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Een blik op de toekomst van de medisch begeleide voortplanting

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Overzicht

- Nieuwe technieken in de dagelijkse praktijk
  - Vitrificatie
  - Pre-implantatie genetische testing = PGT

- Recente nieuwe zorgtrajecten
  - Social freezing
  - Expanded carrier-screening

- De (nabije) toekomst
  - *Individualised medicine in ART*
  - Niet invasief testen van embryo’s

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Everyone here has the sense that right now is one of those moments when we are influencing the future
- Steve Jobs -

Nieuwe technologie in de routine praktijk



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Cryopreservatie

- Essentieel in medisch begeleide voortplanting
  - Overtallige embryo's
  - Sperma
  - Eicellen
  - Ovarieel weefsel



- Twee technieken
  - Slow freezing
  - Vitrificatie

→ Beide technieken zijn gekend sinds de begindagen van IVF

Cryopreservation of human embryos by vitrification or slow freezing: a systematic review and meta-analysis

Kalliopi E. Loutradi, M.Med.Sc., Efstratios M. Kolibianakis, M.D., Ph.D., Christos A. Venetis, M.D., M.Sc., Evangelos G. Papanikolaou, M.D., Ph.D., George Pados, M.D., Ph.D., Ioannis Bontis, M.D., Ph.D., and Basil C. Tarlatzis, M.D., Ph.D.

Human Reproduction, Vol.30, No.8 pp. 1820–1830, 2015
Advanced Access publication on June 18, 2015 doi:10.1093/humrep/dev134

human reproduction ORIGINAL ARTICLE *Embryology*

Vitrification of cleavage stage day 3 embryos results in higher live birth rates than conventional slow freezing: a RCT

S. Debrock*, K. Peeraer, E. Fernandez Gallardo, D. De Neubourg, C. Spiessens, and T.M. D'Hooghe

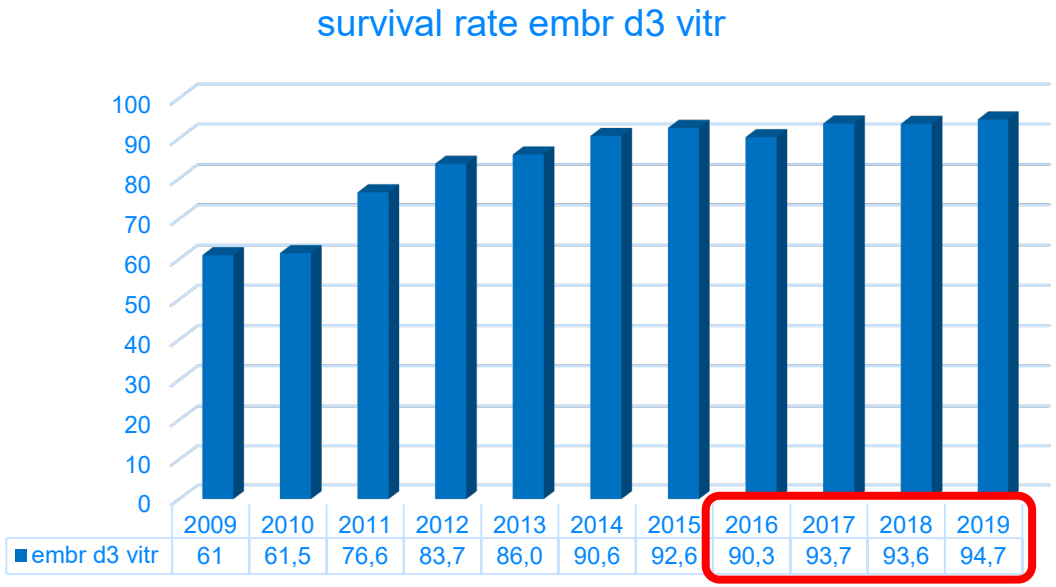
Human Reproduction Update, Vol.23, No.2 pp. 139–155, 2017
Advanced Access publication on November 4, 2016 doi:10.1093/humupd/dmw038

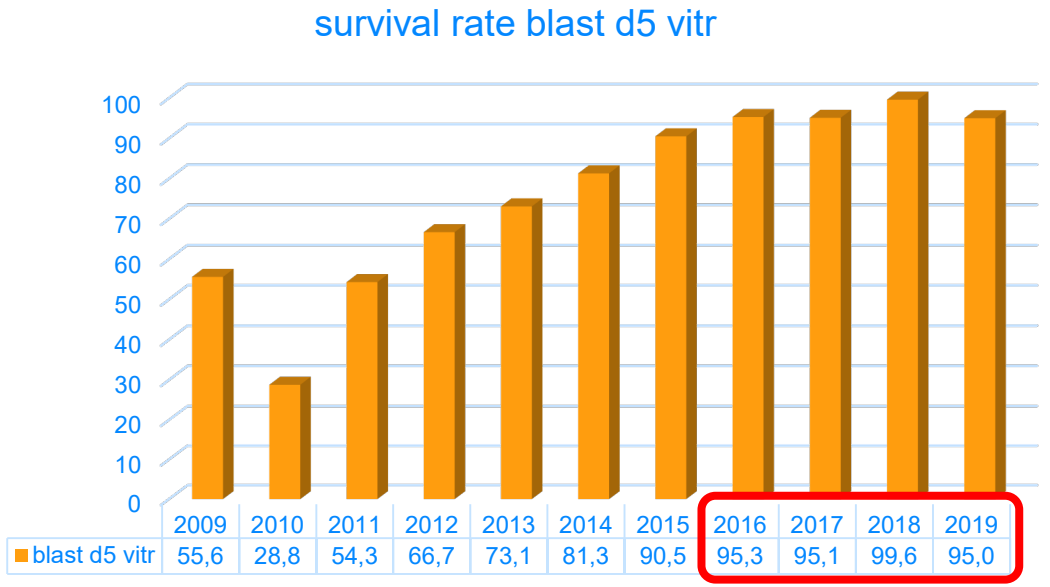
human reproduction update

Oocyte, embryo and blastocyst cryopreservation in ART: systematic review and meta-analysis comparing slow-freezing versus vitrification to produce evidence for the development of global guidance

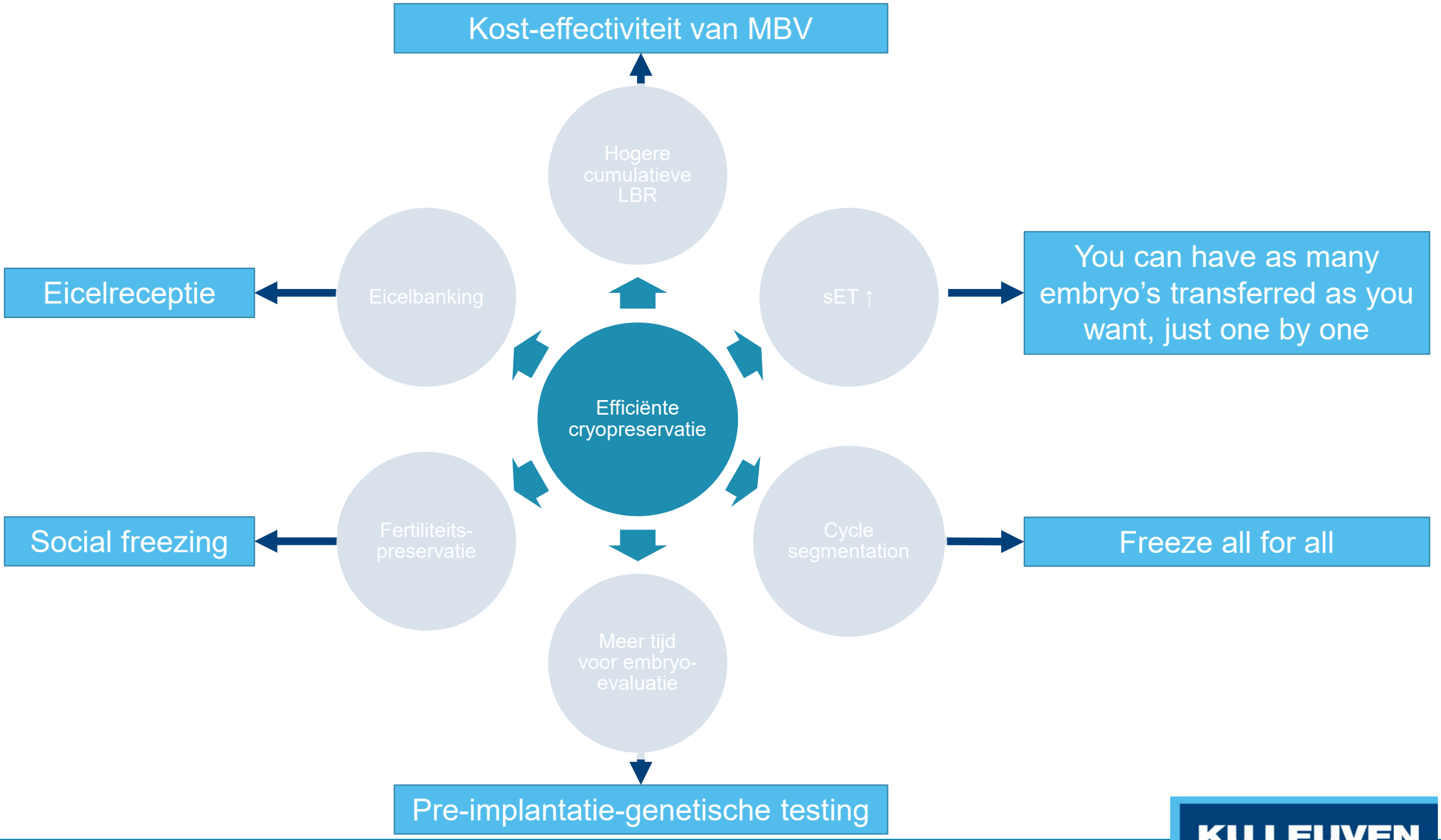
Laura Rienzi[1,*], Clarisa Gracia[2], Roberta Maggiulli[1], Andrew R. LaBarbera[3], Daniel J. Kaser[4], Filippo M. Ubaldi[1], Sheryl Vanderpoel[5,6], and Catherine Racowsky[4]

Resultaten vitrificatie embryo's





Data met dank aan Prof. S. Debrock


Kost-effectiviteit van MBV
Hogere cumulatieve LBR
Eicelreceptie
Eicelbanking
sET ↑
You can have as many embryo's transferred as you want, just one by one
Efficiënte cryopreservatie
Social freezing
Fertiliteits-preservatie
Cycle segmentation
Freeze all for all
Meer tijd voor embryo-evaluatie
Pre-implantatie-genetische testing

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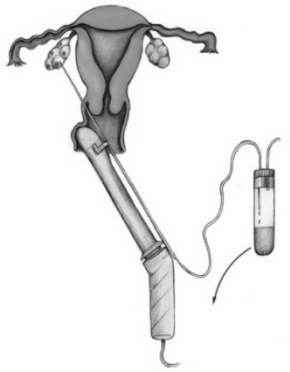
Pre-implantatie genetische testing

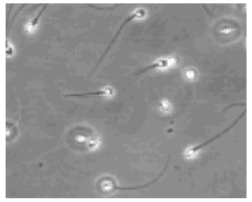
Genetische analyse van embryo's die zijn ontstaan tijdens een IVF-behandeling vooraleer deze embryo's in de baarmoeder worden teruggeplaatst.

- PGT-M: monogenetische aandoening
  - Fertiele koppels met verhoogd risico op kind met een genetische aandoening
- PGT-SR: structural rearrangements
  - Herhaald miskraam of infertiele koppels
- PGT-A: screening voor aneuploïde embryo’s
  - Infertiele koppels
  - Doel: verhogen van de slaagkansen van de IVF behandeling

Pre-implantatie genetische testing

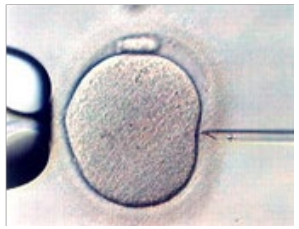
Day 0



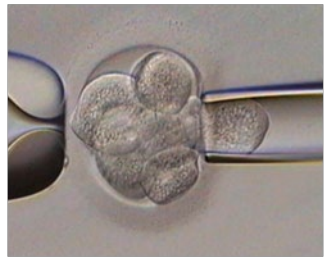


Eicelaspiratie | Sperm prep

ICSI

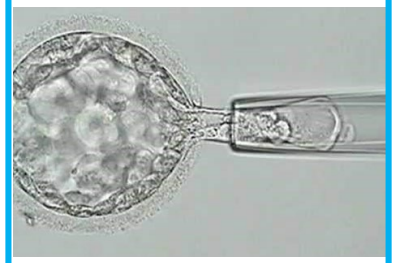


Day 3



Embryo biopsie

Day 5



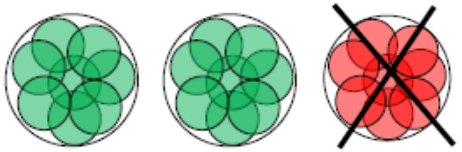
TE biopsie

Day 5



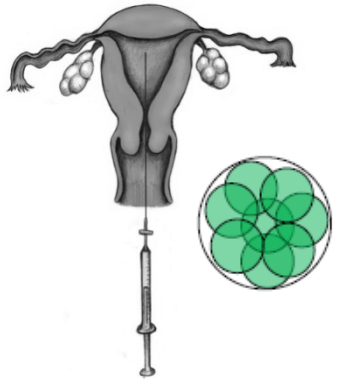
Cryopreservatie

Genetische analyse

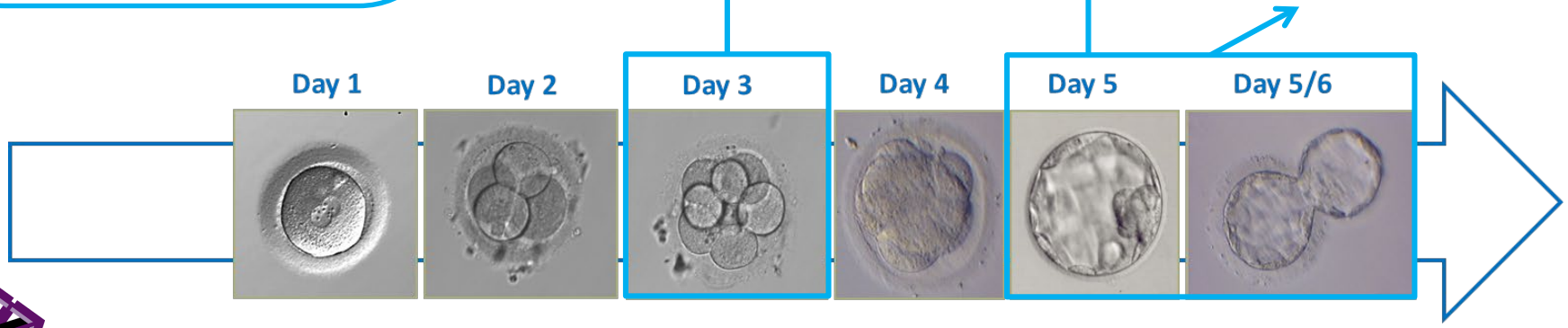


4-6 weken

Ontdooicyclus



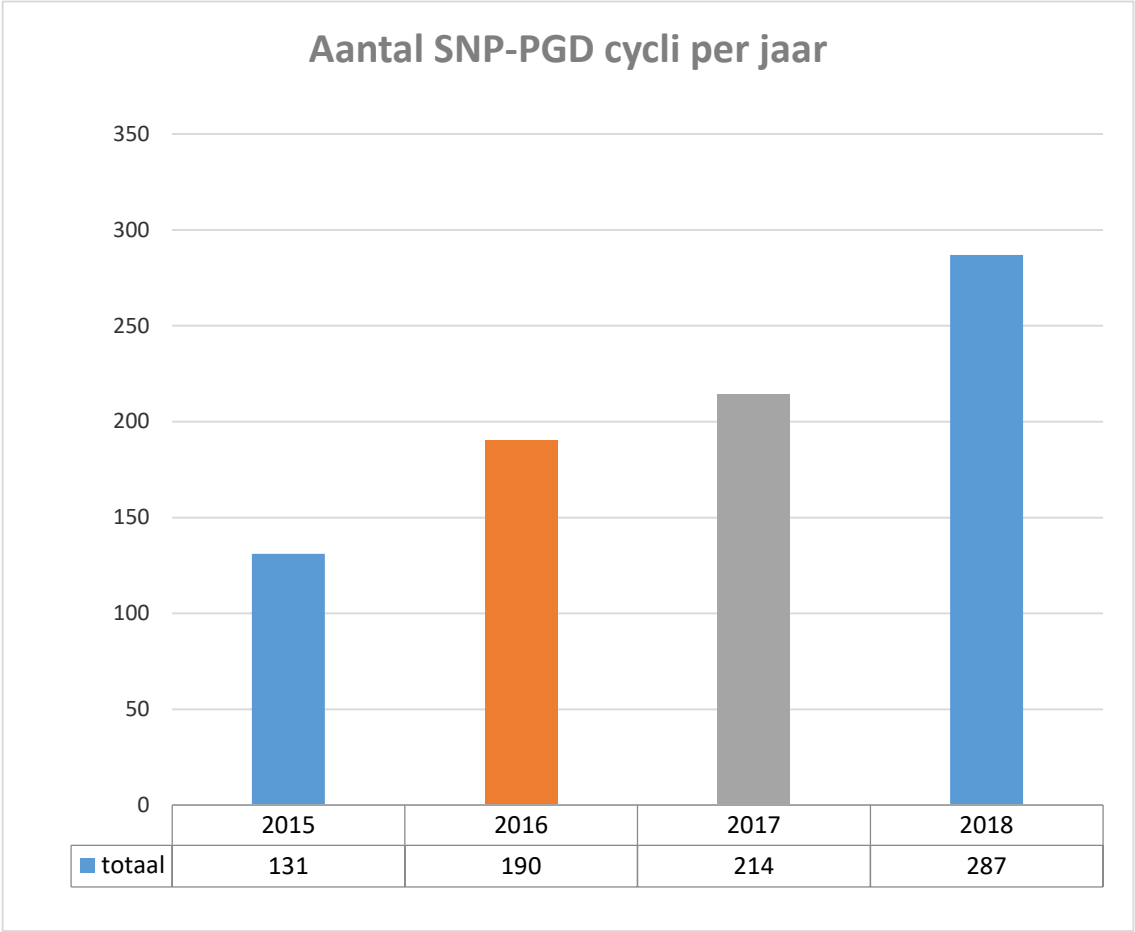
Embryo transfer



Slide met dank aan Prof. S. Debrock

Indicaties voor PGT-M en PGT-SR

- Monogenetische aandoeningen
  - Autosomaal recessief: mucoviscidose, SMA, Sikkelcelanemie
  - Autosomaal dominant: Huntington, BRCA-1, BRCA-2, neurofibromatose
  - X-gebonden: Duchenne musculaire dystrofie, Fragiele–X syndroom, Haemofilie
- Chromosomale afwijkingen
  - Reciproke translocaties
  - Robertsoniaanse translocaties
  - Microdeleties
  - Inversies
  - …



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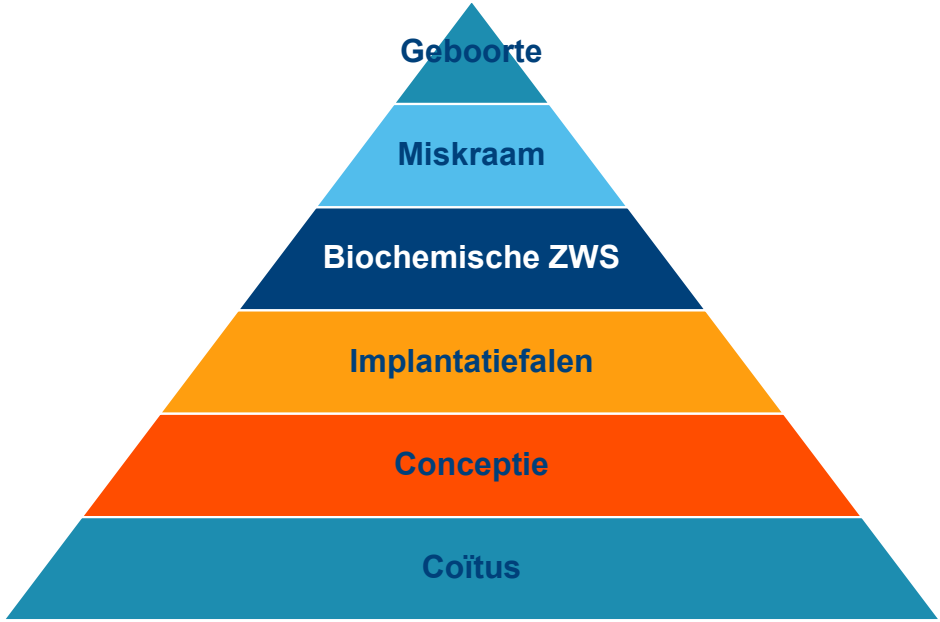
Wat met PGT-A?

- Zelfde techniek
  - TE-biopsie
  - Screening van embryo's voor aneuploïdie
  - Selectieve transfer van euploïde embryo's



- Infertiele koppels

- Doel: verhogen van de slaagkansen/efficiëntie van de IVF-behandeling
  - Cumulatieve live birth rate: onmogelijk
  - Time to pregnancy?

Mosaïcisme

- Exacte prevalentie??
- Klinische data vs research data
- Mosaïek embryo's kunnen resulteren in normale zwangerschappen

Healthy Babies after Intrauterine Transfer of Mosaic Aneuploid Blastocysts

TO THE EDITOR: Chromosomal aneuploidy is recognized as a factor that contributes to unsuccessful embryo implantation and spontaneous abortion. It provides an explanation for the relatively low success rate of in vitro fertilization (IVF) treatments. Preimplantation genetic screening is widely used to identify chromosomally normal (euploid) embryos and select them for intrauterine transfer in order to improve the clinical outcome of IVF.[1]

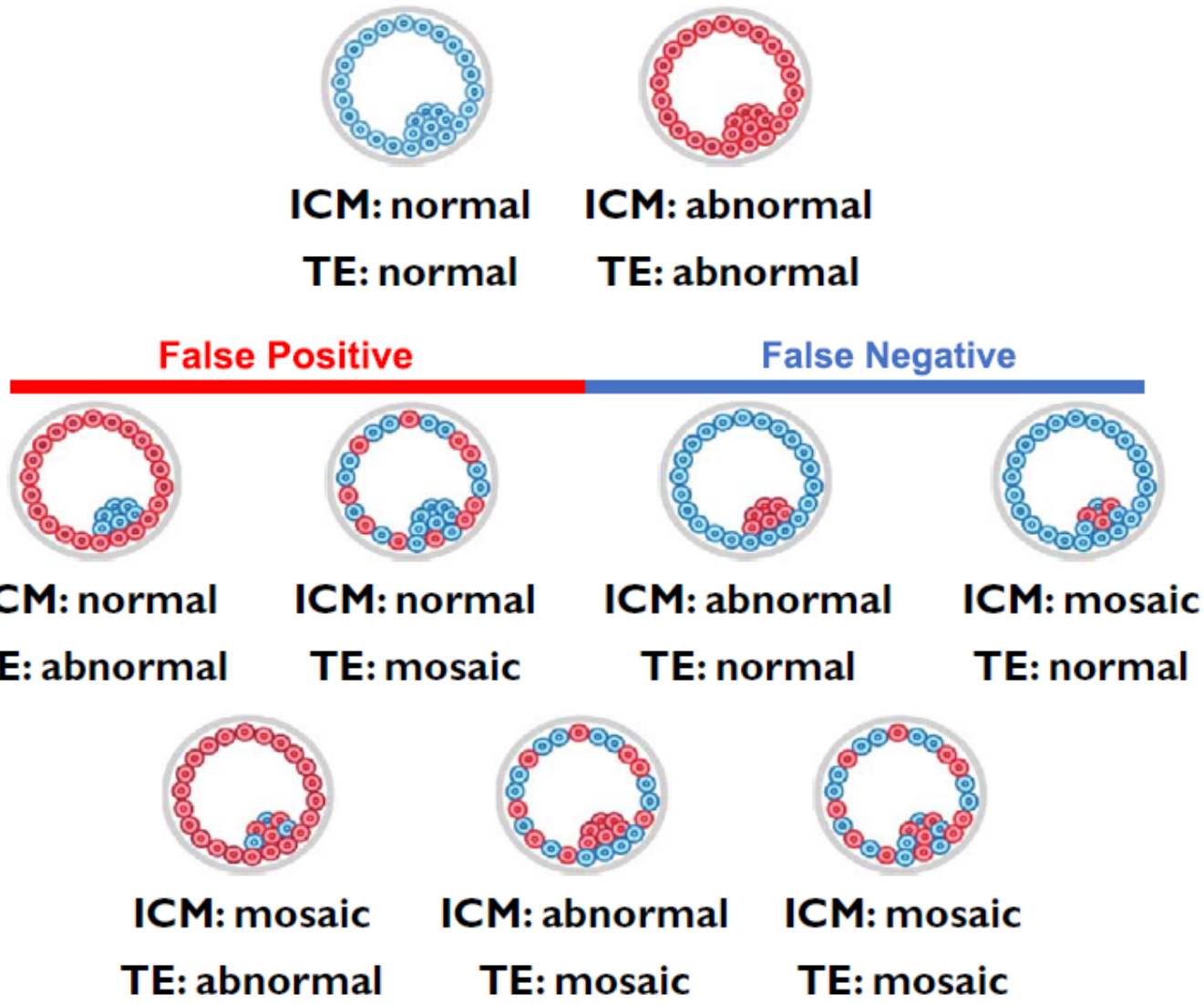
Chromosomal mosaicism is a relatively common finding in IVF-derived human embryos.[2] Mosaic embryos, which are characterized by the presence of a mixture of diploid and aneuploid cell lines, are not usually transferred because they are deemed to be abnormal. Although the effect of mosaicism on implantation and the developmental potential of these embryos is not known, it is reasonable to assume that mosaicism reduces the likelihood of success of IVF.[3]

The low levels of mosaicism reported in prenatal specimens and the reduced incidence of mosaicism with increasing gestational age suggest that there exists a mechanism by which mosaic aneuploidy is corrected or by which aneuploid cells are "outcompeted" by euploid cells.[4] To our knowledge, healthy live births after transfer of mosaic aneuploid blastocysts obtained by means of IVF have not been reported. However, a previous study in which the researchers were unaware of the results of genetic screening may have involved the transfer of mosaic embryos that resulted in clinical pregnancies.[5]

Between May 2013 and July 2014, we analyzed 3802 blastocysts by means of array-comparative genomic hybridization testing (see the Supplementary Appendix, available with the full text of this letter at NEJM.org). We detected chromosomal mosaicism in 181 blastocysts (4.8%). The transfer of mosaic embryos was made available to a consecutive nonselected series of 18 women for whom IVF had resulted in no euploid embryos. We provided the results of the genetic screening to the women and counseled them on the potential consequences of transferring a mosaic embryo. We tailored the counseling according to the type of aneuploidy.

An institutional ethics committee approved the protocol (available at NEJM.org), and we obtained written informed consent from each woman before proceeding with embryo implantation. All the women elected to undergo implantation (only one mosaic blastocyst was available in each case). Eight clinical pregnancies (maternal serum positive for the beta subunit of human chorionic gonadotropin) ensued, of which six resulted in the birth of a singleton infant at term. All pregnancies that went to term were confirmed, by

N ENGL J MED 373;21 NEJM.ORG NOVEMBER 19, 2015



Popovic et al. HRU 2020

STAR-trial

- Populatie
  - Vrouwen 25-40 jaar, autologe eicellen, minstens 2 blastocysten voor TE-biopsie
  - Exclusie: verminderde ovariële reserve, >2 gefaald IVF cycli, >1 miskraam, azoöspermie, ernstige oligospermie
- Interventie:
  - RCT, 1x FRET, embryoselectie PGT-A vs embryoselectie o.b.v. morfologie

TABLE 3

Outcomes in patients undergoing an embryo transfer with embryo selection by means of preimplantation genetic testing for aneuploidy (PGT-A) versus morphology (Control), n (%).

	< 35 y		35–40 y		All patients		
Outcome	PGT-A (n = 152)	Control (n = 168)	PGT-A (n = 122)	Control (n = 145)	PGT-A (n = 274)	Control (n = 313)	*P* value[a]
Negative β-hCG	46 (30.3)	53 (31.5)	34 (27.9)	59 (40.7)	80 (29.2)	112 (35.8)	.0934
Positive β-hCG	106 (69.7)	115 (68.5)	88 (72.1)	86 (59.3)	194 (70.8)	201 (64.2)	ND
Biochemical pregnancy	14 (9.2)	10 (6.0)	15 (12.3)	16 (11.0)	29 (10.6)	26 (8.3)	.3315
Miscarriage	17 (11.2)	14 (8.3)	10 (8.2)	16 (11.0)	27 (9.9)	30 (9.6)	.8979
Elective termination	0	2 (1.2)	1 (0.8)	0	1 (0.4)	2 (0.6)	.6603
Ongoing pregnancy at 20 weeks' gestation	75 (49.3)	89 (53.0)	62 (50.8)	54 (37.2)	137 (50.0)	143 (45.7)	.3177
P value for age subgroups	*P*=.5757		*P*=.0349				

Note: ND = not determined.

[a] *P* value determined by means of Cochran-Mantel-Haenszel test.

Munné. RCT evaluating NGS-based PGT-A. Fertil Steril 2019.

Munné et al. Fertil Steril 2019

PGT-A

- Geen indicatie voor PGT-A in algemene populatie

- Mogelijk benefit in kleine subsets van patiënten
  - Goeie responders >35 jaar
  - Herhaald implantatiefalen?
  - Etc.

- Cave:
  - Grote extra kost voor mogelijk beperkte winst…
  - Mogelijkheid van foute diagnose (mosaïcisme)

"…PGT-A is an expensive technique that makes an already expensive treatment even more expensive…"

Human Reproduction, Vol.35, No.3, pp. 490–493, 2020
Advance Access Publication on February 25, 2020 doi:10.1093/humrep/dez280

human reproduction OPINION

Hidden in plain sight: the overstated benefits and underestimated losses of potential implantations associated with advertised PGT-A success rates

Richard J. Paulson*

RBMO

ELSEVIER

COMMENTARY

Shooting STAR: reinterpreting the data from the 'Single Embryo TrAnsfeR of Euploid Embryo' randomized clinical trial

Luca Pagliardini[1,*], Paola Viganò[1], Alessandra Alteri[2], Laura Corti[2], Edgardo Somigliana[3,4], Enrico Papaleo[2]

Trends in Molecular Medicine

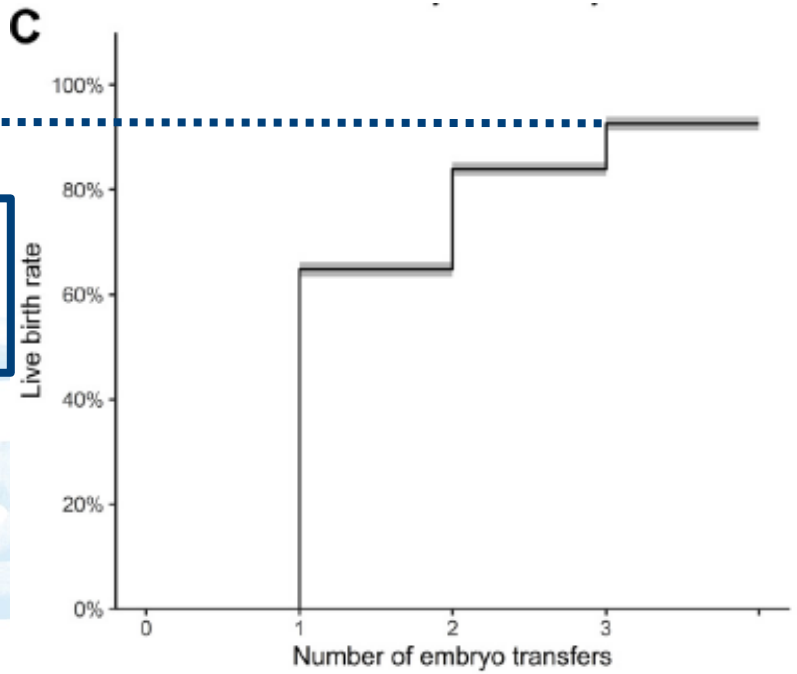
Opinion

Preimplantation Genetic Testing for Aneuploidy – a Castle Built on Sand

Norbert Gleicher,[1,2,3,4,*] Pasquale Patrizio,[1,5] and Ali Brivanlou[3]

Rate of true recurrent implantation failure is low: results of three successive frozen euploid single embryo transfers

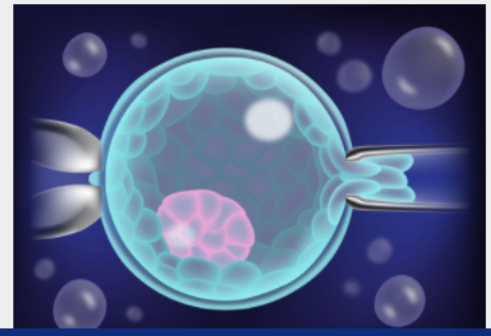
Paul Pirtea, M.D.,[a,b] Dominique De Ziegler, M.D.,[b] Xin Tao, Ph.D.,[c] Li Sun, Ph.D.,[c] Yiping Zhan, Ph.D.,[c] Jean Marc Ayoubi, M.D.,[b] Emre Seli, M.D.,[a,d] Jason M. Franasiak, M.D., H.C.L.D.,[a] and Richard T. Scott Jr., M.D., H.C.L.D.[a]



Cumulative LBR na 3x
FE-sET: 92,3%
(CI:91,2-93,9%)

IMPLANTATION FAILURE

Recurrent implantation failure found to be 'rare' in euploid embryo transfers



A large retrospective study has proposed that recurrent implantation failure is rare and embryonic in its origin - and thus avoidable by transferrring euploid blastocysts.

Published 4 days ago

Large retrospective study of more than 4000 euploid embryo transfers finds very high implantation rates after each of three successive FETs. Recurrent implantation failure likely to be embryonic and not endometrial in its origin, propose investigators.

Prof Peeraer & Dr Geysenbergh: PGT-A bij herhaald implantatiefalen

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The future is already here, it's just not very evenly distributed
- William Gibson -

Nieuwe zorgtrajecten



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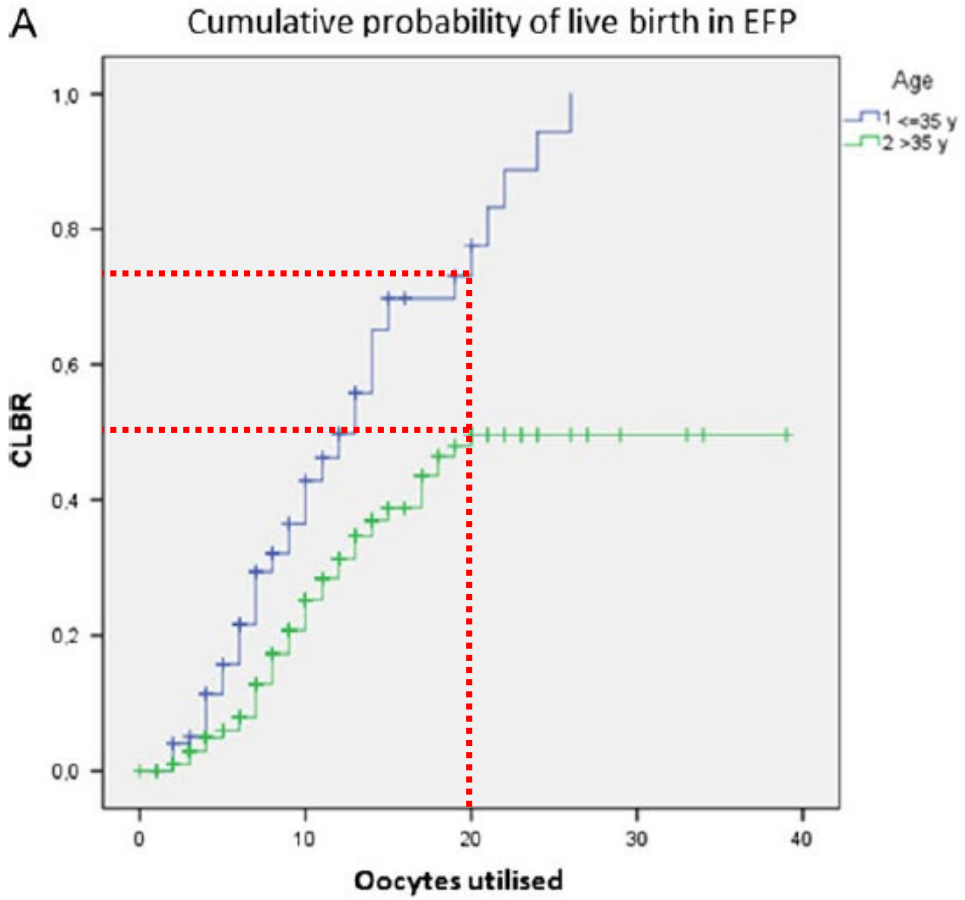
Cryopreservatie van eicellen



- Reproductieve autonomie
- Gendergelijkheid
- Sociale gelijkheid

- Sociale ongelijkheid
- Medische oplossing voor maatschappelijk probleem
- Commercialisatie van MBV

ESHRE Ethics taskforce: 'It is concluded that the arguments against allowing this application of the technology are not convincing'. However, they stress the need, 'for adequate information of women interested in oocyte cryopreservation, to avoid raising false hopes.



Age ≤35. N = 123		Age >35. N = 518	
N°oocytes	CLBR(95%CI)	N°oocytes	CLBR(95%CI)
5	15.8 (8.4-23.1)	5	5.9 (3.6-8.3)
8	32.0 (22.1-41.9)	8	17.3 (13.3-21.3)
10	42.8 (31.7-53.90)	10	25.2 (20.2-30.1)
15	69.8 (57.4-82.2)	15	38.8 (32.0-45.6
20	77.6 (64.4-90.9)	20	49.6 (40.7-58.4)
24	94.4 (84.3-100.4)		

You freeze your oocytes not your fertility!

- *Oocyte aspiration rate*
  - Hoeveel eicellen kan je bekomen per aspiratie?
- *Usage rate*
  - Wat is de kans dat je uw eicellen zal gebruiken?

➔LEEFTIJD

- *"Information is everything"*
  - Medische aspecten
  - Slaagkansen & Risico's
  - Psychologische aspecten
  - Financiële aspecten

Cobo et al. HR 2018

Carrierscreening



Carrierscreening

- Preconceptioneel screenen van koppels voor dragerschap van genetische aandoeningen
- Autosomaal of X-gebonden recessief
- >1000 genen
- 1% van de koppels verhoogd risico
- Kostprijs: 1400€/koppel



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I never worry about the future, it comes soon enough
- Albert Einstein -



De nabije toekomst

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Individualised medicine in ART

- Grote meerderheid van ART studies zijn in patiënten met goeie prognose → extrapolatie naar patiënten met slechte prognose

- Nood aan meer studies in specifieke populaties
  - Maternele leeftijd >38-40
  - Lage ovariële reserve/low responders
  - Endometriose
  - Herhaald implantatiefalen
  - Dun endometrium
  - Etc.

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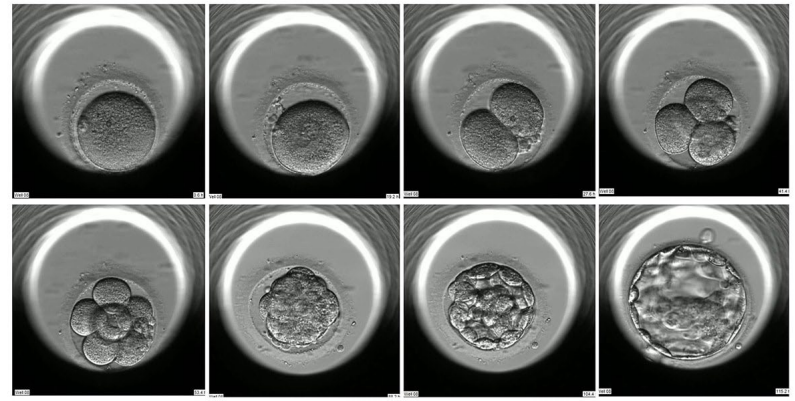
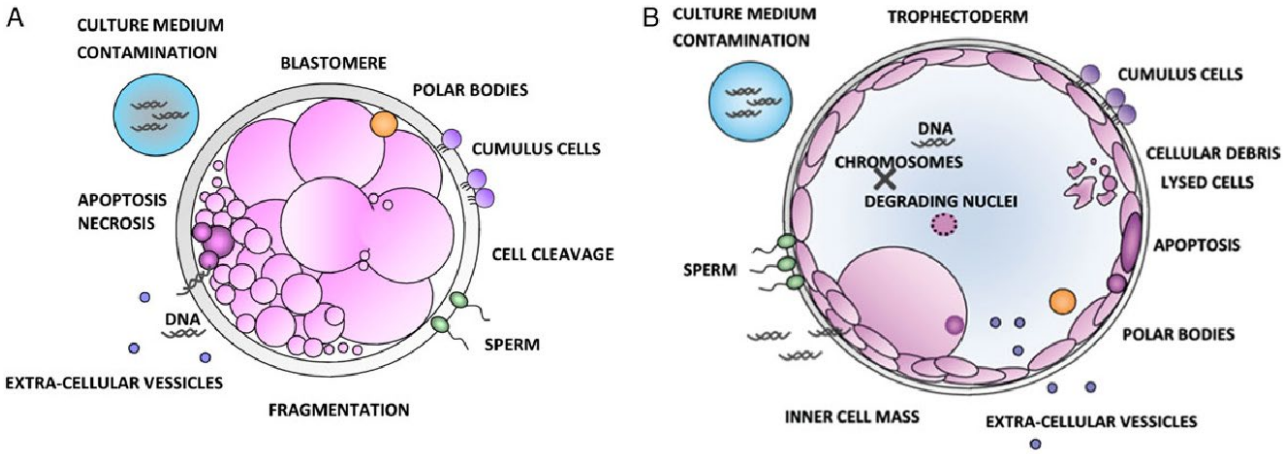
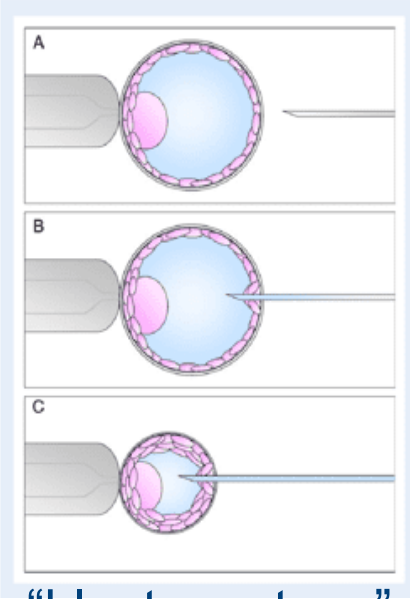
Niet invasief testen van embryo's

- AI-analyse van (beelden van) embryo's
- Cultuurmedium
- Granulosacellen of follikelvocht
- Blastocystvocht





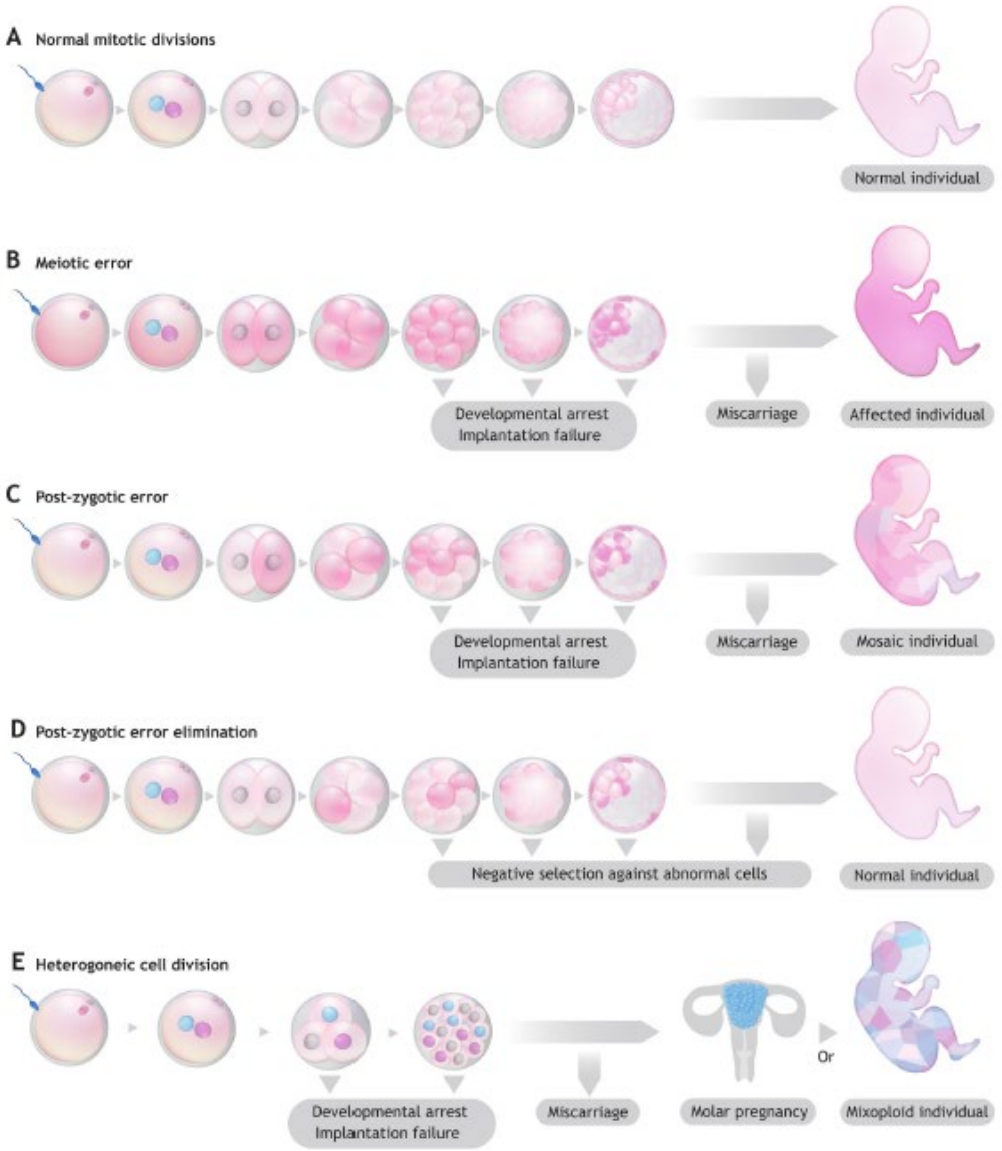


"blastocentese"

Hammond et al. HR 2016

PGT en single-cell genomics

- Nieuwe inzichten over vroege embryogenese
- Optimalisatie van PGT-A technologie
- Nieuwe therapeutische opties?

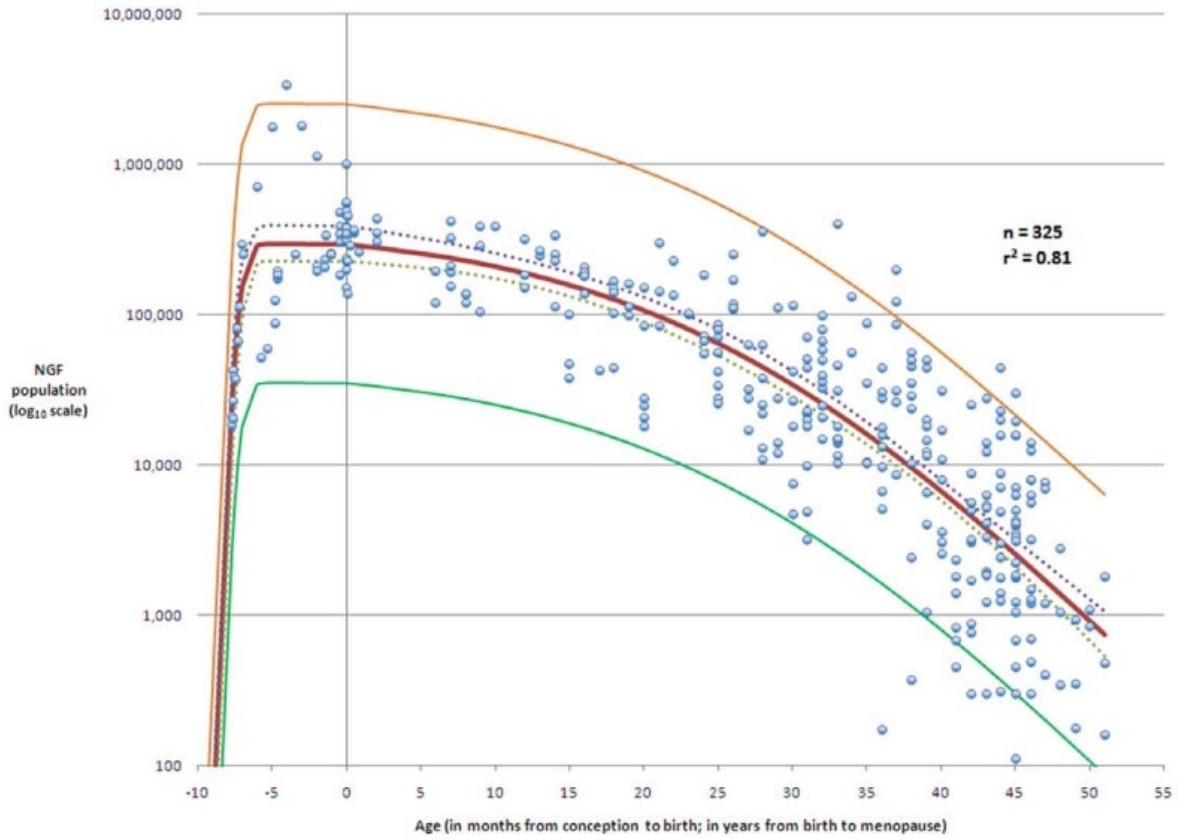


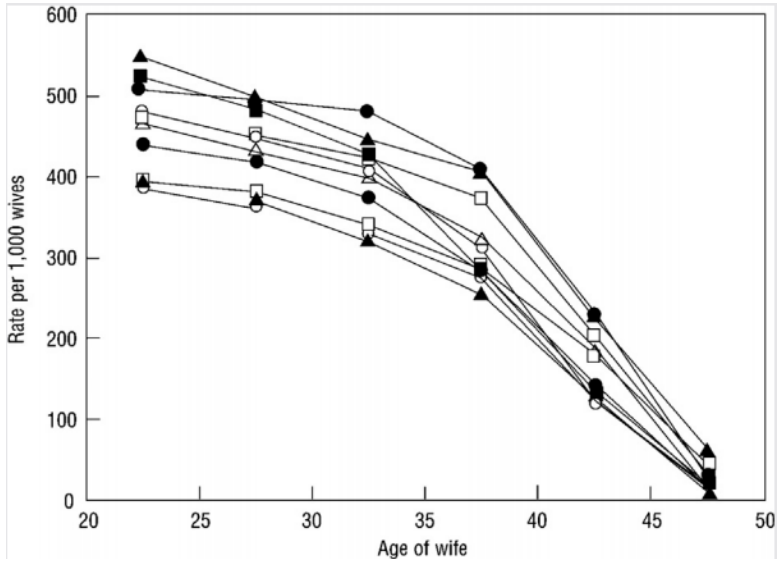
Tsuiko et al. Reproduction 2020

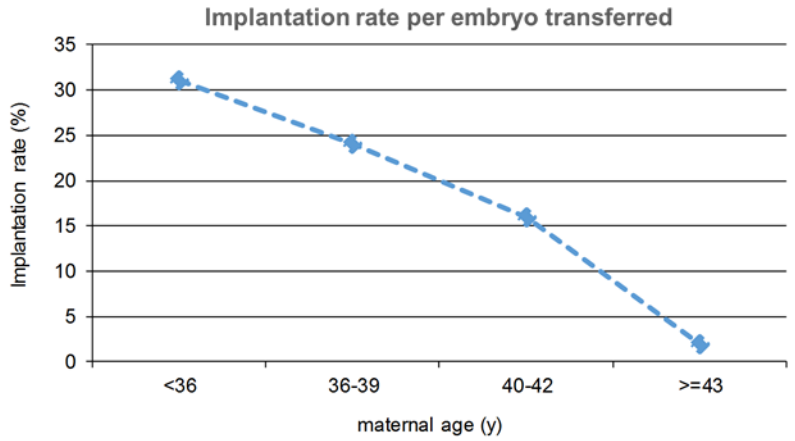
Referenties & *'further reading'*

- Vitrificatie
  - Loutradi et al Fertil Steril 2008; 90(1):186-193
  - Debrock et al. Hum Reprod 2015; 30(8):1820-1830
  - Rienzi et al. HRU 2017;23(2):139-155
- PGT
  - Munné et al. Fertil Steril 2019; 112(6):1071-1079.e7
  - Pagliardini et al. RBMO 2020;40(4):475-478
  - Popovic et al. HRU 2020; 26(3): 313–334
  - Pirtea et al. Fertil Steril 2021; 115(1):45-43
- Social freezing
  - ESHRE Guideline on Female Fertility Preservation
  - Cobo et al. Hum Reprod 2018; 24:1-10
- Niet invasief testen van embryo's
  - Leaver et al. HRU 2020;26(1):16-42
  - Hammond et al. Hum Reprod 2016; 31(8):1653–1661

Afname van de vruchtbaarheid met de leeftijd







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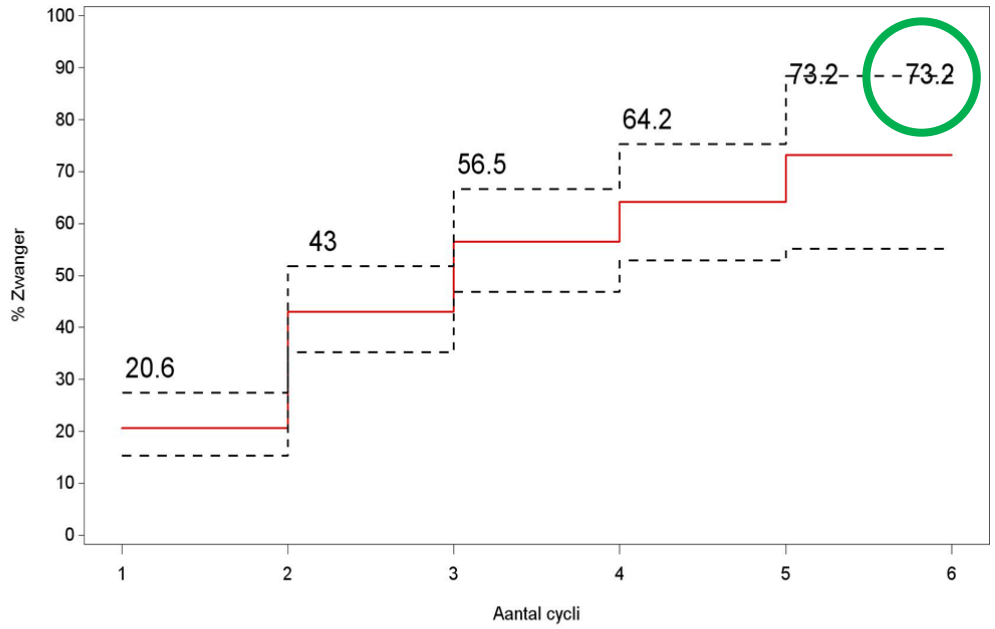
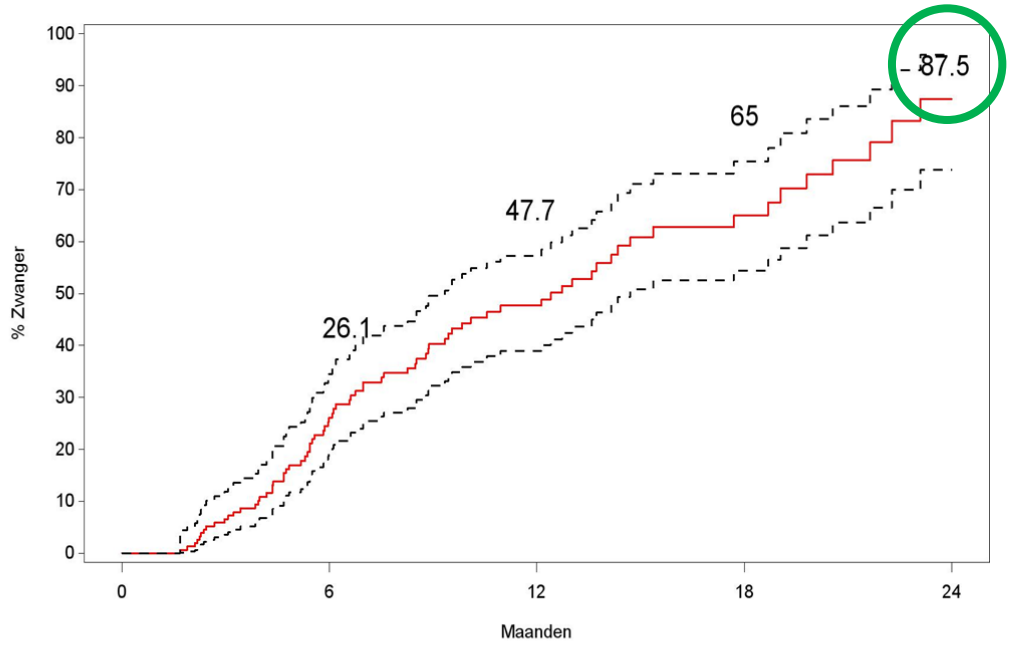


Cumulatieve zwangerschapskans op cyclusniveau



Cumulatieve zwangerschapskans op tijdsniveau

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STAR-trial

SUPPLEMENTARY TABLE 1

Age breakdown for consented patients excluded from the intent to treat population.

Reason for exclusion from ITT Population	25-34 years (N = 510)	35–37 years (N = 269)	38–40 years (N = 205)
Did not have 2 Blastocysts on Day 5/6	70 (13.7)	40 (14.9)	57 (27.8)
Did not meet other inclusion/exclusion criteria	5 (1.0)	1 (0.4)	6 (2.9)
Withdrawal (prior to randomization)	79 (15.5)	37 (13.8)	28 (13.7)

Munné. RCT evaluating NGS-based PGT-A. Fertil Steril 2019.

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