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EMBRYO ANALYSIS OF THE CULTURE ENVIRONMENT

The non-invasive test that allows us to prioritize for transfer the embryos with higher chance of being euploid, avoiding invasive embryo biopsy.

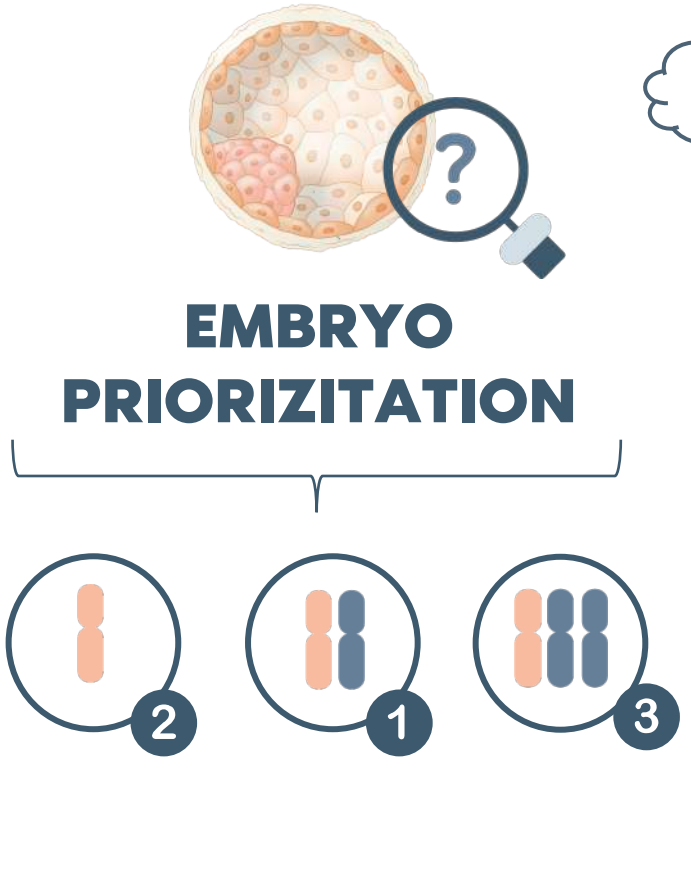
Main menu

1. Introduction
2. Embrace: Definition of the test, procedure and results
3. Igenomix validation
4. Limitations of the test
5. Questions & answers
6. Conclusions

Igenomix®

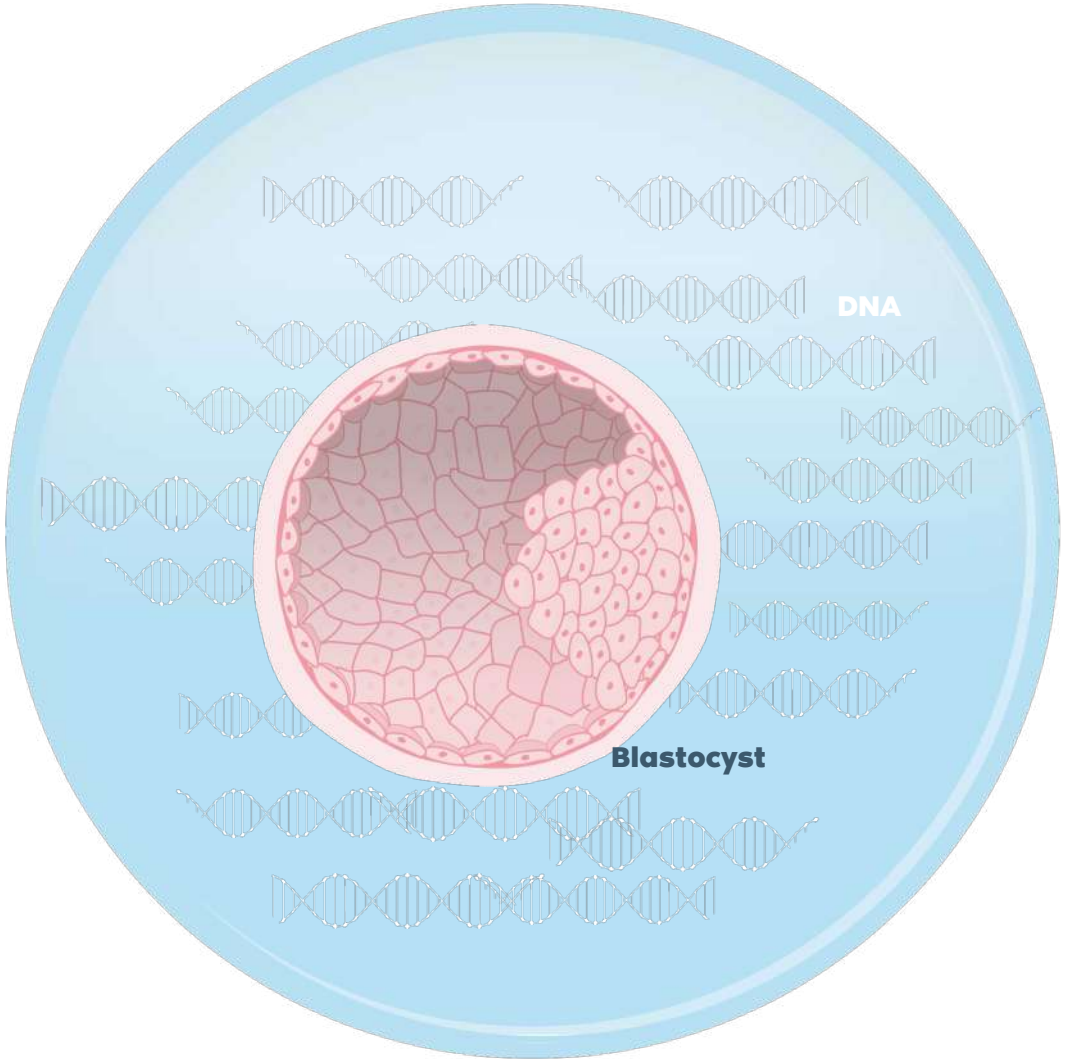
Introduction

Introduction



Embryo cell-free DNA

Embryos obtained from IVF treatment naturally release DNA during their development.



Embrace: definition of the test, procedure and results

What is Embrace by Igenomix?

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A non-invasive test for prioritizing embryo transfer according to their chance of being healthy and leading to a successful pregnancy, which offers an important advantage such us avoiding invasive embryo biopsy, and potentially increasing accessibility for a wider patient population.

- For **all the patients that wish to increase their chances of pregnancy without using invasive methods**.

Benefits:

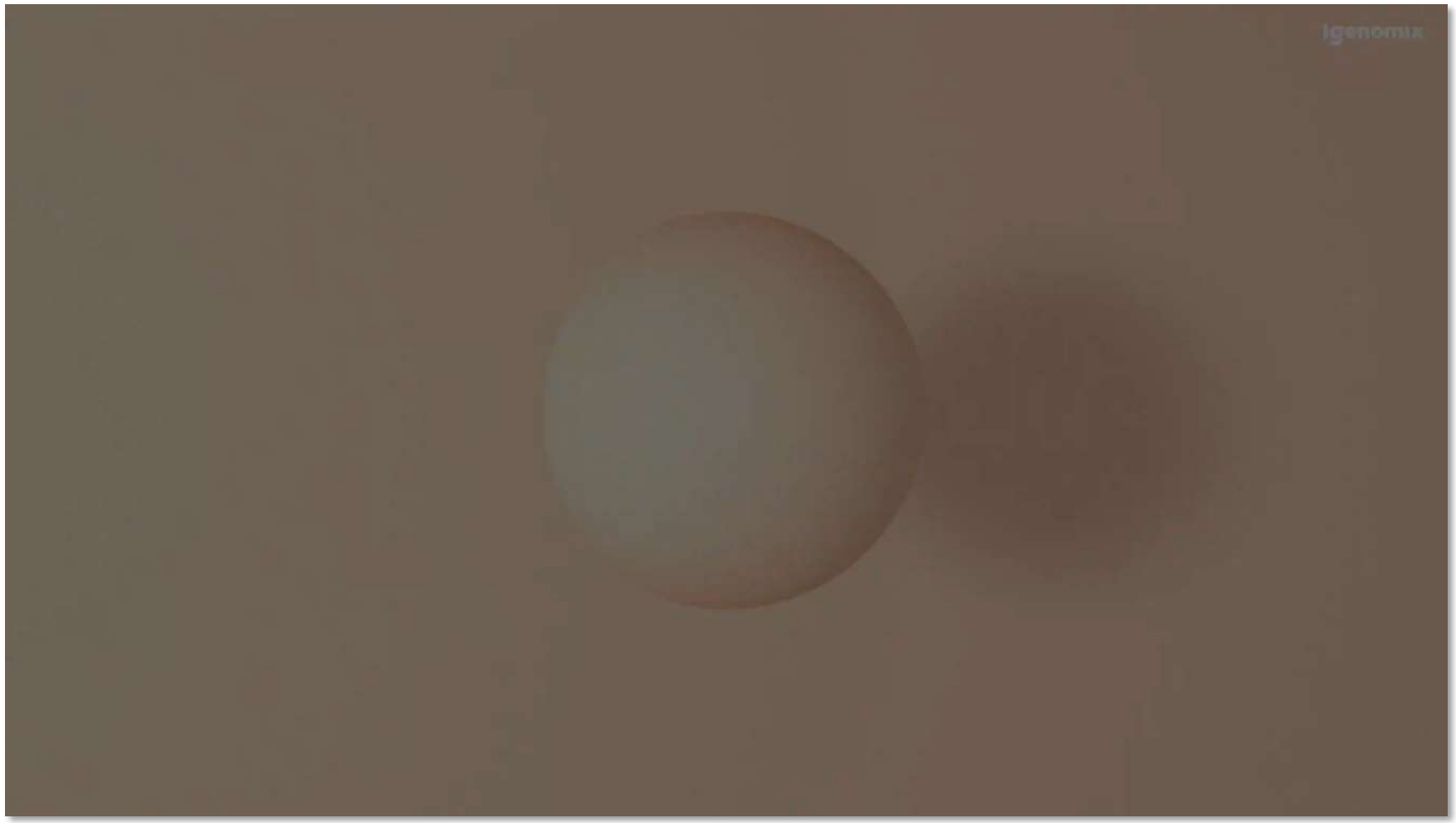
A non-invasive solution that favors a safer and more effective solution.

Avoids the need for embryo biopsies, and therefore reduces clinic costs.

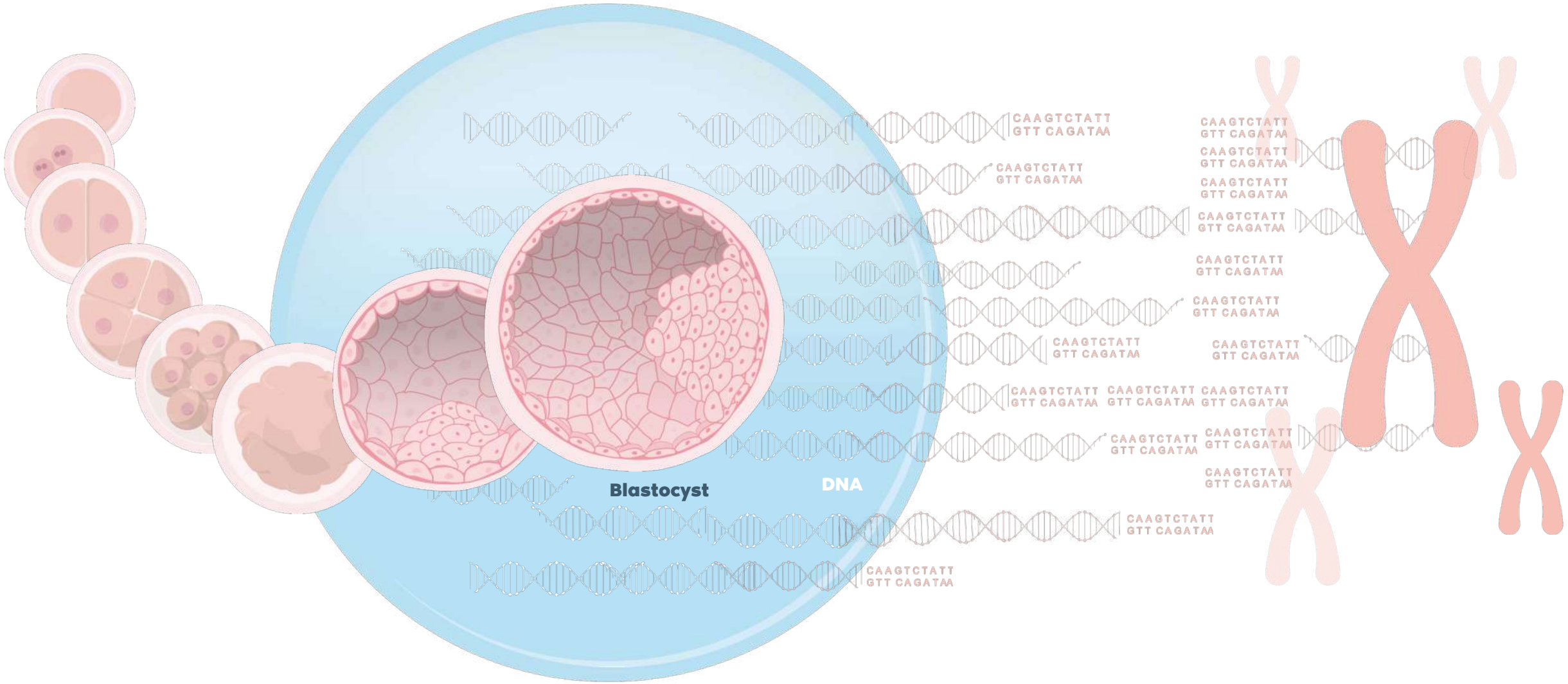
Making the treatment more accessible

How does the test work?

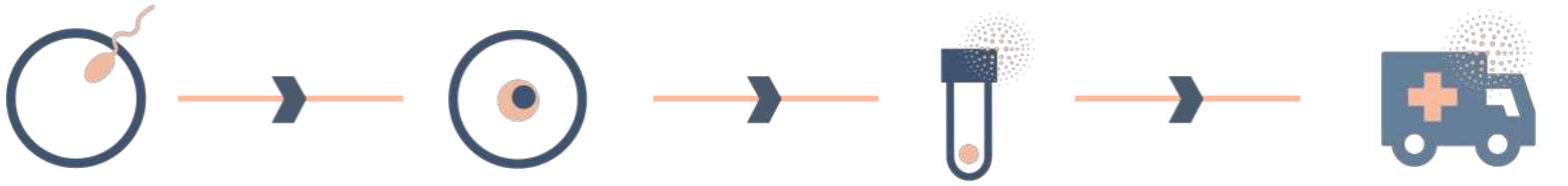
Play video



How does the test work?



What is the procedure?



IVF/ICSI

Embryo culture

Culture Media collection

Sent to Igenomix

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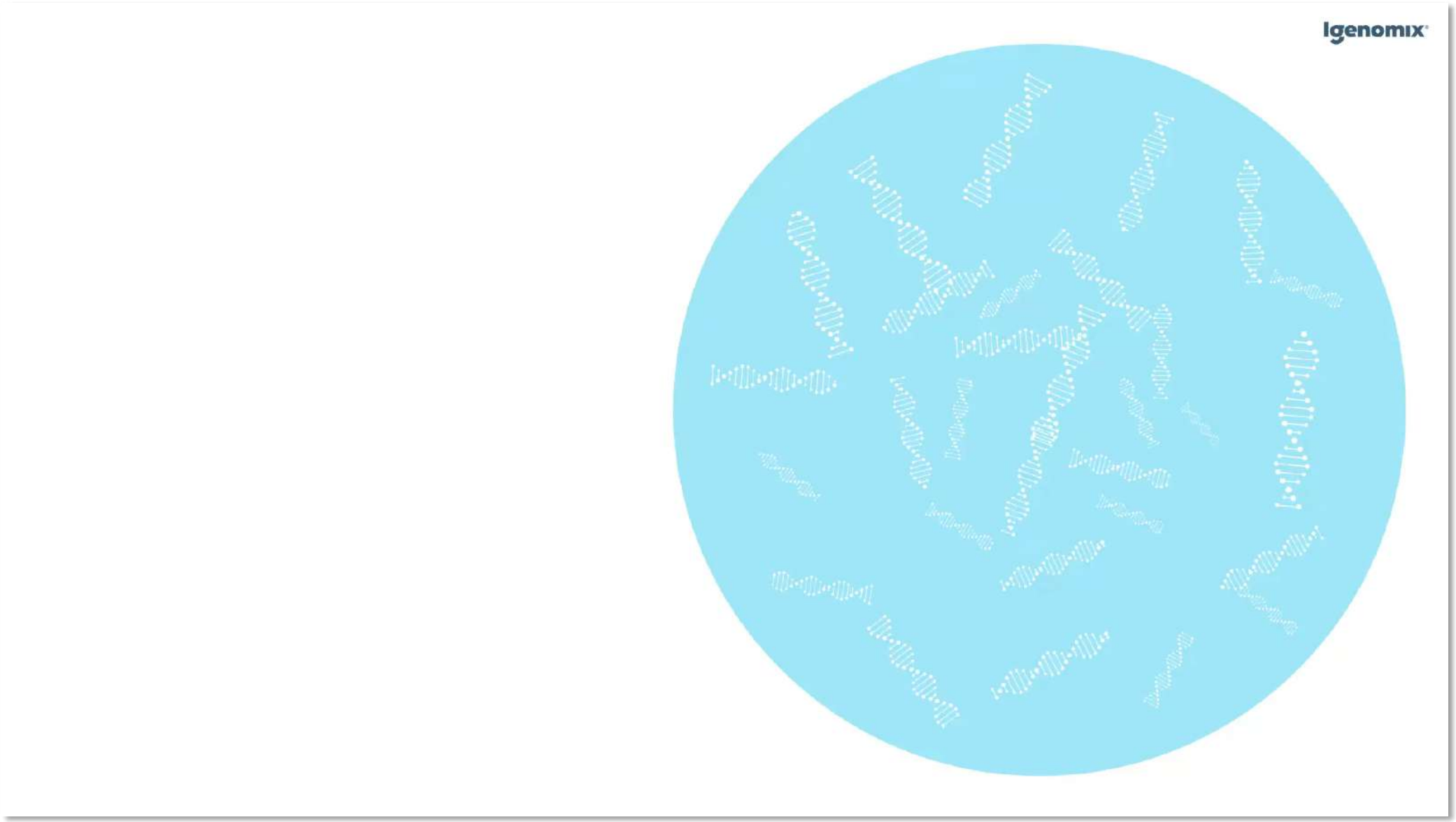
EMBRYO ANALYSIS OF CULTURE ENVIRONMENT

Embryos stay safe in the IVF clinic

What is the procedure?

Play video



Test results

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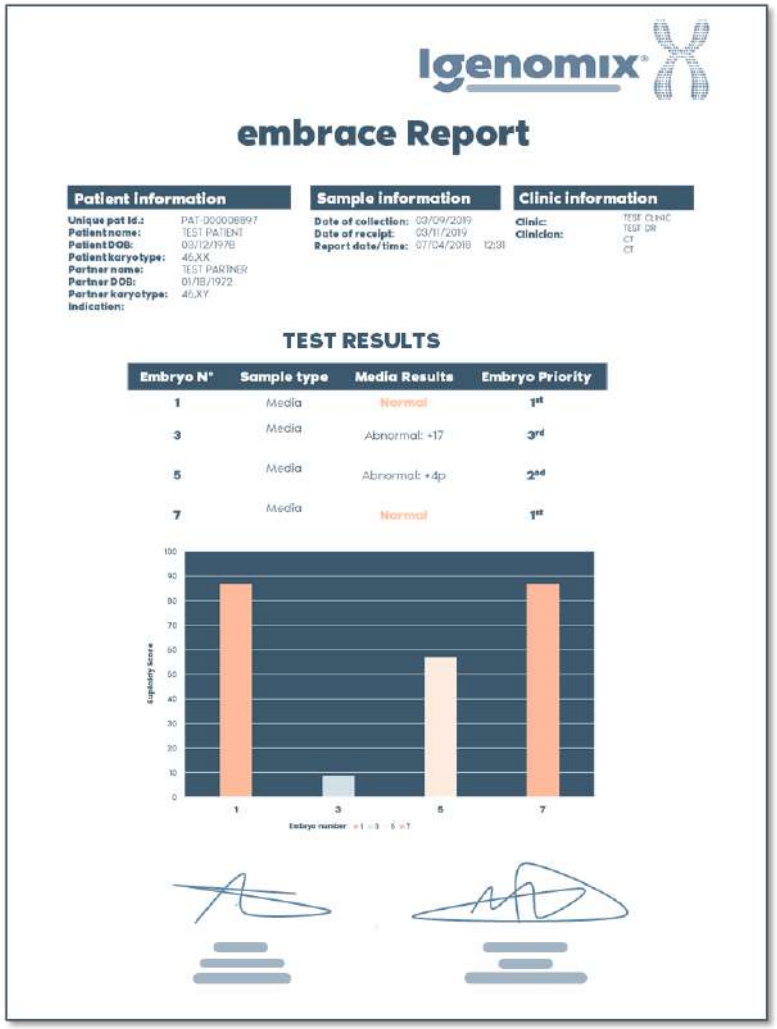
Embrace scores the embryos according to their higher chance of being normal

Embryos with the highest chance will be given the highest score and prioritized for transfer.



Igenomix

embrace Report

Patient information		Sample information		Clinic information	
Unique pat Id.:	PAT-00008897	Date of collection:	03/09/2019	Clinic:	TEST CLINIC
Patient name:	TEST PATIENT	Date of receipt:	03/11/2019	Clinician:	TEST DR
Patient DOB:	03/12/1978	Report date/time:	07/04/2018 12:31		CT
Patient karyotype:	46,XX				CT
Partner name:	TEST PARTNER				
Partner DOB:	01/18/1922				
Partner karyotype:	46,XY				
Indication:					

TEST RESULTS

Embryo N°	Sample type	Media Results	Embryo Priority
1	Media	Normal	1st
3	Media	Abnormal: +17	3rd
5	Media	Abnormal: +4p	2nd
7	Media	Normal	1st

Work-flow for the development of the prioritization system

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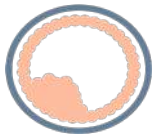
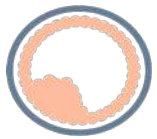
1. **Thresholds for ploidy:** Based in a mathematical calculation (Youden test), to identify the cut-off values for each abnormality to obtain the highest sensitivity and specificities with the trophectoderm biopsies.
2. **Euploidy Score** for different types of abnormalities

Embryo Priority
- Number of aneuploidies
- Type of aneuploidies

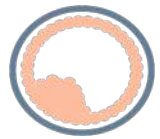
ES: Euploidy Score
LR: Lower range
UR: upper range



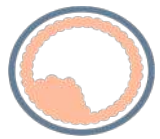
Number-Type aneuploidy
Embryo priority 1



Number-Type aneuploidy
Embryo priority 2



Number-Type aneuploidy
Embryo priority 3



Number-Type aneuploidy
Embryo priority 4

Igenomix validation

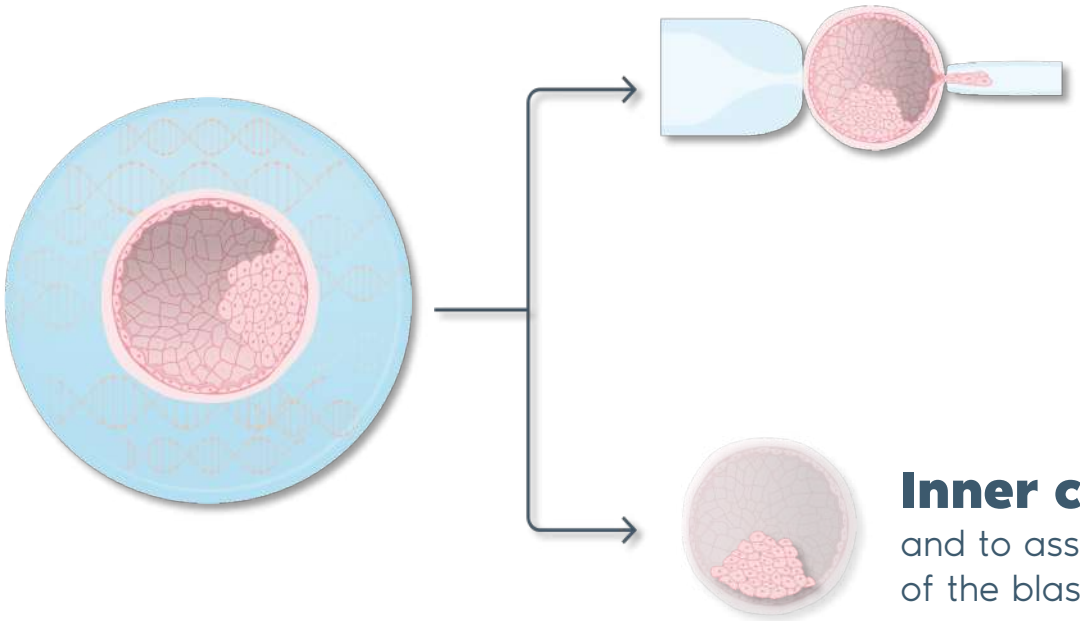
Multicenter prospective study

This is the largest study to date assessing ploidy concordance per embryo between invasive and non-invasive PGT-A

Rubio et al: Multicenter prospective study of concordance between embryo cell-free DNA and trophectoderm biopsies from 1,301 human blastocyst. American Journal of Obstetrics and Gynecology.

Multicenter prospective study

Goals



Trophectoderm DNA

To evaluate the concordance and reproducibility of testing embryo cell-free DNA versus trophectoderm DNA obtained from the same embryo in a large sample of 1,301 day 6 and day 7 human blastocysts,

Inner cell mass DNA

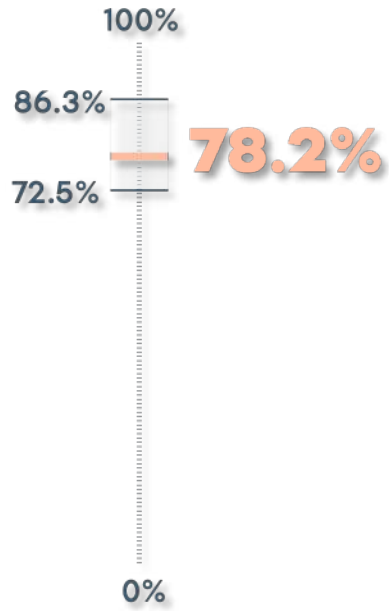
and to assess the concordance rates with the inner cell mass of the blastocysts donated for research.

Rubio et al: Multicenter prospective study of concordance between embryo cell-free DNA and trophectoderm biopsies from 1,301 human blastocyst. American Journal of Obstetrics and Gynecology.

Multicenter prospective study

- **Concordance rates of 1,301 embryo cell-free DNA and trophectoderm DNA**

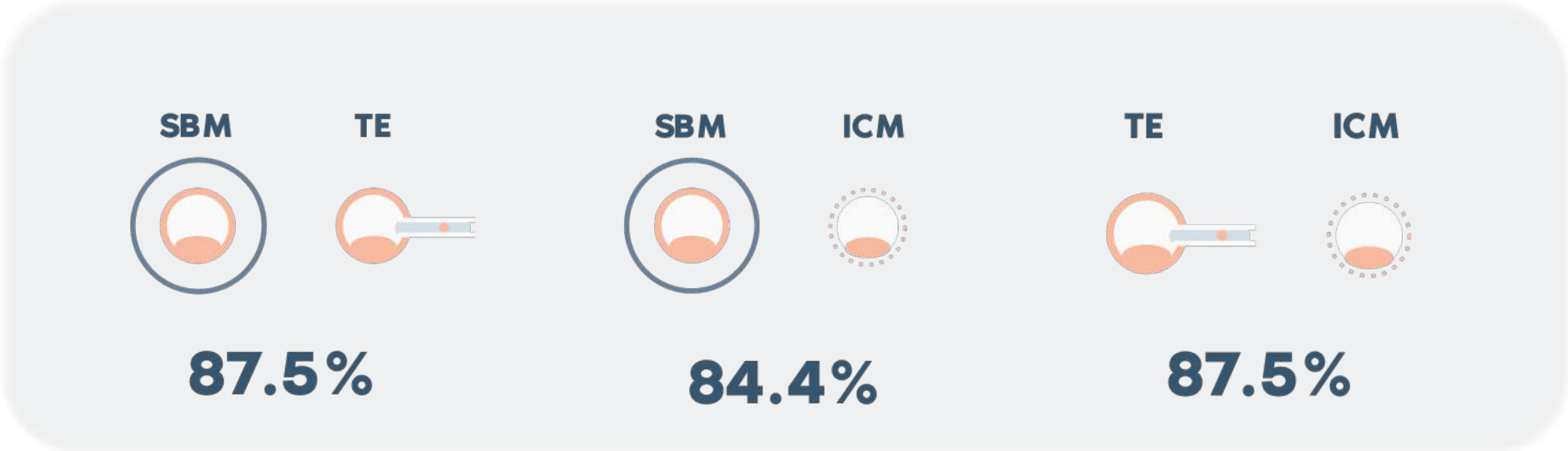
	Center 1	Center 2	Center 3	Center 4	Center 5	Center 6	Center 7	Center 8	TOTAL
Concordance	75.6	77.1	81.8	86.3	84.2	85.0	72.5	77.0	**78.2**
Sensitivity	80.5	84.8	88.2	86.7	91.3	76.7	76.5	78.9	**81.7**
Specifity	69.9	72.7	85.2	87.5	80.0	93.3	64.7	78.1	**77.4**



Rubio et al: Multicenter prospective study of concordance between embryo cell-free DNA and trophectoderm biopsies from 1,301 human blastocyst. American Journal of Obstetrics and Gynecology.

Multicenter prospective study

- **Concordance rates with inner cell mass of 81 blastocysts**



Rubio et al: Multicenter prospective study of concordance between embryo cell-free DNA and trophectoderm biopsies from 1,301 human blastocyst. American Journal of Obstetrics and Gynecology.

Limitations of the test

Considerations and limitations of the test

- Currently, the **concordance rate** of this test with invasive biopsy procedures is **78.2%**.
- The **embryos never leave your clinic**; the genetics laboratory only receives a sample of the fluid in which the embryos have been grown.
- The test is valid only when **embryos have been grown to6 or 7 days of age** and are at the blastocyst stage.
- This test **cannot be used to choose the gender of the embryo**.
- On rare occasions, genetic testing cannot be carried out because of **insufficient or poor-quality DNA in the liquid or contamination from maternal DNA cells.**
- **In some cases, additional genetic assessment may be needed**, which might include an embryo biopsy.

Doctors and Embryologists' comments

Doctors and embryologists' comments

- **Whether the media to be used is the same one which they are using for Embryo culture?**
  Yes, it is the same, the modifications are the culture conditions from day 4-day-6.

- **What if the Blast on D5.5 is an "Early Blast", "Cavitating Blast"?**
  They must keep the embryo in culture one more day until day 6. It should not be a problem in most laboratories.

- **What if Embryos hatch?**
  No problem, few blastocyst Hatch spontaneously on day 6 if they have not been manipulated before.

- **What about "Non-Informative results"? Can the clinics keep 01 extra tube of SCBM at (-20 degree) else in such cases the clinics must thaw and freeze again? In such cases, is the repeat analysis free?**
  All the medium (10 microlitres) is used in the first analysis, there would not be extra media. If not informative, they can transfer according to morphology (offering NACE) or to biopsy.

Doctors and embryologists' comments

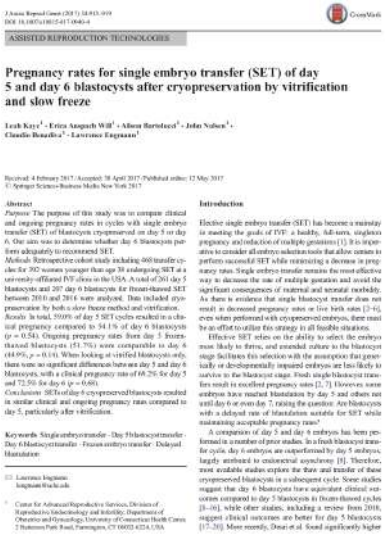
- **Any increase in Price? Price sensitive market.**
  There is an extra cost in reagents, because each cycle requires a control with media, without previous contact with the embryos.
- **What about MCC? How much would cumulus washing reduce the chances of MCC?**
  It is crucial to denude properly the oocytes and to do the washings according to our protocol.
- **In cases of MCC detected, would we do SNP analysis of such samples?** Not at the moment, the protocol we are currently applying do not allow for accurate SNP analysis. We consider that what is really important is to avoid contamination.
- **Some Drs are ok with simple categorisation of reports whereas others said they would appreciate detailed reports which helps in explaining the outcome to patients. Ambiguity.** We are proposing different options of reports according to different opinions.

Doctors and embryologists' comments

- **Is one step media good or the Drs are required to change the droplet everyday?** The IVF Laboratory will need to change the embryos to a fresh drop at least once, on the morning of day 4.
- **Can we use Embryoscope?** It can be used if the use the plates with individual wells. Time-lapse companies are aware of the need of individual culture for this kind of analysis.
- **What media to use?** Any kind of media, albumin, and culture conditions as far as embryos are culture individually in 10 microliters drops.
- **Should we perform ICSI?** No need, IVF insemination can be performed too, as far as zygotes are denuded properly after fertilization.
- **Accuracy: This may be one of the most determining factors since we know it is no above 95%...**
  May be current PGT-A gold standard is not such standard as we believe, and day 6 cell-free DNA might end up providing more significant chromosomal information than we have today

Doctors and embryologists' comments

- **Risks of day 6 culture?** The timing can be adjusted to day 5.5, if ovum pick-ups insemination and/ICSI are scheduled late on the day. Embryos are freeze at this moment, but embryo transfer in a deferred cycles can be scheduled on day 5 or according to ERA results. Below an article showing similar results of day 5, day 6 embryo transfer in vitrified cycles.



ASSISTED REPRODUCTION TECHNOLOGIES

Pregnancy rates for single embryo transfer (SET) of day 5 and day 6 blastocysts after cryopreservation by vitrification and slow freeze

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Received: 4 February 2017 / Accepted: 30 April 2017 / Published online: 12 May 2017
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Abstract

Purpose The purpose of this study was to compare clinical and ongoing pregnancy rates in cycles with single embryo transfer (SET) of blastocysts cryopreserved on day 5 or day 6. Our aim was to determine whether day 6 blastocysts perform adequately to recommend SET.

Methods Retrospective cohort study including 660 transfer cycles for 592 women younger than age 38 undergoing SET at a university-affiliated IVF clinic in the USA. A total of 261 day 5 blastocysts and 207 day 6 blastocysts for frozen-thawed SET between 2010 and 2014 were analyzed. Data included cryopreservation by both a slow freeze method and vitrification.

Results In total, 59.0% of day 5 SET cycles resulted in a clinical pregnancy compared to 54.1% of day 6 blastocysts ($p = 0.54$). Ongoing pregnancy rates from day 5 frozen-thawed blastocysts (51.7%) were comparable to day 6 (44.9%, $p = 0.14$). When looking at vitrified blastocysts only, there were no significant differences between day 5 and day 6 blastocysts, with a clinical pregnancy rate of 68.2% for day 5 and 72.5% for day 6 ($p = 0.80$).

Conclusions SETs of day 6 cryopreserved blastocysts resulted in similar clinical and ongoing pregnancy rates compared to day 5, particularly after vitrification.

Keywords Single embryo transfer · Day 5 blastocyst transfer · Day 6 blastocyst transfer · Frozen embryo transfer · Delayed implantation

Introduction

Elective single embryo transfer (SET) has become a mainstay in meeting the goals of IVF: a healthy, full-term, singleton pregnancy and reduction of multiple gestations [1]. It is imperative to consider all embryo selection tools that allow centers to perform successful SET while minimizing a decrease in pregnancy rates. Single embryo transfer remains the most effective way to decrease the rate of multiple gestation and avoid the significant consequences of maternal and neonatal morbidity. As there is evidence that single blastocyst transfer does not result in decreased pregnancy rates or live birth rates [2–6], even when performed with cryopreserved embryos, there must be an effort to utilize this strategy in all feasible situations.

Effective SET relies on the ability to select the embryo most likely to thrive, and extended culture to the blastocyst stage facilitates this selection with the assumption that genetically or developmentally impaired embryos are less likely to survive to the blastocyst stage. Fresh single blastocyst transfers result in excellent pregnancy rates [2, 7]. However, some embryos have reached blastulation by day 5 and others not until day 6 or even day 7, raising the question: Are blastocysts with a delayed rate of blastulation suitable for SET while maintaining acceptable pregnancy rates?

A comparison of day 5 and day 6 embryos has been performed in a number of prior studies. In a fresh blastocyst transfer cycle, day 6 embryos are outperformed by day 5 embryos, largely attributed to endometrial asynchrony [8]. Therefore, most available studies explore the thaw and transfer of these cryopreserved blastocysts in a subsequent cycle. Some studies suggest that day 6 blastocysts have equivalent clinical outcomes compared to day 5 blastocysts in frozen-thawed cycles [8–16], while other studies, including a review from 2018, suggest clinical outcomes are better for day 5 blastocysts [17–20]. More recently, Dinari et al. found significantly higher

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Table 3 SET for slow frozen and vitrified cryopreserved embryos, overall, and by age group

	Slow frozen			Vitrified		
	Day 5	Day 6	*p* value	Day 5	Day 6	*p* value
Total frozen ETs, *n*	170	156		91	51	
Clinical pregnancy, *n* (%)	91/170 (53.5)	75/156 (48.1)	0.55	63/91 (69.2)	37/51 (72.5)	0.68
<35 years old	70/128 (54.7)	59/114 (51.8)	0.57	54/77 (70.1)	27/34 (79.4)	0.31
35–37 years old	21/42 (50.0)	16/42 (38.1)	0.36	9/14 (64.3)	10/17 (58.8)	0.76
Ongoing pregnancy/live birth, *n* (%)	78/170 (45.9)	61/156 (39.1)	0.22	57/91 (62.6)	32/51 (62.7)	0.99
<35 years old	61/128 (47.7)	49/114 (43.0)	0.47	51/77 (66.2)	23/34 (67.6)	0.88
35–37 years old	17/42 (40.5)	12/42 (28.6)	0.25	6/14 (42.9)	9/17 (52.9)	0.58
Multiple gestation, *n* (%)	1/91 (1.1)	0/75 (0)	1.00	1/63 (1.6)	1/37 (2.7)	1.00
Clinical pregnancy loss, *n* (%)	15/91 (16.5)	15/75 (20.0)	0.81	7/63 (11.1)	6/37 (16.2)	0.55
Biochemical pregnancy, *n* (%)	16/107 (15.0)	23/100 (23.0)	0.14	12/77 (15.6)	1/38 (2.6)	0.06
Ectopic pregnancy, *n* (%)	0 (0)	0 (0)		1/77 (1.3)	0 (0)	1.00

Conclusions

Conclusions

We can conclude that this non-invasive approach could avoid embryo biopsies and reduce costs, while democratizing its use and increasing accessibility for a wider population of patients.

Nevertheless, more studies are needed to understand the origin of the embryo cell-free DNA and the mechanisms involved.

Download the paperwork

Formulario de solicitud de Test

Instrucciones de uso

Ahora los links son de COVID, es para hacer la prueba


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