published as part of the Clinical Practice Guidelines, allowing free and open access to all decision-makers. The NCCN web site, www.nccn.org, attracts over 1.3 million unique visitors per year. Beyond the Clinical Practice Guidelines, NCCN has many other programs and resources to inform and improve decision-making and outcomes for patients whom we serve. NCCN's spectrum of programs and resources emphasizes improving the quality, effectiveness, and efficiency of oncology practice. NCCN hosts educational conferences and symposia for physicians at which the CTI and its results from different panels and settings can be presented to encourage change in practice patterns so that patients receive the best,

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appropriate care. Physicians can also be reached and educated through *JNCCN – The Journal of the National Comprehensive Cancer Network*.

Recommendation: The multidisciplinary experts on the NCCN Guidelines Panels and the NCCN Oncology Outcomes Database Project constitute significant resources to facilitate the identification of high-priority issues for the application of comparative effectiveness research analyses both within the NCCN and nationally.

The Friends of Cancer Research White Paper has recognized the importance of developing a research agenda of “high-priority, clinically important” topics that supports the development of personalized medicine through the analysis of subpopulations or clinical biomarkers and focuses on interventions other than treatment such as screening, diagnosis, and end-of-life care.[5] Keeping these factors in mind, the formation of specific hypotheses for oncology CER studies requires expertise from multidisciplinary clinicians (i.e., medical, radiation, and surgical oncologists) who wrestle with these challenges on a daily basis when caring for their patients. NCCN is able to supply the expertise, as the evidence-based NCCN Guidelines are developed and updated by 44 individual panels, composed of over 800 multidisciplinary clinicians and oncology researchers from the 21 NCCN member institutions geographically dispersed across the country. Panel members possess in-depth knowledge of the biomedical literature and awareness of, if not actual leadership and/or participation in, the trials that provide the evidence for the oncology community and for the NCCN Guidelines.

Additionally, the Friends of Cancer Research White Paper recognizes that CER should also include the analysis of various geographic, ethnic, or socioeconomic factors that may result in disparate care.[5] The NCCN Oncology Outcomes Database Project, with its more than 60,000 patients followed prospectively and longitudinally, represents a significant resource to identify and measure these variations in care across institutions and various types of patient populations. For example, one current use of the Database is for quality improvement purposes, wherein quality measures derived from the NCCN Clinical Practice Guidelines are analyzed for the purpose of improving practice performance. The Database also serves to identify factors that result in variations of care and is a unique resource and repository of data for researchers to access and derive hypothesis-generating research.

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CLOSING STATEMENT

The National Comprehensive Cancer Network (NCCN) is uniquely positioned to assume a leadership role in oncology CER, especially with the translation and adoption of CER. The NCCN is recognized in oncology as the arbiter of high-quality cancer care based upon NCCN world-leading institutions and clinicians and the status of the NCCN Clinical Practice Guidelines in Oncology™, as the standard for clinical policy in oncology in the United States. Based on the identified needs and challenges, there are a number of reasons why the US health care system needs the NCCN to address issues within the arena of oncology CER:

- NCCN has a unique ability to convene panels of oncology thought leaders, evaluate available and emerging scientific data and evidence, facilitate and build consensus among experts, identify research priorities, engage stakeholders throughout the oncology community, and provide and disseminate real world recommendations about policy and process and the implementation of same.
- As leaders in clinical research, NCCN experts understand the research process that achieves and translates findings into improvements for patients, often in an incremental manner.
- NCCN's Oncology Outcomes Database Project would aid in integrating many CER efforts by providing a feedback loop between knowledge generation and the translation and adoption of CER. The NCCN Oncology Outcomes Database Project follows more than 60,000 patients in cancers such as breast, colon/rectal, non-Hodgkin's lymphomas, non-small cell lung, and ovarian with data elements collected on each patient in areas of sociodemographics, clinical interventions, and clinical and non-clinical outcomes. The data is high-quality and research-worthy.
- Through many of NCCN's products and services (NCCN Clinical Practice Guidelines in Oncology™, NCCN Drugs & Biologics Compendium™, and NCCN Chemotherapy Order Templates™), information can be rapidly disseminated to major stakeholders throughout the United States and beyond.
- NCCN's reputation and credibility in the cancer community and among payers properly positions us to take the lead in addressing comparative effectiveness in such a way as to improve patient outcomes, maintain access to effective care, and to enhance the efficiency of such care.

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Proposed Effectiveness Scoring

Score	No impact 0	Minimal 1 – 2	Low 3	Moderate 4	High 5	Weight (%)
Overall survival	No meaningful impact on relevant disease related endpoints	No impact on survival/cure, but sometimes provides control of disease	Little or no impact on survival/cure, but often provides control of disease	Sometimes improves long-term survival or cure	Often provides long-term survival advantage or curative potential	
Progression Free Survival	No meaningful impact on relevant disease related endpoints	No impact on PFS	Little or no impact on PFS	Sometimes improves PFS	Often provides long-term PFS	
Response Rate	No meaningful impact on relevant disease related endpoints	Little impact on RR	Low impact on RR	Moderate impact on RR	Large impact on RR	
Performance Status	No meaningful impact on relevant disease related endpoints	No positive effect on PS but sometimes maintains at current level	Little or no impact on PS, but often maintains at current level	Mostly positive impact on PS and may reverse negative PS due to disease	Dramatically positive impact on PS and very good chance to reverse negative PS due to disease	

Panels will weigh each variable according to each given situation (i.e., cancer, adjuvant or metastatic setting) and use the above scoring system to rate a treatment’s effectiveness. This model is highly dependent on the type and amount of evidence supporting such a judgment. Therefore, the score will be multiplied by a factor (based on the NCCN category of recommendation) adjusting for the quality of data to achieve the final effectiveness score. The multiplying is described below:

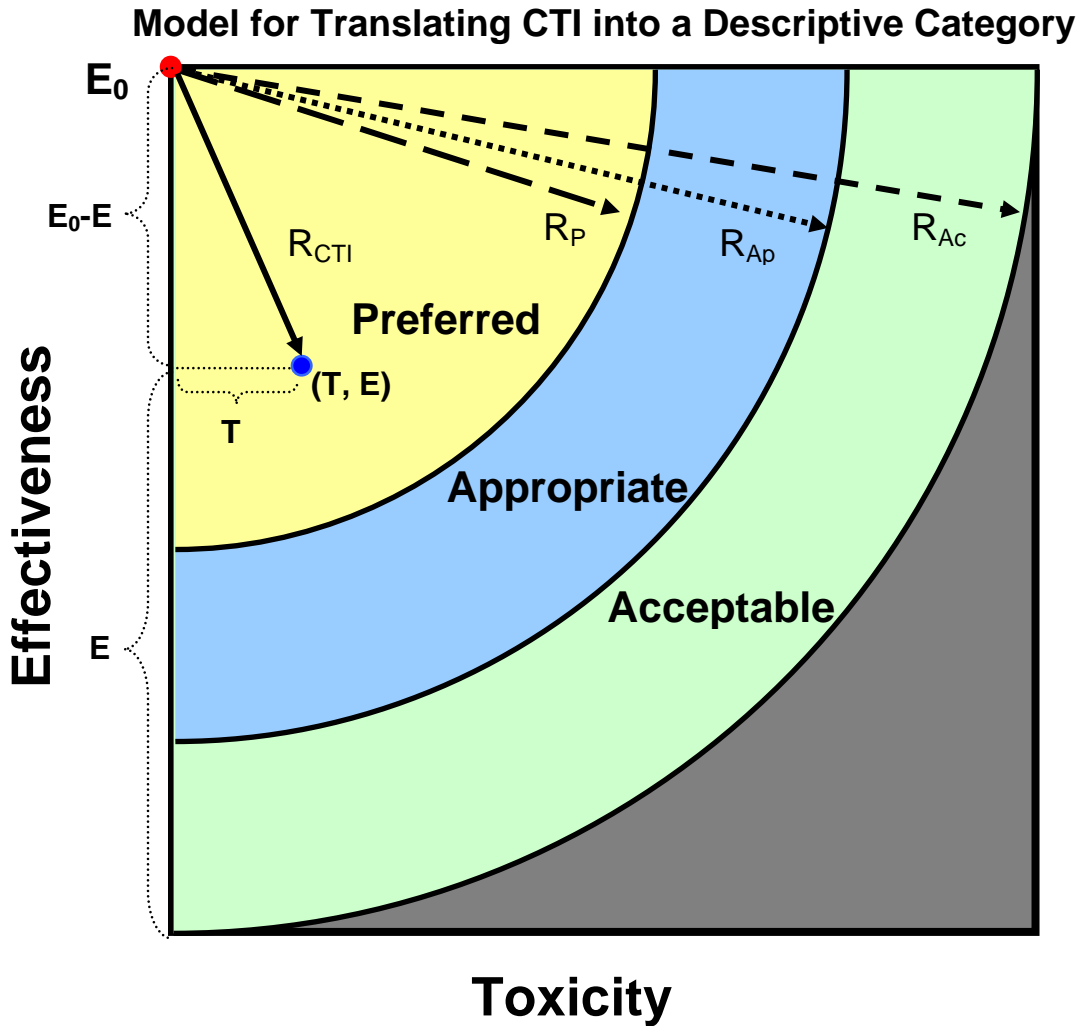
Category of Evidence	NCCN category 3	NCCN category 2B	NCCN category 2A	NCCN category 1
Factor	1	1.5	1.75	2

Proposed Toxicity Scoring

Score	Toxicity Description
0	None
1	Not known to cause death; no Grade 3 – 4 adverse reactions; generally mild, short-term, non-debilitating toxicities and does not decrease health-related quality of life
2	Not known to cause death; low probability of Grade 3 – 4 adverse reactions; generally mild, short-term, non-debilitating toxicities but slightly decreases health-related quality of life
3	Not known to cause death; low probability of Grade 3 – 4 adverse reactions; generally mild, short-term, somewhat debilitating toxicities and slightly decreases health-related quality of life
4	Deaths rarely occur ; low probability of Grade 3 – 4 adverse reactions; generally moderate , short-term, somewhat debilitating toxicities and slightly decreases health-related quality of life
5	Deaths rarely occur; moderate probability of Grade 3 – 4 adverse reactions; generally moderate, moderate-term , somewhat debilitating toxicities and moderately decreases health-related quality of life
6	Deaths rarely occur; moderate probability of Grade 3 – 4 adverse reactions; generally moderate, long-term , somewhat debilitating toxicities and moderately decreases health-related quality of life
7	Deaths may occur ; moderate probability of Grade 3 – 4 adverse reactions; generally severe , long-term, somewhat debilitating toxicities and moderately decreases health-related quality of life
8	Deaths may occur; high probability of Grade 3 – 4 adverse reactions; generally severe, long-term, somewhat debilitating toxicities and severely decreases health-related quality of life
9	Deaths occur ; high probability of Grade 3 – 4 adverse reactions; generally severe, long-term, debilitating toxicities and severely decreases health-related quality of life
10	Unacceptably toxic

Panels will use the above scoring system to rate a treatment’s toxicity. To adjust for the setting of care, this score will be multiplied by a factor to achieve the final toxicity score. The multiplying factor is described below:

	Potentially Curative/ Long-term Control: Primary modality	Potentially Curative/ Long-term Control: Adjuvant/neoadjuvant modality	Disease Control	Palliative/Salvage
Factor	0.7	0.8	0.9	1
Setting of care	The use of this primary modality to achieve a cure or long-term disease control far outweighs toxicity	Elimination/reduction of initial, residual, or micrometastatic disease to achieve a long-term response (or potential cure) outweighs toxicity	The benefit of short- to moderate-term disease control somewhat outweighs toxicity	Improvement of disease-related symptoms or disease control is equivalent to the concerns for toxicity



The above model for translating the CTI into a descriptive category can be conceptualized by first defining E_0 as the theoretical “perfect” treatment option, as it displays the maximum possible effectiveness with no toxicities. Comparatively speaking, any other treatment with a toxicity and effectiveness score of (T, E) will be a distance of R_{CTI} from the theoretical perfect option, this being a ratio of additional toxicity or reduced effectiveness. The boundary curves for the “Preferred, Appropriate, and Acceptable” categories are the thresholds for which one tolerates this ratio of increased toxicity or reduced effectiveness. These curves are semi-circles, with the center of the circle being E_0 with a radius of R_P , R_{Ap} , or R_{Ac} for Preferred, Appropriate, or Acceptable, respectively. A treatment is translated as “Preferred” if $R_{CTI} \leq R_P$, “Appropriate” if $R_P < R_{CTI} \leq R_{Ap}$, and “Acceptable” if $R_{Ap} < R_{CTI} \leq R_{Ac}$. Treatments with $R_{CTI} > R_{Ac}$ will be left off the guidelines. The values for R_P , R_{Ap} , and R_{Ac} are pre-determined by the panel based on the cancer and setting being evaluated. Calculation of R_{CTI} is based upon the Pythagorean Theorem, using the following equation:

$$R_{CTI} = \sqrt{T^2 + (E_0 - E)^2}$$

Regimen	CTI Descriptive Category	Administration setting*	Monitoring intensity*	Special considerations*	Price for 4 weeks of therapy**
FOLFOX + Bevacizumab	To be determined	H; O	☒ ☒	I	\$9,720
CapeOX + Bevacizumab	To be determined	H; O	☒ ☒		\$12,240
FOLFOX + Cetuximab	To be determined	H; O	☒ ☒	K; I	\$14,300
CapeOX + Cetuximab	To be determined	H; O	☒ ☒	K	\$16,827
FOLFOX	To be determined	H; O	☒ ☒	I	\$5,700
CapeOX	To be determined	H; O	☒ ☒		\$8,227
FOLFIRI + Bevacizumab	To be determined	H; O	☒ ☒		\$4,540
FOLFIRI + Cetuximab	To be determined	H; O	☒ ☒	K	\$9,120
FOLFIRI	To be determined	H; O	☒ ☒		\$520
5FU/LV + Bevacizumab	To be determined	H; O	☒ ☒		\$4,080
FOLFOXIRI	To be determined	H; O	☒ ☒		\$6,140

Table 1. Proposed format of displaying resource utilization.

* Please see legend on next page for letter and symbol meaning

** Price is based on Average Sales Price (ASP), assuming a BSA of 1.73 m² or weight of 70 kg as of 9/3/09

Administration setting	Monitoring intensity ¹	Special considerations ²
<p>H – Home administration</p> <p>O – Outpatient administration at infusion center/physician office/hospital</p> <p>I – Inpatient administration</p> <p>S – Inpatient administration with specialty services required</p>	<p>☒ – Some basic monitoring (such as simple blood work, imaging scans) required at a routine outpatient visit or at a predetermined schedule</p> <p>☒ ☒ – Basic monitoring is required more frequently or on a “PRN” basis to monitor for adverse events and/or more advanced tests are routinely required</p> <p>☒ ☒ ☒ – Basic and advanced tests are required at frequent intervals</p>	<p>K – KRAS testing required</p> <p>M – High risk for FN (based on NCCN Myeloid Growth Factor guidelines)</p> <p>I – Intermediate risk for FN (based on NCCN Myeloid Growth Factor guidelines)</p> <p>T – Blood transfusions common with this regimen</p>

Table 1 Legend. Definitions for letters and symbols for Administration setting, Monitoring intensity, and Special considerations

¹ To be defined further in the pilot exercise

² Additional or alternate designations to be determined by the individual panels

Phase I:

Step 1: Work Group

- Determine what variables to consider for effectiveness and toxicity in the scoring system
- Determine what is the hierarchy of evidence and whether it should be based directly on panel assignment of categories of evidence
- Define the descriptive categories (i.e., preferred, appropriate, acceptable, etc.)
- Create an ongoing group (NCCN physicians supported by NCCN staff) to guide the implementation and analysis

Step 2: Pilot Exercise

- Perform trial runs of CTI process in the setting of first-line metastatic breast and colon cancers to evaluate and improve the process
- Not related to Guideline Panel meetings and will not be incorporated into the guidelines
- Groups of 6 – 8 physicians
- Year 2010

Phase II:

Step 3: Pilot CTI process with one Panel

- Apply CTI process as determined by step 2

Step 4: Reliability/validity analysis and quality improvement

- Compare CTI-based recommendations with practice patterns derived from:
 - NCCN Oncology Outcomes Database Project (validity)
 - A survey to physicians at NCCN institutions (validity)
- Examination of the agreement in CTI scores between panel members (inter-rater reliability)
- Examination of correlation between the two separate CTI scores for each panel member (intra-rater reliability)
- CTI scoring process is modified to address concerns

Step 5: Pilot CTI process with three additional Panels

- Apply CTI process as determined by steps 2 and 4

Step 6: Reliability/validity analysis and quality improvement

- Same method as step 4

Phase III:

Step 7

- Each panel should utilize the CTI process one setting initially, incorporating additional settings over time
- Each panel should develop a priority list of settings within their guideline that the CTI process can be practically used
- Data from NCCN Oncology Outcomes Database Project will be used to supplement evidence to be used for CTI evaluation

NCCN Background

The National Comprehensive Cancer Network, a not-for-profit alliance of 21 of the world's leading cancer centers, is an authoritative source of information to help patients and health professionals make informed decisions about cancer care. Through the collective expertise of NCCN member institutions, NCCN develops, updates, and disseminates a complete library of clinical practice guidelines. NCCN's spectrum of programs emphasizes improving the quality, effectiveness, and efficiency of oncology practice. Programs include: NCCN Clinical Practice Guidelines in Oncology™, NCCN Drugs & Biologics Compendium™, NCCN Chemotherapy Order Templates™, Oncology Outcomes Database Project, Oncology Research Program, educational conferences and symposia for clinicians, *JNCCN - The Journal of the National Comprehensive Cancer Network*, and collaborations with managed care organizations. These and other NCCN programs and resources have the overriding objective of informing and improving decisions and outcomes for patients whom we serve.

NCCN Guidelines are widely recognized and used as the standard of care in oncology in both the academic and community settings and significantly influence appropriate practice patterns and prescribing behavior. The evidence-based NCCN Guidelines are developed and updated by 44 individual panels, composed of over 800 multidisciplinary clinicians and oncology researchers from the 21 NCCN member institutions geographically dispersed across the country. Panel members possess in-depth knowledge of the biomedical literature and awareness of, if not actual leadership and/or participation in, the trials that provide the evidence for the NCCN Guidelines.

An NCCN survey in late 2006 demonstrated the value that the NCCN Clinical Practice Guidelines in Oncology™ have to physicians. Ninety-six percent (96%) of professionals who use the NCCN Guidelines agree that they are useful in making patient care decisions. Increasingly, recommendations in both the NCCN Guidelines and in the NCCN Drugs & Biologics Compendium™ are being used by public and private payors to establish coverage policies. As of June 5, 2008, the Centers for Medicare and Medicaid Services (CMS) has recognized the NCCN Drugs & Biologics Compendium™ as a mandated reference for the establishment of coverage policy and coverage decisions regarding the use of drugs and biologics in cancer care. The NCCN Drugs & Biologics Compendium™ will be used by CMS for national coverage determinations and by intermediaries and carriers for locoregional determinations. Further, many private insurers such as UnitedHealthcare and Aetna base their coverage determinations on the NCCN Compendium.

The NCCN Oncology Outcomes Database Project is a network-based data collection, reporting, and analytic system that describes the patterns and outcomes of care delivered in the management of patients with cancer. The concept for the Project was established in 1996, and the operation of the first database in breast cancer was initiated in July of 1997. With the NCCN Oncology Outcomes Database Project, NCCN seeks to implement the NCCN Clinical Practice Guidelines in Oncology™ through performance

measurement. Presently, the NCCN Oncology Outcomes Database Project has five active database components: breast, colon/rectal, non-Hodgkin's lymphomas, non-small cell lung, and ovarian. The Project follows more than 60,000 patients with data elements collected on each patient in areas of sociodemographics, clinical interventions, and clinical and non-clinical outcomes. The data is high-quality and research-worthy as on-site audits of data occur within three months of a site joining the database and on an annual basis thereafter.