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Schleswig-Holstein

Universitäres
Kinderwunschzentrum
Lübeck

Was kann die Medizin?

Georg Griesinger
Universität zu Lübeck

Wissen schafft Gesundheit

Sektion für gynäkologische Endokrinologie und Reproduktionsmedizin

23.05.2014

Reproduktionsmedizinische Versorgung

~ 1,5 x 10^6 ART/Jahr Behandlungszyklen weltweit

~ 550 000 ART Behandlungszyklen in Europa

IVF in Deutschland:

~1,0 - 1,4 x 10^6 Paare mit Subfertilität/Infertilität

~ 80 000 ART Behandlungszyklen/Jahr

~11.000 Kinder/Jahr

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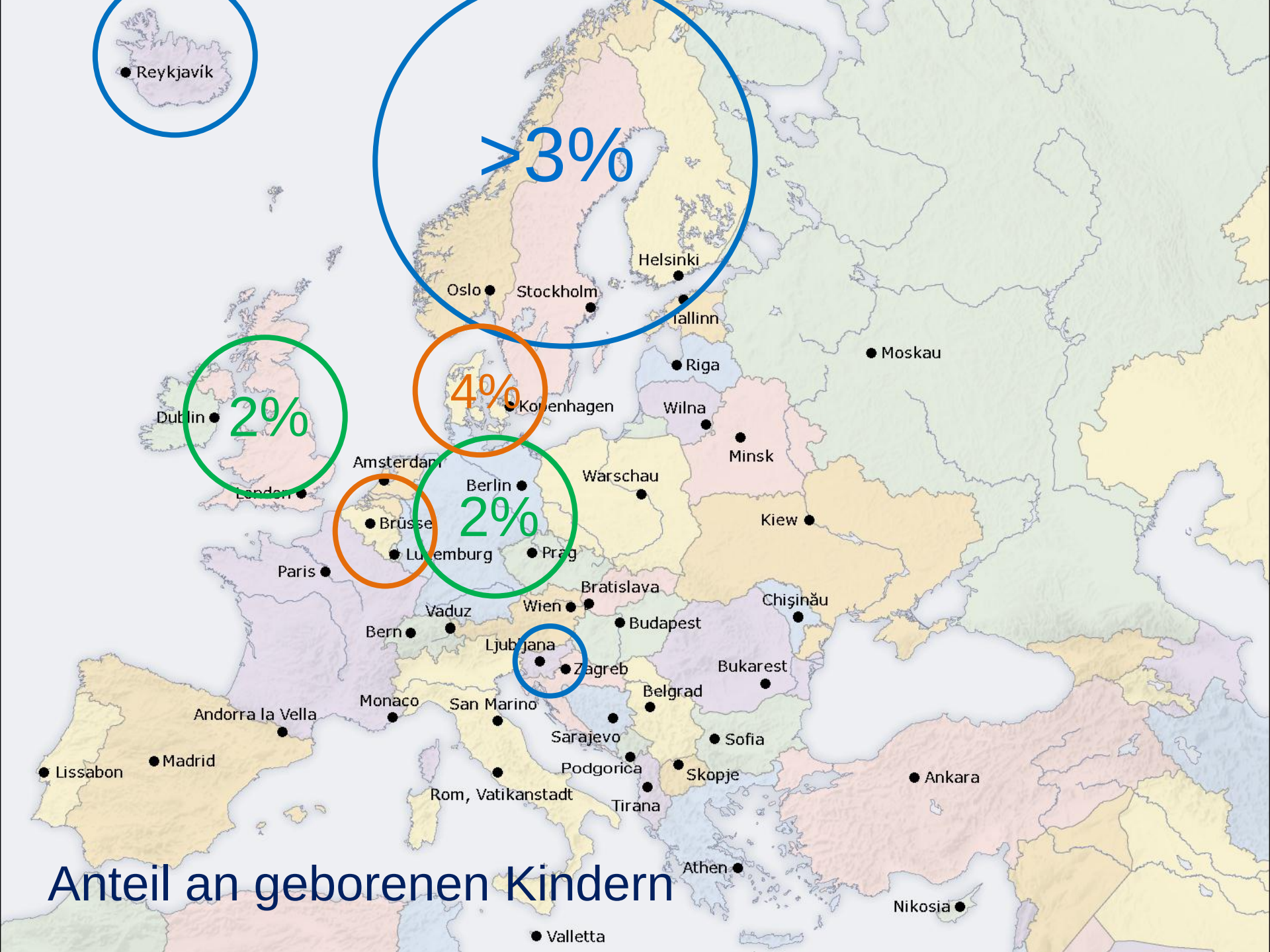


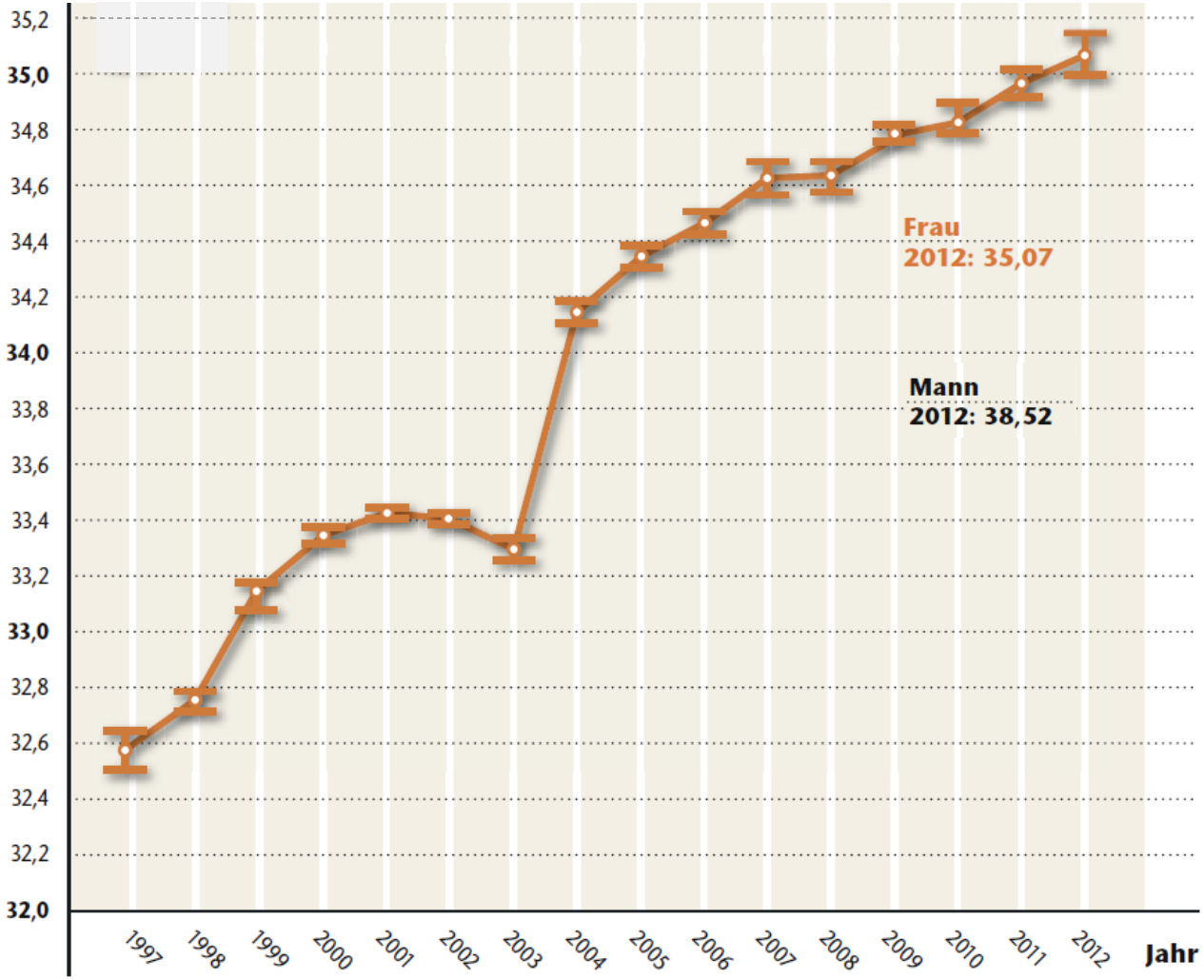
Anteil an geborenen Kindern

Alter

→ Die Paare in Kinderwunschbehandlung werden immer älter

Mittleres Alter der Frauen und Männer 1997 – 2012

IVF, ICSI, IVF/ICSI – prospektive und retrospektive Daten



Deutsches IVF Register, Jahrbuch 2012

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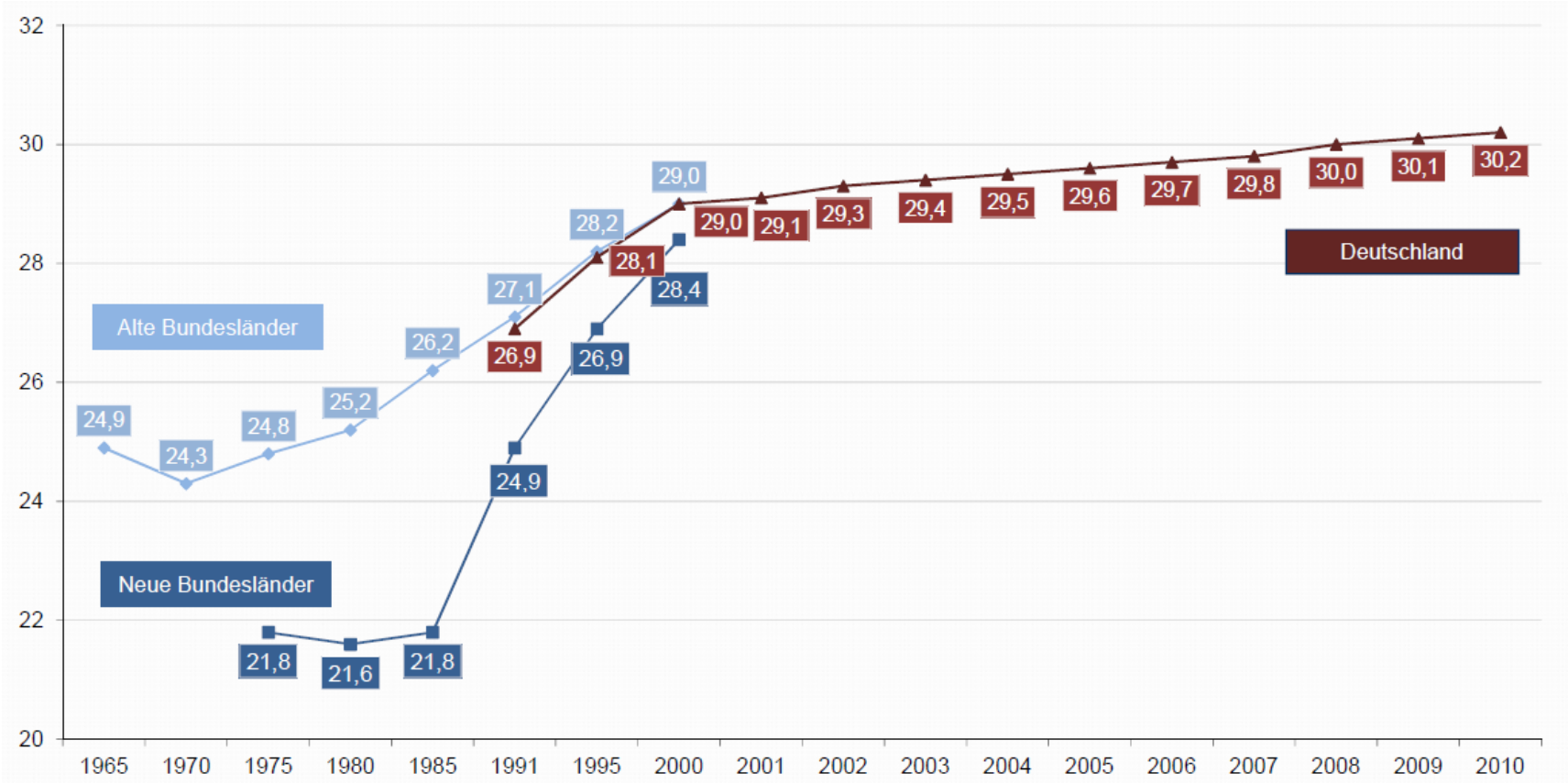
Mittleres Alter der Frauen bei erster ehelicher Geburt, 1965 - 2010



Statistisches Bundesamt, Wiesbaden

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Alter

→ Wer benötigt „*social freezing*“?

Fertilität: Abnahme mit dem Alter

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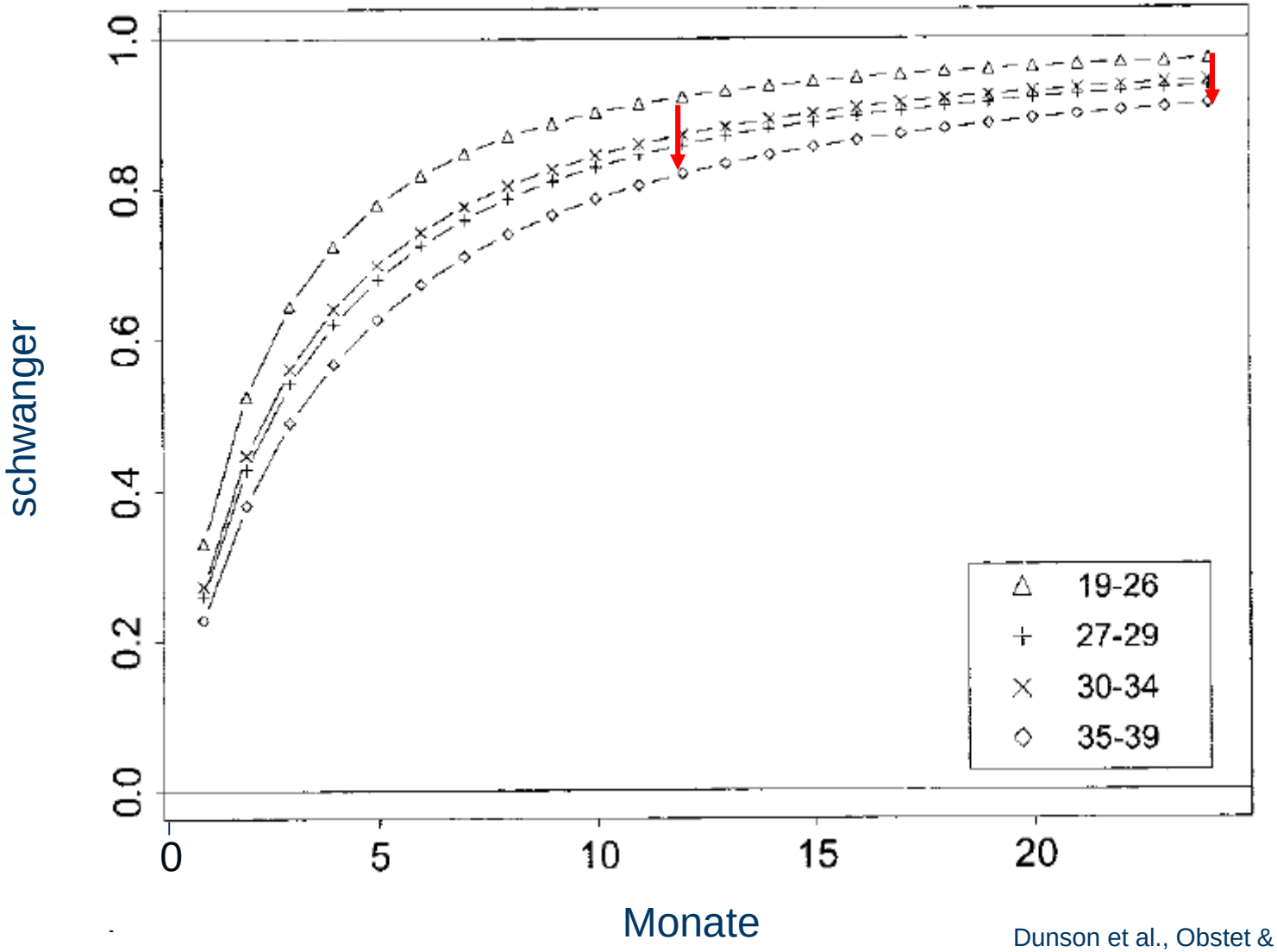
Altersabhängige Schwangerschaftschance über mehrere Zyklen (GV 2x/Woche, n=770)



Dunson et al., Obstet & Gynecol 2004

70-80% schwanger innerhalb von 12 Monaten in der Altersgruppe 35-40

	All women		Intercourse ≥2 times per week		Timing intercourse	
Age (y)	Preg/total	%[a]	Preg/total	%[a]	Preg/total	%[a]
Women						
20–24	314/466	78	237/345	79	132/190	78
25–29	996/1,355	83	692/917	84	402/542	82
30–34	625/791	87	369/460	88	276/334	90
35–40	140/208	72	83/123	73	72/102	78

Number of pregnancies, number of subjects, and cumulative pregnancy proportion within 12 cycles[a] by female and male age at baseline, overall, and by selected volitional factors.

Rothman et al., Fertility and Sterility 2013

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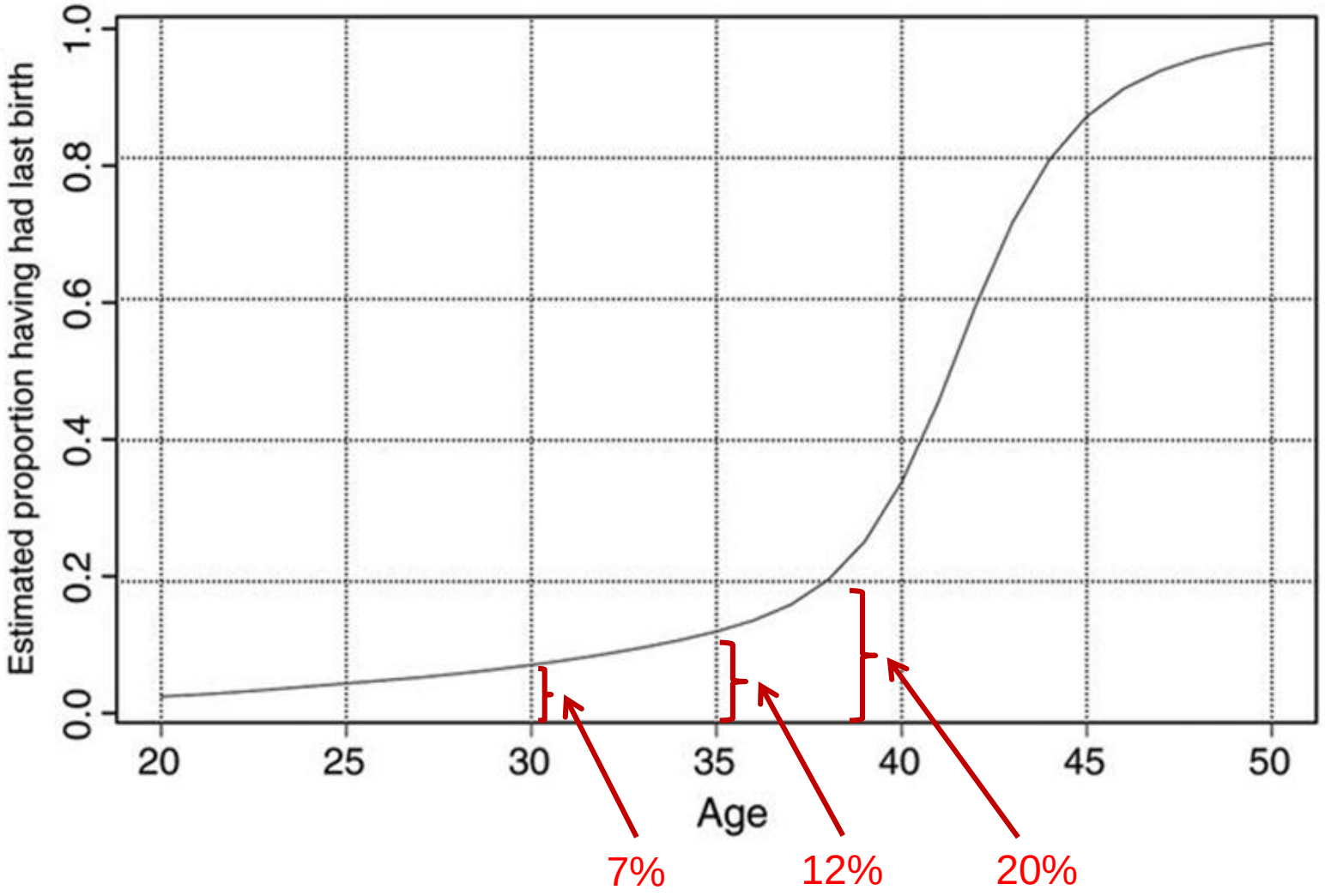
Anteil natürlich steriler Frauen nach Alter



Eijkemans et al. Hum. Reprod. 2014

Risiken der Hormonbehandlung

→Überstimulationssyndrome weitgehend vermeidbar

Schwere ovarielle Überstimulationsyndrome

- 1-4% aller IVF Zyklen
- 3 Todesfälle pro 100.000 Behandlungszyklen [1]
- Neue Behandlungsoption:

  Agonist trigger & elektive Kryokonservierung aller Eizellen/Embryonen

[1] Braat et al., 2010

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Drohende Überstimulationssyndrome sind weitgehend erkennbar und vermeidbar!

→ Eizellspende

Auftreten von Überstimulationssyndromen:

	Konventionelles Vorgehen	Neue Behandlung
Retrospektive Studien[1]	54/1190 (4,5%)	0/1322 (0%)
Randomisierte Studien[2]	25/230 (10,8%)	0/230 (0%)

[1] Bodri 2009; Hernandez 2009; Shapiro 2007
[2] Acevedo 2006; Galindo 2009; Melo 2009; Sismanoglu 2009

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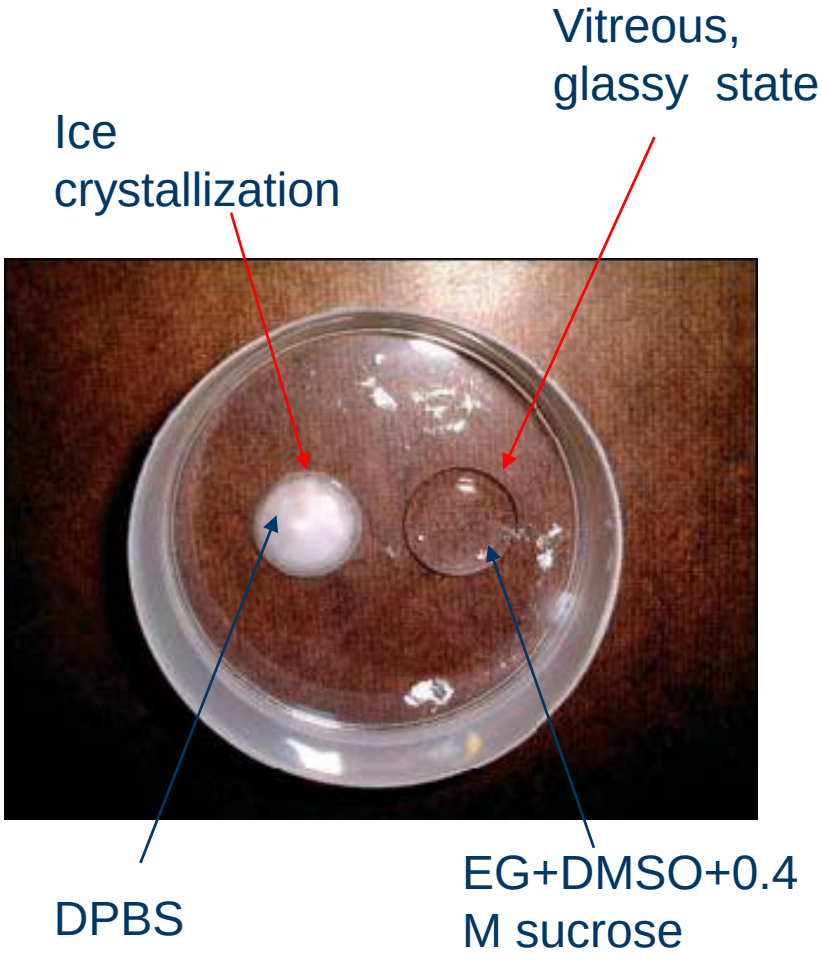
Hocheffiziente Einfriermethoden

→Gefrierlagerung von unbefruchteten Eizellen

→ social freezing

→ Lagerung und Handel mit Eizellen

Die Vitrifikation: Ultra-schnelles Einfrieren



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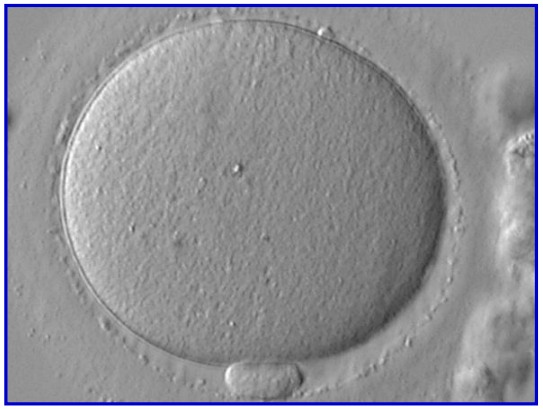
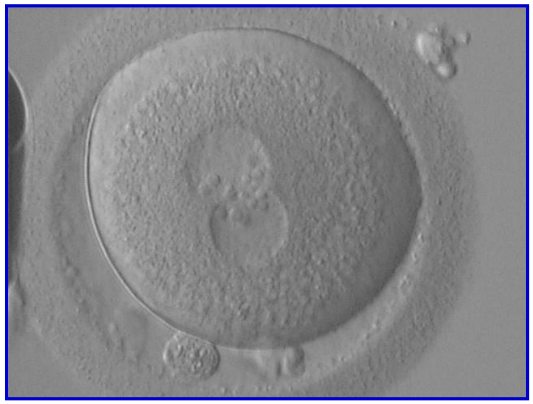
Vitrifikation unterschiedlicher Entwicklungsstadien



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Eizell-Spende

→ „Frisch“ vs. „Gefroren“

Randomisierte Studie: Eizellspende „fresh vs. frozen“

	Vitrifiziert N=231 Eizellen	Frisch N=219 Eizellen	p
Überleben nach Auftau	97%		
Fertilisierung	77%	82%	0,13
Blastulierungsrate	49%	48%	0,87
Schwangerschaftsrate	48%		

Cobo et al., Fertil Steril 2011

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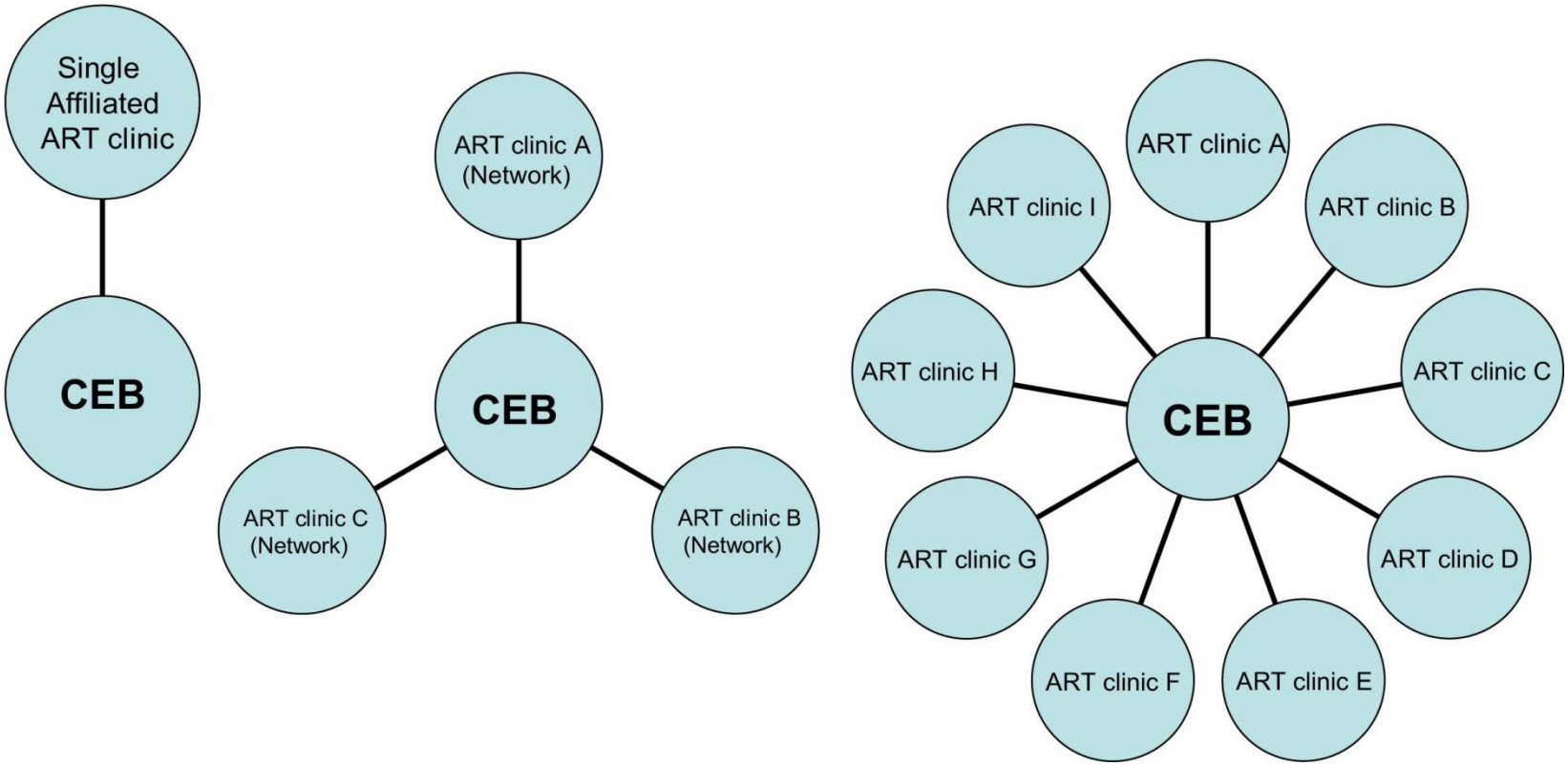
Zukunft der Eizellspende



CEB = commercial egg banks

Quaas et al., Fertil Steril 2013

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Kommerzielle Eizell-Banken in den USA

Characteristics of the seven identified commercial egg banks in the United States.

CEB	Freezing technique	Years in existence	No. of donors used to date	No. of currently available oocytes	No. of oocytes recommended
1	Vitrification	8	18	160	6
2	Vitrification	2	100	100	6
3	Vitrification	2	25	900	6
4	Vitrification	1	6	600	7
5	Vitrification	2	70	1,000	6
6	Vitrification	5	15	120	6
7	Slow freeze	7	60	250	4

Quaas et al., Fertil Steril 2013

Kommerzielle Eizell-Banken in den USA

CEB	Psychological/medical screening, genetic counseling	E_2/FSH testing	AMH testing	AFC testing	Routine karyotyping	Routine CF carrier testing	Routine fragile X carrier testing
1	√	√	√	√	√	√	√
2	√	√		√	√	√	√
3	√	√		√		√	√
4	√	√	√	√		√	√
5	√	√	√	√		√	
6	√	√		√		√	√
7	√	√	√	√		√	

Note: AFC = antral follicle count; AMH = antimüllerian hormone; CF = cystic fibrosis; E_2 = estradiol; FSH = follicle-stimulating hormone.

Quaas et al., Fertil Steril 2013

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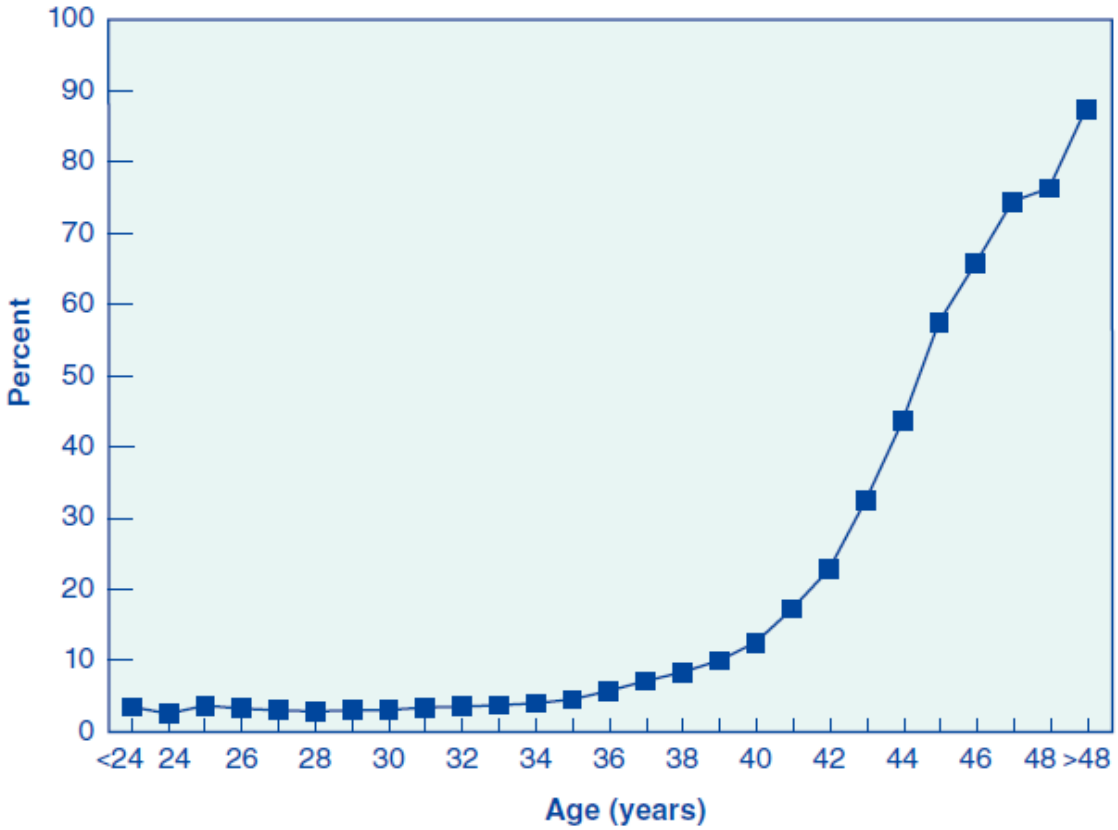
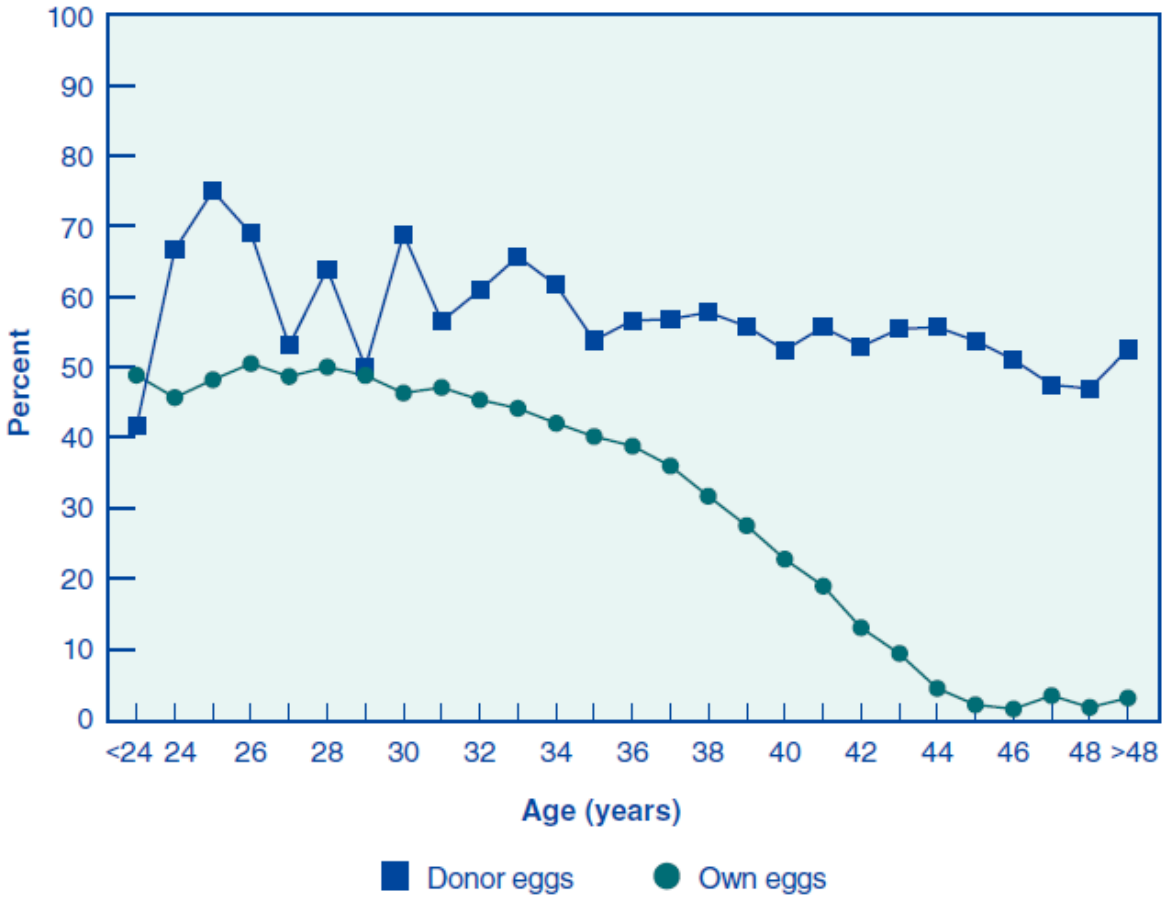
Eizellspende in den USA/Alter der Patientin

Figure 38
Percentages of ART Cycles Using Donor Eggs, by Age of Woman, 2011



SART 2011

Figure 39
Percentages of Transfers That Resulted in Live Births for ART Cycles Using Fresh Embryos from Own Eggs and ART Cycles Using Fresh Embryos from Donor Eggs, by Age of Woman, 2011



SART 2011

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Spender und Empfänger

- Phänotypische Übereinstimmung
- Genetische Übereinstimmung (Array)

Matching

Eizellspenderin

Eizellempfängerin

Partner

Genetische Verwandtschaft?

IVF: Gemeinsame Anlageträgerschaft?

Trägerin von Erkrankungen?

OD: Gemeinsame Anlageträgerschaft?

PID
PND

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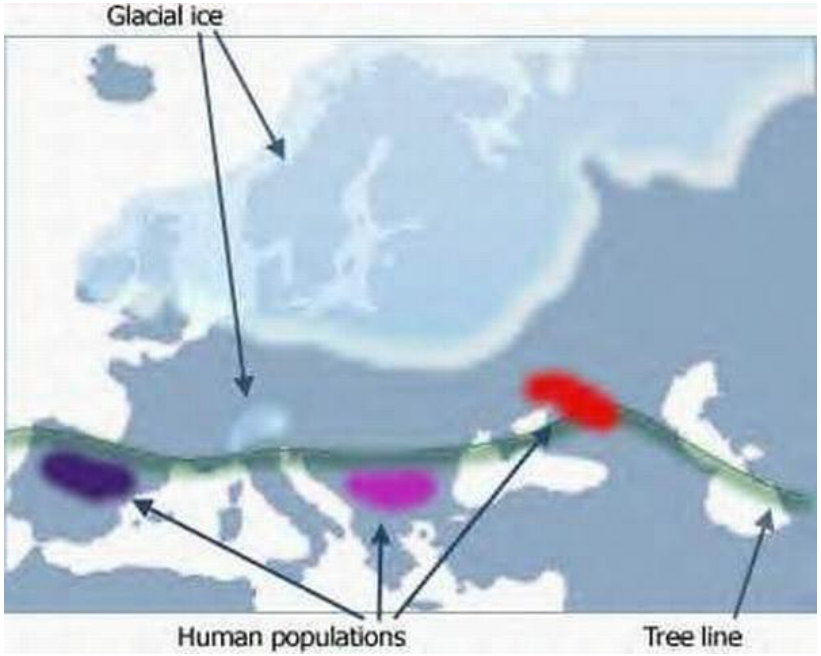
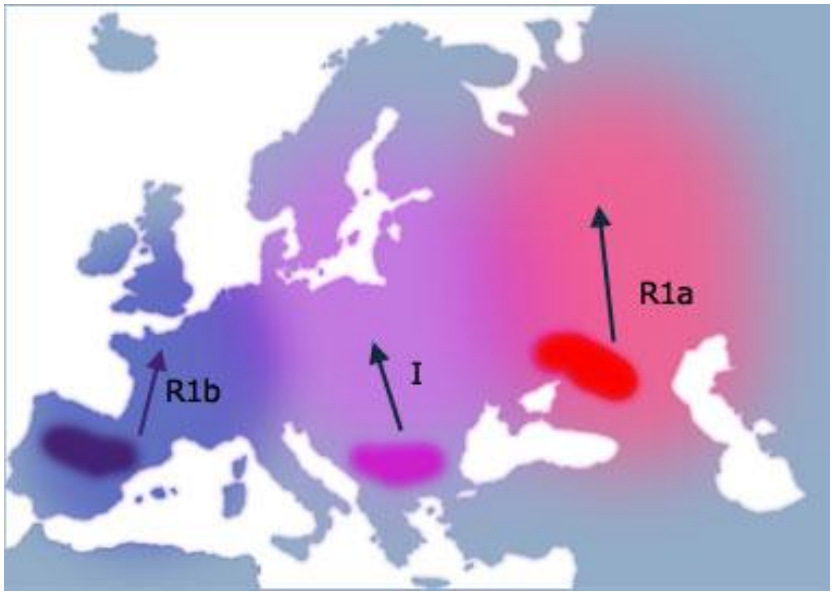
Genetische Übereinstimmung





Bandelt et al., Am J Hum Genet 1998 May;62(5):1137-52

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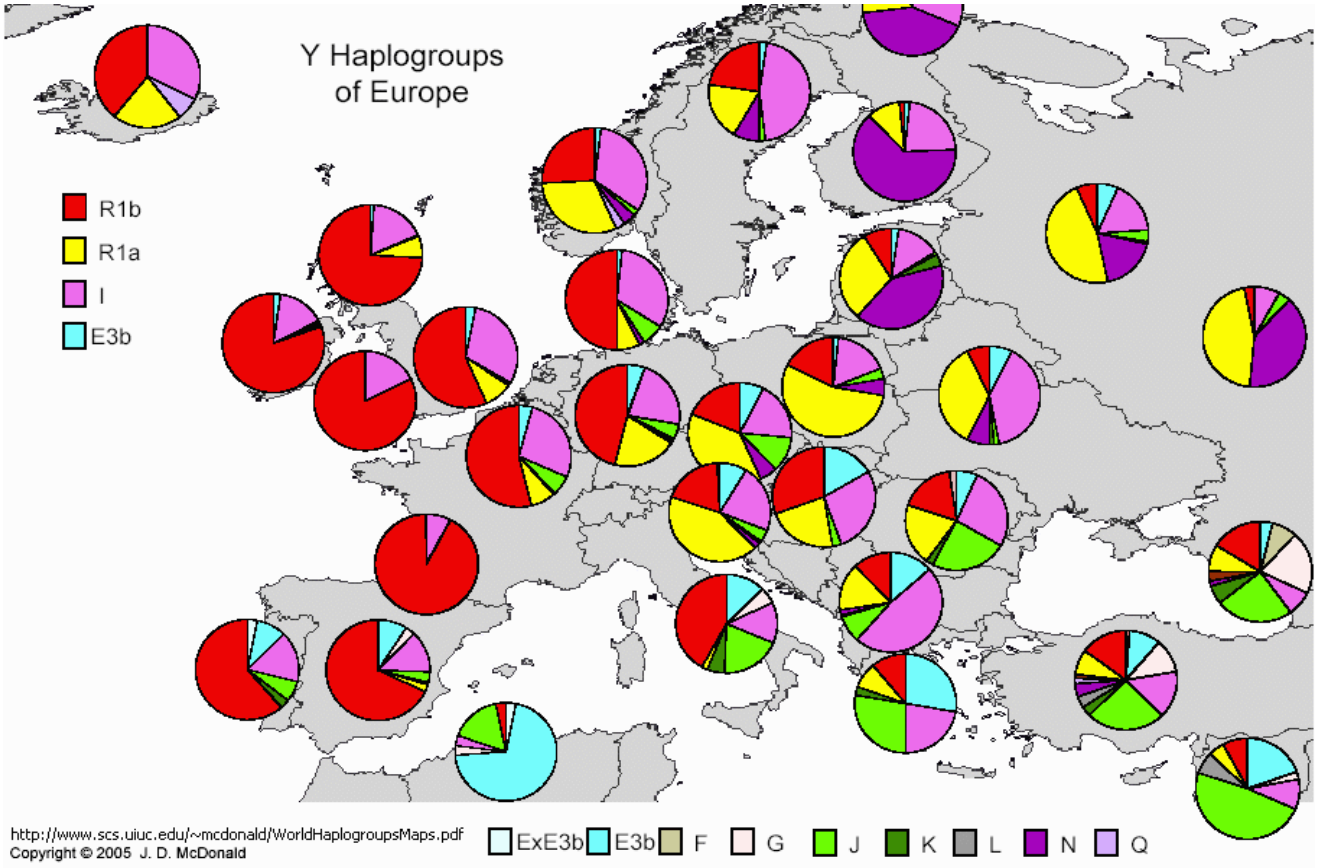
Genetische Übereinstimmung nach Haplogruppen



The American Journal of Human Genetics, Bd. 69, S. 844.

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Plattformen

	Recombine	Counsyl	Good Start Genetics	Natera
Technology	Genotyping (Illumina)	Genotyping (Affymetrix)	Sequencing (Illumina HiSeq)	?
# Diseases	178	107	23	12
# Mutations	984	495	N/A	N/A
SMA	✓	✓	✓	✓
Fragile X	✓	✓	✓	✓
Alpha Thalassemia	✓	✕	✓	✕
Cystic Fibrosis	101 mutations >90% detection	100 mutations <90% detection	550+ mutations >95% detection	127 mutations >90% detection
Jewish Panel	Complete	Incomplete	Incomplete	Incomplete
Customization	✓	✕	✓	✕
Genetic Counseling	✓	✕	✕	✕
Follow-up Information	✓	✕	✕	✕
Cost Per Disease	$1.96	$3.26	$17.17	$29.17

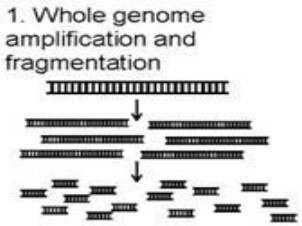
Beispiel: Recombine™

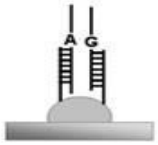
- Recombine: 1500 SNPs covering: 980 SNPs for 213 genetic diseases and 520 random SNPs for genetic matching.

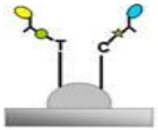
Take the sample

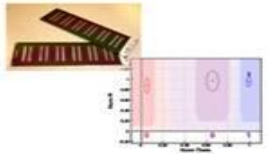
DNA extraction

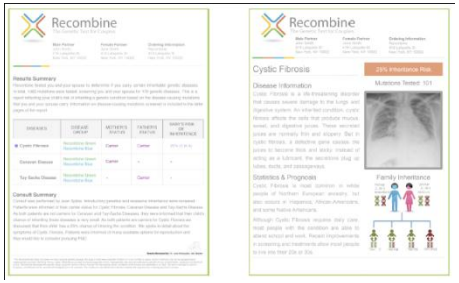
Prepare and process samples











Report

Genetic disorders and screening

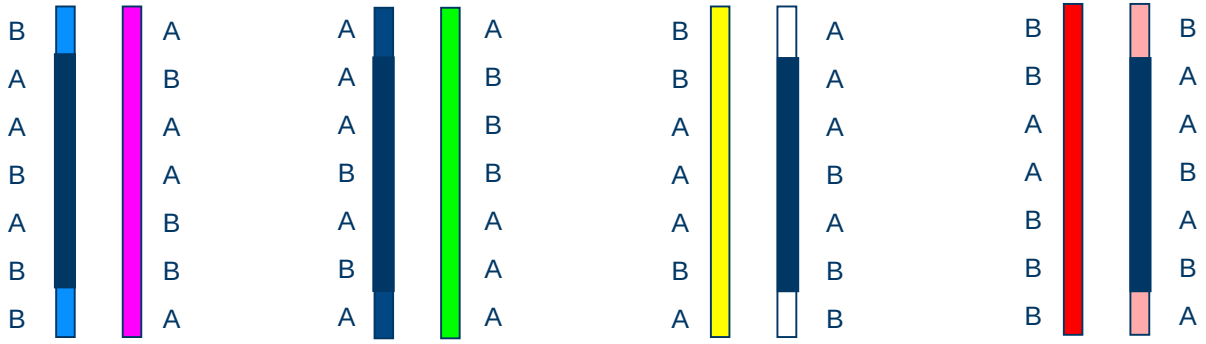
Identification of patients at risk of transmitting a disorder

1. Direct detection of known mutations

    Fully-characterised alteration of DNA sequence

2. Indirect detection

    Haplotype associated with disorder/disease risk

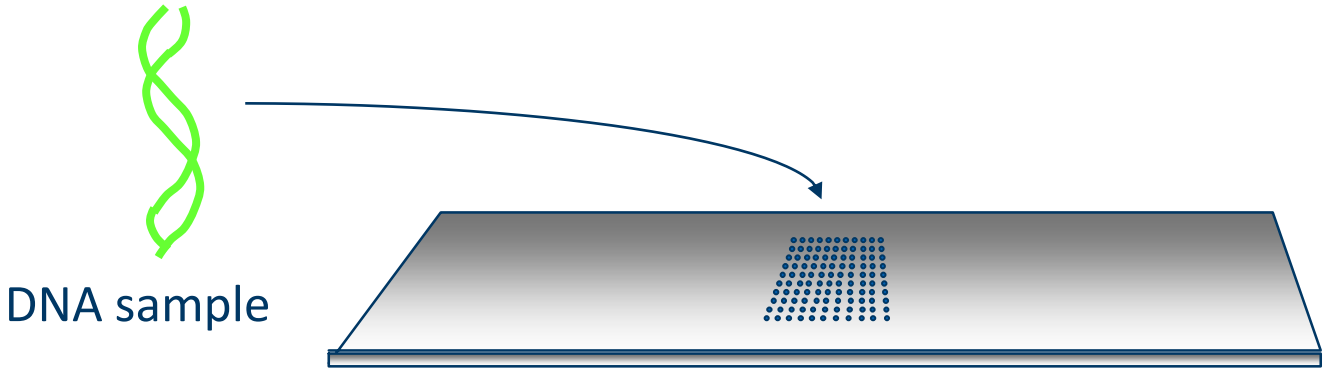


slide courtesy of Prof. Dagan Wells, Oxford University

Single nucleotide polymorphism (SNP) microarrays

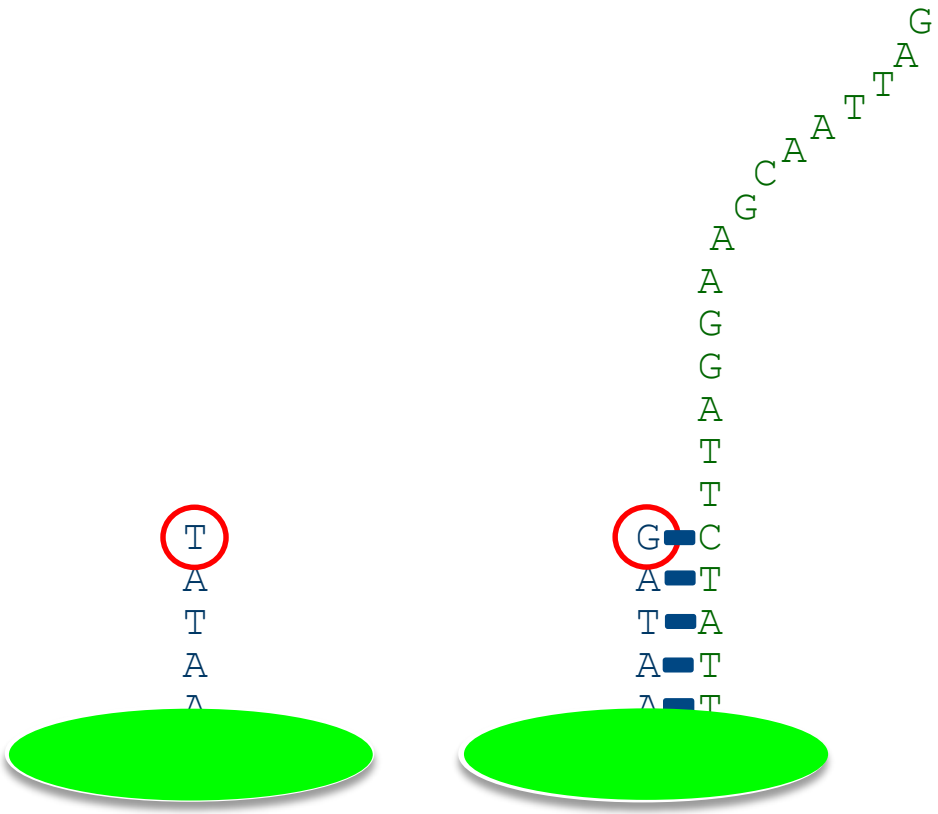
Simultaneous analysis of 1000s of SNPs and/or mutations

Probes for each SNP allele are attached to a slide



slide courtesy of Prof. Dagan Wells, Oxford University

SNP microarrays



Heterozygous C/T

Homozygous for C allele

slide courtesy of Prof. Dagan Wells, Oxford University

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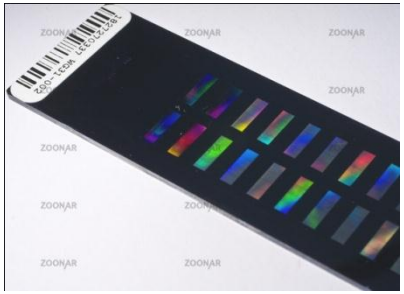
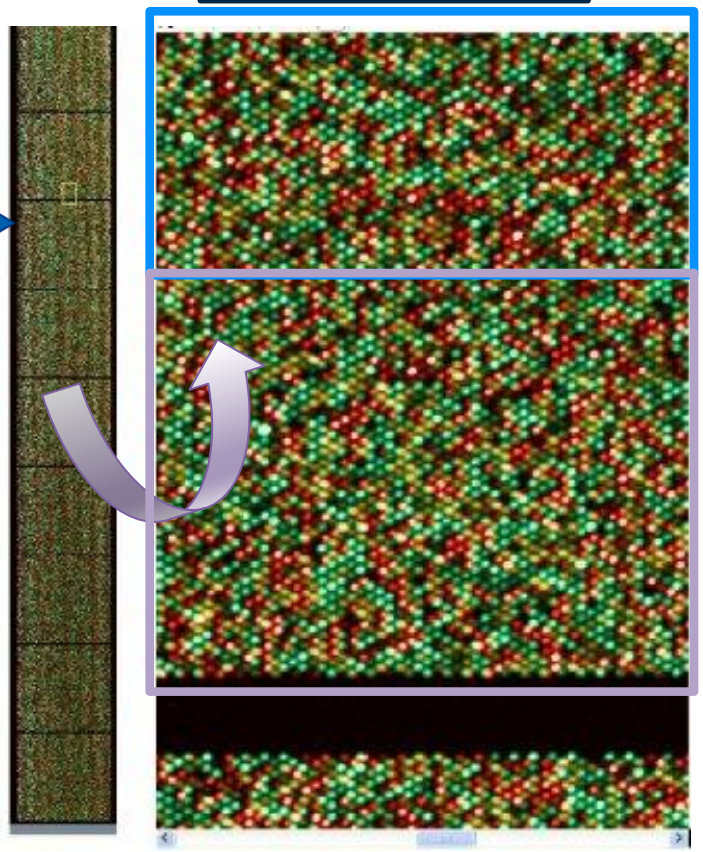


1500 SNPs



520 Random SNPs:
Ancestral
Phenotype

980 SNPs:
Dominant
Recessive

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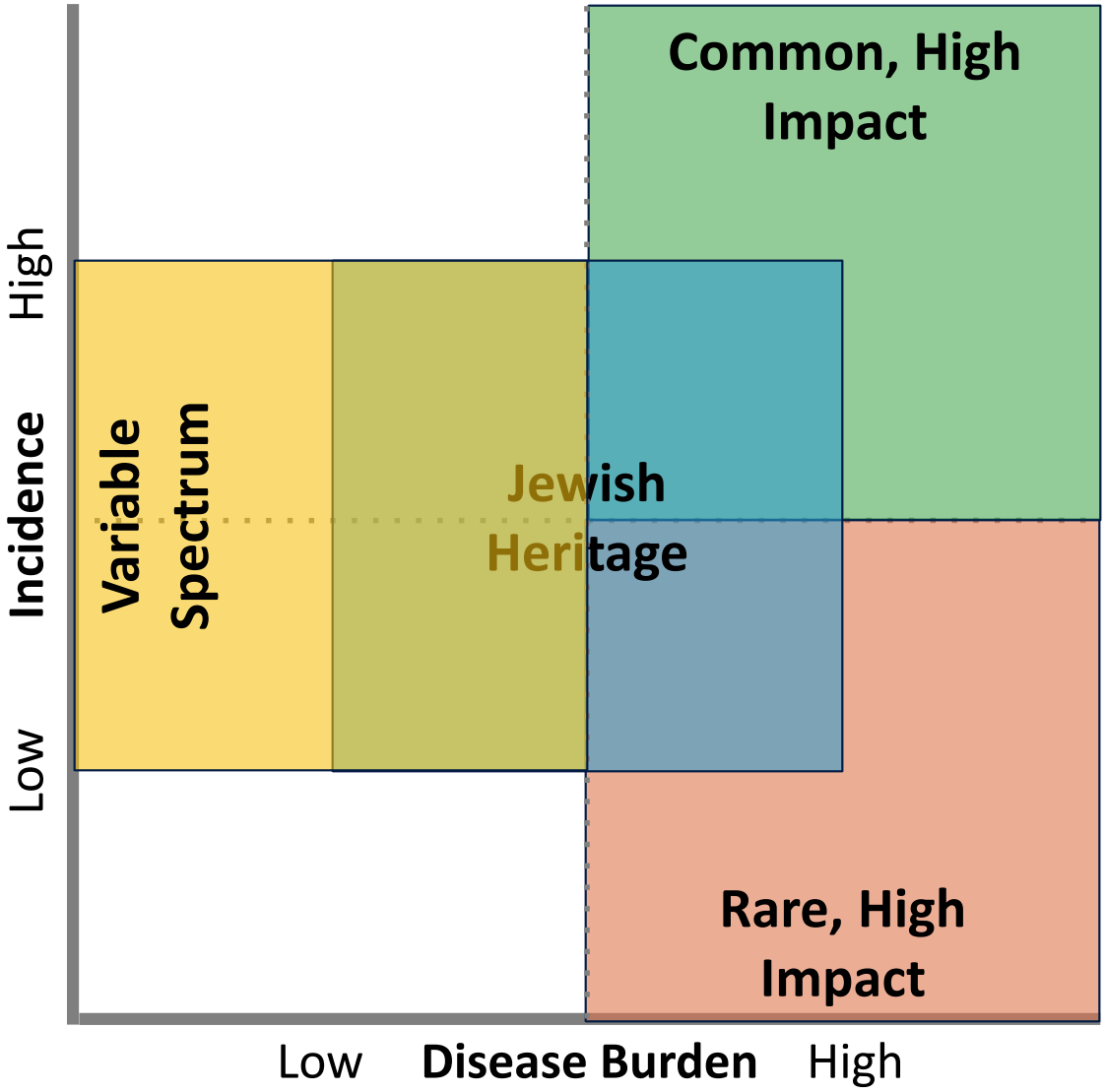
Detektion von 213 Erkrankungen



Groups defined by incidence and disease burden

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Eizellspendeprogramm in Spanien:

400 Spenderinnen → 80 Empfängerpaare

- 2 Spenderinnen ausgeschlossen wg. Anlageträgerschaft für eine dominante Erkrankung

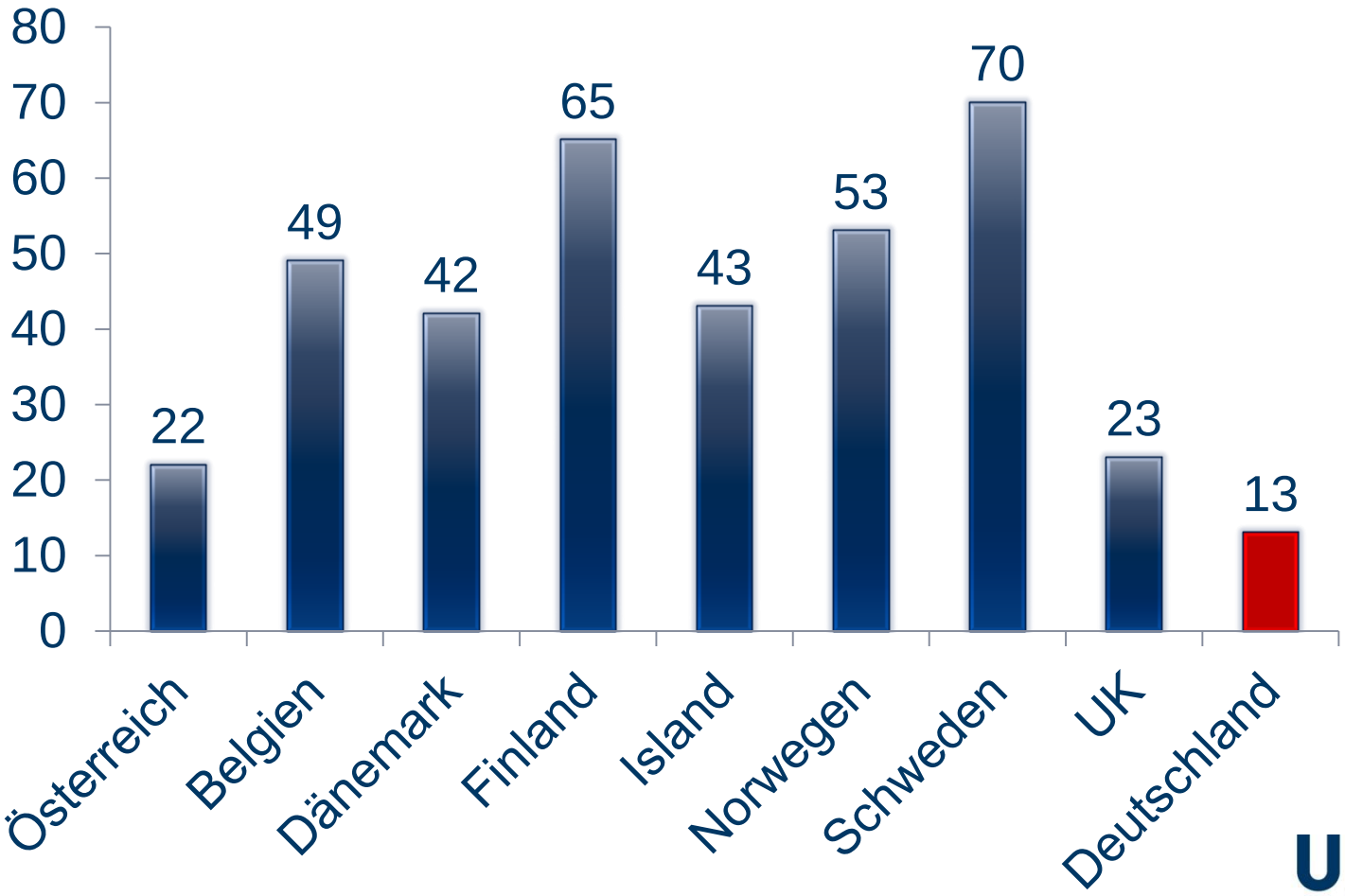
- 5,7% Risiko für autosomal rezessive Erkrankung (Spenderin und Mann)

Aizpurua et al., Hum Reprod 2013 [abstract]

Single Embryo Transfer

→Ausweitung in allen europäischen Staaten

% Single Embryo Transfer 2009



European IVF Monitoring, Hum Reprod 2013

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Single Embryo Transfer in den USA

Figure 51
Percentages of Elective Single Embryo Transfer (eSET) Among all Transfers Using Fresh Nondonor Eggs or Embryos, by Age Group,* 2002–2011

* All ages >40 years are reported together due to the small number of transfers performed with eSET.

SART 2011

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Voraussetzung für den single embryo transfer:

Embryonenauswahl

→Morphologie (Blastozystenkultur)

→Morphokinetik

→Genetik (PGS)

Morphokinetik

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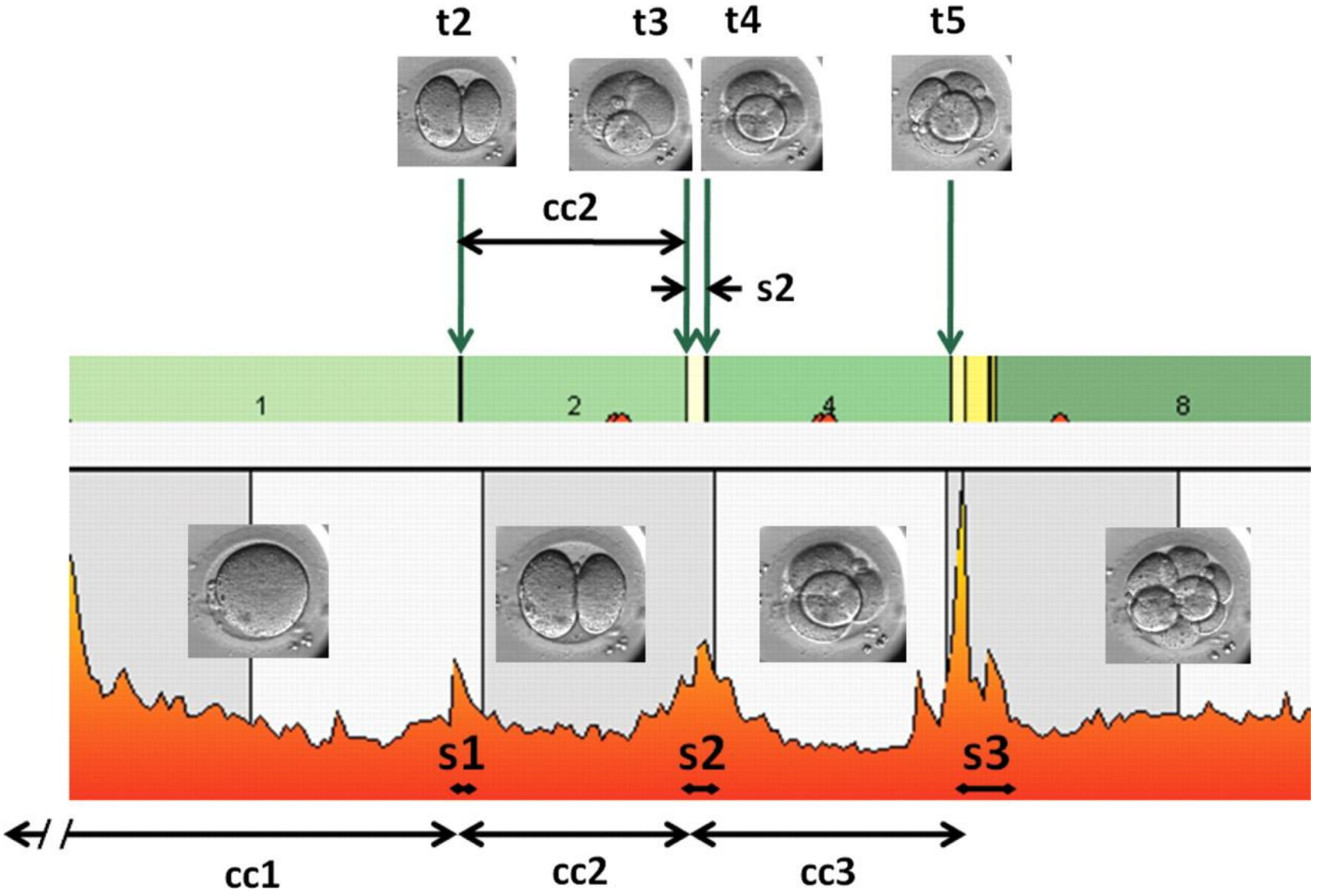
Morphokinetik



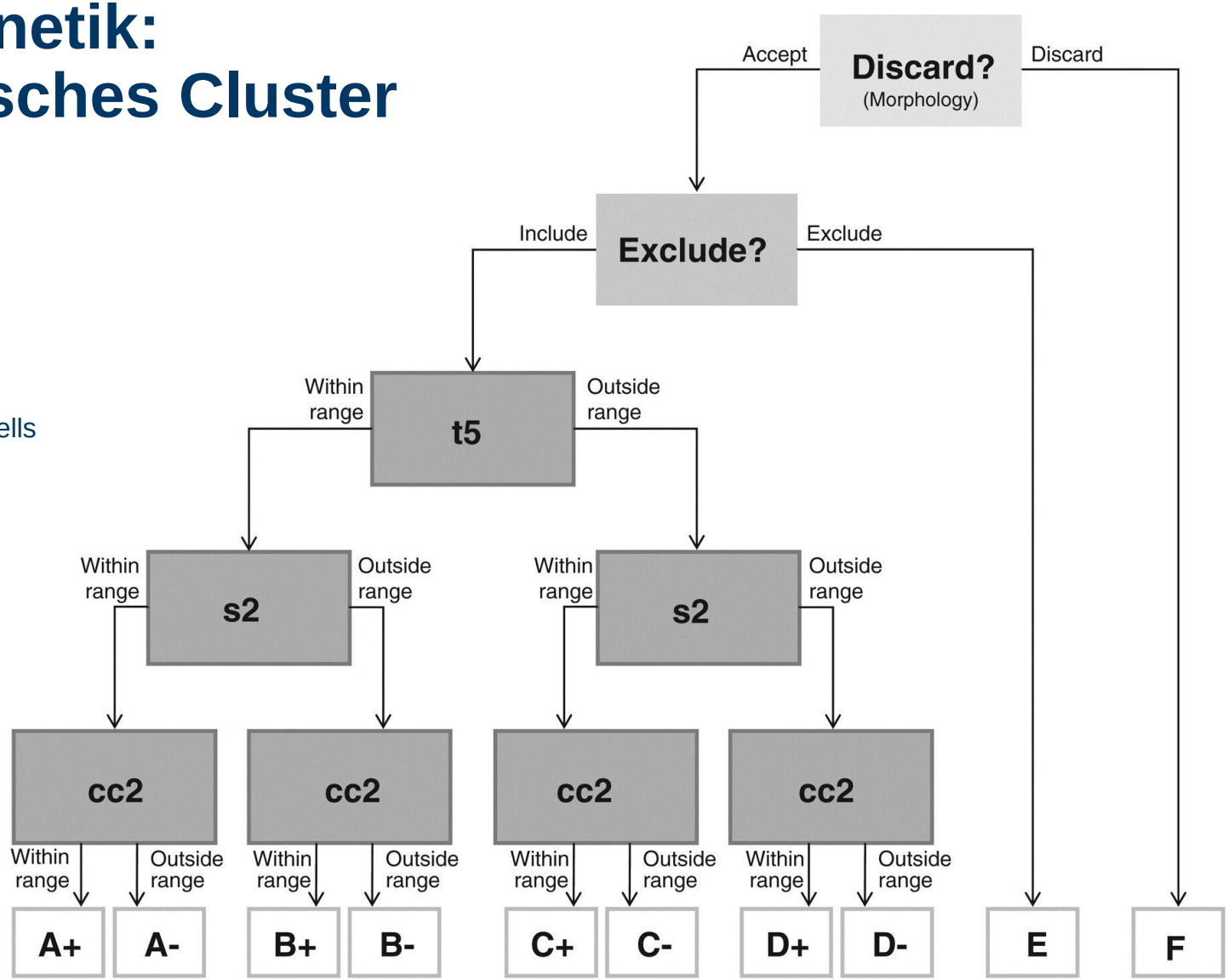
Meseguer et al. Hum. Reprod. 2011

Morphokinetik: Hierarchisches Cluster

timing of cell division to 5 cells

duration of 3 cell stage

duration of
second cell cycle, cc2



Hoch Implantationsrate niedrig

Meseguer et al. Hum. Reprod. 2011

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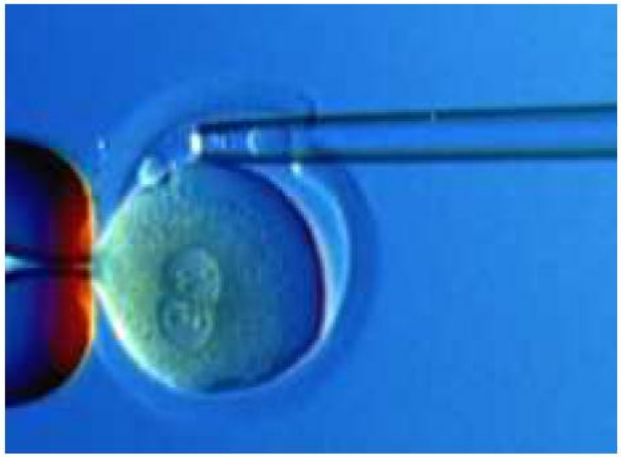
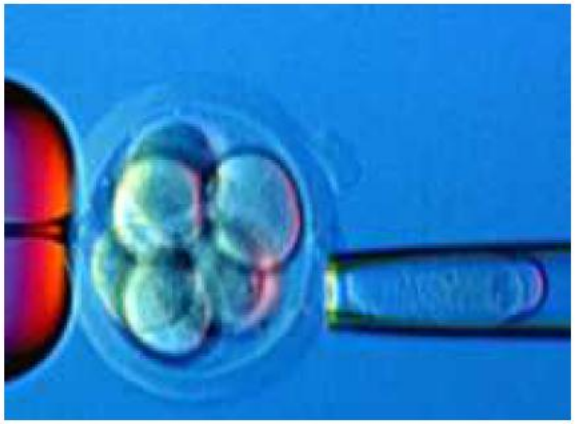
Präimplantationsgenetisches Screening



Polar Body Biopsy

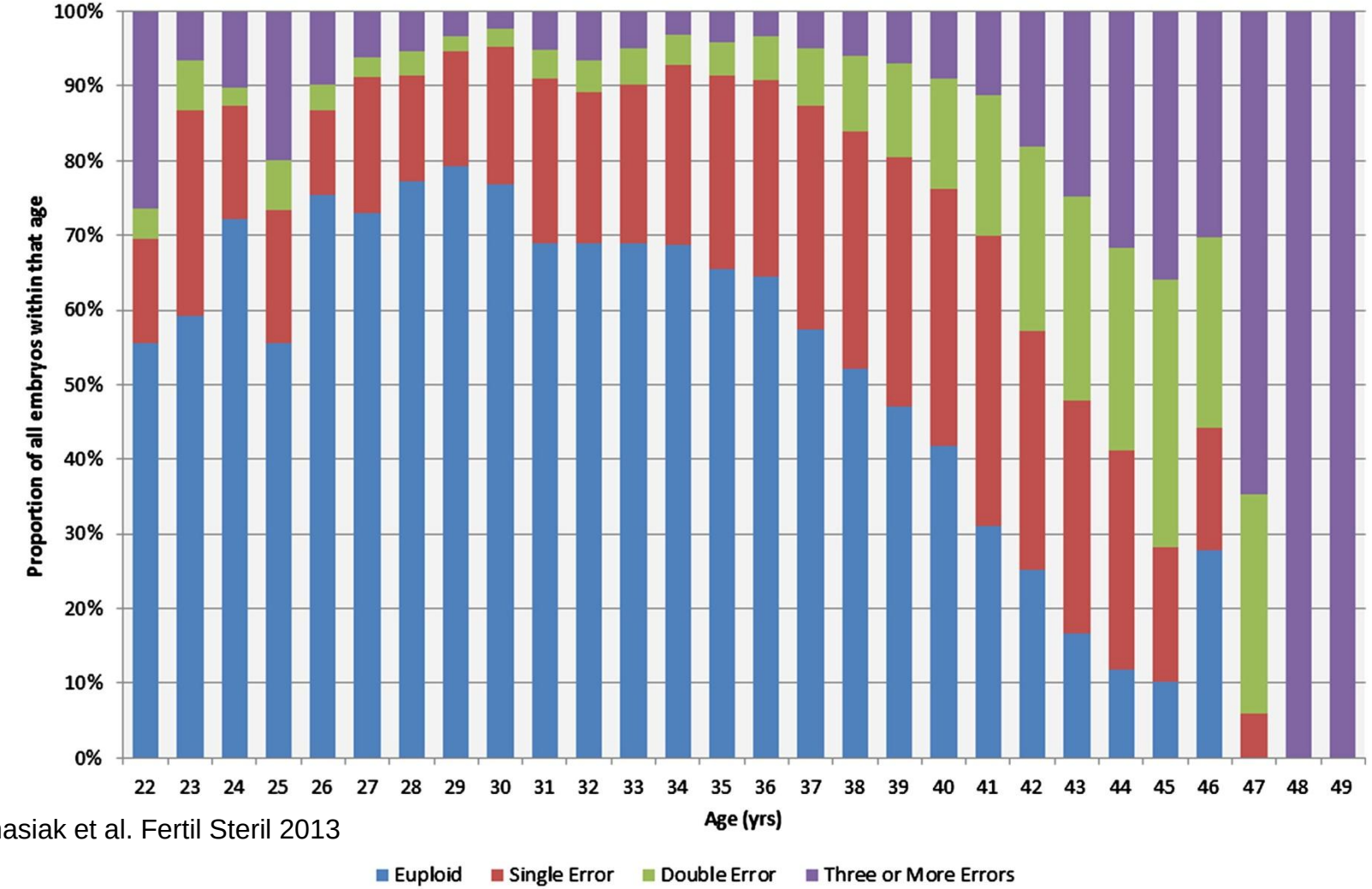


Cleavage Stage Biopsy

Blastocyst Biopsy

Präimplantationsgenetisches Screening

n= 15.169 Blastozysten, comprehensive chromosome screening



Franasiak et al. Fertil Steril 2013

Präimplantationsgenetisches Screening

qPCR

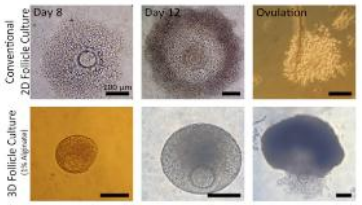
Microarray CGH

Next Generation Sequencing

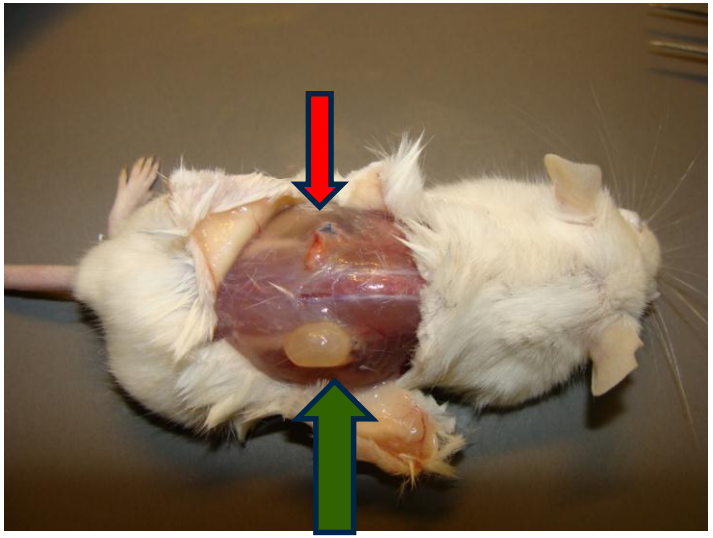
Neue Gameten

- In vitro Follikulogenese
- Xenotransplantationsmodelle
- Oogoniale Stammzellen

5. Encapsulation of preantral follicles in 1% alginate gels maintains follicle morphology and supports in vitro ovulation



In contrast to conventional 2D follicle culture in microwells (upper row) the round follicle shape and morphology is maintained during a twelve day culture of the preantral follicle within a 1% alginate gel and ovulation in vitro can be obtained. Quality and developmental potential of oocytes grown and matured IV in different matrices have to be further assessed.



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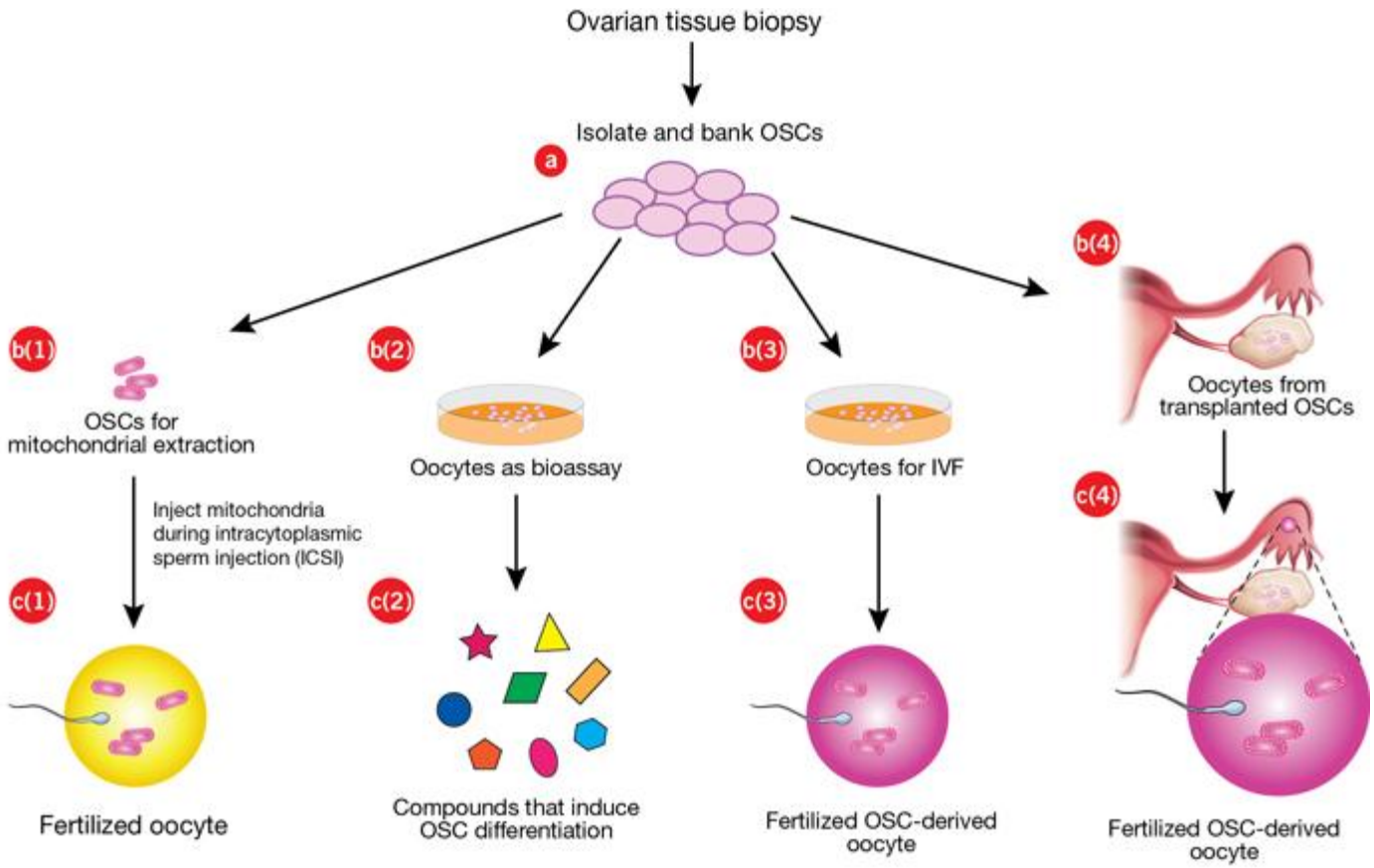
Oogoniale Stammzellen



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