Cancer Outcomes Research and the Arenas of Application

Joseph Lipscomb, Molla S. Donaldson, Robert A. Hiatt

In 2004, an estimated 1.5 million persons in the United States will be diagnosed with cancer; about 560,000 will die from cancer; and more than 9.5 million will be undergoing curative treatment, coping with progressive disease, or living free of cancer after successful therapy (1). But many of these survivors still feel the aftershocks and downstream side effects arising from diagnosis and treatment, and many are fearful of recurrence. Substantial progress in reducing the suffering and death caused by cancer is being pursued by the National Cancer Institute (NCI) and cancer agencies and organizations worldwide through a variety of initiatives, programs, and projects. At the NCI, these efforts emphasize the joint importance of basic and applied scientific discovery, the development and testing of promising interventions, and the delivery of quality care to prevent, detect, and treat cancer and to improve the length and quality of life of cancer survivors (2).

It is therefore vital for decision makers, at all levels, to have a firm understanding of just how effectively the fruits of discovery and development are being applied to enhance cancer care delivery in ways that reduce suffering and death. The scientific pursuit of such decision-relevant information is the central business of cancer outcomes research.

The overall aim of this Monograph is to provide an empirically grounded review and evaluation of the peer-reviewed literature in cancer outcomes research. The intent is to identify both important recent contributions and the challenges that remain in bringing scientifically sound information to bear in cancer care decision making.

DEFINING CANCER OUTCOMES RESEARCH

There is, as yet, no consensus definition of outcomes research, much less cancer outcomes research. But recent statements by the U.S. Agency for Healthcare Research and Quality (AHRQ) and the NCI convey a common sense of purpose and scope of application. According to AHRQ, “...outcomes research seeks to understand the end results of particular health care practices and interventions. End results include effects that people experience and care about, such as change in the ability to function. In particular, for individuals with chronic conditions—where cure is not always possible—end results include quality of life as well as mortality” (3,4).

At NCI, outcomes research “describes, interprets, and predicts the impact of various influences, especially (but not exclusively) interventions, on ‘final’ endpoints that matter to decision makers” (5). These decision makers may include patients, families, individuals at risk for cancer, providers, private and public payers and purchasers of cancer care, regulatory agencies, health care accrediting organizations, and society at large. In cancer, final endpoints (outcomes) include such traditional and important biomedical outcomes as survival and disease-free survival, but also health-related quality of life (HRQOL), perceptions of and satisfaction with health care, and economic burden. Final outcomes are distinguished from “intermediate” outcomes (e.g., whether the individual was screened for cancer, or quit smoking, or received appropriate adjuvant therapy following cancer surgery) and “clinical” outcomes (e.g., whether the patient’s tumor shrank or disappeared, or whether the tumor recurred). Although such measures are frequently pivotal in assessing the proximate success of particular interventions, the ultimate test is, or should be, whether improvement in the clinical or intermediate outcome predicts success in improving final outcomes.¹

Prominent biomedical outcomes like survival and disease-free survival have long been employed both in clinical investigations and in widely circulated reports on progress against the cancer burden at the population level. Although pockets of controversy remain about matters of definition and measurement (for example, the ongoing discussion about cause-specific versus relative survival measures), most researchers and many in the lay public would likely believe they have a basic understanding of what these particular final outcomes mean, if not also how to construct them.² On the other hand, there remains much debate about, and wide variations in the use of patient-reported outcomes like HRQOL and measures of patient satisfaction and economic burden. Consequently, this Monograph focuses largely on the actual, and potential, contributions of such patient-reported outcomes on decision making along the cancer continuum, which includes prevention, early detection, diagnosis, treatment, life after a cancer diagnosis (survivorship), and end-of-life care. As will be seen, the bulk of the existing outcomes research literature is devoted to screening, diagnosis, and treatment applications.

For outcomes research to achieve its potential to enhance care delivery, there are at least three prerequisites: 1) technically sound and decision relevant outcome measures; 2) persuasive evidence about the impact of interventions on those outcomes; 3) the capacity, determination, and ingenuity to translate findings into useful information for decision making (5,6).

There are clear interconnections between outcomes research and health services research, though there is no consensus yet about the precise relationship (owing in part to varying definitions of what these particular final outcomes mean, if not also how to construct them.).

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Moreover, the recent advances in scientific techniques have allowed researchers to explore the complexity of cancer, identifying the multitude of factors that contribute to disease progression and treatment outcomes. This has resulted in a deeper understanding of cancer etiology and the development of targeted therapies, providing hope for improved outcomes.

Despite these advancements, significant challenges remain, particularly in translating research findings into practice and ensuring equitable access to effective treatments. Public health initiatives, policy changes, and increased investment in cancer research are essential to addressing these challenges and improving the outcomes for cancer patients worldwide.

In conclusion, cancer outcomes research is a dynamic field that continues to evolve, driven by the relentless pursuit of scientific discovery and the ultimate goal of improving the length and quality of life for those affected by cancer.
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though this appears to encompass not only what we term final
outcomes but also, . . . abnormal states (such as elevated blood
pressure)” (7). In their detailed review of the history and role of
outcomes research in oncology, Lee et al. (7) appear to settle
upon a definition that does not differ significantly from that of
health services research, as spelled out by the Association for
Health Services Research (AHSR) in the late 1990s.3 In the
introduction to a volume of papers discussing future directions
in cancer outcomes research, Ramsey (10) concluded that it may
be premature to impose a consensus definition “until we know
what matters to whom”4.

To pursue its goal of improving the quality of cancer care by
strengthening the scientific basis for public and private decision
making, NCI has created a research and applications agenda that
is supported by a range of outcomes research and health services
research projects, data resources, and collaborations that extend
well beyond the NCI itself (15). These various efforts are dis-
cussed in the Monograph’s final article. In designing its agenda,
NCI has been guided by the Institute of Medicine’s well-known
definition, “Quality of care is the degree to which health services
for individuals and populations increase the likelihood of desired
health outcomes and are consistent with current professional
knowledge” (16). In this definition, desired means desired by
individuals receiving interventions—underlining the idea of
patient-centered outcomes. NCI’s comparatively broad concep-
tualization of outcomes research, and its recognition of the inter-
play between outcomes research and HSR, underscores the
idea that increasing the likelihood of desired health outcomes
requires sustained and well-coordinated progress in several ar-
areas. Specifically, we should measure outcomes that matter; in-
vestigate the impact of interventions on these outcomes; use
the findings to improve quality of care in the community; and
monitor progress over time to identify successes, shortcomings,
knowledge gaps, and new opportunities for research and appli-
cation.

As Donabedian (17) emphasized years ago, quality of care
may be indexed, alternatively, by structural variables (the quant-
ty and quality of inputs), process variables (what is done, or not
done, to the patient), or outcomes (by which he meant final
outcomes, as defined here). But in the end, the validity of struc-
tural or process variables as quality measures hinges on the
strength of the evidence that they are predictive of outcomes that
matter. As AHRQ has noted, “By linking the care people get to
the outcomes they experience, outcomes research has become
the key to developing better ways to monitor and improve the
quality of care” (3).

With these functional definitions and policy aims in mind,
we turn now to the specific framework employed in this Mono-
graph for categorizing and characterizing the applications of
cancer outcome measures, as seen in the peer-review litera-
ture over the decade of the 1990s. This framework provides a
functionally useful backdrop for our efforts to present a system-
atic review and evaluation of a major segment of that literature
and inferences about future directions for cancer outcomes re-
search.

THE ARENAS OF APPLICATION
The framework adopted here recognizes three broad catego-
ries, or arenas, for the application of cancer outcome measures5
(Table 1).

Macro. Population surveillance of trends in cancer-related
outcomes and progress against the cancer burden—including
survival but ideally also capturing selected patient-reported out-
comes.

Meso. Descriptive and analytical studies to understand the
impact of cancer, patterns of service use, and effects of inter-
vention on cancer-related outcomes. Included are a diverse range
of analyses:

• Randomized clinical trials examining intervention efficacy.

• Observational investigations of the effectiveness of interven-
tions in real-world, community practice and of the burden of
cancer on patients, survivors, and families.

• Patterns-of-care studies that not only examine variations in
service utilization, but also relate these variations to differ-
ces in outcomes across population groups; and studies to
monitor the quality of cancer care by tracking adherence of
individuals or populations to consensus recommendations
about appropriate care.

• Clinical modeling, evaluation, and priority-setting analyses,
which typically integrate and synthesize information on out-
comes (and related explanatory variables) from a variety of
sources to identify the best course(s) of action for the can-
cer-related decision at issue. Included here are clinical decision
modeling analyses to select an optimal intervention for the
population (or subgroup) of interest; cost-effectiveness and
cost-benefit analyses (which may, or may not, employ a de-
cision-model); and studies to evaluate existing cancer inter-
vention programs or to guide the establishment of new ones.

Micro. Patient–clinician decision making enhanced by the
use of patient-reported outcome measures, risk and outcome
prediction models, or other tools to improve the quantity and
quality of information available at the bedside, in the clinic and
office, and in electronic (telephone or computer-assisted) com-
munications.

This Monograph presents 10 invited papers,6 that are distrib-
uted across the arenas of application as follows: one macro,
seven meso, one micro, and one paper that suggests how to
connect the schema in Table 1 to a more general “health out-
comes framework” that envisages a creative interplay among
applications at all levels. Five of the seven meso papers examine
outcomes research applications, in turn, for the four most preva-
lent adult cancer disease sites (breast, colorectal, lung, and pros-
tate) and one major childhood cancer (acute lymphoblastic leu-
kemia). Two additional meso papers provide critical assessments
of the application of HRQOL measures and economic cost mea-
sures, respectively, within and across cancer disease sites. The
Monograph concludes with a paper by NCI staff scientists ref-
lecting on possible future directions for cancer outcomes re-
search.

What follows is a snapshot of these invited papers within the
arenas-of-application framework.

Macro-level. Macro-level studies seek to document varia-
tions in important outcomes to assist decision makers in estab-
lishing and evaluating policies aimed at benefiting entire popu-
lations (20). In particular, Clauser (20) discusses how these
studies typically monitor trends over time, trends within or
Table 1. Arenas of applications for cancer outcomes measures

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<tr>
<th>Arenas</th>
<th>Examples</th>
<th>Potential uses in decision making</th>
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<tbody>
<tr>
<td><strong>Macro</strong></td>
<td>National progress report on changes in cancer-related mortality, morbidity, and health-related quality of life, by state and demographic subgroup</td>
<td>Informs policy discussions and the research agenda by revealing successes, shortcomings, and areas requiring more intensive (meso-level) investigation</td>
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<td><strong>Meso</strong></td>
<td>Descriptive and analytical studies to understand the impact of cancer, patterns of service use, and effects of interventions on cancer-related outcomes</td>
<td>Provides specific research findings, inferences, and recommendations to enhance public and private decisions on cancer care and service delivery, coverage and reimbursement, regulation (especially product approval and marketing), standards setting (including guidelines and quality-of-care measurement and evaluation), and the conduct of new research to assess and improve cancer outcomes.</td>
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<td>A. Efficacy: Experimental investigations to determine the impact of one or more interventions on outcomes of interest, and typically involving the randomization of individuals meeting specific inclusion/exclusion criteria to specific therapeutic, diagnostic, or preventive care regimens.</td>
<td>Randomized controlled trial comparing impact of two competing chemotherapy regimens on survival and health-related quality of life in patients with stage III–IV non–small-cell lung cancer.</td>
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<td>B. Effectiveness: Observational (non-controlled) investigations to draw inferences about the impact of one or more interventions on outcomes of interest, typically in diverse settings that are representative of cancer practice in the community. Study designs include prospective and retrospective cohort, case-control, cross-sectional analyses, case series, and case reports.</td>
<td>Prospective cohort study of individuals newly diagnosed with colorectal cancer to examine the impact of alternative strategies for initial treatment and follow-up care on health-related quality of life, satisfaction with care, and economic burden.</td>
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<td>D. Variations in utilization or performance: Observational studies, either cross-sectional or longitudinal, to identify and interpret significant population differences in use or receipt of cancer services thought to be associated with achieving better cancer outcomes. Included are:</td>
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<td>1. Patterns-of-care studies</td>
<td>Series of cross-sectional analyses in which high-quality cancer registry data are linked to medical records to examine racial/ethnic variations in ovarian cancer treatment, over time and across geographic areas.</td>
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<td>E. Clinical modeling, economic evaluation, and priority setting: Decision-oriented studies that integrate information from a variety of sources (e.g., previously published studies, new work on existing data bases, surveys) into an appropriate analytical framework in order to analyze the impact of each choice option on outcomes important to the decision maker. Included are:</td>
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<td>1. Clinical decision modeling</td>
<td>Decision tree model to analyze the impact of alternative therapeutic options on survival and quality-adjusted survival for children and adolescents diagnosed with acute lymphoblastic leukemia.</td>
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<td>2. Economic modeling, including cost-effectiveness analysis, cost-benefit analysis, and cost-consequence analysis</td>
<td>Cost-effectiveness analysis of program to vaccinate all at-risk women in target population against HPV virus to reduce cervical cancer incidence, morbidity, and mortality—in comparison with current prevention and screening modalities.</td>
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(Table continues)
throughout the literature covering (at least) the 11-year period from 1990 through 2000. And importantly, each paper focuses largely on applications of patient-centered outcome measures—such as health-related quality of life, patient satisfaction, and economic burden—and the conduct of decision-analytic modeling and economic analyses. Thus, articles that examine only survival-related and other biomedical endpoints were not included.

Although the set of five papers differ in their particular findings, conclusions, and recommendations, certain common themes emerge, including the following:

- Patient-centered outcome measures can provide valuable information for interpreting the impact of interventions, e.g., indicating the net effect on patient functioning of treatments that reduce cancer-induced pain while generating toxic side effects.
- There is little consensus about how to measure health-related quality of life for any of the five cancer types examined here. Because multiple competing instruments are used across studies (and sometimes even within a given study), our capability to carry out meta-analyses and other cross-study syntheses of findings is compromised. Underlying this absence of consensus about the most appropriate HRQOL measure is a lack of agreement about the criteria for selecting a “best” measure. Similarly, there is wide variability in how the economic costs of cancer and cancer interventions are defined and computed.
- Compared with HRQOL assessment, many fewer studies measure patient perceptions of the quality of cancer care or their satisfaction with aspects of the care process.
- Greater attention should be paid to measuring patient preferences for outcomes, particularly for those treatment or screening options where HRQOL effects are significant, complex, and important to decision making.

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<td>3. Program evaluation and priority setting</td>
<td>Assessment of alternative strategies (e.g., better therapeutic guidelines for providers, training community outreach workers, broad distribution of educational materials) to improve the delivery of palliative care in rural and medically underserved areas—with the aim of enhancing health-related quality of life for cancer patients and their caregivers.</td>
<td>Improve the quality of patient–provider communication, the quality of the information available for decision making, and hence the quality of cancer care in the clinic, at the bedside, and in community practice.</td>
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<td>Micro</td>
<td>Patient–clinician decision making enhanced by the use of survey instruments and other tools to monitor and predict outcomes, as a function of the intervention selected, patient risk profile, and behavioral characteristics.</td>
<td>Periodic administration of generic, cancer-specific, and/or cancer disease-site specific health-related quality-of-life instruments (e.g., SF-36, EORTC QLC C30, FACT B, respectively) to breast cancer patients, from diagnosis through initial and follow-up care.</td>
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• There is substantial variability in the scientific quality of studies examining patient-centered outcomes, particularly in randomized clinical trials where a biomedical outcome (e.g., short-term cancer-free survival) is the primary endpoint and thus the focus of data collection and analysis. For published findings about HRQOL effects to be taken seriously by decision makers, study sponsors and investigators must measure and analyze these outcomes with the same scientific rigor as more traditional, biomedical endpoints.

In a wide-ranging analysis of the use of HRQOL measures across cancer disease sites, Gotate (26) urges greater attention to understanding the performance of selected, high-quality instruments within specific types of applications. For example, better estimates of the covariation between a generic measure like the SF-36 and cancer-specific measures, like the EORTC QLQ-C30 and FACT G, in cancer treatment trials would enhance understanding of the comparative contributions of each measure. Similarly, the ability to determine whether a given HRQOL change score is “clinically meaningful” would be strengthened by the availability of normative data on the instrument’s performance in diverse populations.

In contrast to the field of HRQOL assessment, defining and measuring the resource burden of cancer and cancer care poses little conceptual problem (because the idea of economic opportunity cost has been long understood and broadly accepted). Yet, again in contrast to HRQOL, Fryback and Craig (27) report that there are virtually no widely used, standardized instruments verifying the accepted standard for cost measurement. This has resulted in significant variation in how cancer costs are defined and measured, which greatly reduces the comparability of findings across studies. These authors recommend developing and testing standardized questionnaires and data collection forms for costs.

Micro-level. Micro-level studies use outcome measurement to understand, evaluate, and improve patient–provider decision making. Donaldson (28) examines the emerging literature on the use, acceptability, and effectiveness of patient-centered measures like HRQOL in enhancing communication, providing feedback on the progression of disease and the impact of therapy, and improving the quality of cancer care. Although there have been methodological advances and reports in the literature of successful applications, HRQOL (and patient-centered outcomes generally) are not yet routinely used in oncology practice in the United States. The way forward, Donaldson argues, is not exhortation or top-down requirements that clinicians do HRQOL assessment. Rather, the focus should be on facilitating adoption by improving information technology in the office setting; efficiently embedding HRQOL assessment into the processes of care delivery; and redesigning cancer care to reduce barriers and improve incentives to assess and use HRQOL data.

The Monograph’s invited papers conclude with Erickson’s (29) proposal for a “health outcomes framework” to link macro, meso, and micro applications by embracing a core set of HRQOL questionnaires for use at all levels, possibly supplemented at each level by additional survey items. The aim is to improve the interpretability and usefulness of HRQOL within each arena of application, whether the focus is a given disease (cancer) or a set of diseases. The framework could apply, as well, to any cancer outcome measure of interest. The key point is that because the core measures are used in all arenas, the interpretability within any one arena benefits from that broader perspective. In turn, the broad use of such core measures would foster a much better understanding of health-related quality of life across multiple populations and diseases.

**Understanding and Informing Cancer Care Decision Making: Ascending the Outcomes Research Pyramid**

In *The Outcomes of Outcomes Research at AHCPR*—a compelling report commissioned by what is now the U.S. Agency for Healthcare Research and Quality—a useful framework was introduced for evaluating progress and identifying future research directions (30). The framework takes the form of a four-level pyramid, with the possible impact of research on final outcomes moving progressively closer as one ascends. Specifically, one moves from research that enhances the knowledge base, and the quality of future research (level 1), but does not directly influence medical policies, practices, or final outcomes; to research that does influence practice policies (level 2); to research that influences care delivery (level 3); to research whose influence on patient outcomes in the community is clearly demonstrable (level 4); see Fig. 1.

From an analysis of survey responses from AHCPR-supported investigators over the 1989–1997 period, the report concluded that outcomes research studies had been most successful in describing health care delivery processes, developing methodological tools for measuring patient-centered outcomes and economic costs, and identifying future research topics—all level-1 analyses. There were impressive advances in such areas as meta-analysis, clinical decision modeling, and cost-effectiveness analysis. But, the report noted, there were “few examples” demonstrating that research findings had influenced medical policies, practices, or final outcomes. [One prominent level-4 success story was the use of data feedback and continuous quality improvement techniques to achieve a substantial reduction in coronary artery bypass surgery mortality rates (30).]

Such conclusions, as well as the myriad findings reported in this Monograph’s papers, underline the importance of develop-
ing and supporting a cancer outcomes research agenda that enables us to scale the pyramid. Although Fig. 1 might suggest that such upward advances are linear, they are more likely recursive, interactive, and dynamic. That is, successful efforts at each level will not only influence activity at the next level, but also inform work at that level and at lower level(s). It is frequently observed that improving the quality of care requires attention not only to the underuse of appropriate interventions but also to the misuse and overuse of services (31). Similarly, advancing up the pyramid means promoting evidence-based decision making that is attentive to overuse and underuse, as well as failure to complete an appropriate plan as intended. In the end, the aim is to produce and provide the right information, at the right time and place, to the right decision maker(s) across the arenas of application. In the Monograph’s final paper, NCI staff scientists draw upon their experiences and perspectives (as further informed by the 10 papers that follow herein) to provide observations about the current state of the science and possible future directions in cancer outcomes research (32).

Our ascent up the pyramid has clearly begun—but is far from complete. As the Monograph’s papers indicate, there has been much progress in recent years toward understanding the impact of interventions on final outcomes, including the patient-centered outcomes emphasized here. However, the literature is thin, and our knowledge more anecdotal than systematized, about exactly how such level-1 information is used (or misused or ignored) in decisions about practice policies (level 2) or the delivery of cancer care (level 3). The challenges in acquiring a deeper understanding of the ways in which information at each level comes to influence decision making, and ultimately the outcomes that matter to decision makers, point to a new “frontier” area for outcomes research. We return to this theme in the Monograph’s final paper (32), illustrating with a cancer example how the pyramid has been scaled—and also the challenges in establishing the chain of evidence that links research to improvement in outcomes.

REFERENCES


NOTES

1 A potentially useful way to conceptualize the idea of final outcomes is to invoke the economist’s traditional model of rational choice: the decision maker acts so as to maximize “utility” subject to whatever constraints on behavior are relevant and binding. In symbols, the decision maker maximizes a function $U(H, x)$ subject to specified constraints, where $H$ is a vector of health-related outcomes and $x$ is a vector of all other goods that affect utility (happiness). Within this
stylized framework, $H$ comprises what we have termed final outcomes, and, likewise, all relevant final outcomes are in $H$. Intermediate and clinical outcomes can then be modeled as influencing the generation of $H$ via the production function $H = f(I, C, Y)$, where $I$ and $C$ are relevant intermediate and clinical outcomes, respectively, and $Y$ is a vector of all other factors influencing final outcomes. Further, the potential interplay between $I$ and $C$ could be modeled, recognizing that achieving particular intermediate outcomes influences clinical outcomes. All this underscores the distinction between final outcomes, which are the “ends” we seek, and intermediate outcomes, which are means to those ends. Note also that what we have termed intermediate outcomes are closely related to what quality-of-care researchers call “process measures” of quality. For the three intermediate measure examples in the text, we can construct the corresponding QOC process measures: percent of eligible population screened for (a particular) cancer, percent of smokers who quit, and percent of patients eligible for adjuvant therapy following surgery who elect to receive it and do.

2To be sure, there is much ongoing discussion and different viewpoints about the appropriate role of such prominent surrogate endpoints as rate of tumor progression in cancer treatment trials. But these are what we would term clinical, not final, biomedical outcomes.

3Academy Health, the successor organization to AHSR, now defines health services research similarly to NLM, and it defines outcomes research in the same spirit as AHRQ and NCI (9).

4Yet another perspective on these matters of definition and function comes from the NCI itself, where its Outcomes Research Branch (ORB) (11) and Health Services and Economics Branch (HSEB) (12) operate in parallel and complementary ways within the Applied Research Program (ARP) (13) of the Division of Cancer Control and Population Sciences (14). In terms of the three prerequisites for effective outcomes research cited earlier, the ORB has focused substantially on assessing and improving outcome measures. HSEB (and ARP more broadly) has initiated a number of projects to strengthen the evidence base and analyze the impact of interventions on outcomes. ORB, with support from HSEB and many units and organizations within and beyond the NCI, has devoted substantial resources to synthesizing and translating evidence for cancer care decision making.

5The macro–meso–micro rubric has been previously used by both Sutherland and Till (18) and Osoba (19), but in each of these papers the terms are defined somewhat differently than in Table 1 here.

6Each of these invited papers was supported through contracts from the National Cancer Institute and was subsequently subjected to the peer review process that is standard for all Journal of the National Cancer Institute Monographs. Two of this paper’s authors, Lipscomb and Donaldson, were designated by the Journal of the National Cancer Institute as the scientific editors for the Monograph.

The authors benefited significantly from comments by Rachel Ballard-Barbash, MD, MPH, and Martin L. Brown, PhD.