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REVIEW ARTICLE

The Childhood Cancer Survivor Study: A National Cancer Institute–Supported Resource for Outcome and Intervention Research

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical Trials repository link available on JCO.org

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ABSTRACT

Survival for childhood cancer has increased dramatically over the last 40 years with 5-year survival rates now approaching 80%. For many diagnostic groups, rapid increases in survival began in the 1970s with the broader introduction of multimodality approaches, often including combination chemotherapy with or without radiation therapy. With this increase in rates of survivorship has come the recognition that survivors are at risk for adverse health and quality-of-life outcomes, with risk being influenced by host-, disease-, and treatment-related factors. In 1994, the US National Cancer Institute funded the Childhood Cancer Survivor Study, a multi-institutional research initiative designed to establish a large and extensively characterized cohort of more than 14,000 5-year survivors of childhood and adolescent cancer diagnosed between 1970 and 1986. This ongoing study, which reflects the single most comprehensive body of information ever assembled on childhood and adolescent cancer survivors, provides a dynamic framework and resource to investigate current and future questions about childhood cancer survivors.

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INTRODUCTION

It is well recognized that survival rates for many of the childhood and adolescent cancers have improved at a remarkable pace over the last four decades. With this success came the need and responsibility to consider the long-term morbidity and mortality associated with treatments responsible for the increases in survival. Early efforts to describe the late effects of treatment in this population included single-institution and limited consortia studies, as well as occasional cooperative clinical trials group investigations of late sequelae. However, by the mid-1980s, it became increasingly clear that there were serious limitations inherent in these approaches, such as small study sizes, incomplete population characterizations, and limited length of follow-up. To overcome these limitations, the Childhood Cancer Survivor Study (CCSS) was proposed and, in 1994, funded by the National Cancer Institute (NCI). The key components of the rationale for initiating the CCSS are summarized in the following sections.

Improved Survival

Today, cure is the likely outcome for most children diagnosed with cancer. Improvements in therapy have increased the 5-year relative survival rate from less than 30% in 1960 to 79% in 2004.[1,2] Long-term survival rates vary substantially according to initial diagnosis, demographic characteristics (eg, age, sex, race), and presenting clinical characteristics (eg, extent of disease, location, morphology, biologic features). Thus, more recent clinical trials are often designed with the general philosophy of intensifying therapy among poor prognosis patients to further increase survival, while reducing/modifying therapy in patients with a good prognosis to decrease the potential for acute and long-term toxicities without compromising survival.

Recognition of Risks Associated With Health-Related and Psychosocial Outcomes

To varying degrees, it has been shown that long-term survivors are at risk of developing a spectrum of adverse outcomes including early death, second neoplasms, organ dysfunction (eg, cardiac, pulmonary, gonadal), impaired growth and development, decreased fertility, impaired cognitive function, difficulties obtaining employment and insurance, and overall reduction in quality of life.[3]

Because of the young age of childhood cancer survivors and thus the potential longevity of survivorship, the delayed consequences of therapy will likely have a substantial impact on their lives, their families, and society at large.

Limitations of Single-Institution Studies, Consortia, and Cooperative Groups

Single-institution investigations provided many of the initial observations on selected sequelae occurring at relatively high frequencies or associated with severe morbidity. However, many of these single-institution and limited consortia investigations are restricted by a small sample size and incomplete patient follow-up and are often derived from patient populations that are treated on a single uniform protocol. Thus, precise quantification of a complete range of possible adverse outcomes is often impossible. Some studies of long-term survivors have been carried out within established cooperative clinical trials groups but with varied success. The pediatric cooperative groups have a primary objective of conducting therapeutic clinical trials, and although questions of health-related outcomes are of interest, the resources do not always exist to provide the necessary support to successfully conduct such nontherapeutic studies.

Table 1. Childhood Cancer Survivor Study Consortium Institutions and Responsible Investigators

Institution	Investigators
St. Jude Children's Research Hospital, Memphis, TN	Leslie L. Robison, PhD*†, Melissa M. Hudson, MD†‡, Greg T. Armstrong, MD, MSCE†, Daniel M. Green, MD†, Kevin R. Krull, PhD†
Children's Healthcare of Atlanta/Emory University, Atlanta, GA	Lillian Meacham, MD‡, Ann C. Mertens, PhD†
Children's Hospitals and Clinics of Minnesota, Minneapolis/St. Paul, MN	Joanna Perkins, MD, MS‡
Children's Hospital and Medical Center, Seattle, WA	Douglas Hawkins, MD‡, Eric Chow, MD, MPH†
Children's Hospital, Denver, CO	Brian Greffe, MD‡
Children's Hospital, Los Angeles, CA	Kathy Ruccione, RN, MPH‡
Children's Hospital, Oklahoma City, OK	John Mulvihill, MD†
Children's Hospital of Orange County, Orange, CA	Leonard Sender, MD
Children's Hospital of Philadelphia, Philadelphia, PA	Jill Ginsberg, MD‡, Anna T. Meadows, MD†
Children's Hospital of Pittsburgh, Pittsburgh, PA	Jean Tersak, MD‡
Children's National Medical Center, Washington, DC	Gregory Reaman, MD‡, Roger Packer, MD†
Cincinnati Children's Hospital Medical Center, Cincinnati, OH	Stella Davies, MD, PhD†
City of Hope Medical Center, Duarte, CA	Smita Bhatia, MD†‡
Cook Children's Medical Center, Ft. Worth, TX	Paul Bowman, MD, MPH‡
Dana-Farber Cancer Institute/Children's Hospital, Boston, MA	Lisa Diller, MD†‡
Fred Hutchinson Cancer Research Center, Seattle, WA	Wendy Leisenring, ScD†‡
Hospital for Sick Children, Toronto, Ontario, Canada	Mark Greenberg, MBChB‡, Paul C. Nathan, MD†‡
International Epidemiology Institute, Rockville, MD	John Boice, ScD†
Mayo Clinic, Rochester, MN	Vilmarie Rodriguez, MD‡
Memorial Sloan-Kettering Cancer Center, New York, NY	Charles A. Sklar, MD†‡, Kevin C. Oeffinger, MD†
Miller Children's Hospital, Long Beach, CA	Jerry Finklestein, MD‡
National Cancer Institute, Bethesda, MD	Roy Wu, PhD†, Nita Seibel, MD†, Preetha Rajaraman, PhD†, Peter Inskip, PhD†
Nationwide Children's Hospital, Columbus, OH	Amanda Termuhlen, MD‡, Sue Hammond, MD†
Northwestern University, Chicago, IL	Kimberley Dilley, MD, MPH‡
Riley Hospital for Children, Indianapolis, IN	Terry A. Vik, MD‡
Roswell Park Cancer Institute, Buffalo, NY	Martin Brecher, MD‡
St. Louis Children's Hospital, St. Louis, MO	Robert Hayashi, MD‡
Stanford University School of Medicine, Stanford, CA	Neyssa Marina, MD‡, Sarah S. Donaldson, MD†
Texas Children's Hospital, Houston, TX	Zoann Dreyer, MD‡
University of Alabama, Birmingham, AL	Kimberly Whelan, MD, MSPH‡
University of Alberta, Edmonton, Alberta, Canada	Yutaka Yasui, PhD†‡
University of California, Los Angeles, Los Angeles, CA	Jacqueline Casillas, MD, MSHS‡, Lonnie Zeltzer, MD†
University of California, San Francisco, San Francisco, CA	Robert Goldsby, MD‡
University of Chicago, Chicago, IL	Tara Henderson, MD, MPH‡
University of Michigan, Ann Arbor, MI	Raymond Hutchinson, MD‡
University of Minnesota, Minneapolis, MN	Joseph Neglia, MD, MPH†‡
University of Southern California, Los Angeles, CA	Dennis Deapen, DrPH†‡
The University of Texas Southwestern Medical Center, Dallas, TX	Daniel Bowers, MD‡
The University of Texas M. D. Anderson Cancer Center, Houston, TX	Louise Strong, MD†‡, Marilyn Stovall, MPH, PhD†

*Project Principal Investigator (supported by Grant No. U24 CA55727).
†Member of Childhood Cancer Survivor Study Steering Committee.
‡Institutional Principal Investigator.

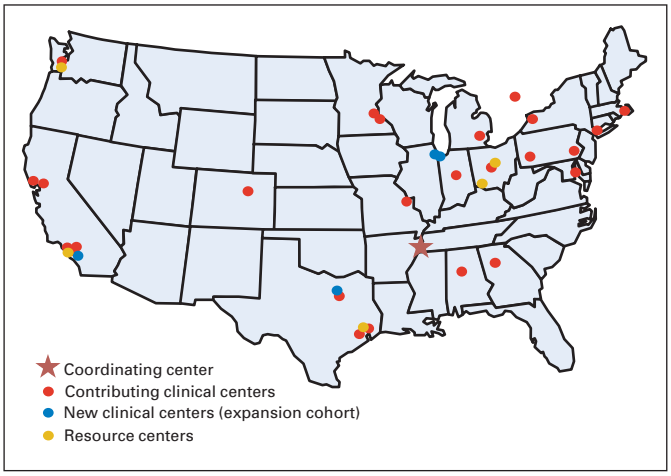

Fig 1. Childhood Cancer Survivor Study consortium centers.

A Large and Increasing Proportion of Survivors Are No Longer Being Observed Systematically

The long-term follow-up of children successfully treated for cancer is challenging, and deficiencies in follow-up may obscure the true frequency and nature of the late effects of therapy. For example, in the majority of survivors, long-term outcomes are not being reported systematically by clinical trials groups.[4] This deficiency is underscored by the fact that when the CCSS was first proposed, the status of 68% of survivors diagnosed between 1970 and 1986 had not been updated within the cooperative groups for more than 10 years. Moreover, among survivors eligible for the CCSS cohort, 39% required extensive tracing (beyond use of telephone directory assistance) because their treating institution no longer had current contact information. To address the potential biases associated with incomplete long-term follow-up of patients, a well-organized and experienced resource like the CCSS is required.

ORGANIZATIONAL STRUCTURE

With the recognition of the need for systematic surveillance of long-term survivors of childhood cancer, efforts in 1990 were begun to form a consortium of institutions and investigators to establish a mechanism to facilitate survivorship research. After a series of organizational and planning meetings, a group of 26 contributing clinical pediatric centers from the United States and Canada was selected to form the CCSS consortium. These centers were chosen based on criteria that included the size of the patient population, investigator expertise and interest in issues relating to childhood cancer survivorship, previous history of successful multi-institutional collaborative research, and geographic location. Over a 2-year period, the consortium investigators developed and agreed on the objectives of the project; eligibility criteria for study participants; and study design, methods, and outcomes. In addition, pilot studies were conducted to demonstrate the feasibility of constructing a retrospective cohort and to generate preliminary data regarding resources required to successfully complete an undertaking of this scope. Subsequent submission and peer review of a grant application resulted in funding by the National Institutes of Health in 1994. Since the original establishment of the CCSS, the project Coordinating Center has been relocated from the University of Minnesota to St Jude Children's Research Hospital, and with the current expansion of the study cohort, four new contributing institutions have been added recently (Table 1 and Fig 1).

Provided in Figure 2 is the organizational structure of the CCSS. Both the population of childhood cancer survivors and most of the scientific input are derived from the contributing/participating centers. Investigators interested in survivorship research, whether or not they are from a contributing CCSS center, can participate in one or more of nine working groups, which provide the primary focus for development and conduct of research initiatives. The CCSS Steering Committee represents the leadership body for the project and is composed of the Principal Investigator, Project Director, Working Group

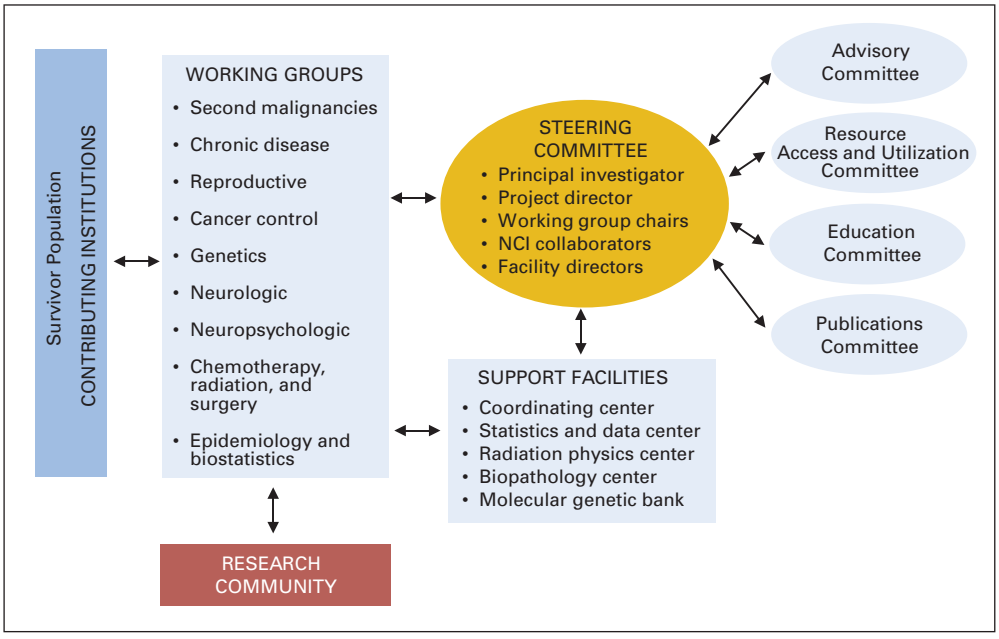

Fig 2. Childhood Cancer Survivor Study organizational structure. NCI, National Cancer Institute.

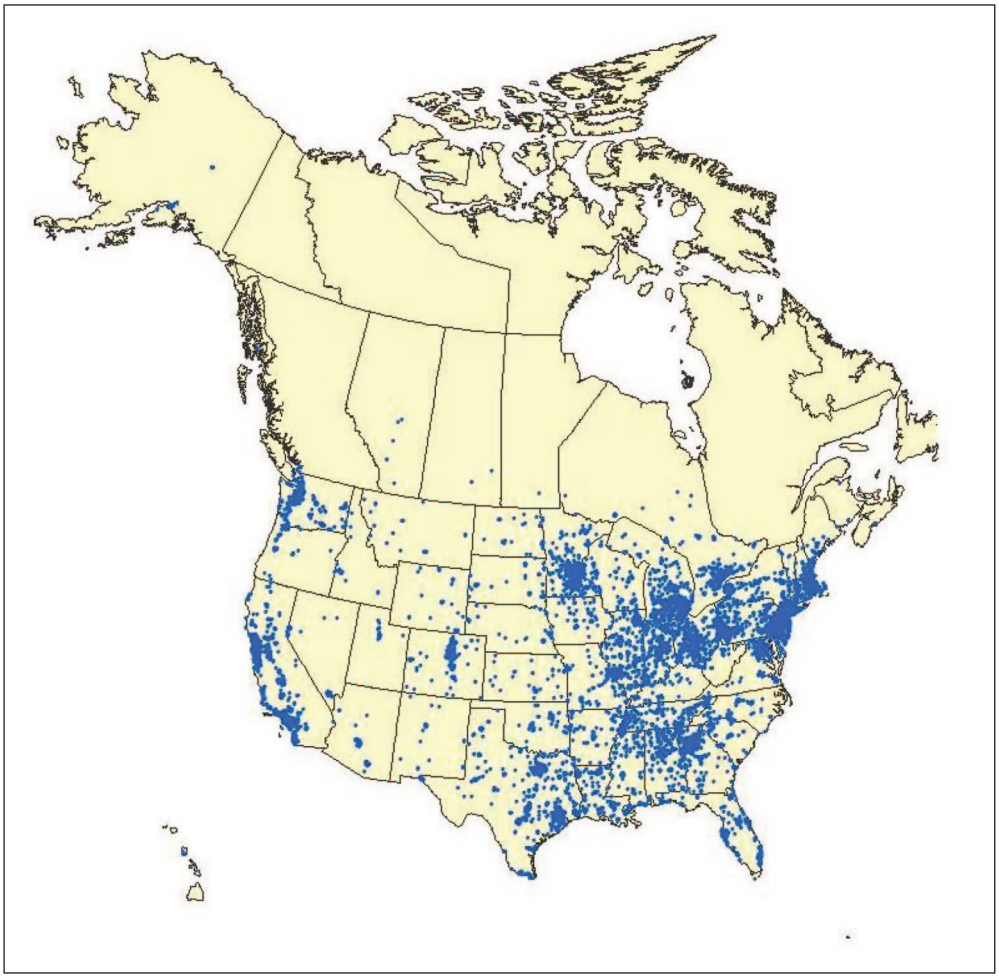

Fig 3. Geographic distribution of survivors participating in the Childhood Cancer Survivor Study.

Chairs/Co-Chairs, NCI Collaborators, and Directors of the support facilities (ie, Radiation Physics Center, Biopathology Center, Data and Statistics Center, and Bio-repository Center). Recently, the Steering Committee was expanded to invite several investigators who are early in their academic careers to participate in leadership activities of CCSS within a mentored environment. A number of committees have been established and charged with oversight of activities related to education of survivors, analysis and publication of results from CCSS, and access and utilization of the CCSS resource. Lastly, an external advisory committee, consisting of survivor advocates and experts in pediatric oncology, epidemiology, biostatistics, and radiation oncology, attend and participate in annual CCSS investigators' meetings and provide input into the current and future activities.

ESTABLISHMENT AND FOLLOW-UP OF THE CCSS COHORT

Details concerning the initial establishment of the cohort, including characteristics of the survivor and sibling cohorts, have been previously published.[5] Briefly, the CCSS cohort is restricted to 5-year survivors of the following diagnoses: leukemia, CNS cancers, Hodgkin's lymphoma, non-Hodgkin's lymphoma, Wilms (kidney) tumor, neuroblastoma, soft tissue sarcoma, or bone tumor. The original CCSS proposal did not restrict eligibility based on type of malignancy, but funding restrictions limited inclusion to only the most common diagnoses among cancer patients diagnosed before the age of 21 years. Eligibility for entry into the cohort required that a patient be diagnosed between January 1, 1970 and December 31, 1986 and have survived 5 years from his or her date of diagnosis (regardless of disease or treatment status). The institutional review board at each participating center reviewed and approved the CCSS protocol, and all study participants provided informed consent. Of the 20,720 eligible survivors identified, 14.6% were deemed to be lost to follow-up after extensive tracing efforts failed to locate them. Of those successfully contacted, 81.2% completed a 24-page baseline questionnaire. The geographic distribution of participating survivors is provided in Figure 3. The demographic-, disease-, and treatment-related characteristics of participants, contacted nonparticipants, and those lost to follow-up were compared to determine the potential for bias.[5,6] To provide a comparison population, a cohort of siblings of survivors was constructed. A randomly selected subset of survivors was asked to identify all their living siblings, from which the sibling closest in age to the survivor was selected and asked to participate. Of the 4,782 eligible siblings, 80.4% participated. Information collected from the sibling cohort is, with the exception of cancer-specific topics, identical to that obtained on the survivor population.

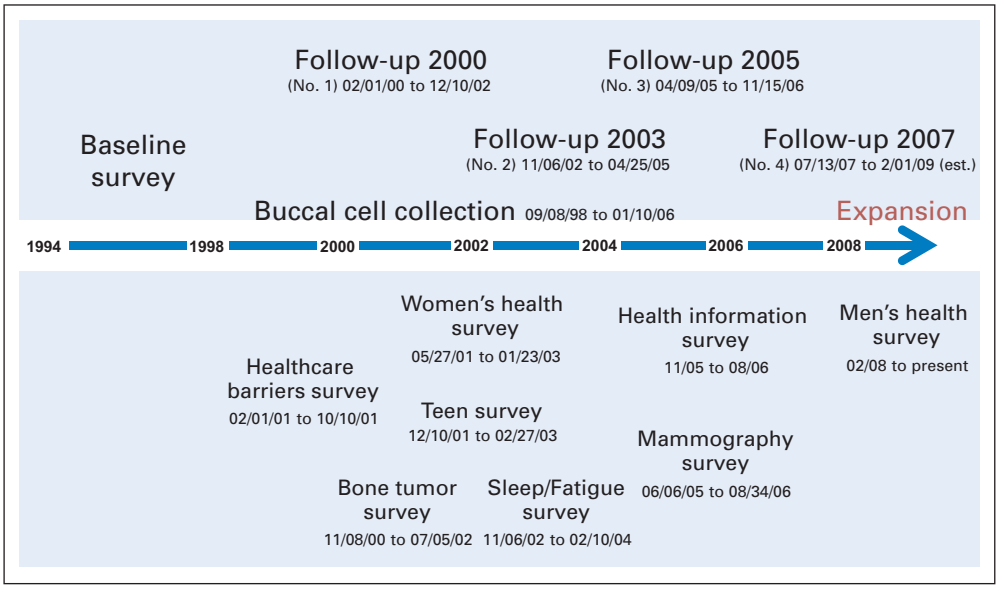

Fig 4. Chronology of Childhood Cancer Survivor Study surveys and specimen collection.

Follow-Up of the CCSS Cohort

As detailed in Figure 4, there were four follow-up surveys conducted after the collection of the baseline data from the study cohort. All study surveys are available on the CCSS Web site (www.stjude.org/ccss). Although the specific content of follow-up surveys has varied, each typically updates major health events in addition to collecting information on focused topics (eg, health utilization, quality-of-life measures, health behaviors, medical outcomes, mental health, psychosocial outcomes, use of complementary and alternative therapies, and so on). Beyond the biannual follow-up surveys, a variety of topic-specific surveys were conducted within the cohort. The majority of these ancillary studies were supported by investigator-initiated grants addressing specific study populations to conduct more in-depth evaluations. Topics of ancillary studies included barriers to health care utilization among survivors, psychosexual function among female and male survivors, health behaviors and quality of life among adolescent survivors, prevalence and risk factors for sleep disorders and fatigue, physical function and quality of life among survivors of lower extremity bone tumors, health information–seeking behaviors, and breast cancer screening practices among female survivors.

Collection and Banking of Biologic Material

To further enhance the scope of research that can be conducted within the CCSS, a biologic repository was established for banking of genomic DNA obtained from buccal cell samples of survivors and siblings, plus peripheral-blood samples from survivors with a second or subsequent neoplasm. Lymphoblastoid cell lines were established from the peripheral-blood samples. Those study participants who provided a biologic sample have given informed consent for the collection, storage, and future use of the material to investigate a spectrum of genetic issues including phase I and II enzymes, DNA repair genes, and other metabolic pathways. Use of the material to investigate genes known to be associated with disease-risk (eg, *p53*, *BRCA*, *ATM*, and so on) require independent informed consent by study participants. The initial collection of buccal cell DNA used a mouthwash-based approach. Currently, the active cohort members are being contacted and asked to provide a saliva sample using an approach that provides a higher quality and quantity of DNA. CCSS investigators at the Biopathology Center have initiated collection and storage of pathology specimens on second and subsequent malignancies. The inventory of available biospecimens is available at the CCSS Web site (www.stjude.org/ccss).

ACCESS AND UTILIZATION OF THE CCSS RESOURCE

With the successful establishment of the CCSS cohort, the potential of this large multidisciplinary project has been realized through the quality and quantity of publications in the peer-reviewed literature, presentations at national and international meetings, and funding of investigator-initiated peer-reviewed grants that use the CCSS resource. As an NCI-funded resource, CCSS has been contacted by more than 100 new investigators (ie, those not previously associated with CCSS) regarding information and/or opportunities involving the cohort. More than a quarter of these new investigators are not from contributing CCSS institutions and the majority of the new investigators contacting CCSS have become actively involved through development of an analysis concept proposal, analysis of study data, submission of a grant application involving CCSS, and/or presentation or publication of CCSS data.

CCSS Publications and Presentations at Scientific Meetings

The CCSS has proven to be a highly used source for data analyses and publications.[5-103] Since establishing the first complete analytic data set containing baseline questionnaire information, completed medical record abstraction, and validation of second malignancies, investigators have conducted analyses on a wide range of outcomes (Table 2). Because of the cohort study design, it has been possible to address issues spanning many topics such as health care utilization, health behaviors, health status, chronic health conditions, psychosocial and quality-of-life factors, second malignancies, endocrine and

Table 2. Childhood Cancer Survivor Study Publications Through 2008

Topic	Population	Citation	Reference No.
Peer-reviewed publications			
Alcohol	All diagnoses	Lown et al. Addiction 103:1139-1148, 2008	7
Chronic health conditions	All diagnoses	Oeffinger et al. N Engl J Med 355:1572-1582, 2006	8
Complementary/alternative therapy	All diagnoses	Mertens et al. Pediatr Blood Cancer 50:90-97, 2008	9
Education/employment/marriage/insurance	All diagnoses	Rauck et al. Med Pediatr Oncol 33:60-63, 1999	10
	All diagnoses	Mitby et al. Cancer 97:1115-1126, 2003	11
	Bone malignancies	Nagarajan et al. Cancer 97:2554-2564, 2003	12
	All diagnoses	Park et al. J Clin Oncol 23:9187-9197, 2005	13
	All diagnoses	Pang et al. Pediatr Blood Cancer 50:104-110, 2008	14
Endocrine and cardiovascular	CNS malignancies	Gurney et al. Cancer 97:663-673, 2003	15
General survivorship	All diagnoses	Robison et al. Cancer 104:2557-2564, 2005	16
	Minority survivors	Castellino et al. J Clin Oncol 23:6499-6507, 2005	17
	Rhabdomyosarcoma	Punyko et al. Pediatr Blood Cancer 44:643-653, 2005	18
	Acute myeloid leukemia	Mulrooney et al. Cancer 112:2071-2079, 2008	19
	Non-Hodgkin's lymphoma	Bluhm et al. Blood 111:4014-4021, 2008	20
	Acute lymphoid leukemia	Mody et al. Blood 111:5515-5523, 2008	21
Genetics/family history	All diagnoses	Boice et al. Health Phys 85:65-85, 2003	22
	All diagnoses	Friedman et al. Cancer Epidemiol Biomarkers Prev 14:1922-1927, 2005	23
	All diagnoses	Kadan-Lottick et al. Pediatr Blood Cancer 46:476-481, 2006	24
	All diagnoses	Blanco et al. Cancer 112:2789-2795, 2008	25
Gonadal function/pregnancy	All diagnoses	Green et al. Am J Obst Gynecol 187:1070-1080, 2002	26
	All diagnoses	Green et al. J Clin Oncol 21:716-721, 2003	27
	All diagnoses	Chemaitilly et al. J Clin Endocrinol Metab 91:1723-1728, 2006	28
	All diagnoses	Sklar et al. J Natl Cancer Inst 98:890-896, 2006	29
	All diagnoses	Signorello et al. J Natl Cancer Inst 98:1453-1461, 2006	30
	Acute lymphoid leukemia	Chow et al. Pediatr Blood Cancer 50:854-858, 2008	31
	All diagnoses	Green et al. J Clin Oncol (in press)	32
	CNS malignancies	Armstrong et al. Cancer (in press)	33
Growth hormone	All diagnoses	Sklar et al. J Clin Endocrinol Metab 87:3136-3141, 2002	34
	All diagnoses	Brownstein et al. J Clin Endocrinol Metab 89:4422-4427, 2004	35
	All diagnoses	Ergun-Longmire et al. J Clin Endocrinol Metab 91:3494-3498, 2006	36
	Acute lymphoid leukemia	Gurney et al. Cancer 107:1303-1312, 2006	37
Health status	All diagnoses	Hudson et al. JAMA 290:1583-1592, 2003	38
Health care utilization/screening	All diagnoses	Yeazel et al. Cancer 100:631-640, 2004	39
	All diagnoses	Oeffinger et al. Ann Family Med 2:61-70, 2004	40
	All diagnoses	Yeazel et al. J Public Health Dent 64:50-54, 2004	41
	All diagnoses	Nathan et al. J Clin Oncol 26:4401-4409, 2008	42
	All diagnoses	Cox et al. Arch Intern Med 169:454-462, 2009	43
	All diagnoses	Cox et al. Oncol Nurs Forum (in press)	44
	All diagnoses	Oeffinger et al. JAMA 301:404-414, 2009	45
Knowledge of cancer history	All diagnoses	Kadan-Lottick et al. JAMA 287:1832-1839, 2002	46
Mortality	All diagnoses	Mertens et al. J Clin Oncol 19:3163-3172, 2001	47
	All diagnoses	Mertens et al. J Natl Cancer Inst 100:1368-1379, 2008	48
Neurologic/neurosensory	CNS malignancies	Packer et al. J Clin Oncol 21:3255-3261, 2003	49
Osteonecrosis	All diagnoses	Kadan-Lottick et al. J Clin Oncol 26:3038-3045, 2008	50
Physical function/quality of life	Bone malignancies	Nagarajan et al. Br J Cancer 91:1858-1865, 2004	51
	All diagnoses	Ness et al. Ann Intern Med 143:639-647, 2005	52
	Wilms tumor and neuroblastoma	Nathan et al. Pediatr Blood Cancer 49:704-715, 2006	53
	Acute lymphoid leukemia	Ness et al. Pediatr Blood Cancer 49:975-981, 2006	54
	Rhabdomyosarcoma	Punyko et al. Psychooncology 16:26-37, 2007	55
	Acute lymphoid leukemia	Florin et al. Cancer Epidemiol Biomarkers Prev 16:1356-1363, 2007	56
	All diagnoses	Ness et al. Arch Phys Med Rehabil 89:128-136, 2008	57
	All diagnoses	Zeltzer et al. Cancer Epidemiol Biomarkers Prev 17:435-446, 2008	58
	All diagnoses	Cox et al. Cancer (in press)	59
	All diagnoses	Ness et al. Cancer [Epub ahead of print on February 17, 2009]	60
	Bone malignancies	Nagarajan et al. J Cancer Surviv 3:59-65, 2009	61

(continued on following page)

Table 2. Childhood Cancer Survivor Study Publications Through 2008 (continued)

Topic	Population	Citation	Reference No.
Psychological	Hematopoietic malignancies	Zebrack et al. Pediatrics 110:42-52, 2002	62
	CNS malignancies	Zebrack et al. J Clin Oncol 22:999-1006, 2004	63
	Solid tumors	Zebrack et al. Pediatr Blood Cancer 49:47-51, 2007	64
	All diagnoses	Schultz et al. J Clin Oncol 25:3649-3656, 2007	65
Pulmonary	All diagnoses	Mertens et al. Cancer 95:2431-2441, 2002	66
Second neoplasms	All diagnoses	Neglia et al. J Natl Cancer Inst 93:618-629, 2001	67
	All diagnoses	Kenney et al. Ann Intern Med 141:590-597, 2004	68
	Hodgkin's disease	Mertens et al. Cancer 101:1463-1472, 2004	69
	All diagnoses	Sigurdson et al. Lancet 365:2014-2023, 2005	70
	All diagnoses	Perkins et al. J Clin Oncol 23:3733-3741, 2005	71
	All diagnoses	Bassal et al. J Clin Oncol 24:476-483, 2006	72
	All diagnoses	Ronckers et al. Radiat Res 166:618-628, 2006	73
	All diagnoses	Neglia et al. J Natl Cancer Inst 98:1528-1537, 2006	74
	All diagnoses	Henderson et al. J Natl Cancer Inst 99:300-308, 2077	75
Sleep/fatigue	All diagnoses	Mulrooney et al. Sleep 31:271-281, 2008	76
Smoking	All diagnoses	Emmons et al. J Clin Oncol 20:1608-1616, 2002	77
	All diagnoses	Emmons et al. J Clin Oncol 21:189-196, 2003	78
	All diagnoses	Butterfield et al. Psychooncology 13:619-629, 2004	79
	All diagnoses	Emmons et al. J Clin Oncol 20:6516-6523, 2005	80
	All diagnoses	Park et al. Prev Med 42:435-442, 2006	81
	All diagnoses	Emmons et al. J Clin Oncol 27:52-60, 2009	82
Stroke	Hodgkin's disease	Bowers et al. J Clin Oncol 23:6508-6515, 2005	83
	Leukemia and CNS malignancies	Bowers et al. J Clin Oncol 24:5277-5285, 2006	84
Survivorship methodology	All diagnoses	Yasui et al. J Clin Epidemiol 52:292-298, 1999	85
	All diagnoses	Robison et al. Med Pediatr Oncol 38:229-239, 2002	5
	All diagnoses	Kadan-Lottick et al. Epidemiology 14:737-740, 2003	86
	All diagnoses	Yasui et al. Am J Epidemiol 158:1108-1113, 2003	87
	All diagnoses	Stovall et al. Int J Radiat Oncol Biol Phys 60:542-552, 2004	88
	All diagnoses	Mertens et al. J Clin Epidemiol 57:933-944, 2004	6
	All diagnoses	Recklitis et al. Psychol Assess 18:22-23, 2006	89
	All diagnoses	Dinu et al. Pediatr Blood Cancer 50:1026-1031, 2008	90
	All diagnoses	Krull et al. Cancer 113:2188-2197, 2008	91
	All diagnoses	Ness et al. Pediatr Blood Cancer 52:379-386, 2009	92
Thyroid function	Hodgkin's disease	Sklar et al. J Clin Endocrinol Metab 85:3227-3232, 2000	93
Weight/height/body mass index	Acute lymphoid leukemia	Oeffinger et al. J Clin Oncol 21:1359-1365, 2003	94
	CNS malignancies	Gurney et al. J Clin Endocrinol Metab 88:4731-4739, 2003	95
	Acute lymphoid leukemia	Ross et al. J Clin Oncol 22:3558-3562, 2004	96
	All diagnoses	Meacham et al. Cancer 103:1730-1739, 2005	97
	Acute lymphoid leukemia	Chow et al. J Pediatr 150:370-375, 2007	98
	Acute lymphoid leukemia	Garmey et al. J Clin Oncol 26:4639-4645, 2008	99
Non–peer-reviewed publications			
General survivorship	All diagnoses	Robison. Minn Med 88:45-49, 2005	100
Mortality	All diagnoses	Mertens. Pediatr Blood Cancer 48:723-726, 2007	101
Second neoplasms	All diagnoses	Davies. Pediatr Blood Cancer 48:727-730, 2007	102
	All diagnoses	Robison. Pediatr Radiol 39:S32-S37, 2009 (suppl 1)	103
Submitted manuscripts			
Cardiac	All diagnoses	Mulrooney et al (submitted for publication)	
Dental	All diagnoses	Kaste et al (submitted for publication)	
Diabetes	All diagnoses	Meacham et al (submitted for publication)	
Education/employment/marriage/insurance	All diagnoses	Janson et al (submitted for publication)	
General survivorship	Neuroblastoma	Laverdiere et al (submitted for publication)	
	CNS malignancies	Armstrong et al (submitted for publication)	
Second neoplasms	All diagnoses	Inskip et al (submitted for publication)	

reproductive outcomes, and late mortality. In addition, the cohort has been the basis of a number of methodologic publications relating to survivorship-based research. Beyond the diversity of topics addressed, it is important to note the generally high impact of CCSS publications. Presentation of CCSS results at national and international meetings has also been a significant method of disseminating findings from the project. More than 120 abstracts have been presented at scientific conferences (full listing available at www.stjude.org/ccss).

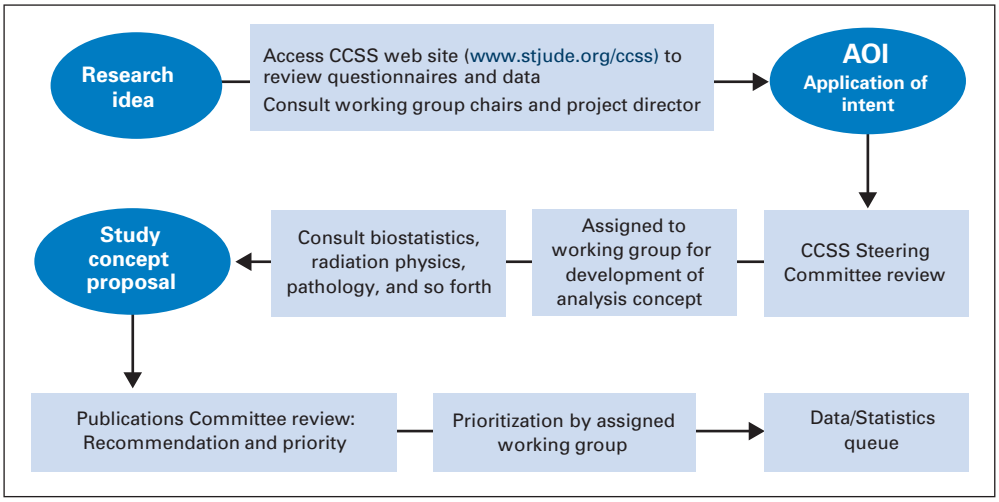

Fig 5. Process for requesting access to the Childhood Cancer Survivor Study (CCSS) resource for analysis and publication.

Mechanism for Using the CCSS Resource

The CCSS is a resource for the scientific community at large. Any investigator interested in using the CCSS resource, whether through analysis and publication of existing data, through use of stored biologic samples, or by investigator-initiated research grant proposals, is encouraged to contact the CCSS Coordinating Center or a Working Group Chair. A formal process has been established to evaluate proposed research involving the CCSS resource (Fig 5). The two-stage process consists of submission of an Application of Intent to conduct research, which is reviewed by the CCSS Steering Committee, followed by completion of an Analysis Concept Form that is reviewed by the CCSS Publication Committee. Details of this process and examples of the Application of Intent and Analysis Concept Form are available at the CCSS Web site (www.stjude.org/ccss). As a resource, CCSS has been well used by investigators to secure funding for survivorship research through investigator-initiated grant applications. To date, 19 externally funded grants have been awarded that use the CCSS resource as a component of the research plan. These grants, totaling more than $14,000,000 in funding, demonstrate the utility of the CCSS to facilitate high-quality, peer-reviewed research from sources including the National Institutes of Health (n = 9) and nongovernmental agencies/foundations (n = 10).

Public Access Data

To further facilitate access to the vast amount of data generated through the CCSS, efforts are underway to establish an extensive library of public access data tables. The initial series of tables are currently available on the CCSS Web site (www.stjude.org/ccss) and will be expanded on an ongoing basis. The aim of the public access data is to allow researchers and health care/public health professionals to determine the frequency of self-reported information among long-term survivors of childhood cancer. These data can then be used for publication/citation and planning of proposed research.

PRIORITIES AND FUTURE DIRECTION OF CCSS

With the passage of time, the aging CCSS cohort increasingly brings new information about the long-term effects of treatment. Although this addresses an important aspect of cancer survivorship (ie, impact of aging among patients exposed during childhood), the treatment-related characteristics of the cohort increasingly reflect a greater historical perspective. To maintain the scientific impact of the CCSS resource, efforts are underway to expand the existing cohort by adding 5-year survivors diagnosed and treated between January 1, 1987 and December 31, 1999. Expansion of the CCSS cohort through recruitment of individuals who achieve long-term survival after more contemporary treatment is important to improve our understanding about evolving late complications associated with new agents and modalities. This includes the potential of altered risk for morbidity or mortality, including the impact of reduction of therapy designed to minimize late effects. Participating CCSS centers have identified 26,093 eligible 5-years survivors, of whom 20,729 were selected for recruitment. Selection criteria for recruitment were based on the goal of enriching the expansion cohort for ethnic/racial minorities and disease/treatment groups of particular interest. Recruitment efforts are underway for expansion of the CCSS cohort.

Another priority for CCSS is a greater emphasis on translation of findings into intervention strategies. A primary focus of CCSS has been to quantify the magnitude of and risk factors for adverse health and quality-of-life outcomes. Although many of these observations have helped define clinical care recommendations and screening guidelines, it is now essential that this information be applied to cancer control efforts, including the development of novel primary risk-adapted interventions for newly diagnosed patients, secondary risk-reducing interventions for long-term survivors at risk of cancer-related morbidity, and risk-based screening guidelines for long-term survivor health care. Each of these aspects of translating CCSS data into intervention strategies will require the development and conduct of clinical trials to test the feasibility and efficacy of the intervention. The CCSS resource represents a strong venue for testing of interventions targeted to long-term survivors.

Lastly, it is well recognized that the strengths of CCSS are many, but reliance on self-reported outcomes imposes limitations on the scope of potential research. CCSS investigators are currently exploring the potential for creating a subcohort of survivors for clinically based assessments. As depicted in Figure 3, there are geographic clusters of survivors within the United States and Canada. Participants who reside within defined geographic areas of selected CCSS centers are

being characterized, with plans to conduct pilot studies to determine the feasibility of performing clinically based investigations.

SUMMARY

Over the last 14 years, the CCSS has significantly expanded our understanding of clinical factors predisposing to cancer-related morbidity and mortality. This accomplishment was made possible by making available information on long-term outcomes in a large, geographically diverse population that is well characterized regarding demographics, treatment exposures, and outcomes.

The importance of the CCSS encompasses the well-being of the cancer survivor, the practice of the pediatric oncologists and primary care physicians who see long-term survivors, and the research questions posed by multidisciplinary teams of investigators. Through the education efforts of the CCSS, participants receive semiannual newsletters summarizing findings of the study and addressing topics of health promotion (available to all interested parties at www.stjude.org/ltfu). The health behaviors of long-term survivors may, compared with the general population, have a greater impact on the quality and length of their lives. For the pediatric treatment team, including surgeons, radiation oncologists, and oncologists, knowledge of the late effects of therapy is critical for choosing initial therapy for current and future patients, as well as recommendations for appropriate follow-up and screening of survivors. For health care providers and planners, CCSS offers the first opportunity to assess in detail the impact of long-term cancer survivorship on the delivery of care as these cancer survivors age. Finally, the cohort provides a critical framework and resource for epidemiologists and biologists to investigate current and future questions regarding consequences of therapy, genetic association, disease processes and causation, and quality of life.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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