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The Nordic ChiCaP Network: An interdisciplinary approach to childhood cancer predisposition

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ABSTRACT

Testing for Childhood Cancer Predisposition (ChiCaP) syndromes is increasingly common in pediatric oncology as early identification can help adapt treatment and initiate surveillance. As such, ChiCaP testing can have medical, ethical, and psychological consequences for both the patients and their families, and present significant diagnostic challenges for pediatric oncologists. In response to these new opportunities and challenges, the Nordic ChiCaP Network was established in 2021, bringing together experts from pediatric and adult oncology, clinical genetics, molecular genetics, bioinformatics, epidemiology, psychology, anthropology, community medicine, law and ethics. Its primary goal is to advance our knowledge of ChiCaP in pediatric oncology research and care through an interdisciplinary approach. The network aims to achieve several key objectives: (1) to improve ChiCaP diagnostics, including gene-associated phenotypes and variant interpretation; (2) to advance understanding of the natural history, cancer risks, adverse treatment reactions, and comorbidities associated with ChiCaP syndromes; (3) to optimize and harmonize treatment protocols and surveillance strategies for affected patients and their families; (4) to address the ethical, legal and psychosocial aspects involved in testing, communication and counseling, diagnosing ChiCaP syndromes, and the impacts of surveillance on patients and their families; (5) to identify novel ChiCaP syndromes and explore their underlying mechanisms; and (6) to facilitate translation of research findings into clinical practice. By gathering interdisciplinary expertise and fostering collaboration across the Nordic countries, the Nordic ChiCaP Network will enhance knowledge and awareness of ChiCaP, improve early diagnosis, patient care, family support, and contribute to a better understanding of these complex genetic conditions.

1. Introduction

Childhood cancer represents a diverse group of rare malignancies [1,2], with treatment outcomes having improved considerably in high income countries during the past decades [3]. However, the underlying causes and mechanisms leading to childhood malignancies have remained poorly understood. As environmental factors rarely cause cancer in children and adolescents, a genetic predisposition to cancer has become an important research focus to unravel the etiology of childhood cancer [4].

Childhood cancer predisposition (ChiCaP) syndromes have increasingly been recognized as key factors in cancer development among children. Numerous studies have revealed that 7 % - 18 % of childhood cancer patients carry germline variants associated with a genetic cancer predisposition [5–10]. Variations in diagnostic rates among these studies largely stem from differences in cohort selections, methods used, gene panel compositions and definitions of positive germline findings. As part of broader genomics initiatives, germline testing has become essential for improving pediatric cancer care [5,11–14]. The detection of a ChiCaP syndrome aids in individualizing therapy, establishing specific surveillance protocols, identifying at-risk family members, and potentially guiding family planning [15]. At the same time, knowledge of cancer predisposition in families can have psychosocial consequences and ethical challenges, as families may experience mixed feelings about implementing cancer surveillance in a healthy child and face uncertainty about what the future holds. [16–18].

Understanding ChiCaP syndromes in childhood cancer is an emerging field, and our knowledge of these newly identified syndromes remains limited. Gene panels and genomic tests currently differ across Nordic and European countries. Genetic counseling practices for this patient group are evolving and need to incorporate findings from studies on the psychosocial impact of genomic testing. Guidelines for implementing such testing in clinical practice and surveillance are scarce, and there is little consensus on best practices. Therefore, the SIOPE Host Genome Working Group has developed consensus-based recommendations for germline genetic testing [19]. Clinical trials are warranted for patients with predisposing genetic variants to improve long-term treatment outcomes by tailoring individualized risk-based therapies appropriately. Furthermore, best practices and guidelines for surveillance are crucial to monitor children with cancer who carry germline cancer predisposition as well as other at-risk individuals. Large cohort studies with advanced statistical methods are both needed to discover novel cancer predisposition genes and inform the implementation of ChiCaP testing in clinical practice. Data sharing across the Nordic countries is a prerequisite for building such large cohorts.

Across Denmark, Finland, Norway, and Sweden, approximately 1100 children receive a cancer diagnosis each year [20,21]. Because $\geq$ 10 % of childhood cancers involve a ChiCaP syndrome, we estimate that at least 100 children diagnosed with cancer each year in the Nordic region harbor an underlying ChiCaP syndrome. In routine clinical practice, more than 190 genes are currently analysed to establish a ChiCaP diagnosis in these countries.

The extent of genetic testing varies across Nordic countries. In Denmark and Sweden, universal germline genome sequencing is offered to all children diagnosed with cancer regardless of cancer type as part of routine diagnostics in healthcare, with analysis focused on *in-silico* gene panels. In Norway, germline genome sequencing with panel-based analysis is offered to all children at diagnosis in most major centers, covering the majority of pediatric cancer patients. Finland uses a phenotype-first driven approach to genetic testing.

We have established the Nordic ChiCaP Network to address several specific challenges: (1) heterogeneous testing protocols and gene panel compositions across Nordic countries, (2) inconsistent surveillance guidelines and follow-up practices, (3) fragmented data collection preventing large-scale outcome studies, (4) limited psychosocial support structures for affected families, (5) difficulties in variant interpretation for rare syndromes, and (6) lack of coordinated approaches to novel gene discovery. The Network provides clinical support, optimize care for affected children and their at-risk relatives, and foster enhanced collaboration across the Nordic countries and internationally.

[1] Equal contribution, shared first authorship
[2] Equal contribution, shared last authorship

The Nordic region is characterized by robust, fully publicly funded, free-for-all healthcare systems, nationwide multiethnic health care registries, and a tradition of interdisciplinary collaboration. This provides an unparalleled opportunity to advance collaboration and research in the field of ChiCaP syndromes. By leveraging these resources, the Nordic ChiCaP Network is well positioned to advance current knowledge in the field, facilitate the integration of clinical expertise, research, and best practices in the management of ChiCaP syndromes, with a focus on improving diagnostic accuracy, counselling support, surveillance and ethicolegal aspects and strategies, and therapeutic outcomes for patients and families. In addition, we want to discover new ChiCaP syndromes, find genetic causes of childhood cancers, and establish a large Nordic dataset based on administrative and quality registries for epidemiological studies of ChiCaPs.

Here we present the Nordic ChiCaP Network as a model for regional collaboration in childhood cancer predisposition. By documenting our organizational structure, interdisciplinary approach, and early achievements, we aim to: (1) provide transparency about our activities to the international ChiCaP community, (2) offer a reproducible framework that other regions might adapt to their local contexts, (3) identify opportunities for international collaboration, and (4) demonstrate how leveraging regional strengths - in our case, the Nordic healthcare infrastructure and registry systems - can advance the field of childhood cancer predisposition research and care.By strengthening Nordic collaborations, we will establish regular in-person meetings and structured discussion forums that allow colleagues to compare management strategies for rare clinical situations, thereby fostering collective learning and continuous improvement.

2. About the Nordic ChiCaP Network

The network began holding monthly virtual meetings in May 2021 after discovering similar research projects on psychosocial studies of ChiCaP syndromes running in Norway, Denmark, and Sweden. Finland joined during the second meeting. The network has so far held two in-person, two-day meetings in Stockholm in September 2022 and September 2024, with the next planned in Oslo in 2026. Each meeting features presentations of ongoing ChiCaP projects, catalyzing rigorous scientific and clinical dialogues that shape the future directions of the network.

Working groups meet in parallel sessions to discuss common goals, needs, projects, and future collaborations. These groups then present their discussion reports to the entire network for feedback. During the second meeting, network members also proposed potential Nordic research projects exploring various aspects of ChiCaP. Specific outcomes from these meetings include: (1) sharing of experiences, (2) harmonization of research projects, (3) agreement on closer collaboration on research projects, (4) finding funding opportunities and (5) establishment of collaborations focused on specific diagnoses or phenotypes.

The Nordic ChiCaP Network also holds regular video conferences to discuss surveillance protocols, treatment recommendations, interpretation of gene variants in ChiCaP syndromes as well as rare challenging cases. In addition, the group addresses patient characteristics, clinical practices, ethical and legal aspects, surveillance guidelines, recent research findings, and opportunities for ongoing and future collaboration. Additionally, nearly half of the Nordic ChiCaP Network members actively participate in international childhood cancer organizations, including the International Society of Pediatric Oncology (SIOP), SIOP Europe (SIOPE), Nordic Society of Paediatric Haematology and Oncology (NOPHO), and European Reference Network for all patients with one of the rare genetic tumor risk syndromes (ERN GENTURIS) and for Paediatric Oncology (ERN PaedCan). Our monthly meetings provide great opportunities to present and discuss new publications and surveillance guidelines from these organizations, as well as local practices for testing, surveillance, genetic counseling, and psychosocial support. Recognizing that this is a rapidly evolving field, the network serves as a forum for learning, developing and reflecting on new knowledge and supporting each other in various aspects.

The network is interdisciplinary, with 40 members including healthcare professionals, legal experts and researchers distributed as follows: pediatric and adult oncology (12), pediatrics (1), clinical and molecular genetics (15), bioinformatics (2), statistics and epidemiology (2), psychology (2), bioethics and law (2), community medicine / public health (2), and anthropology (2). Geographic distribution includes Denmark (6 members), Finland (9 members), Norway (8 members) and Sweden (17 members) according to a survey of members performed in March 2025. New members are welcome to join the network on the website (https://nordicchicap.org).

2.1. International collaboration

The Nordic ChiCaP Network aims to interoperate with international initiatives, including the SIOP/SIOPE Host Genome Working Group, NOPHO, ERN PaedCan and ERN GENTURIS, to align surveillance protocols and genetic counselling guidance while embedding Nordic perspectives in guideline development. Network members hold active roles in these groups, providing established channels for joint case review and consensus drafting. Strategic partnerships with disease-specific consortia, such as Care for CMMRD (C4CMMRD), will enable bidirectional knowledge exchange and access to expanded patient cohorts for research. Collectively, these collaborations will strengthen the evidence base for clinical decision-making and enable participation in larger-scale international studies.

2.2. Working groups (WGs)

Our work is coordinated through seven dedicated WGs: 1) ChiCaP discovery, 2) Surveillance, 3) Epidemiological studies, 4) Ethical, legal and psychosocial (ELP) studies, 5) Constitutional mismatch repair deficiency (CMMRD) syndrome, 6) *TP53*-related cancer syndrome, 7) PhD and postdoctoral studies forum.

1) **ChiCaP discovery:** This WG conducts clinical, molecular genetic, and register-based studies to: 1) identify new gene associations with ChiCaP syndromes, 2) investigate ChiCaP associations in rare diseases, 3) examine ChiCaP associations in known adult cancer predisposition syndromes, 4) study isolated familial cancer syndromes with ChiCaP, 5) explore connections between ChiCaP and congenital malformation and intellectual disability syndromes, and 6) investigate poor outcomes, including severe toxicity reactions and second primary cancers. The working group's aim is to expand the current knowledge about the genetic underpinnings and clinical manifestations of ChiCaP syndromes, providing a broader understanding of how they intersect with other rare diseases, cancer predisposition syndromes, and developmental disorders. The working group consists of clinical geneticists, molecular biologists, epidemiologists, statisticians, and pediatric oncologists.
2) **Surveillance:** This WG aims to: 1) review current surveillance guidelines for known ChiCaP syndromes and adapt them to Nordic conditions, 2) support clinicians with surveillance recommendations of challenging cases that lack established guidelines, 3) update members about newly published surveillance guidelines, and 4) assist in developing new surveillance guidelines for ChiCaP syndromes. The group comprises clinical geneticists, pediatricians, and pediatric oncologists.
3) **Epidemiological studies:** In virtue of the Nordic Health Registries, we have the possibility to initiate large nationwide population-based studies to examine our postulated hypotheses regarding ChiCaP. The WG has two main aims: 1) to discover new ChiCaP syndromes and 2) to explore various associations with ChiCaP. The group brings together epidemiologists, statisticians, clinical geneticists, and pediatric oncologists.

4) **Ethical, legal and psychosocial (ELP) studies:** This WG focuses on the psychosocial, ethical and legal aspects of ChiCaP testing. Using quantitative and qualitative methods, the group explores the psychosocial impact of ChiCaP testing on patients, parents, and physicians with a focus on understanding their unique needs and the particular social and everyday dilemmas arising from the knowledge of a child or adolescent person's predisposition to cancer. Moreover, we also examine the ethical and legal considerations of genetic testing and counseling for families affected by cancer and ChiCaP syndromes. This will help facilitate strategies to enhance family autonomy in decision-making about genetic testing, autonomy of the child, and child's right not to know and right to an open future, enabling more individualized support in clinical practice. The team is multidisciplinary, comprising bioethicists, psychologists, anthropologists, genetic counselors, nurses, pediatric oncologists, and clinical geneticists.
5) **Constitutional mismatch repair deficiency (CMMRD) syndrome:** CMMRD is an extremely rare childhood cancer predisposition syndrome that causes various types of tumors in children and young adults. The WG aims to: 1) collect genetic and clinical data from Nordic CMMRD patients and patients with CMMRD-like diagnoses, 2) establish genotype-phenotype relationships, 3) develop surveillance guidelines, and 4) participate in international research studies. The group works in close collaboration with the surveillance WG, the European consortium "Care for CMMRD" (C4CMMRD) [22] and ERN GENTURIS. The team comprises clinical geneticists, molecular geneticists, pediatric and adult oncologists, and pediatricians.
6) ***TP53*-related cancer syndrome:** This WG has two main aims: 1) to build a database of *TP53* positive findings and penetrance, and 2) to establish genotype-phenotype associations for *TP53* variants observed in Nordic populations. The team includes clinical and molecular geneticists, pediatricians, pediatric and adult oncologists.
7) **PhD and postdoctoral studies forum:** This WG constitutes an interdisciplinary, peer-driven platform for early-career researchers investigating ChiCaP syndromes. It offers a structured yet informal setting in which doctoral candidates and postdoctoral fellows exchange current literature, methodological insights, and practical research experiences, thereby fostering collaborative learning, mutual support, and the refinement of ChiCaP-focused projects throughout their training.

Establishment of working groups: These seven working groups were established through a structured process during our first in-person meeting in Stockholm (September 2022). Network members initially proposed priority areas based on identified gaps in Nordic ChiCaP care and research. Through discussions, we consolidated overlapping themes and identified natural groupings based on expertise and interest. Each working group was required to have representation from different Nordic countries and include both clinical and research perspectives. Working group leadership was determined through self-nomination and consensus, with co-leadership models adopted to ensure geographic and disciplinary diversity.

2.3. Nordic ChiCaP website

The Nordic ChiCaP Network maintains an official member-driven website at https://nordicchicap.org/. The website showcases ongoing Nordic research initiatives on ChiCaP, working group descriptions and memberships, and ChiCaP-related articles published by the network members. Each of the four affiliated Nordic countries runs nationwide projects to advance diagnostics, clinical care, and psychosocial outcomes of childhood cancer predisposition. These projects - ChiCaP (Sweden), PeCCaPS (Finland), PROTECT-CARE (Norway), and STAGING (Denmark) - explore various facets of ChiCaP testing and its clinical and psychological outcomes. The site receives approximately 100 monthly views, primarily from Sweden, Finland, the United States, Norway, the Netherlands, Denmark, and at least 33 other countries worldwide. Researchers interested in joining the network can apply through the website's contact form.

3. Conclusion

The field of ChiCaP is rapidly developing, and our understanding will improve as technologies advance. Discovering ultra-rare genes and establishing associations between ChiCaP and new genes require larger datasets, advanced statistical methods, increased collaboration, and data sharing across countries. Moreover, as technology progresses, it is becoming increasingly important to understand patients' and parents' needs and perspectives on germline genetic testing for children with ChiCaP. The Nordic ChiCaP Network has the potential to drive the field forward by fostering close collaborations not only between Nordic countries but also with European and international initiatives. The Nordic countries' robust healthcare infrastructure, nationwide registries, and standardized clinical practices uniquely position the Nordic ChiCaP Network to make significant contributions to global ChiCaP research. By joining forces, we can drive large-scale research projects that explore various aspects of ChiCaP, from genetic underpinnings to clinical management, surveillance, psychosocial, ethical, and legal considerations. This collaborative approach will enable a more comprehensive understanding of ChiCaP syndromes and help to improve patient outcomes across borders. The network currently operates through members' volunteer work and their research grants. To reach its full potential, it needs long-term funding and partnerships with other organizations.

CRediT authorship contribution statement

Gustaf Ljungman: Writing – review & editing. **Hanne C. Lie:** Writing – review & editing, Writing – original draft, Conceptualization. **Kristina Lagerstedt-Robinson:** Writing – review & editing. **Ann Nordgren:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization. **Monica Cheng Munthe-Kaas:** Writing – review & editing, Supervision, Conceptualization. **Joakim Wille:** Writing – review & editing. **Ekaterina Kuchinskaya:** Writing – review & editing. **Laura S. Korhonen:** Writing – review & editing. **Ida Katrine Knapstad:** Writing – review & editing. **Teresia Wangensteen:** Writing – review & editing. **Andreina Kero:** Writing – review & editing. **Ayo Wahlberg:** Writing – review & editing. **Kirsi Jahnukainen:** Writing – review & editing, Conceptualization. **Wadt Karin A. W.:** Writing – review & editing. **Bushra Ishaq:** Writing – review & editing. **Alexandra Wachtmeister:** Writing – review & editing. **Lauge Holm Sørensen:** Writing – review & editing. **Emma Tham:** Writing – review & editing. **Hildegunn Høberg Vetti:** Writing – review & editing. **Giorgio Tettamanti:** Writing – review & editing. **Ole Haubjerg Nielsen:** Writing – review & editing. **Bianca Tesi:** Writing – review & editing. **Maria Haanpää:** Writing – review & editing. **Alexander Sun Zhang:** Writing – review & editing. **Sonja Strang-Karlsson:** Writing – review & editing. **Ulrik Kristoffer Stoltze:** Writing – review & editing. **Patrick Cairns:** Writing – review & editing. **Kjeld Schmiegelow:** Writing – review & editing. **Andreas Benneche:** Writing – review & editing. **Anna Poluha:** Writing – review & editing, Conceptualization. **Stefan Becker:** Writing – review & editing. **Sara Orrsjö:** Writing – review & editing. **Svetlana Bajalica-Lagercrantz:** Writing – review & editing. **Thale Kristin Olsen:** Writing – review & editing. **Katja Ekholm:** Writing – review & editing, Project administration. **Kristiina Nordfors:** Writing – review & editing. **Joel Janhonen:** Writing – review & editing, Writing – original draft. **Saara Nolvi:** Writing – review & editing. **Fulya Taylan:** Writing – review & editing, Writing – original draft, Conceptualization. **Carolina Maya-González:** Writing – review & editing. **Åsa Grauman:** Writing – review & editing.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used OpenAI ChatGPT o3 in order to improve language and readability. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Ethics Declaration

Ethical approval is not required for this article, as it contains no research involving human participants and solely describes the network of researchers.

Links

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KAWW has received payment for a lecture to Seagen Denmark Aps. The remaining authors declare no conflicts of interest.

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Data availability

No data was used for the research described in the article.

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