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COMMENTARY

Comparative Effectiveness Research in Cancer: What Has Been Funded and What Knowledge Gaps Remain?

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A recent explosion of interest in comparative effectiveness research (CER) has been accompanied by diverse attempts to define CER and specify CER research methods. We explore how CER is relevant across the cancer control continuum, including prevention, screening, diagnosis, treatment, and survivorship. We review cancer CER research funded by the National Cancer Institute by analyzing project characteristics along the dimensions of cancer type, stage of the cancer continuum, position on the T0 to T4 translational continuum, and the size and representativeness of both the settings and populations studied. We also provide an assessment of cost and resources considerations in CER. One hundred three relevant projects on CER were funded by the National Cancer Institute's Division of Cancer Control and Population Science between 2009 and 2011. Prevention studies were most frequent (38.8%), and survivorship grants were least frequent (13.5%). Many projects included economic (35.0%) or simulation modeling (10.7%) approaches as well as multilevel behavioral (53.4%) and/or organizational change (54.4%) interventions. Most studies used convenience sampling (54.3%) and studied two or less settings (50.0%). Cancer CER is active and diverse but could be enhanced by a greater focus on knowledge integration, context, relevance to stakeholders, transparency, and population impact.

Processes for generating and evaluating evidence in cancer and other areas of health care are often slow, costly, or too unrepresentative to provide useful evidence to decision makers (1). Given cancer burden, increasing concerns about cancer treatment costs, and projections about the anticipated number of cancer survivors, there is a clear need for cancer comparative effectiveness research (CER) (2). Recently, CER has been recommended as a practical approach to determining what works in health care (3). As defined by the Institute of Medicine, CER is "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" (3).

Concerns about the effectiveness of health care have promoted interest in CER, culminating in the recently established Patient Centered Outcomes Research Institute (PCORI). PCORI responds to concerns that patients, providers, and caregivers do not have the types of comparative information they need to make choices aligned with their desired health outcomes. Thus, the concepts of personalization and patient-centeredness are embedded in the PCORI (4–6). For example, one of the tenets of this research includes answers to these questions: "Given my personal characteristics, conditions, and preferences, what should I expect will happen to me?" and "What are my options, and what are the benefits and harms of those options?" (7). These same questions apply to personalized or precision medicine that seeks to integrate "-omic" information into health care (7). Personalizing health care according to patient preferences will require incorporating social and behavioral information from the outset, not just when a new application is ready for clinical use. There has been an outpouring of recent articles on CER, including special issues of *JAMA* (April 18, 2012) and the *Journal of Clinical Oncology* (October 15, 2012) that included both conceptual papers and a series of large-scale observational studies, three of which addressed cancer. Given the vast amount of emerging information, it remains to be seen how much evidence will have to come from comparative randomized clinical trials, observational studies, natural experiments, adaptive trials, pragmatic intervention studies, and evidence synthesis and modeling, all of which are tools of CER (7).

Regardless, three things are clear: 1) CER research should be relevant and broadly applicable; 2) it should include information on costs, resources required, and efficiency issues; and 3) it should address public health impact (8,9).

Patient-Centered CER Requires a Strong Role for Public Health

The practice of medicine occurs at multiple levels, including patient–practitioner dyads, health-care organizations, families, communities, and state and federal agencies, all appropriately viewed by the Institute of Medicine as part of the "public health system" (10). With advances in information technology and a strong consumer empowerment movement, health-care systems and public health organizations will have an increasing role in collecting population level data, developing policies for both informing and protecting consumers, and assuring that the most vulnerable segments of the population benefit from CER knowledge (11).

As shown in Figure 1, there are four overlapping, interrelated, and nonlinear phases of research in advancing from basic discoveries to reducing the burden of cancer in populations. This diagram illustrates the highly iterative nature of the scientific discovery to translation cycle. The process starts with the identification of a problem, opportunity, or approach to a health issue (T0). The first research phase (T1) is the more traditional bench-to-bedside model, at the end of which new therapeutics, tests, or other interventions are

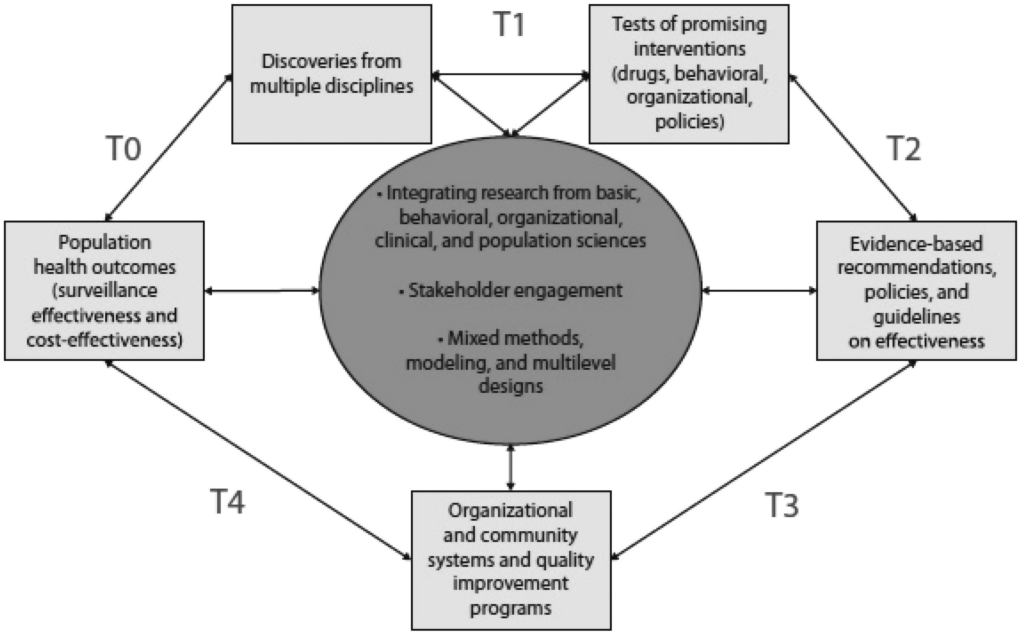

Figure 1. Knowledge integration process (13). This figure depicts the recursive process of integrating knowledge across different types of research so that they inform each other and move toward population health impact in an integrated fashion. Copyright permission from Sheridan Press, *American Journal of Public Health*.

developed (these could also be policy or behavioral interventions). The second research phase (T2) involves analysis and investigation of whether the interventions improve cancer health outcomes (in randomized trials or other study designs). The end result of T2 is evidence-based guidelines and recommendations by professional organizations and independent panels. T3 research includes investigations to increase uptake and implementation of evidence-based recommendations into cancer practice and prevention programs, and T4 research involves evaluation of effectiveness and cost-effectiveness of such interventions in the real world and diverse populations. Some discoveries move rapidly through this cycle, or skip steps and become adopted without evidence-based recommendations. Many others never progress beyond T1 or T2 (12).

This translational framework fits very well with concepts of CER, in T2 to T4 phases. T2-related CER involves comparing the efficacy of different interventions in randomized controlled trials and other designs, T3-related CER involves comparing approaches to implementation and dissemination in practice, and T4-related CER involves comparing effectiveness and population outcomes of various dissemination approaches.

A robust "knowledge integration" (center of Figure 1) is needed to drive the translational cycle. It involves three closely related, iterative components—knowledge management, synthesis, and translation—and includes stakeholder engagement in all components (11). Knowledge management involves an ongoing process of obtaining, organizing, and displaying evolving evidence. Knowledge synthesis involves conducting systematic reviews using mixed methods including meta-analysis, realist review, decision analysis, and simulation modeling that combine information from basic, clinical, and population research. Knowledge translation refers to brokering of the knowledge to influence policy, practice, and research. This model has been recently elaborated on in the context of genomic medicine and implementation science (5,11,13). We apply it to help evaluate and understand the types of cancer CER that have been funded.

The aims of this article are to explain the rationale for CER as applied to cancer, to summarize the types of cancer CER research funded by the National Cancer Institute (NCI), to reflect on how CER research can be best employed to impact population health in the context of the T0 to T4 framework, and to recommend types of research methods that can produce relevant and translatable CER results.

Summary of Recent CER Funded by the NCI

The Research, Condition, and Disease Categorization (RCDC) process of the National Institutes of Health (NIH) was used to generate a preliminary list of 107 grants coded as CER that were funded through the Division of Cancer Control and Population Sciences of the NCI in fiscal years 2009 to 2011. RCDC is a computerized process used by the NIH to identify grants funded in 233 categories of disease, condition, or research area for the purposes of tracking amounts of NIH funding (http://report.nih.gov/rcdc/). Because these grants were selected based on an automated algorithm, abstracts from these grants were then reviewed by a single investigator (V.P. Doria-Rose) to verify that the grants were indeed CER. A second reviewer (M.L. Brown) then reviewed abstracts from grants that were considered either clearly not CER or ambiguous. Based on consensus of the two reviewers, four grants were excluded (three focused on informatics efforts related to electronic medical records that might be applied to CER efforts but were not in themselves CER, and one focused on racial/ethnic disparities in cancer outcomes). A total of 103 research grants were included; career development (K series) and other types of awards were not examined in this analysis. Grants were classified according to several categories, including type of cancer/

Table 1. Number and percentage of National Cancer Institute comparative effectiveness research grants with different characteristics

Topic or issue	Categories	Number of grants*	Percentage of grants
Point(s) on cancer continuum Total No. of grants: 103 Total No. of categories: 111			
	Prevention	40	38.8%
	Screening	24	23.3%
	Diagnosis	3	2.9%
	Treatment	19	18.4%
	Survivorship	14	13.5%
	Multiple	10	9.7%
	Not stated	1	1.0%
Type(s) of cancer No. of grants: 103 No. of categories: 136			
	Breast	23	22.3%
	Colorectal	18	17.5%
	Lung	6	5.8%
	Prostate	13	12.6%
	Gynecologic	1	1.0%
	Cervical	5	4.9%
	Ovarian	1	1.0%
	Not applicable	4	3.9%
	Multiple	14	13.6%
	Other (melanoma, glioblastoma, esophageal, bladder, etc)	7	6.8%
Prevention focused			
	Tobacco	32	30.1%
	Dietary	4	3.9%
	Physical activity	4	3.9%
	Obesity	4	3.9%
	Other (energy balance)	1	1.0%
Place on T2–T4 continuum			
	T2 → recommendations or policies	8	7.8%
	T3 → cancer care/implementation	54	52.4%
	T4 → population cancer impact	29	28.2%
Content area			
	Drug	13	12.6%
	Device	1	1.0%
	Behavioral	55	53.4%
	Organizational system	56	54.4%
	Policy	6	5.8%
	Methods	6930	5.8%
	Multiple		8.7%
	Other (test = 17; surgery = 7; radiation = 5; other = 1)		29.1%
Methods used			
	Experimental, RCT	59	57.3%
	Experimental, other	1	1.0%
	Observational	26	25.3%
	Modeling	11	10.7%
	Cost/economic	36	35.0%
	Infrastructure	12 101	11.7%
	Methods development		9.7%
	Other		1.0%

* Numbers add up to more than 103 in some cases because a given grant fit into more than one category. RCT = randomized controlled trial.

prevention focus, points on cancer control continuum, place on T2 to T4 continuum, content area, and methods used (Table 1).

In addition, we reviewed the full grant proposals to assess information related to the samples and settings studied and the costs and resources involved. These additional analyses were conducted for 94 funded studies for which the entire grant was available in an electronic form. The following criteria for both patient/consumer sample and contextual setting were abstracted: the type of setting (eg, cancer center, clinical setting, workplace, school, community) and the number and recruitment procedures used for both settings and individual participants (ie, convenience sample or no information; some effort to include diverse sample; systematic effort to ensure representativeness). Two factors related to costs were recorded: 1) if there was any report of costs being considered in the design of the study and 2) if non-monetary costs were reported. Finally, three variables were coded related to the transparency of

the grant application: 1) if justification was provided for the inclusion and exclusion of settings, 2) if justification was provided for inclusion and exclusion of individual participants, and 3) if there was any discussion of study limitations or alternative approaches.

Types of CER Currently Funded

A wide range of cancer CER research has been funded by the NCI (Table 1). The vast majority of included grants (92%) were the result of investigator-initiated applications; only eight grants were funded through specific requests for applications or program announcements. The 103 projects were broadly distributed across types of cancers/risk factors, points on the translational continuum, and methods. There were more prevention grants (38.8%) and screening projects (23.3%) than treatment grants and survivorship grants (13.5%; palliative and end-of-life care grants were especially infrequent), and diagnosis studies were funded least often (2.9%). Breast, colorectal, and prostate cancers were all well represented, with 13.6% of the grants studying multiple types of cancer. Among the prevention grants, tobacco studies dominated; there were few grants in other prevention areas.

Funded projects evaluated several types of interventions, the most common being behavioral (53.4%) and organizational/systems approaches (54.4%); these two categories dominated the content areas studied (Table 1). In contrast, only six policy grants were identified, and only two focused predominantly or exclusively on policy issues.

A variety of research methods were proposed, with randomized trials, cost/economic studies, and observational studies all well represented. One area underemphasized was innovative, alternative experimental design methods: all but one of the 60 experimental grants funded were randomized controlled trials. Several grants (10.7%) proposed using simulation modeling or cost/economic analyses (35.0% of the projects). In terms of the grants location on the "translation highway", T1 and likely some T2 grants were excluded because of our focus on cancer control (rather than discovery, which is generally not funded by the Division of Cancer Control and Population Sciences), but there were many grants at both T3 (52.4%) and T4 (28.2%) points on the continuum.

Although there were numerous examples of T3 and T4 research conducted in relevant real-world settings, such as clinical (37.5%) and community (26.0%) (Table 2) settings, few of these reported comprehensively on recruitment at either the setting or patient level, and very few studied an entire region or population-based sample. In contrast, less than 5% of the funded grants focused on worksite or school settings, and very few specifically reported selecting low-resource settings. A majority of grants proposed to report on economic and resources-required issues (50.5%–58.9%). There was variability in the sample sizes studied, with the most common sample sizes being either greater than 1000 (40.4%) or less than 100 (24.6%). In contrast, 50.0% of the grants proposed to study only one or two settings, and only 3.2% included a large number of settings. Sampling strategies at both the setting and patient level were predominantly convenience sampling (54.3%), with only 12.8% using any systematic or representative sampling methods. In terms of transparency, a minority of projects included any justification or discussion of their setting sampling methods or exclusions, and only 28.4% included discussion of limitations or alternative approaches.

Table 2. Setting, sampling issues, representativeness, and resources reporting proposed in cancer comparative effectiveness research crants

Issue and categories within topic	Percentage of grants*
Setting	
Cancer center	11.5%
Clinical	37.5%
Worksite	4.2%
School	0
Community	26.0%
Virtual	6.3%
Other	14.6%
Sampling strategies	
Convenience	54.3%
Some diversity	33.0%
Systematic/representative	12.8%
Sample size	
Of settings	50%
1 or 2	40.4%
3–7	6.4%
8–15	3.2%
Large number of settings	
Of patients	
<100	24.6%
100–499	17.6%
500–599	8.8%
600–999	8.8%
≥1000	40.4%
Missing/not specified	39 grants
Resources reporting	
Considered in design/intervention	58.9%
Report nonmonetary resources required	50.5%
Transparency issues	
Justify setting sampling and exclusions	45.3%
Justify participant sampling and exclusions	61.1%
Report on limitations	28.4%

* Percentages add up to greater than 100% in some cases because a given grant fit into more than one category.

Reflections and Discussion

Our review assessed 103 cancer control CER studies funded across a variety of cancer types, stages of the cancer care continuum, and translational phases of research. These studies should provide a wealth of information for decision makers, including clinicians and patient/families, in the near future. These studies extend well beyond a narrow definition of CER as studying only drugs and devices and have included a large number of studies on systems/organizational interventions and behavioral interventions. Many grants focused on cost and economic issues, and several proposed simulation modeling, an approach capable of producing rapid results and potentially alerting scientists and policy makers to both positive and negative interactions and unintended consequences (11,14,15).

Successful implementation of cancer prevention and care and translation of CER require partnership with and full participation of patients and families, health-care staff, and organizational decision makers, as well as community stakeholders (16–19). Hood and Friend (6) have viewed this participatory role as important in terms of creating the necessary information and information technology to deal with the exponential growth of genomic and biological data on individuals. It also sets the stage for stakeholder engagement,

equity, access, cost and coverage, and choice among alternative approaches (20,21).

Although there were many T3 and T4 studies, only a minority made efforts to ensure that their settings and samples studies were representative. When health-care resources are limited and inequitably distributed (eg, millions of people have no or inadequate health care coverage), there is an ethical obligation to assure that the national investment in research leads to tangible health benefits for all and does not worsen existing health disparities.

Recommended Types of Rapid, Flexible, Contextual CER

The need for rapid, relevant evidence that is actionable by patients and families, clinical teams, and policy makers implies that different and expanded types of research methods will be needed to accomplish the aims of cancer CER (5,8). The recent report of the PCORI Methodology Committee outlines many of the relevant issues (http://www.pcori.org/assets/Preliminary-Draft-Methodology-Report.pdf). Below, we summarize the characteristics of the types of research methods needed by this new field of "CER-T," or CER that will translate into practice and policy (8).

A key characteristic of CER is that it is practical or pragmatic (22–24) and provides information for making real-world decisions. This is why CER requires comparisons that involve real-world options rather than placebo or no treatment. Building on the work of Gierisch et al. (25), we recommend that CER investigators consider inclusion of "minimal interventions needed for change" comparison conditions, in much the same way that evaluations of new cardio-protective medications might include comparisons with aspirin. New and expensive resource-intensive interventions should be demonstrably more effective than standard care or a minimal interventions needed for change comparison before they are recommended for broad adoption (Glasgow RE, Fisher L, Strycker LA, et al, unpublished data).

Other features of pragmatic designs are that they address issues important to stakeholders and that they employ multiple outcomes relevant to these stakeholders (22,26). We encourage cancer CER grantees to address the CONSORT pragmatic trials criteria when reporting their results (23), and the related pragmatic explanatory continuum indicator survey figure (27) can help to increase transparency in reporting results and research methods. Many of these issues, especially those related to unanticipated outcomes or unintended consequences, are best addressed using mixed methods (28) or qualitative assessments (29) (http://obssr.od.nih.gov/scientific_areas/methodology/mixed_methods_research/index.aspx). Measures in a given CER study should address the issues central to that topic but should include among these outcomes both patient-centered measures and broad outcomes such as quality of life (13,30) that allow comparisons across disease and content areas. For example, in the context of genomic medicine, CER offers a variety of methods that can address stakeholders' needs and help ensure translation of genomic discoveries into population health benefits (31).

One of the greatest opportunities to make cancer research CER-T (8) is consistent, comprehensive, and transparent reporting of costs of interventions and resources required and outcomes such as cost-effectiveness and cost–benefit (32,33), especially because comparisons such as cost per quality adjusted life year are explicitly excluded from PCORI (34,35). We recommend that cancer CER research include assessments such as costs of implementing a program and replication costs. Our understanding is that PCORI is not allowed to sponsor any research to produce standard cost-effectiveness analysis results, especially in the form of incremental cost per incremental quality-adjusted life years (34,35). However, because PCORI is mandated to sponsor and carry out research on outcomes of importance to patients and on factors that influence the effectiveness of health care, topics such as health-care cost as a burden on patients and health-care cost and financial arrangements such as coinsurance and copayments can be studied because they affect access and adherence.

To be relevant and actionable, cancer CER-T studies (8) should report results in ways that are understandable and transparent to local health-care organizations, patients/families, and practitioners (Table 3). This includes standardized reporting of the levels

Table 3. Methods recommendations for comparative effectiveness research–translate that will rapidly translate and be relevant

Characteristic	Translational purpose of this feature
Pragmatic or practical*	To answer questions from patients, practitioners, and policymakers to inform real-world decision making
Comparison condition(s) are real alternatives; should include minimal interventions needed for change comparators	To address practical questions in context of currently available (and usually less expensive) alternatives
Collects costs and economic data	To provide information on resources needed to adopt and replicate in different settings
Assesses multiple outcomes using mixed methods	To provide results that recognize the different priorities of multiple audiences(eg, behavior change, quality of life/functioning, health-care use, impact on health disparities, unintended consequences)
Uses flexible and multiple research designs to fit question	To consider and address key threats to internal and external validity and to assess adaptation and evolution over time
Evaluates multilevel participation and representativeness†	To determine breadth of applicability and assess participation rate and representativeness of participants, settings, staff, and subgroups
Modeling and longitudinal evaluation methods to capture adaptation‡	To track evolution of programs, policies, and implementation, including changes over time and adjustments made

* Thorpe et al. (27).

† Keyserling et al. (63).

‡ Des Jarlais et al. (64).

of participation, engagement, and results by key population subgroups. Examples of key subgroups are those related to longstanding health inequities defined by race, ethnicity, education, income, and class and also emerging disparities issues related to factors such as age, number of comorbid conditions, health literacy and numeracy, and place (36–39). The projects reviewed generally studied only a small number of settings and did not describe their sampling methods or rationale for selecting these settings. A fuller, transparent accounting of results, including the settings, clinicians, and patients invited to participate, and comparisons between those who participate vs those who decline and are considered ineligible are needed to help determine generalizability and applicability to various settings (40–42).

Another key issue is reporting of context (43). Because most CER examines how different treatment or prevention approaches work in the real world, they are context dependent. Interventions often have different effects in different settings and patient populations and are affected by differences in the policy environment, community, health-care system, practice, research team, target audience and actual participants, and local cultural factors (20,21,44–46).

Among other tools, simulation modeling can be useful at each stage of the T0 to T4 cycle, especially in examining progression along the cycle in ways that are not possible with single or experimental studies. Systems models are well suited to the dynamic complexity and context dependence that characterize many CER questions (47–49). The use of modeling techniques also allows researchers to ask CER-T questions that better reflect the complexity of CER phenomena, considering multiple interacting diseases and risks, the interaction of delivery systems and at risk populations, and policy and environmental contexts (47,50). The use of participatory group modeling approaches may be particularly helpful in engaging the wisdom of patients and other stakeholders in patient-centered CER (51–53).

We recognize that many are concerned about the limitations of modeling and do not view either those methods or the other recommendations above as a panacea. We do think that such methods have been historically underutilized and deserve consideration as approaches that should be combined with other methodologies, including randomized trials (which are often very expensive, slow, and of limited generalizability) and natural experiments—especially those involving large numbers of representative samples. We do not think that any one method provides perfect answers but that a balance of complementary methods is needed, especially greater use of historically underutilized, less expensive, and innovative methods that produce more rapid and relevant results to produce answers to CER questions (6–9,11).

Finally, almost no experimental or quasi-experimental designs were reported in our review besides randomized controlled trials. We recommend greater emphasis on replication and the convergence of results across different research methods (54). Multimethod research approaches can be helpful when methods are carefully chosen to complement each other (29,55). This complementarity can involve designs and data approaches, sources, and transdisciplinary teams (50,56,57) that have different strengths and limitations. Research using complementary methods can be conducted sequentially or simultaneously (58,59) to triangulate understanding (60). The combined use of qualitative and quantitative methods (61,62) may be particularly helpful both in making real the "patient-centered" in patient-centered outcomes research and in providing contextual understanding in multilevel research (20).

This article provides a summary of recently funded NCI research on CER. It is limited in that it is not a comprehensive review of all cancer CER research funded or reported; several other foundations and groups also fund similar research, and it is too early to evaluate the results and impact of these investments. Also we do not have the "denominator" of all the grants that were submitted but not funded to allow us to make comparisons of the content and characteristics of funded vs unfunded grants, which would be of value. Our portfolio analysis was limited in time and scope to grants funded during the period from 2009 to 2011, which provided us a manageable number of grants for review and covers the primary "spike" in CER funding. There are likely a few grants funded before 2009 and will be many more in the future, so this is a snapshot in time, but we feel it is a useful one to identify general features of the field. Finally, one of the reviewers raised the issue of whether, in this time of fiscal austerity, it is feasible to expect grantees to address the issues recommended above given their likely increased costs. Our response is threefold: 1) such actions are needed to achieve the purpose of CER, and there are likely things now being done that could be dropped; 2) we do not expect every grant to include all of the above recommendations, but rather to think more broadly about these issues and how their reports will be used; and finally, 3) many of the recommendations do not demand added time or resources, but simply increased transparency in reporting.

Conclusion

There is an important need for CER knowledge across both the cancer control continuum and the phases of translational research. Recent cancer CER has spread across most of these dimensions. It is encouraging to see a number of different content areas and research methods being used. Greater emphasis will be needed on survivorship and diagnosis research, as well as more innovation on experimental designs.

We especially encourage cancer CER-T as summarized above and in Table 3. Even more important than multiple types of CER, we need knowledge integration across the T levels and across different experimental methods. A lot is being done at different levels, types, and stages of cancer research, but more effort is needed to integrate resulting knowledge (12). We hope that in a few years, cancer CER funding will have advanced this type of understanding also.

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Notes

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