THE UNIVERSITY of EDINBURGH

Institute for Regeneration and Repair

Centre for Reproductive Health

ORCHID-NET

Optimising male reproductive potential after childhood disease

Fertility preservation for boys and adolescent males with cancer

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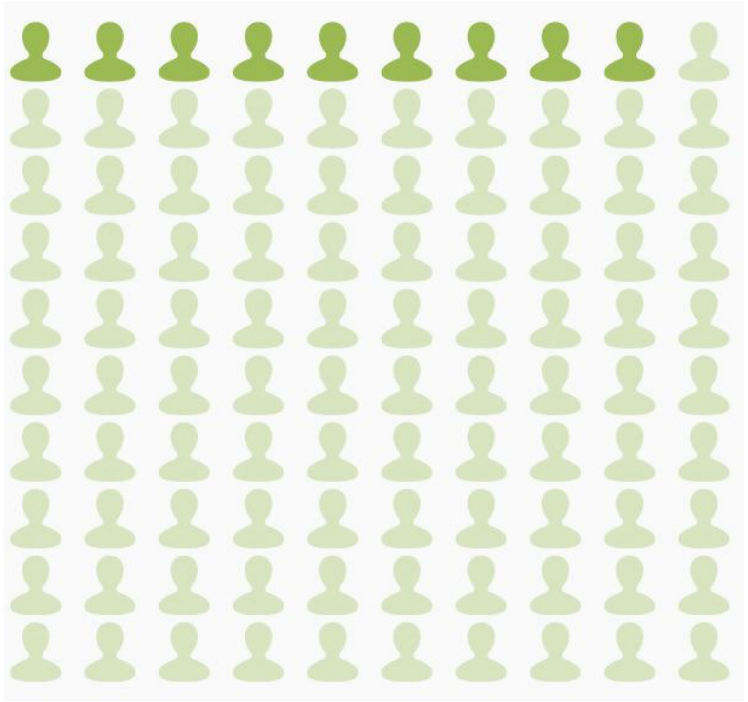
Latvian Association of Obstetricians and Gynaecologists, Riga, May 2025

Most children with cancer will survive

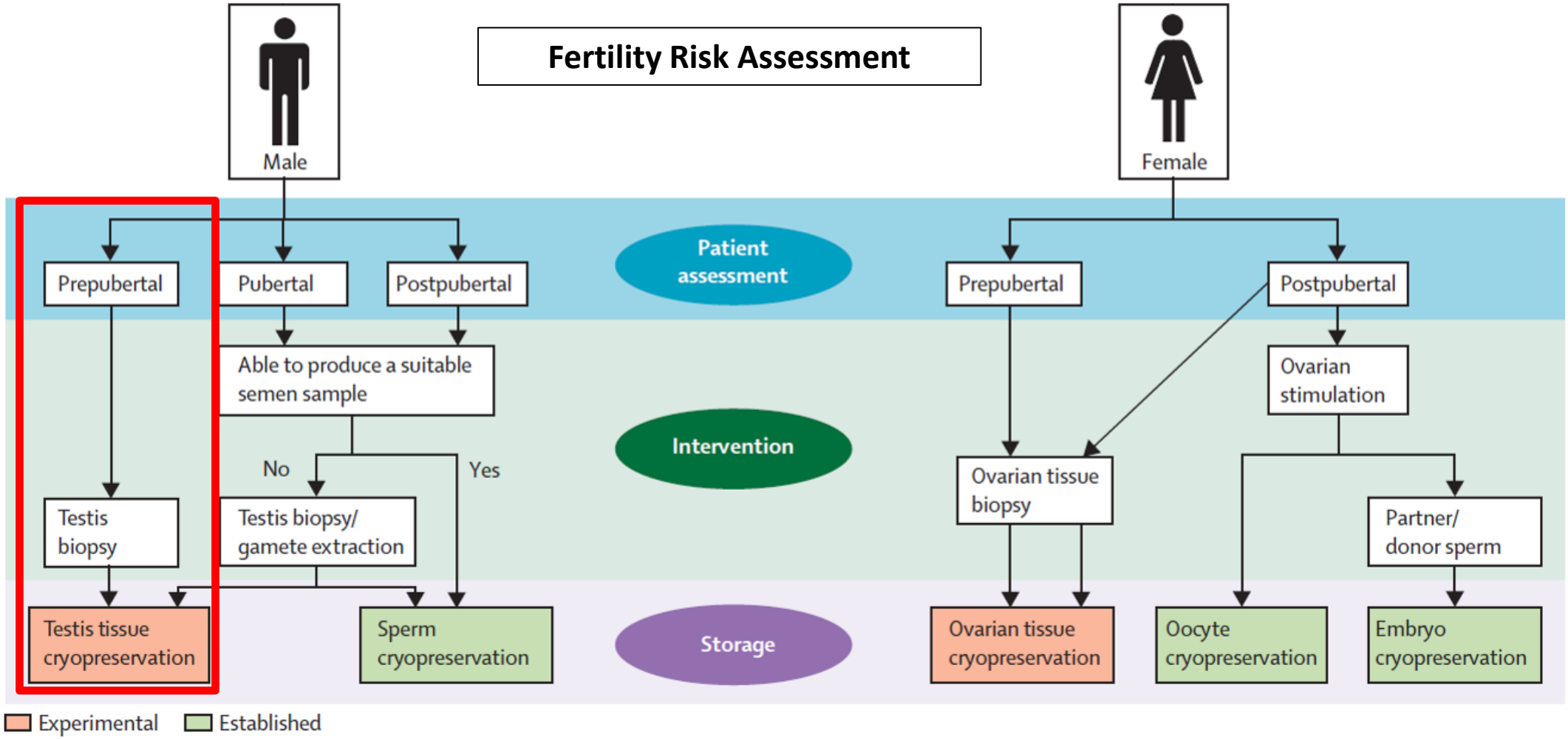
1960



2020

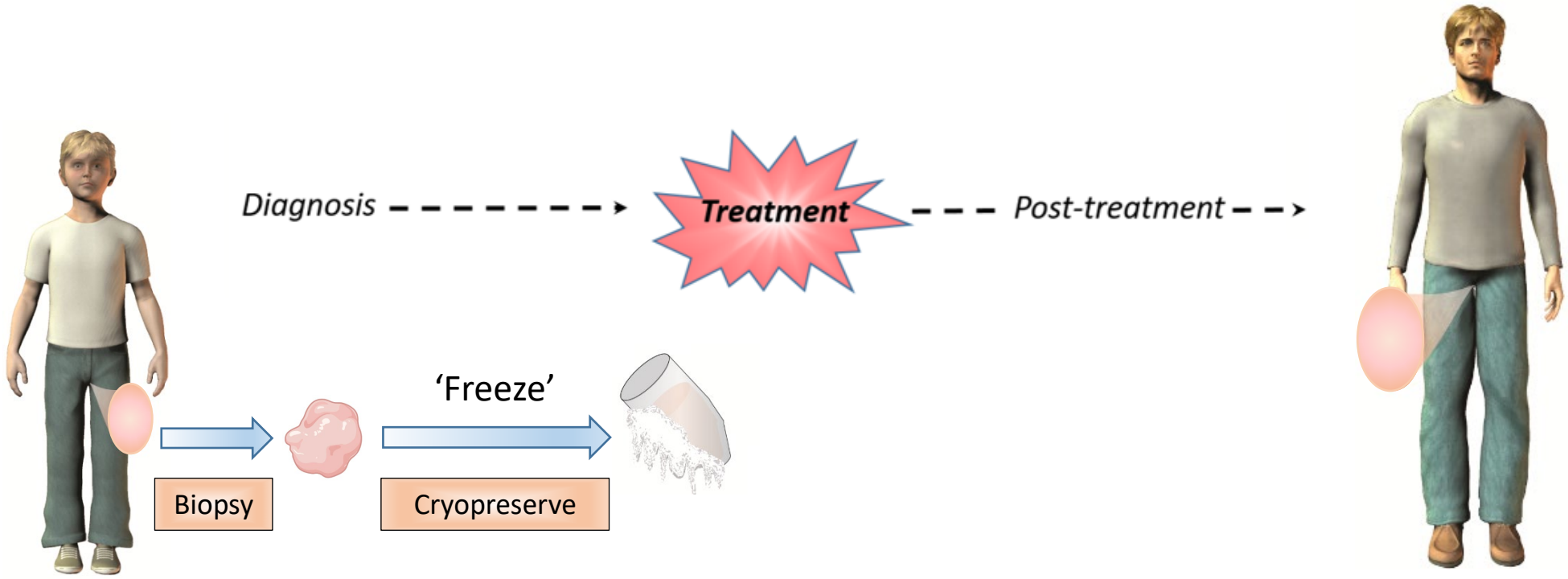
~1:500 young adults is a survivor of childhood cancer

Current options for fertility preservation



Anderson RA* and Mitchell RT* et al. *The Lancet Diabetes and Endocrinology*. 2015

Testicular tissue cryopreservation



Preserve potential for fertility

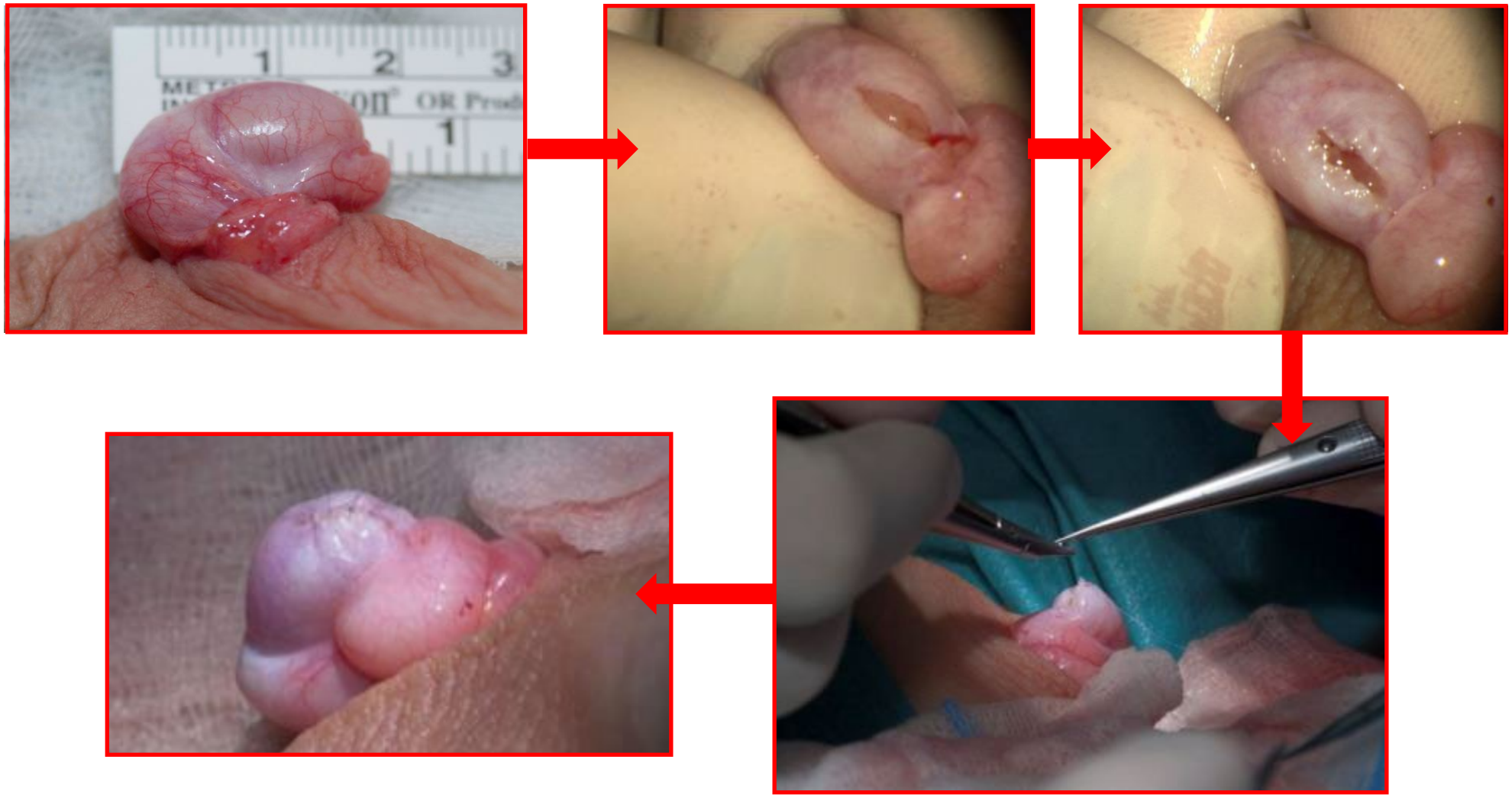
Patient selection criteria

2014 'Edinburgh Criteria'

- Age 0-18 years
- Unable to produce a semen sample
- No testicular pathology
- High (>80%) risk of sub/infertility
  - High dose alkylating agents
  - Radiotherapy to pelvis
- Intention to cure
- Consent (parent +/- patient)

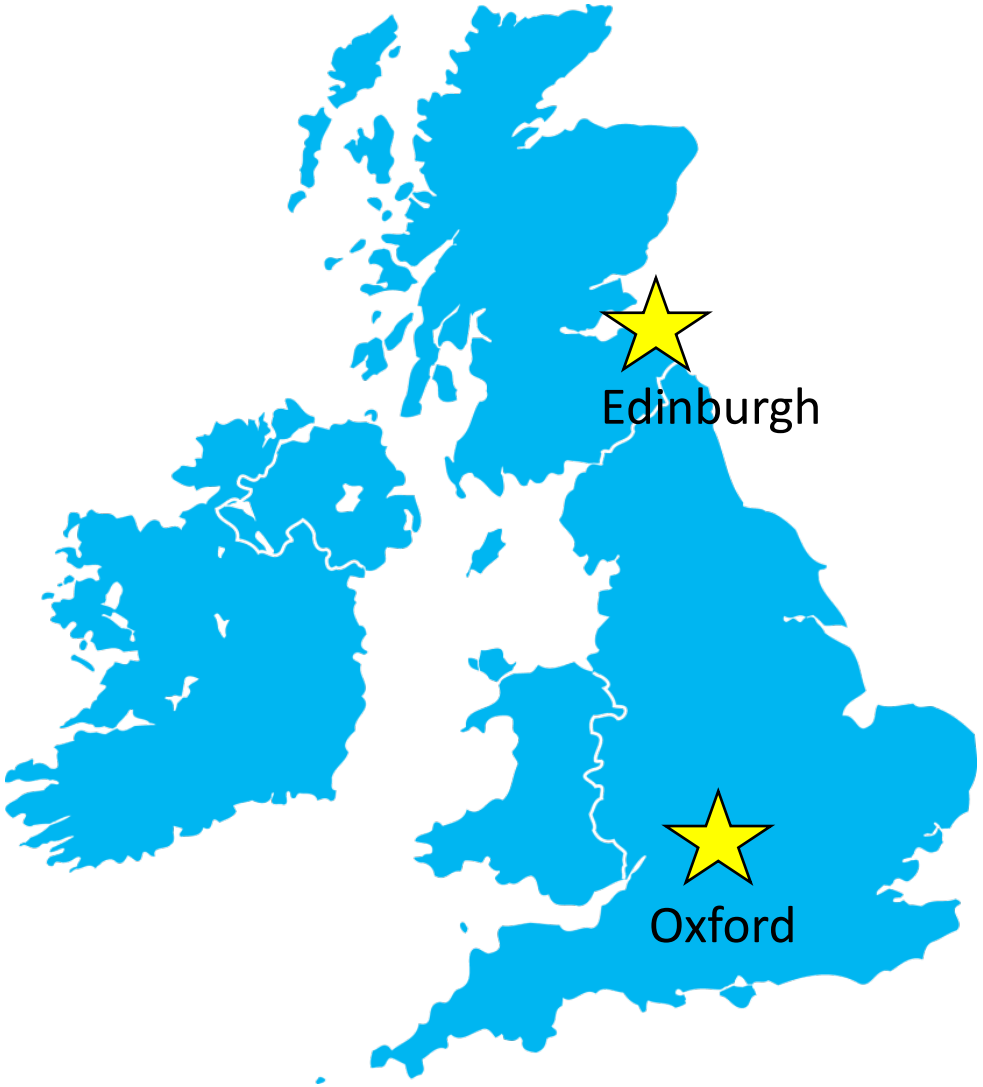
Anderson RA* and Mitchell RT* et al. *The Lancet Diabetes and Endocrinology*. 2015

Testicular biopsy for fertility preservation



Images courtesy or Ans van Pelt, AMC Amsterdam

Testicular tissue cryopreservation in UK



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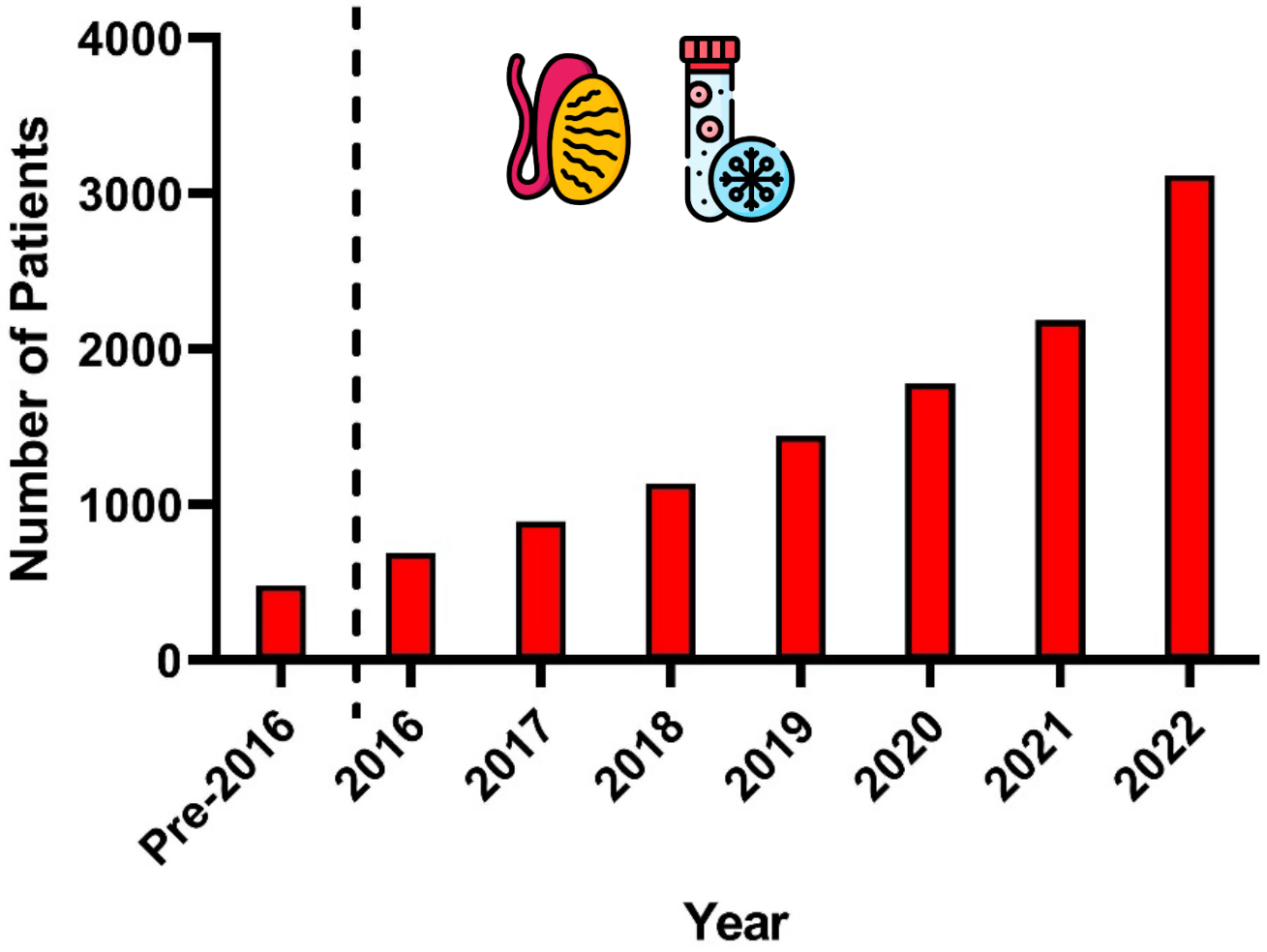
Testicular tissue cryopreservation



>3100 boys

Duffin et al. Human Reproduction Open. 2024

ORCHID-NET survey on fertility preservation in boys

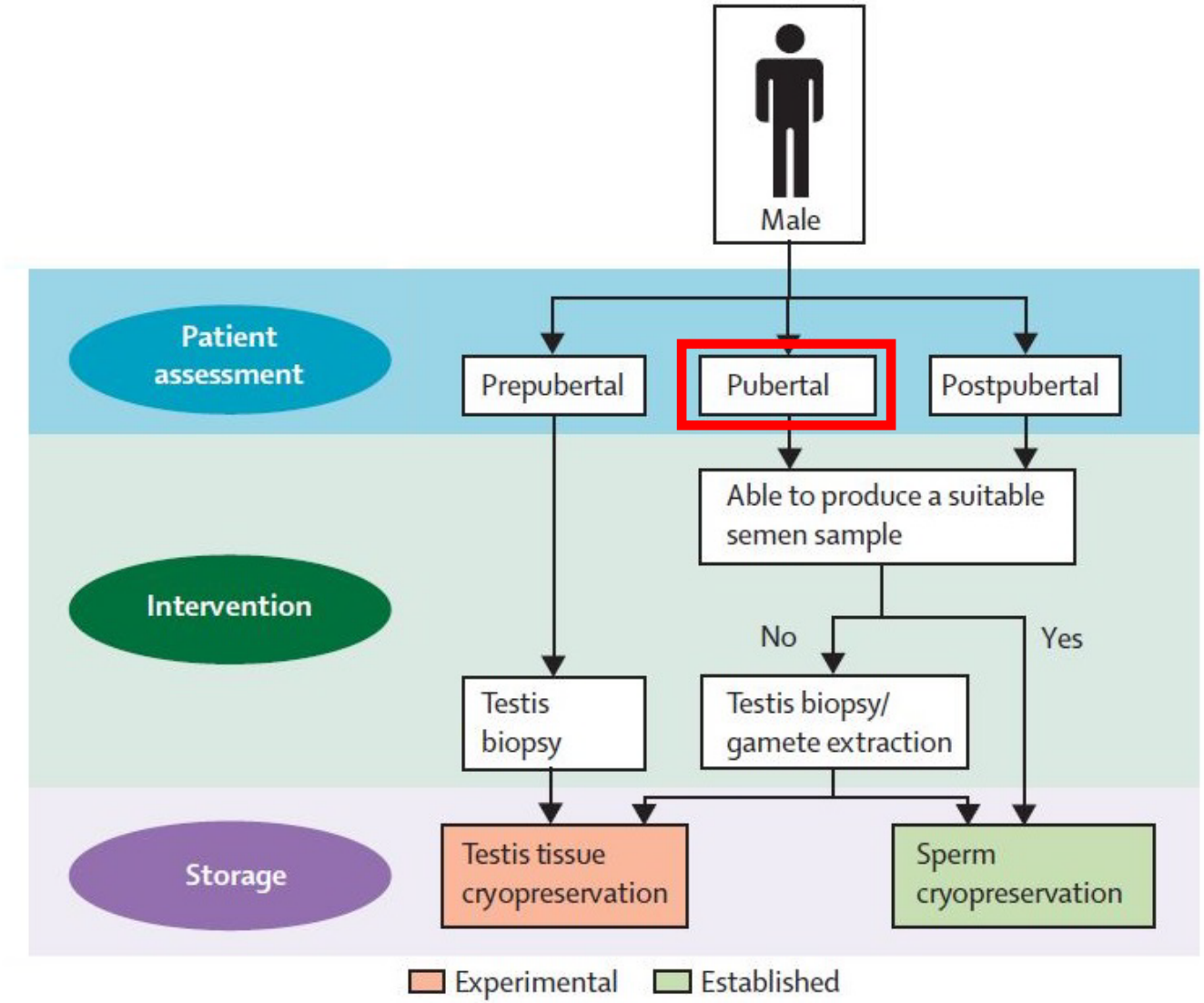
Human Reproduction Open, 2024, **2024(2)**, hoae010
https://doi.org/10.1093/hropen/hoae010
Advance Access Publication Date: February 16, 2024
Original article

A 20-year overview of fertility preservation in boys: new insights gained through a comprehensive international survey

Kathleen Duffin [1,†], Nina Neuhaus [2,†], Claus Yding Andersen[3], Virginie Barraud-Lange [4,5], Aude Braye[6], Cristina Eguizabal [7,8], Aurélie Feraille [9], Jill P. Ginsberg[10], Debra Gook[11,12], Ellen Goossens [6], Kirsi Jahnukainen[13,14], Yasmin Jayasinghe[12,15], Victoria Keros[16,17], Sabine Kliesch[2], Sheila Lane[18], Callista L. Mulder [19,20], Kyle E. Orwig [21], Ans M.M. van Pelt [19,20], Catherine Poirot [22,23], Michael P. Rimmer [24], Nathalie Rives [9], Hooman Sadri-Ardekani [25,26], Myriam Safrai [21,27], Stefan Schlatt [2], Jan-Bernd Stukenborg [13], Marianne D. van de Wetering[28], Christine Wyns [29], and Rod T. Mitchell [24,30,*]

Duffin et al. *Human Reproduction Open*. 2024

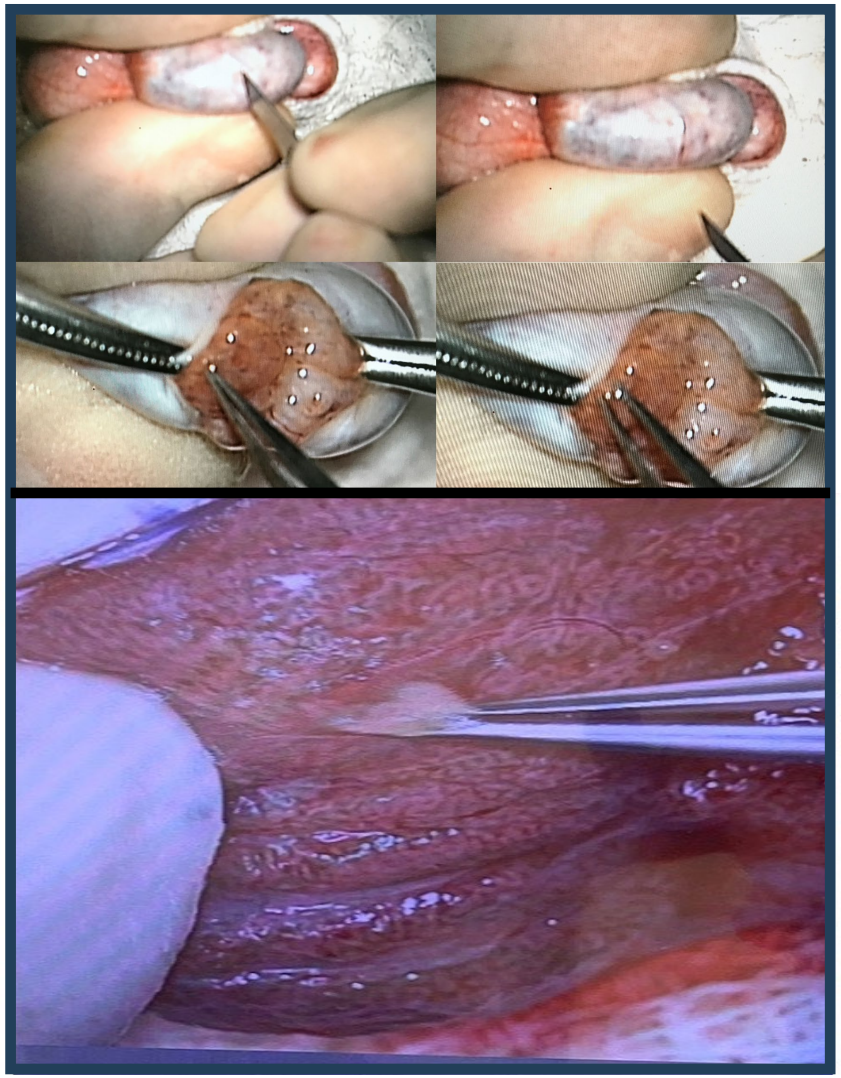
Fertility preservation in pubertal males



Anderson and Mitchell et al. *The Lancet Diabetes and Endocrinology*. 2015

Testicular Sperm Extraction (TESE)

- General anaesthetic
- 3-5 cm scrotal incision
- 45 minute procedure
- Embryologist in theatre



Images courtesy of Pippa Sangster, UCLH, London

Importance of urologist for FP in adolescents

BJU Int 2022; **130:** 637–645 doi:10.1111/bju.15772

BJUI
BJU International

Original Article

The importance of the urologist in male oncology fertility preservation

Lionel A. Micol[1,2,3], Funmi Adenubi[4], Elizabeth Williamson[4], Sheila Lane[5], Rod T. Mitchell[6] and Philippa Sangster[1]

[1]Institute of Andrology and [4]Reproductive Medicine Unit, University College London Hospitals NHS Foundation Trust, London, [5]Children's Haematology and Oncology, Oxford University Hospitals NHS Foundation Trust, Oxford, [6]Centre for Reproductive Health, Edinburgh Royal Hospital for Sick Children, The University of Edinburgh MRC, Edinburgh, UK, [2]Urology, CHUV, and [3]CPMA, Lausanne, Switzerland

Objectives

To demonstrate that surgical sperm retrieval (SSR) and spermatogonial stem cell retrieval (SSCR) in an oncological context are safe and successful.

Patients and Methods

This a retrospective study in a tertiary hospital in the UK. Patients requiring fertility preservation from December 2017 to January 2020 were included. Data were analysed with Microsoft Excel 2016 and the Statistical Package for the Social Sciences (version 20).

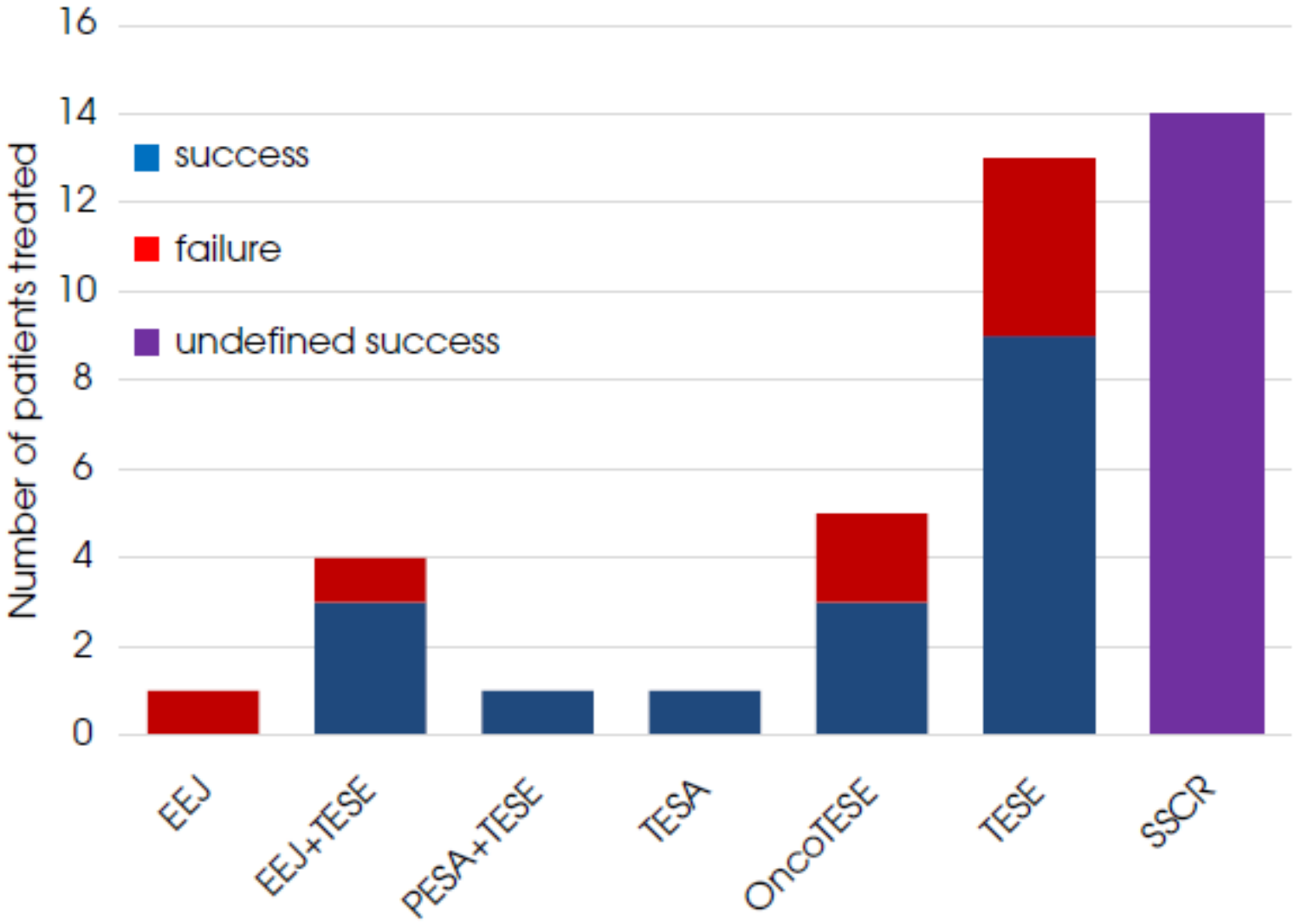
Results

Among 1264 patients referred to the Reproductive Medical Unit at the University College of London Hospitals for cryopreservation prior to gonadotoxic treatment, 39 chose to go forward with SSR/SSCR because they presented as azoo-/cryptozoospermic or an inability to masturbate/ejaculate. Interventions were testicular sperm extraction (23 patients) or

- 1140 patients attended for semen cryopreservation
- 58 (5.1%) were unsuccessful
- 39 underwent SSR or testis biopsy
- Median age 15y (10-65y)

Micol et al. ***British Journal of Urology***. 2022

Success with SSR in patients with cancer



- 39 had SSR or testis biopsy
- Median age 15y (10-65y)
- **Overall success – 17/25 (68%)**

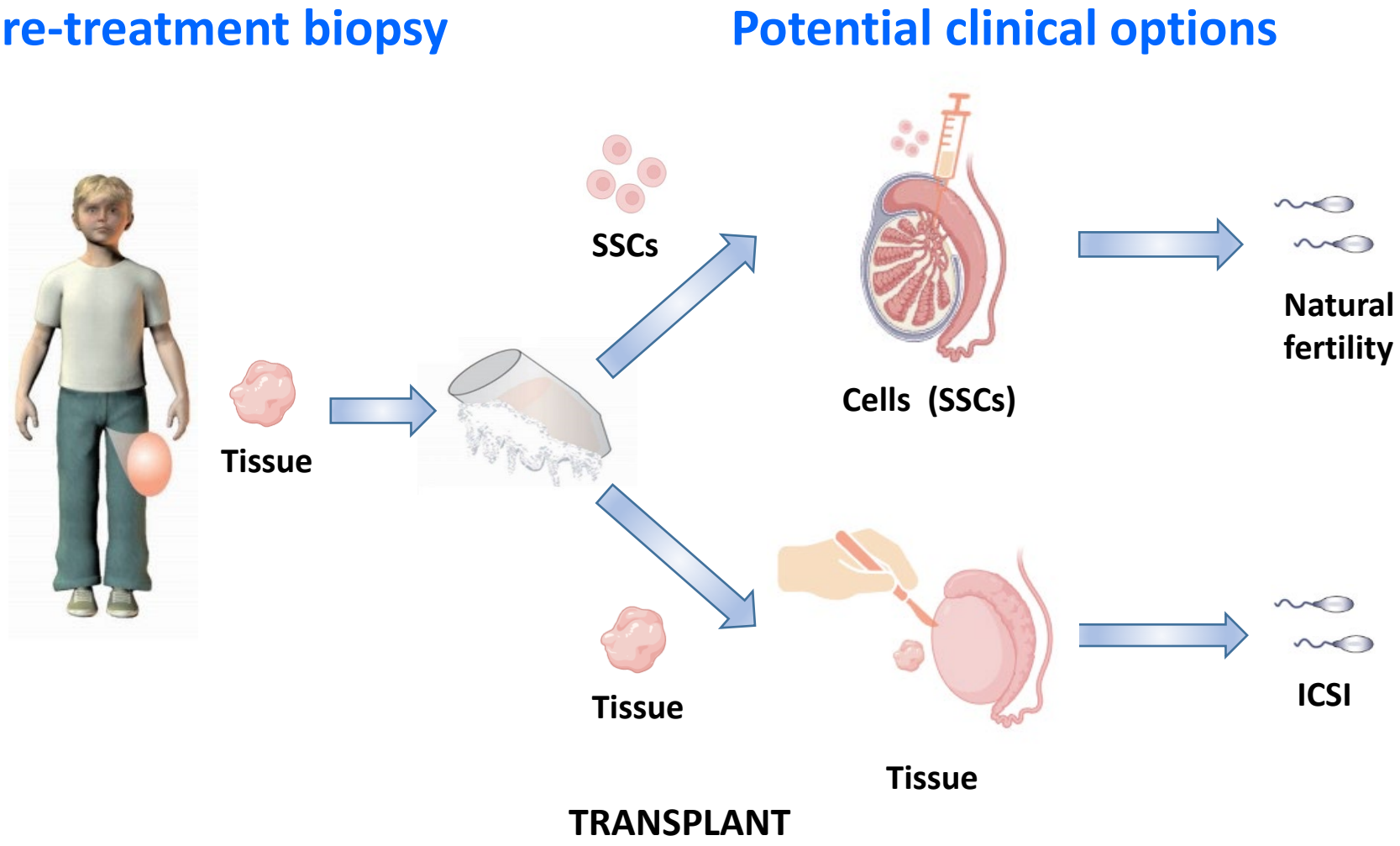
Micol et al. *British Journal of Urology*. 2022

Challenges for SSR in patients with cancer

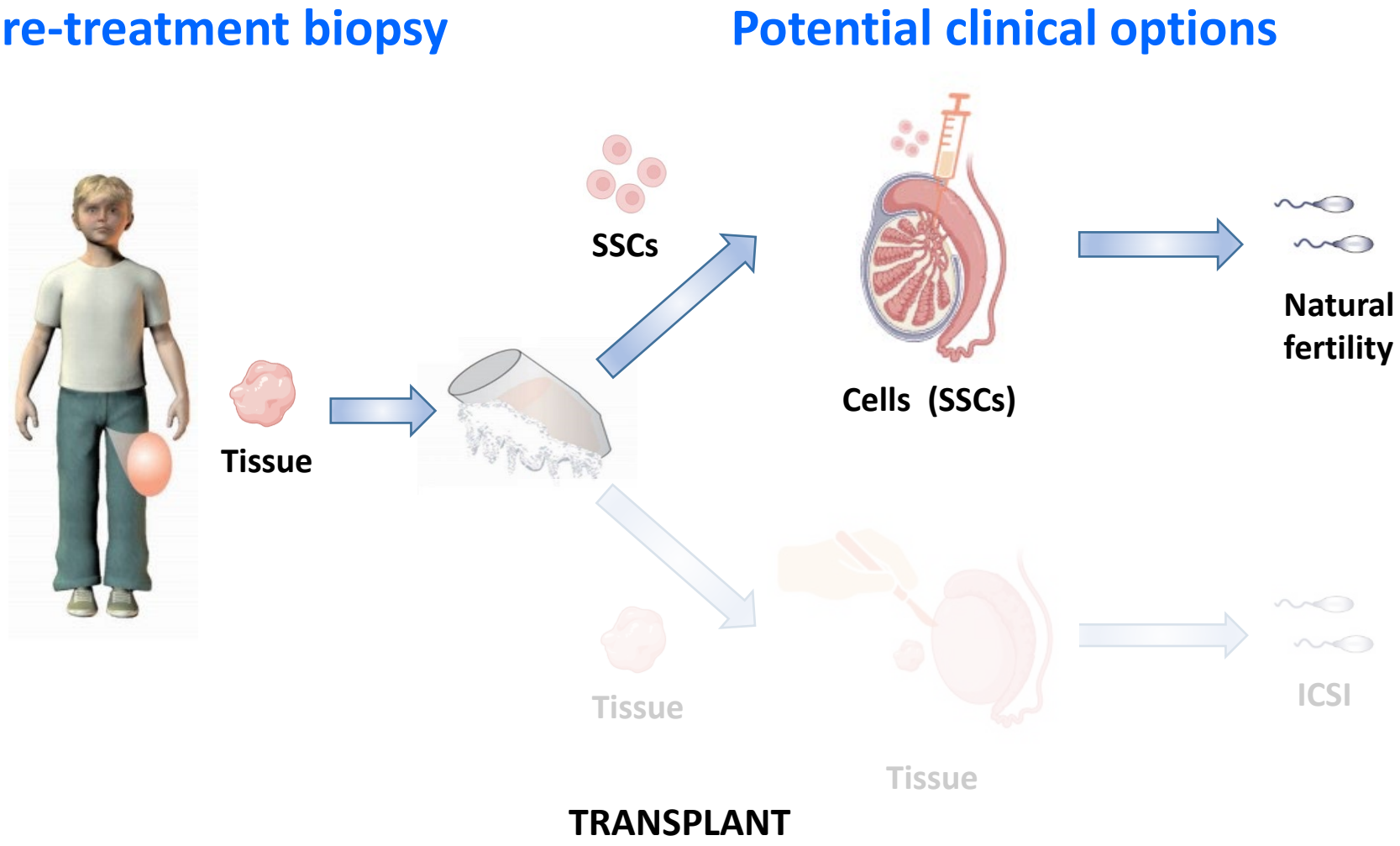
- Time – requires rapid referral and early intervention
- Availability of urologist, embryologist, facilities
- Capacity to consent
- No clear predictor of successful sperm retrieval
- Funding

Testicular transplantation to restore fertility?

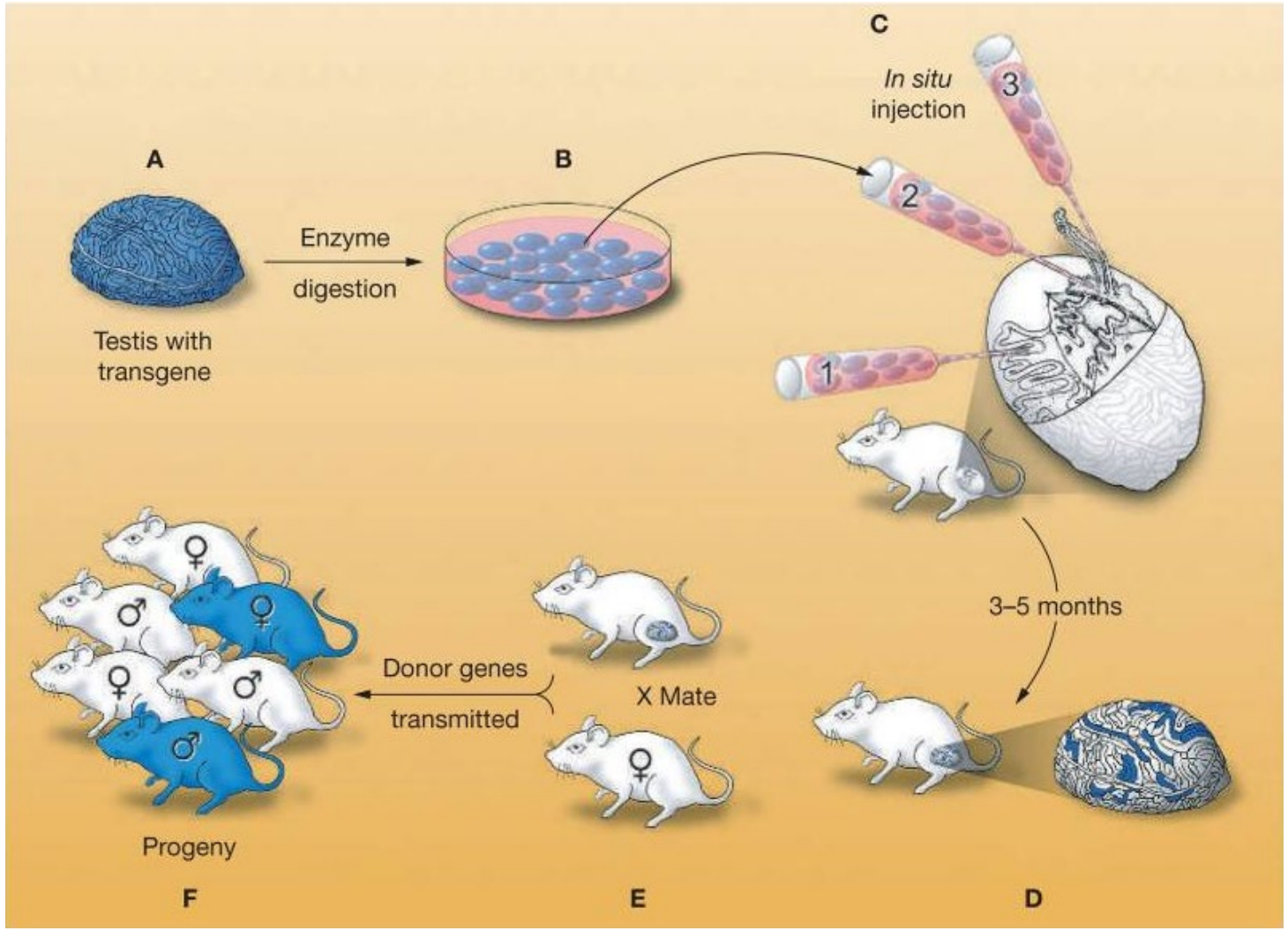
Re-transplantation of testicular tissue/cells?

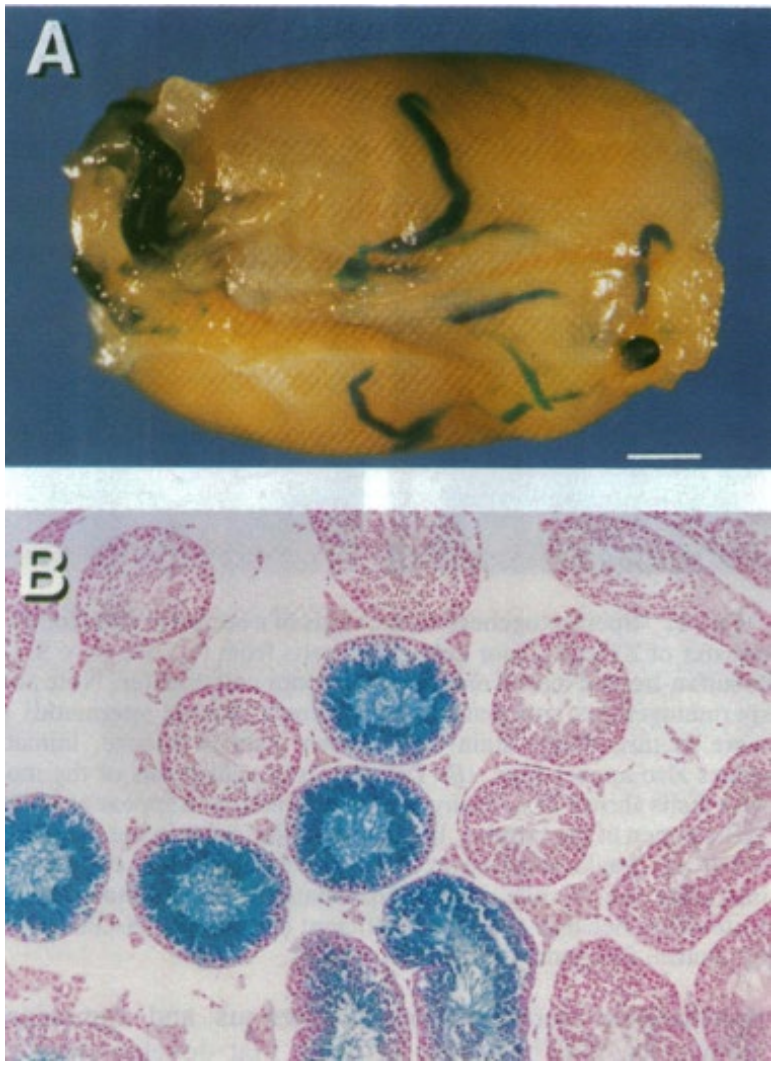


Spermatogonial stem cell transplantation



Spermatogonial stem cell transplantation



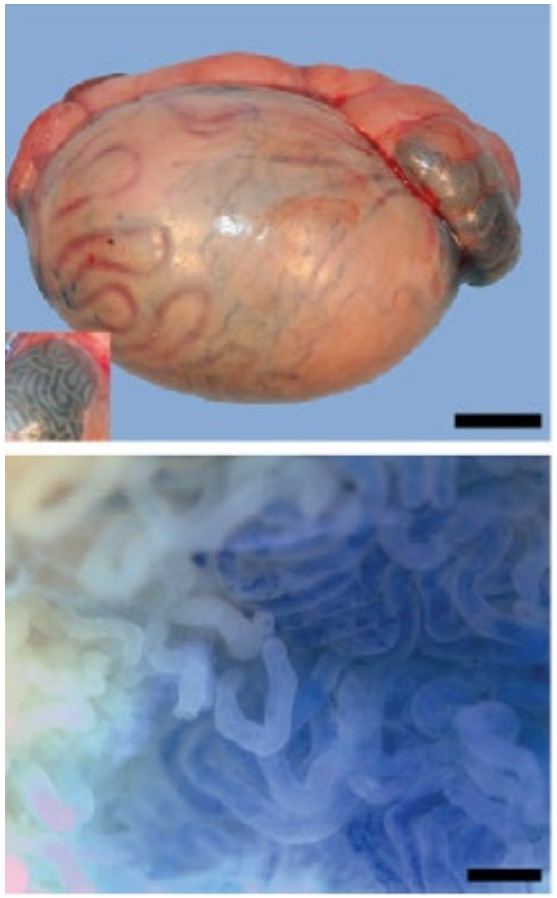


Brinster RL and Avarbock. *PNAS*. 1994

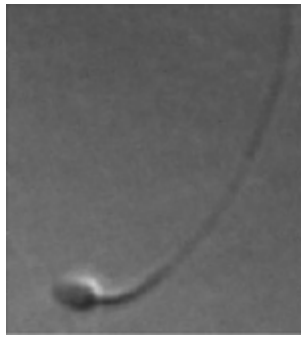
Kubota H and Brinster RL. *Nat Clin Pract Endocrino Metabol*. 2006

Transplantation of Rhesus monkey SSC produces functional sperm

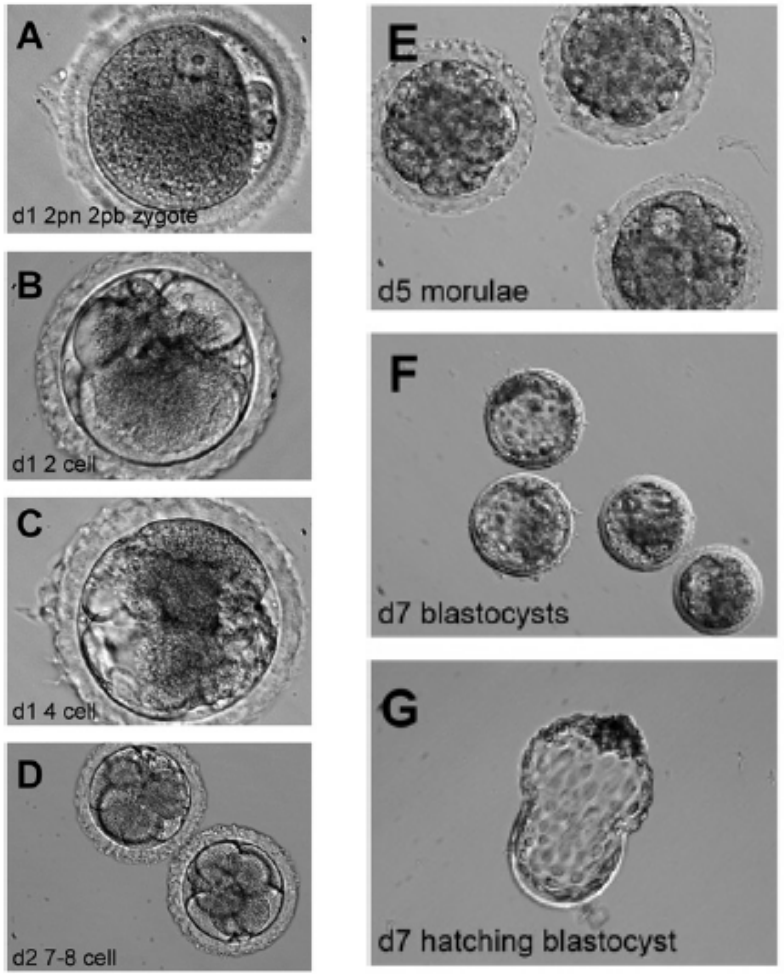
Autotransplantation



Sperm



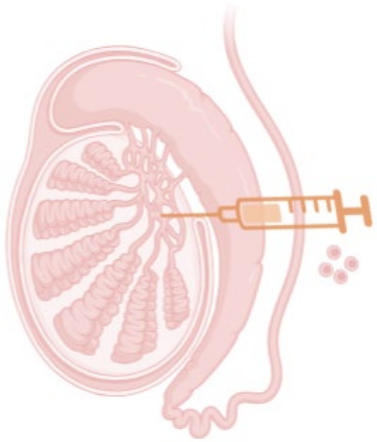
Embryos



Hermann et al. *Cell Stem Cell*. 2012

SSC transplantation – clinical trials

1999



BMJ

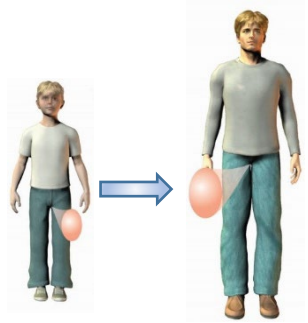
Fertility after treatment for cancer

JA Radford, SM Shalet and BA Lieberman

BMJ 1999;319:935-936

A clinical trial testing this hypothesis is currenuy under way in adults: 11 men have had testicular tissue harvested and cryopreserved as a single cell suspension (J A Radford et al, British Cancer Research meeting, Edinburgh, July 1999, and PF Brook et al, unpublished), and five who have now successfully completed treatment for cancer have had this material injected back into the donor testis. Results of follow up semen analysis are awaited with interest.

2024



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Ultrasound-Guided Rete Testis Approach to Sperm Aspiration and Spermatogonial Stem Cell Transplantation in Patients with Azoospermia

Amanda Colvin Zielen, Karen A. Peters, Gunapala Shetty, Deborah A. Gross, Carol B. Hanna, Serena L. Dovey, Anna Wecht, Glenn M. Cannon, Marvin L. Meistrich, Michael Hsieh, Kathleen Hwang, Kyle E. Orwig

doi: https://doi.org/10.1101/2025.03.25.25324518

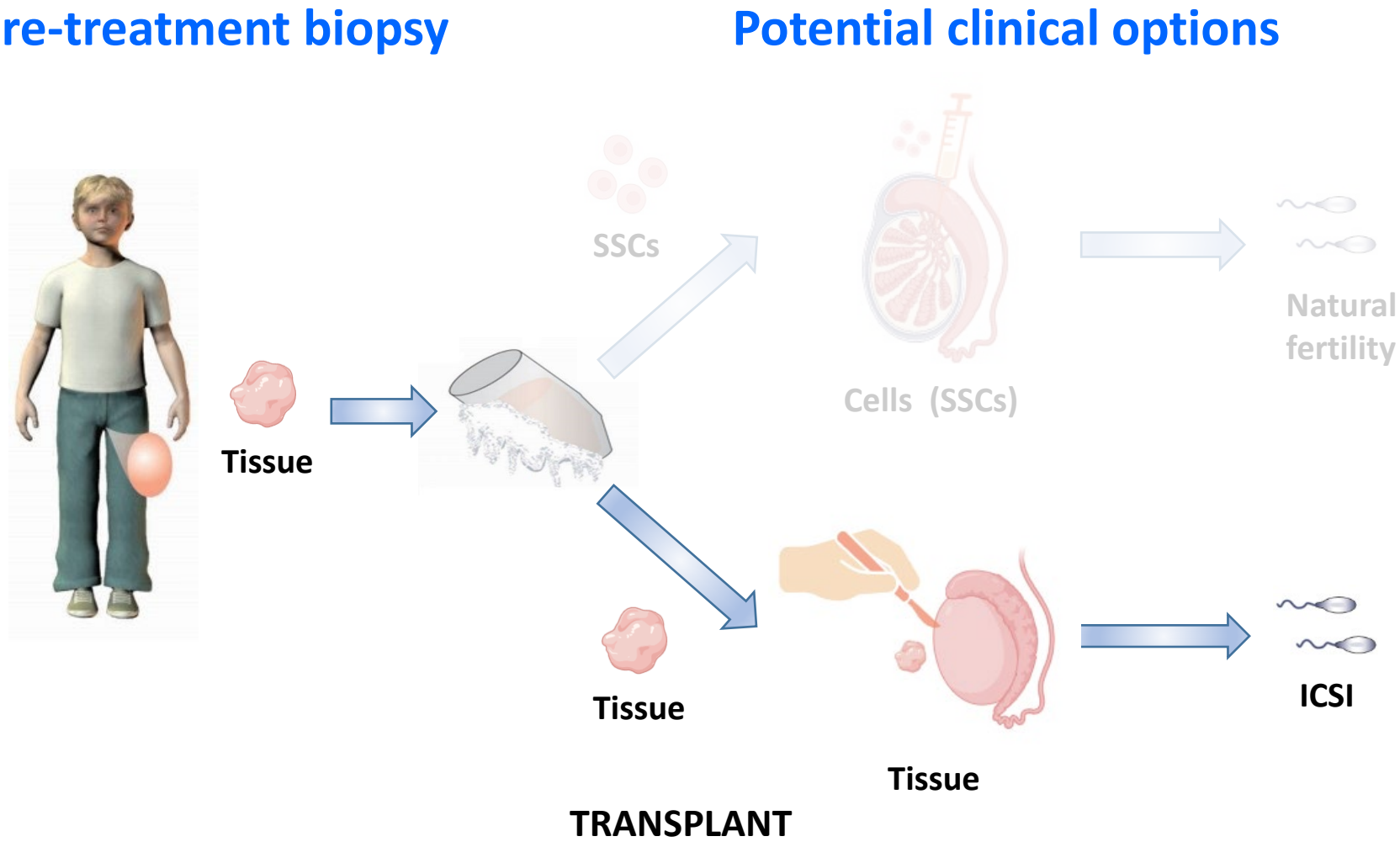
First SSC transplantation in childhood cancer survivor

Results are awaited!

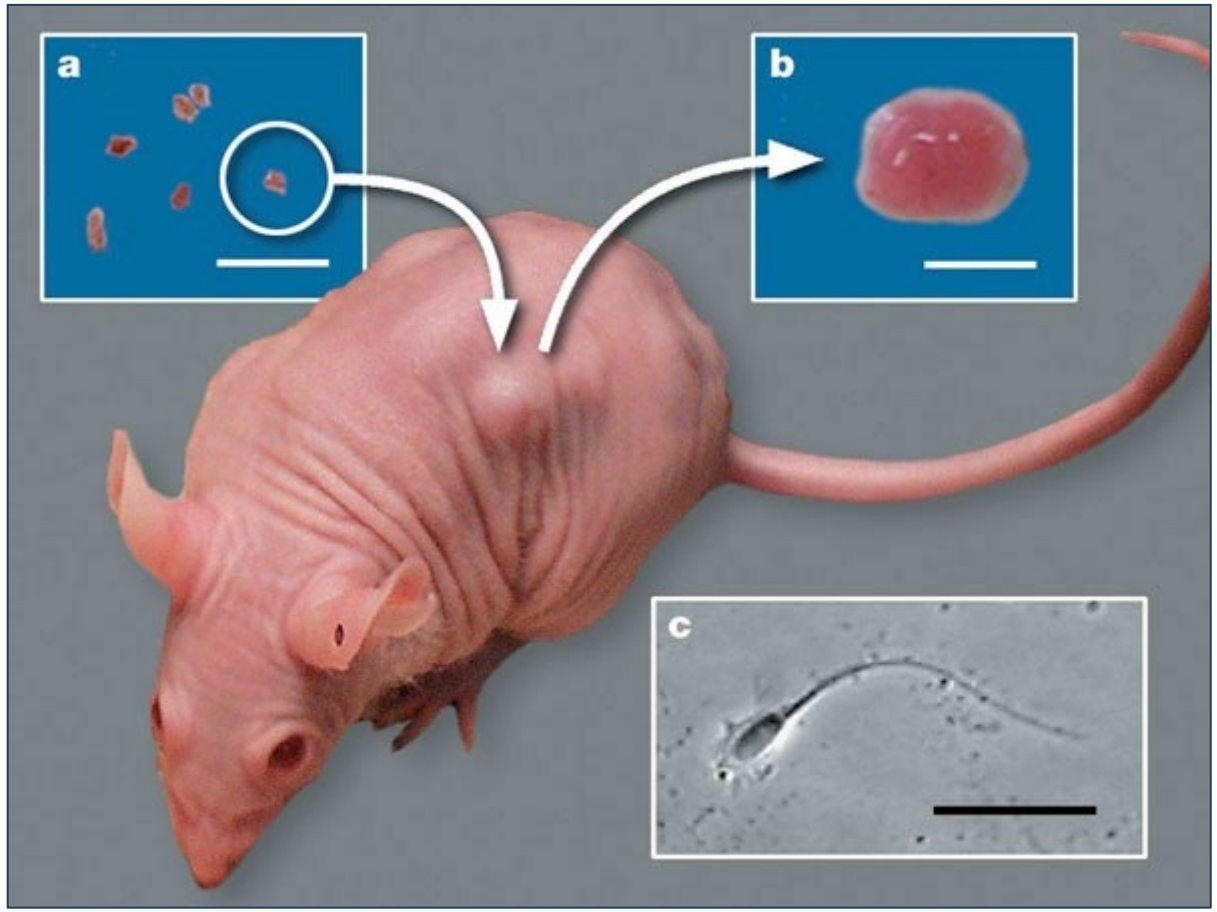
SSC transplantation in human - challenges

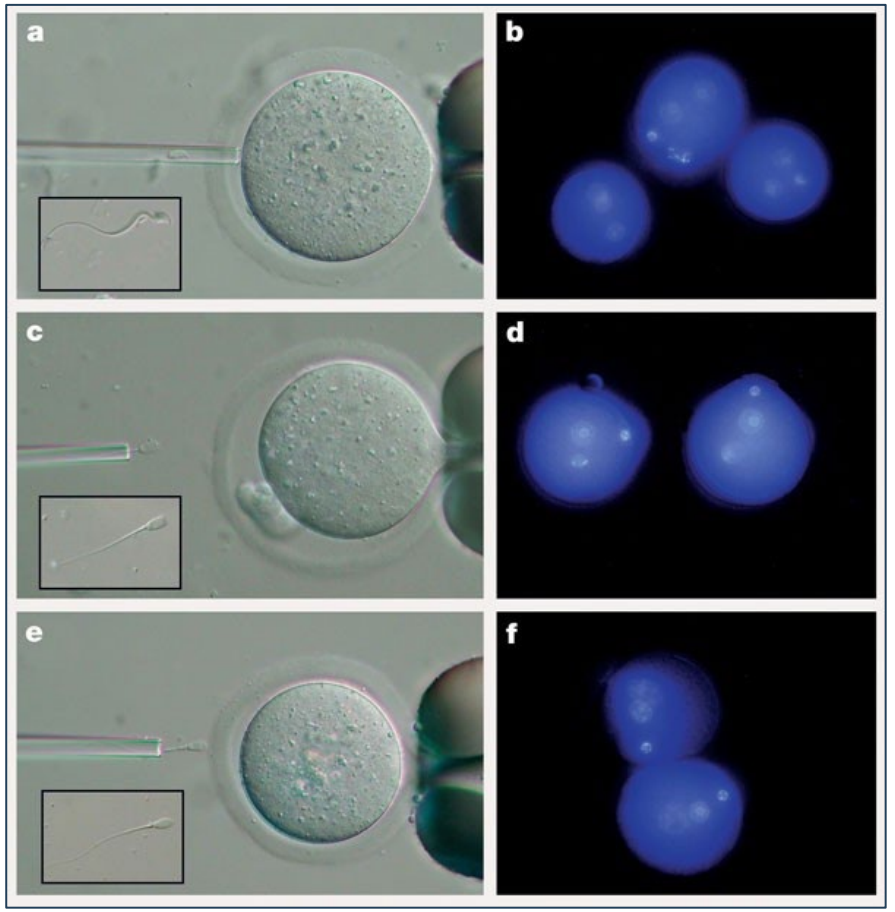
- SSCs represent 1:3000 of the cells in the testis
- Propagation of SSCs may be required for natural fertility
- Isolation of SSCs may improve transplant efficiency but result in SSC loss
- Cannot distinguish sperm from endogenous or transplanted SSCs

Testicular tissue transplantation



Testicular tissue transplantation

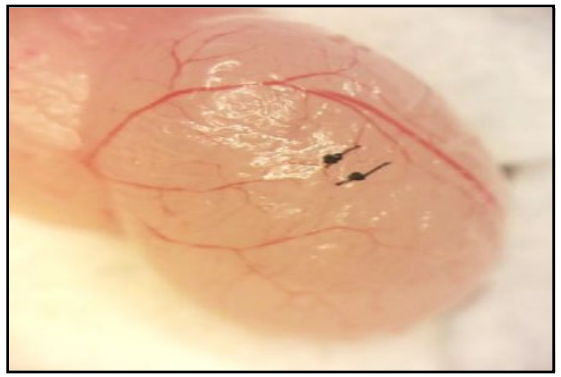




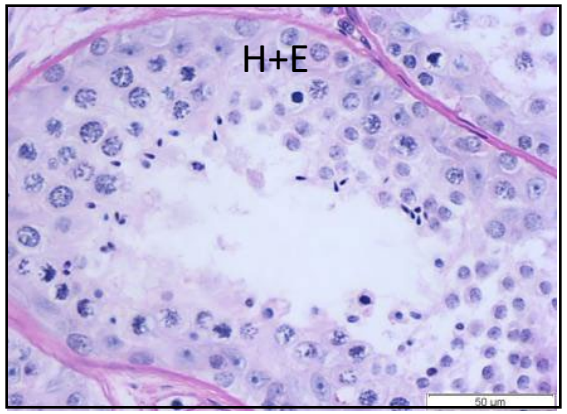
Honaramooz et al. *Nature*. 2002

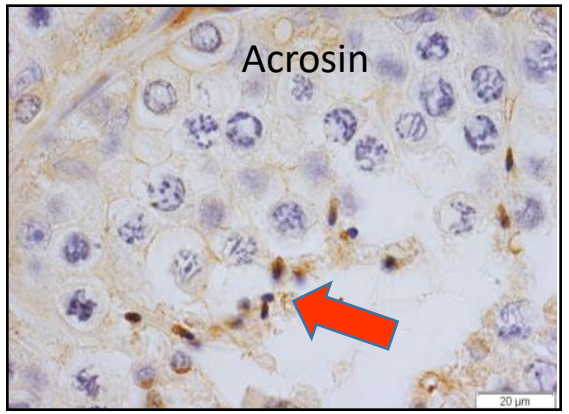
Transplantation of prepubertal testicular tissue from monkeys into mice

Marmoset monkey transplants



Intra-testicular





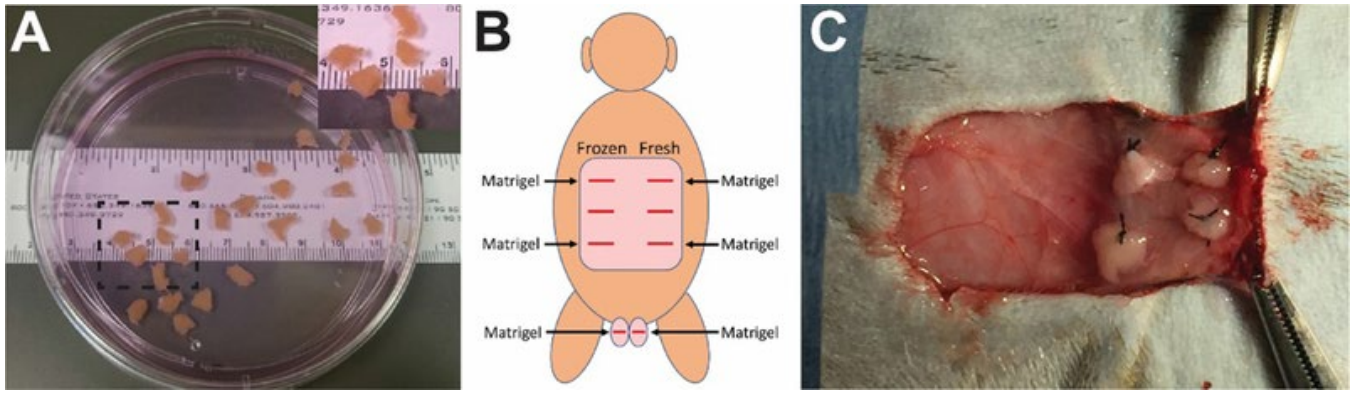
Spermatogenesis occurs in intratesticular monkey testicular xenotransplants.

Ntemou E et al. *Human Reproduction*. 2019

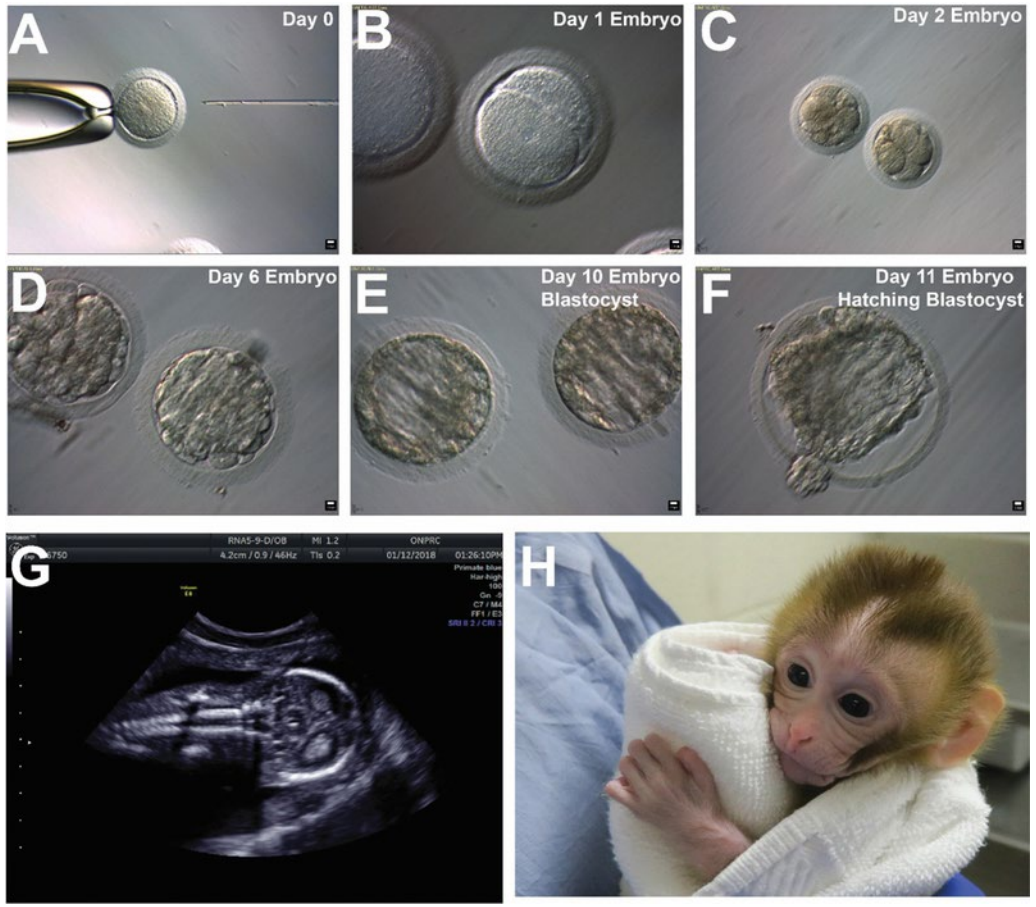
Testis tissue xenotransplantation - challenges

- Most studies using human tissue rely on xenograft model
- Xenografts have so far failed to support complete human spermatogenesis
- Host animal environment may not be compatible with human spermatogenesis
- Clinical applications are likely to require **autotransplantation**

Fertility possible with testis tissue autotransplant



Frozen testicular tissue



Fayomi et al. *Science*. 2019

Testicular tissue transplantation – clinical trials

VUB bite BIOLOGY OF THE TESTIS RESEARCH GROUP

Contact

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GROUNDBREAKING TESTICULAR TISSUE TRANSPLANT ACHIEVED AT THE UNIVERSITY MEDICAL CENTER

FRIDAY 10/01/2025

https://bite.research.vub.be/groundbreaking-testicular-tissue-transplant-achieved-at-the-university-medical-center

Testicular tissue transplantation – clinical trials

Ethical approval obtained 2023

CHILDREN WITH CANCER UK

PSSST! WE ARE RECRUITING! (SPREAD THE WORD)

Eligibility

- **≥18yrs**
- **Testicular tissue stored**
- **Evidence of infertility – e.g. azoospermia**

Autotransplantation of human testis tissue/cells

Title: Is the time right for transplanting immature testicular tissue or cells to restore male fertility?

Expert perspectives on clinical implementation of autotransplantation of cryopreserved testicular tissue or cells for fertility restoration

Authors:
Myriam Safrai[1], Ellen Goossens[2], Rod Mitchell[3,4#], Kyle E. Orwig[5], Callista L. Mulder[6,7], Ans M. M. van Pelt[6,7], Debra A Gook[8,9], Aurélie Feraille[10], Emily Delgouffe[2], Jill P. Ginsberg[11], Jan-Bernd Stukenborg[12,13], Kathleen Duffin[3,4], Kirsi Jahnukainen[12,14], Claus Yding Andersen[15], Marianne D. van de Wetering[16], Michael P. Rimmer[3], Virginie Barraud-Lange[17,18], Nina Neuhaus[19], Sheila Lane[20], Hooman Sadri-Ardekani[21] Nathalie Rives[10*#], Christine Wyns[22*#]

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SEVENTH FRAMEWORK PROGRAMME

MARIE CURIE ACTIONS