Published in final edited form as:
Cancer. 2010 October 1; 116(19): 4440–4449. doi:10.1002/cncr.25248.

Translating Research into Evidence-Based Practice: The National Cancer Institute's Community Clinical Oncology Program

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Abstract

The recent rapid acceleration of basic science is reshaping both our clinical research system and our health care delivery system. The pace and growing volume of medical discoveries are yielding exciting new opportunities, yet we continue to face old challenges to maintain research progress and effectively translate research into practice. The National Institutes of Health and individual government programs are increasingly emphasizing research agendas involving evidence development, comparative effectiveness research among heterogeneous populations, translational research, and accelerating the translation of research into evidence-based practice, as well as building successful research networks to support these efforts. For over 25 years, the National Cancer Institute's Community Clinical Oncology Program has successfully extended research into the community and facilitated the translation of research into evidence-based practice. By describing its keys to success, this article provides practical guidance to cancer-focused provider-based research networks as well as those in other disciplines.

Clinical research and medicine have entered a time of great promise but also are faced with new challenges. The rapid acceleration of basic science, including advances in genomics and proteomics, are elucidating mechanisms of disease, yielding new methods to identify and potentially treat abnormalities, and effectively are transforming acute diseases into chronic ones. These advances signify substantial progress in our national research endeavor; however, they simultaneously are reshaping not only the entire clinical research system, but also our health care delivery system and the practice of clinical medicine. The pace and volume of medical discoveries, and evolving clinical practice and corresponding policy, require the development of new evidence in comparative effectiveness and outcomes, which have recently seen tremendous investment increases through the American Recovery and Reinvestment Act of 2009 and other substantial efforts [1-2]. As we proceed through this transformation and face new research and clinical practice demands, the question of how best to improve the translation

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of clinical research into clinical practice remains unanswered, and the substantial discovery-delivery gap remains.

The National Institutes of Health (NIH) established the NIH Roadmap Initiative to address these challenges and other needs in the scientific community [3]. Through the Roadmap, as one means of restructuring its clinical research enterprise, the NIH is exploring practice-based research networks (PBRNs), to pursue the twin goals of accelerating science and facilitating the translation of research into practice [4-6].

In terms of accelerating the science, PBRNs provide great promise in allowing access both a greater number and a more heterogenous sample of prospective research participants. Both of these elements are increasingly important to accelerating the pace of research progress, for several reasons [4-5]. First, intervention effectiveness is increasingly shown to hinge on specific genotypes expressed in limited subsets of the population. This drives a need for research population heterogeneity to assure inclusion of individuals expressing each of the relevant genotypes. Second, this fuels the need for more clinical trials to examine different agents or approaches that may be effective in treating these multiple population subgroups. Opening more trials testing more agents necessitates more people to enroll on those trials to allow their timely completion. Together with the long-held estimate that less than one percent of Americans seeking health care do so at academic medical centers (heretofore the locus of nearly all clinical trials) [7-8], filling these research needs mandates mechanisms such as PBRNs to extend into the community and access a larger more heterogenous sample of prospective research participants.

PBRNs can also facilitate the translation of research into practice by playing a central role in a critical two-way flow of information [9-10]. First, PBRNs connect academic investigators to community practitioners who contribute “upstream” information to researchers regarding study design and implementation considerations, including insight into the clinical issues and tacit practice-based knowledge that exists in community-based practice settings. Second, PBRNs can facilitate “downstream” dissemination and implementation of research results into community-based clinical practice by promoting a sense of trust and ownership among community-providers who were first-hand participants in the whole process, enhancing providers’ acceptance of research results, and strengthening their commitment to acting on research findings. This level of participation also often encourages practice organizational changes that facilitate the research, and allows access to more, or earlier, information compared with others who did not participate in the research. In this way, PBRNs contribute both evidence-based practice and practice-based evidence, and help close the discovery-delivery gap [11-12].

Despite PBRNs’ promise and substantial federal commitment to develop and support them in a wide range of disease areas[13-22], PBRNs face significant challenges with regard to implementation and sustainability [23-28]. Major challenges include (1) developing and maintaining an infrastructure of clinicians and qualified staff, (2) maintaining adequate and consistent funding for research, (3) developing collaborations with local physicians who manage PBRN functions, and (4) instituting systems of accountability and efficiency [23, 28], all of which are greatly facilitated by (5) establishing a cultural context that values research and scientifically based practice [29]. Recognizing these challenges is important; however, little practical guidance exists in the literature regarding principles for addressing them in establishing and operating effective PBRNs.

The National Cancer Institute (NCI)'s Community Clinical Oncology Program (CCOP) is a cancer-focused PBRN that, since its establishment in 1983, has grown to contribute one third of the NCI's clinical treatment trial enrollment and the overwhelming majority of its prevention

and control trial enrollment (See Figure 1). Moreover, CCOP has been integral to not only core accrual for NCI trials, but also the development of major trials such as the Breast Cancer Prevention Trial (BCPT)[30], the Study of Tamoxifen and Raloxifene (STAR) [31], and the Selenium and Vitamin E Cancer Prevention Trial (SELECT) [32], which was designed by a CCOP Research Base. In addition to providing 31% of BCPT's 13,388 participants, 33% of STAR's 19,747 participants, and 29% of SELECT's 35,534 participants (allowing SELECT to be completed well ahead of schedule), it is widely held that without the CCOP enhanced infrastructure, these studies – most notably SELECT – could not have been started let alone completed [33]. Its current performance and critical centrality to such research is the result of nearly 30 years' direct experience, continuous self-evaluation, adaptation, and learning from other NCI PBRNs and quality enhancement efforts, including the Cooperative Group Outreach Program (CGOP) and the Community Hospital Oncology Program (CHOP) [34-35]. To provide practical guidance for other new and developing PBRNs, we discuss the organizational characteristics and strategies that have contributed to its successfully addressing the challenges of implementation and sustainability, and meeting the needs of clinical research and the translation of research into evidence-based practice. We draw from three decades of evaluation of the CCOP, CGOP, and CHOP programs [24-27, 34-43], and expand upon prior other recent work [28] by discussing the current and evolving practical needs facing practice-based research.

Overview: The NCI Community Clinical Oncology Program

The NCI has established a national clinical trials infrastructure through the Cooperative Groups, which are bodies of researchers, cancer centers, and community physicians who work together to conduct trials. The CCOP is a PBRN and a component of NCI's clinical trials program, through which community physicians participate as full research members in NCI's clinical trials[44] (see Table 1). The CCOP network funds community hospitals and physicians to participate in NCI-funded clinical trials that are designed by NCI cancer centers and clinical cooperative groups (collectively called "CCOP Research Bases"), commonly in conjunction with the CCOP. The community-based networks of hospitals and physicians ("CCOP organizations" or "local CCOPs") and Research Bases are funded through peer-reviewed grants based upon their productivity in developing, conducting, and accruing to clinical trials.

CCOP has a track record of translating findings from NCI-sponsored clinical trials to community practice (see Table 2). It is the academic investigators within the Research Bases who primarily drive the science, but the CCOP physicians participate in the development of the trials and contribute substantial numbers of patients to the trials, and then translate that science into practice by modifying their subsequent practice patterns based upon the results of those trials. In this way, the CCOP program has facilitated the translation of several research-based clinical innovations into practice. For example, Epidermal Growth Factor Receptor (EGFR) inhibitors have demonstrated efficacy in patients with metastatic colorectal cancer that have failed chemotherapy[45]. The CCOP network brought a large heterogeneous population of patients to the trials, facilitating the identification of Kras, a protein in the EGFR pathway, as a predictor of prospective treatment effectiveness [46]. As a result of this study's findings, practicing oncologists and patients considering cetuximab now can prospectively ascertain the probability of treatment effectiveness and thus avoid unnecessary treatment risks, side-effects, and their associated substantial costs. In addition to participating in the study (in terms of offering the trial to his eligible patients), a CCOP investigator was a co-author in the ASCO Guidance for screening patients [47], thus exemplifying the two-way communication between research and practice in the CCOP network.

Similar to this, the CCOP network facilitated the completion of studies in the development of OncoType DX, a genotype scoring system that evaluates patients' risk of cancer recurrence. Specimens and data from previous trials were used to develop and validate OncoType DX[48]

and an ongoing NCI trial (PACCT 1) [49] will evaluate the need for chemotherapy in hormone responsive patients with OncoType DX scores that are difficult to interpret. For physicians and patients considering treatment, the findings of this study will better inform their balancing of the risk of recurrence with other considerations, and whether the prospective chemotherapy treatment benefits will justify the risks [50]. These two examples build upon the enormous success of several foundational adjuvant breast cancer trials, a few of which are presented in Table 2, and demonstrate the centrality of the CCOP program in the evolving cancer research and clinical care environment.

Keys to CCOP Success and Overcoming Challenges

In today's evolving research environment, at least four major challenges must be addressed by PBRNs in order to continue medical progress that benefits patients, providers, and society (see call-out box). Through a combination of experience, deliberation, and serendipity, the CCOP has put into place structures, policies, and practices that address these challenges and have contributed to its strong performance [28, 34-35].

Key Principle 1: Building an Infrastructure

Community-based physicians in a PBRN maintain the critical flow of patients into clinical research studies and collaborate with academically based researchers to test new ideas in the practice setting. In building a research infrastructure, physician interest is essential, but often not sufficient. Community-based physicians face demanding schedules and heavy workloads. A well-trained research staff, particularly research nurses, is critical to the successful integration of clinical research into community oncologists' practice [27, 42].

Research nurses help facilitate and integrate clinical research into physicians' daily activities and ensure that research-related activities offer minimal disruption to clinical practice and care. Research nurses screen charts and flag them for patients eligible for trials, help physicians communicate with patients about clinical research opportunities, and provide assistance with other trial related activities. Physicians and nurses in CCOP trials form a critical mass of health care providers who are comfortable with implementing and delivering the new treatment and care strategies that arise from these trials [42].

In order to maintain high quality research, mechanisms for ongoing training and education for all staff need to be in place. The CCOP research bases provide training and educational opportunities twice a year for all affiliated academic and community-based physicians and research staff. At a local level, CCOP organizations also provide affiliated physicians, research nurses, and staff members with education and training sessions at which nationally known speakers present the latest clinical and research developments. Training includes information about protocol design for specific studies, as well as trial-related skills such as procedures for enrolling participants, collecting and submitting trial data, and reporting adverse events [27]. Education and training activities vary across CCOP organizations depending on how they choose to staff their operations [27, 42]. Education includes continuing medical education sessions for scientific discussions specific to the ongoing clinical trials. Several research bases also offer mentoring programs for newer investigators and certification exams for the Society of Clinical Research Associates. Training by the Research Bases and at the local CCOPs provides an unprecedented opportunity to educate clinicians who might not otherwise be exposed to clinical research, and such exposure also encourages uptake of new treatment modalities.

Key Principle 2: Funding to empower local physicians

Maintaining adequate and consistent funding for research is a persistent challenge in a research enterprise. PBRNs must direct funds to community-based physicians who deliver care and provide accrual for clinical trials. Although academic centers play a large role in a clinical trials program, the CCOP program uses peer-reviewed cooperative agreements to award grant funding directly to local networks of physicians and hospitals, rather than passing the money through academic medical centers or intermediaries, thus contributing a great degree of local flexibility to ensure the money is used to meet each site's specific needs. Providing grants directly to the sites allows the local organizations to plan for multiple years of funding (for stability), permits sites to plan and allocate staff, office infrastructure, and other resources according to the research needs, and brings recognition of NIH funding to a community site. At the same time as the cooperative agreements allow each CCOP flexibility, they also permit substantial NCI management and oversight and provide a framework for regular performance monitoring and financial reporting.

The stability and flexibility conveyed through direct funding is augmented by the CCOP organizations affiliating with multiple research bases for a broad menu of trials that matches the research interests of the organization and the population it serves. CCOP productivity is measured by enrollment of patients to those trials in conjunction with data quality, and typically CCOP will have over one hundred open trials. Budgetary flexibility allows each CCOP organization to manage its staff, time, and other resources to best support the trials it has selected to open, ensuring its ability to meet its accrual goals and otherwise be successful. As an example of how the funding structure empowers decision-making by local communities, the physicians and community served by the Upstate Carolina CCOP (South Carolina) expressed strong interest in the NCI-sponsored prostate cancer clinical trial, the Selenium and Vitamin E Cancer Prevention Trial (SELECT) [51]. Accordingly, they re-allocated a large proportion of their resources and staffing to support enrolling patients in this trial, resulting in remarkably high accrual.

Each CCOP organization's funding is based upon accrual to all trials it has open, rather than any one specific trial, and these accrual targets are set annually based on the availability of trials and historical trends in the CCOP organization's patient accrual. Figure 2 illustrates the funding of the CCOP program and average per-CCOP funding, and underscores the importance of ensuring a relatively consistent, predictable level of funding from one year to the next to enable CCOP organizations to maintain staffing and operations as trials open and close. Despite significant ebbs and flows in levels of federal funding for clinical research and myriad changes in the financing, structure, and delivery of health care [24], the cooperative agreement mechanism helps ensure the viability of this system.

Key Principle 3: Collaboration strengthens research and practice

PBRNs help bridge the gap between academic research and community practice through clinical research that addresses an identified need and will produce usable results. For a two-way communication system between academic research and community practice to be effective, clinicians must understand the importance of the research, and the research must be responsive to the needs of the clinicians.

The CCOP structure provides many opportunities for interaction between clinicians and academic researchers. CCOP research bases hold regular conferences during which academically based researchers and CCOP-affiliated physicians and research staff meet in scientific committees, attend plenary sessions, and participate in training sessions. These conferences provide a forum for learning about clinical research science, planned or ongoing trials, and clinical trial management. Community physicians acquire a greater understanding

of the scientific relevance of particular questions and why certain protocol features may be important for scientific rigor, while simultaneously providing input to the academic researchers, who learn how to design trials that are clinically relevant, feasible in community settings, and reflect the needs of the community itself. For example, minority physicians and those serving minority men were persistent in communicating that African American men were developing prostate cancer earlier than age 55, at the time a common age eligibility criterion for many trials. By lowering the age eligibility criteria for African American men to 50, the recruitment of these men was substantially enhanced [33]. The end result of incorporating input from community physicians is the ability to design scientifically rigorous trials that are feasible to perform in the community, and also more likely to result in uptake into practice as participating physicians have a venue in which to become familiar with the drugs and procedures tested during the trial, observe their benefits for patients, and develop ways to mitigate possible adverse effects.

Key Principle 4: Flexibility in operations of organizations

Individual CCOPs have flexibility regarding their structure and operating procedures, which builds on the stability provided by predictable direct funding and the flexibility provided by selecting which clinical trials to open from a large menu of options. This approach optimizes the skills and interests of local clinicians as they work within the constraints of provider organizations and patient populations. CCOP performance guidelines require that organizations meet overall accrual targets, implement protection for human subjects, and maintain standards for data quality set by their affiliated research bases; however, addressing the reality that these provider organizations and populations vary widely in their characteristics, priorities, and norms, CCOPs have wide latitude in how they do so. There are no requirements regarding a specific organizational structure or size, number of open trials, or even accrual targets for individual trials; rather, CCOPs largely self-design a system that works for them. NCI program staff review each organization annually for overall performance and provide technical assistance as needed, CCOP research bases periodically review each CCOP's data to assure that it is meeting its quality standards, and each CCOP is peer reviewed every 3-5 years when grants are openly competed.

This flexibility in strategies for meeting performance standards provides CCOP organizations with considerable discretion in how they manage their operations. As demonstrated in the case of the Upstate Carolina CCOP, CCOP organizations participate only in those trials that suit the structure, function, needs, and interests of the affiliated providers and provider organizations. Some CCOP organizations operate in a centralized manner from a single office, while others utilize a more decentralized model with an administrative core that coordinates research nurses individually employed by different participating physician practices. CCOP organizations may also participate in non-health care settings, such as health information booths at grocery store entrances or civic events, to distribute information and enroll participants in cancer prevention trials. Many CCOP organizations employ outreach workers to increase trial access for minority populations. These workers staff information booths at minority-focused health events, make presentations in minority churches, and engage in “academic detailing” in community-based organizations serving minority populations [27].

The CCOP program's flexibility is exemplified through the Minority Based CCOP (MBCCOP) program, which evolved out of the recognition that, historically, most cancer care for minorities has been at academic institutions. As such, academic centers were subsequently allowed to be part of the MBCCOP program, in addition to the traditional community-based programs. These sites serve as excellent venues for examining how well new agents, complex trial designs or new technologies can be disseminated and implemented (or not) in special populations. These sites typically have outreach services that inform the MBCCOP of referring physicians’ level

of acceptance for a specific clinical/scientific advancement. Despite being comprised of only 13 local MBCCOP sites (compared to the other 47 CCOPs), the MBCCOP program allows the inclusion of a substantial population of racial and ethnic minorities in studies, as demonstrated in Figure 3, and facilitates their access to practice-based evidence and evidence-based practice.

Discussion

Historically, implementation and dissemination of new health care innovations have been slow. For example, although it was known as early as 1601 that providing citrus to sailors would prevent scurvy, not until 1795 did the British Navy order that citrus fruits be included as part of the rations on all navy ships [52]. More recently, a study of physician awareness and use of the latest hypertension prevention, diagnosis, and treatment guidelines from NIH reported that fewer than half of physicians followed guidelines for use of the latest prevention, diagnostic, and treatment guidelines regarding hypertension, and 40% were not even aware of them [53]. This, despite data showing that more than half of the 50 million Americans with high blood pressure are not being treated to goal even though their physicians understand that high blood pressure is the most preventable cause of heart attack and stroke [54]. There are similar examples of lack of translation in almost all fields of medicine.

The CCOP network is an example of how PBRNs can be mechanisms to effectively address the challenges facing clinical research and practice, continue medical progress that benefits patients, providers, and society, and more effectively translate research into practice. Organizational and funding flexibility together with meaningful, yet adaptable, performance standards allow CCOPs to vary in terms of size, location, provider composition, and the types of trials in which each site chooses to participate. These principles have enabled it to be a vehicle for both including community oncologists as full partners in NCI's clinical trials network and giving them a mechanism to both learn and use state-of-the-art treatments in the context of national standards. In an environment of ever-changing local, state, and federal regulatory burdens that often unintentionally constrict the health care and clinical research, CCOPs' firmly established internal processes enable the consistent and appropriate provision of resources for sites to meet those requirements. These processes also allow for the identification and engagement of competent and knowledgeable young investigators and various support personnel for research careers within this PBRN framework.

Challenges will always face the development and sustainability of CCOPs and other PBRNs, and for their continual adaptation. For example, recent advances in technology and clinical research have resulted in the development of new drugs and methods of treatment that can be increasingly complicated to use, let alone systematically implement as a part of a high quality new standard of care in community practice. Accordingly, special attention needs to be given to providing incentives to bring young clinician-investigators and research nurses into the PBRN arena with their expertise in emerging technologies and practice skills. PBRNs can provide a structured forum to observe and first utilize health care innovations, thus facilitating their initial adoption and their subsequent systematic incorporation into practice.

Looking forward, even the CCOP network will find value in revisiting these principles in the context of its continual evolution and adaptation to the changing landscape of cancer research. Just as clinical cancer care is moving toward individualized therapies and personalized medicine, so too is cancer clinical research. Clinical science is advancing to where antecedent knowledge of individual biological variation is a factor driving not only outcomes, but also treatment selection and even randomization within studies. CCOP practices will have to adapt to these and other changes in order to continue to stay ahead of the curve in research. As the CCOP Program seeks to continue to be on the vanguard of state-of-the-art translational science,

and charts its future course following its recent program evaluation [55], it will benefit from revisiting these guiding principles and grounding itself in them to help it successfully do so.

The CCOP structure has provided a framework for involving community patients and practitioners in clinical research while simultaneously expediting the translation of clinical research results into practice. With ever-growing emphasis on efficiency and, more recently, new pressure to assess differential treatment effectiveness in the broader population, PBRNs in other disease areas may find the CCOP experience useful for developing links between community-based service delivery organizations and academic centers. This is critical for meeting the challenge of translating research into practice.

Condensed Abstract

The National Institutes of Health and other programs are increasingly emphasizing research involving evidence development, comparative effectiveness, translational research, and accelerating the translation of research into evidence-based practice, as well as building successful research networks to support these efforts. This manuscript describes the National Cancer Institute's Community Clinical Oncology Program and its history of successfully extending research into the community and facilitating the translation of research into practice, and provides practical guidance to provider-based research networks in cancer and other disciplines.

(Call out box.)

CCOP Principles for successfully addressing the major challenges facing PBRNs
• Develop and Maintain Infrastructure of Clinicians and Qualified Staff
• Maintain Adequate and Consistent Funding for Research
• Facilitate Collaborations Between Academic and Community Physicians
• Flexible Systems of Accountability and Efficiency

Acknowledgments

We would like to thank Dr Victor Vogel and the peer reviewers for their thoughtful comments as well as acknowledge the support of our DCP colleagues Ms. Lindy Wong, and Drs Leslie Ford and Peter Greenwald.

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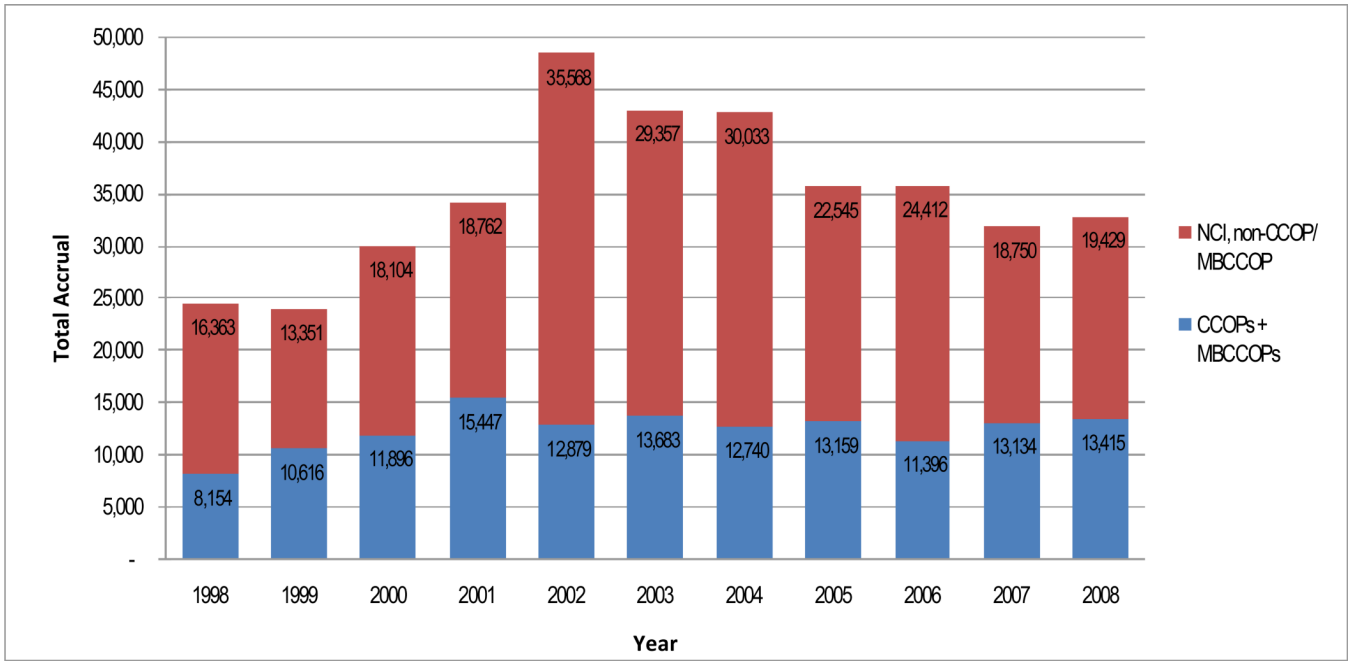


Figure 1.
NCI Trial Accrual 1998-2008: CCOP program vs. all other NCI accrual, 1991-2008.

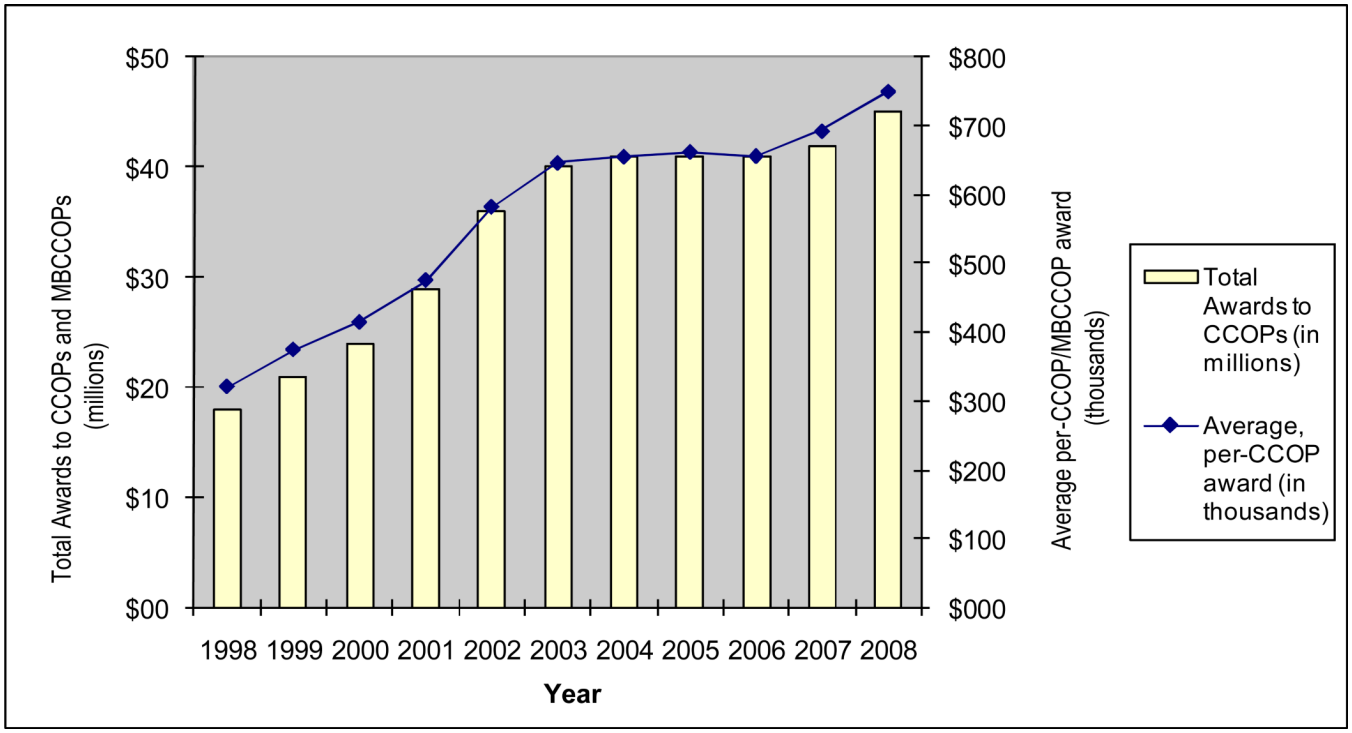
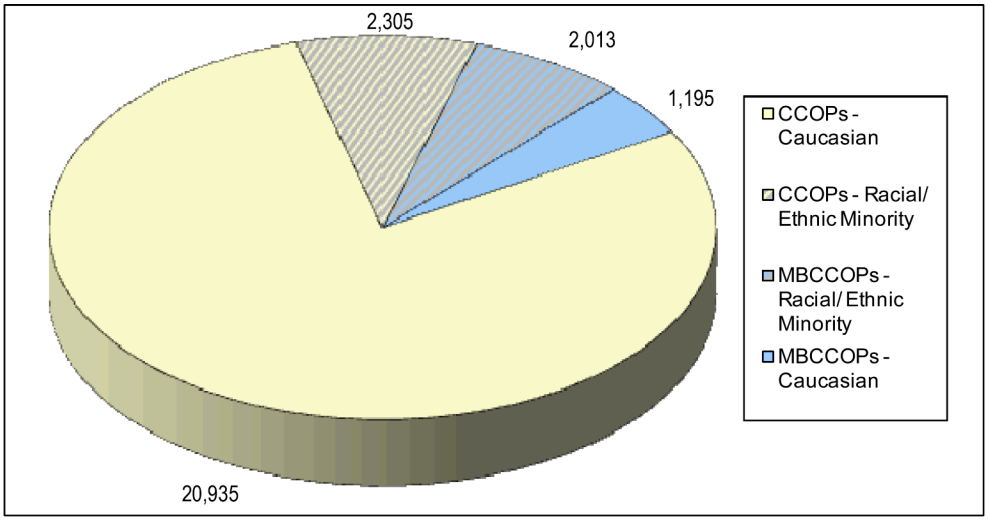


Figure 2.
CCOP Program funding and average per-CCOP funding, 1998-2008.



Note: MBCCOPs include 13 local MBCCOP sites; the CCOOPs include 47 local CCOP sites. Data represent treatment and cancer control accrual.

Figure 3.
2007-2008 CCOP and MBCCOP accrual: Caucasians and Racial/Ethnic Minorities

Table 1

Overview, the NCI Community Clinical Oncology Program

The NCI Community Clinical Oncology Program
• Established in 1983
• Program Funds through Cooperative Agreements (peer reviewed grants)
– Selected *cancer centers and clinical cooperative groups* (“CCOP research bases”) to design, develop and manage clinical trials; and
– *Community hospitals and physicians in local networks* (“CCOP organizations”) to enroll patients onto cancer trials and disseminate study findings in the community setting.
• Includes 47 CCOP organizations and 13 Minority-Based CCOP (MBCCOP) organizations located in 34 states, the District of Columbia, and Puerto Rico **in 2009** [55].
• 60 CCOPs comprise 415 hospitals and nearly 3,440 community physicians **in 2009** [55].
Outcomes
• Currently contributes 1/3 of all enrollment to NCI trials, including 21% minorities [41, 55]
• CCOP trials contribute to evidence-based national standards for cancer care
• CCOP-affiliated physicians participate in the development of clinical trials [25, 27].
• Disseminate national standards to community-based practices

Table 2

Translating Bench to Bedside: Examples of Translation Facilitated by the Community Clinical Oncology Program

Scientific Concept	Clinical Tests and Interventions	Study, and Clinical Impact	CCOP Contribution to Study Accrual
Avoiding ineffective treatment: Kras and Epidermal Growth Factor Receptor (EGFR) Inhibitors	Kras testing to guide introduction of chemotherapy [46]	– CALGB C80405 – Only patients with a wild type Kras benefit from EGFR inhibitors, e.g., cetuximab – Patients who will not benefit from cetuximab can be identified prior to treatment and avoid risks, toxic side-effects, and substantial costs of this chemo.	– 574 (38%)*
Personalized Medicine: OncoType DX	OncoType DX Test to evaluate risk of breast cancer recurrence[56]	– PACCT-1 (TAILORx) – Informing treatment choice: Patients with low risk score are unlikely to have recurrence and may opt to forgo chemotherapy that may yield minimal if any benefit	– 1,718 (25%)*
Breast Cancer Receptor/ Estrogen Receptor	Tamoxifen[57-58]	– NSABP-B-04 – NSABP-B-14 – Improvement in Overall Survival for Early and Late Stage Breast Cancer – Reduction in Recurrence of Early Stage Breast Cancer	– Data not available
Breast Cancer Receptor/ HER-2 Receptor Antibody	Trastuzumab (Herceptin) [59_62]	– NSABP-B-31; – NCCTG-N9831 – Improvement in Survival – Reduction in Recurrence of Early Stage Breast Cancer	– 850 (40%) – 743 (21%)
Preventing the Development of Breast Cancer	Tamoxifen [30] Raloxifene [31]	– BCPT – STAR – Reduction in the Risk of Developing Breast Cancer	– 4,038 (30%) – 6,580 (33%)

*Approximated or estimated contribution based on data to-date; trials are ongoing or data are being finalized.