Testicular cancer as a late symptom of testicular dysgenesis syndrome (TDS)

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Reproductive Trends of Concern

- Industrialized countries have had birth rates below sustainablility levels for several decades and are now facing declining populations
- Infertility is common, 10 % of all children are now born after assisted reproduction in DK
- Semen quality is generally poor. More than 90% abnormal sperm cells are paradoxically considered ‘within normal range’ by WHO
- Serum T-levels have been falling for three or more decades
- Frequencies of genital abnormalities, including cryptorchidism are increasing
- **Testicular germ cell cancer rates have been increasing for decades and are linked to testicular dysgenesis**

Skakkebaek et al. 2022: Nature Reviews Endocrinology Mar;18(3):139-157. doi: 10.1038/s41574-021-00598-8.

Question: What were these cells?

- Years ago I was excited to detect a new type abnormality of germ cells in two infertile men

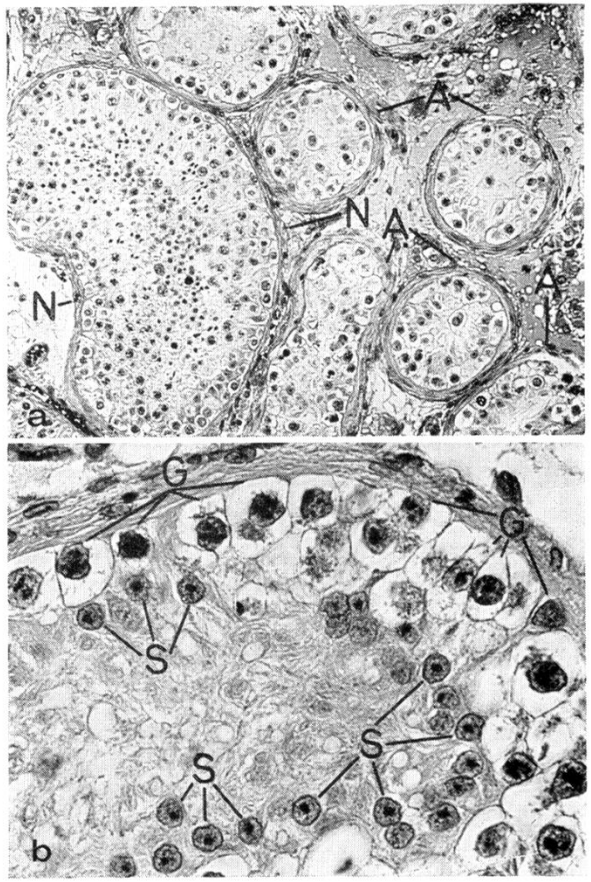

Fig. 1. a, section showing abnormal tubules (A) located together with a normal tubule (N), × 100; b, high magnification of an abnormal tubule showing one layer of abnormal cells (G) along the tubular wall and a series of Sertoli cells (S) with normal appearance, × 400 Iron-haematoxylin stain.

Answer:

Reprinted from THE LANCET, *September* 9, 1972, *pp.* 516-517

POSSIBLE CARCINOMA-IN-SITU OF THE TESTIS

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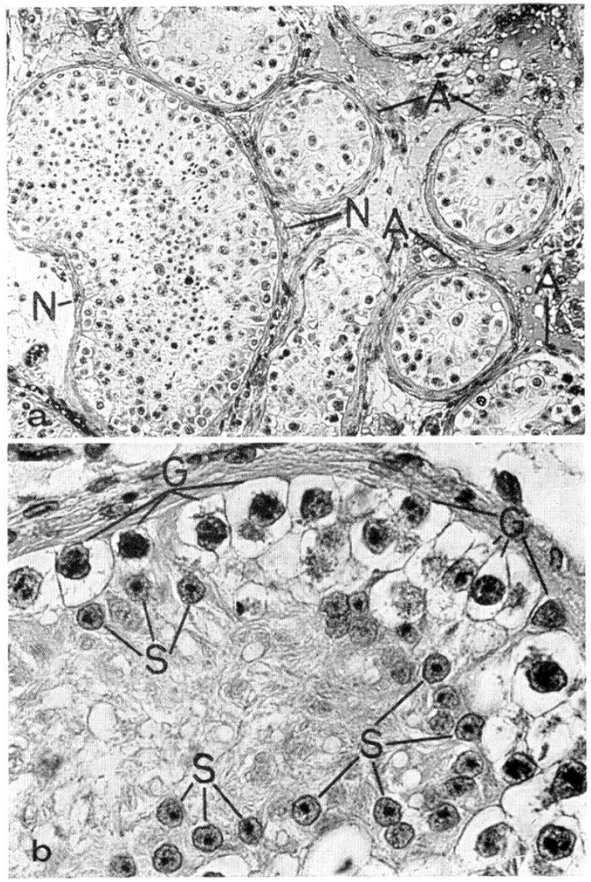
Summary Embryonal carcinoma of the testis was detected in two infertile men in whom testicular biopsies had revealed an abnormal seminiferous epithelium with atypical germ cells. The tumours occurred within 4½ years of testicular biopsy. It is suggested that the atypical germ cells represented a carcinoma-in-situ.

- Controversy for several years
- However, several more infertile men also developed tumors

Since 2016 called Germ Cell Neoplasia In Situ (GCNIS) as WHO- IARC nomenclature



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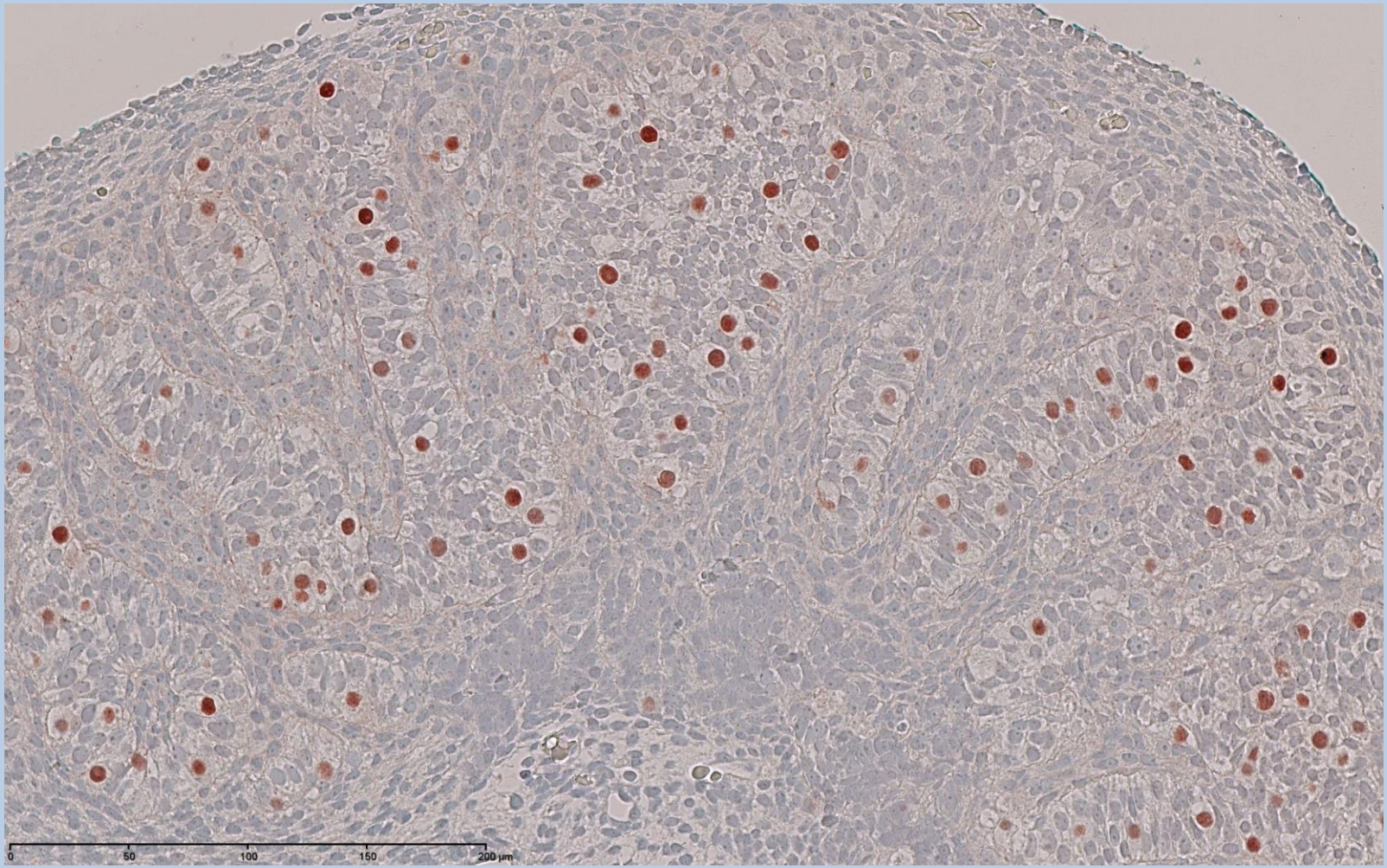
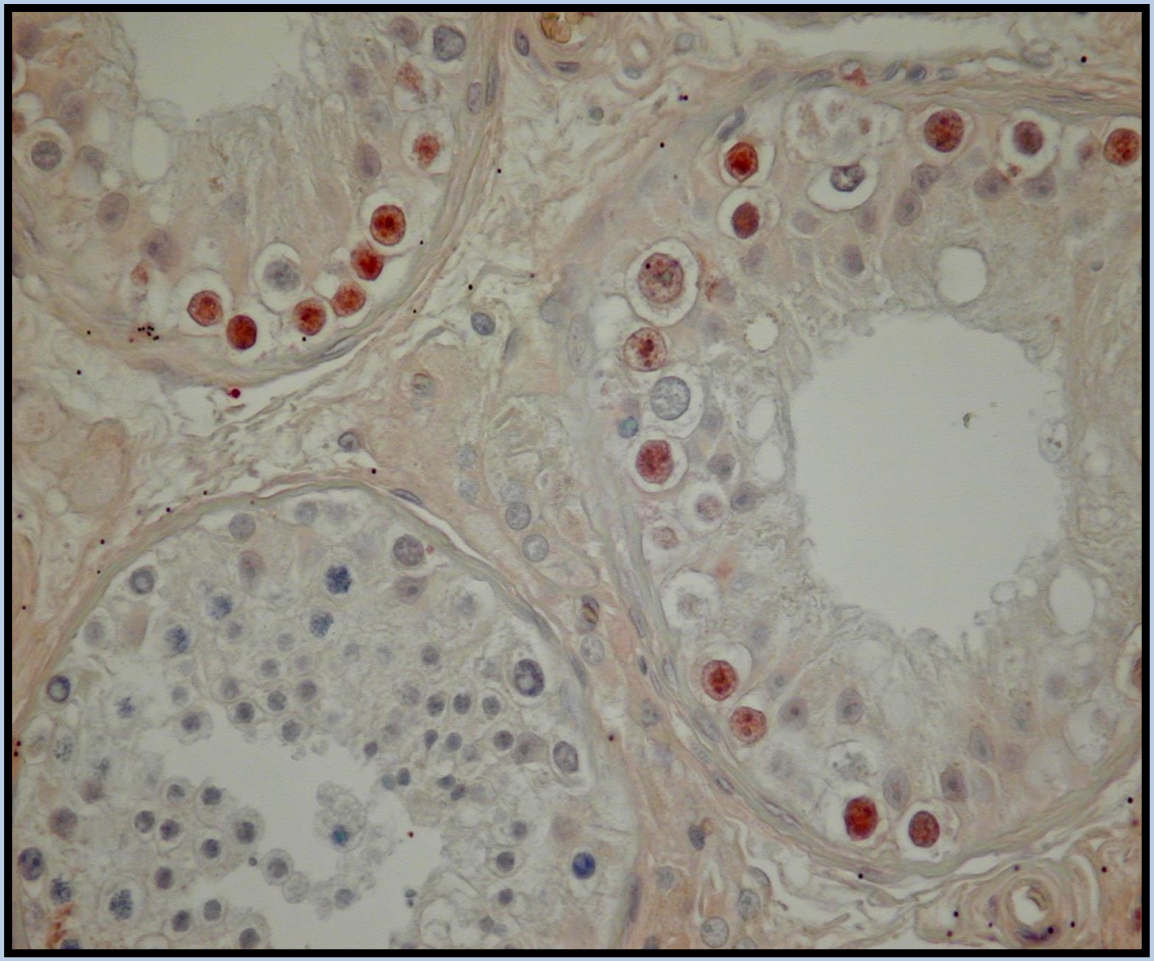
Fetal gonocytes gestational week 10 expressing OCT-4



Courtesy, Anne Jørgensen

Molecular evidence that testis cancer is of fetal origin:

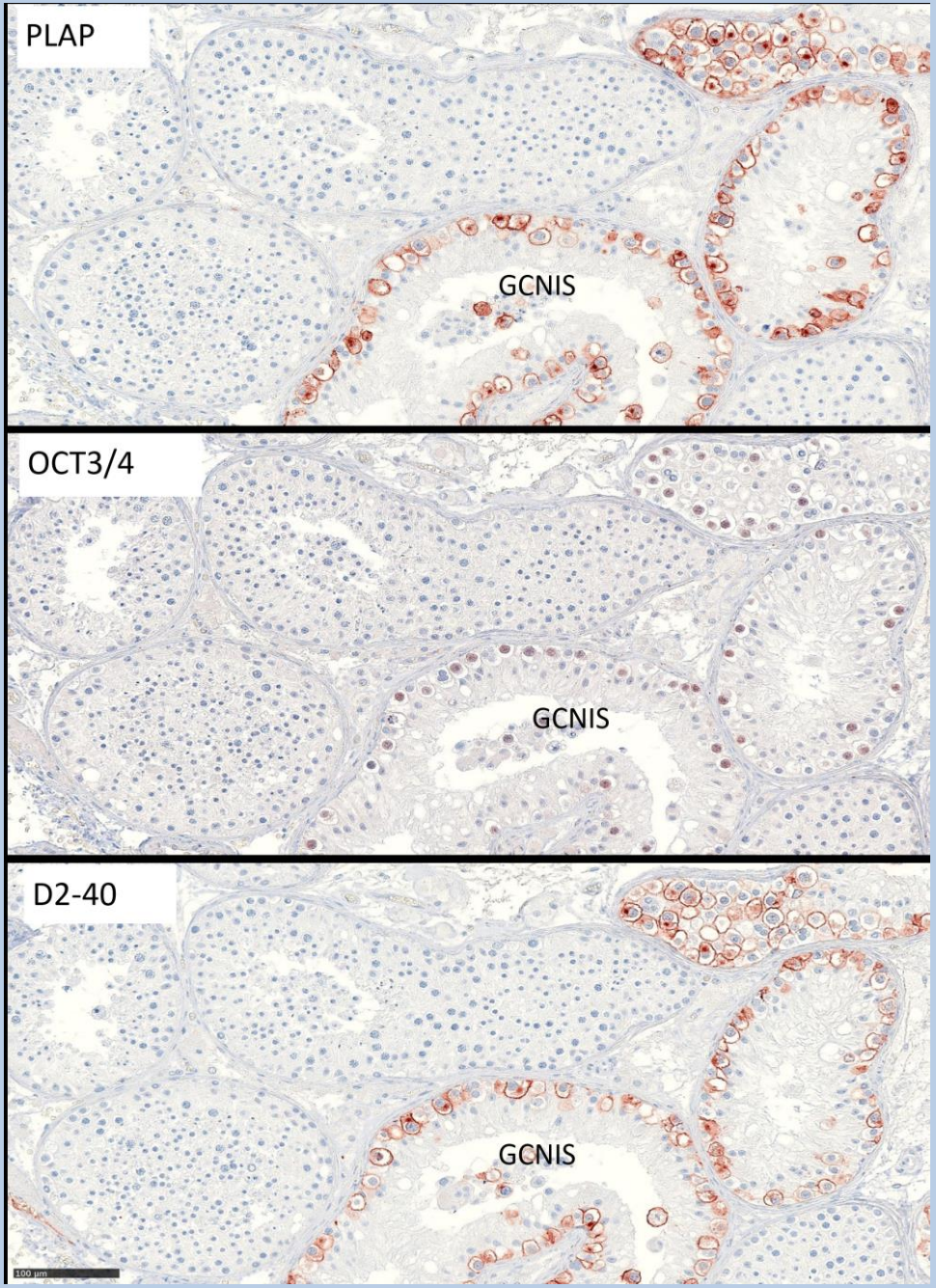
OCT-4 (and other embryonic markers) expressed in Germ Cell Neoplasia In Situ (GCNIS)



OCT-4

Testicular biopsy as a tool to prevent invasive germ cell cancer by screening for GCNIS in at-risk groups

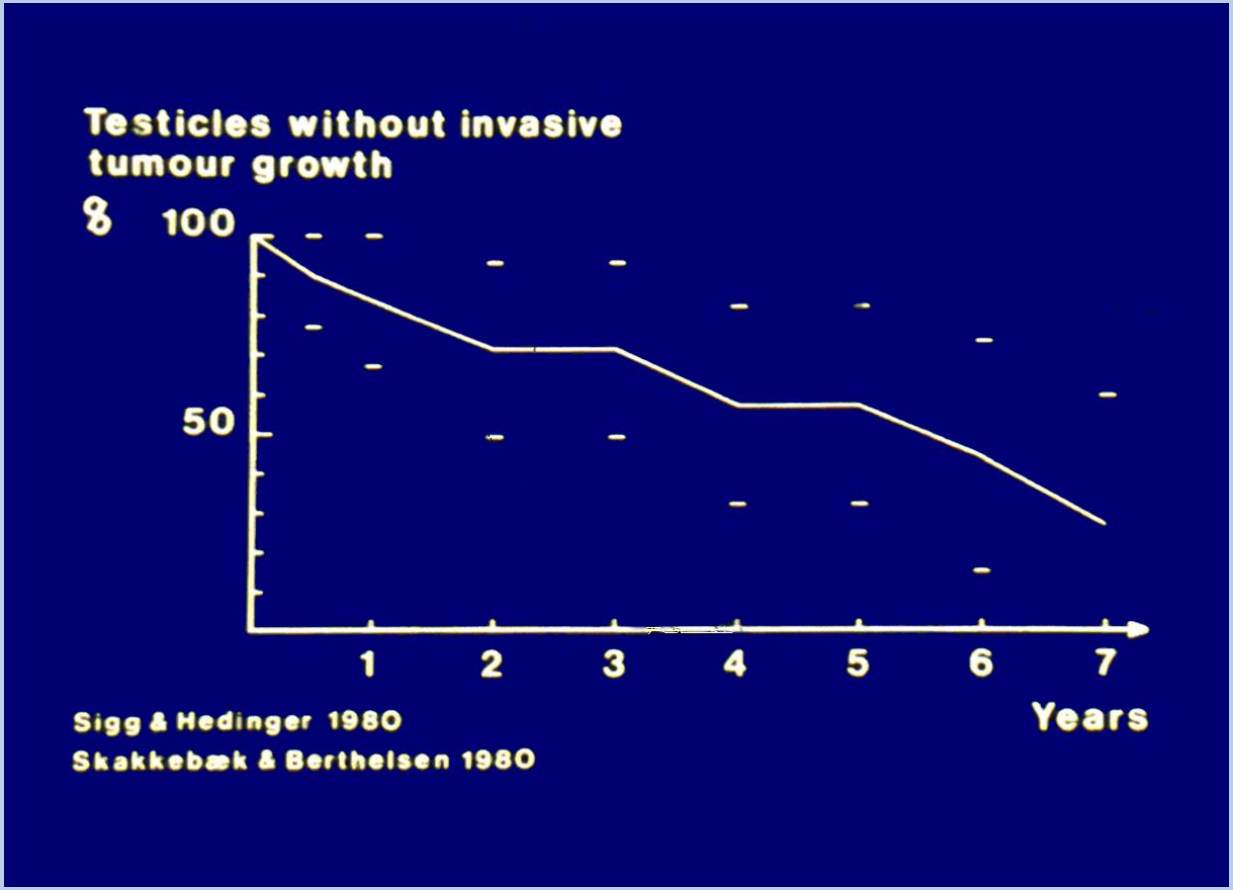
Optimised detection of germ cell neoplasia *in situ* in contralateral biopsy reduces the risk of second testis cancer
Rajpert de Meyts et al. BJU Int. 2022 May 16. doi: 10.1111/bju.15774



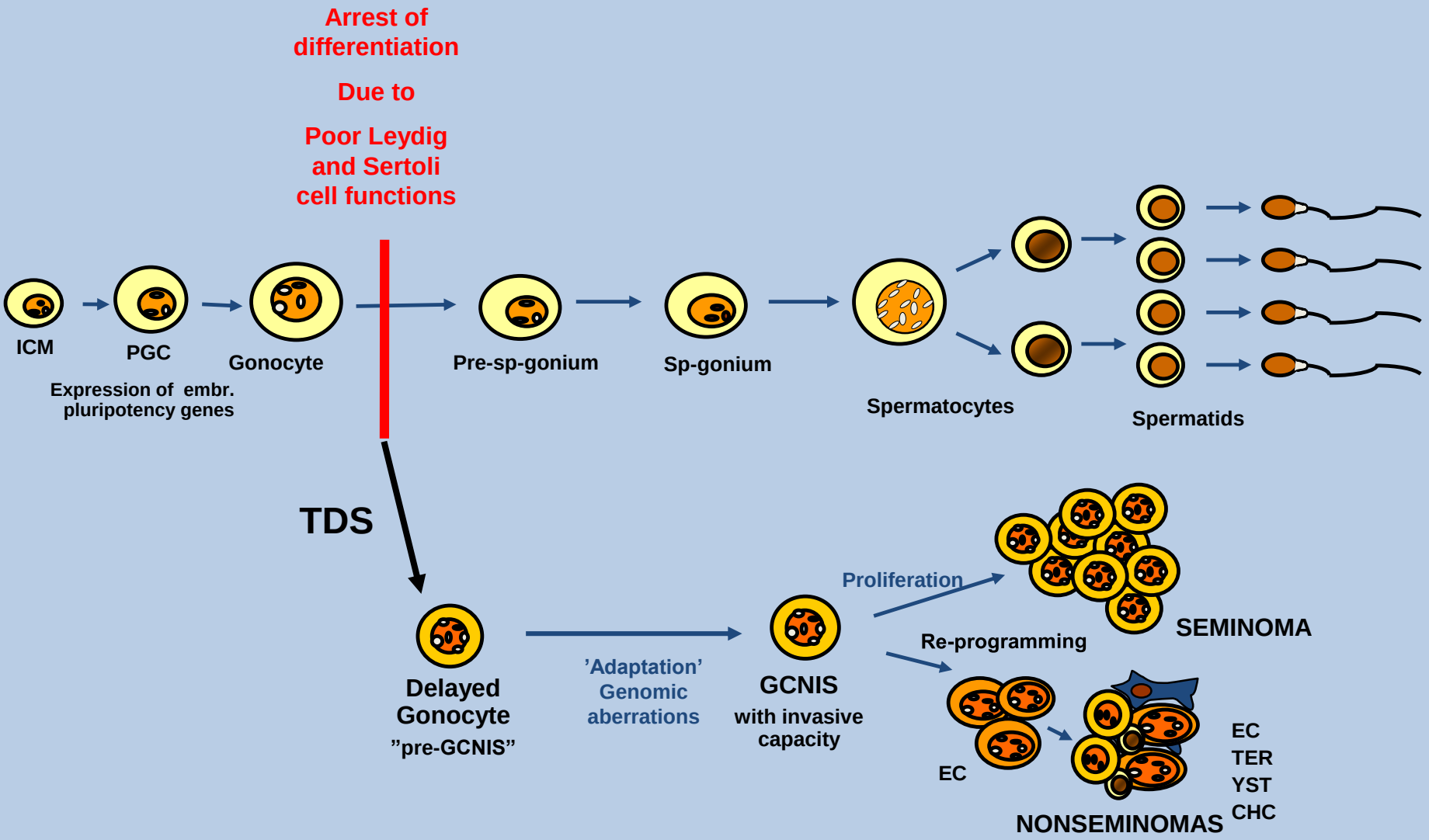
From germ cell neoplasia in situ to invasive testicular cancer

50% invasive within 5 years

70% invasive within 7 years



Current model for the pathogenesis of testicular germ cell tumours



Embryo | Fetus | *Birth* | Childhood | Puberty | Young Adult | Older Adult

Updated from Rajpert-De Meyts, Hum Reprod Upd 2006

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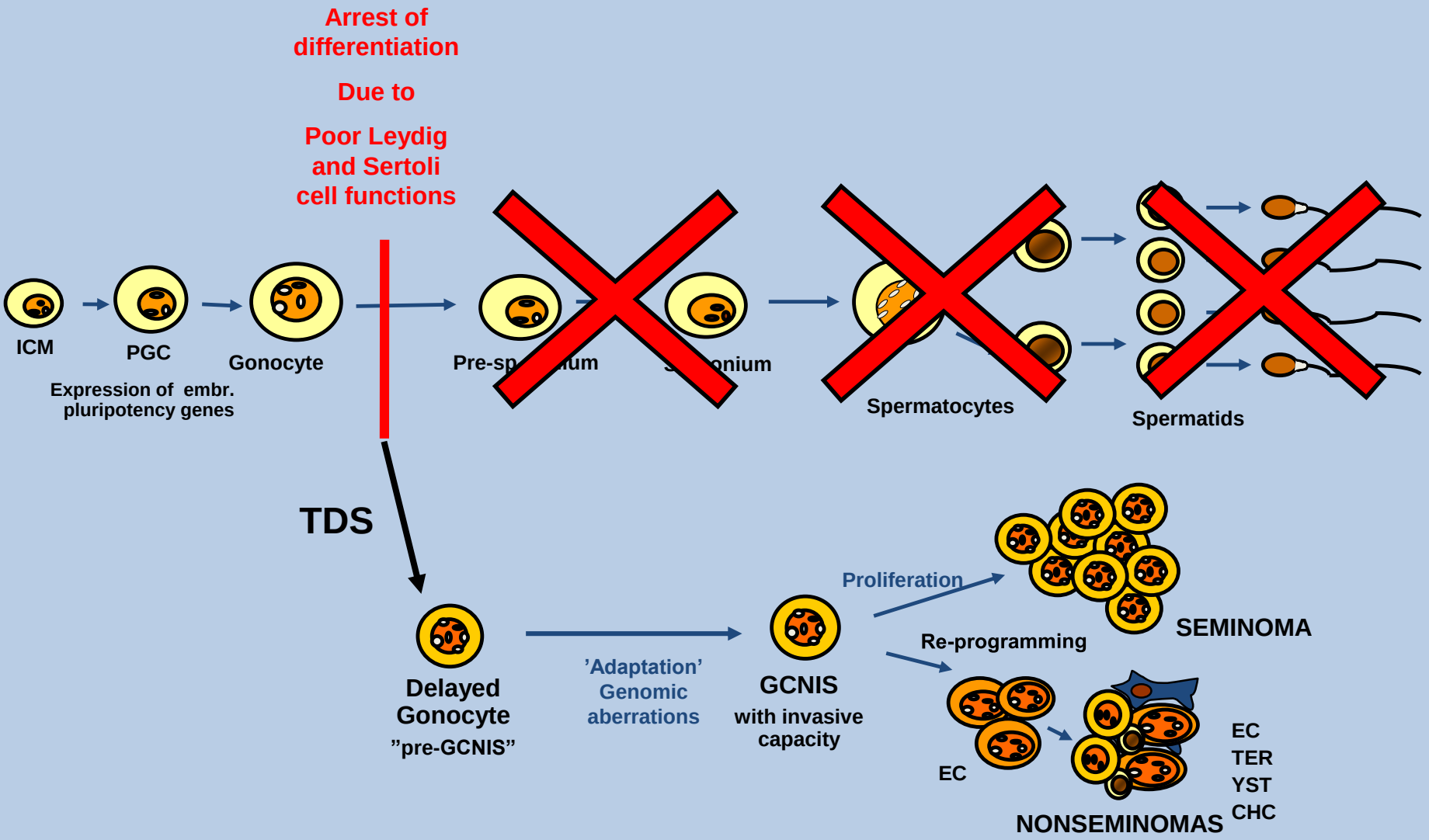

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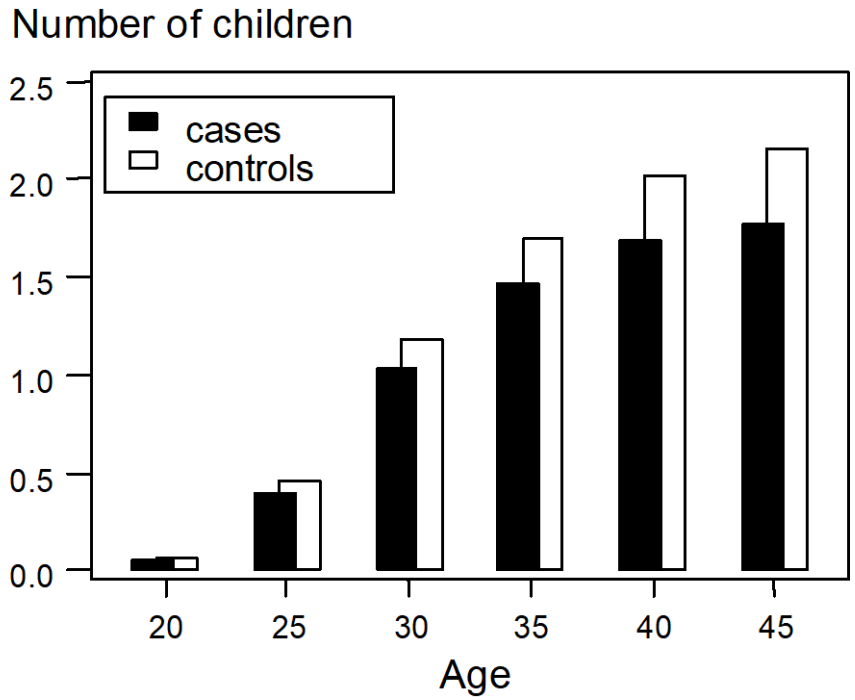
Updated from Rajpert-De Meyts, Hum Reprod Upd 2006

Epidemiological evidence for decreased fertility in men who developed testicular cancer years later



Møller & Skakkebæk, BMJ, 1999

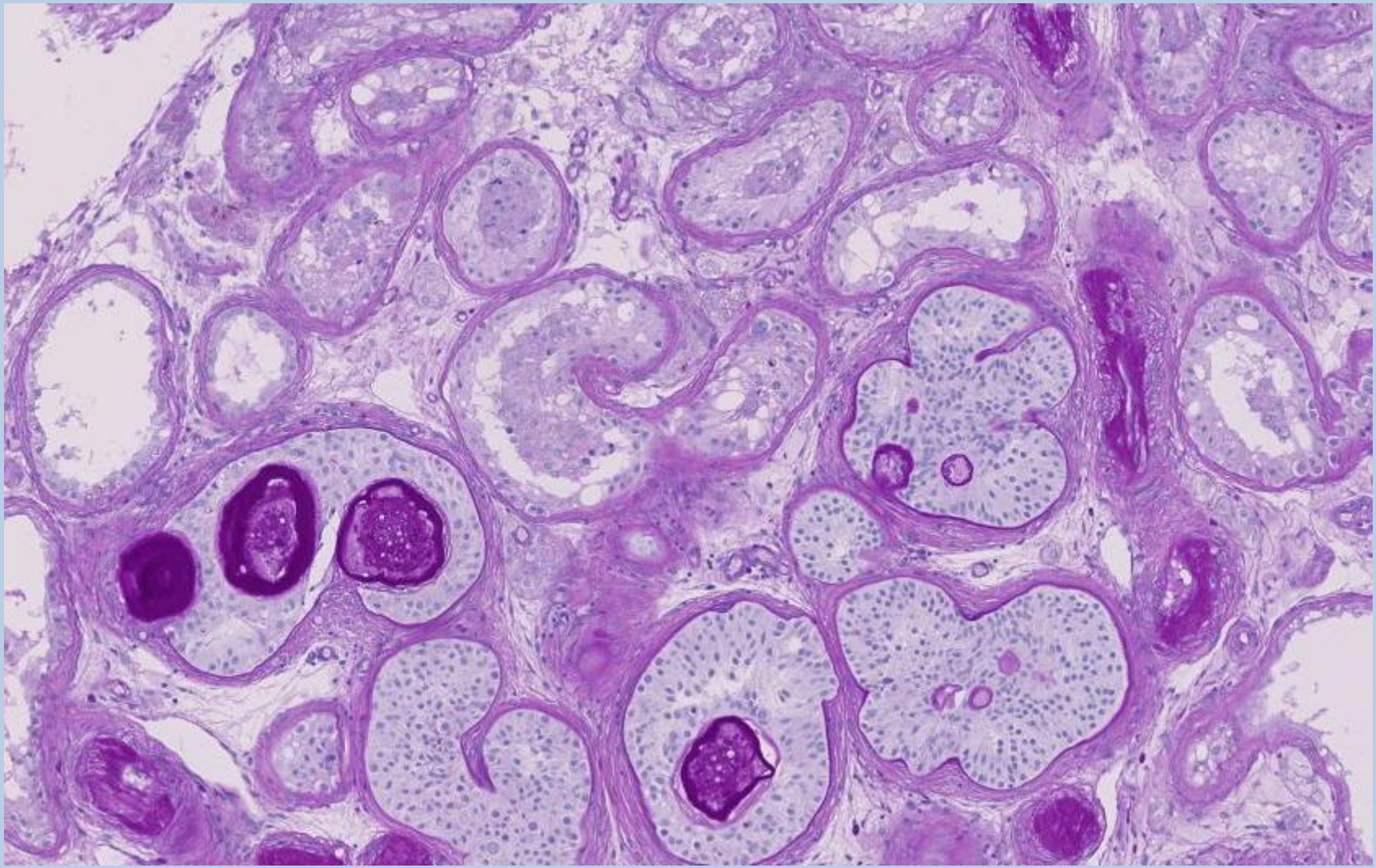
Histological evidence of primary problems with testicular somatic cells in TDS

Dysgenesis of contralateral testis: 218 cases of unilateral testicular cancer

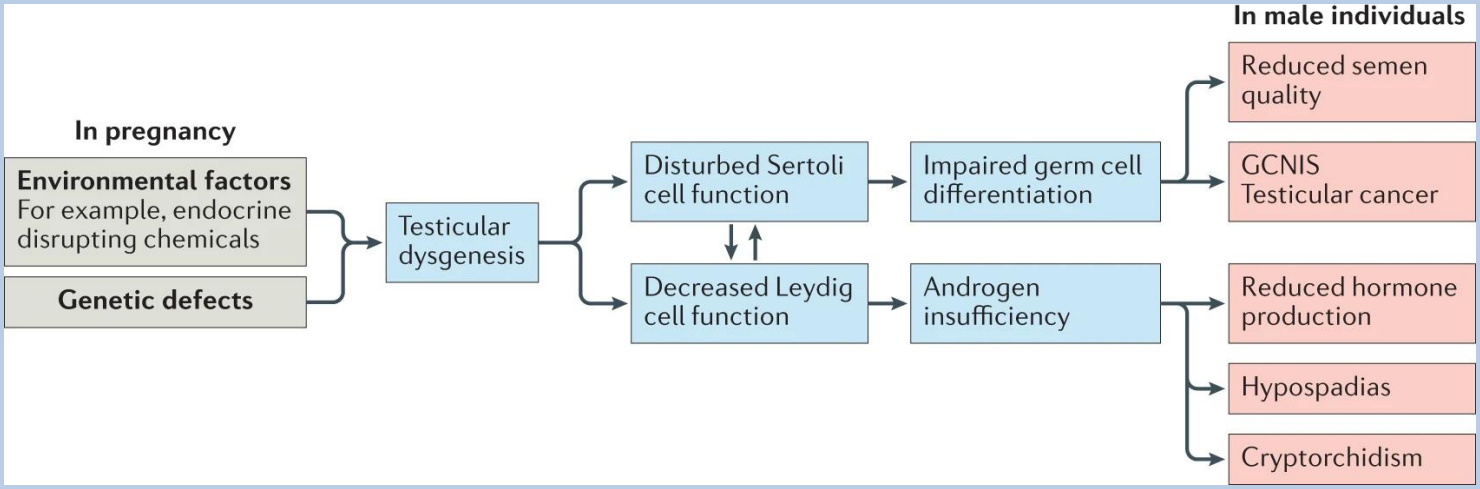
- 38 patients, 13.8%, had Sertoli cell only tubules
- 11 patients, 4.6%, had immature tubules with undifferentiated Sertoli cells
- 14 patients, 6.0%, microliths
- Cumulative presence of one or more signs of TDS: 25.2%
- In addition more than 70% had Leydig cell ”micronodules”

(Hoei-Hansen et al. J. Pathol. 2003)

Histological evidence of testicular dysgenesis



Hypothesis:
Testicular germ cell cancer may be a symptom of **Testicular Dysgenesis Syndrome** due to **Dysfunction of fetal Sertoli and Leydig cells**



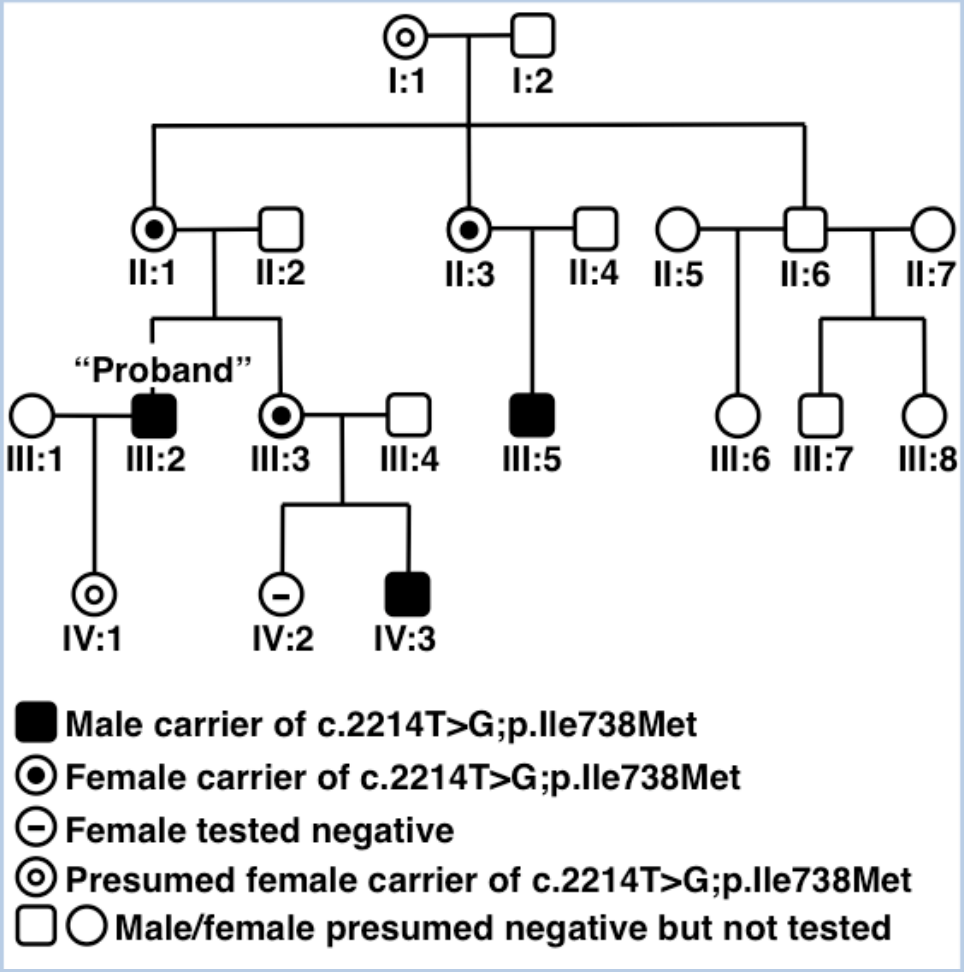
Skakkebaek et al, Human Reproduction, 2001
Toppari et al. EHP, 1996
van den Driesche…,and Sharpe, JCI Insight, 2017
Skakkebaek et al, Nature Reviews Endocrinology, 2022

These six genetic conditions have something in common

- Mutations in the androgen receptor (AR)
- SRY mutations
- Activation mutations in the LH receptor
- 45X/46,XY mosaicism
- Prader Willi syndrome
- Down syndrome

All conditions associated with a combination of gonadal maldevelopment and risk of testicular germ cell cancer

Genetic evidence: AR mutation in a family with multiple cases of testicular dysgenesis syndrome (TDS)



Lottrup et al. JCEM, 2013

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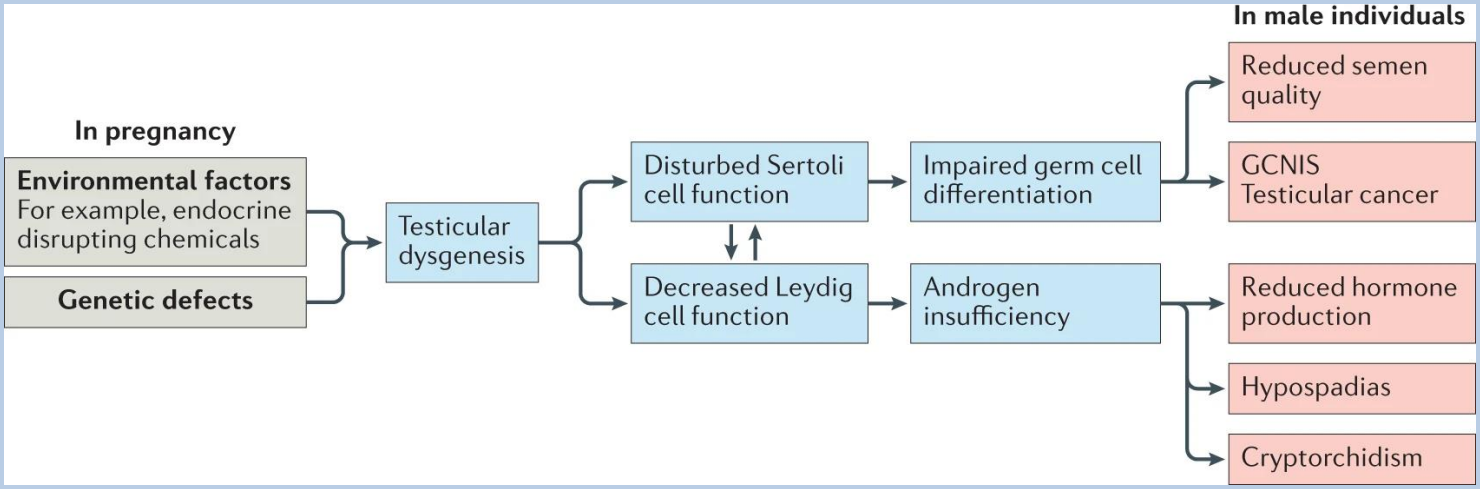

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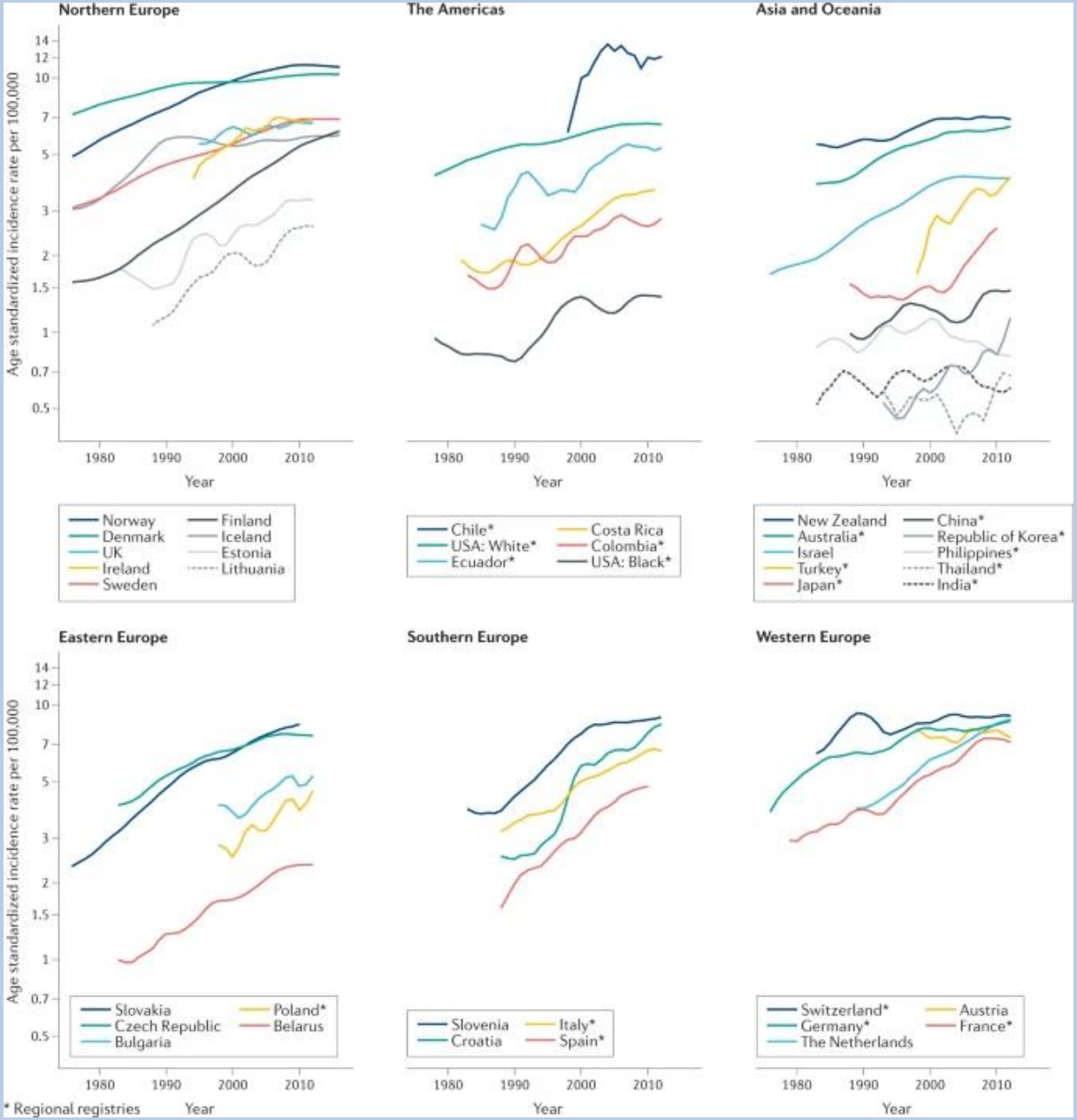
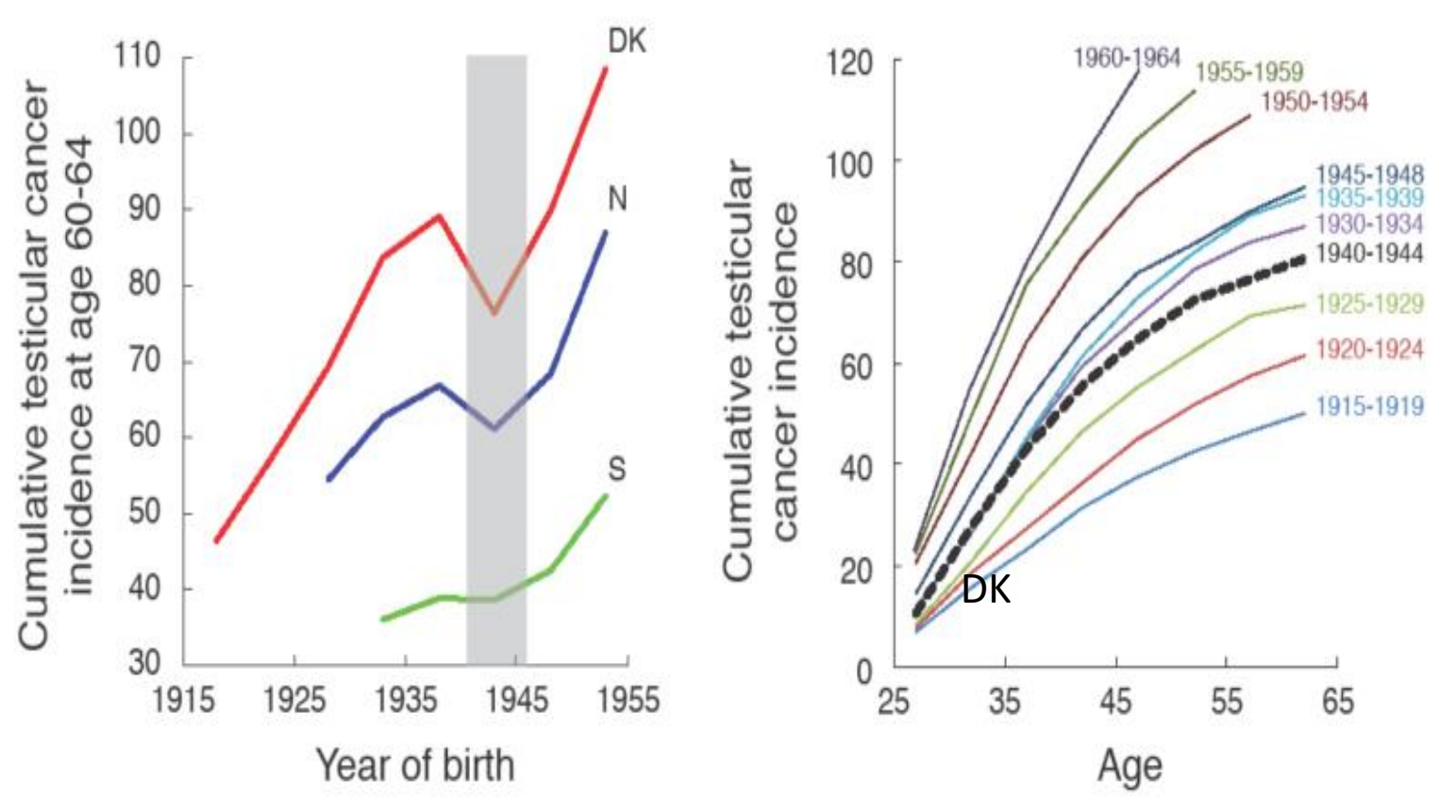
Role of environment: Increasing trends in testicular cancer



Skakkebaek et al. Nature Reviews Endocrinology, 2022

Role of environment
Lower risk of testicular cancer in men born during WWII



Møller, JNCI , 1989
Bergström et al, JNCI, 1996
Skakkebaek et al, Nature Reviews Endocrinology, 2022

Summary/Conclusions

- The rate of testicular germ cell cancer, which is linked to maldevelpment of fetal gonad, is increasing all over the world
- Although the disease occurs in young adulthood, it originates from embryonic germ cells, called germ cell neoplasia in situ (GCNIS)
- These neoplastic precurser cells are similar to fetal gonocytes and express markers for fetal germ cells , includingCT4
- The histological pattern of testicular dysgenesis, incuding GCNIS, immature tubules, Sertoli-cell-only and microlithisasis, which is associated with testicular cancer, has also been linked to male infertility, cryptorchidism and hypospadias
- Our histological observations match epidemiological findings of birth cohort effects in incidences of testicular abnormalities, inclusive testicular cancer, cryptorchidism and poor semen quality
- The role of industrial exposures in the current crisis in male reproduction, including solid data on world-wide increasing rates in testicular germ cell cancer, urgently needs to be explored

More info: Please, go to Skakkebaek et.al **Nature Reviews Endocrinology, 2022, Mar;18(3):139-157. doi: 10.1038/s41574-021-00598-8**.

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