ERN GENTURIS GUIDELINE ON COUNSELLING ON REPRODUCTIVE OPTIONS FOR INDIVIDUALS WITH A CANCER PREDISPOSITION SYNDROME (INCLUDING GENTURIS)

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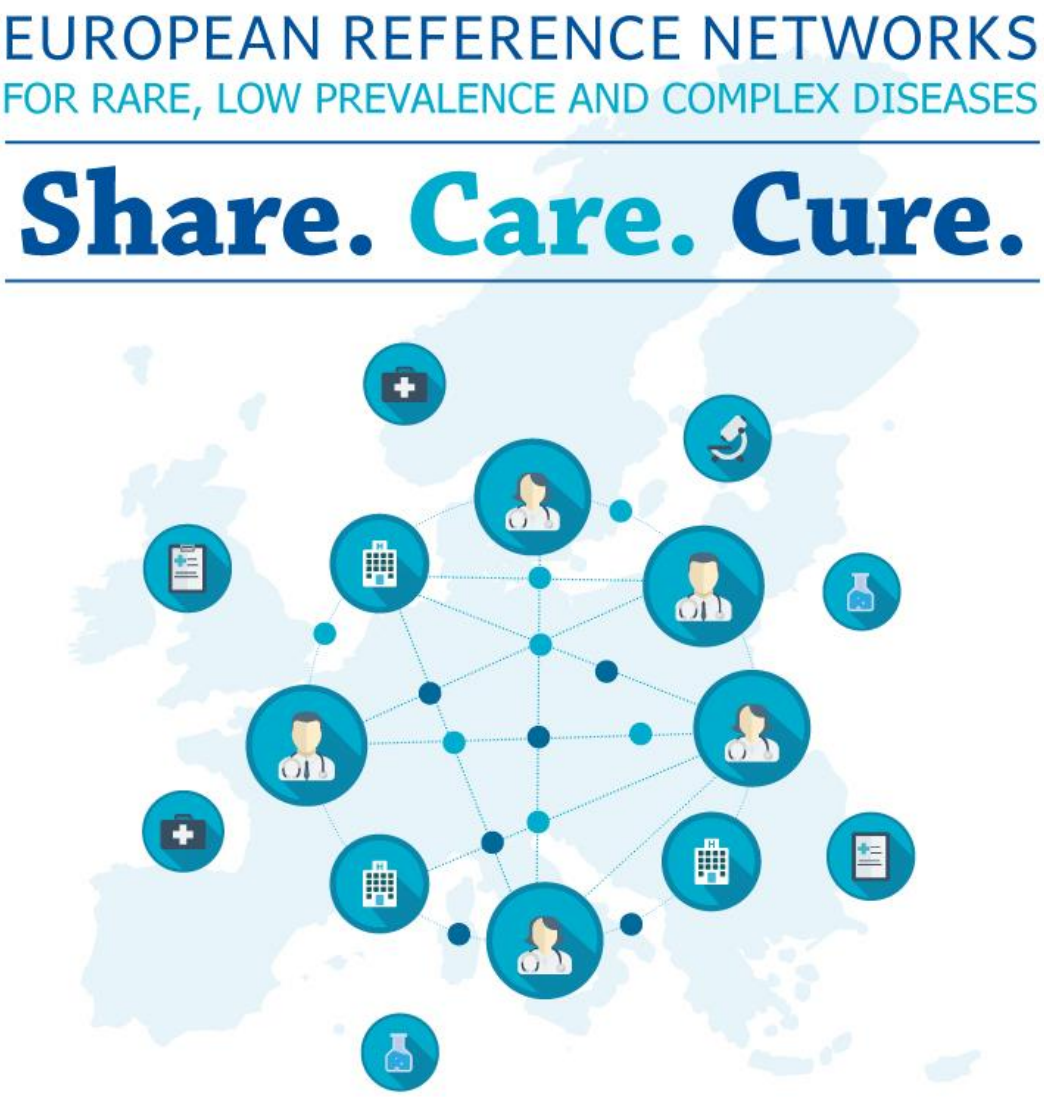

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1. ABSTRACT

Cancer predisposition syndromes (CPSs) are a heterogeneous group of genetic disorders characterised by an increased risk of developing cancer compared to the general population. A subset of CPSs can also be defined as genetic tumour risk syndrome (genturis). Individuals with a CPS have an increased risk of developing tumours. In many CPS families, there is a significant risk of passing the pathogenic variant(s) on to offspring.

An individual with a CPS may therefore not only be concerned about their own cancer risk, but also the risk in (future) children. These individuals have several reproductive options available to them, to avoid having a child with CPS, but decisions concerning reproductive options are complex.

Counselling on reproductive options is essential to support individuals with a CPS to make informed choices and ensure their reproductive autonomy, but few healthcare professionals outside genetics have the specialised knowledge needed to offer complete reproductive counselling.

The aim of this guidelines is to assist healthcare professionals in providing reproductive counselling for individuals with CPS. The recommendations are that individuals with CPS, and those of their family members for whom it is relevant (for example the parents of a child with CPS) receive the offer of reproductive counselling, independent of their healthcare professionals' views and level of knowledge. This reduces disparities in the quality of care for individuals with a CPS. Having multiple opportunities for counselling is recommended, as perspectives and relevance regarding reproduction can change over life.

Due to the complexity of reproductive decisions regarding CPS, access to a multidisciplinary team is recommended.

2. GUIDELINE SUMMARY

This guideline has been drawn from the best available evidence and the consensus of experts in this area and is regularly updated to reflect changes in evidence. The expectation is that clinicians will follow this guideline unless there is a compelling clinical reason to undertake different management, specific to an individual patient.

Recommendations in this guideline are divided into 4 sections: 1. Reproductive decision making – content and framework of reproductive counselling, 2. Timing of reproductive counselling provision, 3. Presentation of reproductive option, 4. Range of assisted reproductive technologies.

Table 1: Key recommendations regarding counselling on reproductive options

Reproductive decision making - content and framework of reproductive counselling	Recommen-dation	Strength*
Reproductive counselling should be offered to all individuals with a cancer predisposition syndrome** and relevant family members.	1,2, 11	Strong (1,2), moderate (11)
Couples should have access to a multidisciplinary team of healthcare experts.	6, 13	Strong
Timing of reproductive counselling provision		
Reproductive counselling should be offered longitudinally with multiple opportunities for counselling throughout life, ideally starting before family planning	7, 8	Strong
Children at risk should be offered counselling once they reach adulthood, or earlier if appropriate	10	Moderate
Presentation of reproductive option		
Reproductive counselling should provide follow-up opportunities, and access to psychological support.	12, 13	Moderate (12), strong (13)
Range of assisted reproductive technologies		
Fertility preservation options should be included in reproductive counselling.	15, 16	Strong (15), moderate (16)

* This grading is based on published articles and expert consensus: strong – expert consensus AND consistent evidence, moderate – expert consensus WITH inconsistent evidence AND/OR new evidence likely to support the recommendation, weak – expert majority decision WITHOUT consistent evidence.

** Counselling is especially relevant in the reproductive age but can be relevant in other age group as well, such as adolescence and older individuals informing their relatives.

3. INTRODUCTION

3.1. CANCER PREDISPOSITION SYNDROMES AND GENETIC TUMOUR RISK SYNDROMES

Cancer predisposition syndromes (CPSs) are a heterogeneous group of genetic disorders characterised by an increased risk of developing cancer compared to the general population. This increased risk is mostly due to a genetic variant that can be either inherited, occur *de novo* or comprise other genetic mechanisms, such as a methylation defect. It is estimated that 5–10% of all tumours have a genetic predisposition. More than 50 CPSs have been described in the literature (Calosci et al. 2023, WHO 2025)

Characteristics for CPSs are that they often cause tumours at a much younger age than equivalent tumours in people without a CPS and that they can cause multiple tumours in one individual. Therefore, they can significantly increase morbidity and mortality.

A subset of CPSs can also be defined as a **genetic tumour risk syndrome** (genturis). Genturis are complex and/or rare, low-prevalence CPSs. These syndromes involve one or more inherited or *de novo* genetic variants that strongly predispose the individuals to the development of benign or malignant tumours amongst other manifestations. Individuals with a genturis have an increased risk of developing tumours, which are often diagnosed at a young age and located in multiple organ systems. If diagnosed with cancer, individuals with a genturis may need different treatment and follow-up compared to cancer patients without hereditary risk. While genturis are characterised by tumourigenesis, development of additional non-tumour related health issues is also frequently observed in genturis patients and should be considered in patient care. In many genturis families, there is a significant risk of passing the pathogenic variant(s) on to offspring. The most up to date list of genturis syndromes can be found on the European Reference Network (ERN) GENTURIS website (www.genturis.eu) and only includes syndromes that have been classified as a genturis by expert members of ERN GENTURIS. Of note, not all CPSs are classified as a genturis, because some of these syndromes have characteristics that better match the inclusion criteria for one of the other European Reference Networks (Engels et al. 2025).

In this document, the slightly broader term CPS will be used. Therefore, the term "individual with a CPS" will refer to individuals that are diagnosed with a CPS, including all individuals with a genturis.

The value and need for reproductive counselling are relevant for all individuals with a CPS, including all individuals with a genturis.

3.2. THE NEED FOR REPRODUCTIVE COUNSELLING

The diagnosis of a CPS has significant clinical, psychosocial, emotional, and familial consequences for these individuals. It also allows access to targeted surveillance programs, which aim to diagnose a tumour at its early stages, start timely specific therapies and improve patients' prognoses as well as to offer appropriate psychological support.

Penetrance and reproductive options vary between different CPSs depending on the risks of the causative genes, specific pathogenic variants, and the mode of inheritance. There are also different risk profiles and therefore reproductive options can be different depending on factors such as the sex of the person or a future child.

An individual with a CPS faces an increased risk of developing cancer and may also be concerned about passing the pathogenic variant associated with the syndrome to their offspring. Some individuals with a CPS may consider not to have children because of the risk of passing the CPS on to a child. Their options include having no children, adoption, surrogacy and gamete donation. Individuals with a CPS who wish to have a biologically related child have several reproductive options available to them, which can be grouped into a number of main categories.

(1) natural conception without genetic testing, which implies accepting the risk of passing on the pathogenic variant to offspring. **This guideline focuses on reproductive counselling and:**

(2) **prenatal diagnosis** (PND), with the possibility to terminate the pregnancy if the foetus is found to carry the pathogenic variant.

(3) **preimplantation genetic testing** (PGT), allowing couples to create embryos through in vitro fertilization (IVF) and test them for the familial pathogenic variant in order to select against transfer of embryos that inherited the pathogenic variant causing the CPS.

Individuals with CPSs face complex decisions, also concerning reproductive options. The emotional, ethical, and practical challenges involved in deciding whether to conceive naturally, opt for PND, or pursue PGT through an IVF process require clear, compassionate, and accessible information. Each healthcare-system sits within a distinct social, cultural, and political system. Each jurisdiction takes a

socio-culturally specific legal and health-economic view regarding the acceptability and potential uses of each approach.

Decisions about reproductive options can carry a significant emotional impact, with individuals with a CPS potentially experiencing long-lasting feelings of guilt or doubt, especially given that there is rarely a definitive "right" answer. Additionally, few healthcare professionals outside genetics have the specialised knowledge needed to offer complete counselling regarding genetic cancer predispositions, and the reproductive options for couples at risk of having children with genetic conditions. Indeed, the limited access to specialists in reproductive counselling was highlighted as the most challenging pregnancy related issue in a recent survey among clinicians and patient representatives from 20 ERNs. Interestingly, in the same survey, pre-conceptional counselling was the topic rated the most important pregnancy related issue (Zucchi et al. 2025).

By providing a framework, healthcare providers can deliver balanced and empathetic reproductive counselling services that emphasise non-directiveness. Supporting patients in making choices that align with their values and beliefs, will minimize the risk of guilt or emotional distress over reproductive decisions. Such guidelines aim to help clinicians navigate complex discussions with patients, enabling them to offer evidence-based options and refer patients to specialized reproductive counselling when necessary. Counselling on reproductive options is essential to help individuals with a CPS to make informed choices and ensure their reproductive autonomy.

In addition, guidelines ensure that patients across different regions or healthcare systems receive standardised care, independent of their healthcare professional views and level of knowledge, including access to reproductive counselling, surveillance programs, and reproductive services like IVF or PGT. Offering standardised care might reduce disparities in the quality of care for individuals with a CPS.

4. COMPOSITION OF THE GUIDELINE GROUP

The ERN GENTURIS guideline group for counselling on reproductive options for individuals with a cancer predisposing syndrome (CPS) including genturis (genetic tumour risk syndrome; ERN GENTURIS counselling on reproductive options guideline group) was established by 20 experts in reproductive counselling from 10 countries as well as 3 (parents of) individuals with a genturis (patient representatives acting as community representatives). The ERN GENTURIS counselling on reproductive options guideline group was supported by a core working group (N=6) which comprised ERN GENTURIS healthcare provider members from different Member States and other experts who are recognised experts in reproductive counselling for genturis syndromes and/or have clinical practice experience and/or specialise in the diagnosis, management, and counselling of reproductive options for individuals with CPSs/genturis.

In order to recruit members for the ERN GENTURIS counselling on reproductive options guideline group, including its core working group, a request for willing participants was made within ERN GENTURIS. ERN GENTURIS members with expertise in counselling on reproductive options and additional non-ERN GENTURIS European experts were selected for the core working group (the requirement to have at least 2 ERN GENTURIS health care providers from at least 2 Member States was met). Afterwards, the core working group suggested European experts in the field (colleagues) for the ERN GENTURIS counselling on reproductive options guideline group.

The core working group met online monthly since April 2024 and drafted the guideline scope, clinical questions, recommendations, and guideline document and obtained feedback from the ERN GENTURIS counselling on reproductive options guideline group. The recommendations were finalised in a modified Delphi approach in which the core working group, guideline group (including patient representatives) and additional experts participated (see chapter 8).

Additional experts to participate in the modified Delphi approach were either suggested by the ERN GENTURIS counselling on reproductive options guideline group or responded to the request to participate in the Delphi survey circulated within the ERN GENTURIS network. When representation from specific European countries was low, ERN GENTURIS national coordinators of the respective country were contacted and encouraged to suggest local experts. During the selection of the final group of experts we took into account the coverage of all specialists and all European countries. However, expertise coverage was leading the selection.

Although the guidelines are primarily written for healthcare professionals involved in the management, treatment, and care of individuals with a CPS - including clinical geneticists, genetic counsellors, oncologists, fertility specialists, treating physicians - they can also be useful for other physicians, individuals with a CPS, and interested parties.

Approach to secure views and preference of target population

The ERN GENTURIS counselling on reproductive options guideline group was supported by 3 patient representatives from a patient advocacy group (community representatives). One patient representative was part of the core working group and present during these meetings. Patient representatives were recruited within ERN GENTURIS.

Involving patient representatives in the development of these guidelines and in the ERN GENTURIS counselling on reproductive options guideline group helped ensure that:

- the addressed questions are relevant to individuals with a CPS including genturis and will make a positive impact on patient care.
- important aspects of the experience of conditions are considered.
- critical clinical and patient focused outcomes are identified and prioritised.
- the balance of the benefits and harms related to the intervention are appropriately considered when recommendations are formulated in conjunction with patient values and preferences.

The representatives from the patient advocacy group advised on the scope, target population, and clinical questions the guideline aimed to address and gave a patient perspective on the findings of the literature review and the consensus recommendations and provided feedback on the plain language summary.

5. CONFLICT OF INTERESTS

All members of the ERN GENTURIS counselling on reproductive options guideline group, including the core working group, have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. Said C. Farschtschi reported receipt of honoraria or consultation fees from Alexion and AstraZeneca. Tamara Hussong Milagre reported receipt of grant/research supports from Gilead Science (EVITA Platform) and receipt of honoraria or consultation fees from Novartis (Advisory Board). Claas Röhl reported receipt of grants/research supports from Boehringer Ingelheim, Alexion, BMS, Novartis, Roche, Tecan and participation in a company sponsored speaker's bureau (Boehringer Ingelheim, Alexion). Anna Sophie Berghoff has research support from Daiichi Sankyo, Roche and honoraria for lectures, consultation or advisory board participation from Roche Bristol-Meyers Squibb, Merck, Daiichi Sankyo, AstraZeneca, CeCaVa, Seagen, Alexion, Servier, Pfizer as well as travel support from Roche, Amgen and AbbVie.

All participants of the ERN GENTURIS Counselling on reproductive options for individuals with a genturis Delphi survey gave provided disclosure statements on all relationships that they have that might be perceived to be a potential source of competing interests.

Rosie O Shea, Kerstin Rhiem, Sophie Frank, Kleoniki Roka reported receipt of honoraria or consultation fees from Astra Zeneca. Rosie O Shea reported participation in a company sponsored speaker's bureau: Astra Zeneca. Kerstin Rhiem received grants/research support from German Cancer Society and received honoraria or consultation fees from Novartis, streamed up GmbH. Susanne Schüler-Toprak reported receipt of honoraria or consultation fees from Pfizer, Roche, GSK, and Celgene. Karin Wadt received honoraria or consultation fees from Seagen Denmark ApS. Sophie Frank reported travel support from Pharma, GSK, Lily, and Pfizer. Hildegunn Høberg Vetti reported receipt of honoraria or consultation fees from Pfizer AS, Novartis Norway AS, and Pierre Fabre Pharma Norden AB. Amedeo Azizi received grants/ research supports form Alexion as well as honoraria or consultation fees from Alexion, Novartis, and Johnson & Johnson.

6. PURPOSE AND SCOPE OF THIS GUIDELINE

6.1. WHY WAS THIS GUIDELINE PRODUCED?

Decision-making regarding reproductive options is complex and nuanced, with no definite 'right answer' applicable to all patients or situations. Healthcare professionals involved with this patient population often express the need for guidance (British Society for Genetic Medicine 2023) to ensure accurate information to patients in these challenging situations.

In families with a hereditary predisposition to cancer, reproductive decision-making may involve additional layers of complexity, as the potential for future risk —rather than certainty— can significantly influence the difficulty of the decision-making process. The patient and their families can have different perceptions of disease burden that depend on local or national factors, which affect access to screening, the availability and acceptance of termination of pregnancy for CPSs, and the impact of penetrance (Julian-Reynier et al. 2009, Carley et al. 2024).

This guideline does not aim to address these issues; instead, it seeks to support specialists in providing timely counselling on reproductive matters to individuals with a CPS and to help ensure their reproductive autonomy. There is currently a lack of awareness regarding reproductive options among both healthcare professionals outside clinical genetics and individuals with a CPS (Brandt et al. 2010, Royal College of Physicians 2022). Not all healthcare professionals have sufficient knowledge, and some may have other clinical priorities; additionally, there may be ethical concerns regarding Assisted Reproductive Technologies (ARTs) for individuals with a CPSs. Consequently, individuals with a CPS might interpret a lack of information on reproductive options as an indication that these options are not recommended for their condition (Kalfoglou et al. 2005). Individuals with CPS generally want to understand their available options, the procedures they and their partners may need to undergo and the associated risks, benefits, and likely success rates (Bracewell-Milnes et al. 2021). Historically, there has been less literature on pregnancy options for those living with a CPS compared to more common conditions (British Society for Genetic Medicine 2023), which may be attributed to a lack of accumulated knowledge in this area. An important aspect of this guideline is to emphasise that reproductive counselling is a crucial and integral part of the treatment of individuals with a CPS.

6.2. WHO IS THE GUIDELINE FOR?

This guideline should be directed to:

Healthcare Professionals:

Genetic counsellors: Professionals who provide detailed information to patients about genetic testing and reproductive options.

Oncologists and geneticists: Doctors involved in diagnosing and treating CPSs should have guidelines to ensure consistent advice and referral regarding reproductive options.

Primary care physicians: Primary care physicians often serve as the first point of contact and need to understand CPSs to identify at-risk patients and make appropriate referrals to specialists.

Fertility specialists: Given the reproductive implications of CPSs, fertility clinics should receive guidance on how to counsel patients about PND, PGT, and the associated risks.

Lay organisations and national disease-specific working-groups: To specify practical guidelines and checklists for the care of specific patient cohorts.

Individuals with a CPS:

At-risk individuals: Individuals diagnosed with or suspected of having a CPS need clear, accessible information about their condition, the potential risks involved, and the preventive or therapeutic measures available to them.

Prospective parents: Couples at risk of having a child with CPS who are considering pregnancy need comprehensive information regarding their reproductive options, including the psychological and ethical dimensions of each choice.

Family members of individuals with a CPS: Given the genetic nature of these syndromes, family members may also be at risk. Educating families is essential to help them understand their own risks, make informed decisions about genetic testing, and navigate discussions regarding surveillance or reproductive choices.

Healthcare institutions and policy makers:

Guidelines directed at institutions and policymakers ensure that CPS-related services, such as genetic testing, reproductive counselling, and surveillance programs, are accessible, affordable, and aligned with best practices. These guidelines could influence healthcare policies and funding for services aimed at individuals with hereditary cancer syndromes.

Public health authorities and advocacy groups:

Advocacy groups and public health organisations that raise awareness of hereditary cancers should use the guidelines to provide up-to-date, evidence-based information to the public. This effort helps destigmatize the condition and promotes early testing and preventive care.

Medical educators and researchers:

Guidelines would also be beneficial for educators involved in training healthcare professionals and researchers investigating CPSs. They serve as a foundational resource for teaching the latest scientific, ethical, and clinical practices related to hereditary cancer predispositions and their reproductive options.

Clinical guidelines are statements to support decision making, based on systematically evaluated evidence for a specified clinical circumstance. Whilst these clinical guidelines are based on the latest published evidence, care of each individual remains primarily the responsibility of their treating medical professionals. Decisions for care should always be based on the individuals needs, personal preferences and individual circumstances of each patient. Clinical guidelines should support clinical decision making, but never replace clinical professional assessment and decision making. Guidelines present recommendations based on expert opinion and published evidence and are not mandates. These guidelines do not signify nor intend to be a legal standard of care.

6.3. WHAT IS THE GUIDELINE ABOUT?

6.3.1 SCOPE

The scope of this guideline is to provide a general framework covering the key concepts related to acceptable and expected options in reproductive counselling specifically for individuals or couples at risk of having a child with a CPS. In most cases, one person in the couple is affected by a CPS (including genturis) with a known pathogenic variant (autosomal dominant inheritance), but other modes of inheritance exist.

6.3.2 HEALTH QUESTIONS

Key clinical questions include, but are not restricted, to:

- What content should counselling regarding reproductive options have for individuals with a CPS?
- How can healthcare professionals aid individuals with a CPS to make informed choices?
- Under what circumstances and at what time in the person's life should healthcare professionals refer individuals with a CPS for counselling regarding reproductive options?

- In what context should counselling for reproductive options be provided to individuals with a CPS?
- Who should perform counselling for reproductive options for individuals with a CPS?
- How should reproductive counselling be performed for individuals with a CPS?

6.3.3 POPULATION

Individuals at an increased risk for developing cancer due to a genetic CPS, along with their partners and the families of those individuals with a CPS.

6.3.4 CARE SETTING

This guideline is intended to support healthcare professionals involved in the care and management of patients with a hereditary cancer predisposition when counselling on reproductive decision making. It may also be used by patients and other interested parties. Implementation and dissemination of the guideline should take place through the national Directorate of Health of each European country, supported by sharing through patient and professional societies and publication in the European Journal of Human Genetics.

6.3.5 EPIDEMIOLOGY & AETIOLOGY

Genetic Basis of Cancer Predisposition

Approximately 27–36 million patients in Europe are affected by one of 5,000–8,000 known rare diseases. A rare disease is defined as a condition that affects fewer than 1 in 2,000 individuals, and it is therefore estimated that it affects about 6–8% of people.

While environmental and lifestyle factors contribute to cancer development, a subset of cancer cases is attributed to hereditary predisposition, where pathogenic variants in a specific gene significantly increase the risk of malignancies. Such a condition is referred to as a cancer predisposition syndrome (CPS) and/or genetic tumour risk syndrome (genturis; rare, low-prevalence and/or complex CPSs identified as falling under the remit of ERN GENTURIS)(Engels et al. 2025).

CPSs are characterized by an increased risk of specific tumour types, an earlier age of onset, and possibly, the presence of multiple tumours within an individual or across family members.

Epidemiological data indicate that CPSs account for approximately 5-10% of all cancer cases and in up to 15% of cancer cases in children. Currently, more than 50 distinct CPSs have been identified. Genetic cancer syndromes often result from pathogenic variants in genes involved in DNA repair, cell division, and apoptosis. Prominent examples include *BRCA1/BRCA2* pathogenic variants in hereditary breast and ovarian cancer, *APC* pathogenic variants in familial adenomatous polyposis, and *TP53* pathogenic variants in Li-Fraumeni syndrome. In some cases, individuals carrying these pathogenic variants face a nearly 100% lifetime risk of developing cancer, but others have only moderate penetrance. Moreover, penetrance can be sex-related, for example in hereditary breast and ovarian cancer. Most of these CPSs follow an autosomal dominant inheritance, whereas others follow an autosomal recessive or X-linked inheritance (Garutti et al. 2023, Engels et al. 2025).

Still, recognizing CPSs remains challenging, as many affected individuals do not present a clear family history due to incomplete penetrance and variable expression of pathogenic variants and due to *de novo* pathogenic variants.

Risk Stratification and Sex-Specific Variable Penetrance

Within genetic CPSs, a distinction is made between high-risk and moderate-risk genes. High-risk genes, such as *BRCA1, BRCA2* and *TP53*, confer a higher cancer risk compared to moderate-risk genes, such as *CHEK2* and *ATM*. Additionally, some pathogenic variants exhibit sex-specific variable penetrance. For instance, *BRCA1* pathogenic variants strongly increase the risk of breast cancer predominantly in women, while in men, they are associated with a more moderately elevated risk of prostate cancer. Some genes display a parent of origin effect, e.g. *SDHD*. Such differences underscore the importance of risk stratification that can be sex-specific and the development of personalized prevention strategies (Garutti et al. 2023).

As some rare cancer predisposition syndromes can exhibit a number of non-tumorous manifestations the clinical work-up of these symptoms is important and may influence genetic counselling and vice versa. These manifestations range from additional clinical and/or psychological burden to hypothetical risks in the future. This may influence the patient's decision upon family planning and consideration of further diagnostic or therapeutic options. Some CPS show a broad range of manifestations, and their respective severity make it challenging to provide decisive prognostic answers. However, the full clinical spectrum of the entity should be discussed. If non-tumour symptoms like neuropsychological or psychiatric disorders impede the genetic counselling, this should be discussed within a multiprofessional team.

Timely recognition of the hereditary character of CPSs allows implementation of risk management strategies (which can be sex-specific), enabling cancer prevention or early detection, enabling improved prognosis for both affected individuals and their family members. Additionally, patients with a CPS can benefit from personalized treatment strategies tailored to their genetic predisposition, as well as from reproductive counselling and options.

7. KEY FINDINGS & RECOMMENDATIONS

7.1. CONTEXTUAL INFORMATION

In the following, the term cancer predisposition syndrome (CPS) will be used. Therefore, the term "individual with a CPS" will refer to individuals that are diagnosed with a CPS, including all individuals with a genturis (see chapter 3.1). The value and need for reproductive counselling are relevant for all individuals with CPS, thus also including genturis patients.

With respect to the hereafter formulated recommendations, the following* should be taken into account:
Healthcare professionals should always: • respect the individual's autonomy and personal readiness while ensuring access to necessary information. • provide information in a timely manner, tailored to the individual's needs and circumstances considering that what is timely may vary based on personal and healthcare system factors. • provide up-to-date information, recognising that clinical screening strategies, treatment guidelines, diagnostic criteria, nomenclature, reproductive methods, and genetic techniques may change at short notice as scientific knowledge evolves.
Healthcare centres providing counselling on reproductive options for individuals with a cancer predisposition syndrome and relevant family members should: • counsel patients prospectively in advance about PND and preimplantation genetic testing, including its medical procedure, limitations, psychological impact, success rates, and the possibility of obtaining only affected embryos/foetuses. • clearly present and explain all available reproductive options to patients, including those beyond prenatal diagnosis and preimplantation genetic testing (such as sperm/oocyte donation, adoption, and postnatal diagnosis). This should include information on reproductive window, waiting times and delays (such as the time required to obtain test results for prenatal diagnosis or the timeline to the first embryo transfer in preimplantation genetic testing)

- ensure realistic expectations and informed decision-making, tailored to the patient's reproductive potential, before initiating any procedures. For example, a 38-year-old woman may have lower success rates in PGT-M procedures due to her ovarian reserve and oocyte quality compared to a 28-year-old woman.
- Provide guidance in accordance with country-specific legal possibilities and processes. For example, some countries may require ethical board approval for PND or PGT in individuals with a cancer predisposition syndrome on an individual basis, and not all cases may be accepted.
- Include information about the availability of public funding for PGT, if applicable.
- Facilitate liaison with IVF clinics regarding fertility potential, including consideration of the patient's age and ovarian reserve (e.g., AMH levels), to set realistic expectations for success rates.

Reproductive counselling

Personal philosophies, religion, cultural values, and individual preferences concerning family and reproduction significantly influence attitudes towards prenatal diagnosis and preimplantation genetic testing. Counsellors should be sensitive to and understand these perspectives, ensuring non-judgemental, personalised, and non-directive support.

* These general statements are based on recommendations included in the first Delphi round which passed the threshold for consensus.

Recommendations in this guideline are divided into 4 sections:

- Reproductive decision making – content and framework of reproductive counselling (section 7.2 & 9.2)
- Timing of reproductive counselling provision (section 7.3 & 9.3)
- Presentation of reproductive options (section 7.4 & 9.4)
- Range of assisted reproductive technologies (section 7.5 & 9.5).

7.2. REPRODUCTIVE DECISION MAKING - CONTENT AND FRAMEWORK OF REPRODUCTIVE COUNSELLING

Recommendations		Strength
Rec. 1	Reproductive counselling should be offered to all individuals with a cancer predisposition syndrome*. It is voluntary for the individual with a cancer predisposition syndrome to accept or decline counselling.	Strong
Rec. 2	All individuals with a cancer predisposition syndrome and relevant** family members of reproductive age should be offered information about their reproductive options.	Strong
Rec. 3	Reproductive counselling must provide individuals with a cancer predisposition syndrome and relevant** family members with comprehensive, balanced, and timely information.	Strong
Rec. 4	Reproductive counselling should be non-directive ensuring patients can freely decline specific or all reproductive options without fear of recrimination, feelings of guilt or social pressure.	Strong
Rec. 5	Couples, at risk for a child with a cancer predisposition syndrome, considering prenatal diagnosis*** should be encouraged to reflect on their views regarding continuation or termination of pregnancy preconceptionally****.	Moderate
Rec. 6	Couples with a cancer predisposition syndrome considering pregnancy should have access to a multidisciplinary team of healthcare experts in an individualised way. This may include: A genetic counsellor or clinical geneticist to assess genetic risk, discuss the feasibility of both prenatal diagnosis (PND)*** and IVF (in vitro fertilization) with preimplantation genetic testing (PGT) ***. A clinician experienced in performing and interpreting prenatal diagnostic tests to explain the risks, benefits, and procedures of PND*** options such as amniocentesis, chorionic villus sampling, and NIPT, if PND*** is considered.	Strong

	A fertility doctor to provide guidance on PGT***, including PGT-M, and other assisted reproductive techniques where relevant. A psychologist trained in reproductive and genetic counselling, given the emotional and psychological impact of these decisions, In difficult or unusual cases, advice should be sought from additional experts.	

* Counselling is especially relevant in the reproductive age but can be relevant in other age group as well, such as adolescence and older individuals informing their relatives.

** Definition: Relevant family members can include first degree relatives, such as parents, children, or siblings but also second- and higher-degree relatives. It depends on the characteristics and the inheritance mode of the syndrome. The healthcare professional will determine who the relevant family members are.

*** Definition: Prenatal diagnosis refers to tests conducted to diagnose a foetus in utero including amniocentesis, chorionic villus sampling, and NIPT (NIPT needs to be confirmed by an invasive test).

**** preconceptionally is before pregnancy.

7.3. TIMING OF REPRODUCTIVE COUNSELLING PROVISION

Recommendations		Strength
Rec. 7	Reproductive counselling should be offered longitudinally to individuals with a cancer predisposition syndrome (and relevant* family members) with multiple opportunities for discussion during reproductive age. At the time of diagnosis, individuals with a cancer predisposition syndrome should receive clear information about the availability of genetic and reproductive counselling services for future family planning.	Strong
Rec. 8	Genetic and reproductive counselling should be available for individuals with a cancer predisposition syndrome and for parents (at risk) of an affected child, ideally beginning before family planning and continuing as needed.	Strong
Rec. 9	Individuals with a cancer predisposition syndrome should be offered age- and context-appropriate genetic and reproductive counselling at the time of diagnosis.	Strong
Rec. 10	Children at risk for cancer susceptibility should be offered counselling** regarding predictive testing and family planning once they reach adulthood, or earlier if they express interest or the condition affects childhood.	Moderate

Rec. 11	Counselling regarding reproductive options is relevant for all individuals with a cancer predisposition syndrome, regardless of whether they already have children, are considering more children, or are not currently planning a pregnancy, since this may influence decisions regarding testing or informing their children/family members.	Moderate

* Definition: Relevant family members can include first degree relatives, such as parents, children, or siblings but also second- and higher-degree relatives. It depends on the characteristics and the inheritance mode of the syndrome. The healthcare professional will determine who the relevant family members are.

** Counselling in minors should be provided with parental consent and involve specialist with expertise in paediatric care. If initiated in childhood, follow-up should be continuous to adapt to the individual's evolving understanding and needs.

7.4. PRESENTATION OF REPRODUCTIVE OPTIONS

Recommendations		Strength
Rec. 12	Reproductive counselling for individuals with a cancer predisposition syndrome should provide sufficient time, follow-up opportunities, and access to psychological support.	Moderate
Rec. 13	Reproductive counselling should take psychological factors into account and be provided by a multi-disciplinary team. This team should include professionals with expertise in reproductive genetics, oncology (when relevant), and psychological support. Access to additional specialists should be tailored to individual patient needs.	Strong
Rec. 14	Reproductive counselling should be offered to both male and female individuals with a cancer predisposition syndrome independently and include their partners, if appropriate.	Strong

7.5. RANGE OF ASSISTED REPRODUCTIVE TECHNOLOGIES

Recommendations		Strength
Rec. 15	Female fertility preservation options, such as oocyte cryopreservation, should be included in reproductive counselling for individuals with a cancer	Strong

	predisposition syndrome, when there is a high risk of infertility due to cancer treatment*.	
Rec. 16	Male fertility preservation options, such as sperm cryopreservation, should be included in reproductive counselling for individuals with a cancer predisposition syndrome, when there is a high risk of infertility due to cancer treatment**.	Moderate

* This discussion should be tailored to the individual's age, ovarian reserve, and the feasibility of fertility preservation in their specific healthcare setting. Ideally, oncologists should address this topic early, before treatment begins.

** This discussion should ideally take place at the time of cancer diagnosis and be led by the oncology team before treatment begins. Counselling should be tailored to individual risk factors and the feasibility of fertility preservation within the specific healthcare setting.

8. METHODS FOR GUIDELINE DEVELOPMENT

8.1. FORMULATING AND GRADING STATEMENTS AND CONSENSUS BUILDING

Literature search

The guidelines were developed based on 851 published articles extracted from PubMed, using the following terms:

- ("reproduction"[MeSH Terms] OR "reproduction"[All Fields] OR "reproductions"[All Fields] OR "reproductive"[All Fields] OR "reproductively"[All Fields] OR "reproductives"[All Fields] OR "reproductivity"[All Fields]) AND ("genetic counselling"[All Fields] OR "genetic counseling"[MeSH Terms] OR ("genetic"[All Fields] AND "counseling"[All Fields]) OR "genetic counseling"[All Fields]) AND ("cancer s"[All Fields] OR "cancerated"[All Fields] OR "canceration"[All Fields] OR "cancerization"[All Fields] OR "cancerized"[All Fields] OR "cancerous"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields] OR "cancers"[All Fields])

  Translations

  reproductive: "reproduction"[MeSH Terms] OR "reproduction"[All Fields] OR "reproductions"[All Fields] OR "reproductive"[All Fields] OR "reproductively"[All Fields] OR "reproductives"[All Fields] OR "reproductivity"[All Fields]

  Genetic counselling: "genetic counselling"[All Fields] OR "genetic counseling"[MeSH Terms] OR ("genetic"[All Fields] AND "counseling"[All Fields]) OR "genetic counseling"[All Fields]

  cancer: "cancer's"[All Fields] OR "cancerated"[All Fields] OR "canceration"[All Fields] OR "cancerization"[All Fields] OR "cancerized"[All Fields] OR "cancerous"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields] OR "cancers"[All Fields]

  829 articles (25th April 2024)

- (("reproduction"[MeSH Terms] OR "reproduction"[All Fields] OR "reproductions"[All Fields] OR "reproductive"[All Fields] OR "reproductively"[All Fields] OR "reproductives"[All Fields] OR "reproductivity"[All Fields]) AND ("genetic counselling"[All Fields] OR "genetic counseling"[MeSH Terms] OR ("genetic"[All Fields] AND "counseling"[All Fields]) OR "genetic

counseling"[All Fields]) AND ("Schwannomatosis"[All Fields] OR "neurofibromatosis"[All Fields] OR "Adenomatous polyposis syndrome"[All Fields] OR "Hamartomatous polyposis syndrome"[All Fields] OR "Lynch syndrome"[All Fields] OR "Hereditary Non-Polyposis Colorectal Cancer"[All Fields] OR "Hereditary Breast and Ovarian Cancer syndrome"[All Fields] OR "PTEN"[All Fields] OR "Li Fraumeni syndrome"[All Fields] OR "Birt-Hogg-Dube Syndrome"[All Fields] OR "BRCA1"[All Fields] OR "BRCA2"[All Fields] OR "Familial Malignant Melanoma"[All Fields] OR "Constitutional Mismatch Repair Deficiency"[All Fields] OR "Carney Complex"[All Fields] OR "Hereditary Papillary Renal Cell Carcinoma"[All Fields] OR "Ataxia-Telangiectasia"[All Fields] OR "Bloom syndrome"[All Fields] OR "Gorlin syndrome"[All Fields] OR "Nevoid basal cell carcinoma syndrome"[All Fields] OR "Werner Syndrome"[All Fields] OR "Hereditary Leiomyomatosis"[All Fields] OR "von Hippel-Lindau disease"[All Fields] OR "Fanconi anemia"[All Fields] OR "Hereditary pheochromocytoma-paraganglioma"[All Fields] OR "Paraganglioma"[All Fields] OR "Heritable TP53-related cancer syndrome"[All Fields])

220 articles (20th May 2024)

In total 851 unique references were screened. Additional articles were requested from experts in the field and references of all the articles were considered. Of these papers, 245 had a full paper review and eventually 85 papers form the basis of this guideline (see appendix 1).

Method for formulating recommendations

In day-to-day practice, clinicians will not have the time to explore the evidence as thoroughly as a guideline group, nor devote as much thought to the trade-offs, or the possible underlying values and preferences in the population. Therefore, the core working group has made recommendations even when confidence in effect estimate is low and/or when desirable and undesirable consequences are closely balanced. These recommendations have been classified as 'weak' and been qualified. The recommendations have been graded on the quality of evidence; balance between benefits and harms, include the values and preferences of patients, and considers the feasibility, equity and acceptability of implementation and use.

Literature was reviewed along with expert opinion to draft recommendations based on literature and experts' experiences and knowledge.

Recommendations were written in one of four stylistic formats: Should, Should Probably, Should Probably Not, Should Not:

- Should & Should Not, were taken to mean most well-informed people (those who have considered the evidence) would take this action.
- Should Probably & Should Probably Not, were taken to mean: the majority of informed people would take this action, but a substantial minority would not.

Grading of the recommendations

As the volume of peer-reviewed evidence for rare diseases is typically limited due to the small population sizes, and it is unlikely that the evidence will ever reach a fraction of a more common diseases, it creates a difficulty when considering the grading of the strength of evidence using Grading of Recommendations Assessment, Development and Evaluation (GRADE).

As is typical for many rare diseases, the volume of peer-reviewed evidence available to consider for these guidelines was small and came from a limited number of articles, which typically reported on small samples or series. If the evidence is categorised and then graded using standard approaches, that are designed to differentiate evidence, in circumstances when there are large numbers of papers and there are likely to be more trials, then its small volume means it would be graded as low. This is not an accurate reflection of the combination of experts' experience and clinical consensus with the available evidence. This is further compounded as there is a low likelihood of additional volumes of evidence that could change the recommendation.

For this reason, and to balance the weight of both published evidence and quantify the wealth of expert experience and knowledge, ERN GENTURIS uses the following scale to grade the recommendations:

Strength	Grading of Recommendation
Strong	Expert consensus AND consistent evidence
Moderate	Expert consensus WITH inconsistent evidence AND/OR new evidence likely to support the recommendation
Weak	Expert majority decision WITHOUT consistent evidence

Expert consensus (an opinion or position reached by a group as whole) or expert majority decision (an opinion or position reached by the majority of the group) is established after reviewing the results of the modified Delphi approach within the core working group.

In addition, strength of recommendation has been determined through a consensus-based approach (modified Delphi) and through active engagement of affected individuals and patient

representatives, specifically balancing the desirable and undesirable consequences of surveillance and alternative care strategies, quality of evidence, and values and preferences held by the patient representatives.

The quantification of strength for a recommendation is composite of harm and benefit. As a general note for these recommendations, the harms that a recommendation seeks to address are often clear, however, the magnitude of the benefit of a specific recommendation are often not as clear.

Consensus building using a modified Delphi approach

After drafting recommendations amongst the core working group, these were subjected to a modified Delphi assessment. Delphi is a structured communication technique or method in which opinions of a large number of experts are asked on a topic in which there is no consensus, and this was used as a consensus building exercise. The goal is to reach consensus after several rounds of questionnaires.

Experts included in this exercise were the members of the ERN GENTURIS counselling on reproductive options guideline group (including three patient representatives, the core working group is part of this guideline group as well), as well as other (external) experts identified by the guideline group or respondents to the request to participate in the Delphi survey circulated within the ERN GENTURIS network.

The survey consisted of 2 rounds, in which the threshold for consensus was defined by a simple majority of the survey participants agreeing with the recommendation (>60% rated "agree" or "totally agree"). Recommendations were graded using a 4-point Likert scale (totally disagree, disagree, agree, totally agree), and a justification for each rating was optional in a free text format. Even if consensus was met, recommendations were still modified if a higher consensus was though achievable from written responses.

All recommendations (n=24) developed by the core working group were selected to proceed in the Delphi procedure. The facilitator of the Delphi survey provided anonymised summaries of the experts' decisions after each round as well as the reasons they provided for their judgements. All recommendations passed the threshold for consensus in the first round. The core working group discussed the anonymised summary of comments given to all recommendations in the first round and decided to accept two recommendations, delete seven recommendations and use them in three general statements in the guideline, combine two recommendations into 1 new recommendation and adjust 13 recommendations for the second round. These were subjected to the expert's opinion in the

second round of the survey, which included 14 recommendations for review. For each recommendation the original recommendation with the overall rating from the first round was presented, as well as the new recommendation, where changes to the original were indicated. All recommendations passed the threshold for consensus and reached similar of higher percentage of agreement. As a result of the modified Delphi, 16 recommendations (agreement higher than 90%) are included in this manuscript.

We would like to thank the experts who were specifically consulted to participate in the Delphi survey:

Name	Speciality / Role	Healthcare provider
Amedeo Azizi, MD	paediatrician	Medical University of Vienna, Vienna, Austria Member of ERN GENTURIS
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Alejandra Cano, MSc	psycho-oncologist	Hospital Universitario Vall d'Hebron, Barcelona, Spain Member of ERN GENTURIS
Melchor Carbonell Socias, PhD	gynaecologist	Hospital Universitario Vall d'Hebron, Barcelona, Spain Member of ERN GENTURIS
Andrada Ciuca, PhD	clinical psychologist and genetic counsellor	Babes-Bolyai University, Cluj, Romania
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Samantha Doyle, MD	reproductive geneticists	The National Maternity Hospital, Dublin, Ireland
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Barbara Laga	psychologist	University Hospital Gasthuisberg, Leuven, Belgium Member of ERN GENTURIS
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Federica Natacci, MD	Clinical geneticist	Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy Member of ERN GENTURIS
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Andrea Ros, MSc	genetic counsellor	Germans Trias i Pujol Hospital, Barcelona, Spain Member of ERN GENTURIS
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Alexander E. Volk, MD	clinical geneticist	Institute of Human Genetics, University Medical Center Hamburg-Eppendorf, Germany Member of ERN GENTURIS
Karin A.W. Wadt, MD, PhD	clinical geneticists	University of Copenhagen, Copenhagen, Denmark Rigshospitalet, Copenhagen, Denmark Member of ERN GENTURIS
anonymous	gyn oncologist	Italy

8.2. Internal and External review

ERN GENTURIS actively involved external experts from different speciality areas that are relevant to the scope of this guideline to review its findings and recommendations developed in this guideline by participation in the guideline group or as a Delphi participant.

In addition, the counselling on reproductive options guideline group submitted a shortened version of the guideline to the European Journal of Human Genetics for independent review.

ERN GENTURIS first published the guideline on counselling on reproductive options for individuals with a CPS on 13 January 2026.

8.3. Timeline and procedure for updating the guideline

Any new evidence published will be reviewed by the ERN GENTURIS clinical leads on an annual basis to determine if the guideline should be updated. New versions will be published on the Network's website and circulated through the ERN GENTURIS Members.

8.4. Funding and Financial support

This guideline has been supported by the European Reference Network on Genetic Tumour Risk Syndromes (ERN GENTURIS). ERN GENTURIS is funded by the European Union. For more information about the ERNs and the EU health strategy, please visit http://ec.europa.eu/health/ern. Potential conflict of interest for the individual authors and Delphi participants are listed in chapter 5.

9. SUMMARY OF EVIDENCE AND GUIDELINE RECOMMENDATIONS

9.1. CONTEXTUAL INFORMATION

In the following, the term cancer predisposition syndrome (CPS) will be used. Therefore, the term "individual with a CPS" will refer to individuals that are diagnosed with a CPS, including all individuals with a genturis (see chapter 3.1). The value and need for reproductive counselling are relevant for all individuals with CPS, thus also including genturis patients.

Receiving reproductive counselling significantly influences a person's reproductive decisions and is associated with a higher degree of knowledge and awareness of the risk of passing on a condition(Warton et al. 2023, Davies et al. 2024).

Lived experiences, personal values, philosophy, religion, belief systems, preferences, and circumstances significantly influence reproductive decision-making. Individuals with a CPS identify the physical and emotional impacts of disease, along with its variability, as factors that affect their attitude towards reproductive options (Vernon et al. 1999, Albar 2002, Forrest et al. 2003, Grover 2003, Quinn et al. 2009, Vadaparampil et al. 2009, Bleiker et al. 2013, Rose et al. 2016, Dason et al. 2022, Shah et al. 2022, Stracke et al. 2022, Patton et al. 2023). The decision-making process regarding reproductive options for individuals with a CPS is complex and includes considerable uncertainties related to the risk, benefits, and likely success rates. There is a clear link between managing this uncertainty - particularly when the information required to understand it is complex and nuanced - and the psychological impacts, in the form of stress and anxiety.

Effective reproductive counselling is a vital skill that requires both training and experience, it is an activity that individuals need to be adequately prepared for (Hallowell et al. 1997). Professionals engaged in reproductive counselling of individuals with a CPS must possess knowledge and training specific to the conditions of the individuals they are counselling. Given the often overwhelming amount of complex and emotionally charged information; preparatory materials, clear language, multiple sessions, and takeaway resources are frequently necessary. Not all professional groups consistently address psychological and informational needs regarding reproductive options (Forbes Shepherd et al. 2020, Forbes Shepherd et al. 2022), making a multi-disciplinary approach the best practice essential. Reproductive counselling is most effectively conducted by clinical geneticist, genetic counsellors, or other health professionals with special training. Given the complexity of CPS, individuals providing reproductive counselling should be supported by a multidisciplinary team.

With respect to the hereafter formulated recommendations, the following* should be taken into account:

Healthcare professionals should always:

- respect the individual's autonomy and personal readiness while ensuring access to necessary information.
- provide information in a timely manner, tailored to the individual's needs and circumstances (Somigliana et al. 2022, Calosci et al. 2023) considering that what is timely may vary based on personal and healthcare system factors.
- provide up-to-date information, recognising that clinical screening strategies, treatment guidelines, diagnostic criteria, nomenclature, reproductive methods, and genetic techniques may change at short notice as scientific knowledge evolves.

Healthcare centres providing counselling on reproductive options for individuals with a cancer predisposition syndrome and relevant family members should:

- counsel patients prospectively in advance about PND and preimplantation genetic testing, including its medical procedure, limitations, psychological impact, success rates, and the possibility of obtaining only affected embryos/foetuses (Insogna et al. 2016, Besser et al. 2019);
- clearly present and explain all available reproductive options to patients (Reynolds et al. 1999), including those beyond prenatal diagnosis and preimplantation genetic testing (such as sperm/oocyte donation, adoption, and postnatal diagnosis). This should include information on reproductive window, waiting times and delays (such as the time required to obtain test results for prenatal diagnosis or the timeline to the first embryo transfer in preimplantation genetic testing)
- ensure realistic expectations and informed decision-making, tailored to the patient's reproductive potential, before initiating any procedures. For example, a 38-year-old woman may have lower success rates in PGT-M procedures due to her ovarian reserve and oocyte quality compared to a 28-year-old woman.
- Provide guidance in accordance with country-specific legal possibilities and processes. For example, some countries may require ethical board approval for PND or PGT in individuals with a cancer predisposition syndrome on an individual basis, and not all cases may be accepted.

• Include information about the availability of public funding for PGT, if applicable. • Facilitate liaison with IVF clinics regarding fertility potential, including consideration of the patient's age and ovarian reserve (e.g., AMH levels), to set realistic expectations for success rates.
Reproductive counselling Personal philosophies, religion, cultural values, and individual preferences concerning family and reproduction significantly influence attitudes towards prenatal diagnosis and preimplantation genetic testing. Counsellors should be sensitive to and understand these perspectives, ensuring non-judgemental, personalised, and non-directive support. (Vernon et al. 1999, Albar 2002, Forrest et al. 2003, Grover 2003, Quinn et al. 2009, Vadaparampil et al. 2009, Bleiker et al. 2013, Rose et al. 2016, Dason et al. 2022, Shah et al. 2022, Stracke et al. 2022)

* These general statements are based on recommendations included in the first Delphi round which passed the threshold for consensus.

9.2. REPRODUCTIVE DECISION MAKING - CONTENT AND FRAMEWORK OF REPRODUCTIVE COUNSELLING

9.2.1 MANAGING ETHICAL CONSIDERATIONS: RISKS AND ISSUES REGARDING 'NATURAL' CONCEPTION FOR INDIVIDUALS WITH A CANCER PREDISPOSITION SYNDROME.

Natural conception without genetic or diagnostic testing implies an acceptance, by individuals with a CPS, of the risk of passing on the pathogenic variant to offspring. In some cases, predictive testing of adult-onset conditions is not offered to children, in respect for the child autonomy. Therefore, a natural pregnancy could also imply an acceptance of not knowing the child's genetic status until the child is an adult and choosing to be tested.

9.2.2 MANAGING ETHICAL CONSIDERATIONS: RISKS AND ISSUES REGARDING PRENATAL DIAGNOSIS (PND) FOR INDIVIDUALS WITH A CANCER PREDISPOSITION SYNDROME.

Prenatal diagnosis (PND) offers the possibility to terminate a pregnancy if the foetus is found to be affected by the pathogenic variant. However, invasive diagnostic procedures carry potential adverse outcomes, such as miscarriage. In the hands of experienced experts, the rates of miscarriage are generally below 0.5% (<1 in 200). Additionally, there is a significant emotional burden associated with pregnancy termination if the foetus is diagnosed with a CPS. Legislation regarding pregnancy termination varies between countries, and in some places, termination because of a CPS condition in the foetus may not be permitted. There are also ethical implications to consider when performing an invasive test that has associated risks if there is no intention to act on the result. In such cases, the invasive test is equivalent to a predictive test on a child, which is not recommended for many adult-onset CPSs, as the individual should have the autonomy to decide if and when to undergo testing. Although some arguments are made for the benefits of 'being prepared', these are only credible for conditions where early interventions in the post-partum period is necessary.

9.2.3 MANAGING ETHICAL CONSIDERATIONS: RISKS AND ISSUES REGARDING PREIMPLANTATION GENETIC TESTING (PGT) FOR INDIVIDUALS WITH A CANCER PREDISPOSITION SYNDROME.

Preimplantation genetic testing (PGT) offers individuals with a CPS the option to obtain embryos by in vitro fertilization (IVF) and test them for the familial pathogenic variant.

PGT-M aims to enable patients to have children unaffected by the same condition and avoid the risk of adverse outcomes associated with invasive prenatal diagnosis (miscarriage) and the burden associated with pregnancy termination in the event of a pathological result. However, ethical issues have been raised about applying PND and PGT-M for specific CPSs. More specifically, when those syndromes have incomplete penetrance (Niermeijer et al. 2008), and variable expressivity, and when there are proven effective surveillance programs available that can reliably reduce the mortality and morbidity of affected patients (Friedman et al. 2005, Harris et al. 2005). Individuals with a CPS understand and raise the dilemma of prenatal tests that are unable to determine severity (Ponder et al. 1998). However, satisfaction is increased for people who choose PGT, specifically satisfaction with the decision regarding PGT is significantly higher than those who did not have PGT (Mor et al. 2018, Han et al. 2023).

9.2.4 Complexities of Reproductive Decision Making

Decisions such as testing for a CPS has consequences that are more far-reaching than a potential carrier can anticipate beforehand (de Vries-Kragt 1998). There is evidence for the psychological impact of specific CPSs (Frebourg et al. 2020, Tischkowitz et al. 2020) at the moment of diagnosis. The psychological impact of continuous surveillance (with associated chronic uncertainty) is an ongoing factor that will have an impact on making reproductive decisions.

The implications of the genetic status go beyond the person being tested and potentially impact their existing extended family as well as their offspring and potential future offspring. These multi-generational impacts magnify the complexity of the required supportive information and complexity of any decisions made, including not to act on it.

Assisted Reproductive Technologies (ARTs) and their use have raised strong emotional responses and continue to raise moral, ethical, and legal concerns (Taguchi et al. 2019). Multidisciplinary reproductive counselling is a vital safeguard for ensuring that these technologies are used in a way that efficiently addresses concerns (Albujja et al. 2024). People affected by genetic syndromes often perceive that they have gaps in their knowledge and understanding of their options even after reproductive counselling (Patton et al. 2023) which limits their ability to make genuinely informed choices. This highlights the need for reproductive counselling for people with a CPS to be viewed as a multi-stage process. Awareness of the applicability of PND and PGT-M for CPSs is limited among both patients and physicians (Calosci et al. 2023) meaning that these approaches are not always offered or used in situations when they would be appropriate.

Effective reproductive counselling is transformative. On the one hand it increases knowledge, perception of personal control and positive health behaviours, and improves risk perception accuracy. On the other hand, it decreases anxiety, cancer-related worry, and decisional conflict (Madlensky et al. 2017, Resta 2019). Reproductive counselling requires a high level of knowledge and skills, and reproductive counselling must not be assumed to be a simple benefit, as psychological harms can also arise from a person gaining knowledge and insight that there is a complex decision to be made (Di Pietro et al. 2004, Wilson et al. 2016, Zirkelbach et al. 2018, Gould et al. 2019).

Technology, technique and understanding progresses rapidly, but the individual outcomes from managing CPSs after diagnosis by screening, prophylactic surgery, or chemoprevention remains uncertain (Frebourg et al. 2020, Tischkowitz et al. 2020, Evans et al. 2022, Carton et al. 2023). This uncertainty is stressful in itself, and certain reproductive options offer individuals with a CPS the

ability to choose if a future child will be born without having an increased risk of cancer (Konstantopoulou et al. 2009, Sagi et al. 2009, Wang et al. 2009). However, there will remain affected individuals who believe that CPSs do not justify termination of pregnancy (Ormondroyd et al. 2012, Albujja et al. 2024). In these cases, PGT can be relevant.

If unaffected embryos are not produced following in vitro fertilization with PGT-M, some patients may request to transfer embryos with positive test results. The majority of such transfers are embryos positive for adult-onset, reduced penetrance diseases. The transfer of embryos tested positive is not an option in all European centres. In many centres, affected embryos are automatically discarded despite any possible request from the patient to transfer. There is no current ethical consensus with regulations differing between countries and even within countries. It is essential to consider the practical and ethical implications of this trend for CPSs (Besser et al. 2019, Cheng et al. 2024) as this would imply that an embryo was implanted that will have a substantially increased risk of tumour development and hence possibly have a significantly reduced quality and quantity of life. Implantation of rescue embryos (affected) may be gender specific e.g. male embryo in *BRCA1*.

With reproductive counselling for individuals with a CPS, issues that are morally problematic, cannot be settled by simply referring to standards of practice and bioethical norms, but rather by collaboration of all stakeholders (Giarelli 2001, Dewanwala et al. 2011). There is no single 'right' answer and all decisions are individual and context dependent.

Recommendations		Strength
Rec. 1	Reproductive counselling should be offered to all individuals with a cancer predisposition syndrome*. It is voluntary for the individual with a cancer predisposition syndrome to accept or decline counselling. (Graumann 1999, Di Pietro et al. 2004, Koch et al. 2005, Wilson et al. 2016)	Strong
Rec. 2	All individuals with a cancer predisposition syndrome and relevant** family members of reproductive age should be offered information about their reproductive options. (Woodson et al. 2013, Calosci et al. 2023, Dallagiovanna et al. 2023, Patton et al. 2023, Villy et al. 2023)	Strong

Rec. 3	Reproductive counselling must provide individuals with a cancer predisposition syndrome and relevant** family members with comprehensive, balanced, and timely information. (Ponder et al. 1998, Reynolds et al. 1999, Patton et al. 2023, Albujja et al. 2024)	Strong
Rec. 4	Reproductive counselling should be non-directive ensuring patients can freely decline specific or all reproductive options without fear of recrimination, feelings of guilt or social pressure. (Noble et al. 2008)	Strong
Rec. 5	Couples, at risk for a child with a cancer predisposition syndrome, considering prenatal diagnosis*** should be encouraged to reflect on their views regarding continuation or termination of pregnancy preconceptionally****.	Moderate
Rec. 6	Couples with a cancer predisposition syndrome considering pregnancy should have access to a multidisciplinary team of healthcare experts in an individualised way. This may include: A genetic counsellor or clinical geneticist to assess genetic risk, discuss the feasibility of both prenatal diagnosis (PND)*** and IVF (in vitro fertilization) with preimplantation genetic testing (PGT) ***. A clinician experienced in performing and interpreting prenatal diagnostic tests to explain the risks, benefits, and procedures of PND*** options such as amniocentesis, chorionic villus sampling, and NIPT, if PND*** is considered. A fertility doctor to provide guidance on PGT***, including PGT-M, and other assisted reproductive techniques where relevant. A psychologist trained in reproductive and genetic counselling, given the emotional and psychological impact of these decisions, In difficult or unusual cases, advice should be sought from additional experts. (Petersen 1996, 2023)	Strong

* Counselling is especially relevant in the reproductive age but can be relevant in other age group as well, such as adolescence and older individuals informing their relatives.

** Definition: Relevant family members can include first degree relatives, such as parents, children, or siblings but also second- and higher-degree relatives. It depends on the characteristics and the inheritance mode of the syndrome. The

healthcare professional will determine who the relevant family members are.

*** Definition: Prenatal diagnosis refers to tests conducted to diagnose a foetus in utero including amniocentesis, chorionic villus sampling, and NIPT (NIPT needs to be confirmed by an invasive test).

**** preconceptionally is before pregnancy.

9.3. TIMING OF REPRODUCTIVE COUNSELLING PROVISION

Navigating reproductive decision-making with a CPS is a complex, unpredictable process and people's understanding, wishes, desires and needs with regard to reproductive information and decisions-making changes throughout the course of their life (Tutty et al. 2023). There are a number of key decision points when genetic reproductive counselling is essential (e.g. prior to diagnostic testing (Petersen 1996, Reynolds et al. 1999, Blandy et al. 2003, Grover 2003, Di Pietro et al. 2004, Terzi et al. 2009, Donnelly et al. 2013), at diagnosis, when actively considering pregnancy). In some cases, the risk of cancer susceptibility is identified in childhood, and reproductive counselling is better postponed until adulthood, unless the child expresses interest. It is imperative that genetic reproductive counselling is not thought of as a 'one and done' intervention, but rather as a process where the intervention (genetic reproductive counselling) is likely to need repetition at different times as the circumstances (and options) are evolving which changes the context for informed decision-making. Different aspects and choices require different emphasis at these different occasions. A person's perception of risk and perspective may change over time. In an evolving situation, assessment of, tolerance to and weighting up risks and possibility and uncertainties change, but it is easy for people to be overwhelmed and too much information all at once is difficult for people to assimilate (Ponder et al. 1998). The majority of people with CPSs who refuse genetic and reproductive counselling at one point in their life might reconsider it in the future (Morand et al. 2022) and have usually refused it due to a temporary barrier rather than an absolute refusal. An offer to come back anytime in the future if the perspective changes is therefore relevant.

Recommendations		Strength
Rec. 7	Reproductive counselling should be offered longitudinally to individuals with a cancer predisposition syndrome (and relevant* family members) with multiple opportunities for discussion during reproductive age. At the time of diagnosis, individuals with a cancer predisposition syndrome should receive clear information about the availability of genetic and reproductive counselling services for future family planning.	Strong

	(Ponder et al. 1998, Emery 2001, Morand et al. 2022)	
Rec. 8	Genetic and reproductive counselling should be available for individuals with a cancer predisposition syndrome and for parents (at risk) of an affected child, ideally beginning before family planning and continuing as needed. (Ponder et al. 1998, Chan et al. 2017)	Strong
Rec. 9	Individuals with a cancer predisposition syndrome should be offered age- and context-appropriate genetic and reproductive counselling at the time of diagnosis. (Petersen 1996, Reynolds et al. 1999, Di Pietro et al. 2004, Chan et al. 2017)	Strong
Rec. 10	Children at risk for cancer susceptibility should be offered counselling** regarding predictive testing and family planning once they reach adulthood, or earlier if they express interest or the condition affects childhood.	Moderate
Rec. 11	Counselling regarding reproductive options is relevant for all individuals with a cancer predisposition syndrome, regardless of whether they already have children, are considering more children, or are not currently planning a pregnancy, since this may influence decisions regarding testing or informing their children/family members. (Somigliana et al. 2022)	Moderate

* Definition: Relevant family members can include first degree relatives, such as parents, children, or siblings but also second- and higher-degree relatives. It depends on the characteristics and the inheritance mode of the syndrome. The healthcare professional will determine who the relevant family members are.

** Counselling in minors should be provided with parental consent and involve specialist with expertise in paediatric care. If initiated in childhood, follow-up should be continuous to adapt to the individual's evolving understanding and needs.

9.4. PRESENTATION OF REPRODUCTIVE OPTIONS

It is crucial for all healthcare professionals to be aware of the complexity of the decision-making process for couples regarding reproductive options (Calosci et al. 2023) and therefore know to whom and when to refer individuals with a CPS considering their options. Health care professionals should also keep in mind that reproductive counselling is equally relevant for male and female patients. It seems that some centres offering reproductive options for CPSs only provide information about a

limited range of (or even only one) reproductive options (Patton et al. 2023). Effective reproductive counselling is a significant skill requiring training and experience (Hallowell et al. 1997). Reproductive counselling for individuals with a CPS requires specific knowledge on the condition and its genetic inheritance, on the relevant reproductive options that can be offered for a specific condition and extensive reproductive counselling skills and experience. Information is often complex with an emotional nature. For this reason, multiple sessions and take away materials are often necessary. Not all professional groups consistently address psychological and informational needs regarding reproductive options (Forbes Shepherd et al. 2020, Forbes Shepherd et al. 2022) so best practice is a multi-disciplinary approach.

Recommendations		Strength
Rec. 12	Reproductive counselling for individuals with a cancer predisposition syndrome should provide sufficient time, follow-up opportunities, and access to psychological support. (Dason et al. 2022)	Moderate
Rec. 13	Reproductive counselling should take psychological factors into account and be provided by a multi-disciplinary team. This team should include professionals with expertise in reproductive genetics, oncology (when relevant), and psychological support. Access to additional specialists should be tailored to individual patient needs. (Reynolds et al. 1999, Grover 2003, Forbes Shepherd et al. 2020, Calosci et al. 2023)	Strong
Rec. 14	Reproductive counselling should be offered to both male and female individuals with a cancer predisposition syndrome independently and include their partners, if appropriate. (d'Agincourt-Canning 2001, Strømsvik et al. 2009, Donnelly et al. 2013, Giles Choates et al. 2020, Wallgren et al. 2021, Law et al. 2022)	Strong

9.5. RANGE OF ASSISTED REPRODUCTIVE TECHNOLOGIES

Assisted Reproductive Technologies (ARTs) is a broad term encompassing medical technologies used to support conception and pregnancy, primarily used to address infertility. This subject involves procedures such as in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), cryopreservation of gametes and embryos, the use of donor gametes of embryos. It can also be used outside of an infertility setting in case of preimplantation genetic testing.

Recommendations		Strength
Rec. 15	Female fertility preservation options, such as oocyte cryopreservation, should be included in reproductive counselling for individuals with a cancer predisposition syndrome, when there is a high risk of infertility due to cancer treatment*. (Somigliana et al. 2022, Calosci et al. 2023)	Strong
Rec. 16	Male fertility preservation options, such as sperm cryopreservation, should be included in reproductive counselling for individuals with a cancer predisposition syndrome, when there is a high risk of infertility due to cancer treatment**. (Calosci et al. 2023)	Moderate

* This discussion should be tailored to the individual's age, ovarian reserve, and the feasibility of fertility preservation in their specific healthcare setting. Ideally, oncologists should address this topic early, before treatment begins.

** This discussion should ideally take place at the time of cancer diagnosis and be led by the oncology team before treatment begins. Counselling should be tailored to individual risk factors and the feasibility of fertility preservation within the specific healthcare setting.

10. WHAT DO OTHER GUIDELINES STATE?

Up to now, only one specific guideline on the topic has been found: In the 2023 UK guideline (British Society for Genetic Medicine 2023) the focus is on the access to reproductive options such as PGT and PND, and the specific circumstances surrounding PND and PGT, especially in UK. The UK guideline also includes practical detailed framework for counselling.

Many of our recommendations are in common with the UK guideline, and none of the recommendations from the two guidelines are in direct conflict with each other.

The UK guideline gives specific guidance, for example to the timing of prenatal diagnosis with referral to the UK Abortion act 1967. Our guideline has more focus on when and how to achieve access to reproductive counselling for CPS individuals - and less on the practicalities of the different reproductive options - since it is to cover all of Europe with different levels of access to for example PGT and different legislation regarding termination of pregnancy.

Other guidelines concerned with the clinical management of different CPSs mention reproductive counselling (for example: "ERN GENTURIS clinical practice guidelines for the diagnosis, treatment, management and surveillance of people with schwannomatosis 2022", rec 6 and "ERN GENTURIS guideline on constitutional mismatch repair deficiency diagnosis, genetic counselling, surveillance, quality of life, and clinical management", rec 7 and 8). In these guidelines, although not very explicitly described, the recommendation is that patients should be offered reproductive counselling, which is also in agreement with the recommendations in this guideline.

11.SUGGESTIONS FOR FUTURE RESEARCH

The field of reproductive counselling is developing (Zakaria et al. 2023), data and research into reproductive counselling and more specifically reproductive counselling for individuals with a CPS still lags behind, with much unknown or untested especially when considering individual conditions. Success rates of ARTs are necessary for guiding reproductive counselling and treatment and are currently only available in the literature for a tiny proportion of CPSs. Current nomenclature for recording ART on the medical pedigree is not sufficient for clinical practice (Lepard Tassin et al. 2021).

The formulation of these guidelines for counselling on reproductive options for individuals with a CPS inevitably highlighted areas in which further research is required in order to guide more definitive conclusions. Examples of topics for further research include:

- Centres providing ARTs for CPSs should collaborate to pool and publish data regarding safety and success rates.
- Current nomenclature for recording ART on the medical pedigree is not sufficient for clinical practice, consensus work is needed to develop and disseminate additional standard symbols and their usage.
- The value of decision-making aids, including coaches, for reproductive decision-making for individuals with a CPS should be investigated.
- The effectiveness of alternative patient education tools to replace or supplement individualised in-person reproductive counselling should be assessed prior to their introduction into clinical care.
- Understanding the ethical, psychological, and moral impact of actions taken when PGT results in only affected embryos.
- Understanding the ethical considerations of CPS patients considering their reproductive options and the long-term psychological impact of choosing PGT/PND/no test/other options.
- There would be value in the community around CPSs (both experts and affected individuals) working together to outline an ethical framework regarding the reproductive options and decision-making.
- Condition specific evidence for each CPS regarding the ideal form that reproductive counselling should take is lacking and further investigation of the important characteristics of conditions, especially their genetic, pathological, and prognostic and the interplay these have

with reproductive decision-making and the associated reproductive counselling would be beneficial.

- The long-term effect on the embryo of single cell biopsy. Currently there is no adequate information (Neelanjana et al. 2008, Okun et al. 2014, Merker et al. 2015, Vernimmen et al. 2023, Albujja et al. 2024)
- The demand of PGT for CPS over time:

  Is there an increasing demand compared to other genetic conditions, and why? Are there differences within the group of CPS, for example more *BRCA* families opting for PGT compared to Lynch syndrome families, and why?
- Establishment of inclusion/ voice for lay organizations in the development of clinical care guidelines
- Linkage between genetic, clinical, and psychological care.
- Consensus on outcome parameters for studies.
- Development of multinational registers.

12.ABBREVIATIONS AND DEFINITIONS

ART	Assisted Reproductive Technologies (ARTs) is a broad term encompassing all technologies used to support conception and pregnancy, including preimplantation genetic testing (PGT) through in vitro fertilisation (IVF).
CPS	Cancer Predisposition Syndrome
ERN	European Reference Network
genturis	Genetic tumour risk syndromes
ICSI	intracytoplasmic sperm injection
IVF	in vitro fertilisation
PGT	**Preimplantation Genetic Testing** (PGT) PGT is a general term including Preimplantation Genetic Testing for Monogenic conditions (PGT-M), Preimplantation Genetic Testing Structural Rearrangements (PGT-SR), and Pre-implantation genetic testing for aneuploidy (PGT-A). PGT-M is a specific type of PGT that allows the detection of causative variants of monogenic disorders. PGT-SR and PGT-A (previously known as preimplantation genetic screening or PGS) involve assessing embryos for chromosomal aberration.
PGT-M	Pre-implantation genetic testing for monogenic disorders
PND	**Prenatal diagnosis** (PND) refers to tests conducted to diagnose a foetus in utero, including amniocentesis, chorionic villus sampling, and NIPT (NIPT needs to be confirmed by an invasive test).

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14.APPENDIX 1

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