Children treated for cancer are living longer than ever and with a quality of life that is steadily improving, thanks in part to the long-running Childhood Cancer Survivor Study (CCSS). But oncologists are now concerned that the updated treatments that have resulted from CCSS research may carry a whole new set of risks and benefits not reflected in the original 20,000-plus childhood cancer survivors enrolled in CCSS.

That group includes children diagnosed with cancer between 1970 and 1986 and who survived at least 5 years, which means that all 72 CCSS publications and 52 study projects have been based on treatment given between 21 and 37 years ago.

Much has changed since then, which is why Les Robison, Ph.D., the researcher who created CCSS and who has championed it ever since, has been lobbying hard in recent years to expand CCSS to patients treated up through 1999. Finally, after 2 years of nail-biting over National Cancer Institute funding, Robison was told early this summer that the study could be updated and its number of participants almost doubled through a new expansion.

In both 2005 and 2006, NCI said that updated participation in CCSS was important and valuable, but it didn’t have the dollars. But in June an NCI executive committee committed almost $20 million to fund the 5-year, $25 million proposal—a turn of events that Robison termed “remarkable in this era of funding.”

What this means to Robison, chair of the department of epidemiology and cancer control at St. Jude Children’s Research Hospital in Memphis, and the 27 research institutions and the hundreds of investigators he works with, is that the expansion will add up to 15,000 new cancer survivors diagnosed and treated between 1987 and 1999 and who have survived 5 years.

“This is a unique asset for any investigator who worries about a long-term effect of how cancer in children is treated,” Robison said. He held a 2-day meeting with 120 CCSS investigators in late August to finalize details of future studies based on the expanded roll of participants, who have already been selected and are now being invited to participate.

“We all have the same goal: to cure cancer in youngsters in such a way that they can have the opportunity for a full and healthy life.”

The CCSS is designed to look for so-called late effects of treatment for childhood cancer. The original group, along with 4,000 healthy sibling controls, answer periodic questionnaires designed to address health status and quality of life, and any researcher can access the CCSS database or propose new studies.

Answers to those questions have often led to changes in treatment that were later tested by the Children’s Oncology Group (COG). For example, given the long-term detrimental effects of radiation that CCSS found, pediatric oncologists today are more likely to use combinations of chemotherapy for hard-to-treat cancers that have “nearly reached the point of maximum benefit and maximum risk of toxicity,” said Gregory Reaman, M.D., professor of pediatrics at George Washington University and chair of COG.

“We found out a great deal from the first CCSS cohort, and our treatment approaches in virtually all diseases changed significantly over the past few years,” Reaman said. “Now it is important to see if those changes have also altered the incidence and results of late complications and side effects.”

Health Issues Found in First Trial
Childhood cancer is unlike adult cancer in both scope and origin. Researchers believe that most of the tumors develop in utero from embryonic tissues that are not fully developed, and they are typically diagnosed at an average age of 6 years. In general, they are relatively rare—one in every 350 people in the U.S. develops a cancer before age 20—but oncologists have pushed up the survival curve by treating these young and resilient patients more aggressively than they would treat many adults.

Advances in pediatric cancer treatment have resulted in an 80% survival rate 5 years after diagnosis, and there are now more than 300,000 childhood cancer survivors in the U.S., according to CCSS research.

But the success comes at a measurable cost, as research examining the original study group—some of whom are now approaching age 60—has demonstrated. Biannual CCSS questionnaires detailing health and psychosocial status have revealed a plethora of health issues later in life, Robison said. “It’s not a rosy picture at all. These studies underscore the need for survivors to receive good medical care and screening,” he said. “If we know what to
look for, hopefully we can detect these problems earlier, treat them, and effectively intervene.”

For example, one major CCSS study on chronic illness, published last year in the *New England Journal of Medicine*, showed that among 10,397 survivors in the CCSS database, almost 75% have a chronic health condition, more than 40% have serious health problems, and one-third have multiple health problems 30 years after a cancer diagnosis. The cancer survivors were eight times as likely as their siblings to have severe or life-threatening health conditions such as heart attacks, congestive heart failure, and severe cognitive dysfunction, the researchers found.

Three groups were at highest risk: survivors of bone tumors, central nervous system (CNS) tumors, and Hodgkin lymphoma. The authors concluded that it is now clear that damage to the organ systems of children caused by chemotherapy and radiation therapy may not become clinically evident for many years. “The incidence of health conditions reported by this population increases with time and does not appear to plateau,” said the study’s lead author, Kevin Oeffinger, M.D., who leads a program for adult survivors of pediatric cancer at Memorial Sloan-Kettering Cancer Center in New York.

Other findings have detailed second cancers in survivors and, unlike many CCSS studies, researchers followed up self-report questionnaires with examination of medical records. One report, published in *JNCI* (J Natl Cancer Inst 2001;93:618–29), found a statistically significant excess of second cancers after all childhood cancers, and girls between 5 and 9 years treated with radiation therapy for Hodgkin disease were at greatest risk of developing breast cancer. Another *JNCI* study (J Natl Cancer Inst 2006;98:1528–37) concluded that exposure to radiation is the most important risk factor for developing new CNS tumors in survivors.

“One thing we have learned from these studies is that the risk of developing a second cancer in childhood cancer survivors does not go away,” said the lead investigator of both studies, Joseph Neglia, M.D., Ph.D., section chief of hematology/oncology at the University of Minnesota Medical School. “Breast cancer seems to be the greatest risk to the cohort, and there is a dramatic dose–response relationship between use of radiation to treat leukemia and occurrence of malignant as well as benign brain tumors decades after treatment,” Neglia said. “We want to make patients aware of these risks so that they have appropriate follow-up and care.”

CCSS findings often lead to small and tailored COG clinical trials that test new treatment protocols that might limit late effects, Robison said. “We function circularly,” Reaman agreed. “The results of CCSS investigations that demonstrate specific long-term complications related to specific therapies are noted by COG as we design new clinical trials. In COG we have worked to decrease toxicities associated with therapy based on what we learned from CCSS.”

For example, pediatric oncologists now reduce or eliminate the use of cranial radiation in treatment of CNS leukemia to lessen the risk of neurocognitive deficits, neuroendocrine dysfunction, and second cancers. Instead, they use high-dose methotrexate, a chemotherapy drug used to
prevent leukemia cells from entering cerebrospinal fluid, said Melissa Hudson, M.D., a pediatric oncologist at St. Jude’s Children’s Research Hospital who is working on national guidelines for later screening of childhood cancer patients. Oncologists have also eliminated or reduced exposure of the breast to radiation in girls being treated for cancer because of the high risk of developing breast cancer, and many institutions have started breast cancer surveillance programs in these survivors, Hudson said.

Focus on Brain Tumors, Minorities

Among other goals, the new research based on the expanded CCSS group is intended to reveal the long-term effects of newer cancer therapies, including chemotherapy agents like ifosfamide, dose-intensive treatment regimens, and the reduction in radiotherapy for Hodgkin disease and childhood acute lymphoblastic leukemia.

CCSS will also selectively increase participation from certain subgroups, Robison said, including brain tumor patients for whom survival has not substantially increased and leukemia patients with a poor prognosis.

“Brain tumor therapy has changed dramatically since 1987, so we are very excited to be looking at this new cohort,” said Roger Packer, M.D., chairman of neurology at Children’s National Medical Center in Washington, D.C. When the original trial participants were treated, chemotherapy was not widely used in medulloblastoma, the most common childhood brain tumor, as well as in other gliomas, and radiation was used at higher doses than it is today, he said. Up to one-quarter of patients experienced substantial late effects, such as stroke, seizures, headaches, motor difficulties, learning difficulties, obesity, and hormonal problems.

“No, now we use more chemotherapy, but we know that these agents carry their own risks. We have also reduced radiation and focused its distribution more narrowly,” Packer said. “We have more survivors, but we need to know whether they are doing better or not as well.”

The answer is not obvious, he said. For example, one unexpected effect of improved surgical techniques to allow better navigation through the brain is that more patients, seemingly, are reporting statistically significant postoperative complications such as loss of speech and balance problems. “This could be because surgeons are being more aggressive, or it may be due to better data collection. We just don’t know.

“This will be a remarkably important cohort that will offer us great insights into what we are doing for childhood tumors,” Packer said.

CCSS is also making a push to include more minorities, Robison said. “The original cohort was 88% white, non-Hispanics, but we want to include 20% minorities in the new cohort,” Robison said. “We are interested in psychosocial outcomes, not just physical, so we need to develop risk profiles according to ethnic, racial, and gender subgroups.”

Reaman, the COG chair, is pleased that CCSS has enough financial assets to take it into the future, but he is worried about whether COG—which enrolls 90% of the childhood cancer patients eligible for clinical trials—will be able to follow up on CCSS’s future findings to further refine therapy. Reaman says that federal funding of pediatric cancer research is at a “crisis stage.” NCI has cut the funding for the COG’s resource grant by 50% over the last 5 years, he said. “So we will be missing a huge chunk of the picture we need to further improve childhood cancer care if CCSS is renewed but COG can’t follow up on what CCSS finds,” Reaman said. “Childhood cancer has long been viewed by many as a small part of the nation’s cancer problem, so it doesn’t get its proportional share,” he said. “But cancer is still the leading cause of death in children, and when we do our job well, we can give a child a long and healthy life to live.”