

## Editorial

# Childhood Cancer Research Network: a North American Pediatric Cancer Registry

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In contrast to adult malignancy, which affects nearly one in two individuals over a lifetime, childhood cancer is rare, affecting only about 1 in 315 children and adolescents under the age of 20 years (1, 2). Investigators have, therefore, needed to work together across many institutions and large geographic areas to capture sufficient numbers for research on the efficacy of new treatment regimens and the biology, epidemiology, and late effects of specific childhood cancers. The success of the cooperative pediatric clinical trials groups in the United States and elsewhere shows how effective these collaborations are, suggesting they could be used as models for similar initiatives in adult malignancy. We focus here on the work of the Children's Oncology Group (COG), specifically the new Childhood Cancer Research Network (CCRN), which is planned to be the basis for a unified pediatric cancer registry within North America.

### Overview of Childhood Cancer in the United States

Nearly 12,500 children under the age of 20 years are newly diagnosed with cancer each year in the United States (3). The incidence of childhood cancer has been increasing slightly, but significantly, over the last several decades, particularly among White children (4). Confirmed risk factors for childhood malignancy are few, but a growing body of evidence suggests environmental exposures play a role (5).

Advances in treatments over the last several decades make it likely that nearly 80 percent of children diagnosed with cancer today will be alive in 5 years (2) compared with 50% in the 1970s. Currently, there are >250,000 childhood cancer survivors in the United States (6). Unfortunately, these life-saving, intensive treatments also increase the risk for second malignancies, cardiovascular disease problems, and other morbidities (7), leading to an ever growing need for more systematic study of childhood cancer survivors.

### COG

Over 200 member institutions of the Children's Oncology Group treat the vast majority of children diagnosed with cancer in the United States and Canada. Depending on the diagnosis and age of the child, estimates are that COG institutions treat upwards of 90% of children under the age

of 15 years (8, 9). Disease-specific committees within COG (e.g., acute lymphoblastic leukemia, neuroblastoma, etc.), comprised of pediatric oncologists, basic scientists, and other specialists, develop standardized patient recruitment, treatment, and evaluation protocols for clinical trials of new therapies. COG also has scientific and discipline committees (e.g., Epidemiology, Late Effects, and Cancer Control) that propose new, nontherapeutic studies that are focused on the COG patient populations, most often with substantial independent external funding. COG Epidemiology studies have been recently described (10).

Conducting nontherapeutic studies in COG has been labor intensive because, in addition to the mandatory protocol approval by an institutional review board and the informed-consent forms required by the study investigators' institution(s), almost every nontherapeutic protocol has also had to be approved by each COG member institution's institutional review board. In addition, approvals for clinical protocols must take precedence over nontherapeutic studies, leading to delay in submission of the application to the local institutional review board. Further complicating recruitment, most COG institutional review boards are now requiring personnel at each site to contact and obtain signed consent forms from parents before they are approached for consent to specific group-approved epidemiology, late effects, and other nontherapeutic studies. Such requirements can introduce bias and result in many patients being lost to follow-up, ultimately influencing the power of studies.

In the face of increased competition for research dollars, the imposition of Health Insurance Portability and Accountability Act requirements, as well as the ever-increasing difficulties of recruitment for nontherapeutic studies in COG, plans are in place to launch a new collaborative initiative: the CCRN.

### CCRN: What is it?

Under development for >5 years, the CCRN is a simple idea with far-reaching potential. It adds an informed-authorization process for parents and patients to the existing COG patient registration system, allowing release of personal identifiers to approved study investigators and obtaining agreement to possible future contact about research participation.

### How It Will Work

Currently, the COG Constitution requires member institutions to register all pediatric patients diagnosed at their institution with a central, secured, electronic data entry system. The limited information collected can include (with appropriate authorization): the child's date of birth, sex, race/ethnicity, type and characteristics of the cancer, date of diagnosis, and

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the family's residential postal or zip code. These data are provided to COG, even if the patient will not be treated on an active COG therapeutic protocol. The new CCRN system will involve the patient and the patient's family at the beginning of the registration process, giving them an opportunity to authorize the collection of personal identifiers and to indicate their wishes regarding future contact for research purposes. Parents and children old enough to understand this process can choose among three options:

- Not to participate at all in the CCRN (limited Health Insurance Portability and Accountability Act-compliant information will be collected);
- To register with CCRN with personal identifiers, which will permit enrollment on a COG therapeutic trial if applicable, but say "no" to future contact for research purposes; and
- To register with CCRN and say "yes" to possible contact about participating in COG-sanctioned, nonclinical research studies.

### Results of Pilot Study for the CCRN

In 2001, funds were received from the National Cancer Institute to pilot the CCRN (as COG AADM01P1) at ~10% of randomly selected COG institutions in North America. Twenty-three institutions participated, including two in Canada. By March 2002, all institutions had obtained institutional review board approval to enroll patients. As of April 2006, 1,990 parents/patients among these institutions have been approached for this protocol. Importantly, 1,901 (~96%) have agreed to both levels of consent (consent for personal identifiers and for possible future contact), and 65 (3%) have agreed to release of personal identifiers only. Only 24 (1%) have refused both consent levels. The pilot of the CCRN is considered a major success. Moreover, many nonselected COG institutions have inquired about opening this protocol as a means to address Health Insurance Portability and Accountability Act concerns and to facilitate enrollment on nontherapeutic research studies.

### Features of the CCRN

Operationally simple, the CCRN incorporates important features. First, it streamlines the informed-authorization process by asking parents and patients 18 years of age and older for permission to contact them about possibly participating in cancer-related research at some point in the future. Currently, individual institutions often ask about possible future contact in a specific protocol (e.g., banking biological specimens), which makes it difficult to determine what is being requested and agreed to regarding "contact" in the future.

Second, the names of parents and patients (and addresses and phone numbers if agreeing to future contact) will be entered at the time of diagnosis, providing a good starting point for locating families, especially if they need to be traced by researchers at some time well into the future. Treatment-related discussions and education about the consent process undoubtedly will inform parents' thinking about participating in the CCRN. Based on experience in the CCRN pilot study, almost all parents will consent to the release of personal identifiers, even if they do not agree to future contact. Every registered patient will be assigned a unique CCRN identifier. Thus, CCRN registration data can assist in studies of cancer clustering and mapping to areas of concern, such as Superfund sites.

Third, the CCRN creates the infrastructure for nationwide, essentially population-based studies and a group approval process discouraging redundancy and encouraging institutional cooperation and support for studies with the most promise. Importantly, COG plans to create a portal for non-COG member institutions to register in the CCRN. Ultimately, the goal is to work with existing state and provincial cancer registries to fill in the gaps in areas not served by COG member institutions.

Lastly, instead of expecting treating institutions to track down patients and families with whom they may have had no contact for years, the new system provides principal investigators of nontherapeutic studies, the major stakeholders of a study, with a much improved way to recruit participants. By removing procedural obstacles, while maintaining all necessary safeguards for patients, the CCRN should result in greater efficiency by investigators and reduced study costs.

Childhood cancer patients and their families will ultimately derive the greatest benefits from the CCRN. On the practical level, it speeds up the process of unraveling the important questions that inspire cancer researchers. In addition, it invites cooperative efforts to address questions that go beyond morbidity and mortality to the causes of childhood cancer and the quality of life and psychosocial wellbeing of survivors. And, on the human level, it does something even more important: the process itself, and the forms that are part of it, communicate respect to children and families at a very difficult time in their lives. Background materials created with input from parent and patient advocates, oncologists, nurses, and others make it clear that protecting patients' and families' confidentiality, not only during treatment but also after, is considered not just a duty but a priority for Network personnel. At any time, families may choose to opt out of the CCRN. Furthermore, the rights of adolescents also are recognized and explained. Parents are told, regardless of what they decide regarding participation in the CCRN, that their child will be asked, upon reaching the age of majority (18 in most states), if he or she would like to continue to be a part of the Network.

In summary, the CCRN is needed, timely, and a potentially powerful catalyst for research breakthroughs that will benefit the 12,500 families affected annually by a child's diagnosis with cancer. And, best of all, the CCRN system is simple enough to serve as a possible model for a registry for adult cancer studies.

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