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Special Article

Future Directions in Oncofertility and Fertility Preservation: A Report from the 2011 Oncofertility Consortium Conference

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Fertility impairment and loss due to cancer or its treatment is a significant survivorship consideration for many pediatric, adolescent, and young adult cancer survivors. Chemotherapeutics, radiation, and surgery can impact the future fertility of men, women, and children with cancer. The field of oncofertility, founded to ensure the reproductive future of cancer survivors, gained momentum with 5 years of funding through a 2007 National Institutes of Health Roadmap Grant for Biomedical Research. This report from working group meetings at the fifth annual Oncofertility Consortium Conference speaks to the present state of oncofertility research and clinical care, existing gaps, and future directions for the field. This summary from conference participants and leaders in the field addresses the science, clinical specialties, and academic scholarship that can guide the field as the Roadmap Grant funding comes to a close.

Keywords: fertility, oncofertility, fertility preservation, research

In 2006, the term "oncofertility" was introduced to describe a new subspecialty focused on the reproductive future for cancer survivors, who may face infertility as a result of chemotherapy, radiation, or surgery.[1] Oncofertility patients include those in pediatric, adolescent, and young adult stages of life, defined here as those aged 39 and younger. Oncofertility encompasses (1) the science needed to develop new fertility preservation options for patients prior to the onset of cancer treatment; (2) the clinical specialties to integrate fertility preservation, family building, and hormonal management throughout survivorship; and (3) the academic scholarship to advance oncofertility communication, social science, and education. In 2007, the United States' National Institutes of Health (NIH) funded a 5-year Roadmap Grant for Medical Research to form the Oncofertility Consortium—an interdisciplinary comprehensive research effort that addresses the complex biomedical condition of fertility impairment in cancer survivors. The Oncofertility Consortium is comprised of researchers based at four core centers—Northwestern University, the University of California at San Diego, the University of Pennsylvania, and Oregon Health & Science University—and its National Physicians Cooperative, which includes more than 50 allied healthcare centers across the United States that implement oncofertility science and scholarship into the clinical setting and provide fertility preservation treatments to cancer patients.[2] The Consortium brings together these diverse scientists, clinical specialists, and scholars to examine and overcome current reproductive barriers for cancer patients (Table 1).[3]

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Table 1. Summary of Progress in Fertility Preservation

- Development of vitrification as a viable method for ooctye cryopreservation[6–8]
- Birth of NuAge and NuBorn, the first mice from follicles grown in vitro from 3D alginate hydrogels[12]
- Establishment of the National Physicians Cooperative, a national network of fertility programs trained to preserve the fertility of young patients[2]
- Development of a virtual community of researchers, clinicians, and scholars through the Oncofertility Consortium to advance the reproductive future of cancer survivors[42]

Oncofertility practitioners and other stakeholders within the cancer and fertility communities meet annually to discuss changes in this rapidly advancing field. At the 2011 Oncofertility Consortium Conference held September 12–13, 2011, more than 120 interdisciplinary scientists, clinical specialists, and scholars participated in working group sessions on a variety of topics to discuss the past 5 years of oncofertility research and practice and identify new priorities for the community. Topics covered oncofertility science, clinical specialties, and additional scholarship through the following working group meetings: Female Fertility Preservation, Male Fertility Preservation, Adolescent and Young Adult Oncology, the National Physicians Cooperative, Information Technology, and Oncofertility Science Education, all of which are areas needed to advance and communicate the emerging field of oncofertility. Leaders in this interdisciplinary field moderated the working group sessions and developed the current report, which can be used by oncofertility scholars and clinicians to identify new research goals, address unmet clinical needs, and develop the next iteration of grant proposals in oncofertility.

Oncofertility Science

Oncofertility scientists work to improve our basic understanding of gamete development and maturation and to apply this understanding to fertility preservation techniques. Working group sessions on female and male fertility preservation summarized some of the past accomplishments of this research and identified opportunities to advance the science over the next few years. In discussing the current state of female fertility preservation research, participants recognized that, for women, embryo banking is the most mature fertility preservation technology, but is not optimal for all females, such as prepubertal girls and women with immediate need of treatment, women with hormone-sensitive cancers, or those who lack an available and suitable sperm donor.[4,5] Although advances in the fast-freezing vitrification of oocytes have led to increased success rates with oocyte banking, this technique still requires hormonal stimulation of patients to retrieve the oocytes, which may not be feasible for girls and some women.[6–8] Ovarian tissue cryopreservation is another fertility preservation option, and may be most appropriate for women and girls who are not candidates for either embryo or oocyte banking.[9,10] For males, working group attendees summarized that fertility preservation options for men have historically been more readily available than for females due to the relatively straightforward technique of sperm cryopreservation for post-pubertal males, which was established in the 1970s.[11] Thus the recent research in fertility preservation has focused on the need to provide equal care to women although considerable clinical efforts are needed to ensure utilization of fertility preservation by male patients.

Female fertility preservation

In discussing the future opportunities for research on female fertility preservation, working group participants identified cryopreservation as the next frontier in fertility preservation technologies. Cryopreservation technology is necessary to support experimental fertility preservation options such as ovarian tissue transplantation and investigational *in vitro* follicle maturation. Ovarian tissue cryopreservation research may also provide insights into optimal protocols for freezing and thawing tissue, and the potential to produce live births from *in vitro*-matured ovarian follicles.[3,12] Advances in ovarian tissue transplantation have resulted in restored endocrine function for some young cancer survivors and the birth of 18 children.[10,13–16] However, the success rate of this technology in patients is still unknown and further research is needed.

Cryopreservation technology has advanced significantly over the past decade with the successful establishment of vitrification freezing methods.[7,8,17] While much effort has been put into understanding the freezing process, working group participants agreed that further research should be devoted toward developing best practices for thawing. A systematic approach might be used to determine the best protocols for preserving ovarian tissue and gametes, as current methods to investigate cryoprotectant concentrations, freezing rates, and thawing protocols are time consuming and expensive. While these technologies are faster and less expensive to investigate in laboratory animal models (e.g., rodents), each species has intrinsic differences in reproductive biology compared with humans. Thus a vertical approach is needed to work in multiple models, including primates, in order to understand the implications of vitrification procedures for later translation to human fertility preservation.

In vitro follicle growth of ovarian tissue is an investigational alternative to ovarian tissue transplantation that may result in preserved fertility without the potential risk of reintroducing cancer cells, as is the case with ovarian tissue transplantation.[18,19] Researchers discussed the need to understand differences between primordial, preantral, and antral follicles and to identify optimal *in vitro* growth conditions of cryopreserved and thawed follicles.[20] Currently, no comparative genomic data have been published to compare specific cell types, such as theca cells, between species; such work may help identify the factors necessary for regulating *in vitro* follicle growth and the critical interactions between developing oocytes and somatic cells.[21] Furthermore, a better understanding of the relationship and interactions between dominant and nondominant follicles during follicular selection in primates is needed.

In discussing future directions for female fertility preservation research, the need to integrate research between different systems and approaches was highlighted. Though the trend in biomedical research is for individual laboratories to specialize in a single organism or experimental approach,

experiences from interdisciplinary research have provided insights into the usefulness of comparing and sharing efforts across model systems. This approach allows researchers to understand differences between species and to develop techniques with an eye toward the common goal of translational application in humans, efforts that can both be applied to female and male fertility preservation science.

Male fertility preservation

Discussions on male fertility preservation included emerging areas of fertility preservation science for male cancer patients. Pre-pubertal males were highlighted as perhaps the most challenging group of male patients in terms of providing fertility preservation care. To date, no proven procedures are available to preserve fertility in this group of patients.[22] However, experimental protocols involving testicular sperm extraction are actively being investigated. Testicular tissue cryopreservation may also provide an opportunity for fertility preservation for prepubertal boys. This cryopreserved tissue could be thawed after gonadotoxic cancer therapy and potentially used to restore sperm production and fertility in 3 possible ways: (1) autotransplantation of spermatogonial stem cells into the survivor's seminiferous tubules; (2) maturation of spermatocytes *in vitro*; or (3) xenotransplantation into an immunodeficient rodent model.[23] Successful utilization of cryopreserved testicular tissue will hinge on the future development of technological advances allowing for the transformation of immature germ cells into mature, functional spermatozoa.[24–26] Future research will also need to examine the feasibility and safety of these investigational techniques, including the risk of reintroducing cancer cells following autotransplantation of cryopreserved testicular tissue.

The Male Fertility Preservation working group also raised concerns that much of the psychosocial research performed regarding sperm cryopreservation has focused on sexually mature adult males,[27,28] though psychologically immature adolescent males may also need guidance with regard to fertility preservation.[29] Communication barriers within this community of patients were identified, especially as adolescent males are often not provided with fertility preservation options despite established options such as cryopreservation of ejaculated sperm.[30,31] Future research will need to focus on the professional guidance that young males need and the integration of these patients' desires with those of their family in order to advance oncofertility care for this underserved patient group. The group discussion ended with recognition that best practice guidelines for male oncofertility needs to be addressed, similarly to how this has been done for female patients.[3] As discussed by other working groups at the conference, one way to disseminate emerging information rapidly, such as clinical practice guidelines, to the clinical community is through integrated networks of clinicians able to provide fertility preservation to cancer patients, such as those described below.

Clinical Specialties in Oncofertility

Though fertility preservation options currently exist for most young cancer patients, few patients participate in fertility preservation prior to cancer treatment.[22,30,32] As discussed by multiple working groups at the 2012 Oncofertility Consortium Conference, one remaining barrier is a lack of communication that ultimately prevents patients from undergoing in fertility preservation. This barrier crosses both sexes, indicating a need for female and male oncofertility research to understand better the communication gaps as well as the best education methodologies to overcome them.[22,30,33] Two clinical working groups—Adolescent and Young Adult Oncology and the National Physicians Cooperative of fertility preservation specialists—discussed how the different communities can address communication barriers in oncofertility.

Adolescent and young adult oncology

The field of oncofertility has significant overlap with another emerging field, that of adolescent and young adult oncology (AYAO), which focuses on advancing research and clinical care to improve outcomes for cancer patients who are diagnosed between the ages of 15 and 39 years—10% of all cancer patients—and survivors of those same ages.[34] As this age range encompasses the primary reproductive years, fertility is of significant concern to AYAO patients and their clinicians.

At a working group session to discuss AYAO in the oncofertility context, participants agreed that the primary barrier to care is the limited number of oncologists that discuss fertility options with their patients, as well as the lack of established resources to facilitate these discussions.[33,35,36] The group identified a two-pronged approach to ensure that adolescent and young adult patients are informed of both the fertility and hormonal effects of cancer treatment as well as their options to preserve reproductive function prior to cancer treatment. First, oncofertility information should be disseminated to oncology practitioners. For example, a comprehensive brochure about AYAO patients including information about fertility and hormonal health could be created. It was agreed that such education should be communicated to a broad range of healthcare providers, not just oncologists. Engaging nurses, clinical psychologists, and other members of the oncology team would allow individual practices to determine which team members providers can best discuss oncofertility issues with patients and provide referrals to reproductive specialists.[18] Second, it was suggested that oncofertility information could be disseminated to the greater AYAO community through partnerships with advocacy groups such as Stupid Cancer and professional organizations such as the American Society of Clinical Oncology (ASCO). As the AYAO working group discussed the need to engage the greater oncology community in oncofertility, a session on the National Physicians Cooperative addressed ways to communicate to and within the reproductive community.

National Physicians Cooperative: a network of fertility preservation specialists

The National Physicians Cooperative (NPC) is a national group of reproductive specialists that provides fertility preservation clinical services to cancer patients and allows for a seamless transition between cancer treatment and fertility preservation. As discussed by the NPC working group, over the past 5 years, the group has grown from four initial core centers to now include more than 50 reproductive clinics. The NPC has three primary purposes: (1) it educates NPC members on the unique temporal, physical, and emotional fertility-related needs of cancer patients; (2) it provides

members with guidelines to incorporate these factors into reproductive care; and (3) it optimizes protocols for established and experimental fertility preservation techniques in order to provide uniform care to patients across the United States.[3] The NPC also supports the research mission of the oncofertility community by participating in a nationwide ovarian tissue registry through which patients undergoing ovarian tissue cryopreservation may contribute part of their tissue to research.[2] Participants in this breakout session also identified three areas of need for the clinical reproductive community: (1) increased communication within and between oncofertility teams; (2) patient education; and (3) collaborative clinical research efforts.

Inter-clinician communication was identified as an important focus for future oncofertility efforts, as a better integration of oncologists and fertility specialists can improve patient care in the cancer setting.[37] Fertility preservation cases are often clinically complex and require collaboration between oncology, fertility, anesthesia, and other medical teams. Working group participants thus expressed that the oncofertility community should encourage clinical teams to include diverse specialists. Collaboration between these diverse stakeholders can occur through the formation of local oncofertility forums, during which discussion of recent cases can include the perspectives of all team members. The working group also indicated that clinician communication between oncofertility teams can further be improved. Even when such teams are dispersed across long distances, discussions of clinical cases can occur virtually via moderated message boards, list serves, or blogs.[38,39] One topic of discussion that teams can share with each other are best practices for communicating with patients about oncofertility.

The NPC working group also identified the need for the community to disseminate oncofertility information better directly to patients and through healthcare providers.[30,35,40] Specifically, the group agreed that some of the most significant patient communication needs concern financial assistance and insurance coverage for fertility preservation services.[41] Social workers, patient navigators, and others who work directly with patients could be called on to identify financial assistance foundations and provide support with insurance appeals. Furthermore, clinical sites should utilize existing materials, such as template fertility preservation brochures and sample letters of insurance appeal.

Finally, the NPC working group discussed that clinical communities can advance oncofertility research by participating in broad-based multicenter studies. As such, large clinical groups, such as the NPC, and others can lead cross-site clinical research protocols on fertility preservation, which can provide the large sample sizes not available at any single institution. Thus the key to success of such research is the engagement of individual fertility programs that may be involved in larger fertility preservation communities. Engaging clinical programs in research integrates oncofertility science and clinical specialties, which can speed the pace of both research and translation to care. Academic scholarship from experts in other fields is also integral to advancing oncofertility efforts.

Oncofertility Scholarship

Scholars from fields outside of science and medicine also contribute to advancing oncofertility. The Oncofertility Consortium involves a diverse array of scholars to identify how oncofertility can be better integrated into the humanities, communication sciences, and other areas of research. These interdisciplinary collaborations can advance oncofertility research in ways not possible through traditional scientific and medical research. As such, working groups in Information Technology and Oncofertility Science Education assembled at the 2011 Oncofertility Conference to discuss how these fields can advance oncofertility research, communication, and clinical care.

Information technology in oncofertility

The Information Technology working group discussed the past experiences and future directions of this scholarship, which can speed the pace of both research and clinical care. They reviewed the past successes of integrating next-generation tools to bring together the diverse oncofertility community across long distances, including websites for professionals (www.oncofertility.northwestern.edu) and patients (www.myoncofertility.org and www.preservefertility.northwestern.edu), an iPhone application (iSaveFertility), a blog (www.blog.oncofertility.northwestern.edu), and social media tools, all summarized elsewhere.[1,42] An information technology infrastructure is also needed to maintain "virtual" (via the internet) oncofertility educational series, such as laboratory meetings between small groups of investigators and seminars (grand rounds) with a large group of viewers. Participants in this working group discussed that information technology experts should be brought into initial conversations about developing new virtual tools, such as message boards and list serves discussed by the NPC working group, to provide insight into these communication modalities. In addition to tangible tools such as technology infrastructure and software, the group identified the importance of having willing participants engaged in the development of the oncofertility community. Information technology can facilitate communication, but it cannot create collegiality where none exists or in the absence of a unified community.[43] The group also discussed security needs for oncofertility communication between researchers, clinicians, telemedicine patients, and providers communicating across long distances. As technology is a moving target, the group stressed the process of following and anticipating technological changes in the future. A cutting-edge technology infrastructure will provide the necessary support for the research, clinical, and scholarly goals of oncofertility.

Oncofertility science education

A second group of scholars met to discuss the science education efforts of the oncofertility community that simultaneously educate young people about oncofertility and promote the study of science and medicine by young students. The group stated that these two missions both ensure that more young people are aware of the reproductive impact of cancer treatment and join the pipeline to become the next generation of scientists and clinicians. In the past 5 years, members of the Oncofertility Consortium have done this by building the Oncofertility National Science Education Network (ONSEN) at four locations across the country: Northwestern University, the University of California, San Diego, the Oregon National Primate Research Center-Oregon Health

Table 2. Future Aims for the Field of Oncofertility

- Determine optimal cryopreservation and thaw techniques for reproductive tissues and gametes
- Advance *in vitro* follicle maturation for primates
- Improve integration of cancer survivors' psychosocial needs into the fertility preservation treatment plan
- Improve provider–patient fertility communication
- Develop broad-based multicenter studies through the infrastructure of the National Physicians Cooperative

& Science University, and the University of Pennsylvania, who together have educated more than 250 high school students.[44] The working group discussed that future ONSEN efforts will include assessment as a major goal, and in particular, evaluation of outcomes in a manner appropriate to the objective of the educational program. Such metrics can be used to better inform educators developing the next generation of oncofertility leaders and inform similar science education programs. Additionally, a "teach the teachers" program has also been launched that allows high school teachers to participate in oncofertility research in the laboratory setting and develop curricula to implement in their classrooms (www.nubio.northwestern.edu). As discussed by the working group, the principle advantage of this program is the ability to teach oncofertility to a greater number of students. Further dialogue identified the need for sustainability and funding to expand both programs and support new sites. Finally, working group participants stressed the need to ensure that the oncofertility educational programs synthesize with the existing local university and school environments in order for sustainability to be achieved.

Summary

The 2011 Oncofertility Consortium Conference marked the culmination of 5 years of effort by researchers supported by critical NIH funding. The current report developed from that conference provides a synthesis of the current state of the field of oncofertility and goals to address moving forward. Improved patient care—the ultimate measure of success of the field of oncofertility, will be achieved by addressing oncofertility science, clinical needs, and academic scholarship. As discussed by the many working groups, scientific, clinical, and communication research are all needed to advance the interdisciplinary field into the future (Table 2).

The oncofertility research community will continue to explore the emerging unmet needs in basic science and clinical care. Federal funding levels remain a challenge for all realms of biological, clinical, and educational research. Thus this report can aid oncofertility investigators looking to identify new opportunities in oncofertility science, translational research, communication, clinical care, and education.

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Disclaimer

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Author Disclosure Statement

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