The Childhood Leukemia International Consortium

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Conflict of interest

None declared.
Abstract

Background—Acute leukemia is the most common cancer in children under 15 years of age; 80% are acute lymphoblastic leukemia (ALL) and 17% are acute myeloid leukemia (AML). Childhood leukemia shows further diversity based on cytogenetic and molecular characteristics, which may relate to distinct etiologies. Case–control studies conducted worldwide, particularly of ALL, have collected a wealth of data on potential risk factors and in some studies, biospecimens. There is growing evidence for the role of infectious/immunologic factors, fetal growth, and several environmental factors in the etiology of childhood ALL. The risk of childhood leukemia, like other complex diseases, is likely to be influenced both by independent and interactive effects of genes and environmental exposures. While some studies have analyzed the role of genetic variants, few have been sufficiently powered to investigate gene–environment interactions.

Objectives—The Childhood Leukemia International Consortium (CLIC) was established in 2007 to promote investigations of rarer exposures, gene–environment interactions and subtype-specific associations through the pooling of data from independent studies.

Methods—By September 2012, CLIC included 22 studies (recruitment period: 1962–present) from 12 countries, totaling approximately 31 000 cases and 50 000 controls. Of these, 19 case–control studies have collected detailed epidemiologic data, and DNA samples have been collected from children and child–parent trios in 15 and 13 of these studies, respectively. Two registry-based studies and one study comprising hospital records routinely obtained at birth and/or diagnosis have limited interview data or biospecimens.

Conclusions—CLIC provides a unique opportunity to fill gaps in knowledge about the role of environmental and genetic risk factors, critical windows of exposure, the effects of gene–environment interactions and associations among specific leukemia subtypes in different ethnic groups.
1. Introduction

Leukemia is the most common cancer among children, representing about a third of all cancers occurring before the age of 15 years; approximately 80% are acute lymphoblastic leukemia (ALL) primarily in children 1–4 years old, 17% acute myeloid leukemia (AML), and 3% chronic myeloid leukemias, with some variation in ALL and AML incidence rates worldwide [1,2]. Further classification of childhood leukemia is made on the basis of cell types for ALL, and cytogenetic/molecular characteristics (e.g., chromosome translocations such as t(12;21), the MLL gene fusion, and aberrant chromosome number such as hyperdiploidy) [3]. These leukemia subtypes exhibit heterogeneity with regard to pathophysiology, clinical manifestations, response to treatment, and prognosis, which suggests distinct etiologies [4]. Biological studies have shown that both prenatal initiating events and postnatal promoting events could be involved in the development of childhood leukemia, consistent with the “two-hit” model confirmed in the natural history of several tumor sites and hypothesized for leukemogenesis [5].

Apart from established associations with rare and specific inherited and congenital genetic instability disorders (e.g., Down syndrome, Fanconi anemia, ataxia telangiectasia and others), prenatal exposure to X-rays and chemotherapeutic agents, epidemiologic studies of childhood leukemia conducted during the last two decades have investigated the role of the child’s immune function, fetal growth and other perinatal characteristics, as well as associations with in utero and early life exposures, including a range of environmental agents. In brief, a decreased risk of childhood B-cell ALL has been associated with surrogate measures of early common infection, such as high levels of social contact in daycare settings [6-9]. Elevated risks of childhood ALL have been reported with high birth weight [10], home use of pesticides [11], tobacco smoking [12-13], diet [14-17], parental occupational chemical exposures such as solvents and hydrocarbons, and some measures of outdoor air pollution [18-23]. Previous studies, mostly limited in scope, have evaluated the role of candidate genes involved in xenobiotic transport and metabolism [24-32], DNA repair [28,33,34], folate metabolic pathways [28,35-38], and immune regulation [28,39-42] including the histocompatibility complex (human leukocyte antigen (HLA) genes) [43-45]. Recent genome wide association studies (GWAS) of childhood B-cell ALL [46-49] and replication studies [50-53] reported associations with genes involved in the transcriptional regulation and differentiation of B-cell progenitors in Caucasian [46-48], Asian [49] and African-American populations [51]. However, it seems unlikely that childhood ALL, like other complex diseases, is determined solely by genetic or environmental factors, but may result from interactions between them. If this paradigm applies to childhood leukemia, the relative rarity of the disease may be explained by interactions between rare genotypes and multiple exposures. While some studies to date have attempted to investigate such gene–environment interactions in childhood ALL [24-27,29,31,36,39,54-62], most have lacked sufficient statistical power.

To overcome the limitations of single epidemiologic studies, the Childhood Leukemia International Consortium (CLIC) was established in 2007, building upon the wealth of data and biospecimens collected in over 20 case–control studies worldwide (https://clic.berkeley.edu). The unprecedented number of children whose data are available for pooling will enhance the statistical power to investigate the contribution of pre- and postnatal exposures to the etiology of childhood ALL, AML, and rarer subtypes, and will
facilitate investigation of gene–environment interactions. The aim of this paper describes the history and organization of CLIC, the participating studies, future directions and challenges.

2. CLIC history and organization

In 2005–2006, the investigator of the US-California childhood leukemia study (PAB) initiated contacts with investigators from Australia (EM), Canada (CIR), and France (JC) to discuss the establishment of an international consortium of epidemiologic studies of childhood leukemia. The primary goals were to share comparable epidemiologic and possibly genetic data in order to enhance statistical power of analyses and, most importantly, to exchange ideas among researchers from different disciplines including epidemiologists, tumor biologists, geneticists, immunologists, toxicologists, clinicians and statisticians about the possible causes of childhood leukemia. In collaboration with the International Agency for Research on Cancer (IARC), CLIC was established in 2007 with its first formal annual meeting. Several other leukemia investigators were invited to outline research priorities and the structure of the consortium, and consortium meetings have taken place each year since then. By September 2012, CLIC had expanded to include 22 existing individual childhood leukemia studies from 18 research groups in 12 countries within North, Central, and South America, Europe, Australia/Oceania, and Africa (https://clic.berkeley.edu). These studies have substantial similarities in research hypotheses and study designs (Table 1).

Two projects were initiated to demonstrate a proof of principle for pooling data within CLIC. One examined the associations between maternal vitamin and folate supplementation during pregnancy and the risk of childhood ALL and AML (supported by funding from the National Cancer Institute, NCI, USA), and the other investigated the association between two measures of fetal growth and childhood ALL (supported by funding from the Cancer Council Western Australia). These initiatives enabled CLIC to develop guidelines and procedures for requesting and pooling data, and guidelines for membership and authorship. The latter were modeled on successful consortia of adult cancers (i.e., the International Lymphoma Epidemiology Consortium, Interlymph, http://epi.grants.cancer.gov/InterLymph/; the International Lung Cancer Consortium, ILCCO, http://ilcco.iarc.fr/), and other references such as the International Committee of Medical Journal Editors (http://www.icmje.org/).

The consortium is governed by the Coordination Group, which comprises the principal investigators and designated co-investigators from CLIC studies. CLIC-wide activities such as those involving data pooling/management, disease classification/pathology, and other emerging needs are supported by the Core Logistics Groups. Research priorities for collaborative projects are set by the Interest Groups, including topics on (by alphabetical order) birth characteristics, environmental and occupational exposures, family history, genetic studies, infection and immunity, rare leukemia subtypes (such as infant leukemia, acute myeloid and promyelocytic leukemia, and T-cell ALL), and survival/outcome studies. The latter group was established as an extension of the etiologic research in leukemogenesis. This Interest Group aims to determine which case series of the case–control studies are (or can be) linked with information on vital status and course of disease. Subsequently, this Group will explore survival in relation to socio-demographic factors, clinical characteristics, and treatment modalities, whenever available. Pooling projects that are approved by the Coordination Group are then implemented by Working Groups. Lastly, the Management Group, which comprises an elected Chair, Vice Chair, and Members, facilitates all CLIC operations. Participation in all groups described above is voluntary (details on CLIC organization are available at https://clic.berkeley.edu/organization).
Members of the Coordination Group who contribute epidemiologic or genetic data are Active CLIC Members, while researchers with relevant expertise, but who do not contribute data, may apply for Associate Membership of CLIC. An individual study may solicit CLIC membership directly or upon invitation by a CLIC Member; inclusion and exclusion criteria include the robustness of the study design and the scope of epidemiologic data and biospecimen available for pooling projects. As a result, CLIC represents a large subset of childhood leukemia studies including most of the large case–control studies worldwide.

Currently, data are held locally by each study principal investigator, who following bilateral data transfer agreements, sends them to the pooling project leader for data harmonization and analyses. Protocols for harmonizing common variables such as parental education and ethnicity are shared between investigators. Now that CLIC has demonstrated its ability to share and analyze data, CLIC has opted to establish a central data coordination center hosted at the IARC, Lyon, France, in order to streamline the exchange of data and relevant study information between CLIC Members, under bilateral data transfer agreements. The short-term goal is to store common variables on socio-demographic characteristics and disease classification, other clinical characteristics and outcomes, as well as variables harmonized for pooled analyses addressing specific hypotheses. These data and their documentation will be checked for consistency and made available for future analyses after approval by principal investigators of each individual CLIC study. In addition, medium-term goals of the central data coordination center are to store original study data when requested by a principal investigator, and to develop an interactive inventory of data and biospecimens available in CLIC studies. Lastly, a long-term goal is to provide support for statistical programming, if requested by the pooling project leader.

3. CLIC studies

Table 1 describes the characteristics of 22 studies participating in CLIC as of September 2012. All individual studies had been approved by their respective ethics committee, and family members who provided data had given informed consent. Leukemia cases were identified from nation/region-wide population-based cancer registries, networks of hospitals or physicians – which in some countries are equivalent to national population-based coverage (14 studies), selected hospitals (6 studies), or clinical trials (2 studies). The source of controls was either population-registry based (14 studies), hospital-based (5 studies), or recruited using random-digit dialing (3 studies). In total, CLIC has accrued information for 31 239 leukemia cases and 50 166 controls (Table 2).

Approximately half of study participants in the CLIC data set (11 157 ALL, 1836 AML, and 21 375 controls) came from 19 case–control studies in which detailed epidemiologic data were obtained using standardized questionnaires to collect information on putative risk factors. The period of enrollment started from 1980, with recruitment ongoing in some studies. Therefore, any tables describing the size of the CLIC studies may be different from what has been published at the time of this manuscript. With few exceptions, children were less than 15 years of age at recruitment. The risk factors studied include medical conditions of the child and mother (e.g., reproductive and birth characteristics, drug use, diagnostic X-rays, infection and other conditions), lifestyle (diet, consumption of alcohol, coffee, and vitamin supplementation, tobacco smoking, markers of social contact), and pre-and postnatal exposures to chemicals (e.g., pesticides, paints, hair dyes, and solvents at home or work). Biospecimens were collected for DNA extraction in 15 of the 19 case–control studies, representing approximately 9400 cases and 7100 controls. Thirteen studies also obtained DNA from child–parent trios (Table 2), which offers a unique opportunity to enhance the validity of genetic association studies. Some CLIC studies have completed genotyping in a subset of cases and/or controls, mostly for selected single nucleotide
polymorphisms (SNPs) in candidate genes involved in xenobiotic and folate metabolism and DNA repair. Other investigators are currently conducting or analyzing data from large-scale genotyping and sequencing studies, or have specimens available for future genetic investigations.

The other half of the participants in CLIC studies (15 075 ALL, 2883 AML, 28 791 controls) were ascertained from two registry-based studies and one study comprising hospital records routinely obtained at birth and/or diagnosis. These studies, with enrollment starting as early as 1962, have limited epidemiologic data available.

Several pooled analyses that maximize the use of existing epidemiologic and genetic data, and possibly outcome data for some studies, are under way (Table 3). Following is an example illustrating the gain in statistical power to examine the association between maternal smoking during pregnancy and childhood AML within CLIC compared to individual studies: given a power of 0.80, an alpha of 0.05, a prevalence of exposure of 20%, and the use of unmatched analysis, the minimum detectable odds ratio is 1.26 for CLIC pooled analyses (930 cases and 7800 controls) vs. 1.69 and 2.96 for individual CLIC studies such as the UKCCS (248 AML cases/492 controls) or the NARECHEM study (105 AML cases/105 controls), respectively.

Classification on immunophenotypes of childhood ALL was available in 19 studies, comprising approximately 9000 B-cell and 1000 T-cell cases (Table 2). Information on molecular lesions, as identified by conventional karyotype at the time of the leukemia diagnosis, was available for most CLIC studies, at least on a subset of cases. Only a few studies have readily available information on gene translocations, duplications and deletions using fluorescence in situ hybridization (FISH) or polymerase chain reaction (PCR) assays, which are mainly available for cases diagnosed after 2000. Quality and completeness of cytogenetic and molecular data in CLIC are currently being evaluated, as methods used for cytogenetic characterization of leukemia cases have evolved over time from conventional karyotyping to more sophisticated molecular biologic methods to detect chimeric gene products using FISH and PCR assays.

Currently, approximately 80% of study subjects in CLIC are classified as White/Caucasian/European, based on self-reports or population demographics when detailed information was not collected. The remaining 20% include children of various ethnic backgrounds, primarily enrolled in studies from the United States, Brazil, and Egypt. We estimate that about 780 cases and 1900 controls are Hispanics. Additionally, a study from Mexico [63] with 980 cases and 750 controls will soon join CLIC. In contrast, the numbers of children reporting Asian and African backgrounds remain low (~200 cases; 800 controls for each group). For a subset of CLIC studies, population admixture will be characterized using ancestry informative markers derived from GWAS.

### 4. Future directions and challenges

CLIC is a maturing consortium that brings together a large community of scientists and clinicians with expertise in childhood leukemia research, a wealth of epidemiologic data, and a substantial amount of genetic data from 12 countries in 5 continents. CLIC is reaching out to additional investigators in Central and South America, and to new studies in Asia and possibly Africa, to expand the participation of these underrepresented ethnic groups.

A number of meta-analyses of published data from childhood leukemia studies have been conducted (e.g., maternal folate [64], pesticides [11], and daycare attendance [6]). Beyond the advantage of pooling data to increase statistical power, CLIC provides access to original published and un-published data (therefore reducing potential for publication bias) and
detailed recruitment statistics. This allows the CLIC investigators to assess the suitability of individual studies in pooled analyses, and to address specific research questions with adequate statistical power, such as estimating risk of rare leukemia subtypes (e.g., understudied AML, T-cell ALL, and cytogenetic subtypes), effects of rare exposures (e.g., some paternal and maternal occupational exposures), multiple time periods of exposure (e.g., sole or combined contribution of exposures occurring during preconception, pregnancy as a whole or by trimester and after birth), dose–response relationships, and possible interactions between socio-demographic (S), environmental (E) and genetic (G) factors (e.g., ExE, ExS, GxG, and GxE interactions).

We acknowledge the challenges in harmonizing existing epidemiologic data collected across a wide range of studies using various designs, and that the limitations of the original studies remain. However, by having access to original data, CLIC investigators are able to conduct comprehensive sensitivity analyses to evaluate the nature and magnitude of various biases related, for example, to non-participation and missing data in individual studies.

To address some methodological limitations of case–control studies, the International Consortium of Childhood Cancer Cohorts (I4C) was established in 2006 to pool data for over 700 000 children from birth cohorts worldwide [65]. The I4C aims to enhance exposure classification through a prospective design; however, cohort studies are not exempt from selection bias and they face challenges in accruing sufficient numbers of leukemia cases in a reasonable time period. Indeed, while the major strength of CLIC is its access to data from several thousand children diagnosed with common and rare leukemia subtypes, the anticipated number of children with leukemia participating in I4C longitudinal studies is ~400 ALL and 100 AML (based on 700 000 children) [65]. Despite the respective strengths and limitations of CLIC and I4C, there are several possible areas for complementary work between the two consortia, such as cross-validation of findings using two methodological approaches, and joint projects to characterize biomarkers of prenatal exposures using pre-natal biospecimens that are available in I4C studies and in some CLIC case–control studies (such as archive newborn blood spots as listed in Table 2). The leaders and members of CLIC and I4C are working closely to maximize the benefits of the two methodological approaches, and to exchange expertise.

Other groups are collaborating to study genetic and/or environmental factors for childhood leukemia [65,66]. The strength of CLIC, however, lies in the availability of both environmental data and the child’s genetic data and/or DNA, as well as parental DNA in a subset of studies. CLIC is currently examining gene–environment interactions with targeted environmental exposure data and functional SNPs (Table 3), and will aim to undertake relevant gene-environment analyses of SNPs with main effects that are replicated by GWAS. Lastly, because CLIC has a unique diversity of ancestries among subjects, it will be feasible to undertake GWAS among specific ethnic groups. This is particularly attractive given that leukemia incidence rates vary substantially between ethnic groups. Several practical concerns will guide the pooling of genetic data in CLIC, including the choice of genotyping platform, central vs. distributed genotyping, and the decision to pursue individual vs. consortium-wide funding.

The overarching objective of CLIC is to influence the focus and priorities for childhood leukemia research through large collaborative efforts. CLIC will continue to seek funding and partnerships to support its expanding research portfolio. CLIC is an open consortium willing to include additional collaborations. Furthermore, CLIC strives to be a dynamic consortium and has established mechanisms for the submission of new research proposals.
and for the development of databases with common core variables and clear data dictionaries to facilitate current and future pooling projects.

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Authorship
Several of the authors contributed to the establishment of CLIC (CMet, EM, JC, CIR, and PAB); others are in the CLIC Management Group (CMet, EM, JC, CIR, LS, JS, and PAB), the coordination of CLIC (AYK), or the writing group of this manuscript (CMet, EM, JC, CIR, EP, MT, PAB, and AYK). All authors (except AYK) are principal investigators, co-investigators or designates of participating CLIC studies described herein and in the tables. All authors were involved in planning this manuscript, have reviewed it for intellectual content and approve of the final version submitted for publication.

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Appendix 1. Acknowledgments by study (listed by location and name in alphabetical order). Further information can be found in study references and websites, and https://clic.berkeley.edu

Australia, Aus-ALL [13,64,67]

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Italy, Studio sulla Eziologia dei Tumori Infantili Linfopoietici (SETIL) [81]

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Corrado Magnani (Università del Piemonte Orientale); Lucia Miligi (ISPO, Firenze); Maurizio A ricò and Gabriella Bernini (AOU Meyer, Firenze); Antonio Acquaviva (AOU di Siena); Giorgio Assennato (ARPA, Bari); Giuseppe Basso, Stefania Varotto and Paola Zambon (Università di Padova); Pierfranco Biddau (Ospedale Microcitemico, Cagliari); Luigi Bisanti (ASL di Milano); Francesco Bochicchio, Susanna Lagorio, Cristina Nuccetelli, Alessandro Polichetti, Serena Risica, and Paolo Vecchia (ISS, Roma); Santina Cannizzaro and Lorenzo Gafà (LILT, Ragusa); Egidio Celentano (ARSan, Napoli); Pierluigi Cocco (Università di Cagliari); Marina Cuttini and Paolo Tamaro (IRCCS Burlo Garofolo, Trieste); Francesco Forastiere, Ursula Kirchmayer, and Paola Michelozzi (Dipartimento Epidemiologia Regione Lazio, Roma); Riccardo Haupt (Istituto Giannina Gaslini, Genova); Franco Locatelli (Università di Pavia); Lia Lidia Luzzatto (Ospedale Pediatrico Regina
Margherita, Torino); Giuseppe Masera and Carmelo Rizzar (Università Milano Bicocca, Monza); Pia Massaglia (Università di Torino); Stefano Mattioli, Guido Paolucci and Andrea Pession (Università di Bologna); Domenico Franco Merlo (INRC, Genova); Liliana Minelli (Università degli Studi di Perugia); Paola Mosciati and Franco Pannelli (Università di Camerino); Vincenzo Poggi (AORN Santobono – Pausilipon, Napoli); Alessandro Pulsoni (Sapienza University, Roma); Roberto Rondelli (Policlinico S.Orsola, Bologna); Giovanna Russo and Gino Schilirò (Università di Catania); Alberto Salvan (IASI-CNR, Roma); Maria Valeria Torregrossa (Università degli Studi di Palermo). **Funding:** Italian Association on Research on Cancer, Ministry of Instruction, University and Research, PRIN Program, Ministry of Health (Ricerca Sanitaria Finalizzata Program), Ministry of Labour and Welfare, Associazione Neuroblastoma, Piemonte Region (Ricerca Sanitaria Finalizzata Program), Liguria Region, Comitato per la vita “Daniele Chianelli”- Associazione per la Ricerca e la Cura delle Leucemie, Linfomi e Tumori di Adulti e Bambini (Perugia).

**New Zealand, New Zealand Childhood Cancer Study (NZCCS) [82-84]**

**Research Investigators**

John D. Dockerty, Peter G. Herbison, David C.G. Skegg, and J. Mark Elwood (University of Otago). **Funding:** Health Research Council of New Zealand (NZ), the NZ Lottery Grants Board, the Otago Medical School (Faculty Bequest Funds), the Cancer Society of NZ, the Otago Medical Research Foundation, and the A.B. de Lautour Charitable Trust.

**United Kingdom, Oxford, Childhood Cancer Research Group (CCRG) [85-87] (www.ccrg.ox.ac.uk)**

**Research Investigators**

Michael Murphy, Kate O’Neill, and CCRG staff (University of Oxford). **Funding:** Department of Health, Scottish Government, National Cancer Intelligence Network, and CHILDREN with CANCER, UK.

**United Kingdom, United Kingdom Childhood Cancer Study (UKCCS) [88-90] (www.ukccs.org)**

**Research Investigators**

Eve Roman and Tracy Lightfoot (University of York), part of a team of ten clinical and epidemiological investigators, and two biological investigators (university departments, research institutes, and the National Health Service in Scotland). **Funding:** Leukaemia and Lymphoma Research.

**United States, California State, California Childhood Leukemia Study (CCLS) [91]**

**Research and Clinical Investigators**

Patricia A. Buffler and Catherine Metayer (University of California, Berkeley); Jonathan Ducore (University of California Davis Medical Center); Mignon Loh and Katherine Matthay (University of California, San Francisco); Vonda Crouse (Children’s Hospital of Central California); Gary Dahl (Lucile Packard Children’s Hospital); James Feusner (Children’s Hospital Oakland); Vincent Kiley (Kaiser Permanente Sacramento); Carolyn Russo and Alan Wong (Kaiser Permanente Santa Clara); Kenneth Leung (Kaiser...
Permanente San Francisco); Stacy Month (Kaiser Permanente Oakland). **Funding:** National Institute of Environmental Health Sciences, USA and the CHILDREN with CANCER, UK.

**United States, Children’s Oncology Group (COG) [92-94]**


**Research and Clinical Investigators**

Logan Spector (University of Minnesota), and research and clinical investigators at the Children’s Oncology Group (COG) and Children’s Cancer Group (CCG) principal and affiliate member institutions. **Funding:** National Cancer Institute, USA, COG Foundation, and the National Childhood Cancer Foundation.

**United States, Texas State**

**Research and Clinical Investigators**

Melissa Bondy, M. Fatih Okcu, and Michael Scheurer (The Childhood Cancer Epidemiology and Prevention Center, Texas); David Poplack (Children’s Cancer Center); Armando Correa and Jean Raphael (Texas Children’s Hospital); Caryn Cohan and Anish Masharani (and the Texas Children’s Pediatric Associates-Bellaire Clinic).

**United States, Washington State [95]**

**Research Investigators**

Beth Mueller, Parveen Bhatti, Eric Chow, Bill O’Brien, Michelle Williams, Danise Podvin, Carrie Kuehn (University of Washington). **Funding:** Washington State Department of Health, the Cancer Surveillance System of Western Washington part of the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute, and the Fred Hutchinson Cancer Center.

**References**


Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL</td>
<td>acute lymphoblastic leukemia</td>
</tr>
<tr>
<td>AML</td>
<td>acute myeloid leukemia</td>
</tr>
<tr>
<td>CLIC</td>
<td>Childhood Leukemia International Consortium</td>
</tr>
<tr>
<td>HLA</td>
<td>human leukocyte antigen</td>
</tr>
<tr>
<td>GWAS</td>
<td>genome wide association studies</td>
</tr>
<tr>
<td>IARC</td>
<td>International Agency for Research on Cancer</td>
</tr>
<tr>
<td>MTHFR</td>
<td>methylene tetrahydrofolatereductase</td>
</tr>
<tr>
<td>SNPs</td>
<td>single-nucleotide polymorphisms</td>
</tr>
<tr>
<td>FISH</td>
<td>fluorescence in situ hybridization</td>
</tr>
<tr>
<td>PCR</td>
<td>polymerase chain reaction</td>
</tr>
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<td>I4C</td>
<td>International Consortium of Childhood Cancer Cohorts</td>
</tr>
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<td>Study location, name</td>
<td>Institution (investigators)</td>
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<td>----------------------</td>
<td>----------------------------</td>
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<tr>
<td>Australia, Aug-ALL [15,6467]</td>
<td>Telethon Institute for Child Health Research (Hume E., Armstrong B.)</td>
</tr>
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<td>Brazil, Brazil/Colombia Collaborative Study Group [BCSG] [14,83,68]</td>
<td>Instituto Nacional de Cerebro (INCB)</td>
</tr>
<tr>
<td>Canada, Quebec [35,69,70]</td>
<td>McGill University (Koifman S.)</td>
</tr>
<tr>
<td>Canada, Qc-ALL, Sainte Justine Hospital, Quebec [71–75]</td>
<td>Université de Montréal, Sainte-Justine Hospital (Séguin D.)</td>
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<tr>
<td>Egypt, Children’s Cancer Hospital Egypt [72,73]</td>
<td>CCHE (Center S.)</td>
</tr>
<tr>
<td>France, ADELE [26]</td>
<td>Inserm U1018, Environmental Epidemiology of Cancer (Clavel J.)</td>
</tr>
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<td>France, ELECTRE [74]</td>
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<td>France, ESACLE [762]</td>
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<tr>
<td>France, ESTELLE</td>
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<tr>
<td>Germany, German Childhood Cancer Registry (GCRR) [75–77]</td>
<td>GCR, Institute for Medical Biostatistics, Epidemiology and Informatics (Beck in M.-F., Schild M.)</td>
</tr>
<tr>
<td>Study location, name</td>
<td>Institution (investigators)</td>
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<td>----------------------</td>
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<td>Greece, Nationwide Registry for Childhood Hematological Maligancies (NARCHEM) [78-80]</td>
<td>Department of Hygiene, Epidemiology and Medical Statistics, Medical School, University of Athens (Nikolau E., Drosianni N.)</td>
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<td>Italy, Studio sulla Eziologia dei Tumori Infantili Linfopema (SETIL) [81]</td>
<td>University of Eastern Piedmont (Magnani C., Miligli L.)</td>
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<td>New Zealand, New Zealand Childhood Cancer Study (NZCCS) [82-84]</td>
<td>Department of Preventive and Social Medicine, University of Otago (Deckerly L.)</td>
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<td>UK, Manchester a</td>
<td>Pediatric and Blood Cancer Research Group, University of Manchester (Buch J., Taylor M.)</td>
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<td>UK, Oxford, Childhood Cancer Research Group (CCRG) (85-87)</td>
<td>CCRG, Oxford University (Murphy M., O’Neill K.)</td>
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<td>UK, United Kingdom Childhood Cancer Study (UKCCS) (88-90) a</td>
<td>Department of Health Sciences, Epidemiology and Evaluation Unit, University of York (Roman E., Lightfoot T.)</td>
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<tr>
<td>US, California State, Childhood Leukemia Study (CCLS) [91]</td>
<td>University of California, Berkeley (Buffler R., Miyakor C.)</td>
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<td>US, Children’s Oncology Group (COG) (Children Cancer Group (CCG) E14, CCG-E15) [92-94]</td>
<td>University of Minnesota, Minneapolis (Spector L.)</td>
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<td>US, Texas State</td>
<td>Baylor College of Medicine, Department of Pediatrics, Section of Hematology- Oncology (Schuster M., Boodle M.)</td>
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</tbody>
</table>

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CL, childhood leukemia of all types; E, environmental studies; G, genetic studies; GxE, gene × environmental interaction studies; GP, General practitioner; RDD, random digit dialing.
aBy alphabetical order.
Possible overlap of cases.

Possible overlap of cases and/or controls.
### Table 2

Number of cases and controls in the Childhood Leukemia International Consortium (CLIC) Studies, April 2006–September 2012.

<table>
<thead>
<tr>
<th>Study location</th>
<th>Number of leukemia cases and controls</th>
<th>Biopspecimens for DNA extraction</th>
<th>Sources of DNA</th>
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<tr>
<td><strong>Study location</strong></td>
<td><strong>Number of leukemia cases and controls</strong></td>
<td><strong>Biopspecimens for DNA extraction</strong></td>
<td><strong>Sources of DNA</strong></td>
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<tr>
<td><strong>Case combined</strong></td>
<td><strong>ALL</strong></td>
<td><strong>B-cell ALL</strong></td>
<td><strong>T-cell ALL</strong></td>
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<td><strong>Australia, Aus-ALL</strong></td>
<td>393</td>
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<td><strong>Brazil, BCSG</strong></td>
<td>406</td>
<td>359</td>
<td>526</td>
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<td><strong>Canada, Quebec</strong></td>
<td>780</td>
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<td><strong>Canada, Qc-ALL</strong></td>
<td>600</td>
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<td><strong>Costa Rica</strong></td>
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<td><strong>Egypt, CCHE</strong></td>
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<td>344</td>
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<td><strong>France, ADELE</strong></td>
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<td><strong>France, ELECTRE</strong></td>
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<td>527</td>
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<td><strong>France, ESCALE</strong></td>
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<td>751</td>
<td>672</td>
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<td><strong>Germany, GCCR</strong></td>
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<td><strong>Greece, NARECHEM</strong></td>
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<td><strong>UK, Oxford, CCRG</strong></td>
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<td><strong>US, California State, CCLS</strong></td>
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<td><strong>US, COG (CCG-E15)</strong></td>
<td>1914</td>
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<td>1165</td>
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<td><strong>US, Texas State</strong></td>
<td>130</td>
<td>123</td>
<td>7</td>
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<td><strong>US, Washington State</strong></td>
<td>1229</td>
<td>953</td>
<td>204</td>
</tr>
<tr>
<td><strong>Sub-total, studies with comprehensive epidemiologic data</strong></td>
<td>15 209</td>
<td>11 157</td>
<td>10 907</td>
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<tr>
<td><strong>Sub-total, studies with limited epidemiologic data</strong></td>
<td>18 030</td>
<td>15 075</td>
<td>540</td>
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<tr>
<td><strong>Total, all CLIC studies</strong></td>
<td>31 209</td>
<td>26 202</td>
<td>3957</td>
</tr>
</tbody>
</table>

**Abbreviations:** ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ANBS, archived newborn blood spots; − denotes estimated numbers of specimens based on surveys completed when studies entered the consortium (e.g., more samples could have been accrued or used since a study joined CLIC).

*By alphabetical order.*
b Possible overlap of cases.

c Immunophenotype data not currently available.

d Possible overlap of cases and/or controls.

e Immunophenotype data is available for ~13,522 ALL cases. Precise count is not presently available.

f Number of leukemia subtypes available upon request.

g All studies except Canada, Qc-ALL; UK, Oxford, CCRG; US, Washington State.

h Only Canada, Qc-ALL; UK, Oxford, CCRG; US, Washington State.
Table 3

CLIC pooled analyses in progress (as of September 2012).

<table>
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<tr>
<th>Risk factors</th>
<th>Outcome</th>
<th>CLIC studies</th>
<th>ALL cases</th>
<th>AML cases</th>
<th>Controls</th>
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</thead>
<tbody>
<tr>
<td>Measures of fetal growth</td>
<td>Risk of ALL</td>
<td>12</td>
<td>7400</td>
<td>n/a</td>
<td>12 500</td>
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<tr>
<td>Maternal vitamin and folate intake before and during pregnancy (and MTHFR variants)</td>
<td>Risk of ALL, AML</td>
<td>11 (5)</td>
<td>6970</td>
<td>600</td>
<td>12 060</td>
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<tr>
<td>Parental smoking (and xenobiotic-metabolizing gene variants)</td>
<td>Risk of ALL</td>
<td>12 (4)</td>
<td>9100</td>
<td>n/a</td>
<td>14 860</td>
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<tr>
<td>Markers of early infections and allergies</td>
<td>Risk of ALL</td>
<td>10</td>
<td>7670</td>
<td>720</td>
<td>12 530</td>
</tr>
<tr>
<td>Indoor sources of benzene and hydrocarbons, xenobiotic transport and metabolic genes</td>
<td>Risk of AML</td>
<td>10 (4)</td>
<td>n/a</td>
<td>930</td>
<td>7800</td>
</tr>
<tr>
<td>Exposure to pesticides at home (and xenobiotic transport and metabolic genes)</td>
<td>Risk of ALL, AML</td>
<td>11 (4)</td>
<td>7650</td>
<td>1150</td>
<td>13 960</td>
</tr>
<tr>
<td>Parental exposure to pesticides at work (and xenobiotic transport and metabolic genes)</td>
<td>Risk of ALL, AML</td>
<td>10 (4)</td>
<td>8900</td>
<td>1400</td>
<td>16 440</td>
</tr>
<tr>
<td>Exposure to paints at home (and xenobiotic transport and metabolic genes)</td>
<td>Risk of ALL, AML</td>
<td>8 (4)</td>
<td>4900</td>
<td>380</td>
<td>6760</td>
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<tr>
<td>Parental exposure to paints at work (and xenobiotic transport and metabolic genes)</td>
<td>Risk of ALL, AML</td>
<td>11 (4)</td>
<td>7650</td>
<td>1150</td>
<td>13 960</td>
</tr>
<tr>
<td>Maternal consumption of coffee and tea</td>
<td>Risk of ALL</td>
<td></td>
<td></td>
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<tr>
<td>Assisted reproductive technologies; time to pregnancy</td>
<td>Risk of ALL</td>
<td></td>
<td></td>
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<td>Geographic distribution of AML, APL and cytogenetic subtypes</td>
<td>AML, APL</td>
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<td>Socio-demographic and clinical characteristics</td>
<td>Survival of ALL, AML</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; APL, acute promyelocytic leukemia.

*Number in parentheses represents the number of studies with genotyping data.

Maximum (rounded) numbers of cases and controls are provided, and numbers may vary by specific risk factor under study.