# What Does Borderline Ovarian Tumor Mean to Your Fertility?

## What Does Borderline Ovarian Tumor Mean to Your Fertility?

Fertility in women diagnosed with borderline ovarian tumors can be reduced or lost due to surgical treatment. Counseling regarding fertility preservation shortly after diagnosis can increase the chance of pregnancy following treatment.

## Borderline-low malignant potential ovarian tumors

The cells in borderline tumors, proliferate more than benign ovarian cysts but less than frank malignant ovarian tumors. Multiple layers of these cells are seen on pathology slides, but they do not invade surrounding tissues as in malignant tumors. They are diagnosed in approximately4000 of women each year in the US and are more commonly encountered in reproductive age women. These tumors are usually cystic, sometimes with surrounding implants. Low malignant potential tumors are treated surgically (removal of cyst, removal of the ovary or sometimes removal of both ovaries and the uterus). They generally do not require chemotherapy for treatment. The majority of these tumors are associated with very high survival (10 year survival >90% in stage I and II ), although some may recur or turn malignant.

There is no difference in survival if borderline tumors were treated with removal of the cyst, removal of the ovary or removal of the uterus and both ovaries. Recurrence may be lower after hysterectomy (5%) compared to salpingoophorectomy (15%) and cyst excision (30%). The high rate for recurrence

after conservative surgery indicates the need for strict and long term follow up (pelvic exams, ultrasound and tumor markers). Some recurrences take place years after initial surgery and are sometimes malignant.

## Fertility risks in women diagnosed with borderline tumors

Fertility risks in women diagnosed with low malignant potential ovarian tumors include loss of ovarian tissue and pelvic scarring that can block the fallopian tubes especially if open approach is used for treatment compared to laparoscopy (minimal acess surgery). Some loss of ovarian tissue does occur even during cyst removal from the ovary. Ovarian reserve can be tested after surgery using transvaginal ultrasound evaluation for ovarian volume and number of antral follicles. Ovarian function can also be assessed using day 2 FSH and estradiol levels and antimullerian hormone (AMH).

## Fertility preservation strategies in women diagnosed with borderline ovarian tumors

### 1. Conservative surgery

Ovarian cystectomy can be considered in reproductive age women, especially in early disease with favorable pathology and absence of implants. Recurrence is relatively high but can be managed with repeat excision if not malignant. If pregnancy is desired following surgery, fertility factors; ovulation, fallopian tubes and sperm factors should be investigated and treated accordingly

### 2. Embryo and oocyte cryopreservation

Women at risk for diminished fertility due to surgery, especially if requiring removal of the ovaries or repeat

excision of cyst, can consider ovarian stimulation, egg retrieval and egg freezing or  IVF and embryo freezing. There is no evidence that ovarian stimulation and exposure to high estrogen increases the risk for recurrence. It is not clear if border line cells are sensitive to estrogen increase during ovarian stimulation. Two options are available to reduce estrogen exposure: to perform IVF in a natural cycle (low egg yield) or to modify the stimulation protocol, through adding an aromatase inhibitor, similar to that used for breast cancer. Alternatively, short stimulation followed by retrieval of immature eggs followed by in vitro maturation can be performed.

Women diagnosed with borderline ovarian tumors are at risk for diminished fertility because of surgical treatment(s). This is especially true if repeat surgical excision is required. Collaboration between a gynecologic oncologist and a reproductive endocrinologist enable adequate surgical treatment, strict follow up and preservation of future fertility in reproductive age women.

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# Frozen Embryo Transfer Vs Fresh Embryo Transfer after IVF

## Frozen Embryo Transfer Vs Fresh Embryo Transfer after IVF

After embryos are created with in vitro fertilization, should you have your embryos transfer 3 to 5 days later or should

embryos be frozen and transferred later in frozen-thaw cycle (FET)? This question became viable after improvement in freezing technology (vitrification) to the extent that the vast majority of embryos (>95%) frozen in The US survive thaw and has high implantation potential.

There are indications to freeze all embryos after IVF i. avoiding ovarian hyperstimulation syndrome,ii. unfavorable uterine lining (thin, fluid..) iii. allow more time for PGD / PGS, iv.personal reasons related to patients.

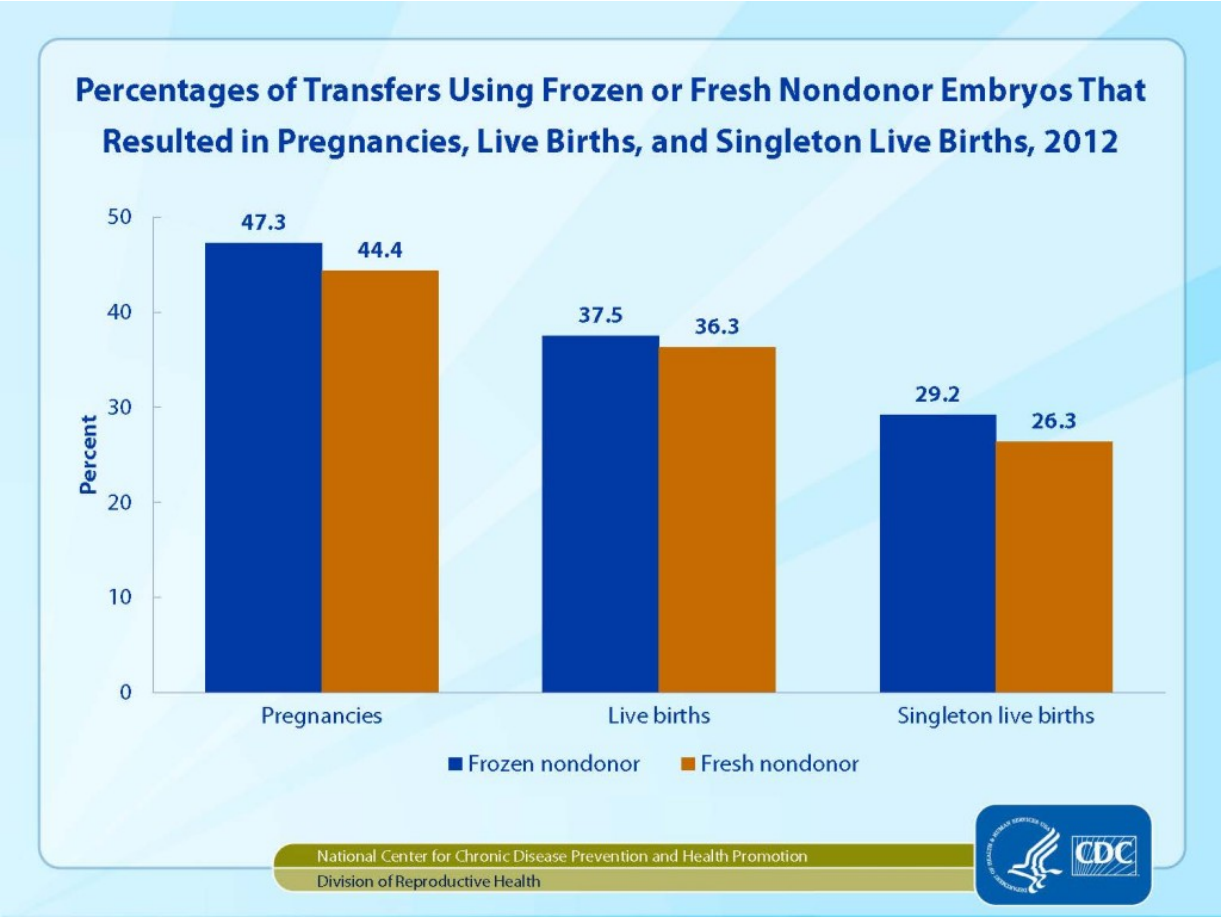
The aim here is to discuss the merits for and against *elective* embryo freezing to transfer the embryo or embryos in a thaw cycle. A thaw cycle involves preparation of the uterine lining, embryo thaw and embryo transfer (no stimulation or egg retrieval). Preparation of the lining of the uterus can be accomplished through one of two main methods

a. Natural Cycle FET : Natural ovulation is monitored using ultrasound and blood work. The time of ovulation need to be accurately defined. Embryos are thawed 3 or 5 days later and transferred. It requires minimal medications but require regular ovulation.

b. Synthetic Cycle FET : Estrogen is administered (patches, pills..etc) till the lining of the uterus reach the desired thickness and pattern. Progesterone is then administered (injections, vaginal tablets) and embryos are thawed and transferred few days later. It does not require ovulation and allows more flexibility in timing of embryo transfer.

There is some evidence that both methods are equivalent with regards to implantation and pregnancy.

## On The Advantages of Elective Frozen Embryo transfer




Fresh embryos vs Frozen Embryos

In the US frozen cycles result in equivalent number of pregnancies and deliveries as fresh embryos.

## Should Elective Frozen Embryo Transfer be Recommended to The General Fertility Population Undergoing IVF?

In other words, do we have enough data to recommend freezing all embryos created after IVF and transfer later?

The possible advantages cited for performing frozen embryos transfer originates from two sources

1. Physiological information: excessive exposure of the lining of the uterus to estrogen may lead to abnormal development of the placenta and

2. Observational studies: when compared to fresh embryo transfer, pregnancies resulting from frozen transfer are less

affected by bleeding and are associated with heavier babies with lower odds for low birth weight.

Conclusions resulting from non controlled studies and physiologic interpretation are not always accurate due to differences between the two groups and cannot be relied upon for definitive conclusions. A definitive study will need to be prospective and patients can be randomly allocated to fresh transfer or elective frozen transfer. This study does not exist at this time

## Can Elective Frozen Embryo Transfer Improve Pregnancy & Delivery Rates?

Three studies showed a trend to improve in pregnancy rates following frozen transfer when compared to fresh IVF transfer. The studies should be interpreted with caution as it included young high or normal responders and not low responders and older women. The studies did show an improve in delivery rate, did not track perinatal outcomes and did not include economic analysis of cost and benefits. So a larger and more comprehensive study is still needed.

*New Ideas in reproductive medicine, though exciting, still require the scientific rigorous study to ensure that the conclusions are correct and define which group will benefit most from freeze all strategy before its general application to women undergoing IVF.*

*If you need to freeze your embryos after IVF to avoid ovarian hyperstimulation syndrome, because of unfavorable uterine lining or other reasons, please do so especially if the clinic has a robust freezing program. Freezing of embryos (especially with vitrification) is unlikely to affect your chance to get pregnant. On the other hand if you want to freeze all your embryos to improve your chance of getting pregnant, know that this strategy is debatable and not backed by solid scientific evidence.*

*When undergoing a frozen transfer cycle and if you have regular ovulation and a favorable lining, consider natural cycle FET over synthetic (medicated) cycle as there is evidence that they are equivalent. Natural cycle avoid external medications and excessive exposure to estrogen*

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# Embryo Selection after IVF

## Embryo Selection after IVF

Many of human embryos produced after in vitro fertilization carry abnormal chromosomes. Placing a chromosomally normal embryo (s) into a normal uterus has a very high chance of achieving a pregnancy. Your eggs have been retrieved and the mature eggs were fertilized. Now You and your reproductive endocrinologist are faced with the critical task of how many and which embryo to transfer to the uterus or which ones to freeze.

### Why do we Need Embryo Selection?

Selection of the most appropriate embryo(s) for transfer aim at i. Maximizing the chance for pregnancy and ii. Minimizing the risk of twins and other multiple pregnancies. Casual inspection of the embryo does not yield accurate information about its chromosome makeup. One can follow an indiscriminate approach where all embryos are transferred. The problem is this approach yields high unacceptable multiple pregnancy rates. On the other hand one can transfer one embryo at a time. This is a much safer approach in terms of markedly minimizing twin rates but may lower the chance for getting pregnant. In addition it also require a robust freezing program so that frozen embryos can survive thawing. Right now

in The US the survival of frozen embryos exceed 95% and the chance for pregnancy with a thawed embryo is approximately equal to a fresh embryo.

## Measure of Success: time to conceive or cumulative chance for pregnancy?

One major issue related to fertility treatment especially IVF is how to measure success? specifically consider this question: if you have three embryos and decided to transfer them one at a time and got pregnant after the third transfer with a singleton, how does that compare to transferring all embryos in the fresh cycle and getting pregnant in twins? before answering it is important to know that twin gestation is associated with higher risk for pre-term delivery, ICU admissions and long term consequences for the babies.

In other words should you consider success as pregnancy taking place after one retrieval (cumulative chance from fresh and frozen embryos) or pregnancy taking place in the fresh cycle only (fresh embryos)? In other words would you like to shorten the time to conceive at the expense of higher risk for multiple pregnancy? Within *reason*, this is a question for you and your reproductive endocrinologist to answer based on your preferences and his practice

## You have a Voice: How should you use your embryos after IVF?

You need to have a voice in the number of embryos transferred to your uterus. Although your fertility specialist can discuss numbers and chances and other technical details as well as long term risks for multiple pregnancy, there are questions that cannot be answered by anyone but you.

- How do you feel about twins? triplets and quads?
- Would you accept fetal reduction (removal of one or more sacs from the uterus and leaving only one or two)?
- Do you have the social support system to take care of

twins?

For these and many other reasons your input in the number of embryos to transfer is paramount.

## Methods of Embryo Selection after IVF

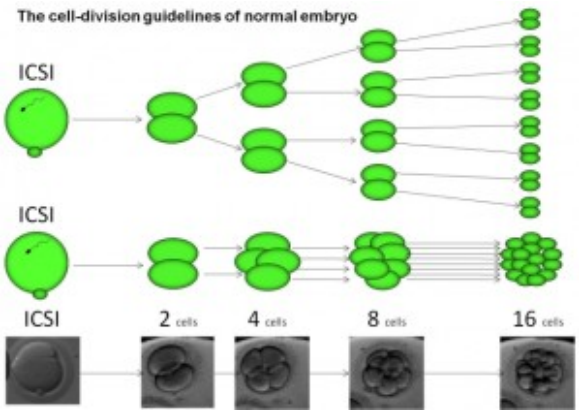
## Embryo Morphology and Female Age

Age is, by far, the strongest predictor of the health of the embryos. Younger women produce more chromosomally normal embryos than older women. An embryo from a woman at age 30 commonly implants 40% of the time as opposed to 5% or less in a woman age 40. For any given cohort, embryos are graded based on specific morphological criteria from the best looking to the worst. These criteria are technical and followed by all embryologists. Embryos are prioritized for transfer based on their shape. Morphology, however is may be 50 to 60% predictive of pregnancy, far from ideal. The combined use of morphology of embryos, stage of development (day 3 or blastocyst) and age is the standard selection method for which embryo is transferred first and how many. This method has the advantage of being sheep, quick and non-invasive. All other methods must prove superior to morphology + age before adoption.

## Extended Culture to Blastocyst Stage (Day 5 Embryo)

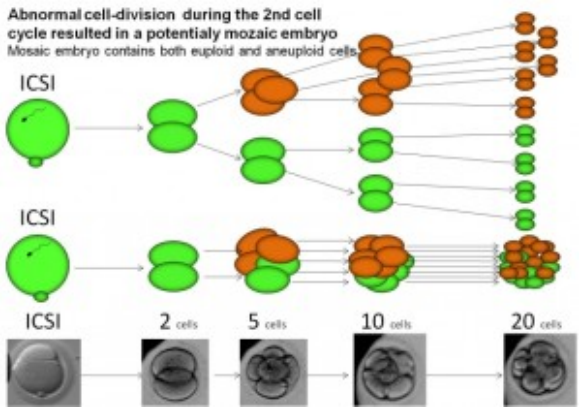
Keeping day 3 embryos in culture may give these embryos may time to develop to blastocysts. Presumably, the better embryos progress to blastocysts or do so faster than less healthy embryos, thus they are preferentially selected for transfer.

## Time Lapse Imaging of Embryos




time lapse embryo imaging- normal embryo division

Embryos are placed in a specific incubator in a specific plate and is observed at predetermined time




time lapse embryo imaging- abnormal embryo division

points using time lapse microscopy / photography. Photos are analyzed manually or through a computer and embryos are graded based on timely division of blastmeres (component cells). There is no evidence so far that pregnancy rate is improved above using morphology. There is extra cost associated with the use of the special plate and is also limited by the number of special incubators available.

## PGS (Embryo Chromosome testing)

New forms of PGS (performing biopsy at the blastocyst stage) and more accurate platforms for analyzing the biopsied cells

are available. However, the concept that better selection will lead to improved IVF results is far from certain.

It success of an IVF cycle is measured after transfer of fresh then frozen embryos till pregnancy ensues (cumulative success) ad patients are will to be patient for 1-2 more months, then any form of embryo selection, PGS or otherwise, will not improve the live birth rates. Moreover, PGS can be harmeful as it may misdiagnose the health of the embryos (see this article on PGS for details). PGS increases the expense of treatment $4000 to 6000

Embryo selection is maybe be able to improve the time to pregnancy, if embryos with the highest implantation potential are transferred first.

> *Based on the available evidence, judicious selection of embryos based on patient age, morphology and the use of extended culture to blastocysts are the standard of care in embryo selection after IVF. Two additional factors to consider is how robust is the freezing program of that specific lab (generally excellent all over the US) and the acceptability of fetal reduction by the couple. Liberal use of single embryo transfer when appropriate should be strongly considered. 'New' ideas should be subjected to rigorous scientific evaluations 'fertility clinical trials' before they are ready for routine use. Thus far, based on published evidence, embryo time lapse imaging and PGS should remain investigational.*

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# Frozen Embryo Transfers (FET)

## Frozen Embryo Transfer

Following IVF, excess **embryos are frozen** for use with second attempts if no pregnancy takes place or to conceive a second child. With improvement of the freezing and thaw techniques: the majority of frozen embryos survive thawing, the implantation potential of a thawed embryo is comparable to a fresh embryo, less embryos or single embryo can be transferred in the fresh cycle and selection of the best embryo for fresh transfer became less important.

Frozen embryo transfer (FET)

Freezing of embryos allow ample time for genetic testing of embryos if needed, transferring embryos to a different locale, delaying transfer due to medical problem, the emergence of an abnormality in the lining of the uterus e.g thin  endometrium, polyp, fluid.. or till a gestational carrier is found.

## Benefits of Frozen Embryo Transfer

1. Pregnancy rate after frozen embryo transfer is comparable to fresh transfer and may even be higher than fresh transfer in some studies. More work is needed to confirm higher live birth rate.

2. Complications: frozen embryo transfer minimize some of the complications related to IVF. Ovarian hyperstimulation syndrome (OHSS) and possibly ectopic pregnancy (pregnancy in the fallopian tube)

3. Lower risk for pregnancy complications and better quality

baby: frozen transfer appear to reduce the risk for preterm delivery, bleeding in pregnancy and low birth weight, possibly due to better placental function.

## How is the lining of the uterus prepared for frozen embryo transfer?

1. Natural cycle: in ovulating women, the follicle in the ovary is monitored till the point of ovulation is accurately identified. The follicle will internally produce the estrogen required to build the lining. When ovulation takes place, the embryos are thawed and transferred in a day comparable to its age e.g a day 5 embryo is transferred 5 days after ovulation. This process require only ultrasound and blood work monitoring

2. Estrogen replacement cycle: ovulation is stopped and estrogen is supplemented externally (patches,oral or vaginal) till the desired thickness and pattern of the uterine lining. Progesterone is then started (injection or vaginal) then embryos are transferred.

Timing of thaw and transfer is a complicated question and it depends on the type of cycle and age of embryos. Sometimes embryos are thawed and cultured for few days before transfer

All method for endometrium preparation yield similar pregnancy rate. At **NYCIVF** we prefer natural cycle with luteal phase support using vaginal estrogen.

### What makes a frozen embryo transfer cycle successful?

Embryo quality: one or more top quality embryo morphology observed at any stage of culture improves the outcome even if high-quality characteristics disappeared before transfer. Transferring more than one embryo increases the pregnancy rate but also multiple pregnancy.

Conclusion: should you intentionally delay transfer to frozen cycle? no but if you need to **freeze the embryos**, expect similar pregnancy rate as in the fresh cycle.

# Should You Test Embryos Created after IVF for Chromosomal Abnormalities?

## Should You Test Embryos Created after IVF for Chromosomal Abnormalities?

Many of the embryos created after IVF carry abnormal chromosomes. Normal embryo cells carry 46 chromosomes. The most common abnormalities are extra chromosome e. +21 (47 chromosomes) or missing a chromosome e.g -X (45 chromosomes). By far, abnormalities in the egg is the source of abnormal chromosome number.

PGD: Testing of embryo chromosomes

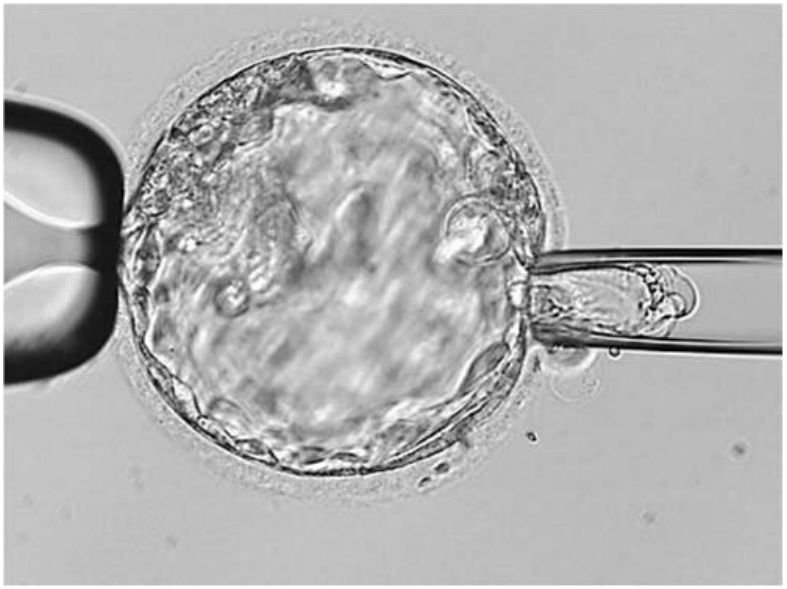
Finding a ‘normal’ embryo is clearly advantages as it will

theoretically lead to 1. The transfer of a single embryo instead of many  embryos and  2. can produce higher pregnancy rate than an embryo selected based on morphology (looks) alone. The process of embryo testing for the purpose of improving pregnancy rate is, however, not simple in relation to the accuracy of testing and many other issues

## Preimplantation genetic screening for chromosomal abnormalites (PGS)

PGS require two steps: 1. Biopsy: obtaining a cell or a group of cells from the embryo and 2. genetic testing of the cells for chromosomes ideally in 1-2 days to obtain results and allow fresh transfer

### Biopsy



Biopsy of trohoectoderm cells of blastocyst

Obtained by removing a. a single cell of a day 3 embryo or b. group of cells from the trophoectoderm (the outer part of the embryo that makes the placenta) of a day 5 embryo (blastocyst). Removal of cells nowadays uses a laser beam. Cells are fixed on a glass slide and sent for analysis.

## Genetic Analysis of Embryos

In the past old technologies (FISH) was limited in its ability to test all chromosomes. Multiple studies in the past few years proved that PGD using FISH actually reduce the chance for pregnancy in many IVF populations and should not be used. Two newer technologies can test all the chromosomes in an embryo: cGH (comparative genomic hybridization) array and SNP (single nucleotide polymorphism) array. Some of these methods can report the results in 3 days allowing for delayed fresh transfer (day 6) and others require about a month for accurate testing, necessitating embryo freezing and transfer in frozen-thaw cycle. Labs offering these methods claim accuracy of 95 to 97%. There are more advanced methods e.g genome screening, that can test embryo chromosomes in as short as 6 hours. The

ultimate method for testing is still evolving.

## Should women test their embryos before transfer to the uterus?

My short answer is no, not routinely. The pros of testing embryos could be transferring less embryos , improving IVF outcomes (pregnancy rates) and avoiding pregnancy with a baby carrying chromosomal abnormalities. The cons are these aims are still not proven facts due to

1. The biopsy may hurt the embryo, reducing its ability to implant

2. The assumption that one cell represent the whole embryo may not be true (mosiacism); the cell may be abnormal while the rest of embryo is normal or vice versa

3. The methods of testing was not validated by independent large studies from multiple centers and maybe less accurate than claimed

4. Delay in transferring the embryo in the fresh cycle may reduce its implantation potential

5. Cost associated with biopsy and testing the embryo is approximately $5500 to $8000

6. Testing of an embryo will not improve the ‘pregnancy’ potential of that embryo. It will just tell you if the embryo is ‘normal’ or not. The potential from all the embryos obtained from IVF after an egg retrieval is not changed by testing. Assuming a very accurate test and an excellent freezing program,  tested embryo transfer should yield similar outcome as transferring untested embryo(s) in multiple cycles. That is the most important point to consider. If you are willing to be patient and transfer one or few embryos resulting from one ovarian stimulation successively in the fresh cycle then frozen cycles, the cumulative pregnancy and

delivery rate should be the same at the end. For example in young women transferring one embryo, approximately 30- 40% of them will just achieve pregnancy in the fresh cycle. In the first frozen-thaw transfer another 30% or so will get pregnant. Frozen cycles are not as demanding as fresh IVF. Many women can have the embryo transferred in a natural cycle with no medications and minimal monitoring.

Embryo testing may help younger women, producing a large number of embryos and want to transfer only one. An alternative approach is to transfer one embryo at a time as their pregnancy rate is high even with a single untested embryo.

Testing of embryos from older women (40 or older) producing few embryos (<6) is of little value as the alternative is to transfer 5 or so untested embryos in that age group because of the very high rate of chromosomal abnormalities in the embryos.

Testing may be helpful for older women (40 or older) producing a very large number of embryos (e.g >10 embryos) to eliminate the need for multiple transfers to get to the healthy embryo. This category (older women and very large number of eggs / embryos) is rare in IVF population.

Women contemplating testing of their embryos after IVF should consider many issues including age, number of embryos, history of unsuccessful fertility treatment if any, cost and sometimes tolerance for multiple pregnancy and fetal reduction. Moreover women should consider all these factors and be ready to modify their decision during the cycle depending on the number of available embryos.

All this does not apply to women testing the embryos for chromosome translocation, a specific genetic disease or sex.