

Oncofertility in adolescent and young adult hereditary cancer: Considerations for genetics professionals

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Abstract

Adolescents and young adults (AYA) with a cancer diagnosis or those at risk for cancer due to hereditary cancer syndromes may benefit from genetic counseling and testing not only to manage personal risk but also to address reproductive concerns, especially fertility. The opportunity for genetic counselors to provide important risk information is relevant to both the newly diagnosed as well as to unaffected carriers and survivors. However, genetic counselors may need additional training in reproductive options related to AYA cancer to provide this valuable counsel. This commentary uses hereditary breast and ovarian cancer syndrome as a model to highlight important considerations when discussing preimplantation genetic diagnosis and prenatal diagnosis, particularly in the context of expanded testing for hereditary cancer risk including multigene panels or whole exome or whole genome sequencing. Other hereditary cancers are also addressed; however, less is known about the psychosocial and fertility concerns in these AYA populations. Additionally, we provide an overview of the concept of "oncofertility" - the linkage between cancer care and reproductive medicine that aims to expand the reproductive opportunities of cancer patients - and offer support for the expansion of guidelines to include genetic counselors in AYA cancer patients' treatment planning related to reproductive health and fertility.

Key words: Fertility; Oncology; Genetic counselors; Decision-making; Oncofertility; Adolescent young adults; Training; Health professionals

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Core tip: Genetic counseling and testing holds great promise for adolescents and young adults (AYA) with cancer or potentially at risk for cancer. Oncofertility, the connection between reproductive medicine and oncology, provides expanded prospects for AYA to achieve childbearing and parenting goals. Genetic counselors and experts may benefit from expanded oncofertility training to provide counsel to AYA and aid in improving quality of life. Newer genomic technologies available for testing such as multi-gene testing and whole exome sequencing combined with advances in assisted reproductive technology offer novel opportunities for AYA to achieve reproductive goals.

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INTRODUCTION

Every year over 70000 adolescents and young adults (AYAs) are diagnosed with cancer in the United States, accounting for approximately 6% of all cases of newly diagnosed invasive cancers. The incidence of specific cancers in the AYA population varies considerably across the age continuum typically defined as between 15 and 39 years^[1]. Hodgkin and non-Hodgkin lymphomas, melanoma, testicular cancer, female genital tract cancers, thyroid cancer, bone and soft tissue sarcomas, leukemia, brain and spinal cord tumors, breast cancer, and non-gonadal germ cell tumors account for 95% of all cancers in this age group^[2]. Importantly, many AYAs with these diagnoses, particularly if they have a family history of cancer, are candidates for genetic counseling and possibly testing for hereditary cancer risk^[3]. Genetic counseling typically entails a comprehensive discussion with a trained genetics professional (*i.e.*, medical geneticist or genetic counselor) to: (1) obtain a risk assessment based on personal and family cancer history; (2) educate about hereditary cancer risks and management; and (3) discuss potential benefits and limitations of genetic testing^[4-8]. Goals of this initial session are to determine the appropriateness of genetic testing based on the patient's history and risk assessment^[9], increase knowledge about hereditary cancer risks and implications, assess and address psychosocial concerns, and facilitate patient decision-making about genetic testing and risk management^[10-12].

One key and highly relevant issue for AYAs is the impact of a cancer diagnosis and associated treatment on future fertility^[13-17]. Numerous organizations including the American Society of Clinical Oncology (ASCO),

the Royal College of Physicians in the United Kingdom, and the Clinical Oncology Society of Australia have developed clinical practice guidelines for fertility preservation for patients of reproductive age^[18-21]. The ASCO guidelines, in particular, recommend that in addition to medical oncologists, the responsibility for discussion of and referral for fertility preservation also extends to other physician specialties and allied health care professionals in the oncology care setting^[18]. However, for the subset of individuals at increased risk for hereditary cancer, there may be the additional concerns about genetic risk for future offspring. The possibility of transmitting a mutation to a child is often a concern among individuals affected with hereditary cancer, perhaps to the extent that some carriers may avoid childbearing^[22-28]. To address this important concern, the National Comprehensive Cancer Network (NCCN) - an affiliation of some of the world's most prominent cancer centers that establishes frequently-updated, expert-reviewed, evidence-based guidelines regarding cancer care and treatment - recommends that patients of reproductive age should be counseled about the options of prenatal diagnosis (PND) and pre-implantation genetic diagnosis (PGD) for several hereditary cancer syndromes^[4,29,30]. Indeed, genetics professionals often see patients at a critical juncture, in which AYA patients are not only acclimating to their diagnosis and treatment, but are also learning about fertility preservation options while considering potential risk to offspring that could impact their future parenting decisions.

This commentary uses hereditary breast and ovarian cancer syndrome as a model to highlight important considerations when discussing PGD and PND, particularly in the context of expanded testing for hereditary cancer risk including multigene panels or whole exome or whole genome sequencing. Other hereditary cancers are also addressed; however, less is known about the psychosocial and fertility concerns in these AYA populations. Additionally, we provide an overview of the concept of "oncofertility" - the linkage between cancer care and reproductive medicine that aims to expand the reproductive opportunities of cancer patients - and offer support for the expansion of guidelines to include genetic counselors in AYA cancer patients' treatment planning related to reproductive health and fertility^[31].

DISCUSSION

Hereditary cancers

Hereditary cancers are those in which increased susceptibility is generally passed down within a family. They result from germline gene mutations and comprise 5% to 10% of all cancers^[32]. Most cancers that affect the AYA age group, particularly those diagnosed under age 30, appear to be "sporadic" - or not arising from any recognized inherited susceptibility or environmental risk factors^[1]. However, AYAs with cancer, and especially those with family histories of cancer suggestive of a

Table 1 Prevalent adolescents and young adults hereditary cancer syndromes

Syndrome	Description	Genetic Testing recommendations
HBOC	Breast cancer or breast and ovarian cancers among multiple family members	Testing for <i>BRCA1</i> and <i>BRCA2</i>
LFS	Increases risk for many cancers including sarcoma, breast, brain, lymphoma, lung, and others	Testing for p53
Retinoblastoma	Intraocular tumors (not always hereditary); nonocular tumors common in hereditary retinoblastoma	Testing for <i>RB1</i>
MEN and FMTC	Increases risk of endocrine tumors; FMTC is a common type of MEN	Testing for <i>MEN1</i> , <i>RET</i> , and <i>CDKN1B</i>
Lynch syndrome	Increases risk for colorectal cancer	Testing for <i>MLH1</i> , <i>MSH2</i> , <i>MSH6</i> , <i>PMS2</i> , or <i>EPCAM</i>
FAP	Increases risk for colorectal cancer; existence of multiple adenomas is passed down within family members	Testing for <i>APC</i> and <i>MUTYH</i>
Cowden Syndrome	Increased risk for breast, thyroid, endometrial (uterine lining), and other cancers	Testing for <i>PTEN</i>
Von Hippel - Lindau Syndrome	Increased risk for kidney cancer and multiple noncancerous tumors, including pheochromocytoma	Testing for <i>VHL</i>
Familial Melanoma	Increased risk for malignant melanoma and pancreatic cancers	<i>CDK2NA</i> and <i>CDK4</i>

HBOC: Hereditary breast and ovarian cancer; LFS: Li-fraumeni syndrome; MEN: Multiple endocrine neoplasia; FMTC: Familial medullary thyroid carcinoma; FAP: Familial adenomatous polyposis.

hereditary cancer syndrome, are good candidates for genetic counseling and testing^[3]. Characteristics of hereditary cancer are dependent upon cancer type and include: Premature onset of cancer, multiple primary cancers within an individual, bilateral cancer in paired organs, rare tumors and uncommon tumor histology, and unusual cancer such as male breast cancer^[4,33-35]. Additional characteristics related to family history include: Clustering of matching cancers in immediate family members, cancers spanning across generations of a family, rare cancers correlated with birth defects, and certain ethnic or geographic populations that are at particular high risk of hereditary cancers^[33,36-38]. Table 1 highlights the most prevalent AYA hereditary cancer syndromes^[4,39-45].

Hereditary breast and ovarian cancer

Hereditary Breast and Ovarian Cancer syndrome (HBOC), primarily caused by mutations in the *BRCA1* and *BRCA2* (*BRCA*) genes, is associated with very elevated risks for breast, ovarian and other cancers, affecting about 5% of women with breast cancer and 10% of women with ovarian cancer having HBOC^[46,47]. While approximately 12% of all women will develop breast cancer during their lifetimes, the inheritance of a harmful *BRCA1* mutation increases this risk to up to 65% and a *BRCA2* mutation increases it to roughly 45%; these mutations increase the likelihood of developing ovarian cancer from 1.3% of all women to 39% for *BRCA1* and up to 17% for *BRCA2*^[45]. Because effective management strategies exist for breast cancer screening and mortality reduction for ovarian and breast cancer vis-à-vis bilateral salpingo oophorectomy, many professional associations recommend *BRCA* counseling and testing for women at high risk of HBOC Syndrome^[4,40,41,48]. For example, the National Society of Genetic Counselors (NSGC) identified critical components of the testing and counseling process that include: The ascertainment of medical and family histories, determination and communication of

cancer risk, assessment of risk perception, education regarding the genetics of HBOC, discussion of molecular testing for HBOC if appropriate (including benefits, risks and limitations) and any necessary follow-up^[9,40]. Additionally, the United States Preventive Services Task Force recommends genetic counseling for women with high risk family histories^[41].

Management of HBOC risk in women may include aggressive and early breast cancer screening with breast magnetic resonance imaging beginning at age 25, mammography starting at age 30, or consideration of bilateral risk reducing mastectomies^[4]. Bilateral salpingo-oophorectomy is recommended by age 35-40 and when childbearing is completed^[4]. These surgeries and therapies have implications for future fertility and parenting considerations. For example, women facing decisions about oophorectomy may wish to know that oocytes can be preserved and through the use of assisted reproductive technology (ART) such as *in vitro* fertilization (IVF), they can still carry a pregnancy^[49-51]. For women recommended to use tamoxifen or undergoing chemotherapy or other adjuvant therapy to manage risk, it is imperative for them to be aware that pregnancy is contraindicated during this time^[52] and oocyte freezing may be a consideration for delayed childbearing^[53-55]. An emerging ovarian cancer risk reduction option includes a two-step surgical strategy that includes bilateral salpingectomy prior to menopause followed by postmenopausal oophorectomy. Ovarian preservation could lead to an opportunity to maintain some fertility preservation options for a more extended period of time, reduce cardiovascular disease and bone loss and improve quality of life. However, this relatively new approach for ovarian cancer risk reduction must be considered in light of limited data regarding optimal timing of the two surgeries and whether timing should differ based on the specific cancer predisposing mutation. Additionally, the short and long term impact of this option on cancer risk reduction, quality of life,

physical and psychosocial functioning, as well as other cancer prevention behavior remains largely unknown^[56,57].

Aside from fertility concerns, a woman who has had bilateral mastectomies will not be able to breastfeed her child. This is an important consideration for women who perceive breastfeeding as an essential parenting role. These women would benefit from counseling about additional ways to establish bonding with their infants and to take this information into consideration when making decisions about risk management^[58]. Each of these examples highlights the importance of women being aware of how hereditary risk may affect fertility and parenting concerns. The genetic counselor is thus important in both providing a woman with personal risk reduction information, and addressing family planning goals with options and strategies.

Fertility and cancer

AYAs with any type of cancer, heritable or not, face several challenges including unique psychosocial consequences. AYA cancer patients and survivors often experience disruption in education, employment, relationships, and personal growth^[59]. One key quality of life issue among this childbearing-aged population is the threat to reproductive health, including risks like loss of fertility, compromised fertility, and concerns about transmission of cancer susceptibility gene mutations to future offspring^[60]. ASCO, NCCN, the Royal College of Physicians, and the European Society for Medical Oncology, as well as other prominent organizations, have all created guidelines suggesting the most effective way to deal with these challenges is to discuss options and preservation methods prior to cancer treatment and document this discussion in the medical record^[18-20,61,62]. However, recent research evidences low rates of documentation, which may equate to low rates of actual discussion^[63].

Established options for fertility preservation include sperm, oocyte, and embryo cryopreservation. Experimental options include testicular and ovarian tissue freezing. Still other options, often referred to as alternative family building, include the use of donor sperm, oocytes or embryos or the use of a gestational carrier. While these options are available for AYA cancer patients and survivors numerous studies have documented poor communication about potential infertility risks and preservation or family building options between patients and health care providers. Additionally, health care providers report discomfort and lack of knowledge regarding some assisted reproductive technologies, like PGD, which may be an important resource for cancer patients concerned about passing on cancer-specific gene mutations to their future offspring^[64-66]. Consequently, many patients do not receive timely and accurate information about the impact of their diagnosis on future reproductive health^[67-70]. Even when these risks are communicated, however,

patients may not be provided with additional resources for related issues beyond immediate treatment impact, including referrals to specialists like reproductive endocrinologists and genetic counselors, who can answer important questions and provide individualized guidance for AYA cancer patients. While oncologists and oncology nurses are necessary primary sources of information on cancer diagnosis and treatment impact on future fertility, sessions with genetics professionals can expand upon this initial information by discussing how hereditary cancer risks may affect the patient's childbearing concerns and goals.

Genetic testing for hereditary cancer syndromes in future offspring

Prior reproductive considerations were largely limited to hereditary cancer syndromes following an autosomal dominant inheritance pattern (e.g., *BRCA*, *PTEN*). Thus, counseling was focused on reproductive implications based solely on the proband's test results. However, with expanded gene panel testing, reproductive counseling must also consider genetic disorders that follow an autosomal recessive inheritance patterns. For example, the addition of the Fanconi anemia (FA) genes (*FANCD1/BRCA2*, *FANCF/BACH1/BRPI1*, *FANCN/PALB2*, *FACNCO0/RAD51C*, and *FANCA*) to cancer testing panels raises the possibility of identifying risk for FA. Thus, reproductive implications for offspring are also informed by the carrier status of the proband's current (or future) partners. If both are heterozygotes, there is a 25% risk that an offspring will be a homozygote and have FA. Similar considerations would arise for probands carrying mutations in *ATM* and *MYH* genes.

For most individuals with autosomal dominant hereditary cancer syndromes (e.g., associated with *BRCA1/2*, *PTEN*, or *TP53* mutations), reproductive options exist for prenatal and PGD to detect heterozygous offspring. However, with the advent of panel testing, more individuals are being identified with heterozygous mutations in a broad array of genes that had been previously identified primarily in homozygotes. These homozygous individuals are biallelic mutation carriers, having inherited a mutation from each parent through autosomal recessive inheritance. For example, female *ATM* heterozygotes are at increased risk for breast cancer, but biallelic carriers have a neurologic condition known as ataxia telangiectasia. Similarly, *BRCA2* homozygotes and others with biallelic mutations in genes in the FA pathway (e.g., *BRIP1*, *PALB2*, *RAD51C*) develop FA. Recently, the rare finding of biallelic *BRCA1* carriers appears to manifest with a similar FA phenotype. Individuals with two mutations in some genes associated with Lynch syndrome may develop a severe condition known as constitutional mismatch repair deficiency. Thus, an individual tests positive for one mutation in genes such as these, counseling about reproductive implications needs to address. Not only the risks associated with autosomal dominant

Table 2 Hereditary breast and ovarian cancer syndrome pre and post treatment options with reproductive implications

Genetic counseling needs for AYAs with a new cancer diagnosis	Genetic counseling needs for AYA cancer survivors
Surgical treatment (e.g., contralateral prophylactic mastectomy at the time of initial diagnosis for <i>BRCA</i> carriers)	Risk reduction surgeries post treatment (e.g., salpingectomy <i>vs</i> bilateral salpingo oophorectomy for <i>BRCA</i> carriers)
Chemotherapy (e.g., clinical trials focused on poly ADP ribose polymerase inhibitors for <i>BRCA</i> carriers)	Use of Tamoxifen for management of disease recurrence among <i>ER</i> + <i>BRCA</i> carriers.

AYA: Adolescents and young adults.

inheritance but also the potential risk to have a child with two deleterious biallelic mutations that could result in a severe condition. Therefore, assessing the tested individual's partner (*i.e.*, his or her personal and family history, as well as ethnicity) is important. In the unlikely event that both parents are heterozygous for specific mutations, there is a 25% risk that a child will be homozygous and could have a severe phenotype. Thus, the couple should be made aware of reproductive options such as PGD.

Preimplantation genetic diagnosis

AYAs with hereditary cancers may have concerns about future offspring and transmission of the hereditary cancer^[22-28,66,71,72]. Technologies exist for individuals with cancer susceptibility gene mutations to avoid the birth of a child with such mutations. PGD is a type of ART allowing couples to choose which fertilized embryos, created through IVF, are implanted into a woman's uterus for further gestation^[73]. These embryos are tested for genetic disorders with the intent that the selected embryo will result in a child who does not carry the genetic mutation^[73,74]. To date, over 20000 cases of PGD use have been reported in the United States and over 200 genetic disorders or conditions can be identified using PGD^[75].

PGD is not without its ethical concerns. Studies of the general public and families with hereditary cancers suggest concerns that PGD is akin to "playing God" and a slippery slope for the creation of "designer babies"^[76,77]. Although oncology healthcare providers may be willing to discuss PGD with patients, many studies show physicians and nurses lack sufficient knowledge and confidence to initiate PGD discussions^[78]. A study of 373 gynecologic oncologists and obstetrics and gynecologists reported that 68% of participants had incorrect or limited knowledge of PGD for hereditary cancer^[79]. Another study with 201 oncology nurses showed more than half of respondents (78%) were unfamiliar with PGD and those familiar with PGD had limited knowledge^[79]. Studies with individuals at increased risk for hereditary cancer syndromes reported low levels of knowledge about PGD for hereditary cancers, moderate rates of acceptability, and high levels of need for information about PGD^[80]. With respect to patients with hereditary cancer, although a few studies indicate some would not consider PGD personally, most individuals

agreed that it is important for health care providers to provide information about the option of PGD^[64,81-83].

PND

PND can be used to identify hereditary cancer risks in the developing fetus. This process typically includes chorionic during the eleventh through fourteenth weeks of pregnancy or amniocentesis in later weeks^[84]. PND has been used to identify gene mutations in *RB1*, which causes retinoblastoma; *NF1* and *NF2*, which cause neurofibromatosis; and a host of others that help determine cancer predisposition^[85]. PND is more likely to be used for childhood onset hereditary conditions like *RB1* and less likely to be used for HBOC, of other adult onset cancer syndromes.

Genetic counseling for cancer risk

As defined by the NSGC genetic counseling is "the process of helping people understand and adapt to the medical, psychological, and familial implications of genetic contributions to disease"^[86]. Through the cancer risk assessment, genetic counselors can navigate patients through the process and provide education and counseling. This opens the floor for discussions regarding potential test results as well as the genetic test's risk and benefits.

Genetic counseling for AYAs at-risk for or with cancer

Although some AYA programs include access to genetic services as part of their umbrella of AYA cancer care, most institutions do not have a specific AYA program. Further, the number of trained oncology genetic counselors is low and may not be available to meet the needs of this growing population. Thus there is great need for genetic counselors in AYA programs and other settings who are trained not only in the discussion and assessment of risk to the individual but who also can discuss fertility, general preservation options for those whose fertility is at risk, and the impact the hereditary cancer may have on future offspring and ways to manage that risk. Expanding the training of genetic counselors to include oncofertility knowledge, resources, and decision-making tools, may greatly improve the quality of life and quality of care for AYA with hereditary cancer risk. Using HBOC, Table 2 provides examples of pre and post treatment genetic counseling and testing options for breast cancer survivors that may have reproductive implications for AYAs.

CONCLUSION

Genetic counselors may benefit from training on communicating about reproductive health risks and options for managing risks in AYA populations. This training should include not only information on fertility preservation, PGD, PND, and ART techniques but also strategies to communicate this information to patients in ways that facilitate informed decision-making and which consider the values and preferences of the patient and if applicable his or her family and partner. Genetic counseling education programs should consider didactic courses for learners on these same reproductive health options so that future genetic counselors are trained to address these important issues with their AYA patients. Improved communication on reproductive health issues and options for patients with hereditary cancers will greatly improve their future quality of life and expand the cadre of oncofertility health care providers.

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