Direct information to at-risk relatives – A randomized controlled trial on direct versus family-mediated information on cancer risk and prevention **(The DIRECT-study)**

Summary

Genetic diagnostics is a clinical field at the frontier of personalized medicine. Today's readily accessible sequencing techniques offer new ways of finding a cause, or predisposition, for certain types of cancers. A carefully selected genetic panel or full genome analysis give physicians a potent tool for diagnosis and guiding treatment options. Results from genetic tests, paired with appropriate preventive measures, can also lead to early detection or prevention of disease – but only if individuals at-risk are informed. Figure 1 illustrates how genetic data from one family member (proband) may reveal data concerning others.

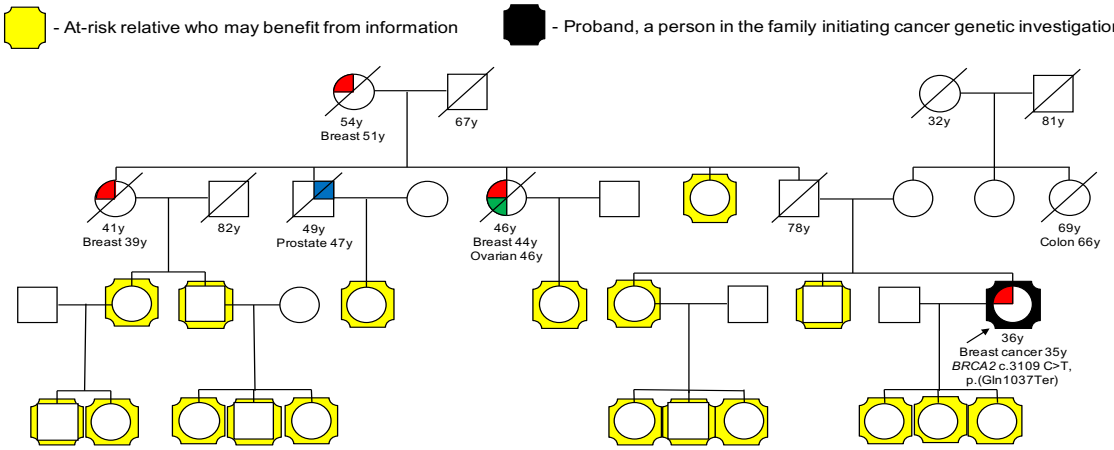

Figure 1. Example of a pedigree (family tree) in a cancer genetic investigation

Research shows that less than half of eligible at-risk relatives in families with hereditary cancer seek genetic councelling for testing or preventive treatment. Lack of evidence on effective genetic councelling methodologies, including ways to reach at-risk relatives, hampers clinical efforts to strengthen cancer prevention.

We want to evaluate and compare the current clinical practice with a new method of hereditary cancer risk communication. We will investigate efficacy, feasibility and acceptance to a more pro-active approach than the one generally used today.

The study's main component is a randomized controlled trial (RCT) conducted at Swedish cancer genetics units involving 600 families with increased risk of developing breast, ovarian or colorectal cancer. The proposed intervention, featuring an offer of mailed letters directly to at-risk relatives, will be evaluated with a mixed-method design. Data sources will include patient registries, questionnaires, narratives and in-depth individual interviews.

The primary outcome measure is comparison of counseling seeking behavior (proportion of at-risk relatives contacting a Swedish cancer genetics unit within twelve months) in both the control and intervention group. We will also investigate potential (adverse) effects and legal and ethical aspects relevant for cancer genetic counselling. The results from our study are expected to be vital in the development of a future model for genetic councelling and implementation efforts at health care providers in the field.

PURPOSE AND AIMS

The overall aim is to compare two different modes of conveying information of a cancergenetic investigation to at-risk relatives belonging to families with increased hereditary risk of developing breast, ovarian or colorectal cancer.

Specific aims are:

1. To assess whether an intervention with direct letters addressed to at-risk relatives impacts on proportion of at-risk relatives contacting Swedish cancer genetics units within 12 months, as compared with standard care with family-mediated information.
2. To explore safety and emotional responses among at-risk relatives after receiving direct letters with information on hereditary health risks in the family and available testing and preventive measures.
3. To explore attitudes towards the offer of direct letters among probands undergoing a cancergenetic investigation.
4. To investigate legal and ethical aspects relevant for the clinical practice of cancer genetic counselling today, and propose a future model for hereditary cancer risk communication to at-risk individuals.

SURVEY OF THE FIELD

About 10% of breast cancer, 20% of ovarian cancer and 20% of colorectal cancer (CRC) cases are attributed to hereditary causes. Targeted surveillance programs to individuals in high-risk families is a cost-effective intervention reducing both cancer incidence and mortality (1-3).

Hereditary breast and ovarian cancer syndrome (HBOC) is caused by pathogenic variants in the genes BRCA1 and BRCA2. Female BRCA1/2-carriers have a 40-80% lifetime risk of developing breast cancer and 30-60% (BRCA1) or 10-20% (BRCA2) lifetime risk to develop ovarian cancer. They are offered surveillance including yearly magnet resonance imaging (MRI) of the breast from the age of 25 and yearly gynaecological examinations from the age of 30. Prophylactic surgery is also an appropriate consideration for these women, with a 90-95% reduction of breast and ovarian cancer risk (1). In families with HBOC, healthy at-risk relatives have the option to undergo predictive genetic testing (cascade screening) to find out if they have inherited the pathogenic variant.

However, only a minority of breast cancer families carry a pathogenic variant in a known breast cancer related gene. If screening for breast cancer related genes is negative, risk estimation is based on cancer family history, including cancer type and age at diagnosis, and calculated with a software prediction tool. When family history indicates a twofold increase in relative risk of developing breast cancer (lifetime risk of 20% or higher), the family is defined as having ***familial breast cancer***. In these families, predictive genetic testing is not possible and mammography is offered to all female at-risk relatives on a yearly basis.

Hereditary CRC associated with pathogenic variants in the DNA mismatch repair-genes accounts for 1-3% of general CRC burden, and about 10% of CRC diagnosed at a young age (<35 y) (4). Carriers have a lifetime risk of 30-70% of developing CRC and female carriers also a highly increased lifetime risk of developing endometrial and ovarian cancer. Surveillance include colonoscopy yearly from the age of 25, with relative reductions of 68% for colorectal cancer incidence and 78% for all-cause mortality (2) Female carriers are also offered gynecological surveillance and later preventive surgery.

If no pathogenic variants in CRC-related genes are detected, familial CRC-risk is predicted based on age of onset and number of CRC-diagnoses in the family. The diagnose ***familial CRC*** is set if a person, based on family history, is predicted to have a twofold increase in relative risk of developing CRC (lifetime risk of 10% or higher). Regular colonoscopy in individuals with familial CRC has been shown to reduce CRC-related morbidity and mortality by 43-80% and 65-81%, respectively (3).

Missed opportunities for prevention
The cost-effectiveness of cancer prevention in high risk families mainly depend on the number of at-risk relatives being notified and included in surveillance program (5). Previous research has shown that predictive testing in at-risk relatives is highly unutilized. In a large study, only a third of relatives in families with hereditary CRC and HBOC actually perform predictive testing (6). In HBOC families, only about half of relatives are informed, with first-degree relatives significantly more likely to be informed compared with more distant relatives (7, 8). Among at-risk relatives with familial CRC the uptake of colonoscopies is reported to be only 34% (3).

Communication about hereditary risk of cancer with at-risk relatives
Probands do recognize their responsibility to share information with relatives (9). Still, factors associated with blocking the information, such as reluctance to contact family members who they have lost contact with, family conflicts and considerations of privacy, leads to limited numbers of relatives informed (10). Gender-related roles and educational level also impact on family communication. It has been shown that even if results are passed on to relatives, errors occur in the information when being transmitted. Relatives who learnt the information from the proband alone recalled significantly less accurate information than relatives informed directly by genetics health professionals (11).

Ethical and legal aspects of disclosure of genetic information to at-risk relatives
When a hereditary cancer risk in a family is confirmed, consideration must be taken regarding other relatives at risk. Disclosure of genetic data raises several ethical issues, mainly concerning autonomy, confidentiality, the duty of beneficance, and moral responsibility. This arguably creates a moral duty to provide this beneficial information (12). The possible duty of beneficance on part of health care professionals to inform at-risk relatives may however conflict with the confidentiality of the doctor-patient relationship. In addition, at-risk relatives may have an autonomy-based right not to receive information that they are at risk, a so called right not to know. The distribution of rights and duties between probands and medical professionals are also unclear. In light of this, it may be debated whether health care professionals should in some way take more responsibility.

From a legal perspective, patient data may be disclosed to another individual, or an authority, if the patient consents to disclosure. In the preparatory works to the Genetic Integrity Act (2006:351), it was noted that health care personnel may inform any at-risk relative about the result of a genetic test, if the proband consents. It is argued that circumstances in each particular case should guide whether the proband should be responsible for informing the relatives or if this task should be carried out by the health care personnel. Hence, there is legal room for clinics to adopt a practice of direct information as standard practice, but in clinical practice today, the proband rarely recieves this offer.
Previous interventions to assist probands in communication with at-risk relatives

Attempts to assist probands in their communication with at-risk relatives comprise e.g. psychoeducational guidance and various written information aids, like letters/leaflets or resource guides. A systematic review has shown that extended genetic counseling improves proband´s knowledge, reduce anxiety and increase intention to inform at-risk relatives (13). The effect on the proportion of relatives that actually receive information has rarely been evaluated in these interventional studies. In addition there are studies showing that information is often misunderstood or distorded along the way (14).

Exploring the option of direct communication between health care and at-risk relatives
Since 1997, the national HNPCC registry in Denmark has been granted an official exception enabling healthcare providers to send unsolicited letters, with information on hereditary colorectal cancer and an invitation to genetic counseling, to members of families with familial and hereditary colorectal cancer. A follow-up study showed that support for direct letters was expressed by 78% of at-risk family members. Regarding route of information, 90% of family members preferred a letter to no information and preferred source of information was in 66% the healthcare system rather than a distant relative (15).

Three previous studies have compared a proactive direct approach to inform at-risk relatives with the standard family-mediated approach (16-18) The overall conclusion of these studies is that genetic uptake improved (in some studies a doubled update of genetic testing was shown) when at-risk relatives are contacted directly, and no adverse psychological effect was identified. However, none of the studies used randomly allocated subjects when assessing the intervention and all included families where predictive testing was possible. Majority of families with increased cancer risk have familial breast cancer or familial CRC, where predictive testing is not possible. The effectiveness of cancer prevention in high-risk families largely depends on if relatives in such families are reached by information and adhere to preventive measures.

Hence, there is a need for a prospective randomized controlled trial, including families with both familial and hereditary cancer syndromes, assessing effectiveness of a proactive direct mode of information compared to family-mediated cancer risk communication to at-risk relatives.

PROJECT DESCRIPTION

Study setting: Current clinical practice, standard care with family-mediated information

The study is being carried out in Swedish cancer genetic units, where majority of families investigated have an aggregation of breast- (and ovarian) or colorectal cancer. The person that brings the family under investigation (proband) is asked to fill in a questionnaire on family history, and to collect written consent from relatives with cancer, allowing for verification of cancer diagnoses by medical records. Genetic analysis of cancer-related genes is offered to the family member with highest risk of having a mutation (e.g. young women with breast cancer).

If a pathogenic variant (mutation) is found, a hereditary cancer syndrome is confirmed in the family and the patient is offered a surveillance program. If no pathogenic variant (mutation) is detected, risk-assessment is based on family pedigree. Families without a mutation, but who

are predicted to have an increased risk of developing cancer based on the pedigree, are considered to have familial cancer syndrome.

After completed investigation, the proband is encouraged to pass on the information to at-risk relatives who are eligible for surveillance or predictive testing. If at-risk relatives are successfully notified about the findings, they can also choose to undergo predictive testing to find out if they are at risk. As support for this family-mediated information pathway the proband is sometimes offered written information that includes a summary of the results from the family investigation.

Preparatory explorative study in related stakeholder groups
As part of the preparations for the planned RCT-study we have performed qualitative and quantitative studies on attitudes, opinions and preferences towards hereditary cancer risk communication in members of the public and patients at the cancer genetic clinic.

Perception and attitudes on risk communication was explored in focus group discussions with informants selected to represent the general population and in individual interviews with patients (both probands and at-risk relatives who have learnt about the familial cancer risk through a family member). Interviews have been recorded and transcribed, and qualitative content analysis is ongoing.

Preliminary results from the focus group discussions with informants representing different gender, age groups, and educational levels, has deepened our understanding of enhancing factors and obstacles when communicating risks. Furthermore, it has help us to identify areas of importance in the design of our intervention, i.e. how to formulate the information letter to at-risk relatives. The data revealed a general interest in being notified of increased individual risk of cancer in order to "be able to do something about it". The informants expressed a wish of hands-on support from the health care providers in spreading of information within families.

We also discovered that people in general were surprised that health care automatically did not take responsibility of informing at-risk relatives. Some suggested that a similar model as practiced for communicable disease control could be in use. Others demanded the legal framework to be updated, and asked for a legal duty to warn relatives, even against the consent of a future proband. Some participants described that even if they had sound relationship with e.g. their parents, they would prefer to be informed directly by health care, whereas others would prefer to be informed by the relatives. Irrespectively of mode of information, the importance of an accessible health care giving prompt answers to questions and uncertainties was pointed out.

The preliminary results from the qualitative analysis aided the design of our questionnaire allowing us to measure the representativeness of the initial qualitative findings. A random sample of the general public was approached through a Swedish citizen web-panel during October 2018. Respondents were given a number of scenarios and related questions; being a potential at-risk relative of a family with an increased risk of colorectal cancer (either 10% risk or 70% risk). Regular colonoscopy was presented as a possible preventive measure to individuals at risk.

Out of 1900 invited, 977 responded (51%). For the scenario of 10% and 70% CRC-risk, 89.2%, and 90.6% respectively, would like to receive information about the fact that a genetic investigation had been conducted in their family. The proportion preferring to be informed was slightly higher among women (91.5%, 93.3%) than men (85.7%, 88.2%), (Chi2, p=0.044, p=0.047). There was no significant difference in age, educational level or place of residence.

Regarding preferences on the source of the information, 79.7% and 74.9%, low and high CRC-risk respectively, would prefer to receive the information from health care and 16.9% and 19.1% from a family member. Hence, a clear majority wanted to be informed about a completed cancer genetic investigation and preferred health care professionals to mediate this information.

Study 1: A prospective randomized controlled trial evaluating an intervention with a proactive approach to at-risk relatives
Study outline: Probands from four Swedish cancer genetic units in Umeå, Stockholm, Lund, Göteborg will be enrolled in the RCT-study.

Inclusion criteria are:

1) New proband beeing offered a cancer genetic investigation or genetic carrier test,
2) submitted written consent to join the study,
3) being over 18 years of age,
4) belonging to a family with
    - familial breast cancer,
    - familial CRC
    - Patogenic variant in PALB2 or BRCA1/2 (Hereditary BC or BOC)
    - Pathogenic variant in MLH1, MSH2, MSH6, PMS2, EPCAM (Hereditary CRC)
5) having at least one at-risk relative who have not previously received information about potential genetic cancer risk in the family.

The probands will be randomly allocated to standard care or intervention group (Figure 2). All probands enrolled receive genetic counselling and written information summarizing the investigation and preventive options. They are encouraged to inform their relatives (standard care).

In the intervention group, probands will be offered the additional service of an information letter being sent directly to the home of the relatives one month after counselling. The proband is asked for written consent to send letters directly from health care to his/her relatives, and direct letters are only sent to those relatives that 1) are eligible for surveillance or predictive testing and 2) relatives that the proband identify as a-risk family members.

The direct letter will inform the relative about the fact that a cancer genetic investigation has been conducted and possible implications for the him/her, and/or his or her family. To facilitate access to further information, contact details to the closest cancergenetics unit are included.

Data collection: For probands in both groups, number of at-risk relatives are identified in the family pedigree. Data on at-risk relatives that actually seek counselling/undergo predictive testing at a Swedish cancer genetic clinic will be retrieved from the cancer genetic clinics' patient data registry at each clinical site. The local genetic coordinator will follow-up the outcomes per proband and report it to the study database as a plain number.

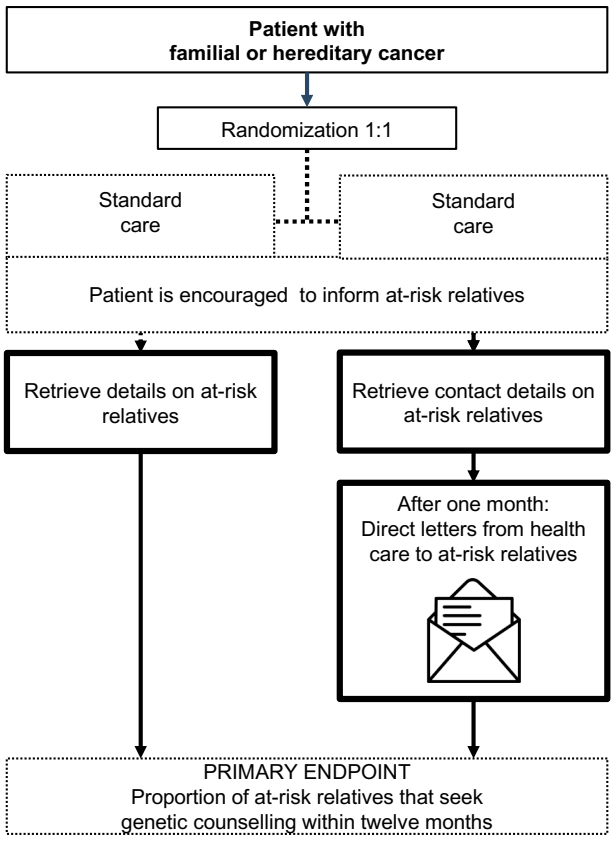

Figure 2. Study outline of the prospective randomized controlled trial comparing clinical praxis with a proactive intervention with direct letters to at-risk relatives

Statistical considerations:
The cancer genetic units who will take part in the RCT-study admit around 700 probands (the individual who initiate a genetic investigation in a family) that meet the inclusion criteria each year. A modest assumption is that half of them will accept an invitation to enroll in our study. Our estimate is that DIRECT needs around 600 probands/families in total to generate a sufficiently large study population.

Our primary outcome measure (in total and for subgroups based on family diagnosis, gender and age) is the proportion of at-risk relatives per family who approach a cancer genetic unit for councelling within 12 months. If three out of four relatives contact a cancer genetic unit in one study arm (e.g. intervention) and two out of four does so in the other study arm (e.g. control/standard care) then we have a power of >0.999 to discover a difference in effect between the two clinical protocols. If instead one extra at-risk relative in every second family approaches a cancer genetic unit in one of the study arms, we reach a power of 0.87.

Regarding the diagnose-specific subgroup analysis we expect around 220 probands to be recruited in each of the familial cancer diagnosis groups (power=0.97) and around 130 in the group with breast and ovarian cancer cases (power=0.85). In the smallest group with Lynch syndrome cases, we can only expect around 30 probands to be included after 28 months at normal patient influx. Thus, this group will be too small, and power subsequently too low, to motivate subgroup specific analysis (power=0.30).

Concerning the subgroup analyses for gender and age the study will have a power between 0.96 and 0.99 to discover differences between the intervention and the control groups, if three instead of two at-risk relatives approach a cancer genetic unit within a year.

Study 2: Mixed method follow-up study of reactions to the intervention in stakeholders
Data collection: In-depth interviews will be conducted with both probands and at-risk relatives, about 15 in each group. Additionally, questionnaires will be administrated to the consenting probands directly after finalized family investigation, and repeated three months later. Receivers of the letters (at-risk relatives) are invited to fill in questionnaires at their first contact with a cancer genetics unit and at 3 months follow-up. The questionnaires include items on attitudes towards cancer risk communication, validated instruments measuring quality of life (RAND -36), anxiety about cancer (cancer worry scale) as well as psychometric testing with State-Trait Anxiety Inventory, (STAI). Emotional reactions and acceptability of the intervention will also be explored in short written narratives.
Analysis: Interviews and short written narratives are transcribed and analysed using qualitative content analysis. Quantitative data (e.g.psychometric measures, cancer worry and attitudes towards the intervention) is subjected to analytical statistics.
Expected outcome: Clarification of potential (adverse) effects of the intervention among probands and at-risk relatives.

Study 3: Investigating the boundaries of hereditary cancer risk communication – legal and ethical perspectives on genetic councelling in Sweden
In order to propose a future model for hereditary cancer risk communication to at-risk individuals, we need to combine our findings from study 1 and 2 with legal and ethical aspects relevant for the clinical practice of cancer genetic counselling. A legislative analysis of legal documents (legislation, preparatory works, case law and legal doctrine) will be conducted by the co-worker Dr. Sandén. We will also conduct an ethical analysis, led by Dr. Grill, of the moral values at stake, and of the result of the explorative study, the RCT and mixed method follow-up study also including existing literature on the ethics of genetic health information.
Expected outcome: The legal and ethical analysis will clarify legal duties and ethical recommendations for health care professionals working with cancer genetic counselling. This data is expected to be vital in the development of future clinical guidelines regarding hereditary cancer risk communication to at-risk individuals.

Infrastructure
The study will be coordinated from Umeå university, but conducted at four cancer genetic units in Sweden (Umeå, Göteborg, Stockholm and Lund). We have already formed a national steering group of involved researchers and clinicans at the participating study sites, and held a national start-up meeting in Stockholm in February 2019.

Research collaborations
The interaction between this project and the cancer genetic units throughout Sweden is crucial for the success of the project, and will be facilitated by the longterm tradition of collaboration between Swedish cancer genetic units. The outline of the proposed study have been drafted in consultation with the collaborating units, who all have expressed a readiness to contribute to recruitment of patients.

Moreover, several of our team members are coordinating or participating in national research projects concerning breast cancer genetics (SWEA-study), management of TP53-mutation carriers (SVEP53) and the development of a national quality registry for the cancergenetic clinics (NOGA-registret). In addition, we collaborate with the newly formed initiative

Genomic Medicine Sweden (GMS), a national approach to strengthen the implementation of translational genomics where we are part of the expert group handling the subfield on hereditary cancer.

The prinicipal investigator (AR) is also involved in research collaborations at the Department of Radiation Sciences concerning the clinical spectrum in families with a BRCA1-founder mutation prevalent in Northern Sweden. Morover, she is also part of another project at the Department of Surgery focusing on the long-term clinical and patient-reported outcomes in women who have undergone prophylactic mastectomy surgery.

Involved research staff
The main applicant **Anna Rosén (AR)** is the principal investigator, and responsible for all aspects of the project. **Barbro Numan Hellqvist (BH)** is a researcher and statistician at the Regional Cancer Centre North and will be responsible for the research database. Specialist nurse, **Senada Hajdarevic (SH)** has expertise in qualitative methodologies and has worked in the explorative study and conducted focus group discussions together with Dr. Rosén. **Carolina Hawranek (CH)** is a Biomedicine major and communication professional, recently admitted as a PhD-student at the Department of Radiation Sciences. CH and SH have conducted individual interviews with patients during 2018, and CH will coordinate the national RCT.

Ulrika Sandén (US) is a LL.D. and lecturer in medical law and will lead the legal study. **Kalle Grill (KG),** senior lecturer in philosophy specialized in normative ethics and political philosophy, including public health ethics is responsible for the ethical study. US and KG will also contribute in development of a proposed future model for hereditary cancer risk communication to at-risk individuals. **Emma Tham (ET)** PhD, MD, Karolinska university hospital, and **Hans Ehrencrona (HE)** PhD, MD, Skåne university hospital and **Anna Öfverholm (AÖ)** Sahlgrenska hospital, are responsible clinical geneticist at their study site, and have contributed in the development of this project. **Beatrice Melin (BM)** is professor in Oncology and contribute with advice in the overall guidance of the project.

Creating a basis for a sustainable translational genomic research group with focus on the clinical utility of genomic applications in clinical practice

The inherent complexity of genetic counselling, coupled with designing and evaluating an intervention in routine cancer genetic care, requires an interdisciplinary approach. The project has assembled a multi-professional team from varied disciplines such as; clinical cancer genetics (AR, AÖ, ET, HE), oncology (BM,SH), public health (AR), epidemiology (AR), nursing (SH), statistics (BH), strategic communications (CH), implementation science (CH), medical law (US), and public health ethics (KG).

Several team members work as health care practitioners and can therefore facilitate diffusion of knowledge between clinical practice and the project. The other team members contribute with a wider perspective, adding strategic communications, law and ethics expertise to our joint effort. As they are not involved in clinical work they have the advantage of positioning themselves with an important outside perspective.

TIMEPLAN

Planned activities per year	**2019**				**2020**				**2021**				**2022**
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1
Project preparation	x	x											
Start-up meeting	x	x											
Study 1: Randomized controlled trial:													
- Recruitment of families			x	x	x	x	x	x	x	x	x	x	
- Data-collection				x	x	x	x	x	x	x	x	x	x
Study 2: Mixed method follow-up study:													
- In-depth interviews with probands and relatives				x	x	x	x						
- Questionnaires to probands and relatives			x	x	x	x	x	x	x	x	x	x	x
Study 3: The boundaries of risk communication													
- Ethical study	x	x	x			x	x	x	x	x	x	x	
- Legal study	x	x	x			x	x	x	x	x	x	x	
Development of a future model for hereditary cancer risk communication										x	x	x	
Dissemination of results							x	x			x	x	x

GRANTS

The study has received grants from the Cancer Research Foundation in Norrland (200 000 SEK), the Swedish Breast Cancer Association (300 000 SEK), and Regional agreement between Umeå University and Västerbotten County Council ("Centrala ALF", 900 000 SEK, "Basenhets-ALF" 306 000 SEK) and FORTE (4 430 000 SEK).

SIGNIFICANCE AND CLINICAL APPLICATIONS

Facilitating communication on cancer risk and prevention to individuals in high risk families is a public health priority, because of the potential of primary or secondary prevention of cancer in these families.

Our aim is to explore a new approach to convey information on preventive measures to at-risk relatives in families with high risk of developing breast and ovarian or colorectal cancer. Surveillance programs aimed at these groups have been proven to decrease cancer-related mortality and morbidity and increase quality-adjusted life years at an acceptable cost.

We ultimately want to propose a future model for hereditary cancer risk communication to at-risk individuals that gives every affected person the same opportunity to know their inherited cancer risk and make informed decisions on possible preventive measures. This could translate into a reduction of cancer incidence and cancer-related death in high-risk families, and we therefore believe that the project is of great value for both the families and the society.

ETHICAL CONSIDERATIONS

A growing body of evidence suggests that the prevailing clinical practice of managing hereditary cancer risk information is insufficient and it has been debated for some time whether health care should have a (more) proactive role in informing relatives. Recently, the Swedish National Council of Medical Ethics (SMER) called for a overview of current regulations governing clinical applications of gene technology for health care.

Ethical dilemmas in the study are closely related to the dilemmas in cancer genetic counselling in general, with conflicting duties between the proband and the relative. The proband is asked for consent before sending direct letters to his/her relatives, and letters are sent only to those relatives that the proband identifies.

In the intervention, we will approach at-risk relatives by a direct letter including information about personal health risk. This may raise worries, and therefore we have balanced the wording in the letter in such a way that the receiver s given a chance of causing lingering anxiety. In the ongoing explorative study informants have underlined the importance of health care professionals being accessible to promptly respond to questions. We will include contact details to a cancer genetics unit in all information letters, and experienced counsellors will be available, limiting potential time of anxiety.

To at-risk individuals for the cancer types in question, effective preventive measures are available. However, even if an ethical justification for the intervention is supported by a duty of beneficence, a dilemma connected to a direct approach is the risk that we violate the relatives' right not to know.

The Regional Ethical Review Board in Umeå has approved the explorative study [Dnr 2016-345-31, 2017-472-32 and 2018-287-32]. Ethical approval of the RCT and mixed-method follow-up study are sought in April 2019.

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