National Cancer Institute

COMMUNITY CLINICAL ONCOLOGY PROGRAM & MINORITY BASED-COMMUNITY CLINICAL ONCOLOGY PROGRAM

ACCOMPLISHMENTS IN CANCER CLINICAL TRIALS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

DEDICATION

This report is dedicated to:

The patients who take part in National Cancer Institute clinical trials

The physicians, nurses, and staff of Community Clinical Oncology Programs and Minority-Based Community Clinical Oncology Programs

The investigators of the CCOP Research Bases

Without their commitment, time, energy, and support, the CCOP Program could not exist.

Ben Klassen, a CCOP patient at the Florida Pediatric CCOP, with his physician, Dr. Emad Salman, in 2003 and 2010. Ben was successfully treated for a childhood cancer in an NCI clinical trial through his local CCOP.

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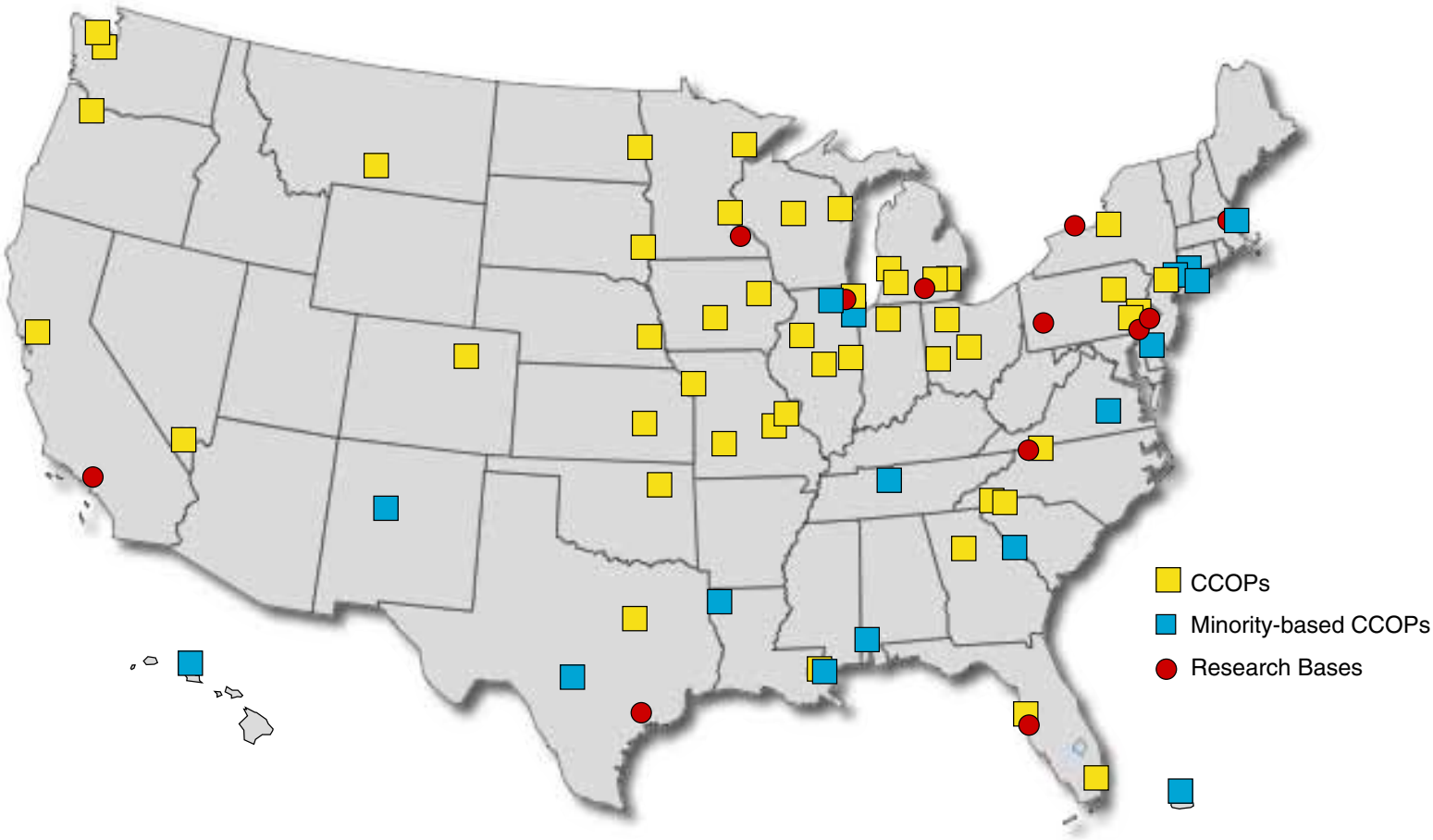
Figure 1: Locations of CCOPs, MB-CCOPs, and Research Bases



OVERVIEW

The Community Clinical Oncology Program (CCOP) was designed 27 years ago to engage community physicians in the National Cancer Institute (NCI) clinical trials programs and thereby facilitate the incorporation of research results into practice. The program was envisioned as a network that would participate in cancer treatment clinical trials and lead the way for innovative cancer prevention and control strategies. The Minority-Based Community Clinical Oncology Program (MB-CCOP) was developed as a means to provide the infrastructure for clinical trials in those institutions which serve communities with large minority and underserved populations.

These two programs have demonstrated substantial success in developing local clinical research infrastructures: accruing significant numbers of cancer patients onto cancer treatment clinical trials and implementing several very large-scale cancer prevention clinical trials. Through the Research Bases (competitively funded Cooperative Groups and Cancer Centers), CCOP and MB-CCOP physicians in practice partner with academic investigators working out of NCI-designated Cancer Centers and Cooperative Groups to test and validate the latest interventions against cancer. These community physicians provide real-world implementation of the trials and subsequently, the successful regimens are rapidly integrated into their practice of medicine.[1] The MB-CCOP program is now almost 20 years old and provides the highest concentration of minority participants accrued onto NCI-sponsored clinical trials.[2]

The CCOP network has three components, each of which competes for peer-reviewed funding through a Request for Applications (RFA).[3] (See page 26 for a listing of currently funded groups.)

1. **A Community Clinical Oncology Program (CCOP)** site is a single community organization or a consortium of community hospitals and private practices spanning one or several states (as shown in Figure 1). These sites enroll patients onto NCI-approved cancer prevention and control clinical trials as well as cancer treatment trials. Each CCOP affiliates with several Research Bases to have access to a choice of studies. CCOPs are required to accrue more than 100 participants per year. In total, the 47 currently funded CCOPs represent 340 hospitals and 2,900 physicians. Twenty-five CCOPs have been continuously funded since 1983.

2. **A Minority-Based Community Clinical Oncology Program (MB-CCOP)** site meets the same requirements as the CCOPs, but must also have a population that is at least 40% minority or underserved. Academic institutions are permitted to be MB-CCOPs. The 16 currently funded MB-CCOPs comprise 55 hospitals and 475 physicians, including 100 minority investigators. Five MB-CCOPs have been continuously funded since 1991.

3. **A CCOP Research Base (RB)** is a Cooperative Group or NCI-designated Cancer Center that designs, develops, and conducts cancer prevention and control clinical trials. Cooperative Group CCOP Research Bases also provide cancer treatment clinical trials. Eight Cooperative Groups and four Cancer Centers are currently funded as CCOP Research Bases.

More than 235,000 people have enrolled in NCI prevention, control, supportive care, and treatment trials through the CCOP network since its inception. In 2009, the network enrolled 12,014 people in NCI clinical trials. Community oncologists are essential to involving both the high-risk participants needed for prevention trials and the patients and survivors needed for treatment, control, and supportive care trials. Table 1 demonstrates the large number of people who participate in trials via the CCOPs. The CCOPs and MB-CCOPs customarily accrue one-third of the patients on all NCI Cooperative Group phase III treatment trials.

Through the CCOP Research Base grants, the Cooperative Groups and Cancer Centers receive funding to expand their research focus to include trials in cancer prevention and control. Cancer control in this program includes symptom management, treatment toxicity reduction, supportive and palliative care, and quality of life, thus extending the NCI clinical trials across the cancer care continuum.

Table 1: CCOP Network Accruals to NCI Clinical Trials, 2000-2009

TYPE OF TRIAL	NUMBER OF TRIALS	PATIENT ACCRUAL AT CCOP AND MB-CCOP SITES
Treatment	1,291	66,758
Cancer Control/ Symptom Management	167	47,565
Prevention	31	15,585
TOTAL	**1,489**	**129,908**

MODEL FOR TRANSLATIONAL RESEARCH IN THE COMMUNITY

Significant strides have been made in the understanding of the human genome. In some cases, the knowledge of genetic-driven mechanisms of disease has led to successful treatment interventions, such as trastuzumab for breast cancer and imatinib for chronic myelogenous leukemia. However, the full impact of genomic medicine has yet to be realized. Clinical studies and trials are needed to identify and validate genomic signatures for tumor response, risk for cancer recurrence and early detection, and to identify host markers for adverse effects and targets for cancer prevention in high-risk individuals. CCOPs have demonstrated their ability to enroll large and varied populations, obtain tumor and host DNA, and record the outcomes following standardized interventions. This creates a wealth of searchable, clinically annotated data that will provide the foundation necessary to build personalized cancer therapies. The CCOP mechanism facilitates the active collaboration between academic investigators and community oncologists, allowing them to take basic science findings and translate them into clinically relevant questions, subsequently adopting the successful research results into medical practice.

The CCOP network has a history of successful dissemination of research results into community medical practice.[4-6] The academic investigators within the CCOP Research Bases bring the science forward through the development of the clinical trials. The community physicians provide additional clinical input regarding the incorporation of the science into practice as they implement the studies in their practices. When the trials report successful results, the community investigators rapidly adopt the findings, which benefits the subsequent patients who are treated.

Examples of translations aided by the CCOP network appear in Table 2 on page 6. The CCOPs and MB-CCOPs accrued between 23% and 40% of patients to these trials. One example of the spectrum of translation is the Oncotype DX® genotype scoring system. CCOPs and MB-CCOPs accrued patients to trials from which specimens were collected that led to the development of the genotyping scoring system. Clinical validation of that scoring system is the focus of an ongoing trial.

Table 2: Examples of Translations Facilitated by the CCOPs and MB-CCOPs

SCIENTIFIC CONCEPT	CLINICAL TESTS, INTERVENTIONS	STUDY	PERCENT OF PARTICIPANTS FROM CCOPS AND MB-CCOPS	CLINICAL IMPACT
Avoiding ineffective treatment: *K-Ras* and EGFR inhibitors	*K-Ras* testing to guide introduction of chemotherapy	Study: Phase III Trial of Irinotecan/ 5-FU/Leucovorin or Oxaliplatin/ 5-FU/Leucovorin with Bevacizumab, or Cetuximab (C225), or with the Combination of Bevacizumab and Cetuximab for Patients with Untreated Metastatic Adenocarcinoma of Colon, Rectum (Karapetis, et al. *N Engl J Med*, 2008[7])	34% of patients from CCOPs and MB-CCOPs	Only patients with a wild type *K-Ras* mutation benefit from EGFR inhibitors (cetuximab). Patients who will not benefit from cetuximab can be identified prior to treatment, and avoid treatments risks, side effects, and costs.
Personalized medicine: Oncotype DX®	Oncotype DX® test to evaluate risk of breast cancer recurrence	Study: Program for the Assessment of Clinical Cancer Tests (PACCT-1): Trial Assigning Individualized Options for Treatment, the TAILORx Trial (Zujewski , et al. *Future Oncol*. 2008[8])	23% of patients from CCOPs and MB-CCOPs	Treatment choice is better informed: patients with a low risk score who are unlikely to have a recurrence can opt to forgo chemotherapy that may yield minimal, if any, benefit.
Breast cancer: HER2 receptor antibody	Trastuzumab (Herceptin)	Study: Randomized Trial Comparing the Safety and Efficacy of Adriamycin and Cyclophosphamide Followed by Taxol to that of Adriamycin and Cyclophosphamide Followed by Taxol Plus Herceptin in Node-Positive Breast Cancer Patients Who Have Tumors that Overexpress HER2 (Romond, et al. *N Engl J Med*, 2005[9])	40% of patients from CCOP and MB-CCOPs	Improvement in survival and reduction in early stage breast cancer recurrence was seen.
Preventing development of breast cancer	Tamoxifen Raloxifene	Study: Study of Tamoxifen and Raloxifene (STAR) for the Prevention of Breast Cancer (Vogel, et al. *JAMA*, 2006[10])	33% of participants from CCOPs and MB-CCOPs	Reduction in the risk of developing breast cancer was demonstrated.
Reducing surgical morbidity	Sentinel node dissection vs. axillary node dissection	Study: NSABP B-32, A Randomized Phase III Clinical Trial to Compare Sentinel Node Resection (SNR) to Conventional Auxiliary Dissection (AD) in Clinically Node-Negative Breast Cancer Patients (Krag, et al. *J Clin Oncol*, 2010[11])	30% of participants from CCOPs and MB-CCOPs	Reduction of lymphedema and other surgical adverse effects was demonstrated.

The CCOP network has also been used as a model for other institutes at the National Institutes of Health (NIH). In 1998, the Institute of Medicine recommended that the National Institute on Drug Abuse (NIDA) and the Center for Substance Abuse Treatment use the CCOP model to develop their community-based trials program of drug and alcohol treatments, the NIDA Clinical Trials Network.

ADDRESSING HEALTH DISPARITIES

The MB-CCOP was established to increase access to cancer clinical trials among racial and ethnic minorities. It evolved from the recognition that most cancer care for minorities took place in the clinics of academic institutions. MB-CCOPs have since been integral to the study and understanding of how new agents, trial designs, and technologies are disseminated and implemented in both minority and special populations. The program's scope of work contributes directly to NCI's efforts to reduce and eliminate the unequal burden of cancer across society.

Table 3: Cumulative Overall and Minority Patient CCOP and MB-CCOP Accrual, 2000-2009

NETWORK COMPONENT	TREATMENT	PREVENTION & CONTROL	OVERALL	MINORITY PATIENTS (#)	MINORITY OVERALL (%)
MB-CCOPs Accrual	6,772	5,769	12,541	8,039	64%
CCOPs Accrual	59,761	57,461	117,222	10,859	9%

The challenges of recruiting minority patients are shared across the entire network. The 60 CCOPs accrue significant numbers of minority patients, but the MB-CCOPs have the highest concentration of minority participants as shown in Table 3. Because the MB-CCOPs provide cancer care in catchments composed of patient populations that are at least 40% minority, much of their focus is on building the outreach and management capacity of the respective institutions. Many of the MB-CCOP institutions are on the front line in confronting the overall health care and cancer care challenges posed by the rapid changes in demographics throughout the United States.

The 1993 NIH Revitalization Act (P.L. 103-43) cites subgroup analyses as a key method of generating hypotheses from clinical trial enrollment of minorities. Accordingly, the Research Bases have successfully reached out to the MB-CCOPs to enhance cohort diversity when designing prevention and control trials. In one trial, the statistical design was overpowered to include 50% enrollment of Hispanics as a means to collect much-needed data on treatment-related stress and its management among patients receiving chemotherapy. All of the trial-related written materials were translated into Spanish, and the quality-of-life tools were validated within a Hispanic population.[13] In another instance, a single institution conducted a study to evaluate the effect of socioeconomic status on breast cancer incidence and the value of *p53* as a prognostic marker among African-American breast cancer patients.[14]

The 2005 published evaluation of the MB-CCOP program stated that between fiscal years 1995 and 2003, minorities comprised 51% to 67% of patients enrolled by the MB-CCOPs to Cooperative Group treatment trials, compared with less than 23% of the patients accrued by other Cooperative Group members and affiliates.[2] Table 4, on page 8, shows the updated information confirming the consistently high level of minority accrual from the MB-CCOPs. Typically, MB-CCOP accrual reflects the demographics of the area in which they are based.

Table 4: Minority Accrual at MB-CCOP Sites, by Year and by Trial Type

FISCAL YEAR	NUMBER OF SITES	TREATMENT ACCRUAL	PREVENTION & CONTROL ACCRUAL	OVERALL ACCRUAL	MINORITY PATIENTS	OVERALL MINORITY
2000	8	425	358	783	427	55 %
2001	10	642	541	1,183	672	57%
2002	11	567	682	1,249	949	76 %
2003	11	521	930	1,451	1,249	86 %
2004	13	673	467	1,140	718	63 %
2005	13	709	428	1,137	569	50 %
2006	13	684	393	1,077	612	57 %
2007	14	805	776	1,581	962	61 %
2008	13	895	733	1,628	1,051	65 %
2009	14	851	461	1,312	830	63 %
Total		**6,772**	**5,769**	**12,541**	**8,039**	**64 %**

MB-CCOPs include minority populations in clinical trials, but also nurture minority researchers.

The NCI Board of Scientific Advisors noted in 2007 that NCI should consider using the MB-CCOP model for other programs that need greater accrual of minority participants.[15] The MB-CCOP provides an invaluable resource to study accrual of underserved populations. During the recent ASCO/NCI Clinical Trials Accrual Symposium: Science & Solutions, sessions on the science of minority and underserved accrual and recruitment planning were chaired by MB-CCOP investigators. One principal investigator presented the experience of enrolling high-risk individuals onto prevention trials,[16] one of four plenary abstracts selected for presentation. Other MB-CCOP investigators have published their experience with co-morbidity as a barrier to accrual among patients who are interested in participating in trials.[17]

MB-CCOP grantees are active in mentoring primary care physicians in institutions geared toward the underserved in order to provide knowledge and increase the workforce for implementing clinical trials in this population. Both of these factors are important in addressing cancer care disparities. Also, community-level safety net institutions that advocate locally for health care can share experiences providing cancer care to immigrants. The MB-CCOPs additionally have the potential to inform clinicians and researchers on the cultural impact of younger minorities and underserved populations residing in communities for whom future cancer care and prevention will be of utmost importance.

CANCER PREVENTION

The CCOP network initiated four large-scale phase III chemoprevention trials over a 15-year period which established the proof-of-principle that an agent can reduce a person's risk for developing cancer. In total, 87,560 participants were enrolled in these landmark prevention studies. Two of the trials resulted in Food and Drug Administration (FDA) drug approvals for tamoxifen and raloxifene for use in breast cancer risk reduction.[10, 18] A third agent, finasteride for use in prostate cancer risk reduction, is under consideration. Three of the four large-scale clinical trials detailed in Table 5 demonstrated the proof-of-principle that an intervention can reduce the risk of developing a cancer. [10, 18, 19]

In order to answer important translational as well as clinical questions, collections of blood and tissue have been established along with the demographic data (including diet and medication information), and clinically annotated outcome information (including adverse events and incidence of multiple cancers). The tissue linked to the outcome data permit multiple translational studies to further characterize cancer risk and potentially validate markers for early detection. The samples collected in conjunction with prevention trials are available to other researchers through the originating Cooperative Group. With better characterization of risk, populations for future studies will become more focused and fewer large-scale trials will need to be conducted.

Table 5: Summary of Results of Large-Scale Prevention Trials

CANCER SITE	INTERVENTION	STUDY AND SIZE	RESULTS
Breast	Tamoxifen vs. Placebo in women at increased risk of breast cancer	Breast Cancer Prevention Trial (BCPT) 13,388 women (Fisher, et al. *J Natl Cancer Inst*, 2005[20] , 1998[18])	Women taking tamoxifen had 49% fewer diagnoses of invasive and noninvasive breast cancers. Women on tamoxifen had increased risk of blood clots and uterine cancers; most side effects are temporary. Tamoxifen approved by FDA in 1998 for reduction of breast cancer risk in women at increased risk.
Prostate	Finasteride vs. Placebo with serial PSA screening and end-of-study biopsy	Prostate Cancer Prevention Trial (PCPT) 18,882 men (Thompson, et al. *N Engl J Med*, 2003[19])	Men taking finasteride had 25% fewer prostate cancers, but seemed to have a slightly higher incidence of aggressive tumors. Further pathological analysis and data have shown that reduced prostate size contributes to finding more high-grade tumors.
Breast	Tamoxifen vs. Raloxifene in postmenopausal women at increased risk of breast cancer	Study of Tamoxifen and Raloxifene (STAR) 19,747 women (Vogel, et al. *Cancer Prev Res*, 2010[21]; Vogel, et al. *JAMA*, 2006[10])	Raloxifene found equivalent to tamoxifen for reducing risk of invasive breast cancer with reduced risk of blood clots and uterine cancers; extended followup also showed raloxifene was able to reduce risk of noninvasive breast cancer. Raloxifene approved by FDA in 2007 for reduction of breast cancer risk in postmenopausal women at increased risk.
Prostate	Selenium vs. Vitamin E vs. both vs. placebos in men age 50 and older	Selenium and Vitamin E Cancer Prevention Trial (SELECT) 35,543 men (Lippman, et al. *JAMA*, 2009[22])	Neither selenium nor Vitamin E separately or together prevented the development of prostate cancer.

STUDY OF TAMOXIFEN AND RALOXIFENE (STAR) AND BREAST CANCER PREVENTION TRIAL (BCPT)

The STAR and BCPT biorepositories continue to enhance the understanding of breast cancer development through studies that further characterize breast cancer risk, including the role of selective estrogen-receptor modulator (SERM) use and time to diagnosis of estrogen-receptor negative breast cancer,[23] and the projection of individualized risk of breast cancer for African-American women.[24]

The NSABP serum and lymphocyte bank has specimens on more than 90% of the 33,000 women in these trials, and tumor blocks on the majority of the breast cancers that have occurred. Being able to link this resource with the clinical data has already allowed studies on the effect of hormones and SERMs on cognition and memory,[25,26] the effect of tamoxifen on specific gene mutations that increase risk of thromboembolic events,[27] and the effect of SERMs on breast cancer risk of those women with *BRCA1/BRCA2* mutations.[28]

The data is also being used in: a Genome-Wide Association Study looking at nearly 600,000 single nucleotide polymorphisms (SNPs) for each breast cancer and matched controls from postmenopausal women in the first breast cancer prevention trials (P-1 and P-2) to determine their relationship to invasive and non-invasive breast cancers; an analysis of the SNP CYP2D6, which affects tamoxifen metabolism to change the drug to its active form, to determine if it has an effect on prevention; an exploration of mammogram density as a risk factor for breast cancer, so that the measure may augment the Gail model risk score to better define breast cancer risk; and a study of sera from BCPT to look at Vitamin D, insulin, and related markers as breast cancer risk factors.

The participant advisory board for STAR.

PROSTATE CANCER PREVENTION TRIAL (PCPT)

The PCPT biorepository and extended data was used to further explore the initial suggestion that some men taking finasteride were at risk of developing high-grade prostate cancers, and to look at the value of prostate-specific antigen (PSA) for early detection. Researchers showed that: finasteride improves the biopsy detection of prostate cancers (by reducing gland volume) and increases the sensitivity of PSA for detecting prostate cancer, in general, and high-grade cancer, in particular;[29 - 31] men taking finasteride may not have increased risk of high-grade prostate cancer;[32 - 34] finasteride prevents cancer for which treatment would be recommended;[35,36] finasteride decreases risk of high-grade prostatic intraepithelial neoplasia (PIN), which may be a precursor to prostate cancer;[37,38] and prostate cancer, including high-grade cancer, can be present even when PSA levels are 4.0 ng/ml or less.[39]

An extensive investigator-initiated program project grant includes studies to evaluate androgen metabolism; diet and diet-related factors; insulin-like growth factor axis and insulin resistance; genotypic and phenotypic studies of inflammation; and oxidative damage and DNA repair.

SELENIUM AND VITAMIN E CANCER PREVENTION TRIAL (SELECT)

As the largest prostate cancer prevention trial ever undertaken, the Selenium and Vitamin E Cancer Prevention Trial, or SELECT, has assembled a substantial biorepository of specimens. To help make SELECT resources available to a wider research community, NCI and the Southwest Oncology Group are developing a plan for prostate cancer biology and nutritional science and micronutrient studies. The trial's biorepository includes toenail clippings, baseline and "year 5" blood samples, linked nutritional data, adherence cohort data, and a vast clinical database from semi-annual visits with each participant. The biorepository also holds prostate biopsies and surgical specimens collected from a subset of the more than 2,100 men who have been diagnosed with prostate cancer during the course of the trial. DNA has been extracted from the serum of these prostate cancer patients and from an age- and race-matched cohort of control subjects.

Highlights of the completed smaller phase III prevention trials supported by the CCOP network on therapies for precancerous lesions and the effect of interventions on subsequent cancers are described in Table 6 on page 12.

The SELECT participant advisory board members.

Table 6: Selected Completed Prevention Trials

CANCER SITE	INTERVENTION	STUDY AND SIZE	RESULTS
Lung	Selenium vs. placebo in people with early stage non-small cell lung cancer	Study of selenium to prevent second lung cancers 1,960 lung cancer patients (Karp, et al. ASCO, *J Clin Oncol* 2010[40])	The intervention appeared ineffective and was stopped. Participants continue to be monitored.
Head and Neck	Low-dose isotretinoin to prevent second cancers in stage I and II head and neck cancer patients	Study of 13-cis retinoic acid to prevent second primary cancers 1,190 head and neck cancer patients (Khuri, et al. *J Natl Cancer Inst* 2006[41])	Isotretinoin did not reduce the number of second primary tumors in this population. Smoking increased the risk of second primary cancers and death.
Lung	Istretinoin to prevent second primary lung cancers in people with stage I non-small cell lung cancer	Study of 13-cis retinoic acid to prevent second primary cancers 1,166 lung cancer patients (Lippman, et al. *J Natl Cancer Inst* 2001,[42] and Lippman et al, *ASCO* 1998[43])	No difference was seen between placebo and intervention in second primary cancers, recurrence, or mortality.
Colorectal	Aspirin vs. placebo in people with surgically-cured early stage colorectal cancer	Colorectal Adenoma Prevention Study (CAPS) 635 colorectal cancer patients (Sandler et al, *N Engl J Med* 2003[44])	Daily aspirin use reduced the development of adenomas by 35%. Aspirin treatment also reduced the number of adenomas and increased the time before adenomas developed, without significant adverse events.

ONGOING PREVENTION TRIALS

The National Ovarian Cancer Prevention and Early Detection Study is an observational cohort of 2,500 women at high risk for ovarian cancer, each of whom chose to undergo prophylactic oophorectomy or quarterly screening.[45] The trial aims to quantify the extent of risk reduction after preventive surgery, assessing both quality of life and incidence of non-cancer diseases related to premature menopause, and to evaluate a novel approach to ovarian cancer screening based on quantitative assessment of changes in CA-125 over time.[46] Blood and tissue have been collected for use in multiple, ongoing Genome-Wide Association Studies evaluating polymorphisms in *BRCA* mutations to refine the risk model. This cohort will include a large subgroup of breast cancer gene mutation carriers and non-carriers to allow the evaluation of differences in risk. The effort represents a unique collaboration with an NCI intramural investigator as the study chair of the Gynecologic Oncology Group study. Results are expected in 2011.

A second ongoing study is the evaluation of a statin to reduce the incidence of colorectal polyps and invasive colorectal cancer in early stage colorectal cancer patients.[47] NSABP P-5 is a randomized phase III trial to compare the effect of rosuvastatin vs. placebo on the 5-year occurrence of adenomas (polyps of the colon or rectum), new colorectal carcinomas, or colon cancer recurrence in patients with resected stage I or II colon cancer. Rosuvastatin may stop the growth of tumor cells by blocking some of the enzymes needed for their growth.

CANCER CONTROL

Cancer control in the CCOP program includes symptom management, toxicity reduction, supportive and palliative care, and quality of life. The toxicities of cancer treatment have changed over the past three decades due to the number of agents that target different mechanisms of action. Thus, nausea and vomiting were important dose-limiting toxicities 20 years ago, and now, peripheral neuropathy, hypertension, and skin toxicities are emerging as toxicities that limit the amount of cancer treatment the patient receives.

The largest growth area for the CCOP network is in the symptom management trials to evaluate strategies for cancer indications, or for toxicities resulting from treatment. In 2009, 21 new protocols were approved. Completed symptom management studies have demonstrated that:

- Equivalent pain relief from bone metastases can be delivered in a single fraction (8Gy) of radiation as compared to the standard of 10 days of lower-dose radiation,[48]
- Venlafaxine[49] and gabapentin[50] provide nonhormonal relief from hot flashes, but soy does not,[51]
- Pilocarpine can decrease xerostomia in patients who have received radiation therapy to the head and neck,[52]
- Megace can improve appetite,[53 - 55]
- Acupressure can successfully treat chemotherapy-induced nausea,[56]
- Testosterone alone (without another hormone) was not effective in treating libido in patients with breast cancer who had major symptoms associated with libido loss,[57]
- Ginger supplements significantly aided in reducing nausea during the first day of chemotherapy,[58] and
- Yoga for cancer survivors significantly improved sleep quality and quality of life while reducing fatigue and need for sleep medication.[59]

The CCOP program supports health-related quality-of-life research in numerous cancer treatment, prevention, and control trials. Investigators within the Research Bases have contributed to the growing knowledge of quality of life, particularly as it pertains to better understanding of toxicities. A review of breast, prostate, colorectal, and lung cancer treatment trials conducted and reported over the past 20 years revealed another shift, from measuring global health-related quality of life to measuring specific symptomatic toxicities that were expected to occur among patients enrolled in trials.[60]

These investigators have demonstrated in published data from CCOP trials that the Common Terminology Criteria for Adverse Events (CTCAE) is an imprecise tool for reporting such toxicities as fatigue, pain, and subjective side effects.[61,62] Consequently, more trials are incorporating patient-reported outcomes to better capture the clinical benefit and risks of therapies. NCI is developing an electronic-based system for patient reporting of symptomatic adverse events in conjunction with clinician reporting. The CCOP network is actively testing the incorporation of this Patient-Reported Outcome version of CTCAE to improve the accuracy of reporting symptomatic side effects.[63]

In addition, the CCOP Research Bases have conducted trials evaluating agents to increase smoking cessation; varying approaches to facilitate understanding of informed consent and patient communication; markers for early detection of colorectal cancer; and methods for exploring how to evaluate exercise for symptom reduction and improved quality of life.

CLINICAL TRIAL DEVELOPMENT

The CCOP network takes part in NCI cancer treatment trials reviewed and approved by the NCI Division of Cancer Treatment and Diagnosis (DCTD) Cancer Therapy Evaluation Program (CTEP). Cancer prevention and control protocols, however, are reviewed and approved by the NCI Division of Cancer Prevention (DCP) Community Oncology and Prevention Trials Research Group (COPTRG) staff. There is great cooperation and collaboration between these programs and their staffs, and the CCOP network sites benefit from the seamless integration of systems.

Cancer prevention trials conducted in the network start with investigator-initiated proposals by the CCOP Research Bases. For the large-scale cancer prevention trials, a peer-reviewed application is submitted. If approved, the cancer prevention trials are developed with NCI involvement. Among the factors considered in beginning the first large-scale prevention trials were a compelling body of scientific evidence from earlier clinical trials; incidence rates for breast and prostate cancer; the feasibility of the interventions; the potential for significant risk reduction; the ability to establish biorepositories; and methods for communicating risk and funding for ancillary studies within the ongoing trials.

As part of NCI's plan to restructure the NCI clinical trials enterprise, the Symptom Management and Health-Related Quality of Life Steering Committee was created in 2006 to: review and prioritize clinical trial concepts of symptom management interventions to be conducted through the CCOP/MB-CCOP mechanisms; provide input to studies with secondary quality-of-life endpoints in Cooperative Group treatment studies; and develop prioritization criteria for quality-of-life studies that are eligible for proposed correlative science/quality-of-life set-aside funds.[64]

Symptom management trials also start with investigator-initiated proposals from academic investigators within the Research Bases. Concepts are reviewed by an internal committee and specified concepts are reviewed by the Symptom Management and Health-Related Quality of Life Steering Committee. The review evaluates the proposal based on whether the research is clinically important; methods are appropriate; existing evidence supports the evaluation; and investigators have the resources to conduct a successful study. After concept approval, the Research Base develops a full protocol, involving the community physicians and nurses in the feasibility evaluation. After protocol approval, the Research Base assumes responsibility for conducting the trial, data collection, analysis, monitoring, and publications.

Out of the Steering Committee, in 2008, the Drug Development Task Force was formed to focus on the development of agents for symptom and toxicity amelioration. The task force's goal is to help identify agents for development and cultivate partnerships among the NCI, industry, and investigators in the CCOP program. Using the NCI Translational Working Group Pathways as a framework, new agents are stringently reviewed by the task force to ensure key information along a "pathway" is clearly identified from: discovery to preclinical data, demonstrating biologic plausibility in ameliorating normal tissue toxicities or symptoms in appropriate animal models; to phase I safety trials; and into phase II and phase III efficacy clinical trials. The task force has facilitated one initial clinical trial agreement between a pharmaceutical partner and the NCI for pilot projects in chemotherapy-induced peripheral neuropathy.

Between 1995 and 2009, the DCP received 367 cancer prevention and control concepts from CCOP Research Bases. Of those, 10 are in review, 210 were approved (146 of which were for symptom management), and 113 resulted in open and accruing clinical trials. The remaining concepts were disapproved or withdrawn.

CLINICAL TRIAL ACCRUAL

To successfully compete for a CCOP grant, community groups must already have a significant infrastructure in place to handle the requirement to accrue at least 50 participants annually to prevention and control trials and 50 patients to treatment trials. Demonstrable factors include: the catchment area of available patient populations; capacity to open trials and to identify and accrue participants; procedures for data management and mechanisms for quality assurance; procedures for investigational drug monitoring; qualifications, training, and experience of the principal investigator or associate; availability of multidisciplinary health professionals; organizational stability; adequate space and facilities; collaborative background; and Research Base affiliation agreements.

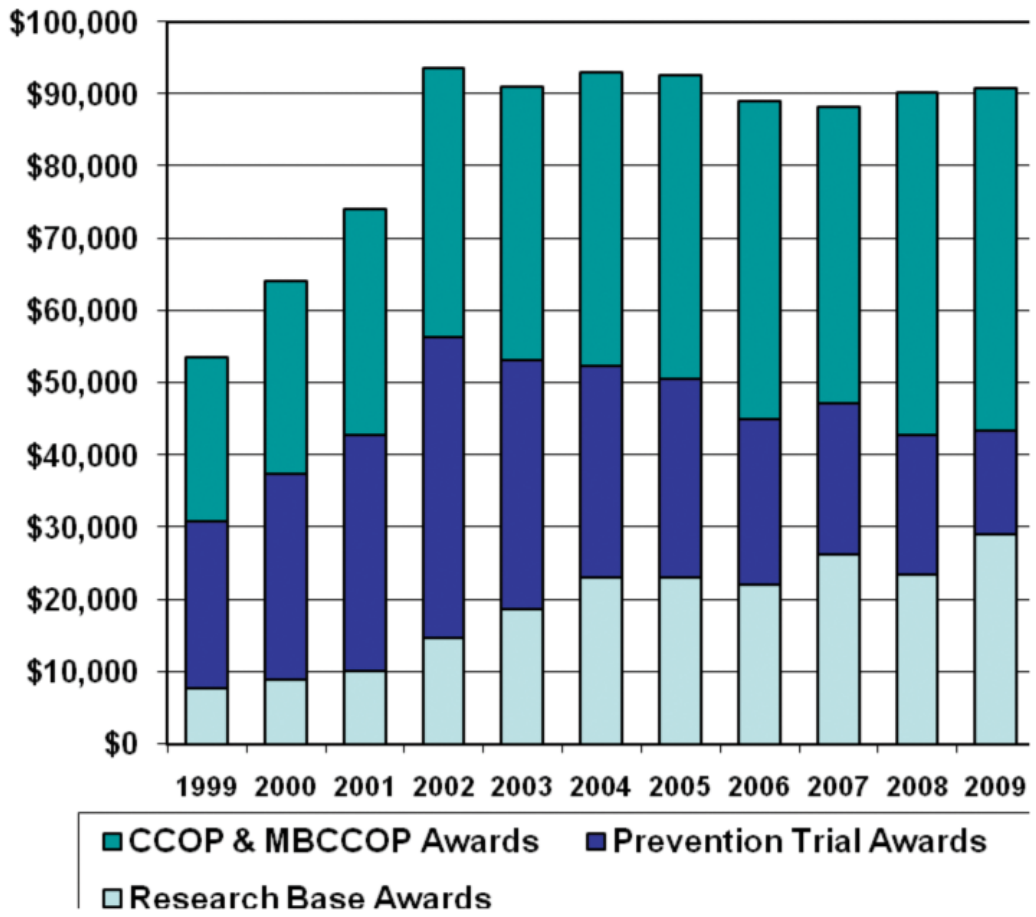
Most CCOPs and MB-CCOPs affiliate with multiple Research Bases. This allows each community group, when choosing trials in which to participate, to respond to changes in clinician interest, patient populations, and the NCI portfolio, as well as to consider future infrastructure needs. Nearly all CCOPs and MB-CCOPs significantly exceed the minimum accrual requirements. A typical CCOP accrues between 200 and 300 patients per year across various studies. Accrual rates vary based on which trials are open at a given time and on community-specific applicability of the available trials. Research nurses are vital to the incorporation of clinical research into physicians' daily activities and to the assurance that research-related activities offer minimal disruption. They screen and flag charts for trial-eligible patients; help physicians communicate study opportunities and assist with related issues such as standardizing treatment orders; facilitate informed consent; act as patient and family advocates; promote patient/participant trial retention; oversee data management; ensure protocol compliance; and serve as liaison with nursing and pharmacy staff .

Research nurses are vital to the incorporation of clinical research into CCOP physicians' daily activities.

PROGRAM SUPPORT

Program funding has been stable for a decade, having increased with the doubling of the NIH budget from 1998 to the present, as shown in Figure 2. This coincided with the launching of two large cancer prevention trials (STAR and SELECT), and provided support for a significant level of accrual. The slight upturn seen in the last 2 years resulted from increased funding for MB-CCOP infrastructure support.

Figure 2. CCOP Network 10-Year Funding Levels (dollars in thousands)



The CCOP network issues three RFAs using the NIH U10 cooperative agreement mechanism: one for CCOPs, one for Research Bases and one for the MB-CCOPs to apply for funding.[3] Applications for the CCOPs and MB-CCOPs are peer reviewed for their organizational structure and ability to accrue at or above the minimum requirements to cancer prevention, treatment, and control trials. Research Bases are peer reviewed for their ability to design and conduct scientifically meritorious and clinically meaningful cancer prevention and control clinical trials.

NCI has determined that the overall funding level for clinical trial accrual across different mechanisms is set at $2,000 per person. This level does not fully pay the costs of conducting trials in either the community or academic sites. CCOPs and MB-CCOPs match NCI funding by approximately 80% of their grant award. These additional dollars come from their institutions, physician practices, industry, private donations, and other sources. The funds pay for infrastructure costs such as additional clinical research associates, laboratory and pharmacy resources, to equipment, and travel expenses. The average CCOP award is $891,052, and the range of $412,592 to $2,186,006 reflects variation in annual accrual and follow-up. The average MB-CCOP award is $620,811 with a range from $427,630 to $879,196.

For the Research Bases, the funding level is based on the size and scope of the clinical trials that are designed and conducted. The average award is $2,591,980 with a range from $1,468,749 to $5,340,154. The totals do not include funding for the large cancer prevention trials, which are supported by a peer-reviewed supplement to the parent grant.

The program operates with eight professional and two support staff who conduct scientific and administrative management and oversee the CCOP portfolio. Staff review concepts and protocols; work with steering committees and Research Bases in the design and development of prevention and control trials; collaborate with other DCP branches and NCI offices (including the DCTD, the Division of Cancer Control and Population Sciences, and the Division of Cancer Etiology); and work with the Center for Health Disparities' Community Network and Navigation Programs using population-specific education and outreach to match navigation with CCOPs and MB-CCOPs where feasible.

Program staff foster formal and informal contacts with the community sites, Research Base investigators, and key personnel; provide feedback on research agendas; assist Research Bases to secure agent-specific data and investigational agents; review study activation, accrual, amendments, and audits; visit communities and Research Bases to monitor program activities and provide guidance; conduct quarterly reviews of the CCOPs' and MB-CCOPs' progress in meeting annual accrual targets; and intercede when there is a lag in projected accruals. Scientific program staff are non-voting members of the Research Bases' data safety and monitoring committees.

FUTURE DIRECTIONS

The CCOP program has undergone multiple evaluations over the past 27 years.[5, 6, 65 - 79] From the initial review which demonstrated successful community physician participation in clinical trials, to a recent review of specific best practices, the network has long been considered an integral component of the NCI clinical trials program.[1] Additionally, successful investigators are using the CCOP network to study the adoption of research results in the community.[80]

In September 2009, the NCI Board of Scientific Advisors reviewed the CCOP and MB-CCOP programs along with an external evaluation; approved the annual release of the CCOP and MB-CCOP RFAs; and strongly endorsed a CCOP strategic planning process in order to ensure the value of this program into the next decade.[81] The planning process began with a one-day retreat in May 2010. Three subcommittees were identified to focus on specific issues pertinent to the network and its three components. The Core Committee is focusing on infrastructure modifications or revisions that may be helpful to facilitate the continued performance of the CCOP network; a Research Priorities Committee is considering future scientific priorities and directions for the CCOP Research Bases; and an Underserved Populations Committee is addressing infrastructure issues pertinent to the accrual of underserved populations and to the scientific agenda to address relevant questions among underrepresented groups in clinical trials. The community and academic investigators have been involved in these committees, discussion of pertinent issues, and directions for the Strategic Plan approved in November 2010 by NCI's Board of Scientific Advisors.

John M. Westfall, et al, have written eloquently about the need to facilitate the translation of research into medical practice by developing practice-based research networks that forge two-way communication between academic and community investigators.[82] He compares the community-level element of these networks to the "blue highways" on maps denoting the back roads to small towns, for it is on those stretches of road where "a lot of life happens…and a lot of health care is delivered." The CCOPs and MB-CCOPs are the NCI's blue highways, with traffic that travels in both directions. The CCOPs and MB-CCOPs bring the science from laboratory, clinical, and population studies to people in their communities, and data from real-world experiences back to researchers.

CCOPs bring the emerging science to the Community.

STRATEGIC ISSUES AND PRIORITIES FOR THE COMMUNITY CLINICAL ONCOLOGY PROGRAM AND THE MINORITY-BASED COMMUNITY CLINICAL ONCOLOGY PROGRAM

NOVEMBER 2010

MISSION

The CCOPs and MB-CCOPs are a community-based clinical trials network, which brings academic investigators (through the Research Bases) together with community physicians to conduct scientifically important and clinically meaningful clinical trials that result in better care for cancer patients and persons at risk for cancer. The MB-CCOPs bring the CCOP structure to communities with greater than 40 percent minority cancer populations to facilitate the inclusion of underserved populations in the same clinical trials.

STRATEGIC GOALS

- Incorporate emerging science and novel trial designs into cancer prevention and control research
- Maximize community resources to conduct complex clinical trials (both cancer prevention and control and cancer treatment trials)
- Use epidemiological and biological data from under-represented populations in clinical trials to address disparate clinical outcomes
- Improve clinical trial access and participation among populations under-represented in cancer clinical research
- Build on the success of the CCOP/MB-CCOP programs to further improve the ability of community institutions to accrue patients to clinical trials

PROGRAM MILESTONES TIMELINE

Pills from the Prostate Cancer Prevention Trial.

Dr. Bernard Fisher with participants in the Breast Cancer Prevention Trial.

1982 CCOP Network is launched with first RFA released.

1983 Original 63 CCOPs in 34 states are funded.

1986 A prospective evaluation published in 1986 demonstrates that community physicians participated successfully in NCI-sponsored treatment trials and their participation accelerated adoption of new treatment regimens in communities.

1987 Second RFA is released; Research Bases required to design and conduct cancer prevention and control clinical trials.

1989 NCI's Board of Scientific Advisors (BSA) determines that the CCOP program should be made a permanent, ongoing part of NCI and voted for an annual release of the RFA.

The BSA also approves a new component of the network, the MB-CCOPs program, to expand into areas with large minority populations lacking access to NCI-sponsored clinical trials.

1990 First MB-CCOP RFA and third CCOP and Research Base RFA are released.

1992 Network initiates first large prevention trial, BCPT.

The second CCOP evaluation demonstrates that cancer control is well integrated into the overall program.

1993 Network initiates second large prevention trial, PCPT.

Network initiates smaller phase III prevention trial, CAPS.

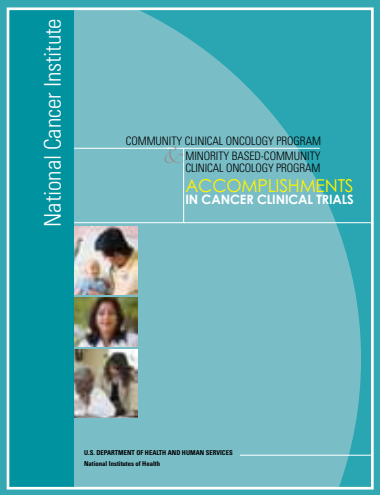
The initial evaluation of the Minority Based CCOP program describes the early implementation and demonstrates that more than 70% of the patients enrolled to NCI clinical trials through the MB-CCOPs were from minority populations.

1997 Enrollment of 18,882 men into PCPT is completed 2 years ahead of schedule. Enrollment of 13,388 women into BCPT is completed 5 years after trial was launched.

1998 BCPT shows tamoxifen reduces invasive breast cancer risk in pre- and postmenopausal women by 49%; tamoxifen is first FDA-approved drug for cancer risk reduction.

1998 Institute of Medicine recommends that NIDA and the Center for Substance Abuse Treatment use CCOP model for community-based trials of drug and alcohol treatments.

The MB-CCOP program is a major mechanism for recruiting minority patients to clinical trials.



1999 Network initiates third large prevention trial, STAR.

2001 Network initiates fourth large prevention trial, SELECT.

2002 CAPS results show daily aspirin use reduced development of adenomas.

2003 PCPT results show that men taking finasteride had 25% fewer prostate cancer diagnoses.

2003 BSA approves the release of the CCOP and MB-CCOP RFAs for 5 years.

2005 NCI Clinical Trials Working Group recommends funding additional MB-CCOPs to address the ongoing need to increase recruitment of minority populations in trials.

The second MB-CCOP evaluation confirms the MB-CCOP program to be a major mechanism to recruit minority participants to trials.

2006 STAR results shows raloxifene works as well as tamoxifen in reducing breast cancer risk in postmenopausal high-risk women without certain serious side effects.

NCI creates the Symptom Management and Quality of Life Steering Committee to review and approve concepts for phase III symptom management trials.

A follow up evaluation demonstrates the CCOP and MB-CCOP programs' success in developing the capacity to conduct cancer prevention clinical trials.

2007 BSA reviews and approves re-issuances of CCOP and MB-CCOP RFAs.

Evaluation shows that over the past decade there continues to be significant interest and viability to the Network consistently meeting program needs.

2008 SELECT results show that neither selenium nor vitamin E prevented prostate cancer.

2009 External evaluation recommends strategic planning process.

2010 Initiated strategic plan and published summary of CCOP as a model for practice-based translational research.

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CCOP, MB-CCOP, RESEARCH BASE LISTING

COMMUNITY CLINICAL ONCOLOGY PROGRAM GROUPS - 2010

CCOP NAME, CITY, STATE (alphabetical by state)		
Bay Area Tumor Institute CCOP OAKLAND, CA	Colorado Cancer Research Program CCOP DENVER, CO	Delaware-Christiana Care CCOP NEWARK, DE
Mt Sinai Medical Center CCOP MIAMI BEACH, FL	Florida Pediatric CCOP TAMPA, FL	Atlanta Regional CCOP ATLANTA, GA
Cedar Rapids CCOP CEDAR RAPIDS, IA	Iowa Oncology Research Association CCOP DES MOINES, IA	Central Illinois CCOP DECATUR, IL
Evanston Northwest Healthcare CCOP EVANSTON, IL	Illinois Oncology Research Association CCOP PEORIA, IL	Carle Cancer Center CCOP URBANA, IL
Northern Indiana Cancer Research Consortium CCOP SOUTH BEND, IN	Wichita CCOP WICHITA, KS	Ochsner Clinical Foundation CCOP NEW ORLEANS, LA
Michigan Cancer Research Consortium CCOP ANN ARBOR, MI	Grand Rapids CCOP GRAND RAPID, MI	Kalamazoo CCOP KALAMAZOO, MI
Beaumont CCOP ROYAL OAK, MI	Duluth CCOP DULUTH, MN	Metro-Minnesota CCOP ST LOUIS PARK, MN
Kansas City CCOP KANSAS CITY, MO	Cancer Research for the Ozarks CCOP SPRINGFIELD, MO	Heartland Cancer Research CCOP ST LOUIS, MO
St. Louis-Cape Girardeau CCOP ST. LOUIS, MO	Montana Cancer Consortium CCOP BILLINGS, MT	Southeast Cancer Control Consortium CCOP WINSTON-SALEM, NC
MeritCare Hospital CCOP FARGO, ND	Missouri Valley Cancer Consortium CCOP OMAHA, NE	Nevada Cancer Research Foundation CCOP LAS VEGAS, NV
Hematology-Oncology Assoc. of Central New York CCOP EAST SYRACUSE, NY	North Shore CCOP LAKE SUCCESS, NY	Columbus CCOP COLUMBUS, OH
Dayton CCOP DAYTON, OH	Toledo CCOP TOLEDO, OH	Warren Cancer Research Foundation CCOP TULSA, OK
Columbia River CCOP PORTLAND, OR	Geisinger CCOP DANVILLE, PA	Main Line Health CCOP WYNNEWOOD, PA
Greenville CCOP GREENVILLE, SC	Upstate Carolina CCOP SPARTANBURG, SC	Sioux Community Cancer Consortium CCOP SIOUX FALLS, SD
Scott & White CCOP TEMPLE, TX	Virginia Mason CCOP SEATTLE, WA	Northwest CCOP TACOMA, WA
St. Vincent Hospital Regional Cancer Center CCOP GREEN BAY, WI	Marshfield CCOP MINOCQUA, WI	

MINORITY-BASED COMMUNITY CLINICAL ONCOLOGY PROGRAM GROUPS – 2009

MINORITY-BASED CCOP NAME, CITY, STATE (alphabetical by state)	
The Gulf Coast Minority-Based CCOP MOBILE, AL	Medical College of Georgia Minority-Based CCOP AUGUSTA, GA
University of Hawaii Minority-Based CCOP HONOLULU, HI	Stroger Hospital of Cook County Minority-Based CCOP CHICAGO, IL
University of Illinois at Chicago Minority-Based CCOP CHICAGO, IL	LSUHSC (New Orleans) Minority-Based CCOP NEW ORLEANS, LA
LSUHSC-Shreveport Feist-Weiller Cancer Center Minority-Based CCOP SHREVEPORT, LA	Boston Medical Center Minority-Based CCOP BOSTON, MA
University of Medicine and Dentistry of New Jersey Minority-Based CCOP NEWARK, NJ	New Mexico Minority-Based CCOP ALBUQUERQUE, NM
The Brooklyn Minority-Based CCOP BROOKLYN, NY	Queens Cancer Center Minority-Based CCOP NEW YORK, NY
San Juan Minority-Based CCOP SAN JUAN, PR	Meharry Medical College Minority-Based CCOP NASHVILLE, TN
South Texas Pediatric Minority-Based CCOP SAN ANTONIO, TX	Virginia Commonwealth University Minority-Based CCOP RICHMOND, VA

RESEARCH BASES FOR THE COMMUNITY CLINICAL ONCOLOGY PROGRAM - 2009

RESEARCH BASE NAME, CITY, STATE (alphabetical by state)	
Children's Oncology Group CCOP Research Base ARCADIA, CA	SunCoast CCOP Research Base at the University of South Florida TAMPA, FL
Cancer and Leukemia Group B CCOP Research Base CHICAGO, IL	Eastern Cooperative Oncology Group CCOP Research Base BOSTON, MA
Southwest Oncology Group CCOP Research Base ANN ARBOR, MI	North Central Cancer Treatment Group CCOP Research Base ROCHESTER, MN
Wake Forest University Cancer Center CCOP Research Base WINSTON-SALEM, NC	University of Rochester Cancer Center CCOP Research Base ROCHESTER, NY
Gynecologic Oncology Group CCOP Research Base PHILADELPHIA, PA	Radiation Therapy Oncology Group CCOP Research Base PHILADELPHIA, PA
National Surgical Adjuvant Breast and Bowel Project CCOP Research Base PITTSBURGH, PA	M. D. Anderson Cancer Center CCOP Research Base HOUSTON, TX

PROGRAM STAFF

Lori Minasian, M.D., is a board-certified medical oncologist who runs the Community Clinical Oncology Program and is the branch chief for the Community Oncology and Prevention Trials Research Group in the NCI Division of Cancer Prevention. She manages and oversees the program, provides scientific leadership in cancer prevention and control specifically in symptom management, health-related quality of life, and the large cancer prevention trials. She provides expertise on clinical trials to NCI and advises other institutes on clinical trial issues with an emphasis on community participation. She sees patients in the NIH Clinical Center and is part of the Medical Ovarian Cancer Clinic Team.

Worta McCaskill Stevens, M.D., M.S., is a medical oncologist with a focus on breast cancer control and prevention. She is the program director for several DCP research bases and for the Minority-Based Community Oncology Program. She is the program director for the STAR trial and is a member of the NCI Breast Cancer Steering Committee and other committees related to risk prediction and disparities in clinical research. She chaired the NIH State of the Science conference on Ductal Carcinoma In Situ.

Joseph Kelaghan, M.D., M.P.H., is chair of the protocol review committee for all Community Clinical Oncology Program studies and works on symptom management issues both inside and outside the group. He works with the NCI Symptom Management and Quality of Life Steering Committee to improve the quality of studies available in the CCOP program. A Commander in the U.S. Public Health Service, he was called to emergency duty after Hurricane Katrina.

Ann M. O'Mara, Ph.D., R.N., is an oncology nurse scientist and heads Palliative Care Research in the Division of Cancer Prevention. She manages the portfolio of symptom management and palliative and end-of-life care research projects, and provides expertise in several trans-NIH symptom-specific committees.

Joanna Brell, M.D., is a medical oncologist and the program director for symptom management and drug development. Her background includes conducting phase I and II therapeutic clinical trials. She has served as member and chair of the ASCO Annual Meeting Scientific Program Committee for the Patient and Survivor Care Track and as a member of the ECOG Pain and Symptom Management Subcommittee.

Diane St. Germain, R.N., M.S., C.R.N., is a nurse consultant and practitioner with expertise in palliative care, pain, and symptom management. She provides nursing expertise in planning and supporting CCOP-supported clinical trials and is a member of the NCI Community Cancer Centers Program (NCCCP) Advisory Committee and the Clinical Trials Subcommittee.

Marge Good, R.N., M.P.H., recently joined COPTRG after working for more than 20 years as a CCOP administrator at the Wichita CCOP. She brings significant practical information to the management of the program as it moves forward.

Cynthia Whitman, B.S., M (ASCP), is a program specialist responsible for financial management of the portfolio of CCOP, MB-CCOP, and Research Base cooperative agreements. She is a subject-matter expert on CCOP Program policies and related NIH grant policies. She is a Program Director for approximately one-quarter of the CCOP cooperative agreements.

This report was written by the Community Oncology and Prevention Trials Research Group of the National Cancer Institute's Division of Cancer Prevention. Lori Minasian, M.D., chief of the Community Oncology and Prevention Trials Research Group, would like to acknowledge the following individuals for their assistance in its creation:

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