XVIII JORNADA PAULISTA DE UROLOGIA

29-31 MAIO 2025

Um olhar para o FUTURO REPRODUTIVO DA HUMANIDADE

Edson Borges Jr.

Fertility Medical Group
FERTGROUP
Instituto Sapientiae

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25 ANOS Instituto Sapientiae

Declaração

Sem conflito de interesse para divulgar relacionado ao assunto desta palestra

Resolução do Conselho Federal de Medicina
nº 1.595/2.000

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Agenda

- ❑ Fertilidade no Brasil e no mundo
- ❑ Meio ambiente e fertilidade
- ❑ Técnicas de RA – Diagnóstico Genético Pré-Implantacional
- ❑ Novas propostas terapêuticas
- ❑ Perspectivas futuras

Global fertility in 204 countries and territories, 1950–2021, with forecasts to 2100: a comprehensive demographic analysis for the Global Burden of Disease Study 2021

*GBD 2021 Fertility and Forecasting Collaborators**

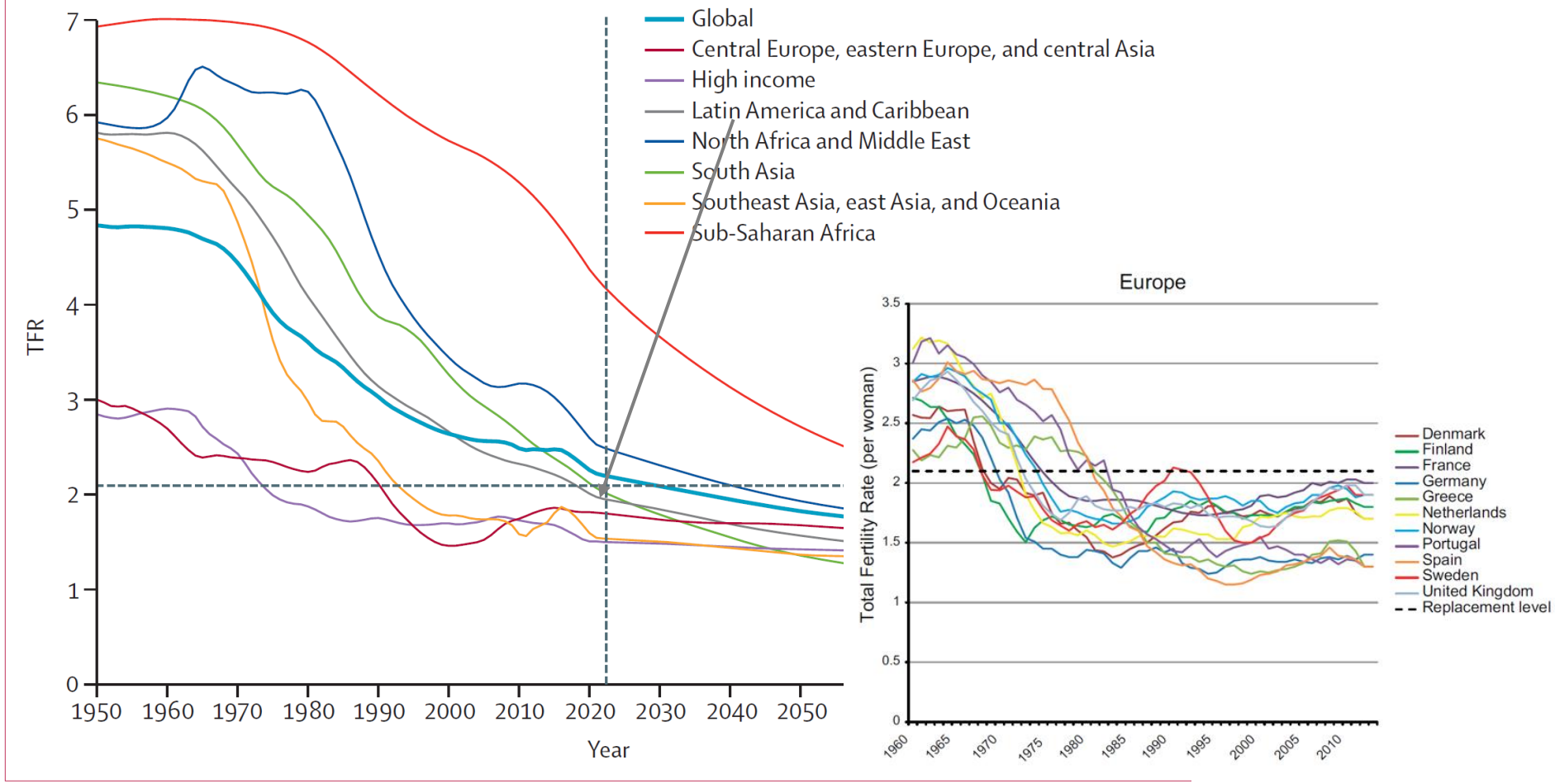

Figure 1: **TFR, globally and by GBD super-region, 1950–2100**

The dashed horizontal line indicates replacement TFR (2·1), and the dashed vertical line indicates the year 2022 (the first forecast year). GBD=Global Burden of Diseases, Injuries, and Risk Factors Study. TFR=total fertility rate.

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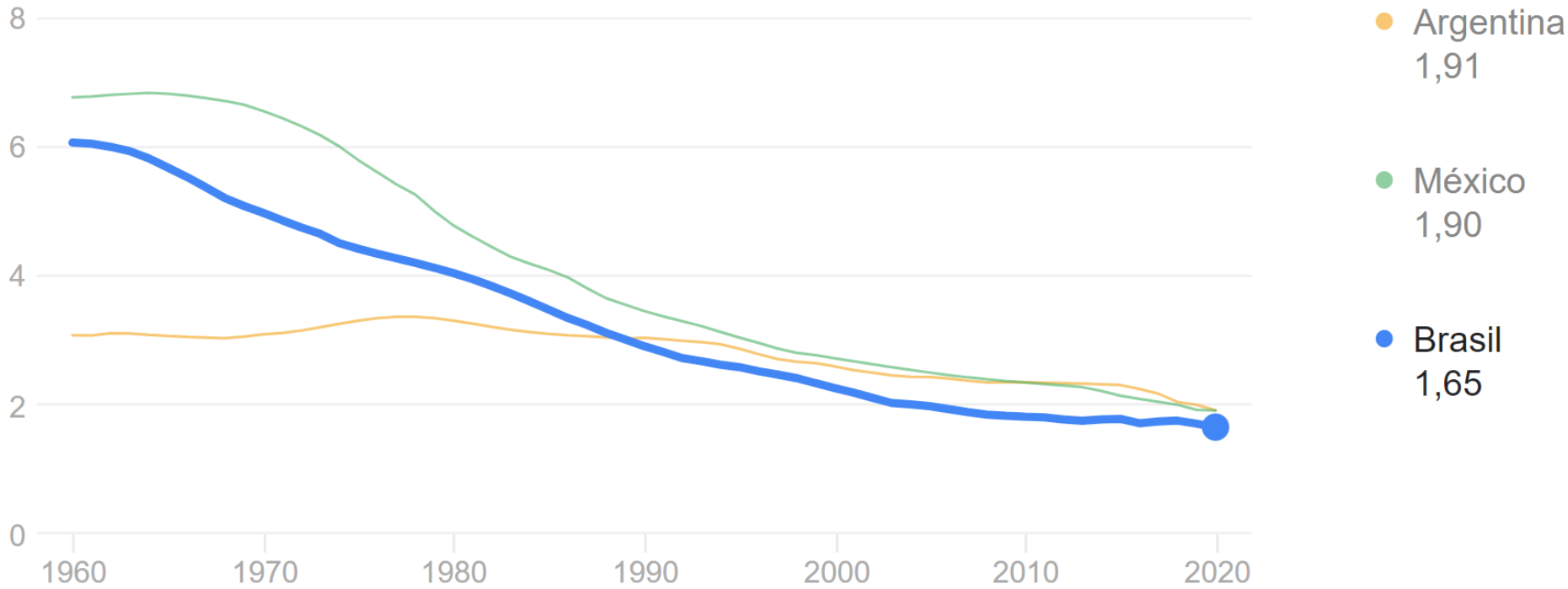
www.thelancet.com **Published online March 20, 2024 https://doi.org/10.1016/S0140-6736(24)00550-6**

1,65 nascimentos por mulher (2020)



Fontes: Banco Mundial

Feedback

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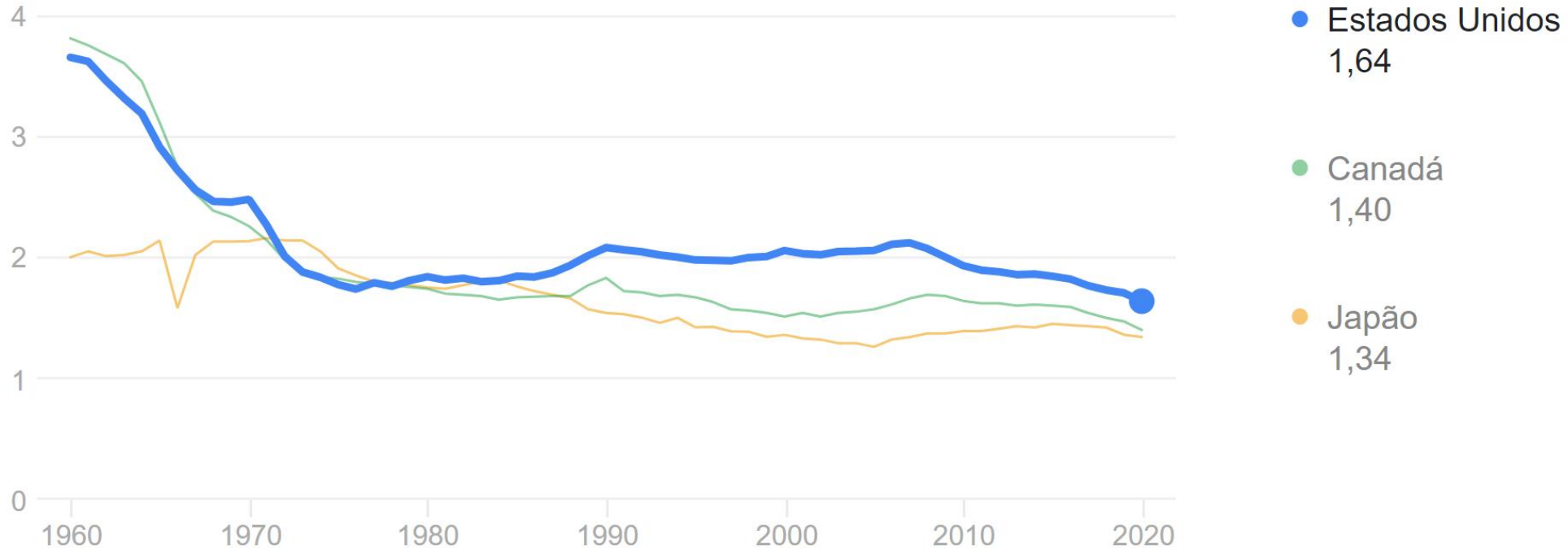
1,64 nascimentos por mulher (2020)



Fontes: Banco Mundial

Feedback

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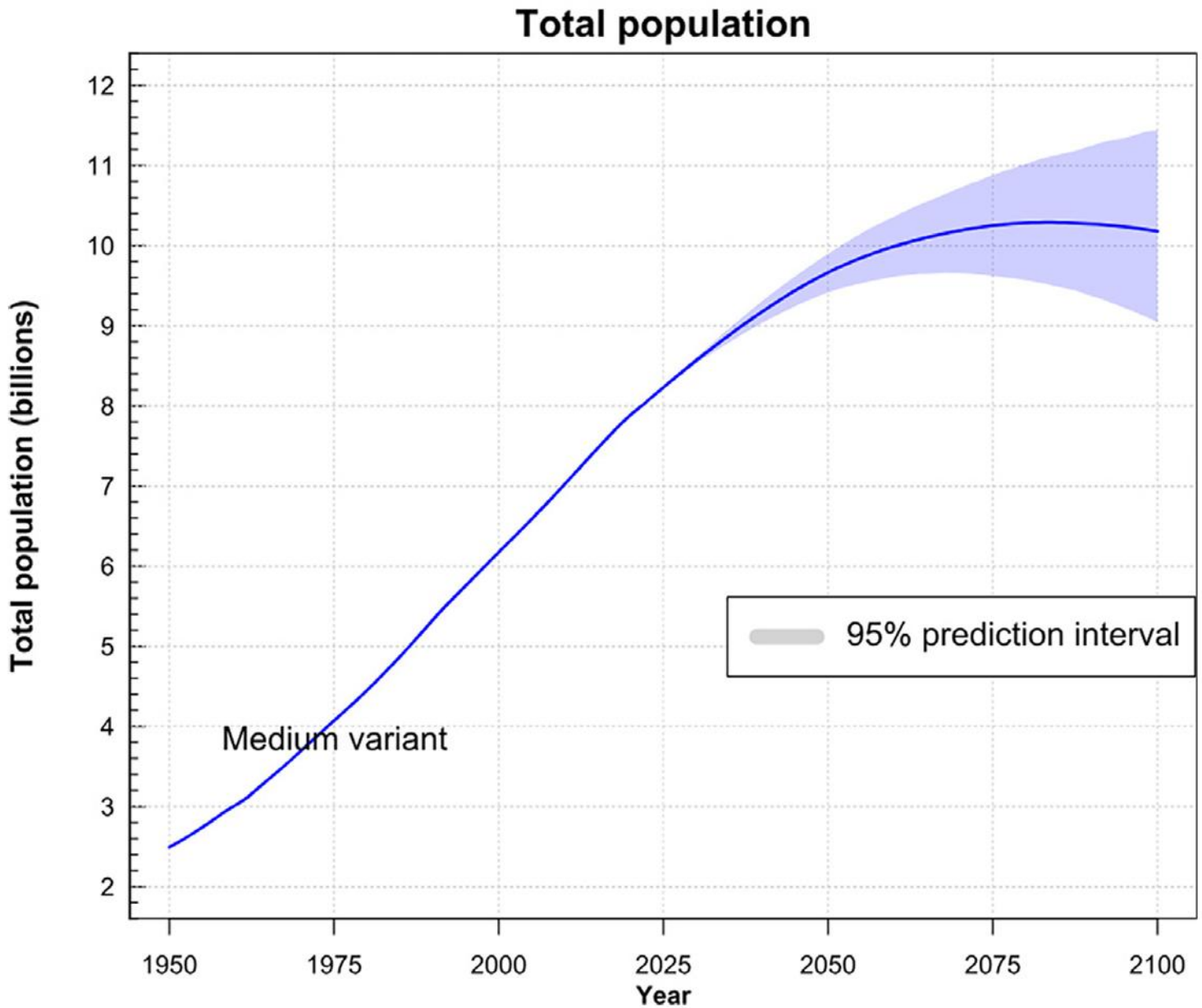
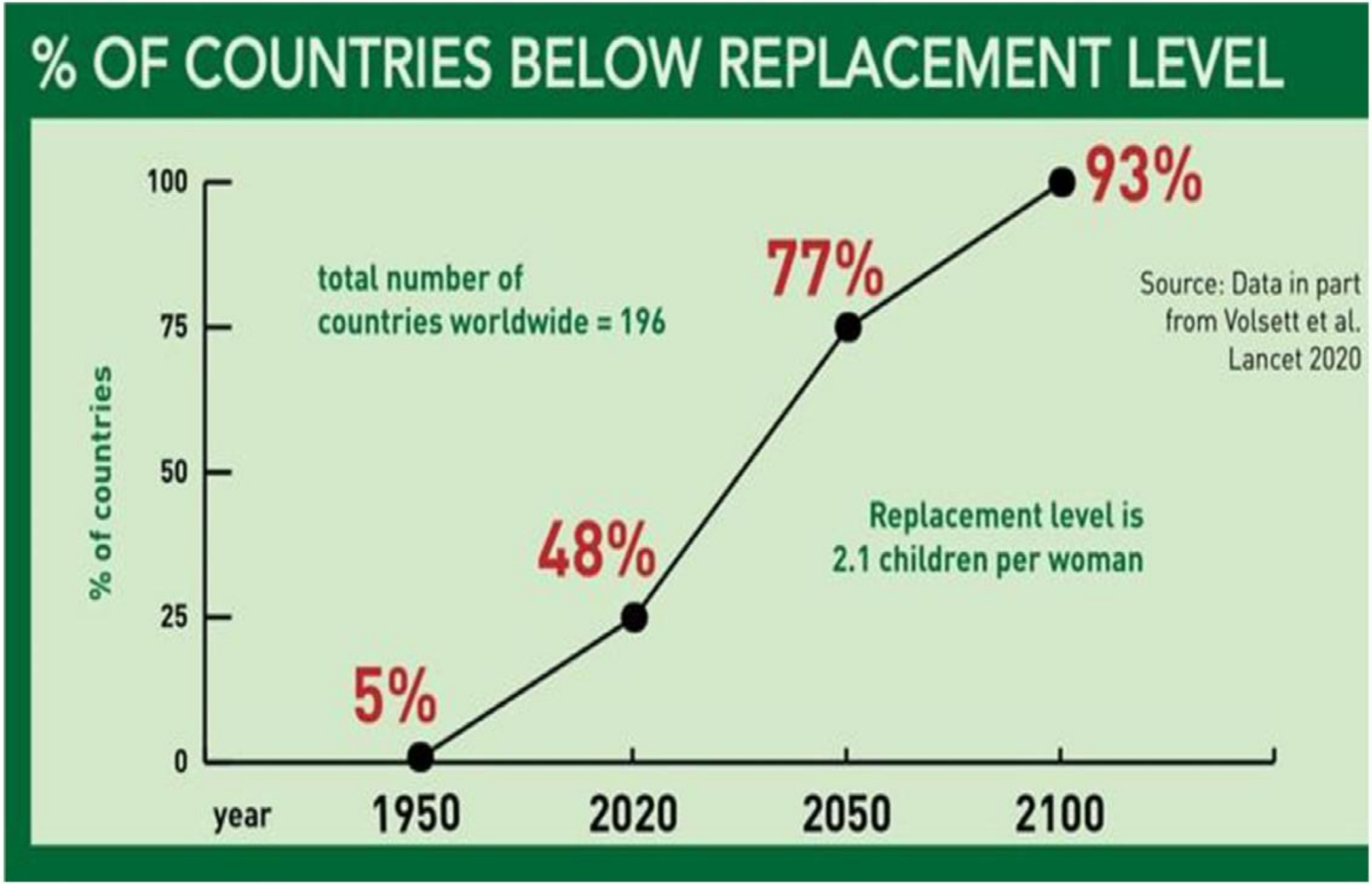

Total population
Total population (billions)
12
11
10
9
8
7
6
5
4
3
2
1950
1975
2000
2025
2050
2075
2100
Year
95% prediction interval
Medium variant


% OF COUNTRIES BELOW REPLACEMENT LEVEL
100
75
50
25
0
% of countries
total number of
countries worldwide = 196
5%
48%
77%
93%
Replacement level is
2.1 children per woman
Source: Data in part
from Volsett et al.
Lancet 2020
year
1950
2020
2050
2100

Article

H E T

Human and Experimental Toxicology
1–9

DOI: 10.1177/0960327117703690
journals.sagepub.com/home/het
SAGE

Decline in sperm count in European men during the past 50 years

P Sengupta[1,2], E Borges Jr[3], S Dutta[4] and E Krajewska-Kulak[2]

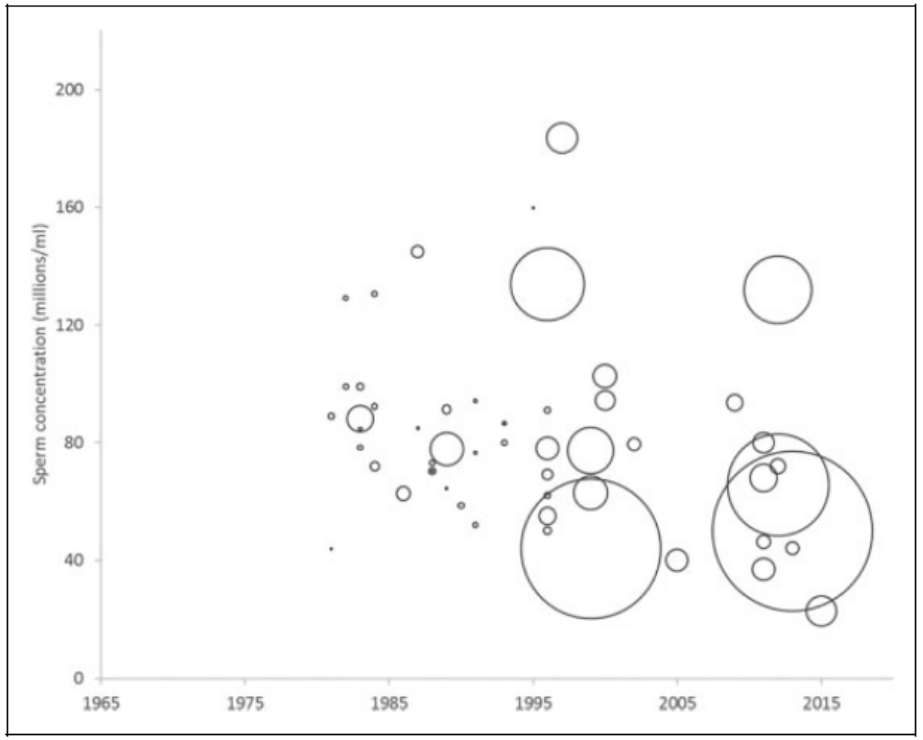


Figure 1. Temporal decline in sperm concentration ($\times 10^6$/ml) from 1965 to 2015, bubble size corresponds to the number of men in the study.

A time dependent decline in sperm concentration was observed from 1965 to 2015 (r=0.307, p=0.02)

An overall 32.5% decrease in mean sperm concentration

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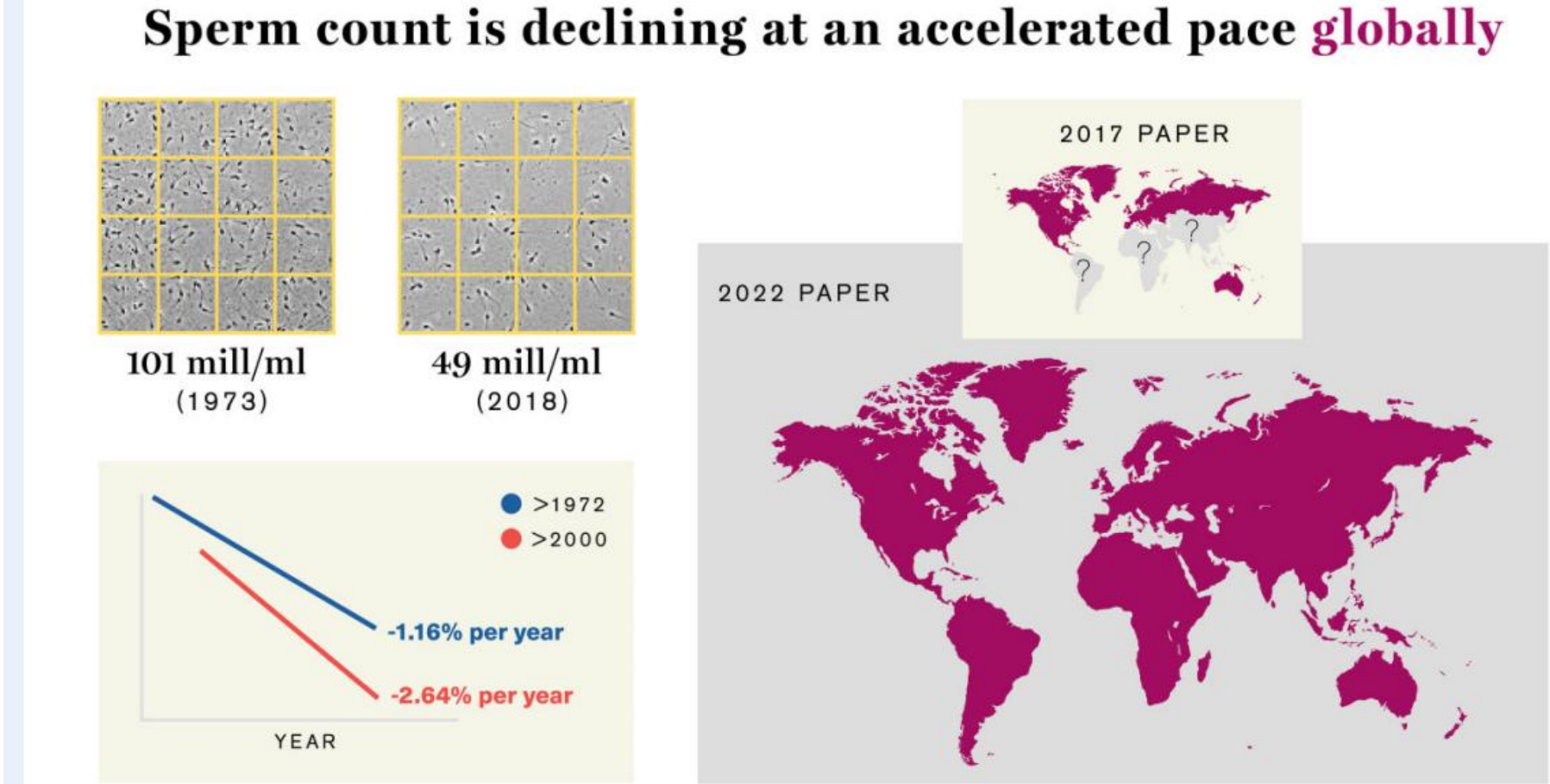
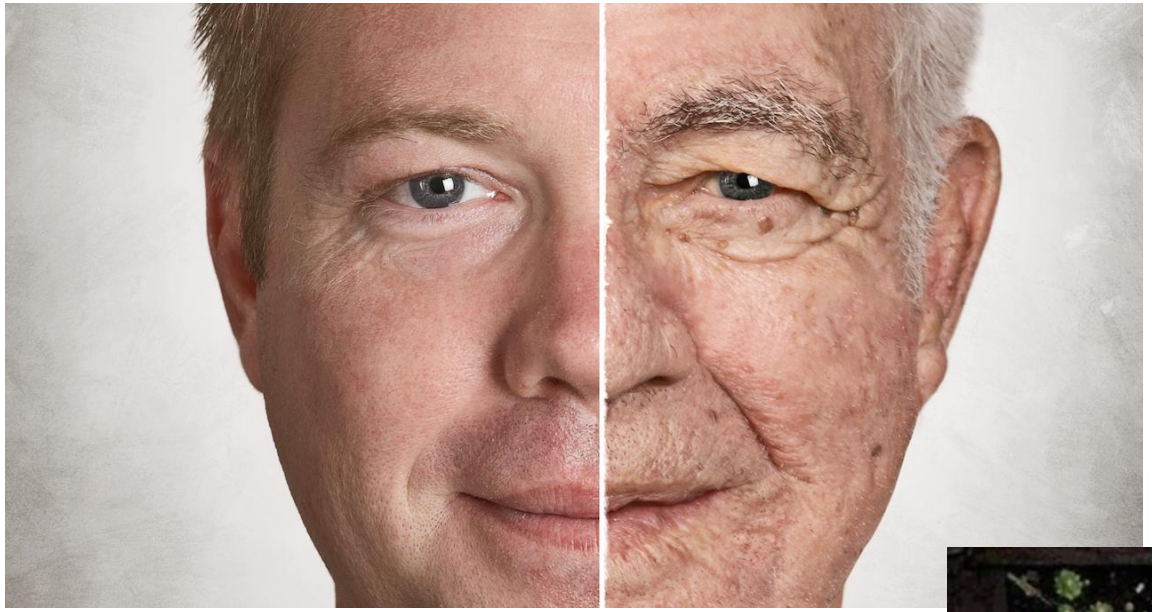
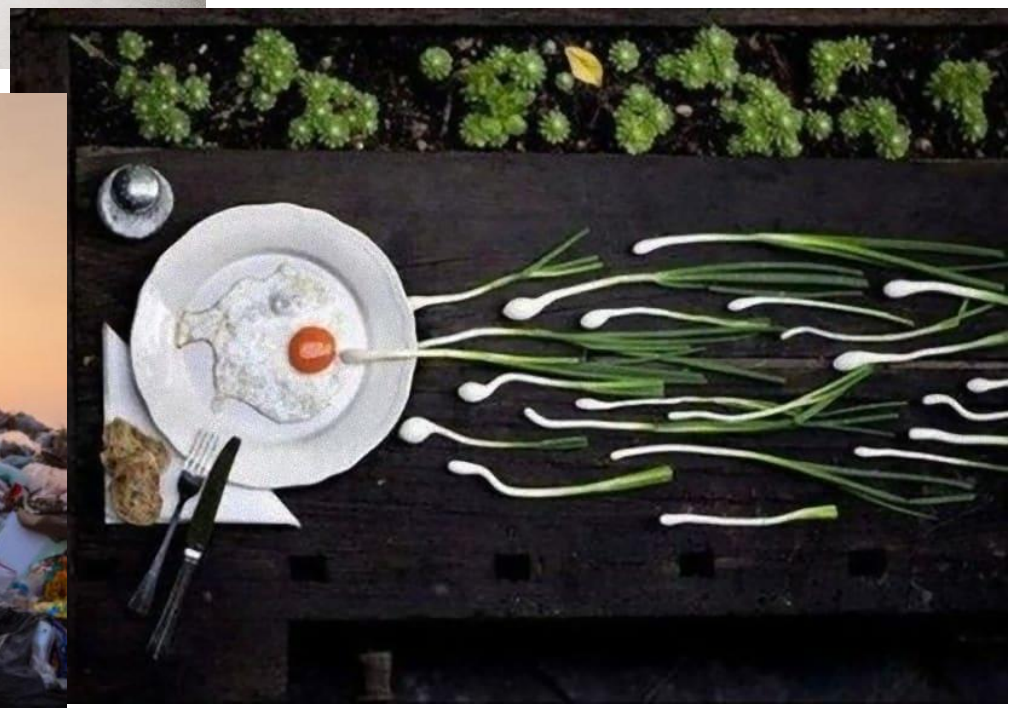
GRAPHICAL ABSTRACT



Sperm count is declining at an accelerated pace globally.

Human Reproduction Update, Vol.29, No.2, pp. 157–176, 2023
Advance Access Publication on November 15, 2022 https://doi.org/10.1093/humupd/dmac035





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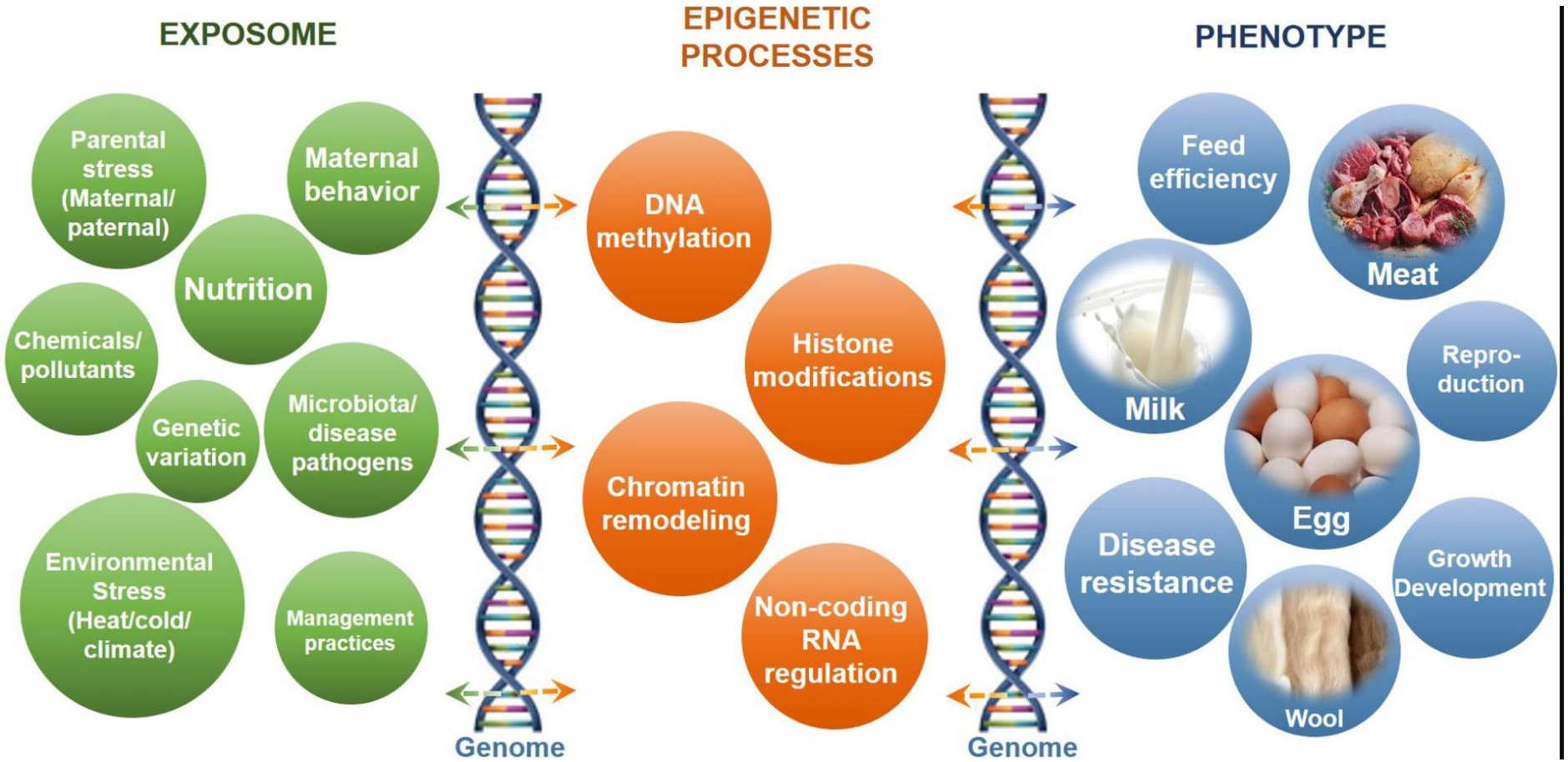
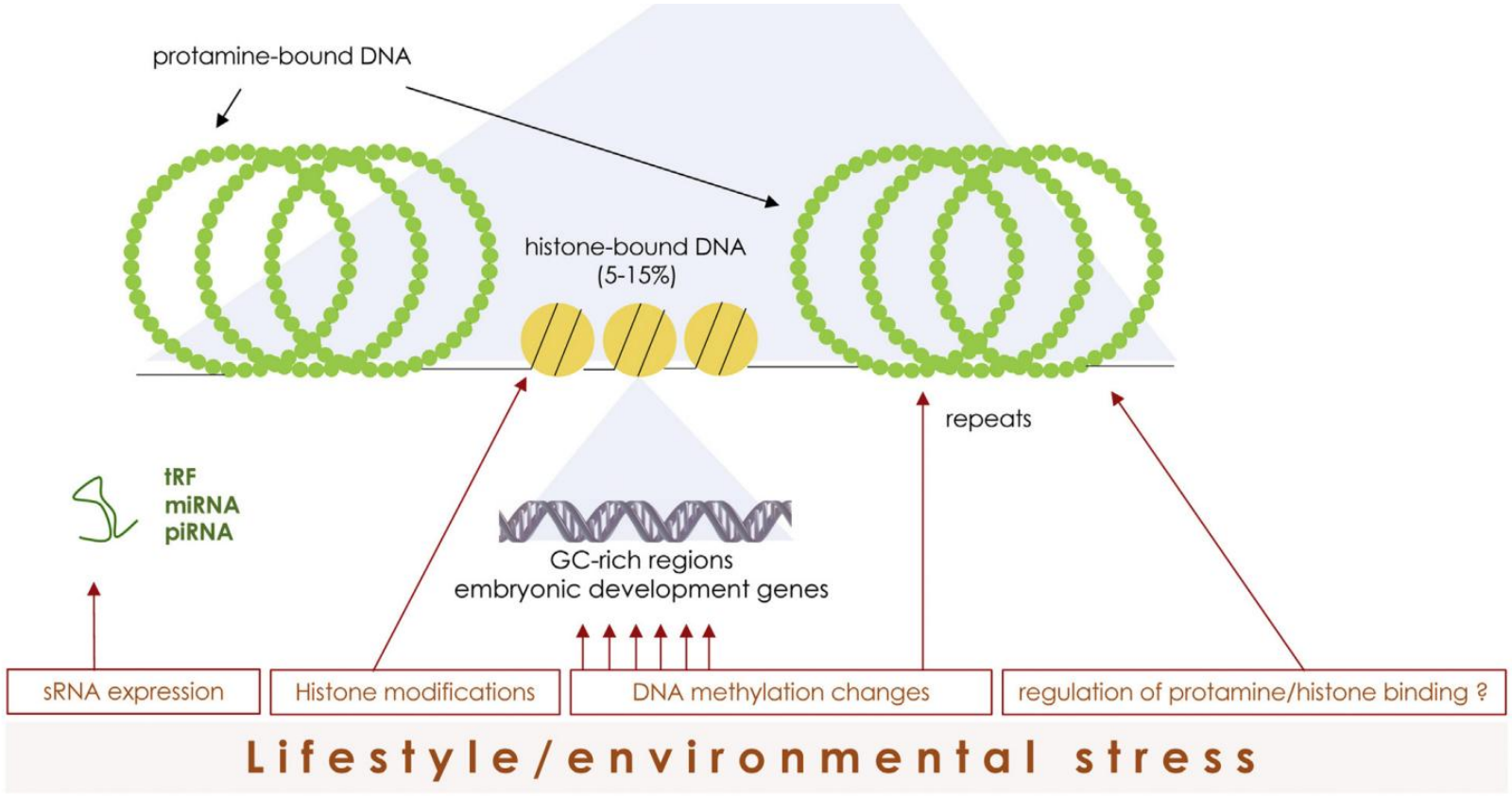
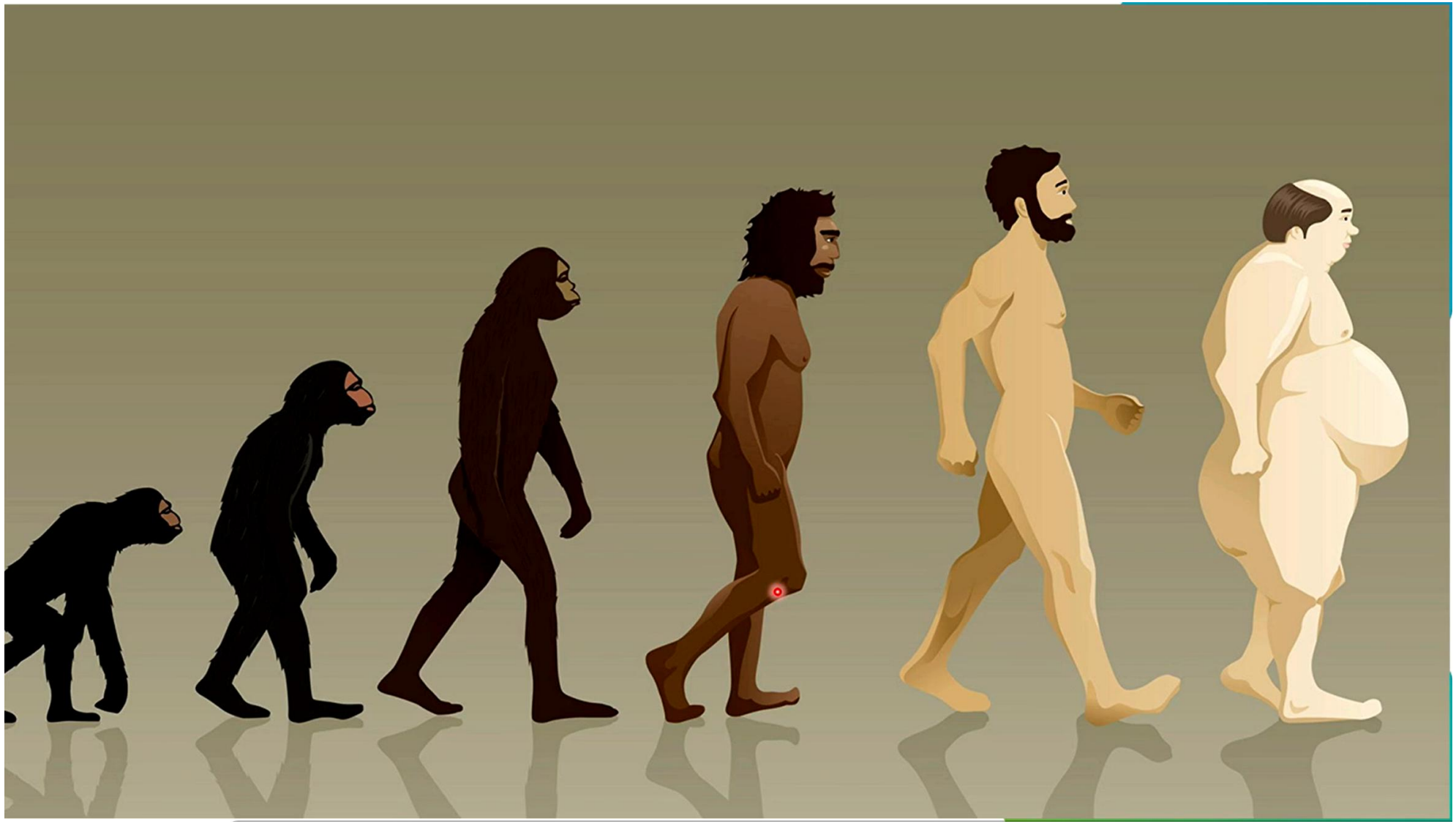

EXPOSOME
EPIGENETIC PROCESSES
PHENOTYPE
Parental stress (Maternal/ paternal)
Maternal behavior
Nutrition
Chemicals/ pollutants
Genetic variation
Microbiota/ disease pathogens
Environmental Stress (Heat/cold/ climate)
Management practices
Genome
DNA methylation
Histone modifications
Chromatin remodeling
Non-coding RNA regulation
Genome
Feed efficiency
Meat
Milk
Repro-duction
Egg
Disease resistance
Growth Development
Wool

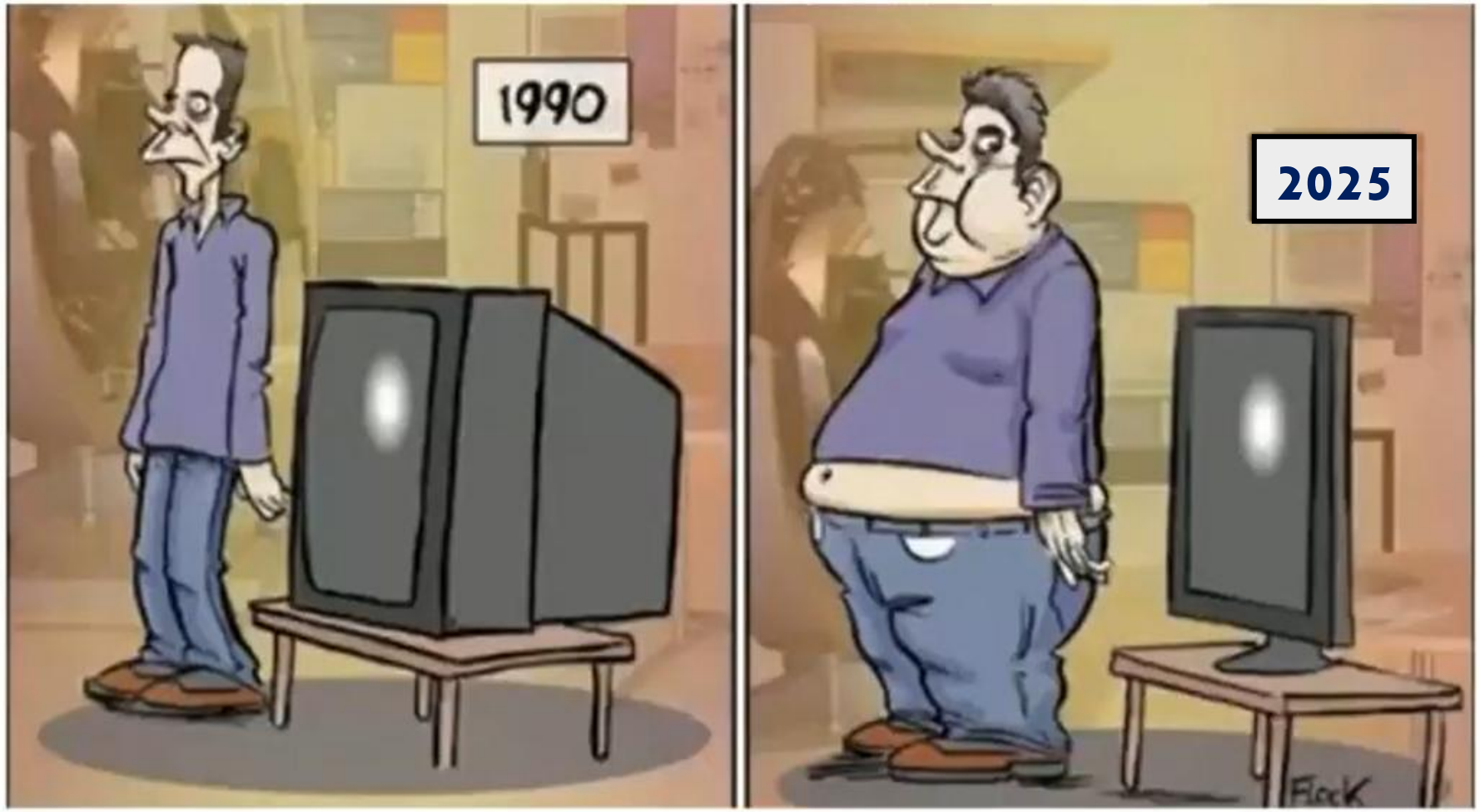


- Em termos evolutivos, essas mudanças criam ***a diversidade fenotípica que alimenta a seleção natural***.

- Existem fortes evidências ***de fatores epigenéticos causados pelo ambiente e transmitidos pelos espermatozoides***, capazes de ***alterar o fenótipo da próxima geração***.

MOLECULAR METABOLISM 14 (2018) 1e11
https://doi.org/10.1016/j.molmet.2018.02.006




1990
2025
FlocK

OBESITY

Paternal obesity—a risk factor for autism?

Susan K. Murphy

The aetiology of autism-spectrum disorders is partly explained by genetic factors, but a substantial component is attributed to environmental exposures. New evidence suggests that paternal obesity increases the risk of having a child with autism, which raises the possibility that obesity-driven, autism-related shifts in epigenetic reprogramming occur during spermatogenesis.

Murphy, S. K. *Nat. Rev. Endocrinol.* **10**, 389–390 (2014); published online 3 June 2014;
doi:10.1038/nrendo.2014.81

"**Paternal obesity** was associated with a **73% increased risk** (OR 1.73, 95% CI 1.07–2.82) of having a child diagnosed with autism, compared with the risk of autism in children of **non obese fathers** (BMI ≤25 kg/m2)."

Strongest form of autism!!

Murphy, **Nat Rev Endocrinol**, 2014

Garrido et al. Clin Epigenet (2021) 13:6
https://doi.org/10.1186/s13148-020-00995-2

Clinical Epigenetics

RESEARCH Open Access

Sperm DNA methylation epimutation biomarker for paternal offspring autism susceptibility

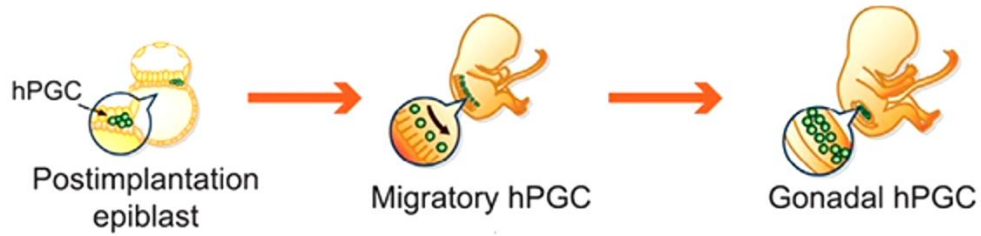
Nicolás Garrido[1], Fabio Cruz[1], Rocio Rivera Egea[1], Carlos Simon[2,3], Ingrid Sadler-Riggleman[4], Daniel Beck[4], Eric Nilsson[4], Millissia Ben Maamar[4] and Michael K. Skinner[4*]

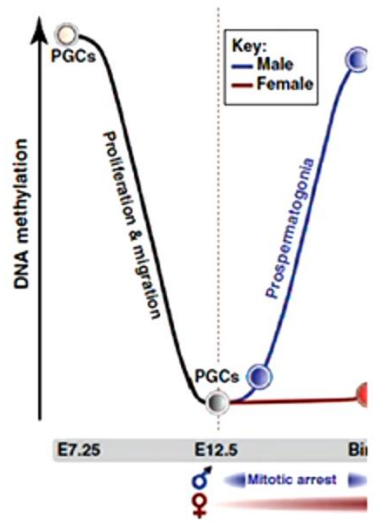
- *Exposições paternas ou dos ancestrais no início da vida que alteram a epigenética da linhagem germinativa*

- *Componente molecular da etiologia do TEA.*

A Unique Gene Regulatory Network Resets the Human Germline Epigenome for Development

Walfred W.C. Tang,[1,2,3,5] Sabine Dietmann,[3,5] Naoko Irie,[1,2,3] Harry G. Leitch,[3] Vasileios I. Floros,[4] Charles R. Bradshaw,[1] Jamie A. Hackett,[1,2,3] Patrick F. Chinnery,[4] and M. Azim Surani[1,2,3,*]

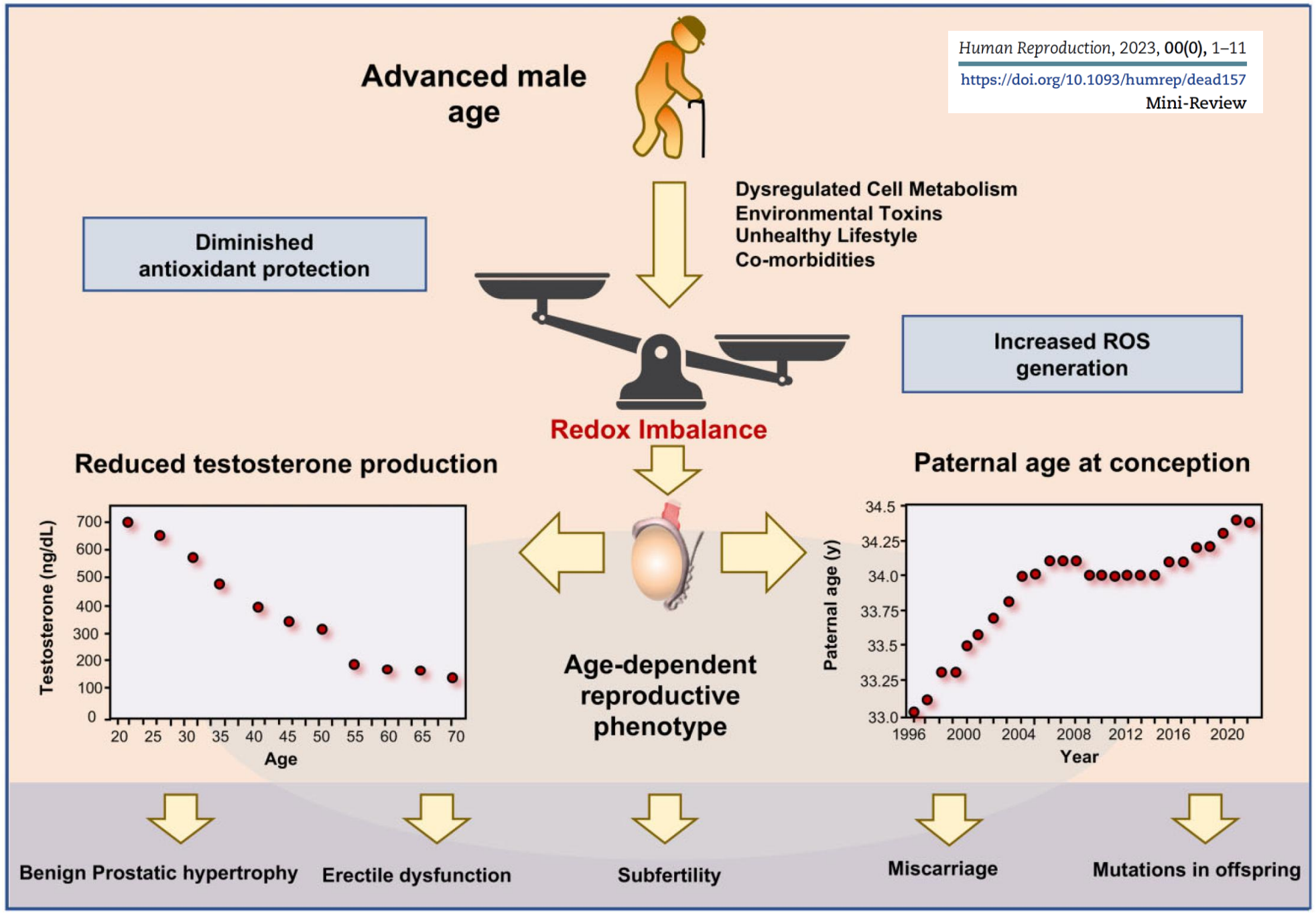


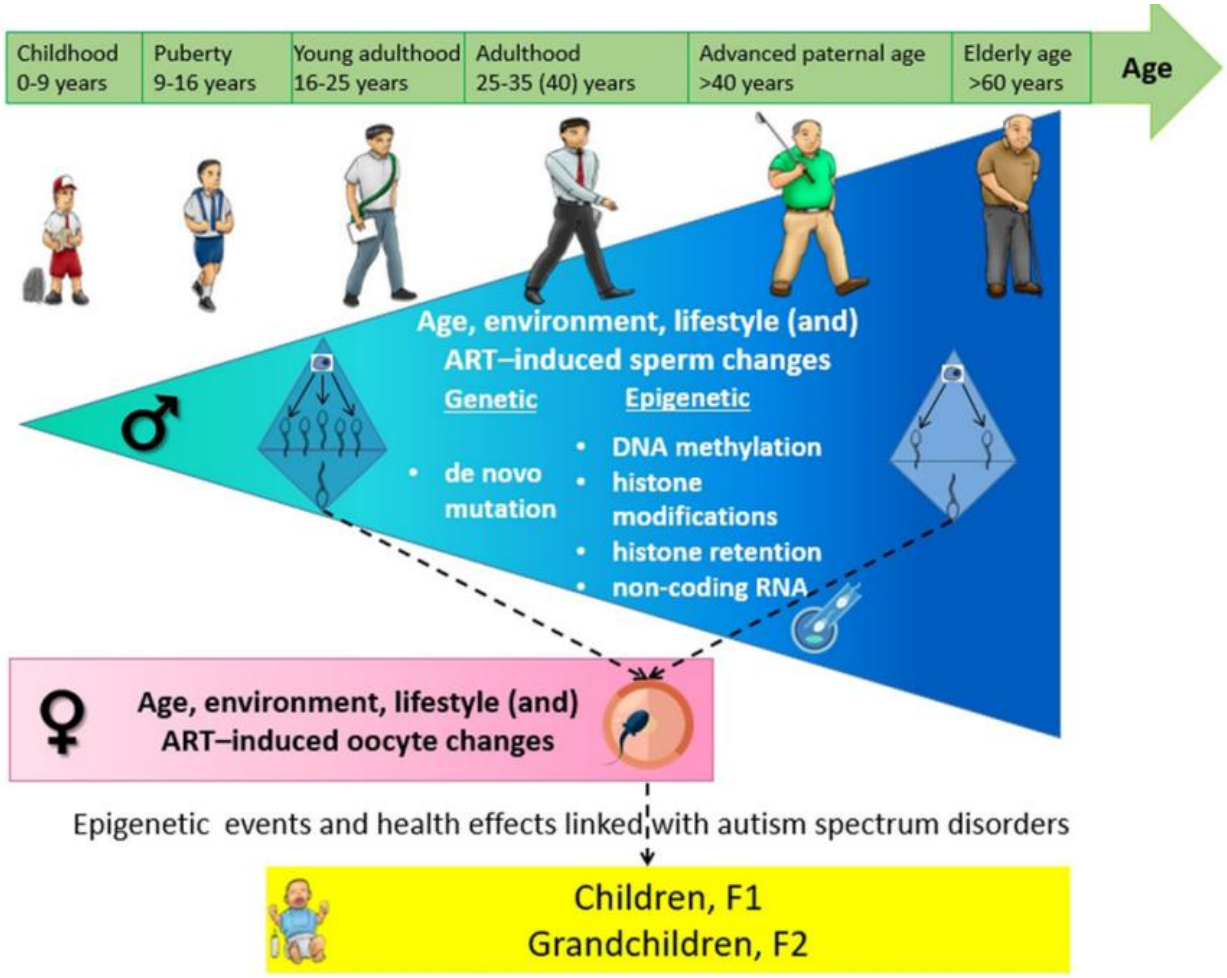


Region escaping reprogramming were related to "[…] genes expressed in brain and participated in neural development. Comparison of the escapee geneswith the NHGRI GWAS catalog revealed characteristic trait and disease associations, such as "obesity-related traits," "schizophrenia," […]"

Tang et al., **Cell**, 2015.

Human Reproduction, 2023, **00(0)**, 1–11
https://doi.org/10.1093/humrep/dead157
Mini-Review





- *Age is a powerful factor* in humans and rodent models associated *with increased de novo mutations and a modified sperm epigenome.*

- *Age affects all known epigenetic mechanisms*, including DNA methylation, histone modifications and profiles of small non-coding (snc)RNA.

Human Reproduction Update, Vol.24, No.3 pp. 320–389, 2018
Advanced Access publication on February 15, 2018 doi:10.1093/humupd/dmy005

human reproduction update

The effect of paternal factors on perinatal and paediatric outcomes: a systematic review and meta-analysis

Nan B. Oldereid [1,*], Ulla-Britt Wennerholm[2], Anja Pinborg[3], Anne Loft[4], Hannele Laivuori[5,6,7,8], Max Petzold[9], Liv Bente Romundstad[10,11], Viveca Söderström-Anttila[12], and Christina Bergh[13]

[1]Livio IVF-klinikken Oslo, Sørkedalsveien 10A, 0369 Oslo, Norway [2]Department of Obstetrics and Gynaecology, Institute of Clinical Sciences, Sahlgrenska Academy, Gothenburg University, Sahlgrenska University Hospital East, SE 416 85 Gothenburg, Sweden [3]Department of Obstetrics and Gynecology, Hvidovre Hospital, Institute of Clinical Medicine, Copenhagen University Hospital, Copenhagen, Denmark [4]Fertility Clinic, Section 4071, Copenhagen University Hospital, Rigshospitalet, Blegdamsvej 9, DK- 2100 Copenhagen, Denmark [5]Department of Obstetrics and Gynecology, Tampere University Hospital, Teiskontie 35, FI-33521 Tampere, Finland [6]Faculty of Medicine and Life Sciences, University of Tampere, Arvo Ylpön katu 34, FI-33520 Tampere, Finland [7]Medical and Clinical Genetics, University of Helsinki and Helsinki University Hospital, Haartmaninkatu 8, FI-00290 Helsinki, Finland [8]Institute for Molecular Medicine Finland, Helsinki Institute of Life Science, University of Helsinki, Tukholmankatu 8, FI-00290 Helsinki, Finland [9]Swedish National Data Service and Health Metrics Unit, University of Gothenburg, 405 30 Gothenburg, Sweden [10]Spiren Fertility Clinic, Norwegian University of Science and Technology, Trondheim NO-7010, Norway [11]Department of Public Health, Norwegian University of Science and Technology, Trondheim, Norway [12]Mehiläinen Felicias, Mannerheimintie 20A, 00100 Helsinki, Finland [13]Department of Obstetrics and Gynaecology, Institute of Clinical Sciences, Sahlgrenska Academy, Gothenburg University, Reproductive Medicine, Sahlgrenska University Hospital, SE-413 45 Gothenburg, Sweden

Table XI Summary results of the meta-analyses of the association between paternal factors and perinatal and paediatric outcomes.

Exposure	Outcome	Pooled estimate (with 95% CI)	Certainty of evidence GRADE
Paternal age	PTB	1.02 (1.00–1.05)	⊕⊕◯◯
	Low BW	1.00 (0.97–1.03)	⊕⊕◯◯
	Stillbirth	1.19 (1.10–1.30)	⊕⊕◯◯
★	Children with any birth defects	1.05 (1.02–1.07)	⊕⊕⊕◯
★	CHDs	1.03 (0.99–1.06)	⊕⊕⊕◯
	Orofacial clefts	0.99 (0.95–1.04)	⊕⊕◯◯
		1.14 (1.02–1.29)*	
★	Gastroschisis	0.88 (0.78–1.00)	⊕⊕⊕◯
★	Spina bifida	0.97 (0.90–1.04)	⊕⊕⊕◯
★	Trisomy 21	1.13 (1.05–1.23)	⊕⊕⊕◯
★	Acute lymphoblastic leukaemia	1.08 (0.96–1.21)	⊕⊕⊕◯
★	Autism and ASDs	1.25 (1.20–1.30)	⊕⊕⊕◯
★	Schizophrenia	1.31 (1.23–1.38)	⊕⊕⊕◯
Paternal BMI	No meta-analysis		
Paternal smoking	PTB	1.16 (1.00–1.35)	⊕⊕◯◯
	Low BW	1.10 (1.00–1.21)	⊕⊕◯◯
	SGA	1.22 (1.03–1.44)	⊕⊕◯◯
	CHDs	1.75 (1.25–2.44)	⊕⊕◯◯
	Orofacial clefts	1.51 (1.16–1.97)	⊕⊕◯◯
	Brain tumours	1.12 (1.03–1.22)	⊕⊕◯◯

*Exposure: Paternal age >45 years.

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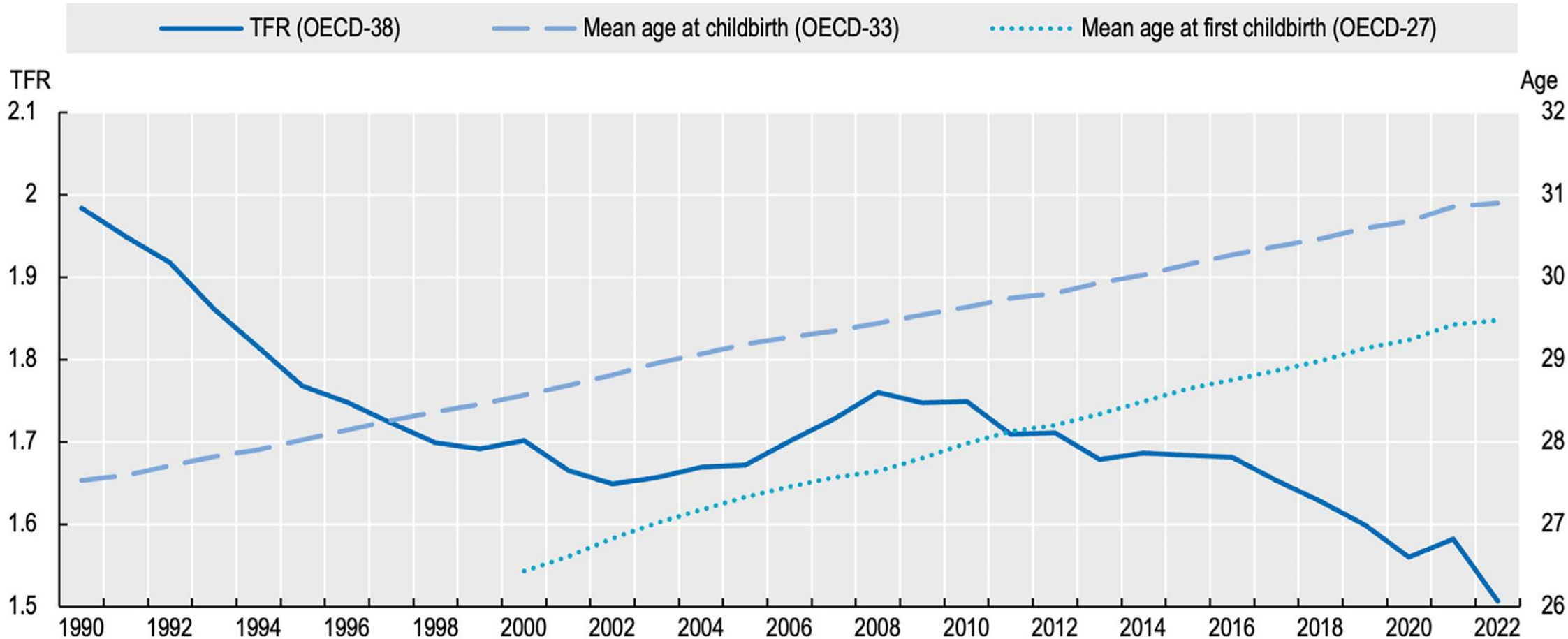
TFR (OECD-38)
Mean age at childbirth (OECD-33)
Mean age at first childbirth (OECD-27)
TFR
Age
2.1
2
1.9
1.8
1.7
1.6
1.5
32
31
30
29
28
27
26
1990
1992
1994
1996
1998
2000
2002
2004
2006
2008
2010
2012
2014
2016
2018
2020
2022

- Brasil: 39.762 ciclos FIV/ICSI 2023
- 68.001 embriões transferidos provenientes OVORECEPÇÃO DESCONGELAMENTO EMBRIÕES , OVÓCITOS DESCONGELADOS

~ 2.500.000 nascimentos / ano 2023 no Brasil

~ 24.000 crianças nascidas FIV/ICSI/DESCONGELAMENTO

~ 0,96% crianças nascidas Brasil

- USA: 4%
- Europa: 7% – Japão: 9%
- Dinamarca – Finlândia: 10%

IA nas T.R.A.

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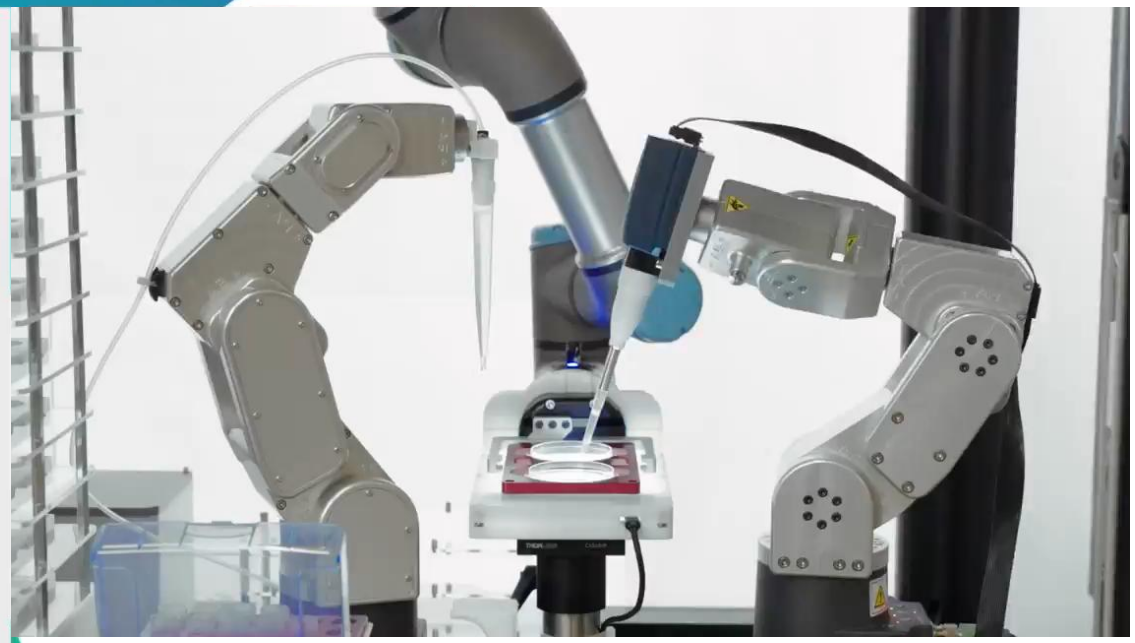
FIGURE 4 Diagram illustrating the diverse potential applications of artificial intelligence (AI) in fertility treatment procedures.

eshre SCIENCE MOVING PEOPLE MOVING SCIENCE | European Society of Human Reproduction and Embryology

Fully automated IVF lab

Launching January 2025

AURA



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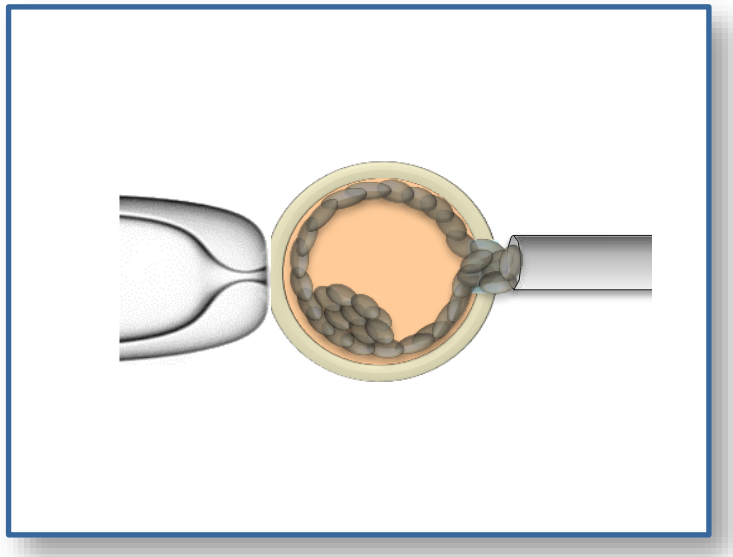
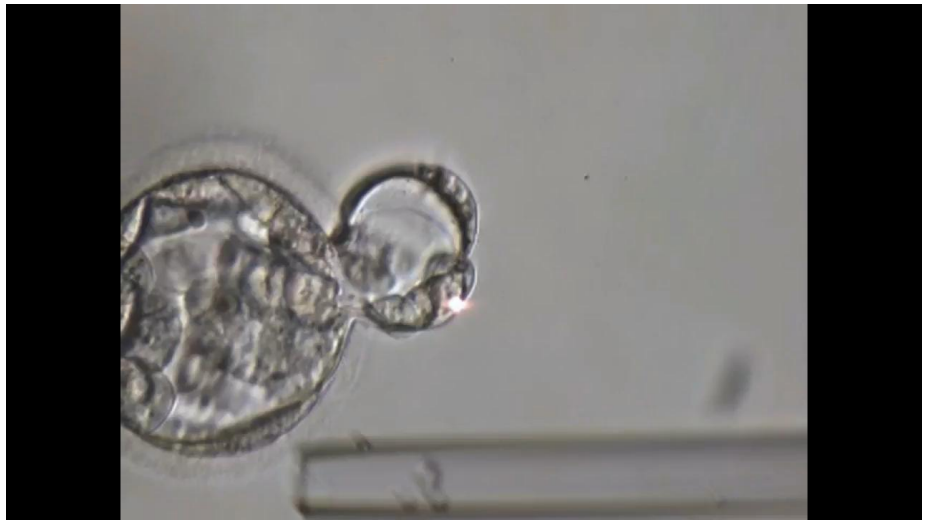
Diagnóstico Genético Pré-Implantacional

Retirada de 4 - 8 células do embrião dia +5 (120 células)
durante seu desenvolvimento laboratorial para análise genética





Diagnóstico Genético Pré-Implantacional

❖ Análise genética para os 24 cromossomos (PGT-A)

- ***array*SNP** (single nucleotide polymorphism), **NGS** (next-generation sequency)
  Aneuploidias: Sind Down, Edwards, Patau, Klinefelter, Turner, etc..

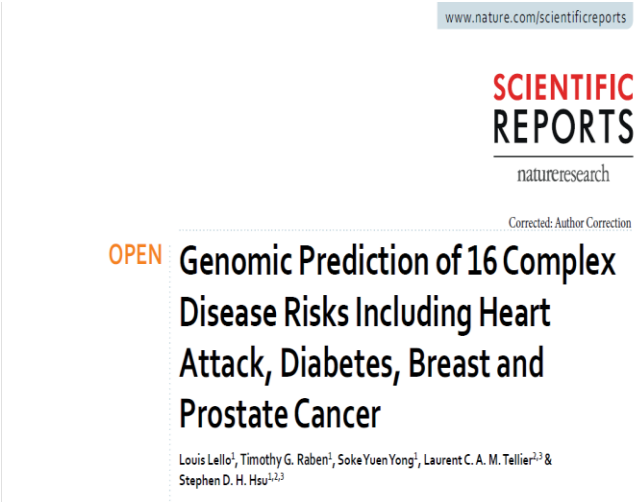
❖ Diagnóstico de doenças genéticas (PGT-M)

- **qPCR (**real-time quantitative polymerase-chain-reaction)
  Anemia falciforme, VHL (neurofibromatose), talassemia beta, atrofia muscular espinal, Huntington, Duchene, fibrose cística, X frágil, hemofilia A e B, "sexagem" , HLA typing

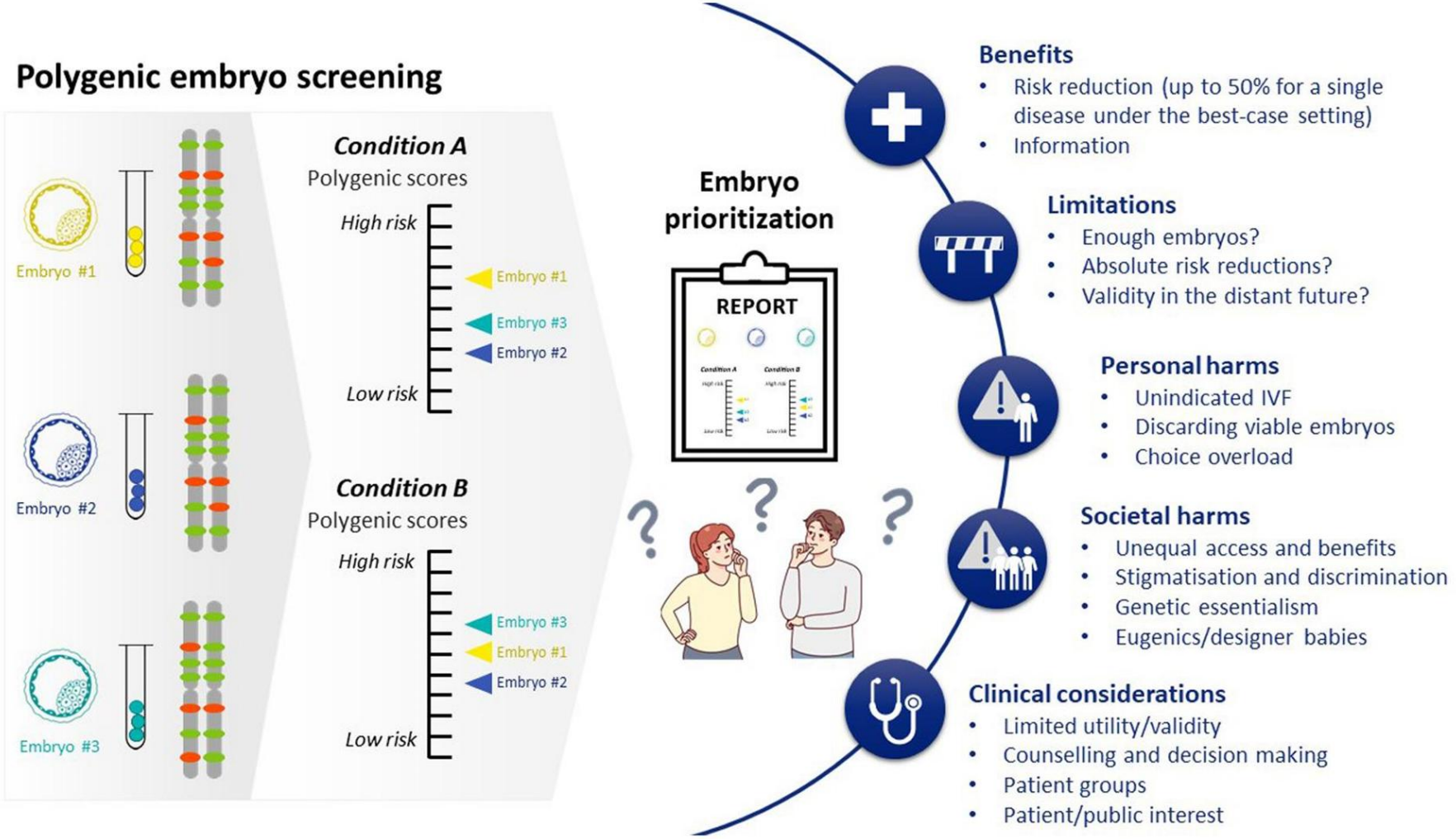
Diagnóstico Genético Pré-Implantacional

- Diagnóstico das Doenças Poligênicas (PGT-P)

Hypothyroidism, (Resistant), Hypertension, Type 1 and 2 Diabetes, Breast Cancer, Prostate Cancer, Testicular Cancer, Gallstones, Glaucoma, Gout, Atrial Fibrillation, High Cholesterol, Asthma, Basal Cell Carcinoma, Malignant Melanoma, Heart Attack, Schizophrenia, Autisms.



GRAPHICAL ABSTRACT



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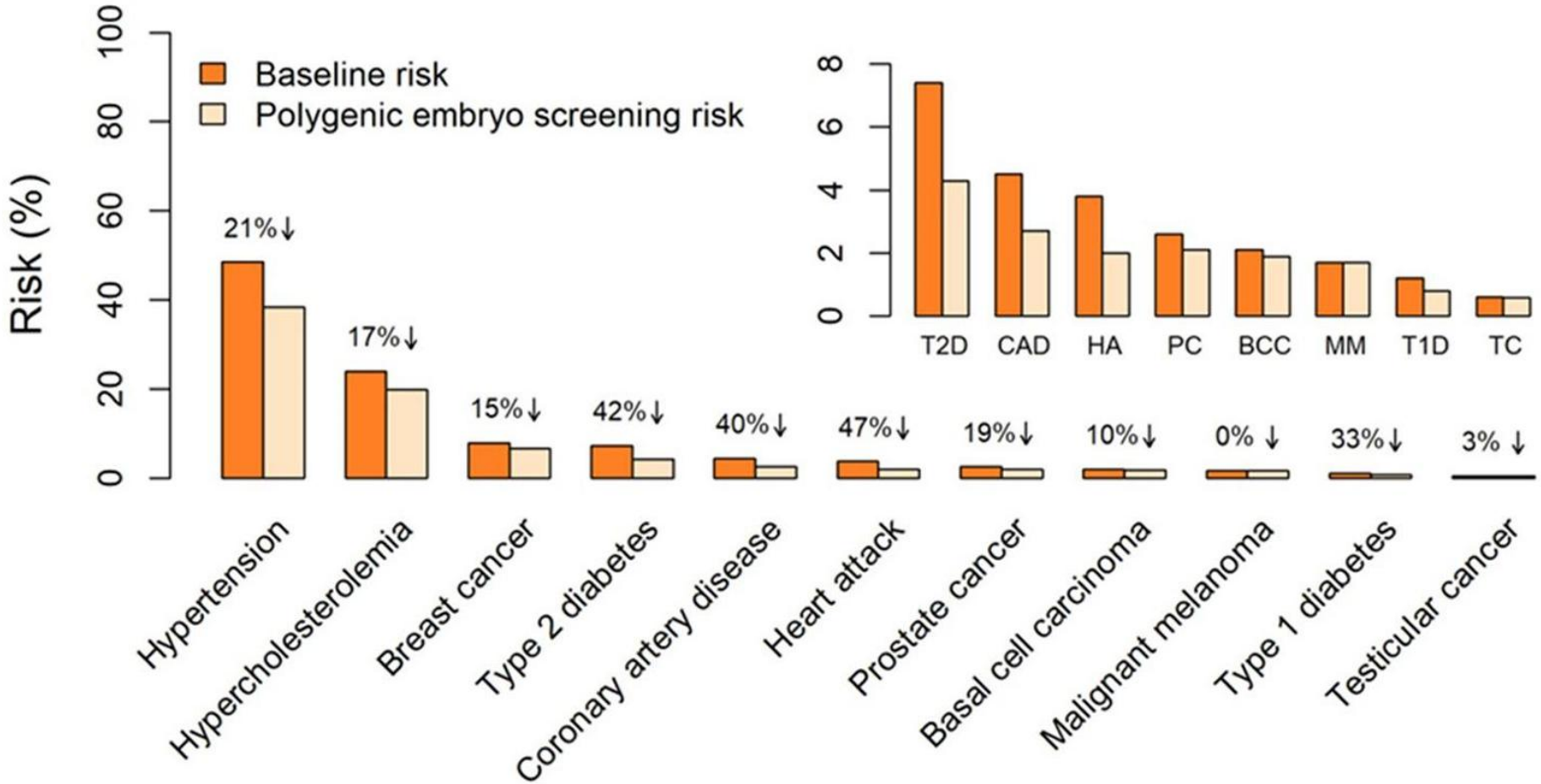
Human Reproduction Update, 2024, 30(5), 529–557
https://doi.org/10.1093/humupd/dmae012


Risk (%)
0
20
40
60
80
100
Baseline risk
Polygenic embryo screening risk
21%↓
17%↓
15%↓
42%↓
40%↓
47%↓
19%↓
10%↓
0% ↓
33%↓
3% ↓
Hypertension
Hypercholesterolemia
Breast cancer
Type 2 diabetes
Coronary artery disease
Heart attack
Prostate cancer
Basal cell carcinoma
Malignant melanoma
Type 1 diabetes
Testicular cancer
0
2
4
6
8
T2D
CAD
HA
PC
BCC
MM
T1D
TC

Genomic Prediction (offering PES commercially under the name ***LifeView***) (Treff et al., 2019a,b), ***Orchid Heal***th (Xia et al., 2022, 2024) and ***MyOme*** (Kumar et al., 2022)

ORCHID

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MONOGENIC SCREENING

Neurodevelopmental disorders	Intellectual disability Autism spectrum disorders Global developmental delay Epilepsy
Pediatric and adult-onset cancers	Breast cancer Prostate cancer Pancreatic cancer Retinoblastomas Ovarian cancer Colorectal cancer Wilms' tumor
Birth defects	Heart, skeletal, cranial defects Neuromuscular disorders Vision and hearing loss
Chromosomal abnormalities	Whole chromosomes Microduplications/deletions Molar pregnancies

GENETIC PREDISPOSITION SCREENING

Brain health

- Alzheimer's disease
- Bipolar disorder
- Schizophrenia

Heart health

- Artial Fibrillation
- Coronary artery disease

Cancers

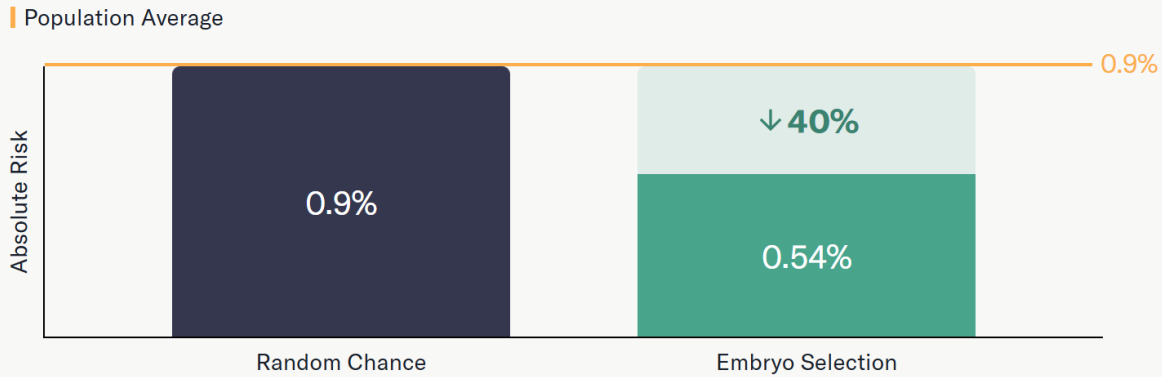
- Breast cancer
- Prostate cancer

General health

- Celiac disease
- Inflammatory bowel disease
- Type I diabetes
- Type II diabetes

Help protect my child from Schizophrenia

Selecting your healthiest embryo could **reduce your child's risk by 40%.**



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Genome Editing

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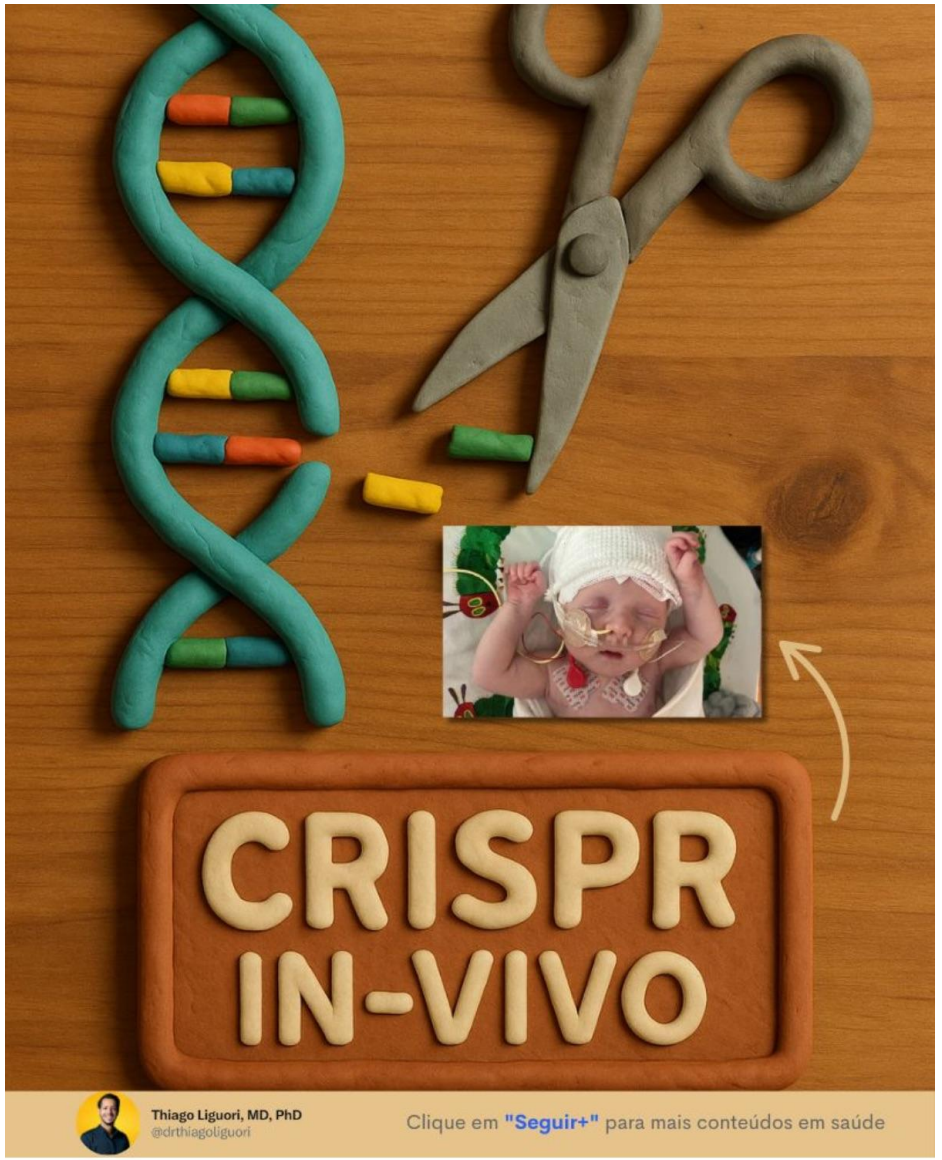
Existem cerca de 75 mil mutações que causam doenças nos seres humanos.

"prime editing" tem o potencial para corrigir 89% delas....



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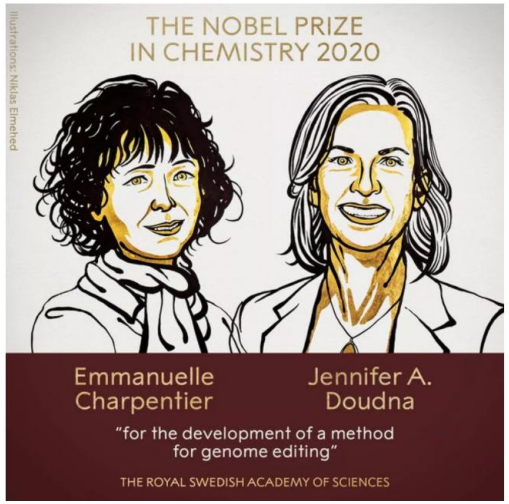

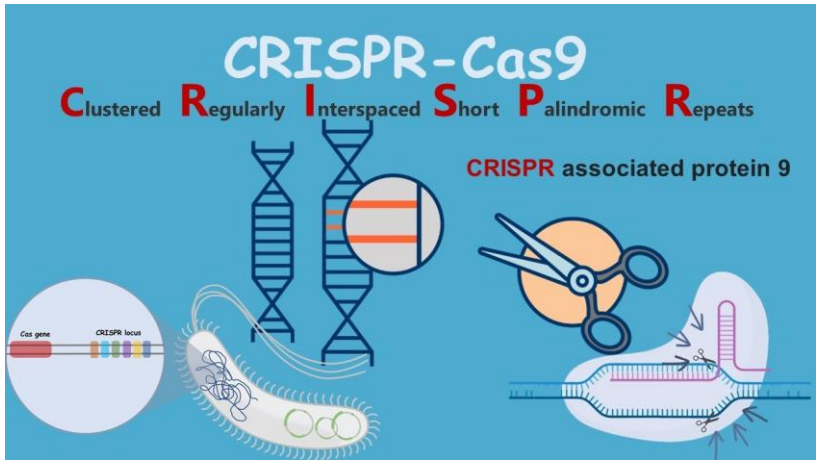

Patient KJ. (Children's Hospital of Philadelphia)

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Ectogenesis

‘ectogestation’, ‘extra-corporeal gestation’ and ‘artificial womb technology’

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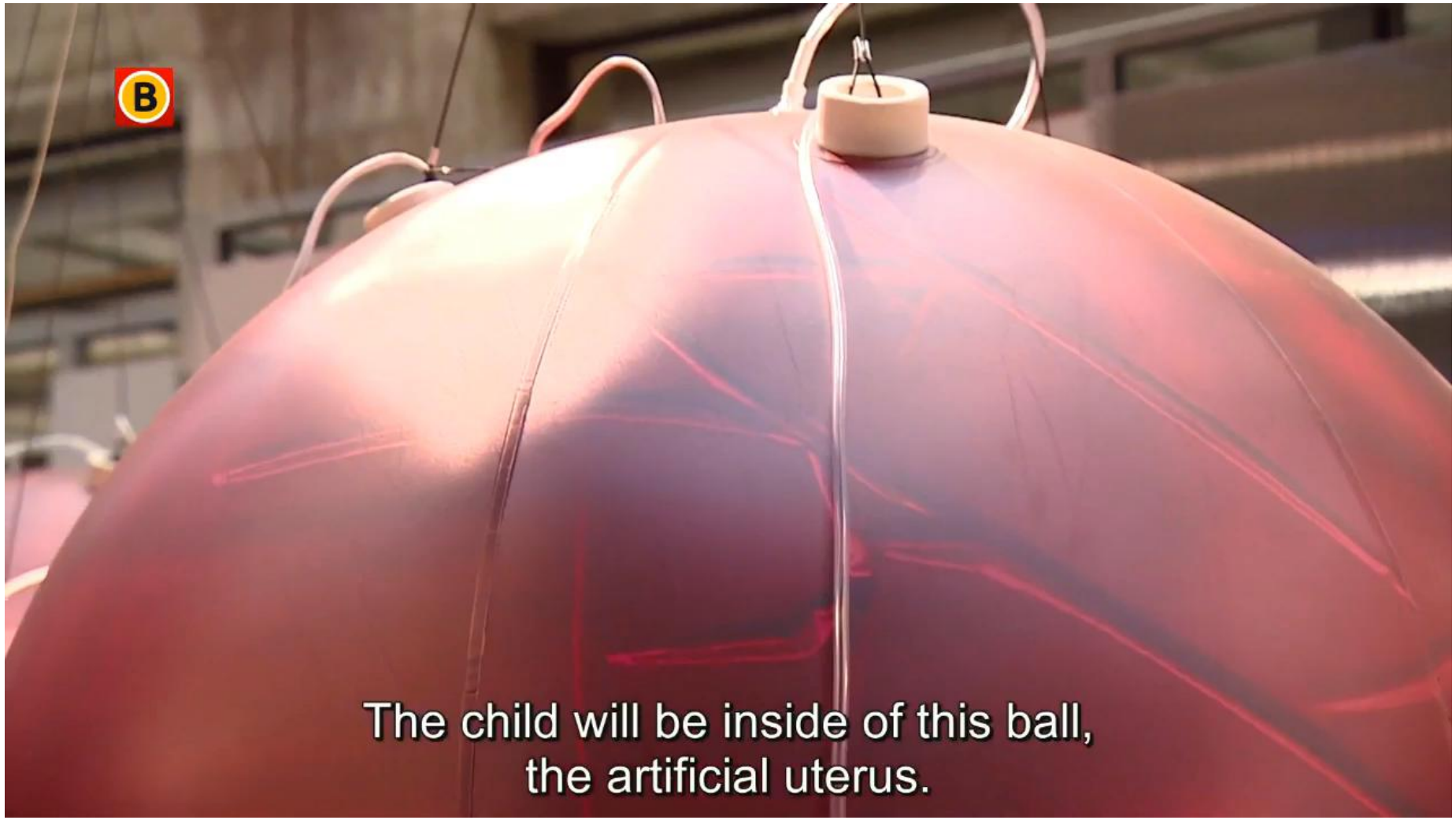
The child will be inside of this ball,
the artificial uterus.

Ectogenesis (Artificial Wombs)

What it is:

Developing fetuses outside of the human body in a controlled environment, potentially replacing or supplementing natural pregnancy.

Potential benefits:

Could offer solutions for conditions where natural pregnancy is impossible or dangerous, and could even allow for "multi-parent" or "design" of

Ethical concerns:

Raises questions about the definition of birth, the rights of the fetus, and potential social implications of "design" babies

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In vitro-derived Gametes

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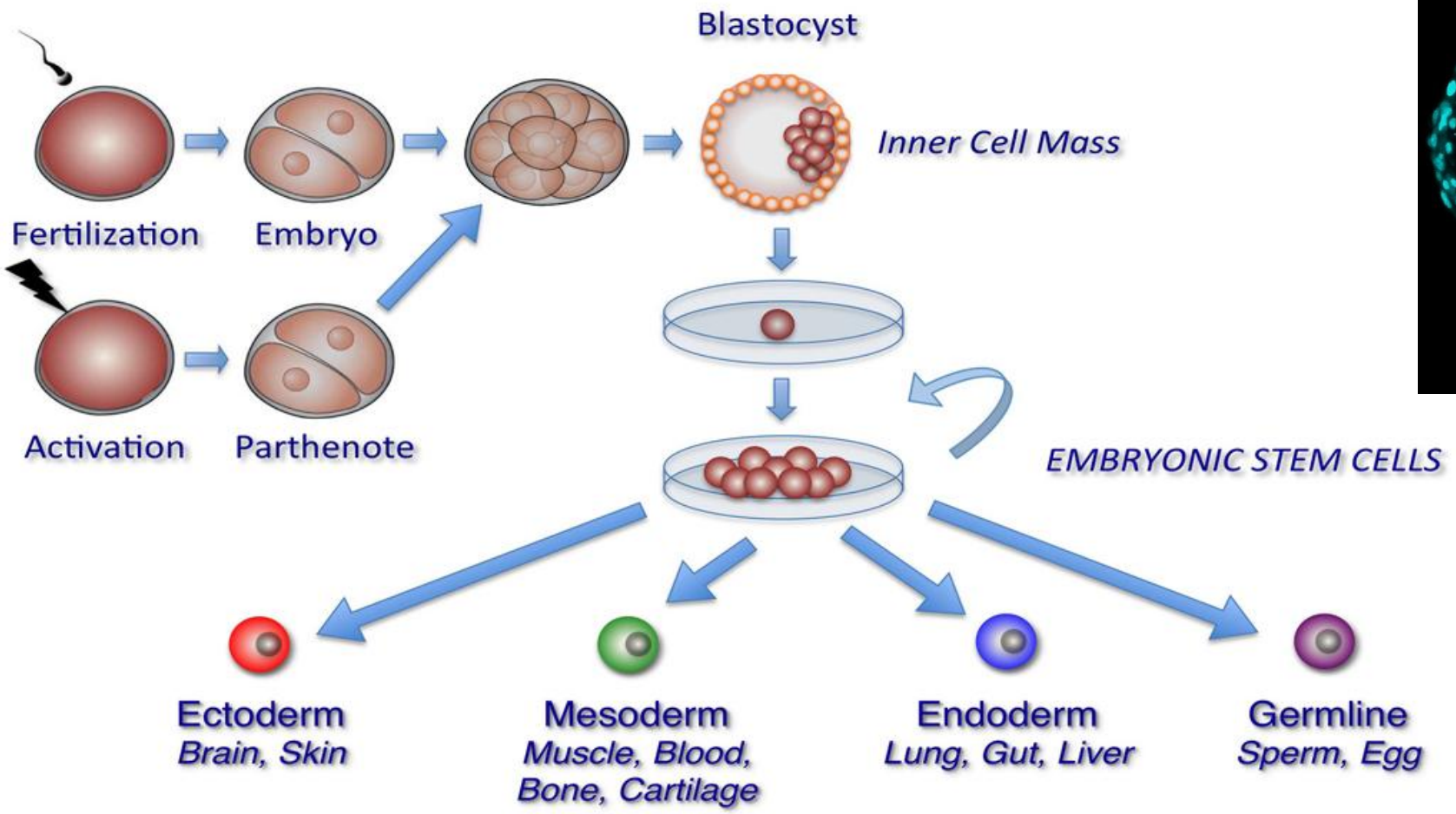

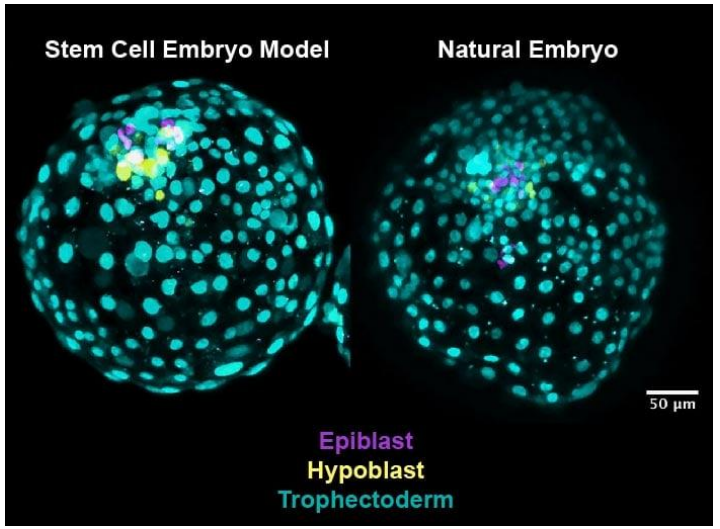

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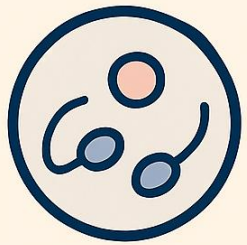
Stem Cell Rev Rep. 2025 May 20. doi: 10.1007/s12015-025-10890-z

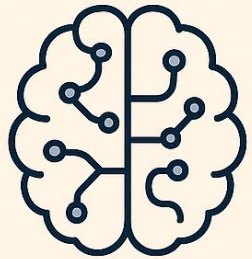
IN VITRO-DERIVED GAMETES

What itis	Potential benefits
	Creating eggs and sperm artificially from cells, like skin cells, opening up possibilities for same-sex, multiplex (multi-parent), or singular genetic parenting
Potential benefits 	Could provide solutions for infertility, enable same-sex couples to have biological children, and potentially allow for more diverse genetic combina-tions
Ethical concerns 	Raises questions about the definition of parenhood, the implications for genetic diversity, and potential societal biases related to reproductive technology

Scientists create mice with two fathers after making eggs from male cells

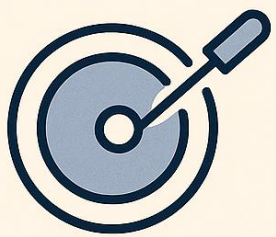
Creation of mammal with two biological fathers could pave way for new fertility treatments in humans

FUTURO REPRODUTIVO DA HUMANIDADE – CURTO PRAZO



Inteligência Artificial
modelos preditivos

Automatização completa do laboratório



Grande uso do Diagnóstico Genético Pré-Implantacional

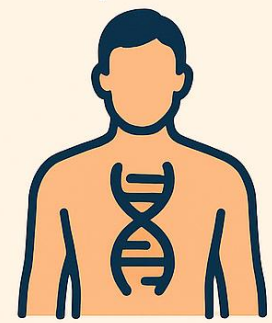
FUTURO REPRODUTIVO DA HUMANIDADE – LONGO PRAZO

Edição genética

Gametas artificiais

Ectogênese

Nova espécie??
os “geneticamente enriquecidos”



FER

Impactos sociais e éticos

- Desigualdade de acesso à tecnologia
- Desumanização da reprodução?
- "Fábricas de bebés" e controle populacional

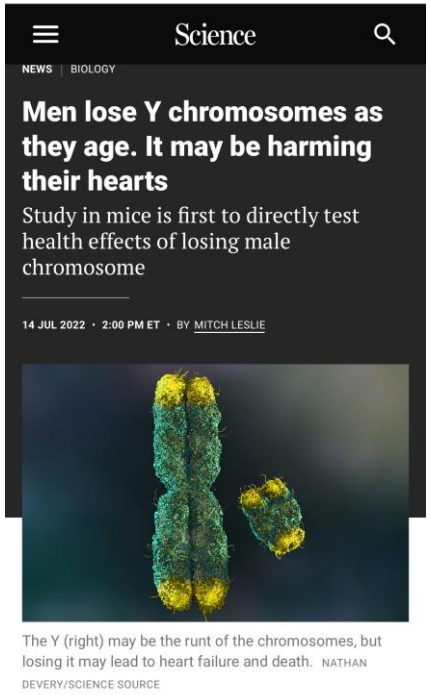
Reprodução natural

Reprodução artificial

The Y chromosome is disappearing. Is this the end of men?

The Y chromosome, responsible for creating the male sex, is on the way out. But something appears to be taking its place.

Originally, the Y chromosome was similar to the X and had over 900 genes. Now just 45 are left


Science

NEWS | BIOLOGY

Men lose Y chromosomes as they age. It may be harming their hearts

Study in mice is first to directly test health effects of losing male chromosome

14 JUL 2022 · 2:00 PM ET · BY MITCH LESLIE

The Y (right) may be the runt of the chromosomes, but losing it may lead to heart failure and death. NATHAN DEVERY/SCIENCE SOURCE

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O CROMOSSOMO Y FRÁGIL

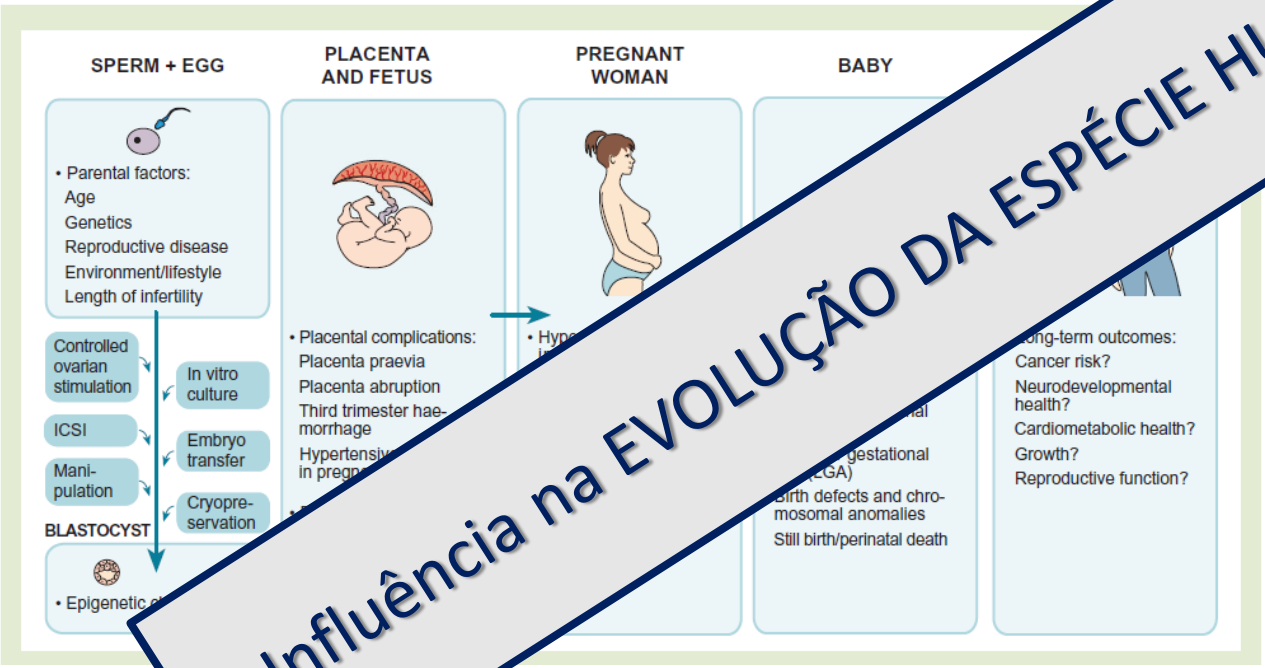
- O cromossomo Y carrega o gene SRY, o interruptor da determinação do sexo masculino
- Contém pouquíssimos outros genes e não é essencial para a vida
- As mulheres vivem muito bem sem ele

LINHA DO TEMPO DA DEGENERAÇÃO

- Tinha o mesmo tamanho e número de genes que o cromossomo X
- Perdeu a maioria dos genes devido à falta de recombinação
- Pode desaparecer em ~ 4,6 milhões de anos (se a degeneração continuar)

Importante: Sim, os homens ainda existem – mas por quanto temp mais?

FIV / ICSI



Human Reproduc… 137–158, 2019

Influência na EVOLUÇÃO DA ESPÉCIE HUMANA ???

…CSI pode interromper
…s epigenéticos normais com
…equências para o desenvolvimento e
saúde a longo prazo;

- Aumenta a aptidão reprodutiva de casais subférteis, removendo tecnologicamente vários tipos de barreiras seletivas e alterando outras barreiras;

- De acordo com o princípio básico da evolução, as gerações subsequentes serão, assim, geneticamente e epigeneticamente adaptadas a um ambiente em qual reprodução depende cada vez mais da intervenção tecnológica.

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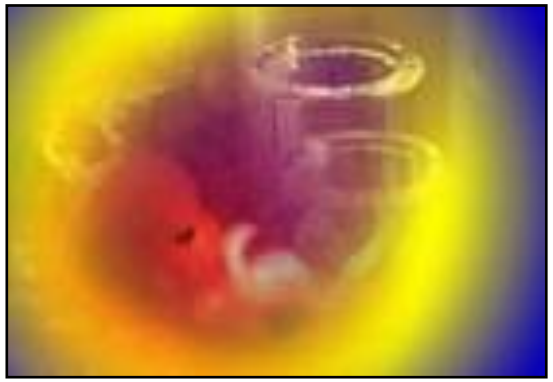
Como os bebês nascerão
num futuro próximo!

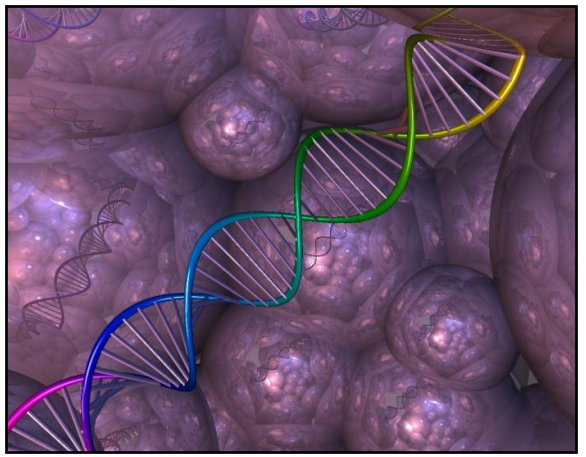
“Perspectivas Futuras”

Sexo virtual

Útero artificial



Bebês por RHA



Engenharia Genética

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“Perspectivas Futuras”

clique aqui
para comprar
um bebê

VISA

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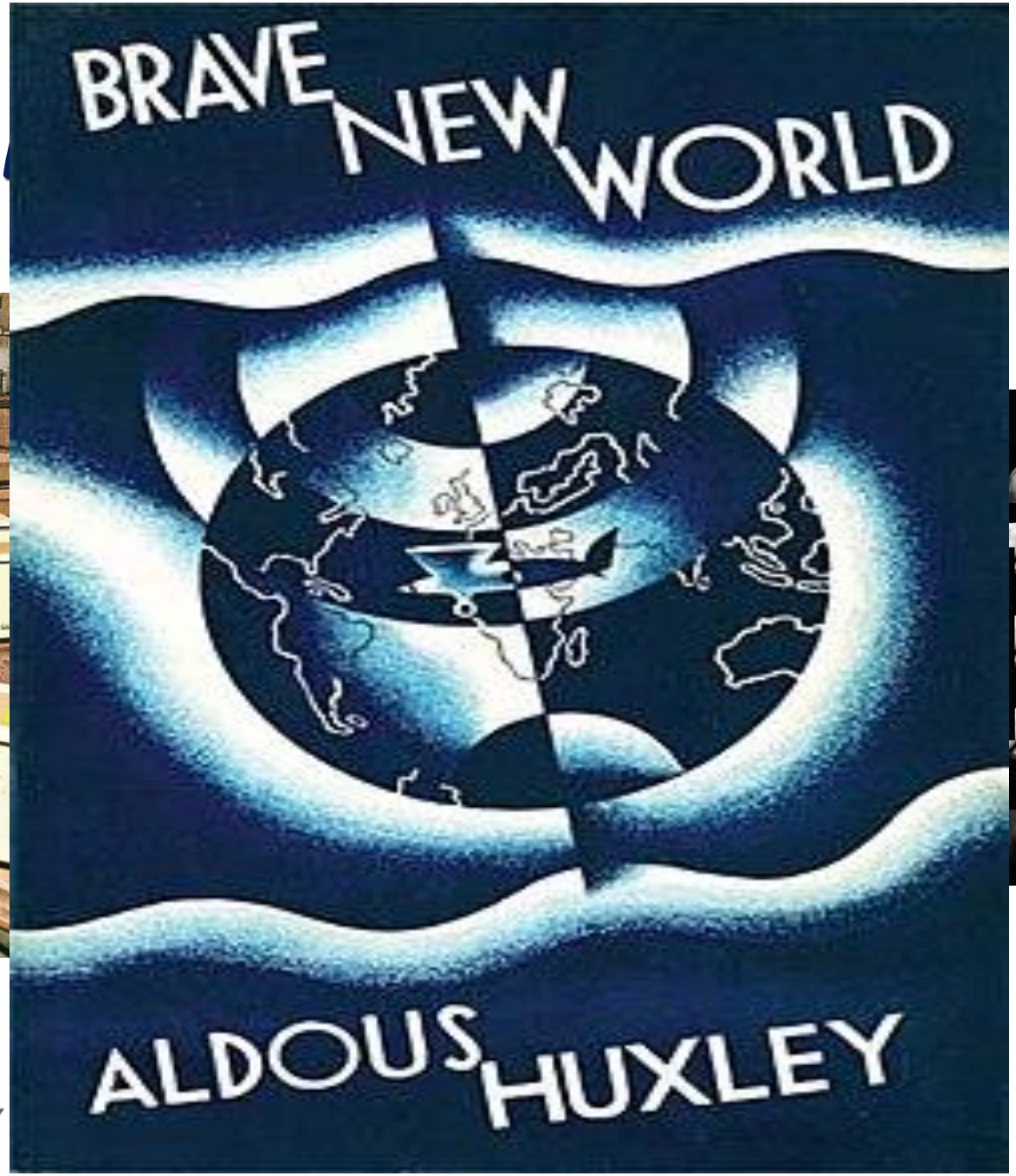

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Obrigado!

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