

To: Hon Peter Dunne

Cc: Hon Dr Jonathan Coleman

Title: Advice that the use of cryopreserved ovarian tissue become an established procedure

A. EXECUTIVE SUMMARY

1. The purpose of this report is to advise you, pursuant to section 6 of the Human Assisted Reproductive Technology Act 2004 (HART Act), on the use of cryopreserved ovarian tissue to restore ovarian function. Section 6 relates to procedures or treatments that may be declared established procedures. The Advisory Committee on Assisted Reproductive Technology (ACART) recommends this procedure become an established procedure.
2. Section 35(1)(b)(ii) of the HART Act requires ACART to advise the Minister of Health whether a procedure should become an established procedure under the HART Order. ACART must first consult the public on the proposed advice (s.39).
3. Once ovarian tissue has been cryopreserved it may be thawed and transplanted into the woman from whom it was excised. The reimplanted tissue can restore ovarian function with the aim of restoring hormonal activity and hence the production of eggs suitable for fertilisation. The primary intention for restoring ovarian function is to provide a potential option for restoring a woman's fertility.
4. ACART has kept a watching brief on developments in the use of cryopreserved ovarian tissue. An estimated 200 women have received transplantation worldwide. There is growing awareness that in addition to providing gametes, transplanted tissue may serve an important endocrine function for the woman.
5. ACART has considered the known risks and benefits associated with the use of cryopreserved ovarian tissue to restore ovarian function. It has applied its risk acceptability framework to assess the acceptability of the risks, and considers that the risks fall within a level that is acceptable in New Zealand.
6. We consulted the public on our proposed advice during May and June 2016, and received submissions from 14 individuals and organisations. Submitters included one fertility services provider, Fertility New Zealand, the Northern Regional Fertility Service and a number of women's health advocacy groups.
7. Our main recommendation is that the procedure should become an established procedure and we note the implications of the recommendation and the need for monitoring. Our recommendations, rationales and the effects of our recommendations are presented in the table on the next page.
8. Our advice does not address the use of cryopreserved ovarian tissue in human reproductive research other than to comment on the status quo.

9. We have given a copy of the advice to the Ministry of Health, in case you decide to seek parallel advice. I am available to discuss the advice with you, if you wish. We plan to publish the advice on ACART's website early in 2017.

Table 1: Recommendations, rationale and effects

	ACART recommends	Rationale	Effects
1	Agree that the use of cryopreserved ovarian tissue, to restore ovarian function, should become an established procedure.	Currently not allowed but evidence now shows it is likely to be a safe and effective means of restoring ovarian function.	<ul style="list-style-type: none"> For the procedure to be declared an established procedure the HART Order would need to be amended. Currently between 20 and 30 girls and women cryopreserve their ovarian tissue per year. We anticipate this increasing to between 100 and 200 if the use of cryopreserved ovarian tissue becomes an established procedure though it will be some years before we have data on the number of girls and women using their tissue. Volumes and indications would need to be considered by the Ministry of Health.
2	Agree that the procedure be limited to the woman from whom the tissue was excised.	There are some clinical risks associated with transplanting the tissue to women other than the woman from whom the tissue was excised.	<ul style="list-style-type: none"> Only the woman from whom the tissue was excised could have the tissue reimplanted.
3	Agree that ACART work with the Ministry of Health on the wording that would be in the HART Order.	ACART does not want to expose women to risks that are greater than those in existing procedures. As the legislation will set out the legal requirements it is important ACART's recommendations are not overlooked.	<ul style="list-style-type: none"> ACART would work with the Ministry of Health on the wording for the HART Order.

B. RECOMMENDATIONS

10. We recommend that you:

- | | | |
|---|--|----------|
| 1 | agree that the use of cryopreserved ovarian tissue, to restore ovarian function, should become an established procedure | Yes / No |
| 2 | agree that the procedure be limited to the woman from whom the tissue was excised | Yes / No |
| 3 | agree that ACART work with the Ministry of Health on the wording that would be in the HART Order. | Yes / No |

Alison Douglass

**Chair
Advisory Committee on Assisted Reproductive Technology**

Minister's signature

Alison Douglass		Isabel Ross	
Chair, Advisory Committee on Assisted Reproductive Technology		Policy Analyst	
Phone	03 477 3488 (business)	Phone	04 816 2088
Cellphone		Cellphone	N/A

C. PURPOSE OF THIS REPORT

11. This report provides you with advice that the use of cryopreserved ovarian tissue, to restore ovarian function, should become an established procedure. By making the procedure an established procedure¹ ovarian tissue could be used by fertility clinics to restore a woman's own reproductive function without the need for ethical approval by the Ethics Committee on Assisted Reproductive Technology (ECART).

Recommendation for established procedure

12. One of ACART's roles under the HART Act is to advise you on aspects of, or issues arising out of, different kinds of assisted reproductive procedures (ARPs) or human reproductive research. The HART Act enables us to recommend that the use of cryopreserved ovarian tissue to restore ovarian function be one of the following:
- a. an established procedure
 - b. subject to ethical approval on a case-by-case basis (therefore requiring guidelines)
 - c. subject to a moratorium
 - d. prohibited.

¹ An established procedure is a procedure that is declared established under section 6 of the HART Act and that can be routinely undertaken by fertility clinics, without the clinic having to seek ethical approval from ECART on a case-by-case basis.

13. Section 35(1)(b)(ii) of the HART Act requires us to advise you following public consultation on the proposed advice (s.39). We have undertaken analysis as required under Section 6 of the HART Act.
14. In developing our advice we have taken into account:
 - the principles of the HART Act, including the health and wellbeing of women and children; the right of donor offspring to access information about their genetic origins; and the needs, values and beliefs of Māori
 - other common ethical principles, including autonomy, wellbeing of families, and transparency
 - wider public policy considerations, including the Code of Health and Disability Services Consumers' Rights (the Code)
 - feedback from public consultation in 2016
 - evidence and information from local and international sources.

D. STRUCTURE OF THIS REPORT

15. Our report discusses:
 - E. cryopreserved ovarian tissue could be used to restore ovarian function
 - F. the current status of using cryopreserved ovarian tissue in New Zealand
 - G. our consultation process
 - H. the scope and focus of our advice
 - I. the known risks and benefits of using cryopreserved ovarian tissue to restore ovarian function
 - J. acceptability of the risks of using cryopreserved ovarian tissue to restore ovarian function
 - K. ethical analysis
 - L. our advice and recommendations
 - M. next stepsAppendices:
 - list of submitters
 - summary of submissions.Glossary

E. CRYOPRESERVED OVARIAN TISSUE COULD BE USED TO RESTORE OVARIAN FUNCTION

Ovarian tissue can be cryopreserved

16. Ovarian tissue cryopreservation is a technology that has been developed for preserving reproductive potential in pre-pubescent girls and women with medical conditions such as

cancer. Pre-pubescent girls or women who undergo cancer treatments, such as chemotherapy or radiotherapy, may experience adverse consequences to their fertility, for example early onset of menopause or gonadotoxic effects reducing their fertility.

17. Ovarian tissue cryopreservation has been used internationally since the late 1990s. Currently, the ovarian tissue cryopreservation procedure is most commonly used in young girls (ie. pre-pubescent) and women facing the possible loss of their fertility from cancer treatment.
18. Cryopreservation is sometimes also used by pre-pubescent girls and women with a genetic disease, or non-malignant disease where treatment may adversely affect their fertility.

The tissue can be used to restore ovarian function

19. Once ovarian tissue has been cryopreserved it may be thawed and transplanted into the woman from whom it was excised. The reimplantation of the tissue can restore ovarian function. The main aim of restoring the ovarian function is to restore hormonal activity and production of eggs suitable for fertilisation, and the primary intention is to provide a potential option for restoring a woman's fertility.
20. In addition to restoring hormonal activity and producing eggs, other physiological processes are interrelated with ovarian function. For example, preventing early onset of osteoporosis and cardiovascular disease in young women, enabling pre-pubescent girls to undergo puberty at the appropriate age, preventing early onset menopause, and reducing hormone therapies following gonadotoxic treatment.
21. Ovarian function has been restored following transplantation of the tissue to the ovaries and/or transplantation to a site outside of the ovaries.
22. In most European countries, cryopreserved ovarian tissue must only be used by the woman from whom it originated and it is illegal to treat another person with the tissue.
23. It is estimated that internationally more than 10,000 women have stored cryopreserved ovarian tissue for fertility purposes. It is also estimated that 200 women have received transplantation worldwide. There is growing awareness that, in addition to providing gametes, transplanted tissue may serve an important endocrine function for the woman.
24. A 2016 study found that in 49 women with a follow up more than one year after transplantation, the ovaries were active in 67 percent of cases and the pregnancy and delivery rates were 33 percent and 25 percent, respectively.²

ACART has been monitoring the use of ovarian tissue

25. ACART has kept a watching brief on developments in the use of cryopreserved ovarian tissue. In 2010 the Committee commissioned a technical report to review the use of cryopreserved ovarian tissue and obtain further information.³ ACART at the time concluded that the limited evidence did not support further work to enable the use of the tissue in New Zealand.

² Van der Ven H, et al. 2016. Ninety-five orthotopic transplantations in 74 women of ovarian tissue after cytotoxic treatment in a fertility preservation network: tissue activity, pregnancy and delivery rates. *Human Reproduction*. 2016 Sept;31(9):2031-41. doi: 10.1093/humrep/dew165. Epub 2016 Jul 4.

³ Anderson R. 2010. Report on the Current Status of the Use of Cryopreserved Ovarian Tissue.: <www.acart.health.govt.nz/report-current-status-use-cryopreserved-ovarian-tissue-2010>

26. In 2014 ACART commissioned a further technical report “Report on the current status of the use of cryopreserved ovarian and testicular tissue for the Advisory Committee on Assisted Reproductive Technology of New Zealand” by Professor Claus Andersen of Oslo University.⁴ Based on the report’s findings, ACART agreed to develop advice to the Minister that the use of cryopreserved ovarian tissue to restore ovarian function should become an established procedure.

F. THE CURRENT STATUS OF USING CRYOPRESERVED OVARIAN TISSUE IN NEW ZEALAND

Cryopreservation is permitted

27. As part of implementing the HART Act, and before ACART was established, an independent committee, the Advisory Group on Assisted Reproductive Technologies (the Advisory Group) advised the Director-General of Health on the risks and benefits of various assisted reproductive technologies. In 2005, the Advisory Group recommended that ovarian tissue cryopreservation become an established procedure.
28. The Advisory Group considered that the risks of ovarian tissue cryopreservation were confined to those associated with the surgery to retrieve the tissue, and were therefore minimal. The procedure offered pre-pubescent girls and women about to undergo cancer treatment the opportunity to store their reproductive potential.
29. The Advisory Group’s recommendation was accepted and in 2005 ovarian tissue cryopreservation was declared an established procedure under the HART Order 2005. The established procedure includes:
- a. collecting and preparing ovarian tissue for freezing
 - b. freezing and storing the tissue
 - c. thawing and discarding the tissue.

Reimplantation is not permitted

30. In its 2005 report, the Advisory Group did not recommend that the subsequent use of cryopreserved ovarian tissue should become an established procedure. The Advisory Group advised that the safety of such use was in doubt due to the novelty of the procedure and limited evidence available at the time.
31. An effect of excluding the use of cryopreserved ovarian tissue as an established procedure is ECART must approve the use of the tissue as an assisted reproductive technology. To date, ACART has not issued any guidelines or advice on the use of cryopreserved ovarian tissue, therefore ECART has not been able to consider any applications on the use of cryopreserved ovarian tissue.
32. As a result, women in New Zealand may cryopreserve and store ovarian tissue, but are unable to use it in New Zealand. In 2012 provider brought to ACART’s attention that women are going overseas to use their tissue.

⁴ Professor Andersen is a Professor of Human Reproductive Physiology at the University of Copenhagen. He was commissioned to produce the technical report due to his significant and recent expertise in both ovarian and testicular cryopreserved tissue, including safety and outcomes. He is a leading fertility treatment clinician and has headed the Danish programme on fertility preservation since it began in 1999.

How assisted reproduction is regulated in New Zealand

33. New Zealand's requirements for assisted reproduction are set out in:

- the HART Act and the HART Order
- the Code of Health and Disability Services Consumers' Rights
- guidelines issued by ACART to ECART
- the Fertility Services Standard.

The HART Act

34. The HART Act is the principal law regulating human assisted reproductive technology and human reproductive research in New Zealand. The HART Act requires ACART to advise the Minister of Health on a number of matters related to assisted reproduction. This advice must not be inconsistent with the Code.

The HART Order

35. The HART Order lists the established procedures and the exceptions to those procedures. The HART Order specifies the collection, storage and disposal of ovarian tissue as established procedures.

The Code of Health and Disability Services Consumers' Rights

36. Any medical procedure a person undergoes is also subject to the Code. The Code extends to any person or organisation providing or receiving health and disability services in New Zealand. Rights 5, 6 and 7 of the Code give every consumer the right to effective communication, to be fully informed, to make an informed choice and to give informed consent. Right 7 also gives every consumer the right to make decisions about what happens to their body parts or bodily substances removed or obtained in the course of a health care procedure.

37. While the Code does not address all matters of informed consent for assisted reproductive technology, any regulations or guidelines must be consistent with the Code.⁵

Guidelines issued by ACART

38. None of the guidelines issued by ACART apply to the collection, storage, use of or disposal of ovarian tissue. The guidelines are for ARPs that need to be considered by ECART. In this advice, ACART is not proposing that the procedure would require ethical approval from ECART.

The Fertility Services Standard

39. Providers of fertility services in New Zealand must operate in accordance with the Fertility Services Standard 2007 (the Standard), which sets out requirements for the safety and quality of fertility services in New Zealand. The Standard is a form of regulation issued under the Health and Disability Services (Safety) Act 2001. Providers are audited and certified against the Standard, which is administered by the Ministry of Health.

Informed consent

40. The use of cryopreserved ovarian tissue to restore ovarian function would need to comply

⁵ HART Act s.76(1)(a)(i).

with the usual requirements for informed consent.

41. A well-established body of law and practice concerning informed consent for medical procedures upholds the principle that autonomous individuals have the right to make decisions about procedures carried out on them.
42. Informed consent is addressed in s.4 of the HART Act (Principles), which provides:

(d) . . . no assisted reproductive procedure should be performed on an individual and no human reproductive research should be conducted on an individual unless the individual has made an informed choice and given informed consent.
43. When carrying out any medical procedure, providers must ensure that consumers⁶ receive information about all important aspects of their procedures. Appropriate consent forms for the procedure are required, and providers must have clear policies and procedures to obtain informed consent from consumers.

G. OUR CONSULTATION PROCESS

44. On 21 April 2016, we advised you about our intended public consultation on our proposed advice to you about the use of the tissue, giving you a copy of the consultation document.
45. We consulted the public from 9 May to 4 July 2016. We received written submissions from 14 individuals and organisations including one fertility services provider, Fertility New Zealand (a consumer group), the Bioethics Centre (University of Otago), and a number of women's health advocacy groups. These submitters are those we would normally expect to hear from when consulting on fertility matters.
46. In addition to receiving written submissions, we held three meetings—one with staff members from a fertility services provider (Fertility Associates), one with Fertility New Zealand and the third with the Northern Regional Fertility Service.
47. We published the meeting notes and submissions on our website.
48. Overall, submitters supported our proposal. Submitters raised a number of matters, many of which were addressed in the consultation document. Our recommendations and advice to you take their comments into account. A list of submitters and interviewees is included as **Appendix 1**. A summary of submissions is included as **Appendix 2**.

H. THE SCOPE AND FOCUS OF OUR ADVICE

In scope

49. Our advice focuses on the use of cryopreserved ovarian tissue by the woman from whom the tissue was excised, for her own treatment, to restore ovarian function.

Restoring ovarian function

50. The aim of restoring ovarian function is to restore hormonal activity and production of eggs suitable for fertilisation. The primary intention for restoring ovarian function is to provide a

⁶ In this document we use the word “consumer” in relation to ART in accord with the definition in the Glossary of the Fertility Services Standard: “A user or participant in the service, including client, patient, gamete or embryo donor. Where appropriate this may include the family/whānau or other representatives.”

potential option for restoring a woman's fertility. In addition to restoring hormonal activity and producing eggs, other physiological processes are interrelated with ovarian function. For example, preventing early onset of osteoporosis and cardiovascular disease in young women, enabling pre-pubescent girls to undergo puberty at the appropriate age, preventing early onset menopause, and reducing hormone therapies following gonadotoxic treatment.

Out of scope

51. The use of frozen eggs and embryos is out of scope because these are already established procedures.

Donation of cryopreserved ovarian tissue to another individual

52. Based on current evidence, ACART does not support the transplantation of cryopreserved ovarian tissue to another individual. The potential benefits to be gained are outweighed by the uncertainties and potential risks to the recipient, including rejection of the transplanted tissue or the possible transfer of malignant cells and disease.
53. One submitter suggested allowing the transplantation of cryopreserved ovarian tissue between identical twins. ACART is not proposing this. The incidence of true identical twins is 4/1000 births and although there is no basic risk of tissue rejection two factors must be considered. First, if one twin develops cancer there is a very high risk of the second twin developing the same cancer, and second, as identical twins age there are more dissimilar epigenetic⁷ changes that take place in their DNA. There is very little information on the epigenetic changes and the influence on tissue transplant.

Use of cryopreserved ovarian tissue for research purposes

54. Women may decide not to use their cryopreserved ovarian tissue. In this case, they may choose to discard the tissue or donate it for research purposes. Where the subsequent use of stored ovarian tissue is intended for research, this falls within the scope of human reproductive research.⁸ ACART is not making any proposal about the use of surplus cryopreserved ovarian tissue in human reproductive research.
55. Any research proposal involving the use of donated ovarian tissue is covered by ACART's Guidelines for Research on Gametes and Non-Viable Embryos and will require ECART approval.⁹
56. This situation is comparable to individuals with stored eggs or sperm. If there are eggs or sperm that they do not intend to use, they have the option to donate them to others, discard them, or donate them to research. However, in light of the current evidence, ACART considers that cryopreserved ovarian tissue should not be donated to another individual for their therapeutic use.

⁷ 'Epigenetic' is defined as the inheritable changes in the pattern of gene expression cause by by factors other than changes in the DNA sequence.

⁸ Guidelines for Research on Gametes and Non-viable Embryos

⁹ Section 16, HART Act.

I. THE KNOWN RISKS AND BENEFITS OF USING CRYOPRESERVED OVARIAN TISSUE TO RESTORE OVARIAN FUNCTION

57. This section summarises the known risks and benefits associated with the use of cryopreserved ovarian tissue to restore ovarian function as discussed in the Anderson report “Report on the current status of the use of cryopreserved ovarian and testicular tissue for the Advisory Committee on Assisted Reproductive Technology of New Zealand.” The report was included in full as an Appendix to our consultation document.¹⁰

Benefits

58. The use of cryopreserved ovarian tissue to restore ovarian function has made significant advances. It is gaining ground as a valid method for restoring ovarian function, including restoring fertility. Benefits from the use of cryopreserved ovarian tissue include the following.
- It might be the only opportunity for some pre-pubescent girls and women undergoing gonadotoxic treatment to regain their ovarian function in the future.
 - It has the potential to increase quality of life following cancer treatment because fertility is valued by many girls and women.
 - Ovarian function can be restored in a woman for years at a time following reimplantation. One study reported this to be the case for 93% of patients with transplanted ovarian tissue. Another study in Denmark reported 18 women have so far regained, and continue to maintain, their ovarian function for at least seven to nine years. Restoring ovarian function includes the return of endocrine function, menstrual cycles, production of eggs suitable for fertilisation, and the possibility of pregnancy – both assisted and spontaneous.
 - For younger women, regaining their menstrual cycles is not only consistent with restoring their potential fertility, but it would help delay the onset of osteoporosis and other menopausal related conditions.
 - An ovarian tissue transplant can allow for a pregnancy to occur as long as the tissue remains active.
59. These benefits are only possible if the subsequent use of cryopreserved ovarian tissue is permitted.

Risks

Risks to the tissue

60. There are no reports that suggest the cryopreservation procedure itself imposes any change in the tissue that could lead to unwanted side effects upon transplantation. In addition, there are no reports on any potential risks to a woman’s health through the use of cryopreserved ovarian tissue in terms of oocytes and subsequent embryos being abnormal or less viable as compared to mature oocytes obtained in in vitro fertilisation (IVF) treatment.

¹⁰ Note that the technical report discussed the use of both cryopreserved ovarian and testicular tissue. In this proposed advice, ACART is only addressing the use of cryopreserved ovarian tissue. The use of cryopreserved testicular tissue will be considered in the future as a separate project when sufficient international studies have indicated the utility and safety of this tissue.

61. Currently, it is not possible to predict who will conceive, and who will not, from their transplanted tissue. This in turn has an effect on understanding pregnancy rates.
62. It is not yet possible to detect the number of follicles present without destroying the tissue in the process, nor is there solid information of the survival rate of follicles following transplantation to a woman. The chances of conception will depend in part on the age of the woman at the time of tissue cryopreservation. The older the woman, and therefore her ovarian tissue, the lower her chance of conceiving. In addition to age, the collected amount of tissue may correspond to the number of follicles that could develop, and affect the subsequent success of the treatment. There is a risk of damage to oocytes and follicles in the ovarian tissue during the cryopreservation procedure. Data suggest that women who undergo IVF treatment following transplantation of thawed tissue have lower rates in oocyte retrieval and embryo formation. Consequently, this has an effect on pregnancy rates.

Recipient health outcomes

Concerns with transplanting tissue excised at the time of disease

63. The safety of transplanting ovarian tissue that was excised when the patient had active disease is currently uncertain. There is a potential risk of malignant cells from the original cancer being present in the transplanted tissue.
64. There is currently no way to detect with certainty malignant cells in the ovarian tissue. Nor is it known whether there is any correlation between the development of malignant cells, following the transplantation of the excised tissue, and the number of malignant cells being transplanted.
65. To date, women with grafted ovarian tissue excised when the disease was active do not appear to experience relapse more often than cancer survivors without transplanted ovarian tissue do. In Denmark, 15 women who had their cryopreserved ovarian tissue transplanted more than five years ago have not shown signs of relapse following their transplantation.
66. Based on an estimated 200 cases of transplanted ovarian tissue worldwide, there have been six reported cases of a woman experiencing relapse following transplantation. Approximately 120 to 150 women had cancer at the time of tissue retrieval. The reported tumour relapses occurred at the original site of the tumour and there has been no indication of the ovarian tissue causing relapse. A recent study of 41 Danish women with transplanted ovarian tissue reported three cases of relapse but all cases appear to be unrelated to the transplant.¹¹
67. Several submitters raised concerns about the risk of using this procedure with pre-pubescent girls and women with leukaemia or haematological cancer. Leukaemia is usually considered the highest risk for relapse in connection with grafting because leukaemia is a disease of the blood, and malignant cells will almost invariably be present in the tissue. The literature recommends that collection of ovarian tissue from leukaemia patients occur when they are in complete remission. Recent research however, indicates that it is possible to dissect follicles from the ovarian tissue and mature them in-vitro thereby reducing the possible risk of malignant cell transfer.

¹¹ Jensen AK, Kristensen SG, Macklon KT, et al. 2015. Outcomes of transplantations of cryopreserved ovarian tissue to 41 women in Denmark. *Human Reproduction* 30: 2838–45.

68. ACART recommends caution when considering the transplantation of cryopreserved ovarian tissue for pre-pubescent girls and women with leukaemia or haematological cancer, in consultation with their oncologist.

Pregnancy-related risk

69. There are no known higher pregnancy-related risks for women with transplanted ovarian tissue. The only risk is that their cancer treatment may have affected their ability to carry a pregnancy, for example, damage from irradiation of the pelvis.

Surgical risk

70. There is a risk with any surgical procedure, for example, infection, bleeding, or damage to adjacent organs. However, there are no reported additional risks specific to the transplantation of thawed ovarian tissue.
71. The procedure of removing and replacing ovarian tissue is considered low risk, and no major complications from the operation have been reported.

Outcomes for children born following transplantation of cryopreserved ovarian tissue

72. Currently more than 35 children in eight countries have been born following transplantation of cryopreserved ovarian tissue. All babies born have been reported to be healthy. There is no information to suggest children born from cryopreserved ovarian tissue are any different from children conceived naturally.
73. At this time, there is no systematic reporting of pregnancy and birth data. Consequently, this limits the information available about pregnancy outcomes, and has implications for the monitoring and assessment of longer-term health outcomes on babies born following transplantation of cryopreserved ovarian tissue.
74. There are also no long term follow-up studies on these children and their development at present. It is too early to identify whether there are any adverse observations of a child's development or psychological outcomes, given the current ages of children born to date. There is insufficient information on resultant chromosomal abnormalities or congenital malformations or epigenetic disorders. Current evidence about children conceived from frozen eggs indicates the cryopreservation process has no deleterious effects on their health.
75. Any trans-generation effects on the children born from mothers who become pregnant following ovarian tissue transplantation are unknown.
76. ACART concludes that the evidence at this stage suggests that health outcomes for children born following the use of cryopreserved ovarian tissue are similar to those for children born as a result of other IVF procedures including frozen eggs. However, ACART recognises that further research is needed in this area.

Monitoring

77. The HART Act requires ACART to monitor the application and health outcomes of ARPs and established procedures, and also to monitor developments in human reproductive research.¹²
78. The lack of evidence discussed above highlights the need for ACART to keep a watching brief on international developments and reported findings in the use of cryopreserved ovarian tissue to restore ovarian function, particularly regarding outcomes for children born from the procedure and health outcomes for women.
79. ACART notes that it will be difficult to collect data on the outcomes for the use of cryopreserved ovarian tissue to restore ovarian function. For example, when collecting data on pregnancy rates, a pregnancy may occur spontaneously, independent of the graft itself; the graft may fail; the cryopreserved tissue may never be used; or there may be an extended length of time from the grafting until the woman becomes pregnant.

Submissions and response

80. Several submitters raised concerns about the newness of the procedure and absence of conclusive evidence and long-term results, noting that there needs to be careful monitoring. Submitters also said that the excision of tissue during active disease and treatment, and the effects of reimplantation, need to be monitored.
81. ACART agrees that monitoring is crucial. Doing so will be part of standard practice.
82. Notwithstanding the difficulty of data collection, ACART would support the establishment of an international database to monitor both cryopreserved ovarian tissue transplants and outcomes for children born from transplanted tissue. One submitter, a fertility clinic, wrote that it is establishing a database with Australian clinics; these data will be analysed and published.

J. ACCEPTABILITY OF THE RISKS OF USING CRYOPRESERVED OVARIAN TISSUE TO RESTORE OVARIAN FUNCTION

83. This section presents ACART's analysis of the acceptability of the risks associated with the use of cryopreserved ovarian tissue to restore ovarian function.
84. ACART has applied its risk acceptability framework to consider and assess the acceptability of the risks associated with the use of cryopreserved ovarian tissue to restore ovarian function (see attached **Appendix 3**).
85. As discussed in section I of this document, ACART has identified very few known health risks associated specifically with the use of cryopreserved ovarian tissue to restore ovarian function. ACART's analysis indicates that these risks fall within a level that is acceptable in New Zealand.

Indicators of acceptability

86. There are very few known risks in the use of cryopreserved ovarian tissue that are similar to those of other, more common, assisted reproductive technologies.

¹² Section 35(2) HART Act 2004.

87. ACART's assessment of the acceptability of the risks includes an examination of:
- the international acceptability of the procedure
 - the potential demand for the use of cryopreserved ovarian tissue in New Zealand
 - who should make decisions about the use of the procedure
 - risk reduction and management
 - the benefits.

International acceptability of the procedure

88. ACART considers the increasing uptake of the procedure in other countries as an indication of a worldwide acceptability of the risks associated with the technology. Twenty-six countries are currently reported to use cryopreserved ovarian tissue.¹³ In particular, ACART notes that the regulatory frameworks for assisted reproduction in Australia and the United Kingdom allow for the transplantation of cryopreserved ovarian tissue.
89. Some countries require ethical approval of the procedure, but no country has banned the procedure except for Bulgaria, where there is a moratorium until formal regulations have been approved.
90. Worldwide, more than 10,000 women have had ovarian tissue cryopreserved, and of these an estimated 200 women have received a subsequent ovarian tissue transplant. Recent reports indicate that more than 35 babies worldwide have been born following the transplantation of cryopreserved ovarian tissue.¹⁴
91. The uptake for ovarian tissue cryopreservation and subsequent transplantation is significantly lower than other assisted reproductive technologies used for fertility preservation. The first choice for fertility preservation of cancer patients is egg freezing when there is enough time to undergo egg collection before beginning cancer treatment.¹⁵

Potential demand in New Zealand

92. Fertility preservation is rapidly becoming an integral part of treatment for cancer patients, particularly as survival rates for cancer increase. ACART recognises that ovarian tissue cryopreservation as a method of fertility preservation will increase. It therefore follows that there will be an increasing demand for women to be able to take advantage of their stored tissue in order to try and have children. In 2015, a New Zealand fertility clinic reported having ovarian tissue samples stored for 67 women.
93. At present, women in New Zealand who wish to have their cryopreserved ovarian tissue transplanted need to travel overseas, for example, to Australia. ACART considers it would be preferable for women to use this procedure in New Zealand because of the proximity to family, other support networks, clinical supervision and support.

¹³ Denmark, Norway, United Kingdom, Israel, Germany, Switzerland, Sweden, Finland, Holland, Belgium, France, Spain, Italy, United States, Austria, Australia, Japan, Portugal, Poland, Hungary, Singapore, South Africa, Vietnam, Russia, China, India.

¹⁴ Jensen AK, Kristensen SG, Macklon KT, et al. 2015. Outcomes of transplantations of cryopreserved ovarian tissue to 41 women in Denmark. *Human Reproduction* 30: 2838–45.

¹⁵ Kawamura K, Cheng Y, Sun Y, et al. 2015. Ovary transplantation: to activate or not to activate. *Human Reproduction* 30: 2457–60.

Who should make decisions about the use of the procedure

94. ACART's analysis is that the identified risks and ethical issues are acceptable, and should not require ethical oversight by ECART. ACART considers that the risks and ethical issues could be addressed in discussion between a patient and her clinician.
95. Section K of this document sets out a detailed ethical analysis of the procedure.

Risk reduction and management

96. There are some concerns about the use of cryopreserved ovarian tissue that was excised at the time of active disease. The risk of malignant cells from the original cancer being present in the transplanted tissue cannot be excluded, but is considered to be very low. To date, animal and primate studies suggest the development of malignant cells following the transplant of malignant cells may be considerably lower than anticipated and dependent on the number of malignant cells being transplanted. The number of women to date who have experienced relapse is reassuringly low, and the relapse is most likely unrelated to the ovarian tissue in these cases.
97. ACART has identified precautionary measures undertaken overseas to reduce the risk of transplanting malignant cells. One example is with leukaemia patients. Leukaemia is considered to have the highest risk of causing relapse in connection with grafting, and therefore ovarian tissue may only be collected from women with leukaemia when they are in complete remission. In Denmark, transplantation of cryopreserved ovarian tissue is not undertaken in leukaemia patients. Furthermore, transplanting tissue is usually considered only when a woman is well and has been disease-free for at least two years.
98. ACART is recommending caution when the procedure is used for pre-pubescent girls or women with leukaemia or haematological cancer, in consultation with their oncologist.
99. In light of this, ACART considers the risk of malignant cells being present in the transplanted tissue to be acceptable.

Benefits

100. Overall, ACART considers that the benefits associated with the use of cryopreserved ovarian tissue to restore ovarian function are significant and outweigh the risks.
101. The primary benefit associated with the use of cryopreserved ovarian tissue to restore ovarian function is no different to that of other assisted reproductive technologies such as IVF, or the use of frozen eggs; it is a potential opportunity for a woman to conceive and give birth to a child.
102. A distinguishing benefit of the use of cryopreserved ovarian tissue to restore ovarian function is that it may be the only opportunity for restoring ovarian function and fertility in women who have had potentially gonadotoxic cancer treatment. As ovarian tissue can be cryopreserved at short notice, it can be preferable to egg freezing if there is urgency to commence cancer treatment and may be the only opportunity for a woman to conceive and give birth.
103. Additional benefits include its potential to:
 - enable a pregnancy to occur as long as the ovarian tissue remains active
 - restore ovarian function in women, and this can deliver health benefits other than fertility

- establish ovarian function in pre-pubescent girls when they reach puberty.
104. These additional benefits make the risks associated with the technology more acceptable.

Effect of data uncertainty

105. In ACART's risk acceptability assessment, the following areas of uncertainty have been identified.
- There are no long term follow-up developmental studies of babies born from transplanted cryopreserved ovarian tissue currently available.
 - There is limited information and data on pregnancies and births following the transplantation of cryopreserved ovarian tissue.
 - The overall success rate of transplanted tissue is unknown, and will only be known once a large cohort of women have used their cryopreserved ovarian tissue.
 - There is a need for information on potential negative consequences or adverse health outcomes for pre-pubescent girls and women following transplantation.
 - The safety of the tissue, especially in connection with leukaemia and tumours originating in the ovary itself, remains unknown. There are no studies to date to confirm that transplanted tissue does not develop into malignancy later on.
 - Excluding the potential risk of malignant cells from the original cancer disease being present in the transplanted tissue, there is no information to suggest that the transplanted tissue should increase the risk of cancer or lead to adverse side effects.
106. ACART will continue to review international developments associated with the use of cryopreserved ovarian tissue to restore ovarian function.

Relevant principles of the HART Act

107. ACART's decision-making is guided by the principles of the HART Act, listed below.
- The health and wellbeing of children born as a result of the performance of an ARP or an established procedure should be an important consideration in all decisions about that procedure.
 - The human health, safety and dignity of present and future generations should be preserved and promoted.
 - Although all persons are affected by ARPs procedures and established procedures, women, more than men, are directly and significantly affected by their application, and the health and wellbeing of women must be protected in the use of these procedures.
 - No ARP should be performed on an individual, and no human reproductive research should be conducted on an individual, unless the individual has made an informed choice and given informed consent.
 - Donor offspring should be made aware of their genetic origins and be able to access information about those origins.
 - The needs, values and beliefs of Māori should be considered and treated with respect.
 - The different ethical, spiritual and cultural perspectives in society should be considered and treated with respect.

108. All of these principles are relevant to a risk-acceptability analysis.
109. ACART considers that the use of cryopreserved ovarian tissue to restore ovarian function is consistent with the purposes and principles of the HART Act.
110. In particular, ACART has considered the health and wellbeing of children born as a result of the use of cryopreserved tissue and considers that, at this stage, the evidence does not indicate there are any adverse implications for a child's development or psychological outcomes.
111. Allowing the use of cryopreserved ovarian tissue to restore ovarian function gives pre-pubescent girls and women who face gonadotoxic treatment another opportunity to preserve their fertility by having the opportunity to produce oocytes in their future, thereby protecting their health and wellbeing.

ACART's conclusion about the acceptability of the risks

112. ACART considers that the increasing use of cryopreserved ovarian tissue overseas indicates the international acceptability of the known risks associated with this procedure. This international acceptability supports ACART's analysis of the level of risk as acceptable in New Zealand. ACART also considers that the known risks, such as recipient or child health outcomes, do not justify the need for case-by-case ethical review by ECART, and could be addressed in discussions between a patient and her clinician.
113. ACART acknowledges that while there are known risks and areas of uncertainty, there are risk reduction measures to help ensure these remain at an acceptable level in New Zealand. ACART will maintain a watching brief for developments in the procedure to better understand areas of uncertainty. The literature will indicate clinical practices that may help reduce the risk of transplanting malignant cells into women.
114. ACART is of the opinion that while there are risks associated with the use of cryopreserved ovarian tissue to restore ovarian function (see section I) these fall within a level of risk that is acceptable in New Zealand.

K. ETHICAL ANALYSIS

115. ACART must identify and consider ethical issues that arise from assisted reproductive treatment. ACART is guided by its ethical framework,¹⁶ which incorporates principles of the HART Act and generally accepted ethical principles, to make these ethical deliberations.

Principles of the HART Act

116. ACART's ethical analysis is guided by the principles of the HART Act.¹⁷ Overall, ACART has not identified any ethical issues that are inconsistent with the health and wellbeing of children; human health, safety and dignity; donation and donor offspring; or the health and wellbeing of women. While recognising that there are unconfirmed implications and data uncertainties for the health and wellbeing of women and children born, ACART considers

¹⁶ Ethical framework for ACART (2012)

<<http://acart.health.govt.nz/publications-and-resources/acart-publications/ethical-framework-acart>>

¹⁷ Section 4 HART Act 2004.

that the use of cryopreserved ovarian tissue to restore ovarian function is consistent with the ethical principles of the HART Act.

Informed consent

117. The HART Act requires that no assisted reproductive procedure be performed on an individual unless the individual has made an informed choice and given informed consent. This requirement is supported by the Code of Health and Disability Services Consumers' Rights, and the Fertility Services Standard which sets out specific informed consent requirements for assisted reproductive technology.
118. Any woman seeking to use cryopreserved ovarian tissue to restore ovarian function must be provided with full information about the procedure to enable her to make an informed choice.
119. This procedure involves two stage consent, as informed consent is required both before tissue is excised, and before tissue is reimplanted. Obtaining this would be standard practice.
120. Individuals might be minors at the time of undergoing this procedure. In New Zealand, when children reach the age of 16 they have the right to consent to or decline medical treatment. In addition to parental consent, children under 16 who have capacity are entitled to make decisions about their care. Even when a child is considered to not yet have sufficient understanding to make their own decisions, attempts should be made to maximise their involvement in decisions about their care.
121. ACART is of the view that a woman seeking the procedure should be able to make an informed decision through discussions with her clinician. The clinician would explain the procedure, including the benefits and risks, and that there are areas of uncertainties associated with this procedure—for example, the limited evidence about health outcomes for children born following the transplantation of cryopreserved ovarian tissue. Other information such as the best transfer technique and the amount of tissue transplanted would be clinical decisions and vary from patient to patient.

Respect for the needs, values and beliefs of Māori

122. Principle 4(f) of the HART Act requires that the needs, values and beliefs of Māori should be considered and treated with respect. This does not mean that ACART supports the idea that a pan-Māori perspective exists. There is rarely one single viewpoint representative of Māori concerns, any more than there is a single religious viewpoint. Policy should reflect New Zealand's cultural diversity.
123. ACART acknowledges the primary significance of whakapapa and the effects on broader family networks associated with the use of assisted reproductive treatment. There may be concern that whakapapa could be disrupted through such treatment. In relation to the use of cryopreserved ovarian tissue to restore ovarian function, ACART notes this procedure may assist Māori women facing limited fertility treatment options, to both preserve and strengthen their whakapapa, because it offers an opportunity to have genetically related children.
124. Women must be able to maintain the mana of their cryopreserved ovarian tissue. In this context, ACART acknowledges the concepts of whakapapa, whanaungatanga and kaitiakitanga in relation to the storage and use of cryopreserved ovarian tissue. Regardless

of the length of time between collection, storage and subsequent use of the cryopreserved tissue, there must be sufficient time to discuss any cultural implications and the opportunity to address restoration of her ovarian function and fertility.

Ethical principles from ACART's ethical framework

125. These principles are consistent with and complementary to the principles of the HART Act. They include consideration of the welfare of those affected by the procedure, and the autonomy of those involved, altruism, social trust and responsibility, the special status of the embryo, justice and equality.

Welfare and autonomy

126. ACART's proposed advice, that the use of cryopreserved ovarian tissue to restore ovarian function become an established procedure, supports women's existing freedom to choose from the fertility preservation options available to them. ACART is of the view that women can consider the benefits and risks to decide whether this procedure is in their best therapeutic interests.

Justice and equality

127. It would be unfair to further limit the options for people who are unable to have a child on cultural or financial grounds.
128. While ACART's functions do not involve responsibility for the costs of reproduction, ACART acknowledges the submissions it received about equity matters. ACART acknowledges that there may be concerns about access to the technology in terms of costs restricting who may be able to access it. Costs would likely include ovarian tissue collection and freezing, storage of tissue and transplantation of thawed tissue. However, ACART considers that the issue of cost for this procedure is no different from the issue of cost and access to other assisted reproductive treatments.
129. Although funding and equitable access to procedures is not within the scope of this advice, and we did not address the matter in our consultation, it was mentioned by several submitters. We suggest that you ask the Ministry of Health to investigate this matter should you accept our advice that the use of cryopreserved ovarian tissue becomes an established procedure.
130. ACART considers that the use of cryopreserved ovarian tissue to restore ovarian function is suitable as a potential fertility preservation option for women. However, ACART recommends that the use of cryopreserved ovarian tissue be restricted to the woman from whom the tissue was excised for her own treatment. This position is taken in most European countries where this procedure is permissible.

ACART's conclusion about the ethics of the procedure

131. ACART is of the view that the ethical issues identified and considered do not justify restricting the use of cryopreserved ovarian tissue to restore ovarian function. The potential benefits to be gained outweigh the ethical issues identified.

L. OUR RECOMMENDATIONS

132. Our principle recommendation is that the procedure should become an established procedure. We note the implications of the recommendation and the need for monitoring. We also note the matter of the two stage nature of consenting, which was not specifically addressed in our consultation.

Recommendations 1 and 2

ACART recommends you agree that

- the use of cryopreserved ovarian tissue to restore ovarian function should become an established procedure
- the tissue can only be reimplanted into the woman from whom the tissue was excised.

Recommendation 3

ACART recommends you agree that

- ACART work with the Ministry of Health on the wording that will be in the HART Order.

133. If you agree, the decision may be given effect by amending the HART Order in Council 2005:
- a. Part 1 to include a statement that the thawed ovarian tissue can be grafted into the woman from whom it was excised
 - b. Part 2 to remove the exclusion of the use of ovarian tissue that has been cryopreserved.

M. NEXT STEPS

134. We have given a copy of the advice to the Ministry of Health in case you decide to seek parallel advice.
135. I am available to discuss the advice with you, if you wish.
136. We plan to publish the advice on ACART's website early in 2017.

APPENDIX 1

SUBMITTERS AND INTERVIEWEES

1. AWHC: Auckland Women's Health Council
2. Peart: Nicola Peart, Bioethics Centre
3. ECART: the Ethics Committee on Assisted Reproductive Technology
4. FWHC: Federation of Women's Health Councils Aotearoa – New Zealand
5. FA: Fertility Associates
6. FNZ: Fertility New Zealand
7. Forman: John Forman
8. France: John France
9. HSNZ: Humanist Society of New Zealand
10. Hunter: Sarah Hunter
11. MoH: Two individual submitters from the Ministry of Health
12. Nathaniel: The Nathaniel Centre: The New Zealand Catholic Bioethics Centre
13. NCWNZ: National Council of Women of New Zealand Te Kaunihera Wahine o Aotearoa
14. NRFS: Northern Regional Fertility Service
15. NZNO: New Zealand Nurses Organisation
16. Name withheld by request

Introduction

- ACART consulted the public in 2016 on its proposed advice to the Minister of Health about the use of cryopreserved ovarian tissue becoming an established procedure.
- The HART Act requires ACART to advise the Minister of Health on a range of matters relating to human assisted reproductive technology. Before giving the advice, ACART must give interested members of the public an opportunity to make submissions about the proposed advice.
- A discussion document including the draft advice was sent to a range of health professionals and other stakeholders identified as having an interest in this work. The discussion document was also put on ACART's website. This report summarises the feedback ACART received.
- ACART is very grateful to everyone who provided feedback. The information provided was extremely helpful for finalising ACART's advice to the Minister of Health.

Note:

- the responses have been summarised
- the only responses presented here are those that introduce ideas that were not presented in the discussion document
- when respondents have only agreed or disagreed those responses have been counted and noted.

Summary

Question/submission	Submitter
<p>Question 1 a Do you agree with ACART's assessment of the known risks and benefits to health associated with the use of cryopreserved ovarian tissue to restore ovarian function?</p>	
<p>Yes</p>	
FWHC believes the risks of future outcomes are yet to be confirmed and women must be clearly told this.	FWHC
Yes. The assessment is comprehensive and issues around monitoring the application have been identified. Monitoring must be consistent to detect any increases in relapses.	NCWNZ
<p>ACART summary</p> <ul style="list-style-type: none"> • Almost all submitters agreed with ACART's assessment, while those that did not comment on ACART's assessment commented on specific matters such as the legal status of the procedure, rather than the clinical or ethical nature of the procedure. • No submitters disagreed with ACART's assessment. • Two of the 16 submitters commented on the need to monitor the use of the procedure in the event that it is introduced. • One submitter noted the uncertainty about the long term outcomes of the procedure and said that women should be told about this uncertainty. The uncertainty about the procedure was mentioned by several submitters on several occasions. 	
<p>Question 1 b Are there any risks and/or benefits associated with the use of cryopreserved ovarian tissue to restore ovarian function that ACART has not identified or assessed?</p>	
<p>No</p>	
We trust that ACART will continue to monitor the situation and report on future developments as more evidence is published.	AWHC
This is still experimental treatment for which we have minimal longer term data. We must be careful not to tell people the procedure is guaranteed to work. There will always be a risk that the woman's expectations exceed the supporting evidence. Nevertheless, the procedure gives a prospect of restoration of ovarian function and we agree that women should not have to travel overseas to access this treatment procedure.	FWHC
<p>ACART summary</p> <ul style="list-style-type: none"> • Almost all submitters agreed with ACART's assessment, while those that did not comment on unidentified risks commented on specific matters such as the need for monitoring. • No submitters said that there were any risks ACART had not identified or assessed. • One submitter (the AWHC) again commented on the need to monitor the use of the procedure in the event that it is introduced. • One submitter noted that the treatment is experimental and there is no long term data yet. They said that, consequently, it is important not to promise women the treatment will be successful, and women should be told about this uncertainty. 	
<p>Question 2 a Do you agree with ACART's conclusion that the risks associated with the use of cryopreserved ovarian tissue to restore ovarian function fall within a level that is acceptable in New Zealand?</p>	
<p>Yes</p>	
I believe that with appropriate information about the risks to the women from whom the tissue was taken that the risk benefit balance is appropriate.	Peart

Question/submission	Submitter
ACART's observation that the risks and ethical issues could be addressed in discussion between a patient and her clinician would be very appropriate.	FA: written submission
<p>ACART summary</p> <ul style="list-style-type: none"> • Almost all submitters agreed with ACART's assessment, while those that did not comment on risk acceptability commented on specific matters such as the need for informed consent. • No submitters said that the level of risk was unacceptable. • Two submitters commented on the need to discuss the risks with the patient. 	
No	
While the FWHC agrees that, in most cases, the procedure will be acceptable they have concerns for women who have had blood-borne diseases such as leukaemia, or lymphatic cancers, even if the woman is deemed to be in remission. The reintroduction of the tissue might reintroduce the disease. For women with these cancers, the risk/benefit ratio is not acceptable. They note that Denmark does not allow this procedure for women with these cancers, and they believe NZ should take this precaution.	FWHC
<p>ACART summary</p> <ul style="list-style-type: none"> • One submitter said that the level of risk was unacceptable for women who have had blood-borne diseases such as leukaemia, or lymphatic cancers, even if the woman is deemed to be in remission. The submitter suggested that NZ should not allow the procedure for women with those diseases. 	
<p>Question 2 b Do you have any other comments?</p>	
The AWHC emphasises the importance of women being provided with good information to enable them to give informed consent to the use of their cryopreserved ovarian tissue. This means the risks must not be downplayed and the potential benefits oversold.	AWHC
We would like to see 'risk reduction measures' identified and considered with a view to promoting consistency of practice according to the highest possible standards throughout New Zealand. We believe this should be part of the ongoing monitoring brief taken on by ACART (n. 102, p. 23). We would like to see serious consideration given to the suggestion that one laboratory carry out the actual cryopreservation procedure for the whole country in order to maximise the necessary expertise and experience required (see D.23, p. 59).	Nathaniel
We support the recommendation that patients with leukaemia should only undergo ovarian tissue freezing during remission.	FA: Written submission
<p>ACART summary</p> <ul style="list-style-type: none"> • One submitter commented on the need for women to receive suitable information so they can make informed choices. • Another submitter suggested having only one laboratory freezing the tissue to ensure expertise is developed and available. • A clinic supported the idea that, for women with leukaemia, tissue should be stored but not yet used. • All three of these comments were also made by other submitters in other parts of the feedback. 	
<p>Question 3 a Has ACART identified all the relevant areas to monitor the use of cryopreserved ovarian tissue to restore ovarian function?</p>	
Yes	
Ongoing monitoring will be required to determine whether donation of cryopreserved tissue to other women should be permitted.	Peart

Question/submission	Submitter
I assume the health outcomes for the women concerned include any arising from the surgical procedures. ACART presumably will establish a system for monitoring the outcomes of the use of the procedure in New Zealand.	France
It is important that an accurate register is kept so that outcomes may be clearly identified. Areas to monitor should include method of freezing, method of tissue transfer, whether assisted reproductive technology was subsequently used, and long term health of women and children.	FA: Written submission
<p>ACART summary</p> <ul style="list-style-type: none"> • Nine submitters commented on the need to monitor. • Some said the monitoring is needed so we can: <ul style="list-style-type: none"> ○ identify the optimal methods of freezing and transferring the tissue and whether ART was subsequently used ○ determine whether the donation of tissue (to other women) might become acceptable ○ understand the long term outcomes for women and offspring. 	
No	
<p>The FWHC supports the monitoring of outcomes, but states that New Zealand women must be allowed to decide whether their data are sent overseas and their consent for this should be recorded. Further, those women should not be denied access to treatment on the basis of any refusal to have their data shared internationally. Data sharing will also affect the offspring.</p> <p>The FWHC asks how the situation is managed at present where NZ women undergo the re-implantation of cryopreserved ovarian tissue procedure in other countries, i.e. where is their data held and what controls do they exercise over who it is shared with?</p>	FWHC
<p>ACART summary</p> <ul style="list-style-type: none"> • One submitter stated that women must be given the choice of sharing their data, and that of their offspring, in an international database. • The same submitter also asked how NZ women are monitored at present if they have ovarian tissue reimplanted overseas. 	
<p>Question 3 b Are there any other areas ACART should monitor?</p>	
Yes	
<p>It is unclear whether ACART will continue to monitor the situation where transplanting tissue is excised at the time of active disease. We believe this is an area which should continue to be monitored to inform future use.</p> <p>We also strongly recommend a New Zealand database is established to assist with ongoing monitoring.</p>	AWHC
<p>Stage and site of cancer and any associated treatments. This may wellFWHC believes this may indicate a cut-off point for whether 'reinstatement for cryopreserved tissue' is a recommended intervention for certain types of cases in future.</p>	FWHC
<p>We would like ACART (or another health-related body) to collect and report on specific data on treatment outcomes within New Zealand including, as far as is possible, future fertility rates (even if it will be impossible to determine if subsequent pregnancies derive from the endogenous stores of follicles or from the transplanted tissue: see C.20.4.2, p. 55).</p>	Nathaniel
<p>We are participating in setting up an international oncofertility database and guidelines with Australian colleagues.</p>	FA: Written submission

Question/submission	Submitter
We believe it is most important that monitoring for misuse (e.g. transfer of tissue to other women) must also be carefully monitored. We consider the risks around the eventual disposal of stored tissue need to be carefully considered and carefully monitored.	NCWNZ
<p>ACART summary</p> <ul style="list-style-type: none"> One submitter stated that it would be helpful to monitor the extent to which tissue is excised when disease is active, and related to that, two submitters stated that it would be helpful to monitor the stage and site of cancers and their treatment. One submitter, a clinic, noted it is establishing an international database with Australian colleagues. One submitter said the potential misuse of the tissue should be monitored. 	
No	
<p>ACART summary</p> <ul style="list-style-type: none"> Two submitters said nothing needs to be monitored other than the matters discussed in the consultation document. 	
<p>Question 4 a Has ACART identified all the ethical issues relevant to the use of cryopreserved ovarian tissue to restore ovarian function?</p>	
Yes	
The submitters agreed and said the procedure should be permitted provided fully informed consent is given	Hunter. Peart.
While the values and beliefs of Maori have been recognised, it is essential that other major ethnic/religious values and beliefs also be considered – e.g. Muslim, Asian and Pacific women.	NCWNZ
<p>ACART summary</p> <ul style="list-style-type: none"> Two submitters said all ethical issues have been addressed and they stressed the importance of women giving their fully informed consent. One submitter said the beliefs of other ethnic and religious groups need to be considered. 	
No	
Ovarian tissue freezing is not publicly funded, and that women seeking fertility preservation after diagnosis will be referred to private fertility clinics. Our preference is that the storage of tissue be handled within the public health system.	Nathaniel
<p>ACART summary</p> <ul style="list-style-type: none"> One submitter said the absence of public funding is an ethical matter as it affects the equity of access to the treatment. 	
<p>Question 4 b Do you agree with ACART's ethical analysis that there are no significant ethical issues associated with the use of cryopreserved ovarian tissue to restore ovarian function?</p>	
Yes	
Use of cryopreserved ovarian tissue for restoration of ovarian function, provided fully informed consent is given, holds no greater ethical concern than other established assisted reproductive technologies.	Hunter. Peart.
The processes associated with providing full information and gaining consent will be particularly important to consider in cases where children are involved and where there is the potential for disagreement between parents/guardians and a child/young person or between parents/guardians of a child/young person regarding the necessity (or even affordability) of such treatment. The implications for future fertility decisions are permanent and of such a serious nature that thought should be given to providing independent counselling in these cases.	Nathaniel

Question/submission	Submitter
Preventing the use of cryopreserved ovarian tissue to restore ovarian function would create significant ethical issues.	HSNZ
<p>ACART summary</p> <ul style="list-style-type: none"> • Three submitters said all ethical issues have been addressed and they stressed the importance of women giving their fully informed consent. • One submitter noted that parties might disagree over whether a girl/woman should use the procedure. The submitter said independent counselling could be necessary for such situations. • One submitter said it could be unethical to <i>prevent</i> the use of the procedure. 	
No	
FWHC believes ‘treatment creep’ could occur if the procedure is introduced, for example as a backstop option against conditions such as osteoporosis. We do not support this potential future use option.	FWHC
<p>ACART summary</p> <ul style="list-style-type: none"> • One submitter cited treatment creep as an ethical issue as it may lead to unsupported future use purposes. 	
<p>Question 5 a Do you agree that the use of cryopreserved ovarian tissue to restore ovarian function should become an established procedure?</p>	
Yes	
Yes, provided the women are fully informed, their autonomy should be respected.	Peart
Given that the risks are primarily personal and clinical, we see no useful role for ethical oversight: that oversight would add time and expense to the process for no clear benefit.	AWHC
There would be a significant benefit from (potentially) restoring endocrine function for a woman’s general physical wellbeing; restoring fertility potential is another layer of benefit. Only the woman concerned will be able to answer that QALY matter.	FWHC
The Consultation Document notes that the benefits of restoring ovarian function are much wider than the restoration of fertility. Consequently, as the procedure becomes more common worldwide, and presuming there are no significant negative outcomes discovered, we believe there will be a good case for regarding the removal, storage and transplantation of ovarian tissue as a standard part of the ‘treatment’ of all women undergoing cancer treatments that are potentially gonadotoxic (see also our comments in Question 7 below).	Nathaniel
Yes, so long as monitoring is in place and rigorously applied.	NCWNZ
<p>ACART summary</p> <ul style="list-style-type: none"> • Almost all submitters said they agreed the procedure should become an established procedure. • No submitters said they disagreed with ACART’s assessment. • One submitter commented on the need to monitor the use of the procedure in the event that it is introduced. • Two submitters commented on the potential for the treatment to also help women to recover from cancer treatments, whether or not they propose to have children. • One submitter noted there is no need for ethical oversight of such a procedure and that requiring that oversight would cause delays in treatment. 	
<p>Question 5 b Do you have any other comments?</p>	

Question/submission	Submitter
<p>If the procedure becomes an “established” one it might send a message to women that there are few if any risks, when in fact the current thinking is based on a small number of cases over a relatively short time span.</p> <p>While we agree that the benefits outweigh the risks, it is important that women are fully informed about the current level of uncertainty. The information they receive at the time of surgery (both removal and transplantation) should reflect the latest developments related to cryopreservation and transplantation—both the broader health benefits as well as information concerning pregnancy rates and the known outcomes for children born from cryopreserved ovarian tissue.</p> <p>Also, we believe there should be a system of notification/communication so that women who have gone through the procedure continue to be provided with any new information as it comes to hand, particularly any potentially significant developments relating to risks and benefits.</p>	Nathaniel
<p>Permission from women, for the use of their tissue for research purposes, should become an established procedure. Permission must also be obtained, as an established procedure, for the destruction of the tissue should the woman have no further requirement for it. This decision should be solely that of the woman concerned.</p>	NCWZN
<p>ACART summary</p> <ul style="list-style-type: none"> • One submitter reiterated the need for fully informed consent, and that women must be told that the procedure is new and the results not yet conclusive. • One submitter commented on whether the tissue could be used in research and that, if so, women’s permission would be needed. The same submitter said that the decision to destroy the tissue, if it is no longer needed, should be entirely that of the woman. 	
<p>Question 6 Do you agree with ACART’s position that the scope for the use of cryopreserved ovarian tissue to restore ovarian function be limited to the woman from whom the tissue was excised, for her own treatment?</p>	
<p>Yes</p>	
<p>Until there is more evidence about the risk of the tissue containing malignant cells, I support the ACART’s position that donation should not be permitted.</p>	Peart
<p>We believe extension of use beyond that opens up both clinical and ethical issues and risk which are not currently acceptable.</p>	AWHC
<p>Though the risk of inclusion of malignant cells in the transplanted tissue and the resultant development of a cancer appears to be very low, it is still a risk. The transplantation procedure, therefore, should be restricted to the woman from whom the tissue was excised.</p>	France. Name withld.
<p>Yes. Also, the transplantation of donated ovarian tissue from a ‘healthy’ woman to a third party raises additional and unique ethical issues of a medical, ethical, cultural and spiritual nature related to the introduction of a genetic ‘third party’ that are not fully explored in the Consultation Document. While third party gamete donation for IVF is already allowed in New Zealand, it should not be assumed that the issues related to consent and knowledge of genetic origins would be exactly the same in the case of donated ovarian tissue donation. Such issues would need to be explored as part of a separate consultation.</p>	Nathaniel
<p>Yes. Also, in the future, there may be the possibility of using the tissue in women other than the woman from whom the tissue was excised. Until evidence suggests this is safe and effective we would recommend that this procedure be restricted to the woman from whom the tissue was excised.</p>	NCWZN
<p>We believe extension of use beyond that opens up both clinical and ethical issues and risk which are not currently acceptable.</p>	AWHC

Question/submission	Submitter
Though the risk of inclusion of malignant cells in the transplanted tissue and the resultant development of a cancer appears to be very low, it is still a risk. The transplantation procedure, therefore, should be restricted to the woman from whom the tissue was excised.	France. Name withld.
Yes. Also, the transplantation of donated ovarian tissue from a 'healthy' woman to a third party raises additional and unique ethical issues of a medical, ethical, cultural and spiritual nature related to the introduction of a genetic 'third party' that are not fully explored in the Consultation Document. While third party gamete donation for IVF is already allowed in New Zealand, it should not be assumed that the issues related to consent and knowledge of genetic origins would be exactly the same in the case of donated ovarian tissue donation. Such issues would need to be explored as part of a separate consultation.	Nathaniel
Yes. Also, in the future, there may be the possibility of using the tissue in women other than the woman from whom the tissue was excised. Until evidence suggests this is safe and effective we would recommend that this procedure be restricted to the woman from whom the tissue was excised.	NCWNZ
<p>ACART summary</p> <ul style="list-style-type: none"> • Almost all submitters agreed that the procedure should only be for autologous use, citing the risks of malignancy and other ethical and clinical matters. • One submitter noted the ethical questions, not covered in the document, that would arise if non-autologous reimplantation was allowed. The questions would be about the offspring that might be born from third party eggs and the genetic heritage of that offspring. 	
No	
There may be cases where a transfer of cryopreserved ovarian tissue to another woman is warranted and desirable; for instance, a transplant from a healthy woman to her monozygotic (identical) sibling who has been treated for cancer. Transplants between other close relatives, such as siblings, may also be worthy of consideration in some cases. We recommend that any restriction should be subject to periodic review, perhaps at five year intervals, as future medical developments may make such procedures desirable. Rather than an outright ban now it may be better to subject all transplants to an unrelated woman to ethical review.	HSNZ
<p>ACART summary</p> <ul style="list-style-type: none"> • One submitter argued there might be cases in which transplants to other women could be ok and that these would need to be subject to ethical assessment. The submitter also suggested the restrictions on the procedure be periodically reviewed as evidence emerges. 	
<p>Question 7 Do you have any further comments to share with ACART?</p>	
The funding/equity of access to the whole process associated with the use of ovarian tissue must be addressed for those with no other option for fertility preservation (those with truly no alternative option being a relatively small group).	Hunter
Two stage consent needs to be discussed in the advice. Consent is initially obtained when the patient is a child. While the parents are entitled to decide on the initial surgery it is likely that the child, now a competent adult will be required to complete the process. Current consent standards require that assent is obtained from the child, and that she is able to participate meaningfully in the decision to her level of capacity. It is essential that there is sufficient information provided to her to make an informed decision when she is older, and that resources are available. It would be unethical to remove ovarian tissue and then not ensure that the woman to whom it belongs is able to make use of it.	Tuohy

Question/submission	Submitter
<p>Disposal of the ovarian tissue needs to be discussed in the advice. There will be situations where the disposal of the tissue will be needed, such as death or a decision not to use the tissue. The advice should comment on who is responsible for making decisions and what the rules are. A related issue is storage, who pays for this and what provisions are made for ensuring that the child, now an adult woman is aware of the existence of the tissue.</p>	MoH
<p>Non-medical use of the tissue needs to be discussed in the advice. "Non-medical" use of the procedure, such as preserving younger ova, in the situation where a healthy woman wants to delay conception for social or economic reasons, but wants to ensure that her ova remain young to reduce the risk of age related genetic defects such as down syndrome or autism. The document is silent on this and it should be addressed.</p>	MoH
<p>The FWHC would like to know about the following matters.</p> <ol style="list-style-type: none"> If/when the procedure becomes standard practice, what criteria will determine eligibility? Will the re-implantation procedure be publicly funded? Who will do the outcomes monitoring? Will the private sector also be able to provide the reimplantation if the women are willing to pay for it privately, and will these women have the same "rules of limitation" applied as those who come through the publicly funded pathway? 	FWHC
<p>Some parts of the consultation document refer to 'restoring ovarian function', while other parts describe the procedure more narrowly as 'fertility preservation'. Given the multiple health benefits of the transplantation (notably the return of endocrine function and the regaining of menstrual cycles which can assist in delaying the onset of osteoporosis and other menopausal related conditions) there is a strong case for regarding the process as a standard part of the 'treatment' for all women requiring health interventions that are potentially gonadotoxic. We suggest that the procedure should ultimately be more broadly promoted as an element of the 'best practice' treatment in such circumstances, rather than as a specialised procedure aimed primarily at restoring the fertility of women for whom fertility is important.</p> <p>This constitutes for us a further reason why the storage of such tissue should be handled within the public health system rather than by fertility clinics. If the freezing and storage costs are not covered by a DHB, as currently seems to be the case, the benefits of ovarian tissue transplantation (both fertility and other health-related benefits) may be available only to those with the financial means to pay such costs. This is unjust. We would like to see both the surgical and storage costs covered by the New Zealand health system for all women likely to benefit from the transplantation of cryopreserved ovarian tissue.</p>	Nathaniel
<p>HSNZ repeated its assertion that the procedure should be allowed for a monozygotic (identical) twin and that ACART should allow for future developments that could make the procedure desirable between siblings or other close relatives. They cite the paper by Andersen in the consultation document: the transplant of fresh ovarian tissue between monozygotic twins is already a well established practice and pregnancies have resulted with good results (see section A6 on page 39 of the consultation document). Consideration might also be given to the possibility that it will soon be possible for a very small sample of ovarian tissue taken from one monozygotic twin to be grown or multiplied outside her body before being cryopreserved and then used at a later time to restore ovarian function to her twin.</p>	HSNZ

Question/submission	Submitter
It is important that an international database be established with clear criteria for the data to be collected, to enable consistent reporting. Problems have arisen in other fields where there has been misrepresentation and rendered the information collected spurious. Good quality information needs to be available to the women/girls accessing this procedure and also for the clinicians/specialists involved so that informed decisions can be made by all parties.	NCWNZ
Fertility New Zealand noted the importance of ensuring that separate funding is allocated for consumers to have this procedure undertaken (separate to the funding that is allocated for IVF treatments for example).	FNZ
ACART should consider the costs associated with the process including the initial tissue retrieval, processing and storage, which, although an approved procedure, is currently not funded in New Zealand. This has resulted in inequity of access to preservation of fertility for those with no other option – particularly pre-pubescent girls.	Hunter
The less affluent in our society may have no or limited access to this procedure. Accepting that the initial surgery to remove ovarian tissue for cryopreservation may take place through the public hospital system at no cost to the individual, ongoing storage and the eventual transplantation procedure and follow-up will involve significant costs if carried out by private fertility services. The document notes on page 20 that ACART has no responsibility for the costs of reproduction.	France
We would hope that, if ovarian tissue cryopreservation and its use becomes an established procedure, the Ministry of Health will consider funding the service.	FA: Written submission
FWHC is adamantly opposed to women freezing their ovarian tissue for later use just because there might be a future need/benefit arising, e.g. where a woman delays childbearing for social/economic reasons; or to counter increased risks to her future hormonal or fertility wellbeing through other personally adopted behaviours such as smoking uptake or risky alcohol consumption (both known carcinogenic factors).	FWHC
<p>ACART summary</p> <ul style="list-style-type: none"> • One submitter repeated the argument made earlier that there might be cases in which transplants to other women could be ok and that these be subject to ethical assessment. The submitter also suggested the restrictions on the procedure be periodically reviewed as evidence emerges. • Seven submitters said that funding should be available for the procedure through the public health system. One submitter said the funding should be separate to IVF funding. Some submitters noted that although the purpose of the document was not to consider how funding could be provided the matter will need to be addressed. • Two submitters commented on social use of the procedure while a third repeated a comment made earlier about the potential for the procedure to help in treating other medical conditions. (Distinction between social and medical.) • One submitter repeated a comment about the need for monitoring and fully informed consent. • One submitter said the disposal of the ovarian tissue needs to be discussed in the advice. (This matter was also raised in one other place.) • One submitter said the two stage consent needs to be discussed in the advice. 	

APPENDIX 3 RISK ASSESSMENT OF THE USE OF CRYOPRESERVED OVARIAN TISSUE TO RESTORE OVARIAN FUNCTION

ACART has applied its risk acceptability framework¹⁸ to help it assess the known risks to health in the use of cryopreserved ovarian tissue to restore ovarian function. The framework sets out a process and considerations for ACART to take into account in its analysis of whether or not the risks fall within a level that is acceptable in New Zealand.

Below ACART sets out its comparison of the risks associated with the use of cryopreserved ovarian tissue to restore ovarian function, the principles of the HART Act 2004 applied, and the questions used in its analysis of whether the level of risk is acceptable. Note the consequences table is simply a tool for presenting and comparing information. ACART's analysis is set out in section 4 of this document.

Risk

'Risk' is a combination of two concepts:

- the likelihood of an effect occurring
- the consequences of an effect if it occurs.

Likelihood and magnitude can be described qualitatively or quantitatively.

Likelihood

To consider the likelihood of risks associated with the use of cryopreserved ovarian tissue to restore ovarian function, ACART has used the following categories.

	Descriptor	Description
A	Frequent	Is expected to occur again either immediately or within a short period of time (likely to occur most weeks or months)
B	Likely	Will probably occur in most circumstances (several times a year)
C	Possible	Possibly will recur – might occur at some time (may happen every one to two years)
D	Unlikely	Possibly will recur – could occur at some time in two to five years
E	Rare	Unlikely to recur – may occur only in exceptional circumstances (may happen every five to 30 years)

Consequences

To assess the consequences of the risks associated with the use of cryopreserved ovarian tissue to restore ovarian function, ACART has used the following descriptors of consequences.

¹⁸ <<http://acart.health.govt.nz/publications-and-resources/acart-publications/risk-acceptability-framework-used-acart>>

Descriptor	Descriptions (risks and costs)
Serious	Patients whose death is unrelated to the natural course of the illness and differs from the immediate expected outcome of the patient's management
Major	Patients suffering a major permanent loss of function (sensory, motor, physiological or psychological) unrelated to the natural course of the illness and differing from the expected outcome of patient management
Moderate	<p>Patients with permanent reduction in bodily function (sensory, motor, physiological or psychological) unrelated to the natural course of the illness and differing from the expected outcome of patient management or any of the following:</p> <ul style="list-style-type: none"> • increased length of stay as a result of the incident • surgical intervention required as a result of the incident
Minor	Patients requiring an increased level of care, including review and evaluation, additional investigations, or referral to another clinician
Minimum	Patients with no injury or increased level of care or length of stay

Comparing the risks

ACART has used the following table to quantify and compare each aspect of the risk associated with the use of cryopreserved ovarian tissue to restore ovarian function.

Legend:

E = extreme risk	H = high risk	M = moderate risk	L = low risk
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	Consequences				
Likelihood	Serious	Major	Moderate	Minor	Minimum
A (frequent)	E	E	H	M	M
				<p>Surgical risk</p> <p>There are no reported increased procedural risks with transplanting thawed ovarian tissue. The procedural risks are considered low risk and no major complications from the operation have been reported. There is however a risk with any surgical procedure, for example, infection, bleeding or damage to adjacent organs.</p>	
B (likely)	E	E	H	M	L
			<p>Risk of damage to the tissue</p> <p>No reports suggest the cryopreservation procedure imposes any change in the tissue and could lead to unwanted side effects upon transplantation. There are no reports on any potential risks to a woman's health through the use of cryopreserved ovarian tissue in terms of oocytes and subsequent embryos being more abnormal or less viable as compared to mature oocytes obtained in IVF treatment.</p> <p>There is a risk of damage to oocytes and follicles in the ovarian tissue during the cryopreservation procedure. This in turn has an effect on rates of oocyte retrieval and embryo</p>		

	Consequences				
Likelihood	Serious	Major	Moderate	Minor	Minimum
C (possible)	E	H	H Pregnancy-related risks There are no known higher pregnancy-related risks for women with transplanted ovarian tissue. The only risk is that their cancer treatment may have affected their ability to carry a pregnancy, for example damage from irradiation of her pelvis.	M	L
D (unlikely)	E	H Concerns with transplanting tissue excised at the time of disease The safety of grafting ovarian tissue excised at the time when the patient experienced active disease is unresolved. To date, there are no studies or reports to secure that the transplanted tissue does not develop or increase the risk of malignancy later on. There is a potential risk of malignant cells from the original cancer being present in the transplanted tissue. If the tissue was excised at the time of active disease, the transplanted tissue may cause a relapse.	M	L	L
E (rare)	H	M Outcomes for children		L	L

	Consequences				
Likelihood	Serious	Major	Moderate	Minor	Minimum
		<p>All babies born so far from transplanted cryopreserved ovarian tissue have been reported healthy. There is no information to suggest children born from cryopreserved ovarian tissue are any different from children conceived naturally</p> <p>There are no long term follow-up studies on the children and their development at present, and it is too early to identify any adverse observations of a child's development or psychological outcomes. There is also no systematic reporting of pregnancy and birth data.</p> <p>There is not enough information regarding resultant chromosomal abnormalities, congenital malformations or epigenetic disorders.</p> <p>Due to the lack of this information, future monitoring of health outcomes for children born from the use of cryopreserved ovarian tissue is required.</p>			

GLOSSARY

Advisory Committee on Assisted Reproductive Technology (ACART)	The advisory committee established under New Zealand's Human Assisted Reproductive Technology Act 2004.
Assisted reproductive procedure	The Human Assisted Reproductive Technology Act 2004 defines an assisted reproductive procedure as a procedure performed for the purpose of assisting human reproduction that involves: <ul style="list-style-type: none">• the creation of an in-vitro human embryo, or• the storage, manipulation or use of an in-vitro human gamete or an in-vitro human embryo, or• the use of cells derived from an in-vitro human embryo, or• the implantation into a human being of human gametes or human embryos.
Cryopreservation	The freezing and storage of tissues and cells at extremely low temperatures.
Epigenetic	The inheritable changes in the pattern of gene expression caused by factors other than changes in the DNA sequence.
Established procedure	A procedure that is declared established under section 6 of the Human Assisted Reproductive Technology Act 2004 and therefore does not require approval from ECART.
Ethics Committee on Assisted Reproductive Technology (ECART)	The ethics committee established under New Zealand's Human Assisted Reproductive Technology Act 2004.
Fertility Services Standard	A standard issued under the Health and Disability Services (Safety) Act 2001 that sets out the safety and quality measures that all fertility services provided by New Zealand fertility clinics must meet.
Gamete	An egg or sperm, whether mature or not, or any other cell (whether naturally occurring or artificially formed or modified) that (i) contains only one copy of all or most chromosomes and (ii) is capable of being used for reproductive purposes.
Gonadotoxic	Having a harmful effect on the gamete-producing organs ie. the ovary in the female or the testis in the male.
Human Assisted Reproductive Technology Act 2004 (HART Act 2004)	An act to secure the benefits of, and regulate, assisted reproductive technology and human reproductive research.
Informed consent	A person's voluntary agreement, based on adequate knowledge and understanding of relevant information, to participate in research or to undergo a diagnostic, therapeutic or preventive procedure.

In-vitro fertilisation (IVF)	The uniting of egg and sperm outside the body (in the laboratory).
Kaitiakitanga	Guardianship.
Mana	A concept that implies authority, influence and prestige, as well as the recognition of these qualities.
Oocyte	An egg produced by the ovary.
Ovarian function	The ability of the ovary to produce reproductive hormones and potentially release eggs.
Ovary	The egg-producing reproductive organ found in females.
Whakapapa	The genealogical descent of all living things from the gods to the present time.
Whanaungatanga	The obligation of care and support among relatives.