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Installing oncofertility programs for common cancers in optimum resource settings (Repro-Can-OPEN Study Part II): An extrapolation for best practice models.

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Installing oncofertility programs for common cancers in optimum resource settings (Repro-Can-OPEN Study Part II): An extrapolation for best practice models.

Abstract

Purpose: The main objective of Repro-Can-OPEN Study Part 2 is to learn more about oncofertility practices in optimum resource settings to provide a roadmap to establish oncofertility best practice models.

Methods: As an extrapolation for oncofertility best practice models in optimum resource settings, we surveyed 25 leading and well-resourced oncofertility centers and institutions from the United States, Europe, Australia and Japan. The survey included questions on the availability and degree of utilization of fertility preservation options in case of childhood cancer, breast cancer, and blood cancer.

Results: All surveyed centers responded to all questions. Responses and their calculated oncofertility scores showed three major characteristics of oncofertility practice in optimum resource settings: (1) strong utilization of sperm freezing, egg freezing, embryo freezing, ovarian tissue freezing, gonadal shielding, and fractionation of chemo- and radiotherapy, (2) promising utilization of GnRH analogs, oophoropexy, testicular tissue freezing, and oocyte in vitro maturation (IVM), (3) rare utilization of neoadjuvant cytoprotective pharmacotherapy, artificial ovary, in vitro spermatogenesis, and stem cells reproductive technology as they are still in preclinical or early clinical research settings. Proper technical and ethical concerns should be considered when offering advanced and experimental oncofertility options to patients.

Conclusions: Our Repro-Can-OPEN Study Part 2 proposed installing specific oncofertility programs for common cancers in optimum resource settings as an extrapolation for best practice models. This will provide efficient oncofertility edification and modelling to oncofertility teams and related healthcare providers around the globe and help them offer the best care possible to their patients.

Keywords: oncofertility; cancer; optimum resource settings; best practice; childhood cancer; breast cancer; leukemia; lymphoma.

1. Introduction

Several malignancies occur at a young age and may necessitate aggressive anticancer therapies including alkylating chemotherapy and ionizing radiation that could lead to gonadotoxicity and subsequent fertility loss as a devastating side effect. According to the most recent international guidelines of the American Society of Clinical Oncology (ASCO) and the American Society for Reproductive Medicine (ASRM), several established, debatable and experimental oncofertility options can be offered to young female and male patients with cancer to preserve and restore fertility [1, 2]. Established oncofertility options include sperm freezing, embryo freezing, egg freezing, and recently ovarian tissue freezing and autotransplantation. Debatable oncofertility options include GnRH analogs and hormonal suppression, oophoropexy, gonadal shielding, and fractionation of chemotherapy and radiotherapy. Experimental oncofertility options include oocytes in vitro maturation (IVM), artificial ovary, testicular tissue freezing and autotransplantation, in vitro spermatogenesis, neoadjuvant cytoprotective pharmacotherapy, stem cells reproductive technology and others.

However, such oncofertility international guidelines face several challenges in practice. Over the past years, the Oncofertility Consortium has studied oncofertility practice in many countries within its Oncofertility Professional Engagement Network (OPEN). Our previous studies identified a variety of standards in oncofertility practice around the globe due to limited resource settings, shortage of reproductive care services provided to young patients with cancer, lack of awareness among providers and patients, cultural and religious constraints, lack of insurance coverage, high out-of-pocket costs for patients,

and lack of funding to support oncofertility programs [3, 4, 5, 6, 7, 8, 9]. Despite these challenges, many opportunities exist and create a significant potential for the future including improved cancer survival rates and improved success rates of many oncofertility options as well as emergence of new promising technologies. Therefore as a practical approach, the Oncofertility Consortium recommends installation of specific oncofertility programs for common cancers such as childhood, breast and blood cancers according to the contemporary challenges and opportunities. This practical approach will provide efficient oncofertility edification and modelling to oncofertility teams and related healthcare providers around the globe and help them offer the best care possible to their patients. To carry out this practical approach, the Oncofertility Consortium has designed its new **Repro-Can-OPEN Studies (Reproduction and Cancer in the Oncofertility Professional Engagement Network)**.

Recently in our **Repro-Can-OPEN Study Part 1** published at *Journal of Assisted Reproduction and Genetics (JARG)* [10], we proposed installation of specific oncofertility programs for common cancers in limited resource settings amidst a current global crisis of the COVID-19 pandemic as well as in 14 developing countries from Africa, Asia and Latin America. As a further step to reflect the actual wide spectrum of oncofertility practice around the globe and to help provide plausible oncofertility best practice models, we propose here in our **Repro-Can-OPEN Study Part 2** installation of specific oncofertility programs for common cancers in optimum resource settings. Our **Repro-Can-OPEN Study Part 2** is based on the practical experience of 25 leading and well-resourced oncofertility centers and institutions from the United States, Europe, Australia and Japan.

2. Methods

The Oncofertility Consortium sent the Repro-Can-OPEN Study Part 2 questionnaire via email to 25 leading and well-resourced oncofertility centers and institutions from the United States, Europe, Australia and Japan (Table 1) to be proposed for childhood cancer, breast cancer and blood cancer. The Repro-Can-OPEN Study Part 2 questionnaire included questions on the availability of fertility preservation options provided to young female and male patients with cancer and whether these options are always, commonly, occasionally or rarely used. The responses for childhood cancer, breast cancer, and blood cancer from the surveyed centers were collected, reviewed, and analyzed.

To analyze the collected data, our coauthor Dr. Salama from Northwestern University developed the new scoring system 'oncofertility score'. As previously described [10], the oncofertility score, is a new diagnostic tool to measure the availability and utilization of oncofertility options for cancer patients in a treating center, country, or group of centers or countries. It is also a prognostic tool to follow up on the development of oncofertility options and strategies provided to cancer patients over time. The oncofertility score is calculated as a percentile ratio between the actual and maximal points of utilization that an oncofertility option might have (Table 2 & Fig 2). When a fertility preservation option is available and always used for cancer patients, it is given (Yes +++) that weighs 100 actual points (25 points per each +). When a fertility preservation option is available and commonly used for cancer patients, it is given (Yes ++) that weighs 75 actual points (25 points per each +). When a fertility preservation option is available but occasionally used

for cancer patients, it is given (Yes ++) that weighs 50 actual points (25 points per each +). When a fertility preservation option is available but rarely used or only used in research settings for cancer patients, it is given (Yes +) that weighs 25 actual points (25 points per each +). When a fertility preservation option is not available, it is given (No) that weighs 0 actual points. When the fertility preservation option is not available to cancer patients because it is still in the preclinical research stage, it is marked with (No*). The maximal points of utilization that an oncofertility option might have is 100 when it is available and always used for cancer patients and is given (Yes +++++), (25 points per each +).

In this study of 25 surveyed centers, the oncofertility score is calculated as a percentile ratio between the total actual points and the total maximal points of utilization that an oncofertility option might have. The total actual points for an oncofertility option equal the sum of actual points for this option in all 25 surveyed centers. The total maximal points for an oncofertility option equal 100 points multiplied by 25 (number of surveyed centers in this study) resulting in 2500 points.

3. Results

All 25 surveyed centers responded to all questions. Each surveyed center has the same serial number in all tables (Table 1 & 3-5). Responses for childhood, breast and blood cancers and their calculated oncofertility scores are listed in Tables 3-5.

The oncofertility scores for options provided to children with cancer in all 25 surveyed centers were as follows; gonadal shielding in case of irradiation (69%),

ovarian tissue freezing (63%), fractionation of chemo- and radiotherapy (61%), oophoropexy in case of pelvic irradiation (42%), testicular tissue freezing (41%), GnRH analogs in case of old child (9-14 year) (35%), oocyte in vitro maturation (IVM) (18%), neoadjuvant cytoprotective pharmacotherapy (6%), artificial ovary (2%), in vitro spermatogenesis (2%), and stem cells (0%). (Table 3 & Fig 3).

The oncofertility scores for options provided to female patients with breast cancer

in all 25 surveyed centers were as follows; egg freezing (77%), IVF/ICSI of frozen oocytes (75%), gonadal shielding in case of irradiation (75%), embryo freezing (66%), frozen embryo transfer (64%), fractionation of chemo- and radiotherapy (62%), GnRH analogs (61%), ovarian tissue freezing (49%), autotransplantation of frozen ovarian tissue (43%), oocyte in vitro maturation (IVM) (23%), neoadjuvant cytoprotective pharmacotherapy (5%), artificial ovary (2%), and stem cells (0%). (Table 4 & Fig 4).

The oncofertility scores for options provided to patients with blood cancer in all 25

surveyed centers were as follows; sperm freezing (83%), gonadal shielding in case of irradiation (75%), egg freezing (68%), fractionation of chemo- and radiotherapy (62%), embryo freezing (58%), ovarian tissue freezing (57%), GnRH analogs (57%), oophoropexy in case of pelvic irradiation (46%), testicular tissue freezing (38%), oocyte in vitro maturation (IVM) (23%), neoadjuvant cytoprotective pharmacotherapy (7%), artificial ovary (2%), in vitro spermatogenesis (2%), and stem cells (0%). (Table 5 & Fig 5).

4. Discussion

In our Repro-Can-OPEN Study Part 2, the responses and their calculated oncofertility scores (Tables & Figs: 3-5) showed three major characteristics of oncofertility practice in optimum resource settings: (1) strong utilization of sperm freezing, egg freezing, embryo freezing, ovarian tissue freezing, gonadal shielding, and fractionation of chemo- and radiotherapy, (2) promising utilization of GnRH analogs, oophoropexy, testicular tissue freezing, and oocyte in vitro maturation (IVM), (3) rare utilization of neoadjuvant cytoprotective pharmacotherapy, artificial ovary, in vitro spermatogenesis, and stem cells reproductive technology as they are still in preclinical or early clinical research settings.

Proper technical and ethical concerns should be considered when offering advanced and experimental oncofertility options to patients including gonadal tissue freezing and autotransplantation, in vitro maturation of gametes, artificial gonad technology, neoadjuvant cytoprotective pharmacotherapy and stem cells reproductive technology. Technically, the aforementioned advanced oncofertility options are sophisticated procedures that require well-resourced oncofertility centers with expert teams of oncologists, reproductive endocrinology and infertility specialists, pediatric and adolescent gynecologists, urologists, pediatric endocrinologists, biologists, embryologists, scientists, and transplantation surgeons. That is why they should be performed only at highly specialized oncofertility centers in optimum resource settings. Early referral of cancer patients to such highly specialized oncofertility centers is strongly recommended. Ethically, most of these advanced oncofertility options are experimental

or have limited data on efficacy, and it is essential that they are offered to patients under clear ethical regulations. Special ethical and legal considerations need to be considered in children [11, 12]. Obtaining ethical approval from the Institutional Review Board (IRB) or the equivalent ethics committee is essential, as is obtaining informed consent from the patients or the legal guardians in the case of a minor. Informed consent for experimental medical treatments and interventions should include the explanation of the procedures, benefits, risks, alternative treatments, and information about the expected outcome and costs. Several oncofertility options are expensive and not fully covered by health insurance in some states and countries, leaving many patients under critical financial pressure. In such complex situations, doctors and patient navigators as well as patient support and advocacy organizations can play an important role in reassuring and guiding patients or legal guardians of minors during counseling [13, 14, 15, 16, 17, 18].

Installing oncofertility programs in optimum resource settings:

Based on the responses and their calculated oncofertility scores (Tables & Figs: 3-5), we will try here to tailor and install plausible oncofertility programs for common cancers in optimum resource settings as an extrapolation for best practice models (Table 6). Previous international oncofertility guidelines and recommendations were considered as well [19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35]. Immediately after cancer diagnosis, we recommend early referrals of patients to oncofertility specialists to check the anticancer therapy plan and estimate the related risk of gonadotoxicity and subsequent fertility loss. The risk of anticancer therapy induced gonadotoxicity and fertility loss depends mainly on the type and stage of the disease, type and dose of anticancer

therapy as well as the age of the patient at the time of treatment. If the risk of gonadotoxicity and fertility loss is detected or even unknown, a comprehensive multidisciplinary oncofertility strategy should be offered before, during and after anticancer therapy.

From a practical point of view, an effective oncofertility strategy should be individualized and tailored to the patient's circumstances and it may integrate various established, debatable, and experimental options after proper counselling and obtaining informed consent from the patient or the legal guardians of a minor. It is recommended that the proposed oncofertility strategy should include at least one cryopreservation option. After complete cure from cancer, and when the patient decides to have biological children, a new assessment of reproductive functions should be performed. If anticancer therapy induced gonadal dysfunction exists, fertility restoration may be achieved by using the cryopreserved gametes or gonadal tissue.

I. Installing oncofertility programs for childhood cancer in optimum resource settings:

The common forms of childhood cancers that may require aggressive gonadotoxic anticancer therapy and hence necessitate prior fertility preservation measures are leukemia, central nervous system cancers, lymphoma and sarcomas. Unique medical challenges in oncofertility programs for childhood cancer exist and include (1) freezing of gonadal tissues is the only suitable cryopreservation option before puberty, (2) autotransplantation of frozen gonadal tissue may carry the risk of reintroducing malignant

cells, especially in leukemia which is the most common childhood cancer [36, 37, 38, 39, 40, 41, 42].

According to the aforementioned unique medical challenges, as well as the responses and their calculated oncofertility scores (Table 3 & Fig 3), we suggest installing the following oncofertility programs for childhood cancer in optimum resource settings.

Before initiation of anticancer therapy, freezing of prepubertal gonadal tissues (ovarian or testicular tissue) should be encouraged and attempted when possible. In vitro maturation and further vitrification of gametes (oocytes or spermatozoa) and artificial gonad technology (ovary or testis) are still experimental and cannot be relied upon as effective oncofertility options in children. Although experimental, these emerging technologies of in vitro maturation of gametes and artificial gonads aim to provide safe alternatives to avoid future gonadal tissue autotransplantation and potential reintroduction of malignant cells. Oophoropexy before female pelvis irradiation should be attempted when possible. **During anticancer therapy**, gonadal shielding in case of irradiation should be attempted. Fractionation of chemo- and radiotherapy could be attempted whenever deemed feasible by the oncologists. Use of GnRH analogs to preserve fertility during chemotherapy in case of older children (9-14 year) is widely debated and needs more research to inform evidence-based practice. Neoadjuvant cytoprotective pharmacotherapy is still experimental and not yet clinically proven as an effective oncofertility option. **After anticancer therapy**, gonadal function should be monitored to ensure appropriate growth, pubertal development and reproductive function, with hormone replacement introduced in those with gonadal failure. Furthermore, regular

follow-up in survivorship offers a window of opportunity for interval fertility and sexual healthcare, linking patients in with the tissue storage laboratory, and discussing expectations around relationships, pregnancy and parenthood [43]. When the patient becomes an adult and wishes to have children, fertility restoration may be possible using stored gonadal tissue or gametes. Autotransplantation of gonadal tissue can be offered to restore fertility but it should be handled with caution in patients with leukemia due to possible contamination of gonadal tissue with leukemic cells. According to few reports, harvesting gonadal tissue after the first cycles of anticancer therapy and during complete remission followed by proper gonadal tissue assessment for minimal residual disease (MRD) may reduce the risk of reintroducing leukemic cells with autotransplantation [44, 45]. For additional safety measures, it may be a possible option for patients with leukemia to remove the transplanted gonadal tissue later after restoring fertility and having biological children [46, 47]. Stem cells reproductive technology may be promising in research settings but it is not yet clinically proven as an effective oncofertility option (Table 6).

II. Installing oncofertility programs for breast cancer in optimum resource settings:

Breast cancer is the most common cancer in women during their reproductive years. Breast cancer may require aggressive gonadotoxic anticancer therapy and hence necessitate prior fertility preservation measures. Women with *BRCA1* or *BRCA2* mutations carry significantly higher risks to develop breast and ovarian cancers (Hereditary Breast-Ovarian Cancer Syndrome; HBOC), and they should receive appropriate oncofertility care as well. According to a recent large study, the cumulative

breast cancer risk is 72% for *BRCA1* and 69% for *BRCA2* carriers, while the cumulative ovarian cancer risk is 44% for *BRCA1* and 17% for *BRCA2* carriers [48]. Unique medical challenges in oncofertility programs for breast cancer exist and include (1) conventional ovarian stimulation prior to egg or embryo freezing results in elevated serum estradiol levels that should be avoided in estrogen sensitive malignancies such as breast cancer, (2) autotransplantation of frozen ovarian tissue in patients with *BRCA* mutations should be handled with caution due to significantly higher risks of developing ovarian cancer [49, 50, 51, 52, 53].

According to the aforementioned unique medical challenges as well as the responses and their calculated oncofertility scores (Table 4 & Fig 4), we suggest installing the following oncofertility programs for breast cancer in optimum resource settings. **Before initiation of anticancer therapy**, freezing of eggs or embryos should be attempted with a random-start protocol for controlled ovarian stimulation and using letrozole or tamoxifen to avoid high estradiol levels. Freezing of ovarian tissue should be attempted when possible. In vitro maturation and further vitrification of oocytes retrieved in-vivo or ex-vivo from the extracted ovarian tissue (ovarian tissue oocytes in vitro maturation; OTO-IVM) could be attempted [54, 55, 56]. Artificial ovary technology is still experimental and cannot be relied upon alone as an effective oncofertility option. Although experimental, oocyte IVM and artificial ovary technology aim to provide safe alternatives to avoid future ovarian tissue autotransplantation and potential reintroduction of malignant cells. **During anticancer therapy**, GnRH analog administration before and during chemotherapy can be considered. Fractionation of chemo- and radiotherapy could be attempted whenever

deemed feasible by the oncologists. Gonadal shielding might be needed in case of combined irradiation to ovaries. Neoadjuvant cytoprotective pharmacotherapy is still experimental and not yet clinically proven as an effective oncofertility option. **After anticancer therapy**, fertility restoration may be achieved by frozen embryo transfer, or in vitro fertilization of stored oocytes. Patients with *BRCA* mutations could be advised to use preimplantation genetic testing (PGT) during in vitro fertilization to avoid transmitting the mutation. Autotransplantation of frozen ovarian tissue can be offered to restore fertility but it should be handled with caution in patients with *BRCA* mutations due to significantly higher risks of developing ovarian cancer. Proper ovarian tissue assessment in patients with *BRCA* mutations is mandatory to reduce the risk of reintroducing malignant cells with autotransplantation. For additional safety measures, it may be a possible option for patients with *BRCA* mutations to remove the transplanted ovarian tissue as well as the remaining ovary (if any) after childbearing is complete and at the time of an elective caesarian section. Stem cells reproductive technology may be promising in research settings but it is not yet clinically proven as an effective oncofertility option (Table 6).

III. Installing oncofertility programs for blood cancer in optimum resource settings:

The common forms of blood cancers that occur during the reproductive age and may require immediate aggressive gonadotoxic anticancer therapy and hence necessitate prior fertility preservation measures are acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), Non-Hodgkin lymphoma (NHL), and Hodgkin lymphoma (HL). Unique medical challenges in oncofertility programs for blood cancer exist and include (1) most cases of blood cancer especially leukemia necessitate immediate initiation of anticancer

therapy leaving very short time to offer fertility preservation options, thus may be precluded by the health status of the patient and the time available, (2) autotransplantation of frozen gonadal tissue may carry the risk of reintroducing malignant cells, especially in leukemia [57, 58, 59].

According to the aforementioned unique medical challenges as well as the responses and their calculated oncofertility scores (Table 5 & Fig 5), we suggest installing the following oncofertility programs for blood cancer in optimum resource settings. **Before initiation of anticancer therapy**, freezing of embryos or gametes (oocytes or spermatozoa) should be attempted when possible. Freezing of gonadal tissues (ovarian or testicular tissue) should be attempted after proper tissue assessment to exclude contamination with malignant cells. In vitro maturation and further vitrification of gametes retrieved in-vivo or ex-vivo from the extracted gonadal tissue could be attempted. Artificial gonad technology is still experimental and cannot be relied upon alone as an effective oncofertility option. Although experimental, these emerging technologies of in vitro maturation of gametes and artificial gonads aim to provide safe alternatives to avoid future gonadal tissue autotransplantation and potential reintroduction of malignant cells. Oophoropexy before female pelvis irradiation should be attempted when possible. **During anticancer therapy**, gonadal shielding in case of irradiation should be attempted. Fractionation of chemo- and radiotherapy could be attempted whenever deemed feasible by the oncologists. Use of GnRH analogs to preserve fertility during chemotherapy in case of hematological malignancies is widely debated and needs more research to inform evidence-based practice. Neoadjuvant cytoprotective pharmacotherapy is still

experimental and not yet clinically proven as an effective oncofertility option. **After anticancer therapy**, fertility restoration may be achieved by frozen embryo transfer, or in vitro fertilization of stored gametes. Autotransplantation of frozen gonadal tissue can be offered to restore fertility but it should be handled with caution in patients with leukemia due to possible contamination of gonadal tissue with leukemic cells. According to a few reports, harvesting gonadal tissue after the first cycles of anticancer therapy and during complete remission followed by proper gonadal tissue assessment for minimal residual disease (MRD) may reduce the risk of reintroducing leukemic cells with autotransplantation. For additional safety measures, it may be a possible option for patients with leukemia to remove the transplanted gonadal tissue later after restoring fertility and having biological children [46, 47]. Stem cells reproductive technology may be promising in research settings but it is not yet clinically proven as an effective oncofertility option (Table 6).

After installation of these specific oncofertility programs for common cancers in optimum resource settings, we encourage using the 'oncofertility score' as a prognostic tool to follow up on the development of these new oncofertility programs over time.

In cases where oncofertility options are rejected, contraindicated, infeasible, unsuccessful or unavailable, adoption and third-party reproduction, such as sperm, egg, and embryo donation and surrogacy can be offered as family building alternatives.

Next steps and future directions of Repro-Can-OPEN Studies:

In our next Repro-Can-OPEN studies, we are planning to investigate in detail the oncofertility programs offered to leukemia and lymphoma patients according to their gender and age group. We are planning also to investigate other cancers as well as other patients groups (e.g. LGBTQ population: lesbian, gay, bisexual, transgender and queer or questioning) who were not included in our previous studies. We will provide further discussions on the advanced and the emerging oncofertility options, and highlight the recent achievements in the related preclinical research [60, 61, 62, 63, 64, 65]. The Oncofertility Consortium will continue to engage more stakeholders from the United States and abroad to help build a sustainable oncofertility core competency worldwide.

5. Conclusion

Our Repro-Can-OPEN Study Part 2 proposed installing specific oncofertility programs for common cancers in optimum resource settings as an extrapolation for best practice models. Responses for childhood, breast and blood cancers and their calculated oncofertility scores showed three major characteristics of oncofertility practice in optimum resource settings: (1) strong utilization of sperm freezing, egg freezing, embryo freezing, ovarian tissue freezing, gonadal shielding, and fractionation of chemo- and radiotherapy, (2) promising utilization of GnRH analogs, oophoropexy, testicular tissue freezing, and oocyte in vitro maturation (IVM), (3) rare utilization of neoadjuvant cytoprotective pharmacotherapy, artificial ovary, in vitro spermatogenesis, and stem cells reproductive technology as they are still in preclinical or early clinical research settings. Proper

technical and ethical concerns should be considered when offering advanced and experimental oncofertility options to patients. Dissemination of our study results and recommendations will provide efficient oncofertility education and modelling to oncofertility teams and related healthcare providers around the globe and help them offer the best care possible to their patients.

Tables and Figures

Table 1: Surveyed Oncofertility Centers

N	Surveyed Oncofertility Centers
1	Oncofertility Consortium, Feinberg School of Medicine, Northwestern University, Chicago, IL 60611, USA. Ann & Robert H. Lurie Children's Hospital of Chicago, 225 East Chicago Ave, Box 63, Chicago IL, 60611, USA.
2	Yale Fertility Center and Yale Fertility Preservation program, 200 West Campus Dr., Orange, CT 06477, USA.
3	Karolinska Institutet, Department of Oncology-Pathology and Karolinska University Hospital, Department of Reproductive Medicine, Division of Gynecology and Reproduction, SE-14186, Stockholm, Sweden.
4	Department of Obstetrics and Gynecology, St. Marianna University School of Medicine, 2-16-1, Sugao, Miyamae-ku, Kawasaki, Kanagawa, Japan.
5	Department of Medical Oncology, UOC Clinica di Oncologia Medica, IRCCS Ospedale Policlinico San Martino, Genova, Italy. Department of Internal Medicine and Medical Specialties (DiMI), School of Medicine, University of Genova, Genova, Italy.
6	Fertility Preservation Service, Reproductive Services Unit, Royal Women's Hospital, Parkville, 3051, Australia. Fertility Preservation Service, Melbourne IVF, East Melbourne, 3002, Australia.
7	Children's National Hospital, 111 Michigan Avenue NW, Washington, DC 20010, USA. (ZIA# HD008985)
8	Center for Reproductive Medicine, Michigan Medicine, 475 Market Place, Building 1, Suite B, Ann Arbor, MI 48108, USA.
9	Fertility Research Centre, Royal Hospital for Women, Barker Street, Sydney, Australia.
10	Stanford University Medical Center, 300 Pasteur Drive, Stanford, CA, USA.
11	University of Edinburgh, Edinburgh, UK. Royal Infirmary of Edinburgh and Royal Hospital for Children and Young People, Little France Crescent, Edinburgh, UK.
12	Nationwide Children's Hospital, 700 Children's Dr., Columbus, OH 43205, USA.
13	University of Pennsylvania, Division of Reproductive Endocrinology & Infertility, 3701 Market Street, Suite 8000, Philadelphia, PA 19104, USA.
14	New York University, NYU Langone Fertility Center, 660 First Ave, 5th Floor, New York, NY 10016, USA.
15	UniKID - Center for Reproductive Medicine, UniCareD - Center for Fertility Preservation, Düsseldorf University Hospital, Moorenstrasse 5, D-40225 Düsseldorf, Germany.
16	Laboratory of Reproductive Biology, Juliane Marie Centre for Women, Children and Reproduction, University Hospital of Copenhagen, Blegdamsvej 9, DK-2100 Copenhagen, Denmark.
17	Fertility Preservation Service, The Royal Children's Hospital, Flemington Rd, Parkville, Melbourne, Vic 3054, Australia.
18	University of California, San Diego, 3855 Health Sciences Drive, La Jolla, CA 92039-0901, USA.
19	Cliniques Universitaires Saint Luc, Université Catholique de Louvain, Avenue Hippocrate, 10, 1200 Brussels, Belgium. Université Catholique de Louvain, Avenue Mounier 52, 1200 Brussels, Belgium.
20	Fertility Clinic and Research Laboratory on Human Reproduction, CUB-Erasme Hospital, Université Libre de Bruxelles (ULB), 808 route de Lennik, 1070 Brussels, Belgium.
21	Centre for Reproductive Medicine of UZ Brussel, Laarbeeklaan 101, 1090 Brussels, Belgium.
22	Gynecological Endocrinology and Reproductive Medicine Division, Obstetrics and Gynecology Department, Cologne University Hospital, Cologne, Germany.
23	Center for Reproduction and Transplantation, Magee-Womens Hospital, University of Pittsburgh Medical Center, 300 Halket Street, Pittsburgh, PA 15213, USA.
24	University of Cincinnati, Department of Obstetrics and Gynecology, Division for REI, Cincinnati, OH 45229, USA. Cincinnati Children's Hospital Medical Center, Division of Pediatric Adolescent Gynecology Pediatric, Cincinnati, OH 45229, USA.
25	Urology Department, UCSF Medical Center, University of California, San Francisco, CA 94143, USA. Obstetrics and Gynecology Department, UCSF Medical Center, University of California, San Francisco, CA 94143, USA.

Figure 1: Merger of American and global networks into one unified network, the Oncofertility Professional Engagement Network (OPEN).



Table 2: Oncofertility Score calculation

Availability and utilization of an oncofertility option	Available and always used for cancer patients	Available and commonly used for cancer patients	Available but occasionally used for cancer patients	Available but rarely used or only used in research settings for cancer patients	Not available
Scale Symbol	++++	+++	++	+	-
Actual Points (AP) (25 points per +)	100	75	50	25	0
Maximal Points (MP) (100 points per ++++)	100	100	100	100	100
Oncofertility Score = AP/MP (%)	100%	75%	50%	25%	0%

Figure 2: Oncofertility Score calculation

$$\text{Oncofertility Score} = \frac{\text{Actual Points (AP) of utilization that an oncofertility option might have}}{\text{Maximal Points (MP) of utilization that an oncofertility option might have}} \%$$

Table 3 & Figure 3: Oncofertility Options and Scores (%) for Childhood Cancer in All 25 Surveyed Centers

Oncofertility Center	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	Total Actual Points	Oncofertility Score (%)	
Available fertility preservation options for girls with cancer																												
- Ovarian tissue freezing	Yes (+++)	Yes (+)	Yes (+++)	Yes (+++)	Yes (+++)	Yes (++)	Yes (++)	No	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	No	Yes (++)	Yes (+++)	Yes (++)	No	Yes (++)	Yes (+++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	1575	63
- Oophoropexy in case of pelvic irradiation	Yes (++)	Yes (++)	Yes (++)	No	Yes (+++)	Yes (+)	Yes (+)	Yes (++)	Yes (++)	Yes (++)	No	Yes (+)	Yes (++)	Yes (++)	No	Yes (++)	Yes (+)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (+)	Yes (++)	1050	42
- Oocyte in vitro maturation (IVM)	No	No	Yes (+)	Yes (+++)	No	Yes (+)	No	No	Yes (+)	Yes (+)	No	No	No	No	No	Yes (++)	Yes (++)	No	Yes (+)	Yes (+)	Yes (++)	Yes (+)	No	No	Yes (+)	450	18	
- Artificial ovary	No*	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes (+)	Yes (+)	No	No	No	50	2
Available fertility preservation options for boys with cancer																												
- Testicular tissue freezing	Yes (++)	Yes (+)	Yes (+)	No	No	Yes (++)	Yes (++)	No	No	Yes (+)	Yes (++)	Yes (+)	Yes (++)	No	Yes (+)	Yes (++)	Yes (++)	Yes (+)	Yes (++)	No	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (+)	Yes (+)	1025	41
- In vitro spermatogenesis	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes (+)	No	Yes (+)	No	No	50	2
Available fertility preservation options for both girls and boys with cancer																												
- GnRH analogs in case of old child (9-14 year)	Yes (++)	Yes (++)	No	No	Yes (++)	No	Yes (++)	Yes (++)	Yes (++)	Yes (++)	No	Yes (++)	Yes (+)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	No	No	No	No	Yes (+)	No	Yes (++)	875	35
- Gonadal shielding in case of irradiation	Yes (+)	Yes (++)	Yes (++)	Yes (+)	Yes (++)	Yes (++)	No	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (+)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	1725	69
- Fractionation of chemo- and radiotherapy	Yes (++)	Yes (++)	Yes (++)	No	No	Yes (++)	No	Yes (++)	Yes (++)	Yes (+)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	1525	61
- Neoadjuvant cytoprotective pharmacotherapy	No	No	No	No	No	No	No	No	Yes (+)	No	No	No	Yes (+)	No	No	Yes (+)	Yes (++)	No	No	No	No	No	No	Yes (+)	No	No	150	6
- Stem cells reproductive technology	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	0	0

(+++ Available and always used for cancer patients, (++) Available and commonly used for cancer patients, (++) Available but occasionally used for cancer patients, (+) Available but rarely used or only used in research setting for cancer patients, (No) Not available, (No*) Not available because it is still in the preclinical research stage.

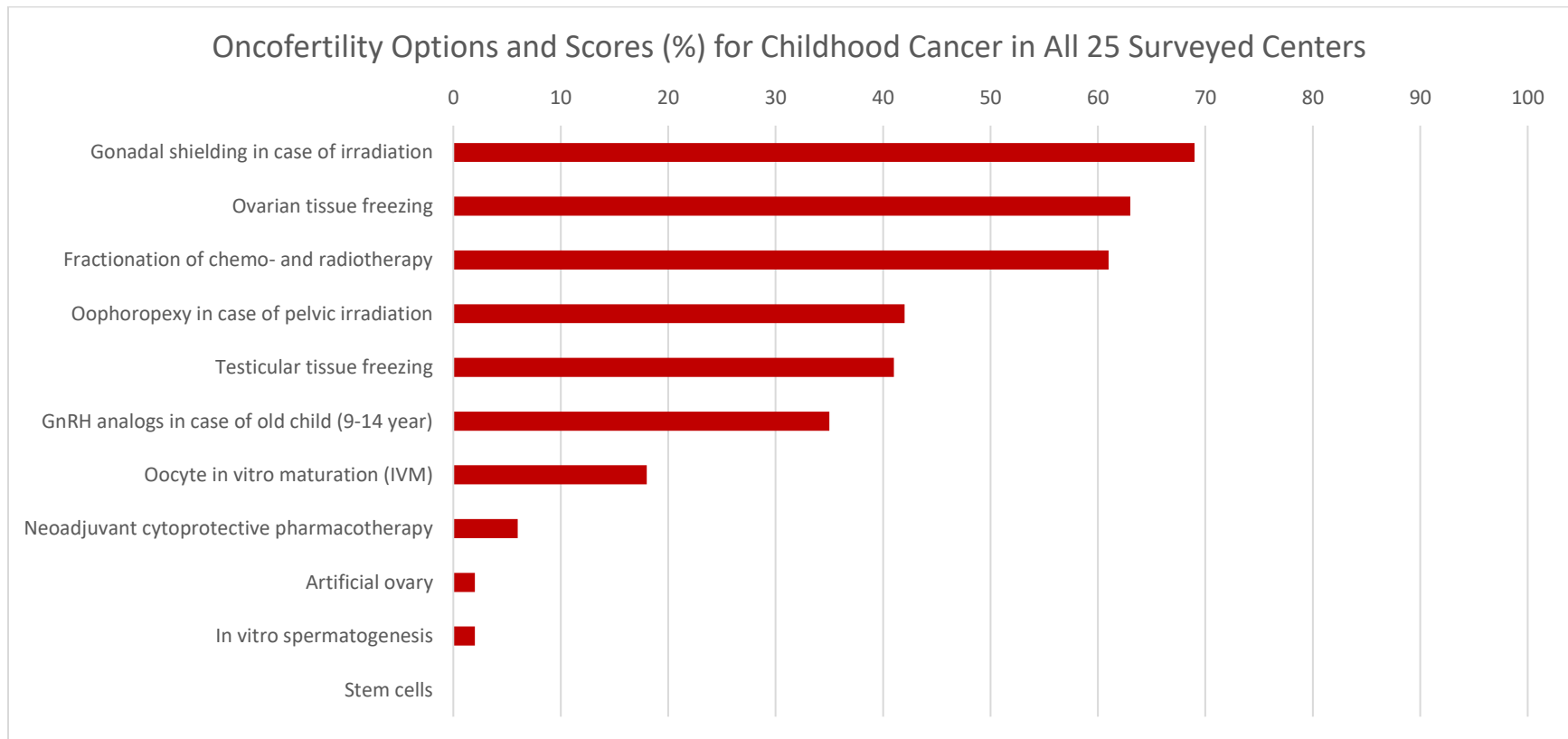


Table 4 & Figure 4: Oncofertility Options and Scores (%) for Breast Cancer in All 25 Surveyed Centers

Oncofertility Center	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	Total Actual Points	Oncofertility Score (%)	
Available fertility preservation options before anticancer treatment																												
- Embryo freezing	Yes (++++)	Yes (++++)	Yes (+++)	Yes (++)	No	Yes (++++)	Yes (+)	Yes (+++)	Yes (++)	Yes (++)	Yes (++)	Yes (+)	Yes (+++)	Yes (++)	Yes (++)	Yes (++)	Yes (++++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	1650	66
- Egg freezing	Yes (++++)	Yes (++++)	Yes (+++)	Yes (++)	Yes (++++)	Yes (++++)	Yes (+)	Yes (+++)	Yes (++)	Yes (++)	Yes (++)	Yes (+)	Yes (+++)	Yes (++)	Yes (++)	Yes (++)	Yes (++++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	1925	77
- Ovarian tissue freezing	Yes (+)	Yes (++)	Yes (+++)	Yes (++)	Yes (++)	Yes (+++)	Yes (++)	No	Yes (++)	Yes (+)	Yes (++)	Yes (++)	Yes (++)	No	Yes (++)	Yes (++)	Yes (++)	No	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	1225	49
- Oocyte in vitro maturation (IVM)	Yes (++)	Yes (+)	Yes (+)	Yes (+)	No	Yes (++)	No	No	Yes (++)	Yes (+)	No	No	Yes (+)	Yes (+)	No	Yes (+)	Yes (++)	No	No	Yes (+)	Yes (++)	Yes (+)	No	No	Yes (++)	575	23	
- Artificial ovary	No*	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No*	No	No	Yes (+)	Yes (+)	No	No	50	2	
Available fertility preservation options during anticancer treatment																												
- GnRH analogs	Yes (++)	Yes (++)	Yes (+)	No	Yes (++++)	Yes (++++)	Yes (+)	Yes (++)	Yes (++++)	Yes (++)	Yes (++)	Yes (+)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	1525	61
- Gonadal shielding in case of irradiation	Yes (++)	Yes (++)	Yes (++)	No	Yes (++++)	Yes (++++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	1875	75
- Fractionation of chemo- and radiotherapy	No	Yes (++)	Yes (++)	No	No	Yes (++++)	Yes (++)	Yes (++)	Yes (++)	Yes (+)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	1550	62
- Neoadjuvant cytoprotective pharmacotherapy	No	No	No	No	No	No	No	No	Yes (+)	No	No	No	No	No	No	Yes (++)	No	No	No	No	No	No	No	Yes (++)	No	No	125	5
Available fertility restoration options after anticancer treatment																												
- Frozen embryo transfer	Yes (++++)	Yes (++++)	Yes (++)	Yes (++)	No	Yes (++++)	Yes (+)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (+)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	1600	64
- IVF/ICSI of frozen oocytes	Yes (++++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (+)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (+)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	1875	75
- Autotransplantation of frozen ovarian tissue	Yes (+)	Yes (++)	Yes (++)	Yes (++)	Yes (+)	Yes (++)	No	No	Yes (++)	Yes (+)	Yes (++)	No	Yes (+)	No	Yes (++)	Yes (++)	Yes (++)	No	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	1075	43
- Stem cells reproductive technology	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	0	0

(++++) Available and always used for cancer patients, (+++) Available and commonly used for cancer patients, (++) Available but occasionally used for cancer patients, (+) Available but rarely used or only used in research setting for cancer patients, (No) Not available, (No*) Not available because it is still in the preclinical research stage.

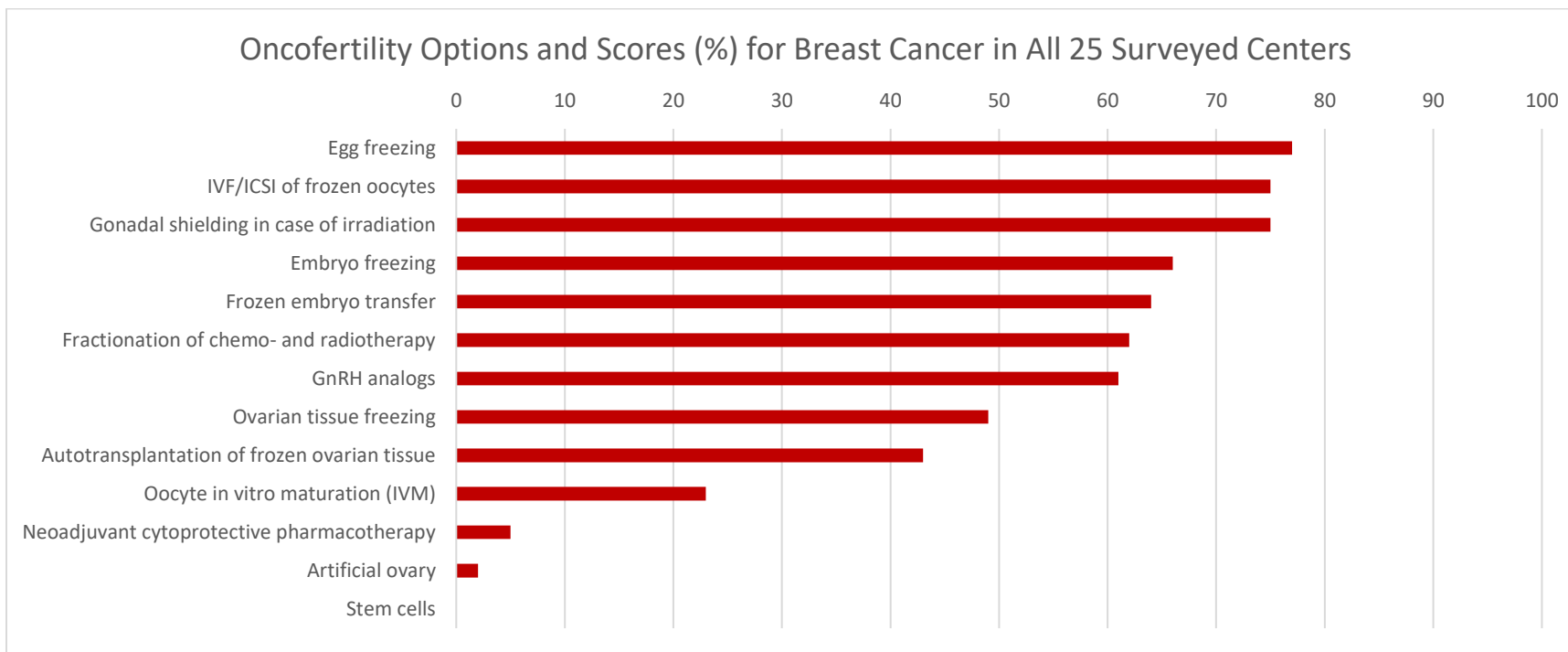


Table 5 & Figure 5: Oncofertility Options and Scores (%) for Blood Cancer in All 25 Surveyed Centers

Oncofertility Center	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	Total Actual Points	Oncofertility Score (%)	
Available fertility preservation options for female patients																												
- Embryo freezing	Yes (++++)	Yes (+++)	Yes (+++)	Yes (+++)	No	Yes (++++)	Yes (++)	Yes (+)	Yes (++)	Yes (++)	Yes (++)	Yes (+)	Yes (++)	Yes (++)	Yes (++)	Yes (+)	No	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	1450	58
- Egg freezing	Yes (++++)	Yes (++)	Yes (+++)	Yes (+++)	Yes (++++)	Yes (++++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (+)	Yes (++)	Yes (++)	Yes (++)	Yes (+)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	1700	68
- Ovarian tissue freezing	Yes (++)	Yes (+)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (+)	No	Yes (++)	Yes (+)	Yes (++)	Yes (++)	Yes (++)	No	Yes (++)	Yes (++)	Yes (++)	No	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	1425	57
- Oophorectomy in case of pelvic irradiation	Yes (++)	Yes (++)	Yes (+)	No	Yes (++)	Yes (+)	Yes (+)	Yes (++)	Yes (++)	Yes (++)	Yes (+)	Yes (+)	Yes (+)	Yes (++)	Yes (++)	Yes (+)	Yes (+)	Yes (+)	Yes (+)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	1150	46
- Oocyte in vitro maturation (IVM)	Yes (++)	Yes (+)	Yes (+)	Yes (++)	No	Yes (++)	No	No	Yes (+)	Yes (+)	No	No	Yes (+)	Yes (+)	No	Yes (+)	Yes (++)	No	No	Yes (+)	Yes (++)	Yes (+)	No	No	Yes (++)	575	23	
- Artificial ovary	No*	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No*	No	No	Yes (+)	Yes (+)	No	No	50	2
Available fertility preservation options for male patients																												
- Sperm freezing	Yes (++++)	Yes (++++)	Yes (++++)	Yes (++++)	Yes (++++)	Yes (++++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	2075	83
- Testicular tissue freezing	Yes (++)	Yes (+)	Yes (+)	No	No	Yes (++++)	Yes (+)	No	No	Yes (+)	Yes (++)	Yes (+)	Yes (+)	No	Yes (++)	Yes (+)	Yes (++)	Yes (+)	Yes (+)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	950	38
- In vitro spermatogenesis	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No*	No	Yes (+)	No	Yes (+)	No	No	50	2
Available fertility preservation options for both female and male patients																												
- GnRH analogs	Yes (++)	Yes (++)	Yes (+)	No	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	1425	57
- Gonadal shielding in case of irradiation	Yes (++)	Yes (++)	Yes (++)	No	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	1875	75
- Fractionation of chemo- and radiotherapy	Yes (++)	Yes (++)	Yes (++)	No	No	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	1550	62
- Neoadjuvant cytoprotective pharmacotherapy	No	No	No	No	No	No	No	No	Yes (+)	No	No	No	No	No	No	Yes (++)	Yes (++)	No	No	No	No	No	No	Yes (++)	No	No	175	7
- Stem cells reproductive technology	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	0	0

(++++ Available and always used for cancer patients, (+++) Available and commonly used for cancer patients, (++) Available but occasionally used for cancer patients, (+) Available but rarely used or only used in research setting for cancer patients, (No) Not available, (No*) Not available because it is still in the preclinical research stage.

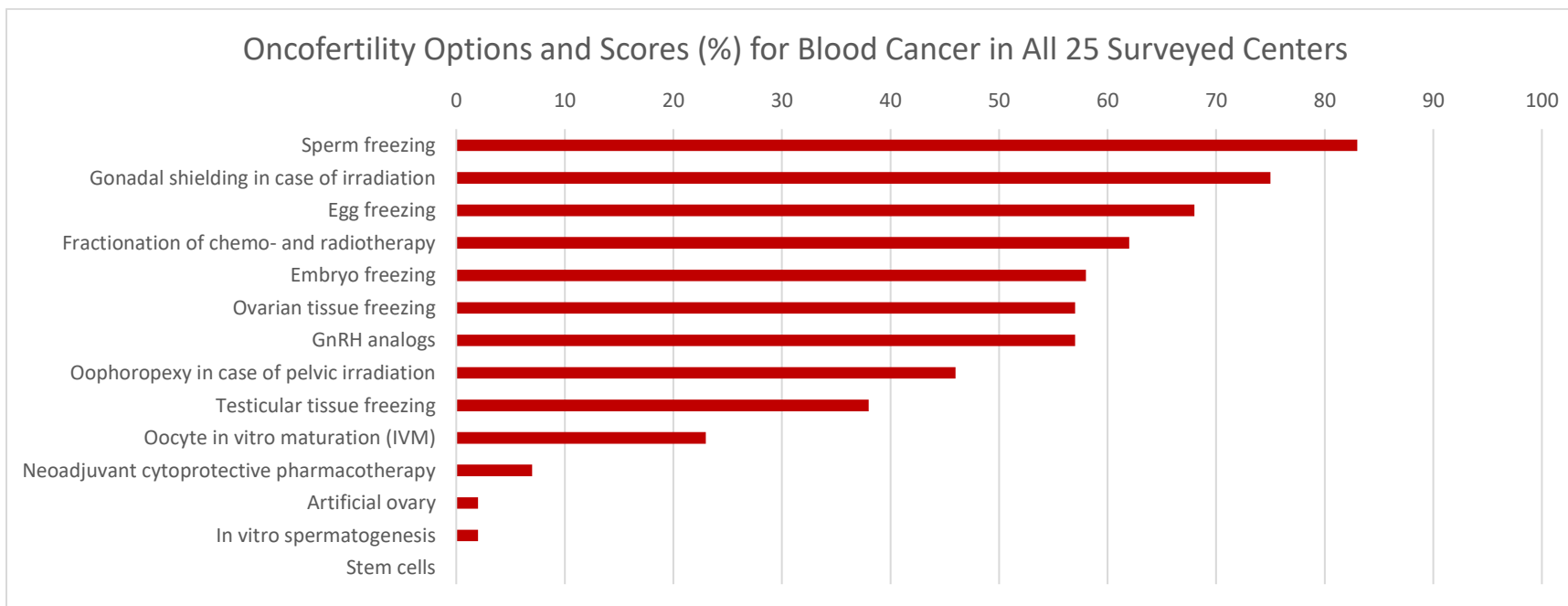


Table 6: Suggested best practice models: Plausible fertility preservation and restoration strategies for cancer patients

Cancer Patients	Before anticancer therapy (Fertility Preservation)	During anticancer therapy (Fertility Preservation)	After anticancer therapy (Fertility Restoration)
<p>Childhood Cancer (♀ & ♂)</p> <p>Leukemias, central nervous system cancers, lymphoma and sarcomas</p>	<ul style="list-style-type: none"> - Freezing of gonadal tissue - In vitro maturation and vitrification of gametes (promising in research but not yet clinically proven in children) - Oophorectomy in case of female pelvic radiation - Artificial gonads technology (promising in research but not yet clinically proven) 	<ul style="list-style-type: none"> - Gonadal shielding - Fractionation of chemo- and radiotherapy - GnRH analogs in case of old child (widely debated) - Neoadjuvant cytoprotective pharmacotherapy (promising in research but not yet clinically proven) 	<ul style="list-style-type: none"> - IVF/ICSI of frozen gametes - Autotransplantation of frozen gonadal tissue (should be utilized with caution in leukemia) - Stem cells (promising in research but not yet clinically proven)
<p>Breast Cancer (♀)</p> <p>Patients with or without BRCA mutations</p>	<ul style="list-style-type: none"> - Egg freezing - Embryo freezing - Ovarian tissue freezing - In vitro maturation (IVM) of oocytes and vitrification - Artificial ovary technology (promising in research but not yet clinically proven) 	<ul style="list-style-type: none"> - GnRH analogs - Fractionation of chemo- and radiotherapy - Gonadal shielding - Neoadjuvant cytoprotective pharmacotherapy (promising in research but not yet clinically proven) 	<ul style="list-style-type: none"> - Intrauterine transfer of frozen embryo - IVF/ICSI of frozen oocytes - Autotransplantation of frozen ovarian tissue (should be utilized with caution in BRCA mutations) - Stem cells (promising in research but not yet clinically proven)
<p>Blood Cancer (♀ & ♂)</p> <p>Leukemia (ALL, AML), and Lymphoma (NHL, HL)</p>	<ul style="list-style-type: none"> - Freezing of gametes (when possible) - Freezing of gonadal tissue - In vitro maturation and vitrification of gametes - Oophorectomy in case of female pelvic radiation - Artificial gonads technology (promising in research but not yet clinically proven) 	<ul style="list-style-type: none"> - GnRH analogs (widely debated) - Gonadal shielding - Fractionation of chemo- and radiotherapy - Neoadjuvant cytoprotective pharmacotherapy (promising in research but not yet clinically proven) 	<ul style="list-style-type: none"> - Intrauterine transfer of frozen embryo - IVF/ICSI of frozen gametes - Autotransplantation of frozen gonadal tissue (should be utilized with caution in leukemia) - Stem cells (promising in research but not yet clinically proven)

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