# Female fertility and ovarian function in young people with cancer: who is at risk?

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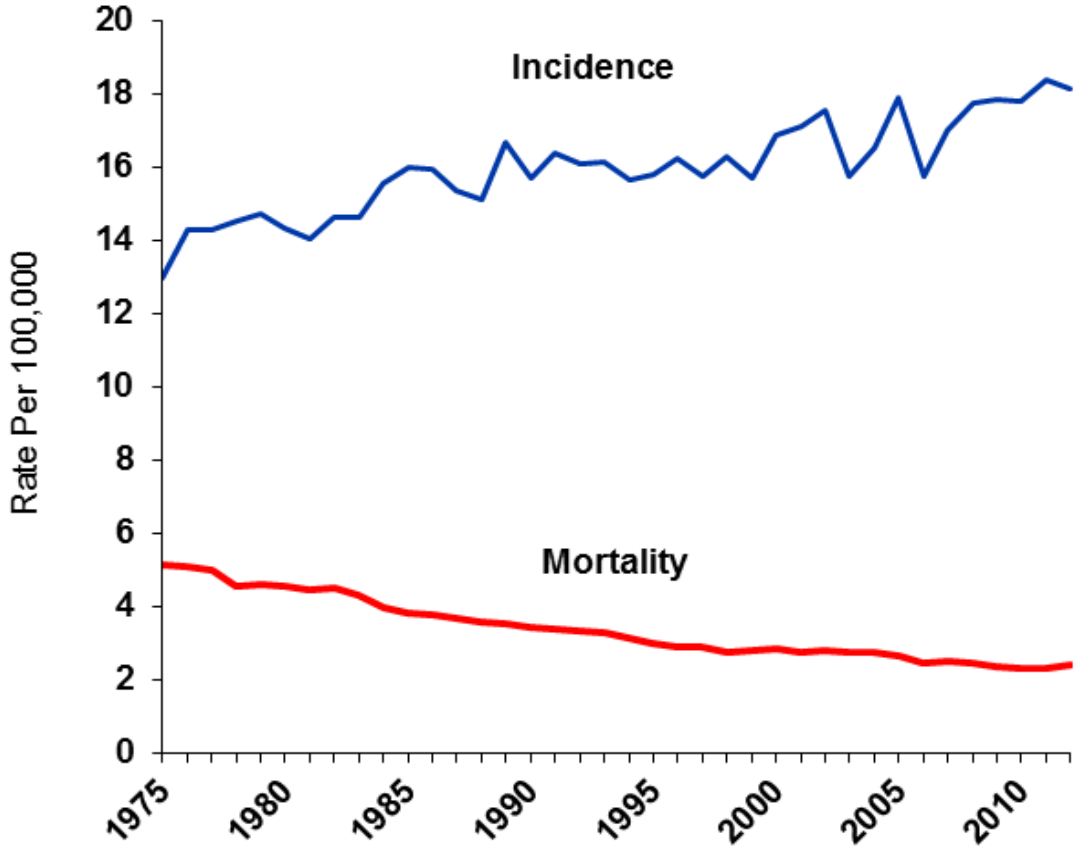
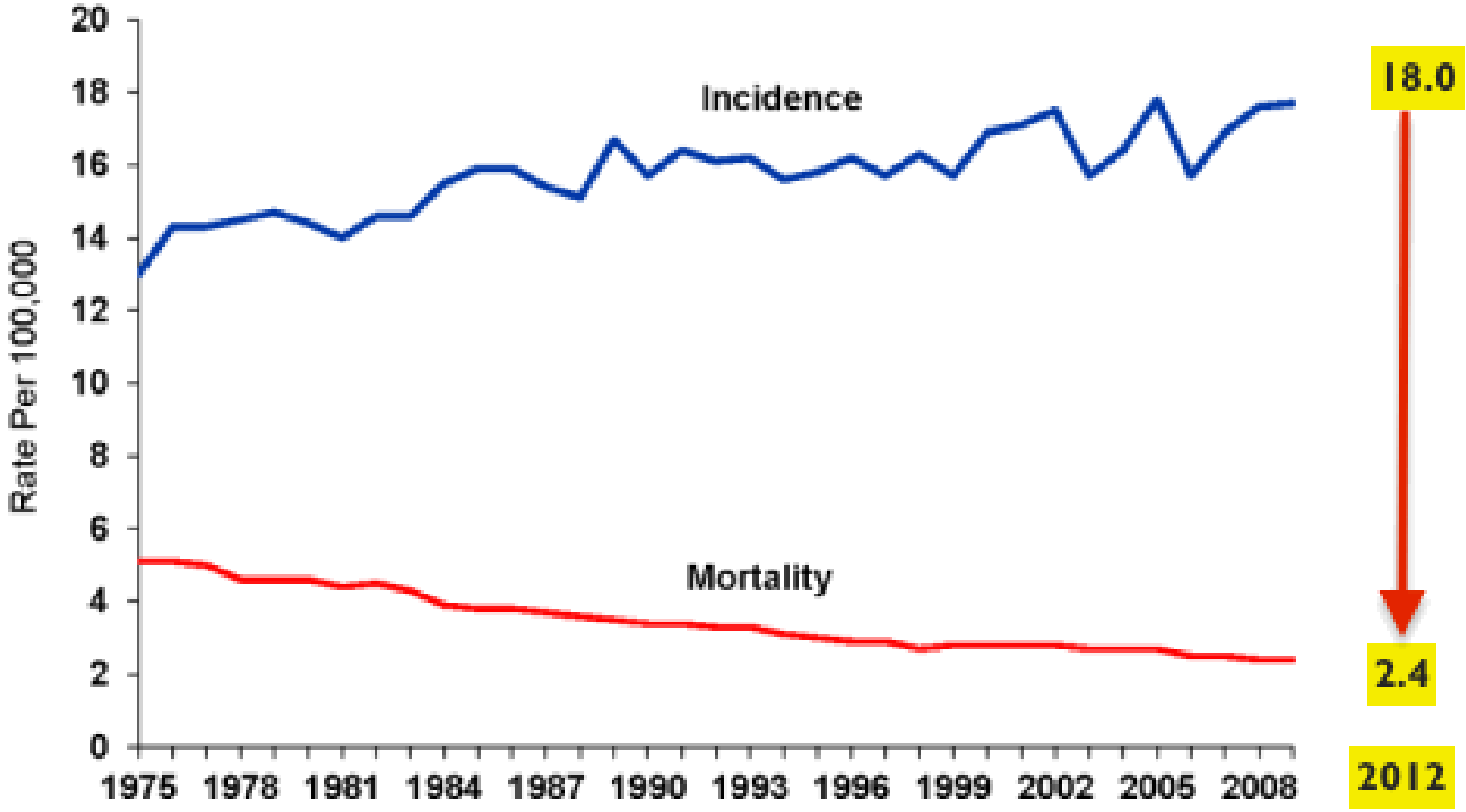
Oncofertility, ESHRE, Paris 2016

# Trends in Cancer Incidence and Death Rates* in Children and Adolescents (0-19 Years), 1975-2012




*Age-adjusted to the 2000 standard population. Incidence rates are adjusted to account for delays in reporting.
Sources: Incidence – Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute, 2015. Mortality – National Center for Health Statistics, Centers for Disease Control and Prevention, 2015.

# Cancer Incidence and Death Rates* in Children 0-19 Years, 1975-2009

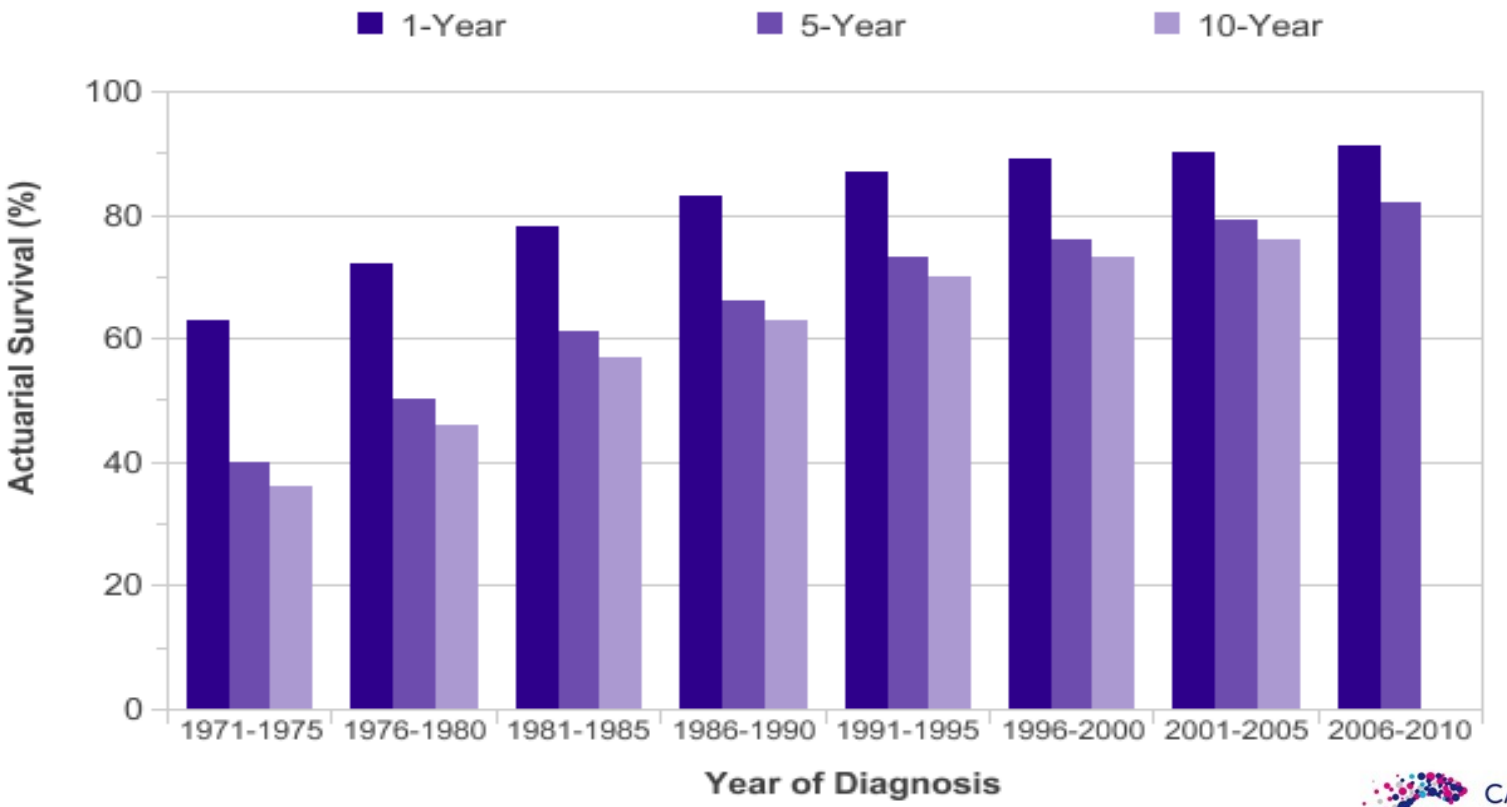



*Age-adjusted to the 2000 Standard population.

Source: Incidence -Surveillance, Epidemiology, and End Results Program, Delay-adjusted Incidence database: SEER Incidence Delay-adjusted Rates, 9 Registries, 1975-2009, National Cancer Institute, 2012.
Mortality – National Center for Health Statistics, 2012.

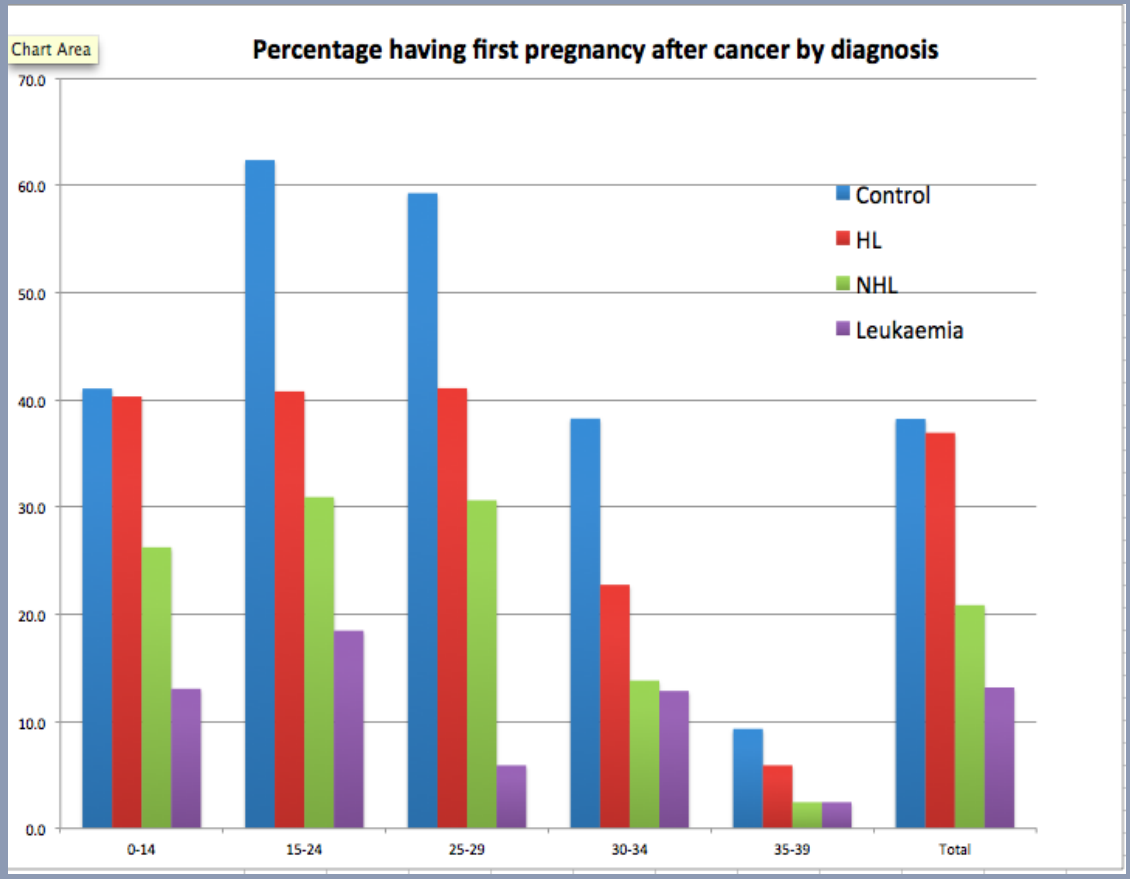
# Childhood Cancer 1971-2010

## One-, Five- and Ten-Year Actuarial Survival (%), Children (Aged 0-14), Great Britain




CANCER RESEARCH UK

# Scottish (population-based) study of first pregnancy after cancer diagnosis (<39 years)




Anderson R et al. unpublished

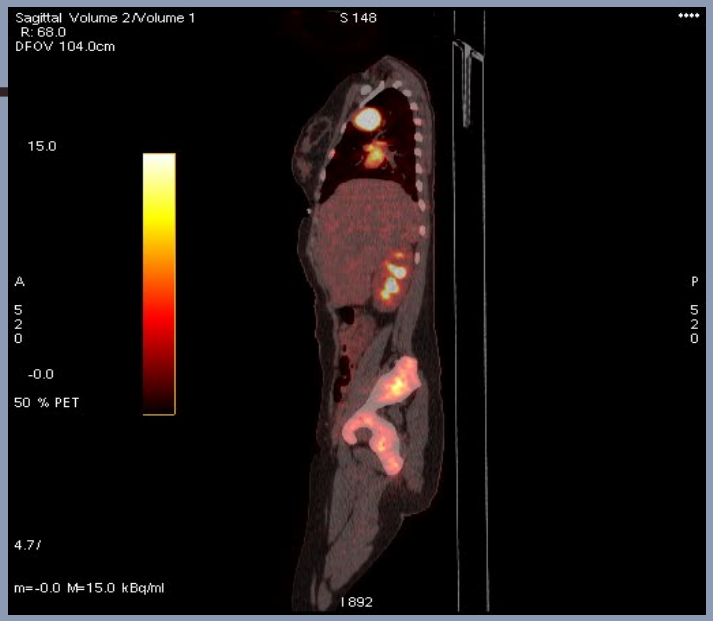
# A Patient

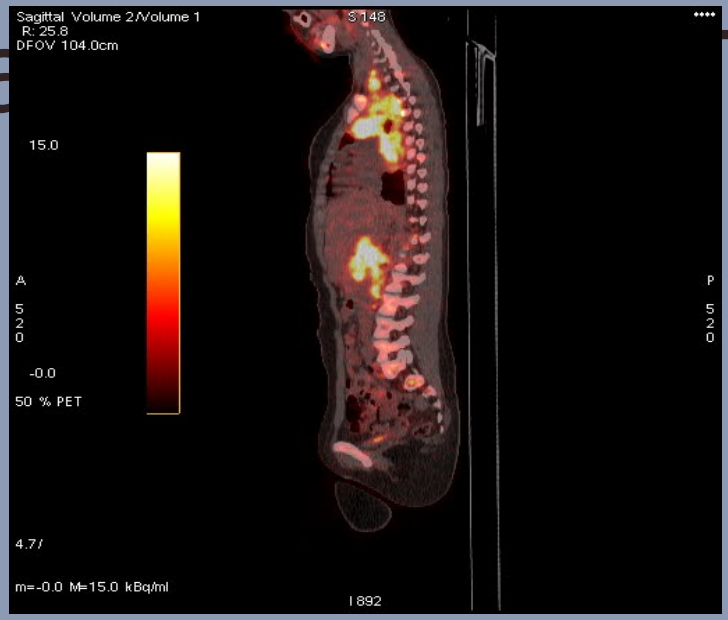
March 2011 (age 15 years)

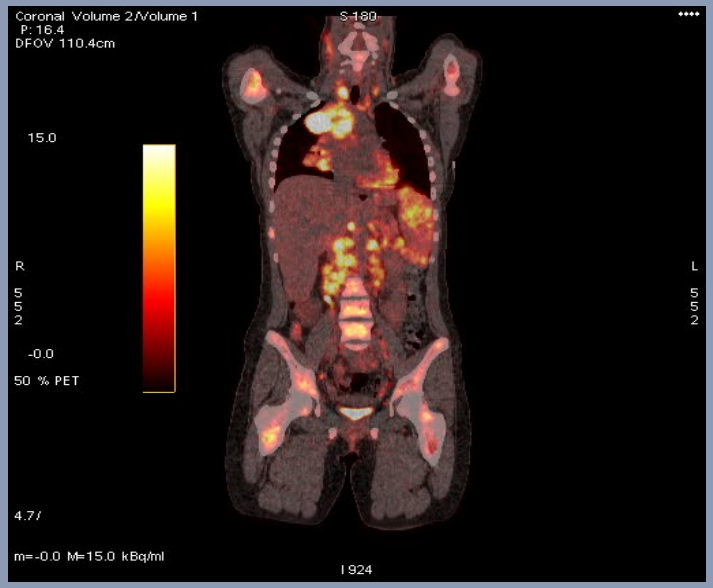
Six month H/O of intense pruritis of her feet

Three month H/O fever, night sweats, lethargy, pallor, poor appetite and weight loss

Widespread LN – lower cervical, mediastinum, abdomen


Sagittal Volume 2/Volume 1
S 148
R: 68.0
DFOV 104.0cm
15.0
A
P
-0.0
50 % PET
4.7/
m=-0.0 M=15.0 kBq/ml
I 892


Sagittal Volume 2/Volume 1
S 148
R: 25.8
DFOV 104.0cm
15.0
A
P
-0.0
50 % PET
4.7/
m=-0.0 M=15.0 kBq/ml
I 892


Coronal Volume 2/Volume 1
S 180
P: 16.4
DFOV 110.4cm
15.0
R
L
-0.0
50 % PET
4.7/
m=-0.0 M=15.0 kBq/ml
I 924


Coronal Volume 2/Volume 1
S 180
P: 7.0
DFOV 110.4cm
15.0
R
L
-0.0
50 % PET
4.7/
m=-0.0 M=15.0 kBq/ml
I 924

# Diagnosis and Staging

Mediastinal lymph node biopsy

- Hodgkin's lymphoma

Insertion of double lumen portacath

Laparoscopic ovarian biopsy and cryopreservation of ovarian cortical strips

# Laura

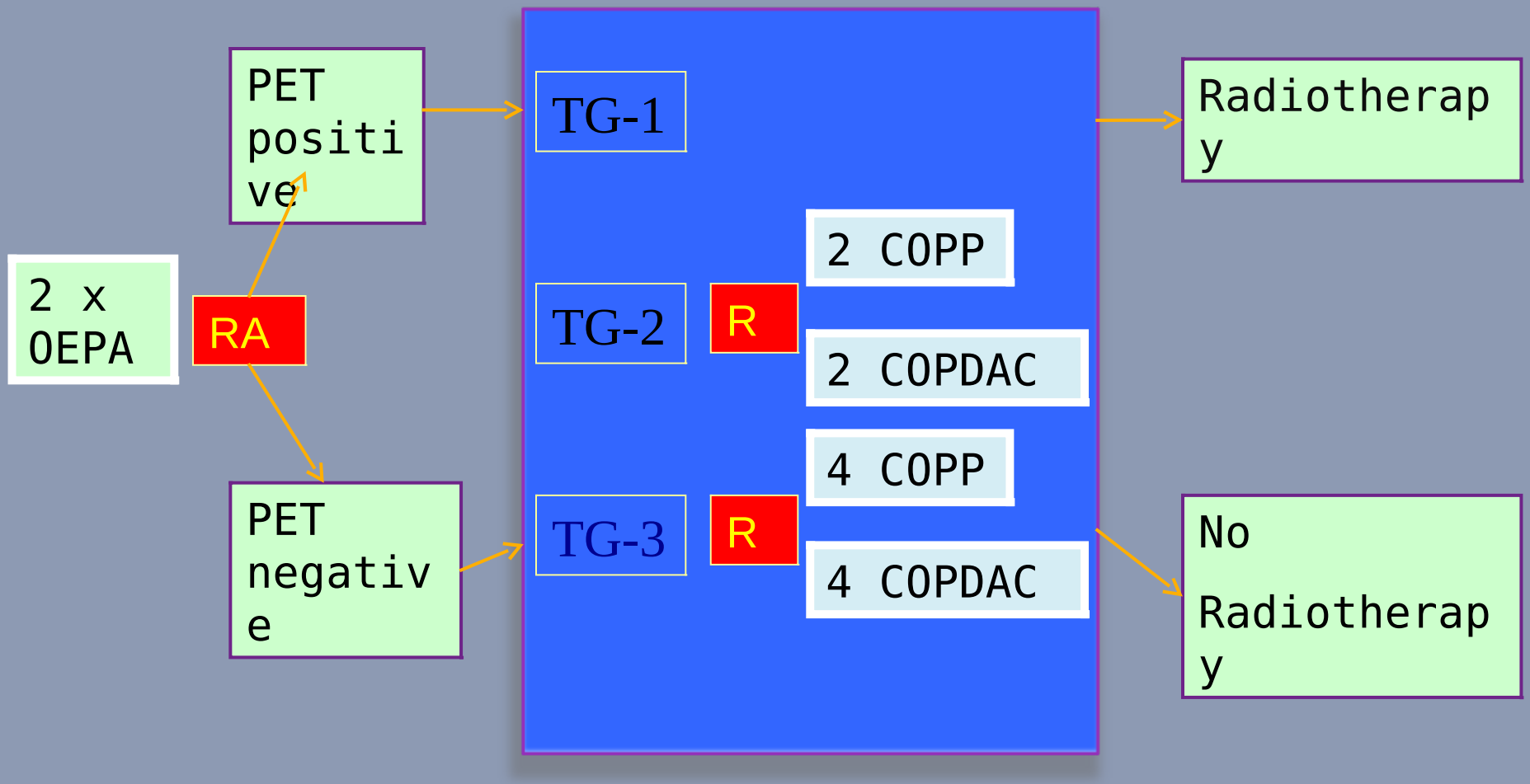
EuroNet-PHL-C1 Protocol:

Treatment Group 3 (TG3)

Two cycles of OEPA

Four cycles of COPDAC or COPP

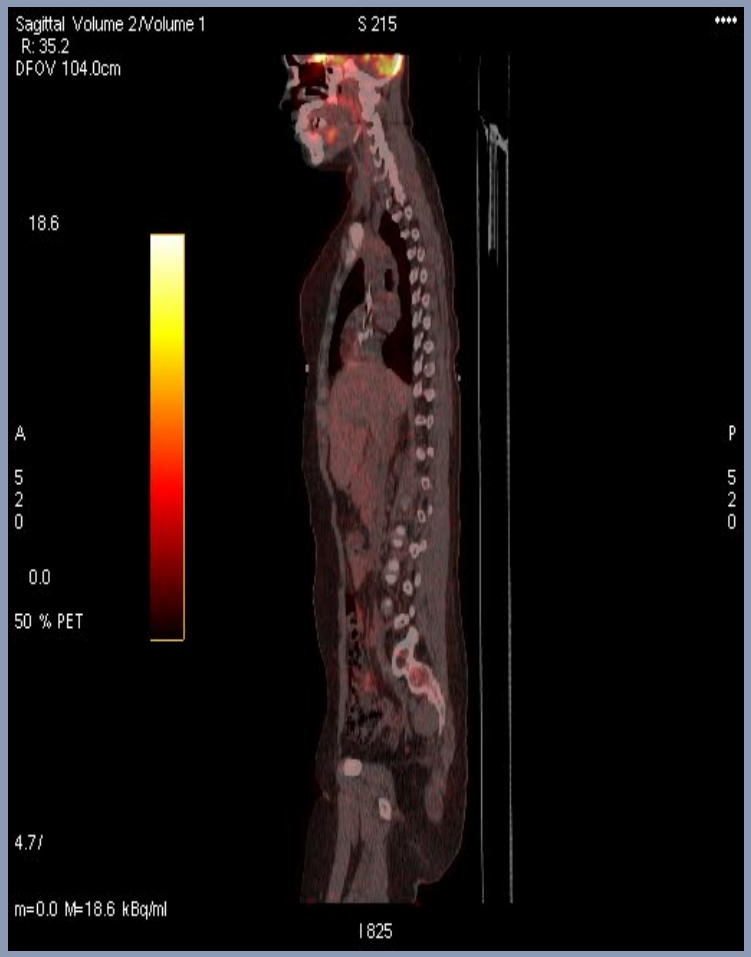
# EuroNet-PHL-C-1

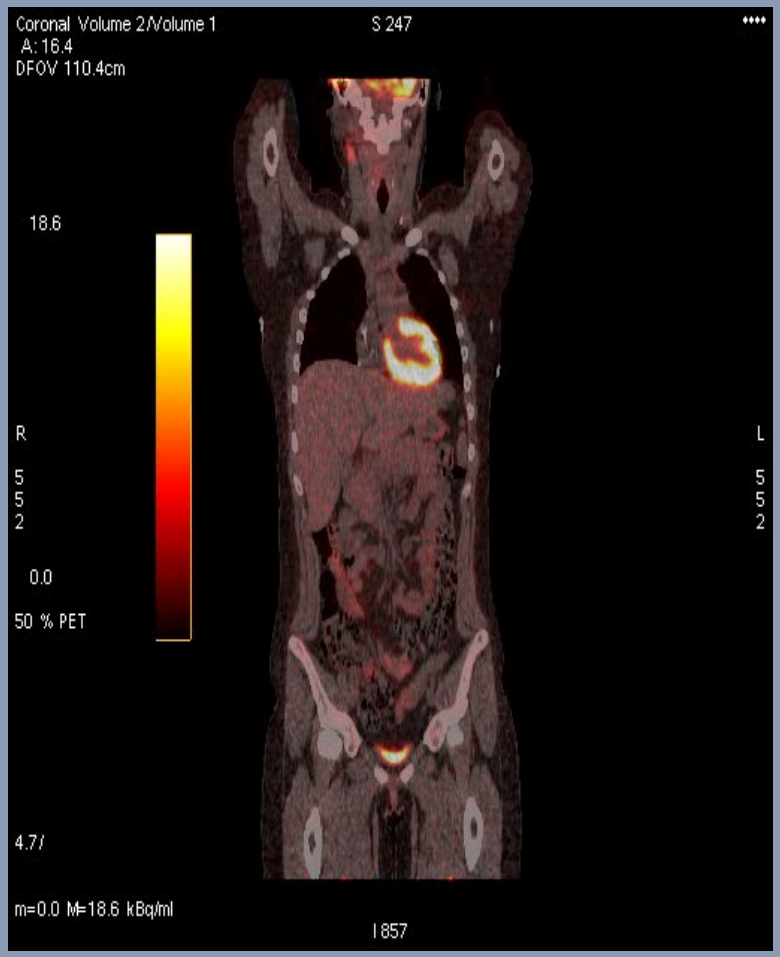



Wallace WH. UK Chief Investigator

CRUK support 400K

# Early Response Assessment PET scan



# Radiotherapy Field and estimated doses to organs at

| Organs at risk | Maximium dose received | Mean Dose |
|---|---|---|
| - spinal cord | 2139.7 cGy | 1916.2 cGy |
| - heart | 2116.1 cGy | 1701.4 cGy |
| - left kidney | 2169.1 cGy | 1439.8 cGy |
| - right kidney | 2022.2 cGy | 639.3 cGy |
| - lung | 2148.5 cGy | 1168.9 cGy |
| - right breast | 2195.1 cGy | 476.7 cGy |
| - left breast | 2156.4 cGy | 654.6 cGy |
| - liver | 2153.4 cGy | 830.2 cGy |
| - thyroid | 2047.2 cGy | 1999.0 cGy |

# Risk of infertility

| Low risk (<20%) | Medium risk | High risk (>80%) |
|---|---|---|
| ALL<br>Wilms' tumour<br>Brain tumour<br>Sx, RT < 24Gy<br>Soft tissue sarcoma (stage1)<br>**Hodgkin's Lymphoma HL(Low stage)** | AML<br>Osteosarcoma<br>Ewing's sarcoma<br>STS: stage II/III<br>Neuroblastoma<br>NHL<br>Brain tumour<br>RT>24Gy<br>**HL (High Stage)** | Total Body Irradiation<br>Pelvic/testes RT<br>Chemo pre BMT<br>Metastatic Ewing's<br>**HL (Pelvic RT)** |

Wallace, Anderson, Irvine. Lancet Oncology 2005

**Panel 1: Intrinsic and extrinsic factors for fertility preservation strategies in children and young adults[9]**

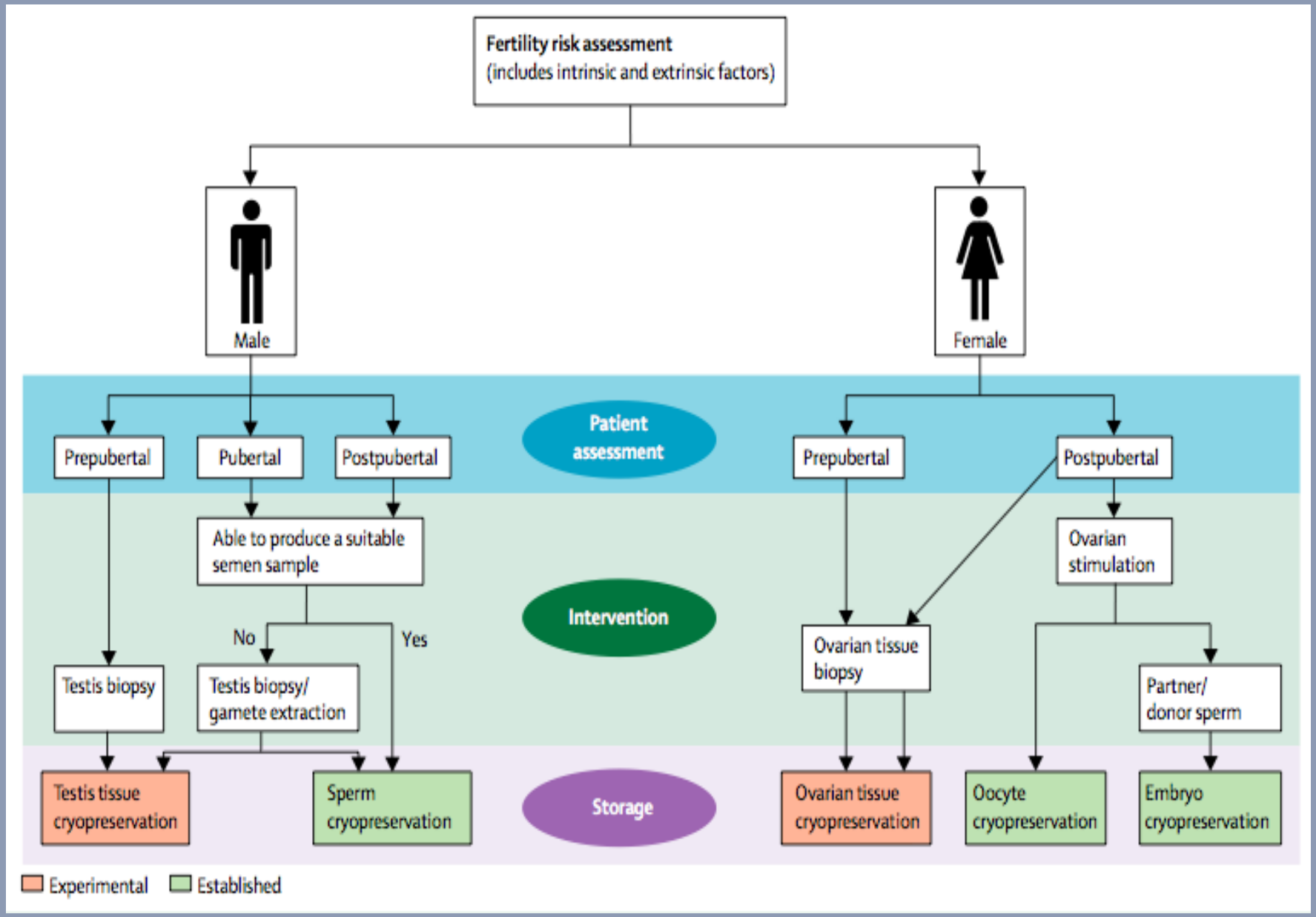
**Intrinsic factors**

- Health status of patient
- Psychosocial factors
- Consent (patient or parent)
- Assessment of pubertal status
- Assessment of ovarian reserve (female patients)

**Extrinsic factors**

- Risk of predicted treatment (high, medium, low, or uncertain risk)
- Time available
- Expertise and technical options available

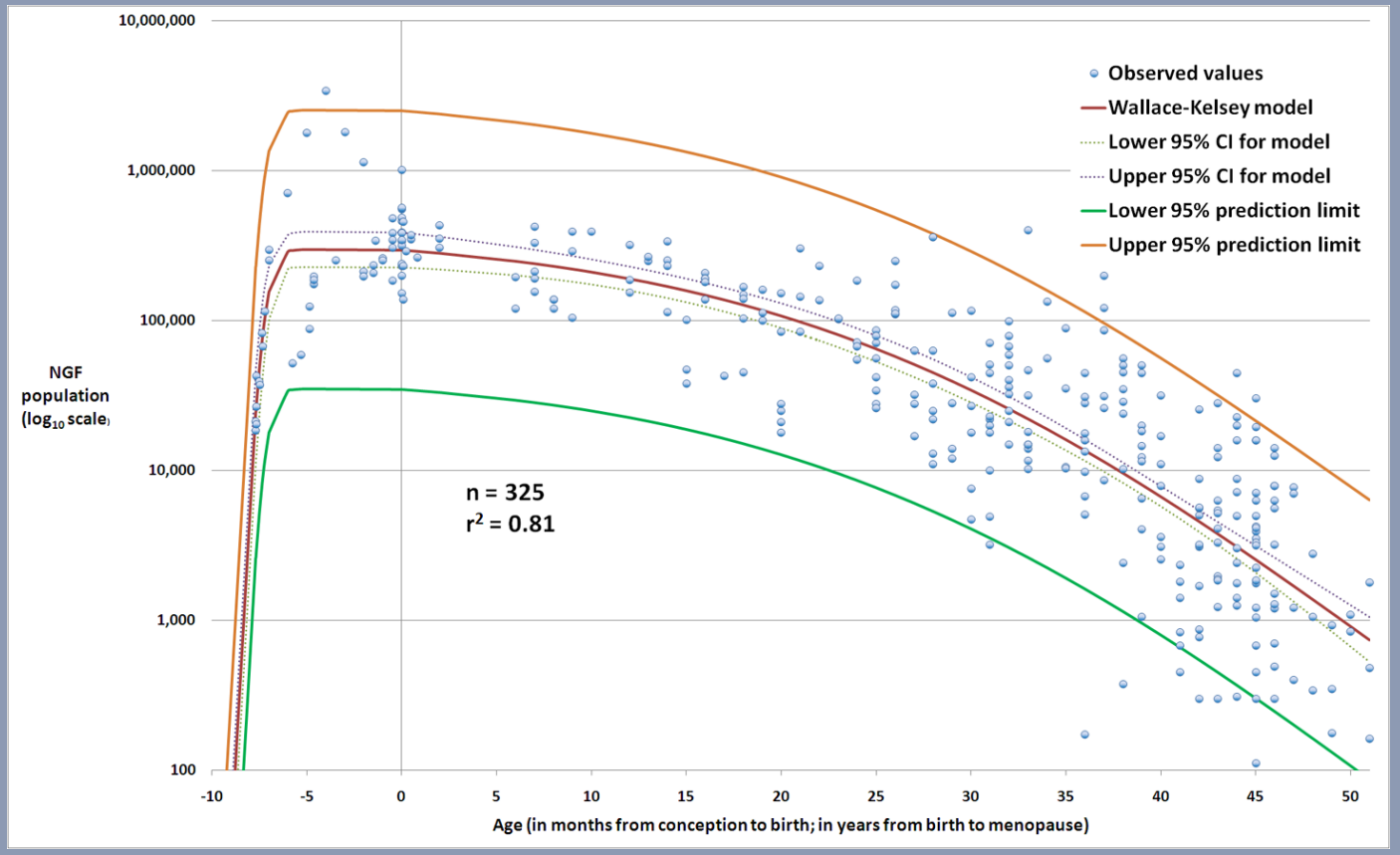
Anderson RA…Wallace WH. Lancet Diabetes Endocrinol. 2015




Anderson RA…Wallace WH. Lancet Diabetes Endocrinol. 2015

# Ovarian Reserve?

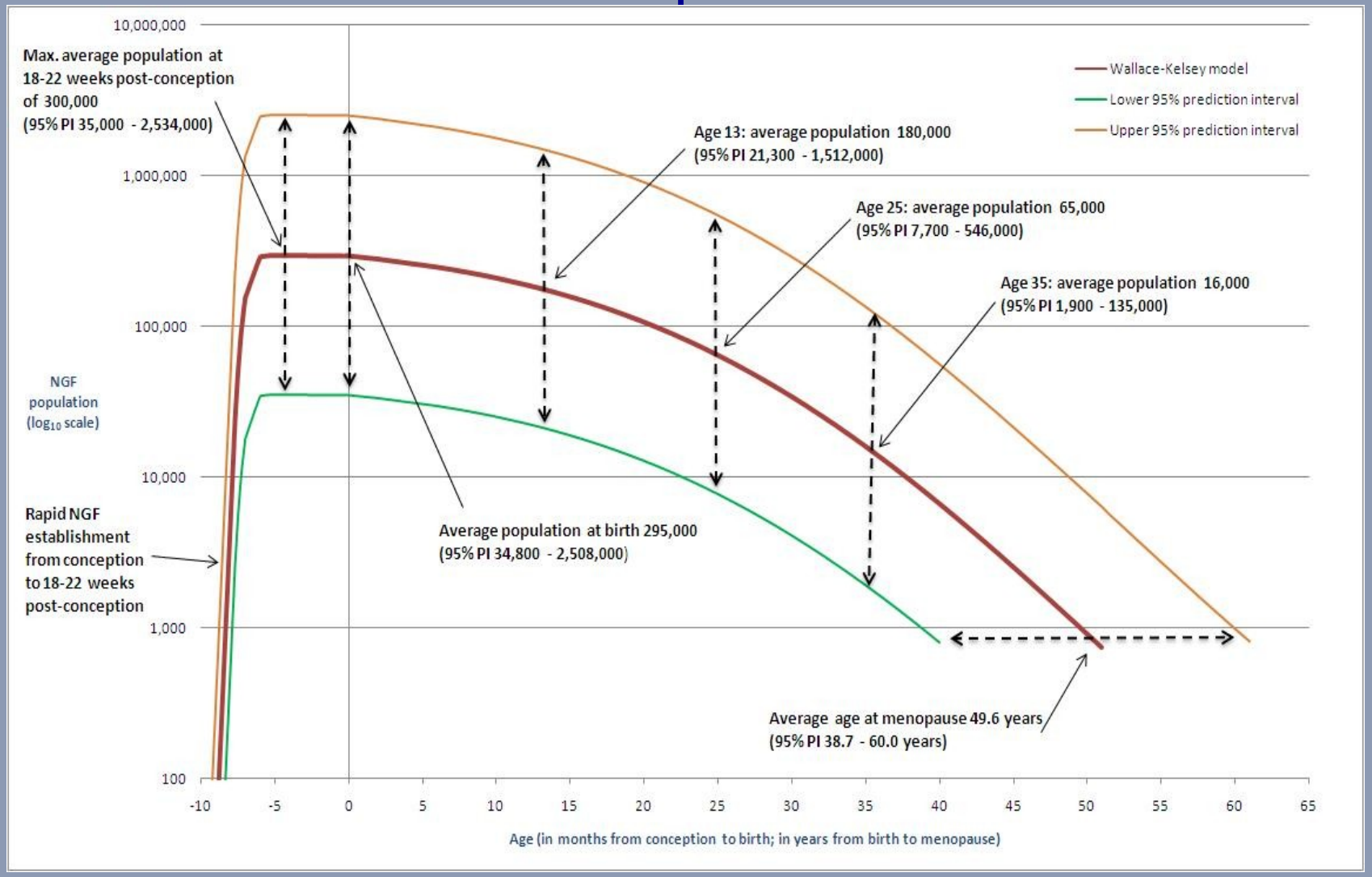
# The Wallace-Kelsey Model
## (Five parameter asymmetric double-Gaussian cumulative curve)




$$log_{10}(y) = \frac{a}{4}\left[1 + \mathrm{Erf}\left(\frac{x+b+\frac{c}{2}}{d\sqrt{2}}\right)\right]\left[1 - \mathrm{Erf}\left(\frac{x+b-\frac{c}{2}}{e\sqrt{2}}\right)\right]$$

Wallace &Kelsey (2010) PloS ONE

# Ovarian reserve: Conception to Menopause

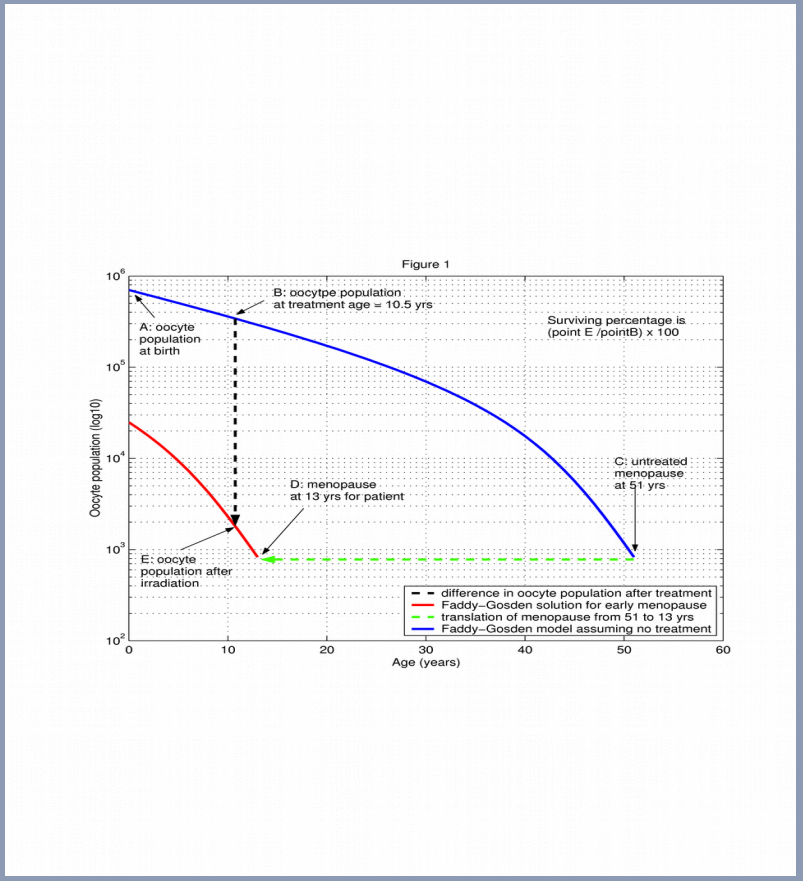



Wallace &Kelsey (2010) PloS ONE

# Radiation-induced ovarian damage

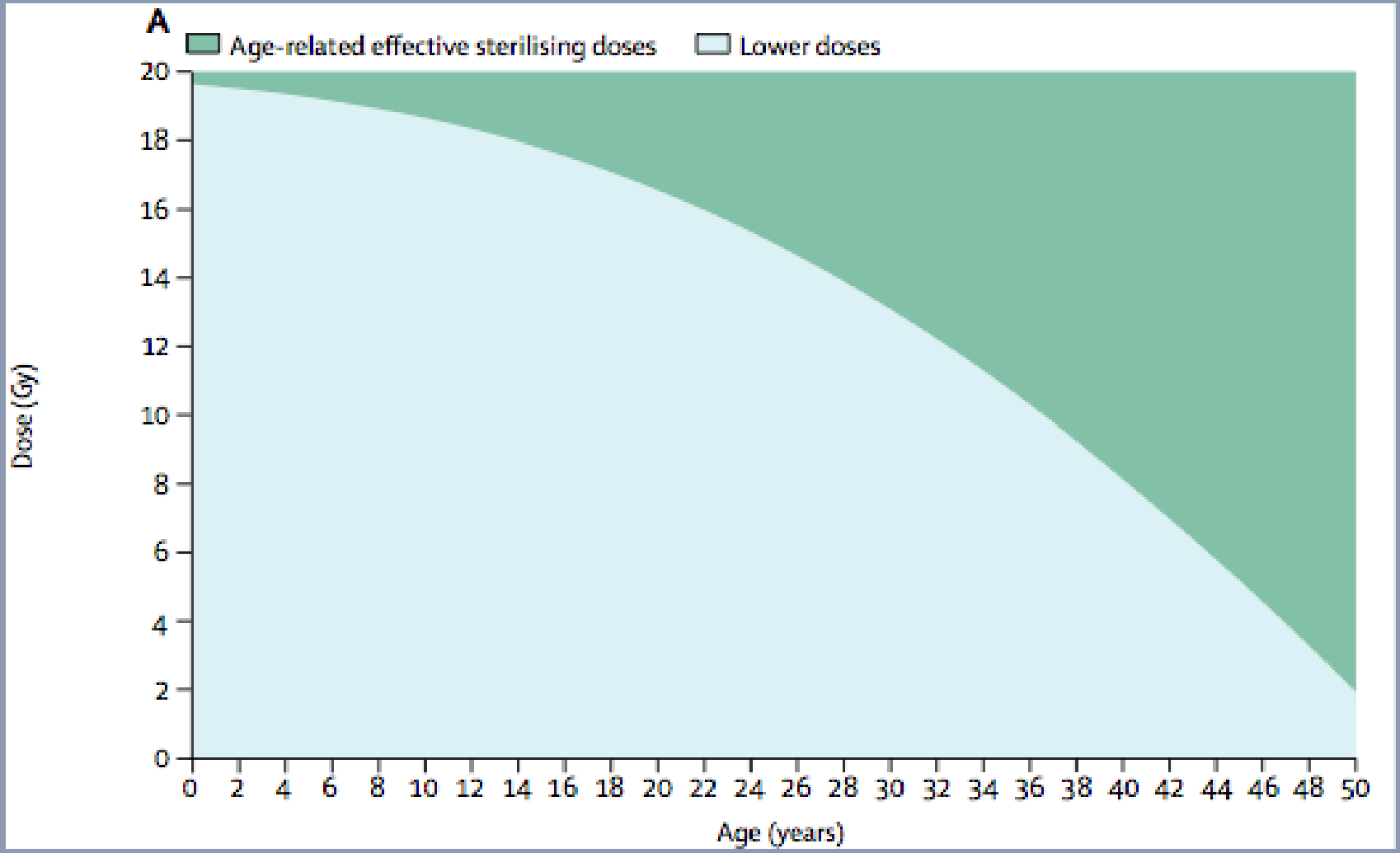
Human oocyte (Primordial follicle)

$LD_{50} < 2$ Gy

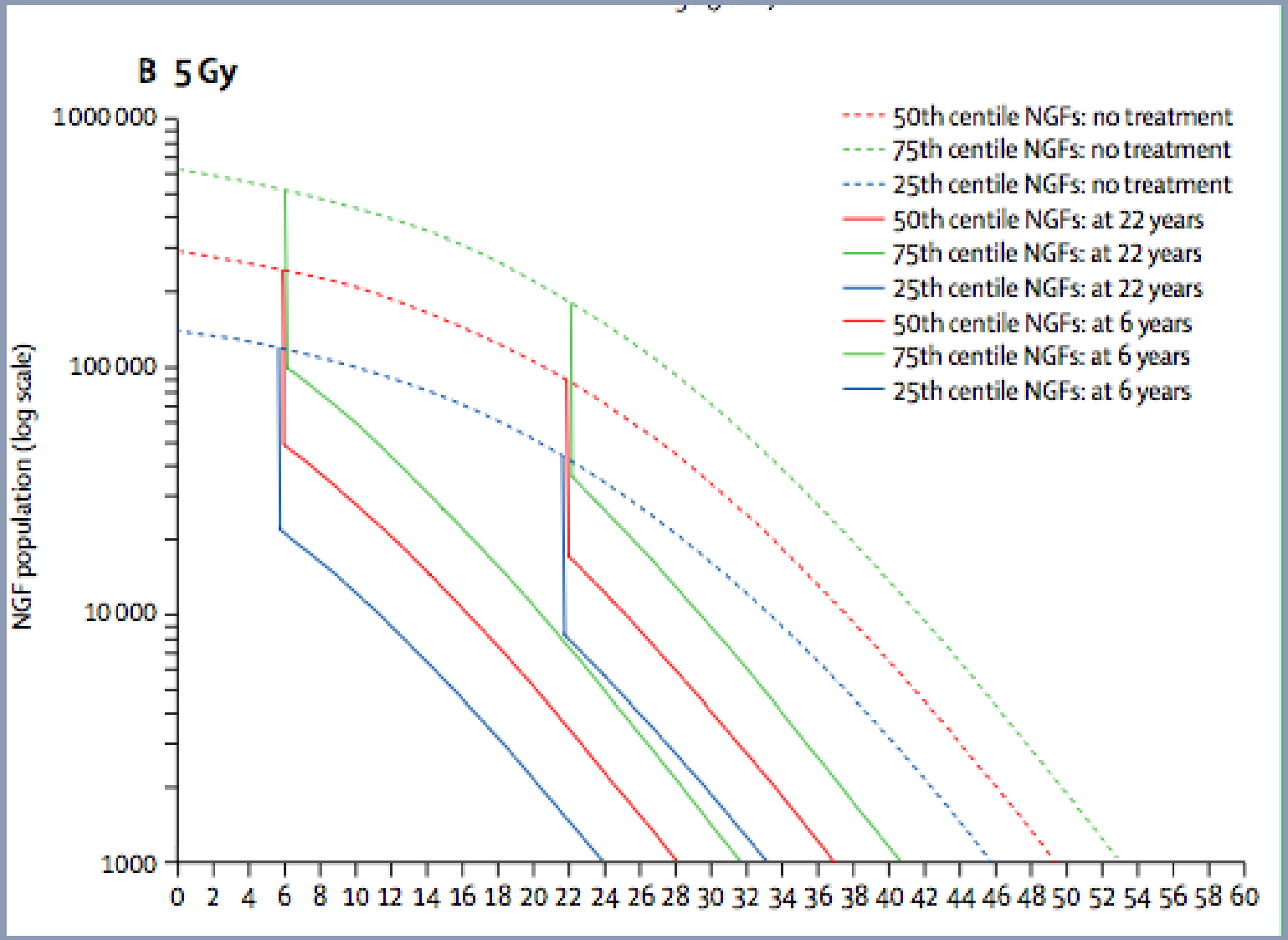



**Wallace, Thomson, Kelsey. (2003) Hum Reprod.**

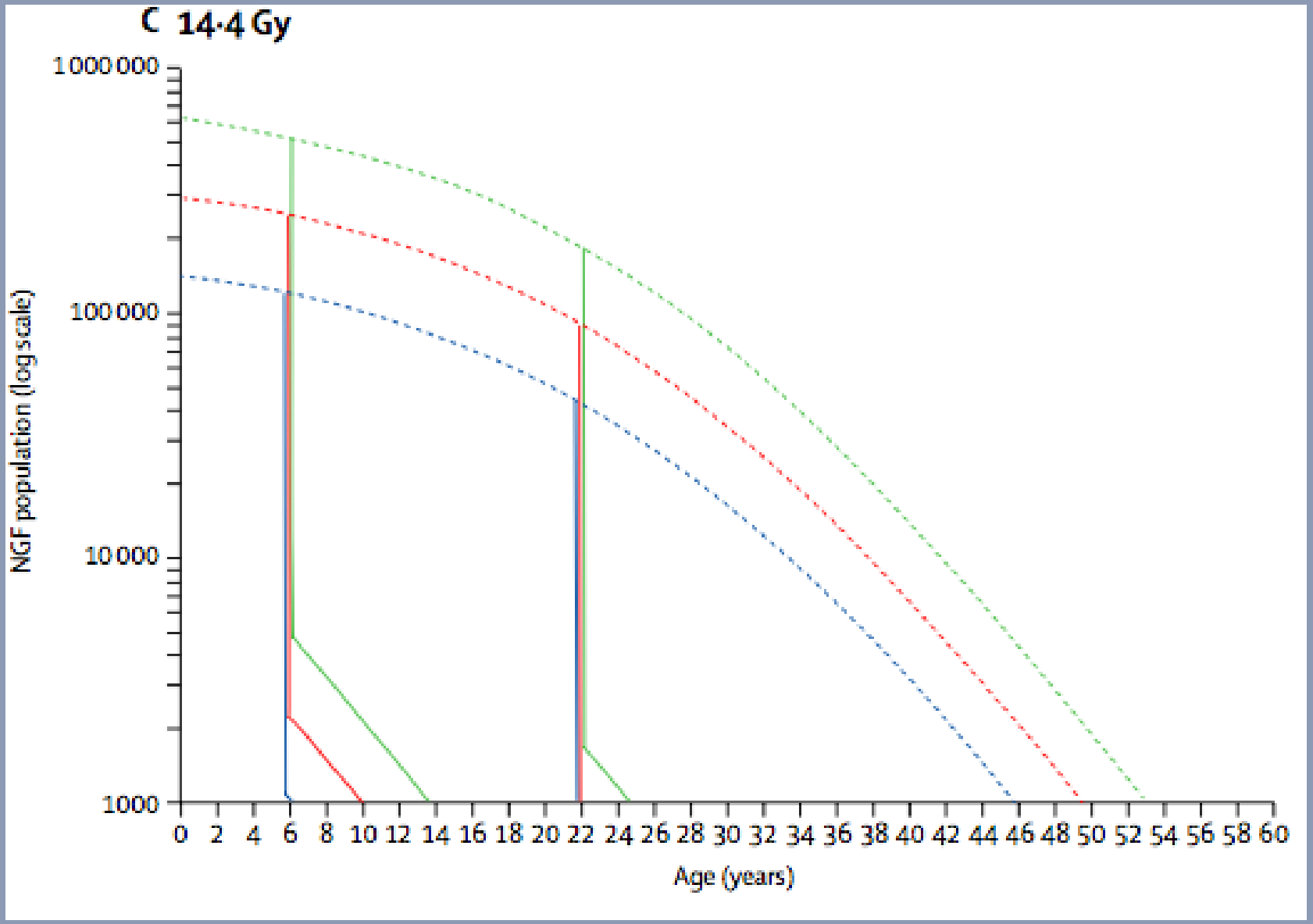
# Effective ovarian sterilizing doses of radiotherapy with increasing age




Anderson RA…Wallace WH. Lancet Diabetes Endocrinol. 2015




Anderson RA…Wallace WH. Lancet Diabetes Endocrinol. 2015




Anderson RA…Wallace WH. Lancet Diabetes Endocrinol. 2015

# Prediction of Ovarian Reserve (AMH)

Anti Mullerian Hormone (AMH) is an important product of the adult ovary, produced by the granulosa cells of small growing follicles

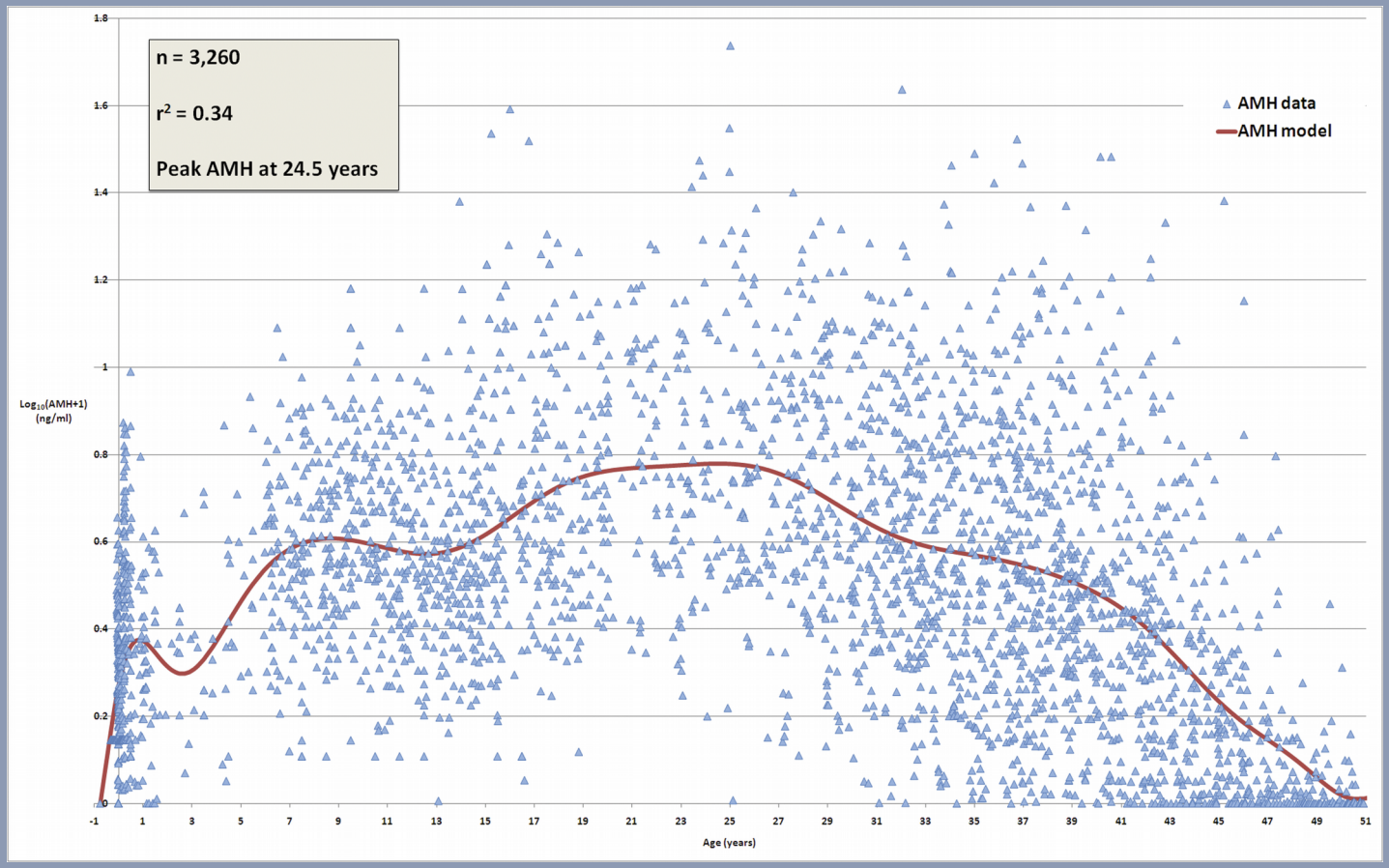
AMH has little variation across and between menstrual cycles

AMH is the best currently available marker of the number of small-growing follicles in the ovary

But there was no validated reference model for AMH available

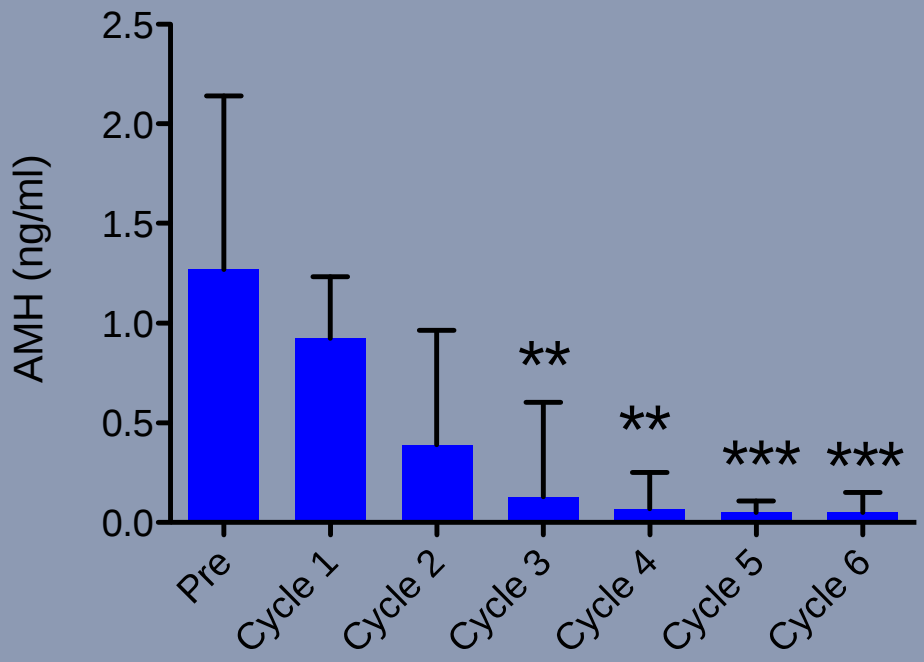
Anderson, Nelson, Wallace (2011) Maturitas

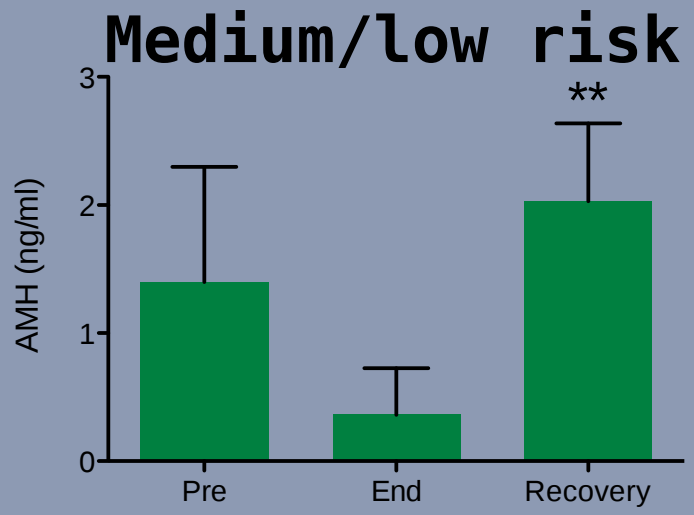
# A validated model of serum anti-Mullerian hormone (AMH) from conception to menopause

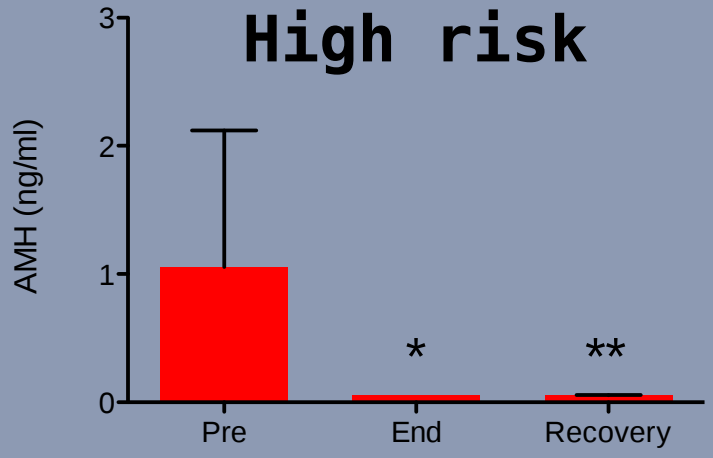



Kelsey et al. PLoS ONE 2011

# AMH in childhood cancer



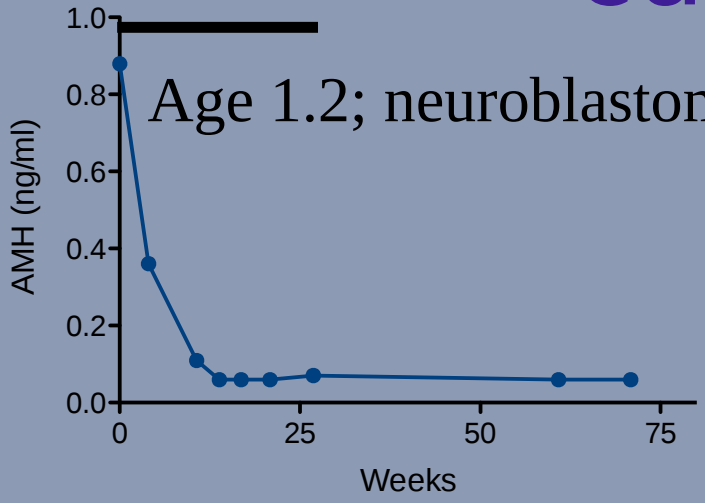



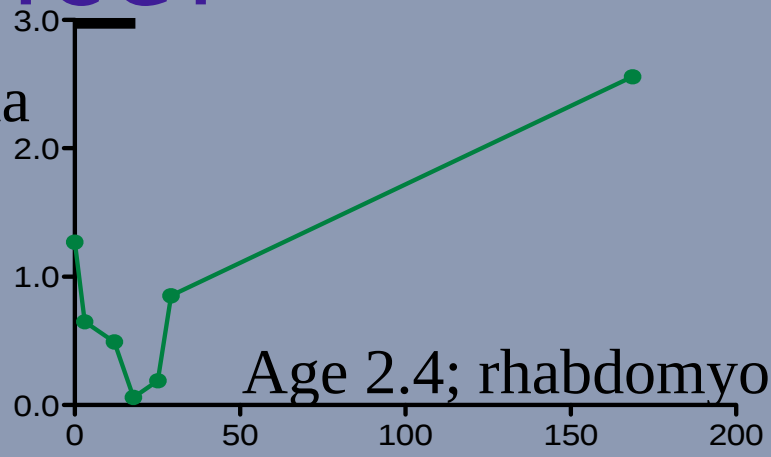



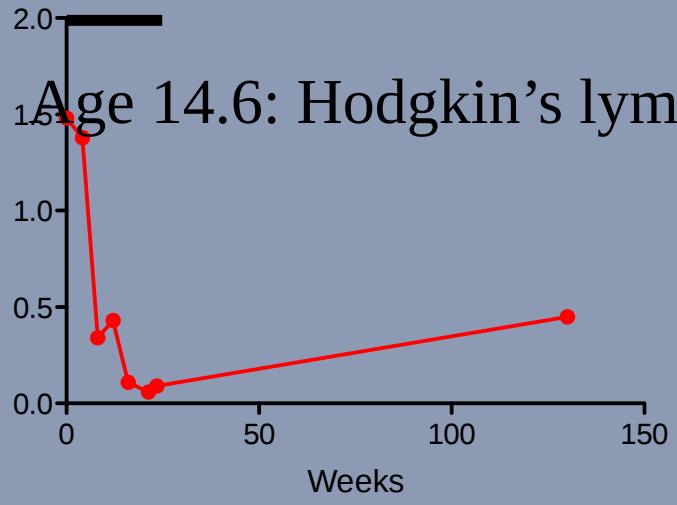

22 girls age 0.3-15yr
17 prepubertal

Brougham et al 2012 JCE&M

# AMH in 3 girls with cancer




Brougham et al 2012 JCE&M

# Summary

AMH is detectable before puberty

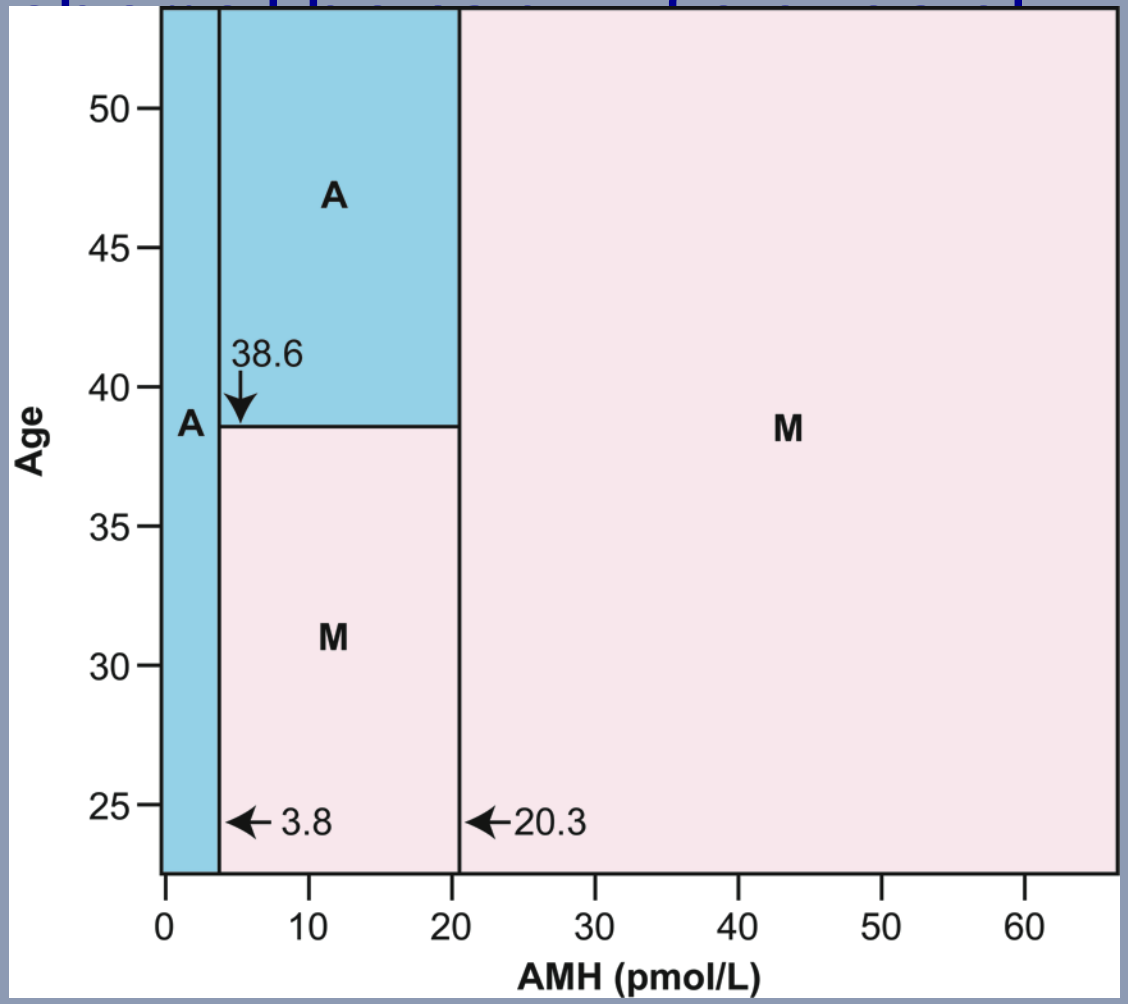
AMH falls rapidly during cancer treatment in both pre-pubertal and pubertal girls

AMH levels recover in those patients at low/medium risk of gonadotoxicity

AMH fails to recover in those at high risk. This could be indicative of future reproductive impairment

Brougham et al 2012 JCE&M

# Pretreatment anti-Müllerian hormone predicts for loss of ovarian function after [illegible] breast




sensitivity 98.2%
specificity 80.0%
for correct classification
of amenorrhoea

n=75

Anderson and Cameron 2011 JCE&M
Anderson et al 2013 Eur J Cancer

# Ovarian Cryopreservation & Ovarian Function

Edinburgh experience  in children (< 18 yrs) 1996-2012

***Panel 2:* The Edinburgh Selection Criteria for gonadal tissue cryopreservation**

These criteria were established with ethics committee review and approval because they refer to experimental procedures, and should be regarded as a starting point for future discussion, research, and refinement.

**Female patients**[112]

- Age younger than 35 years
- No previous chemotherapy or radiotherapy if aged 15 years or older at diagnosis, but mild, non-gonadotoxic chemotherapy is acceptable if younger than 15 years
- A realistic chance of 5-year survival
- A high risk of premature ovarian insufficiency (>50%)
- Informed consent (parent and, when possible, patient)
- Negative HIV, syphilis, and hepatitis serology
- Not pregnant and no existing children

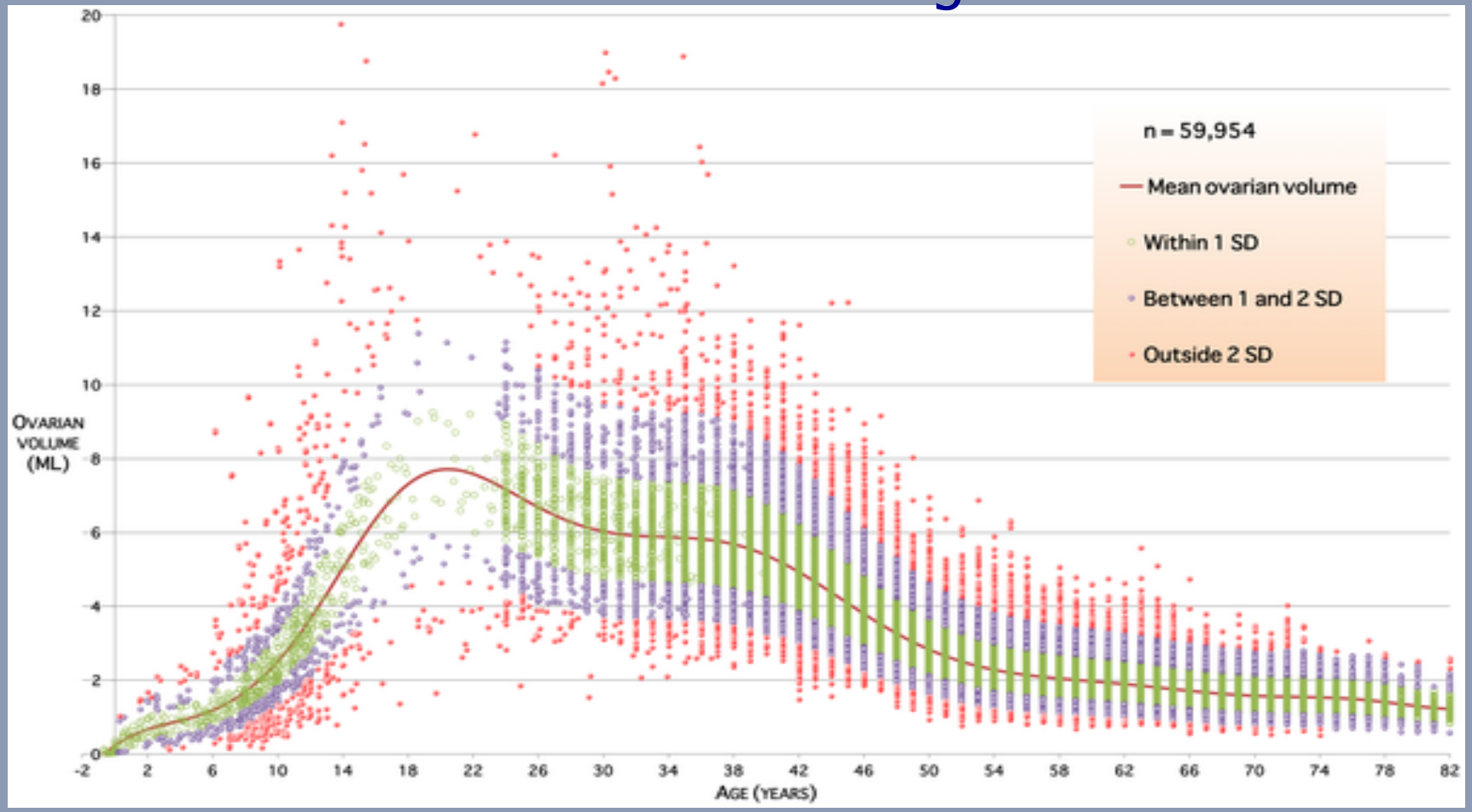
**Male patients**

- Age 0–16 years
- A high risk of infertility (>80%)
- Unable to produce a semen sample by masturbation
- No clinically significant pre-existing testicular disease (eg, cryptorchidism)
- Informed consent (parent and, when possible, patient)
- Negative HIV, syphilis, and hepatitis serology

Anderson RA…Wallace WH. Lancet Diabetes Endocrinol. 2015

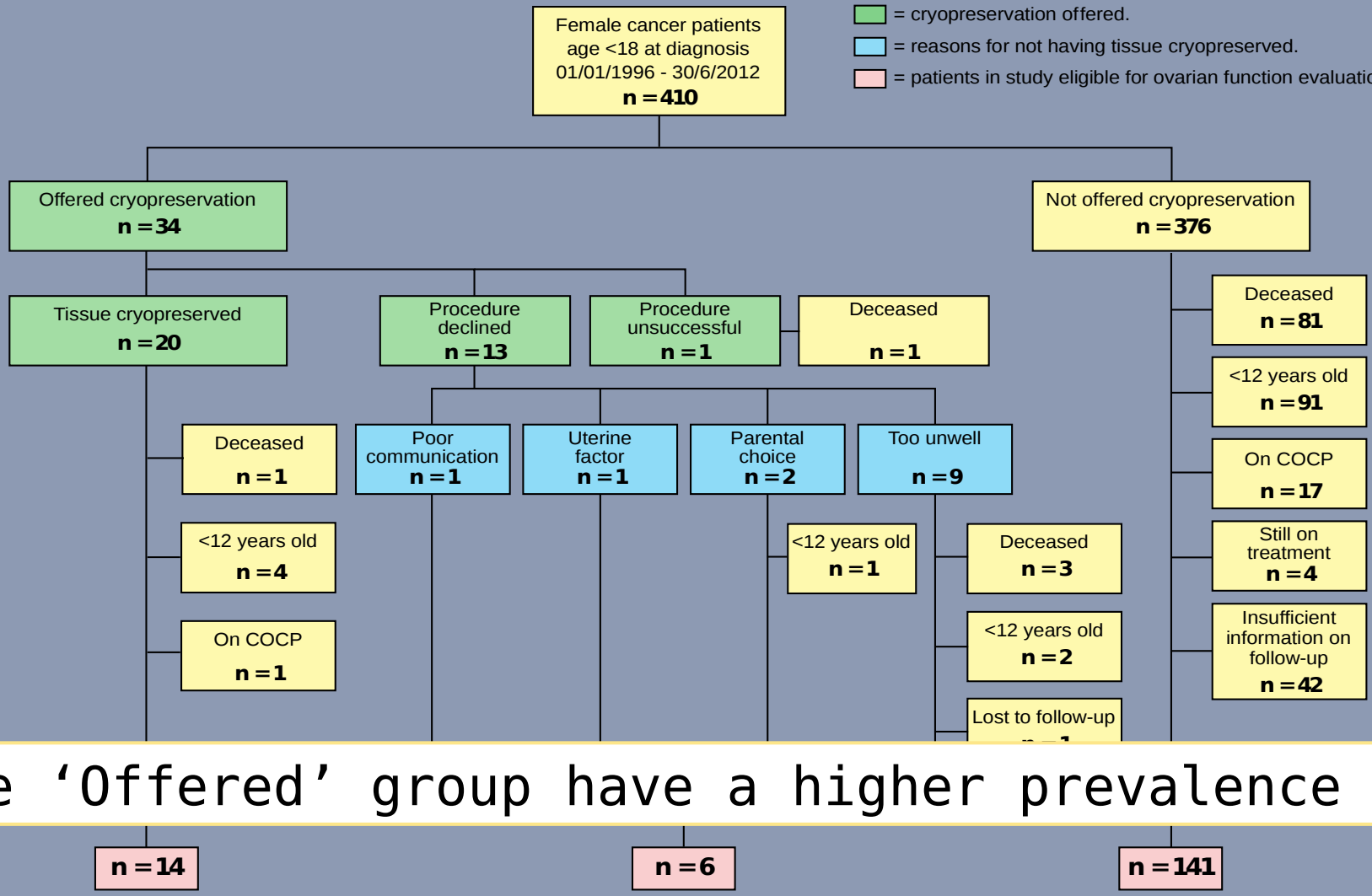
| Patient No. | Diagnosis | Age at cryopreservation (years) | Method of ovarian tissue collection | Complications from procedure | Duration since cryopreservation (years) | Age at last assessment (years) | Current Ovarian Function |
|---|---|---|---|---|---|---|---|
| 1 | Hodgkin's Lymphoma[◊] | 14.9 | Laparoscopic Cortical Strip | None | 15.8 | 30.2 | Not POI |
| 2 | Ewing's Sarcoma (pubic bone) | 14.9 | Laparoscopic Cortical Strip | None | 16.6 | 25.6 | POI (+1 child) |
| 3 | Sacral Ependymoma | 11.3 | Laparoscopic Cortical Strip | None | 15.8 | 24.5 | Not POI |
| 4 | Hodgkin's Lymphoma | 13.7 | Laparoscopic Cortical Strip | None | 15.6 | 28.9 | Not POI |
| 5 | Hodgkin's Lymphoma | 11.0 | Laparoscopic Cortical Strip | None | 14.7 | | On COCP |
| 6 | Chronic Granulocytic Leukaemia | 9.9 | Laparoscopic Cortical Strip | None | 12.2 | 21.7 | Not POI |
| 7 | Rhabdomyosarcoma | 5.3 | Laparoscopic Cortical Strip | None | 8.2 | 13.1 | POI |
| 8 | Ewing's Sarcoma (pelvic) | 9.8 | Laparoscopic Cortical Strip | None | 6.7 | 15.6 | POI |
| 9 | Uterine Cervix Rhabdomyosarcoma* | 16.4 | Laparoscopic Cortical Strip | None | 5.1 | 17.5 | Not POI |
| 10 | Hodgkin's Lymphoma[θ] | 14.0 | Laparoscopic Cortical Strip | None | 3.2 | 17.2 | POI |
| 11 | Abdominal Embryonal Rhabdomyosarcoma | 7.9 | Laparoscopic Cortical Strip | None | | | Deceased |
| 12 | Ewing's Sarcoma | 12.1 | Laparoscopic Cortical Strip† | None | 3.9 | 15.2 | POI |
| 13 | Hodgkin's Lymphoma | 12.7 | Laparoscopic Cortical Strip | None | 3.3 | 14.3 | POI |
| 14 | Metastatic Medulloblastoma | 8.1 | Laparoscopic Cortical Strip | None | 2.9 | | Not assessed |
| 15 | Hodgkin's Lymphoma | 15.2 | Laparoscopic Cortical Strip | None | 1.9 | 16.9 | Not POI |
| 16 | Alveolar Rhabdomyosarcoma | 10.5 | Laparoscopic Cortical Strip | None | 1.4 | | Not assessed |
| 17 | Embryonal Rhabdomyosarcoma | 3.0 | Oophorectomy | None | 1.4 | | Not assessed |
| 18 | Ewing's Sarcoma | 12.0 | Laparoscopic Cortical Strip | None | 1.4 | 13.5 | Not POI |
| 19 | Undifferentiated Sarcoma | 12.3 | Laparoscopic Cortical Strip† | None | 1.0 | 13.4 | Not POI |
| 20 | Wilm's Tumour | 1.2 | Oophorectomy | None | 0.6 | | Not assessed |

# The normative validated model of ovarian volume throughout life




Kelsey TW, Dodwell SK, Wilkinson AG, Greve T, Andersen CY, et al. (2013) Ovarian Volume throughout Life: A Validated Normative Model. PLoS ONE 8(9): e71465. doi:10.1371/journal.pone.0071465

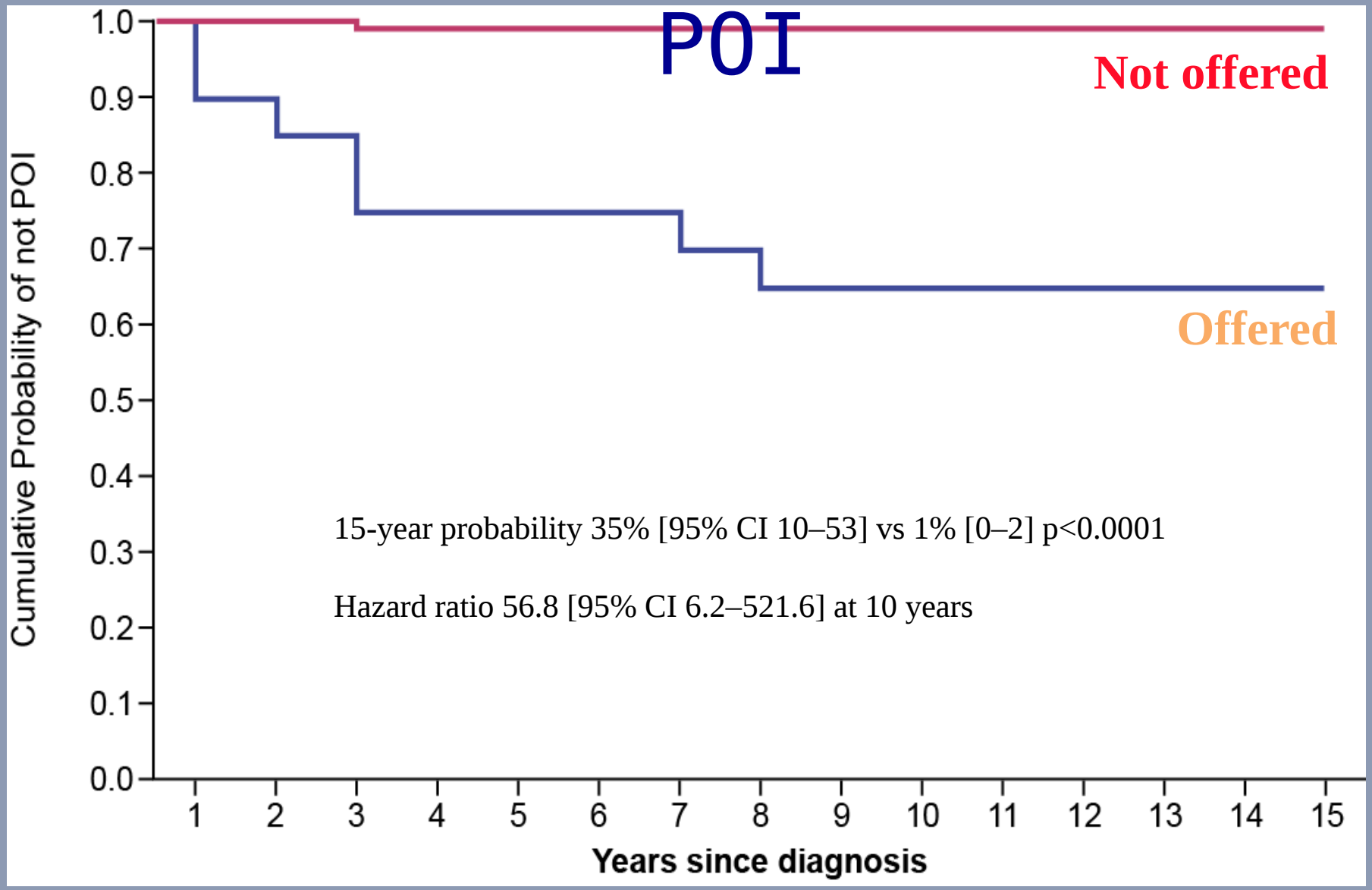
# 15 year, population-based analysis of criteria for ovarian cryopreservation




the ‘Offered’ group have a higher prevalence of PC

Walllace WH et al. 2014 Lancet Oncology

# Cumulative incidence of POI




Walllace…..and Anderson 2014 Lancet Oncology

# Conclusion

Ovarian cryopreservation was offered to 9% of our patients, and performed in 5%

The procedure was safe and without complications

No patients have asked for re-implantation of their tissue – to date

All patients who have thus far developed premature ovarian insufficiency were identified except one patient

The Edinburgh Selection Criteria have proved to be helpful in selecting those patients at highest risk of POI

Wallace WH…..and Anderson 2014 Lancet Oncology

# Challenges

Provide fertility counseling to all young patients with cancer

Cryopreserve ovarian and pre-pubertal testicular tissue from the right (high risk) patients

Define the success rate of the procedures

Develop IVG/M as a safe alternative to re-implantation through basic research

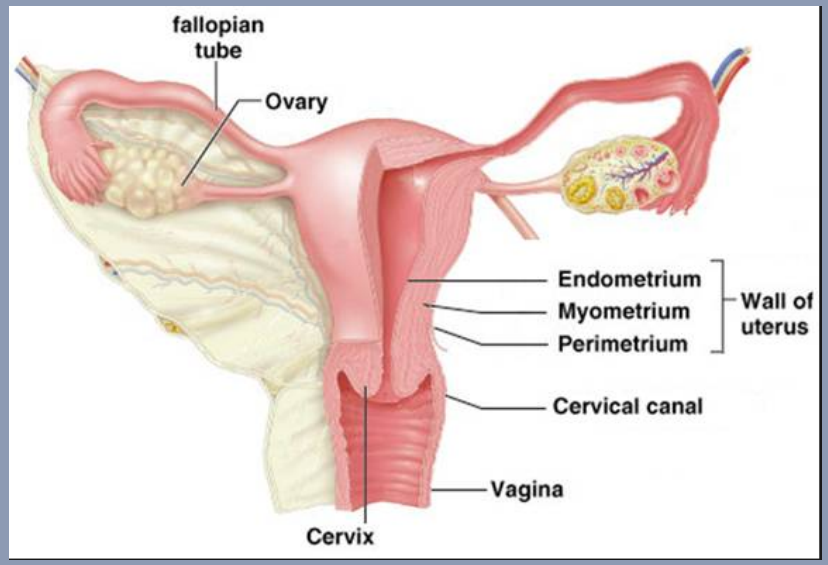
# Acknowledgements

Richard Anderson
David T Baird
Tom Kelsey
Evelyn Telfer
Marie McLaughlan
Alice Grove Smith

Rod Mitchell
Louise Bath
Angela Edgar
Mark Brougham
Fraser Munro

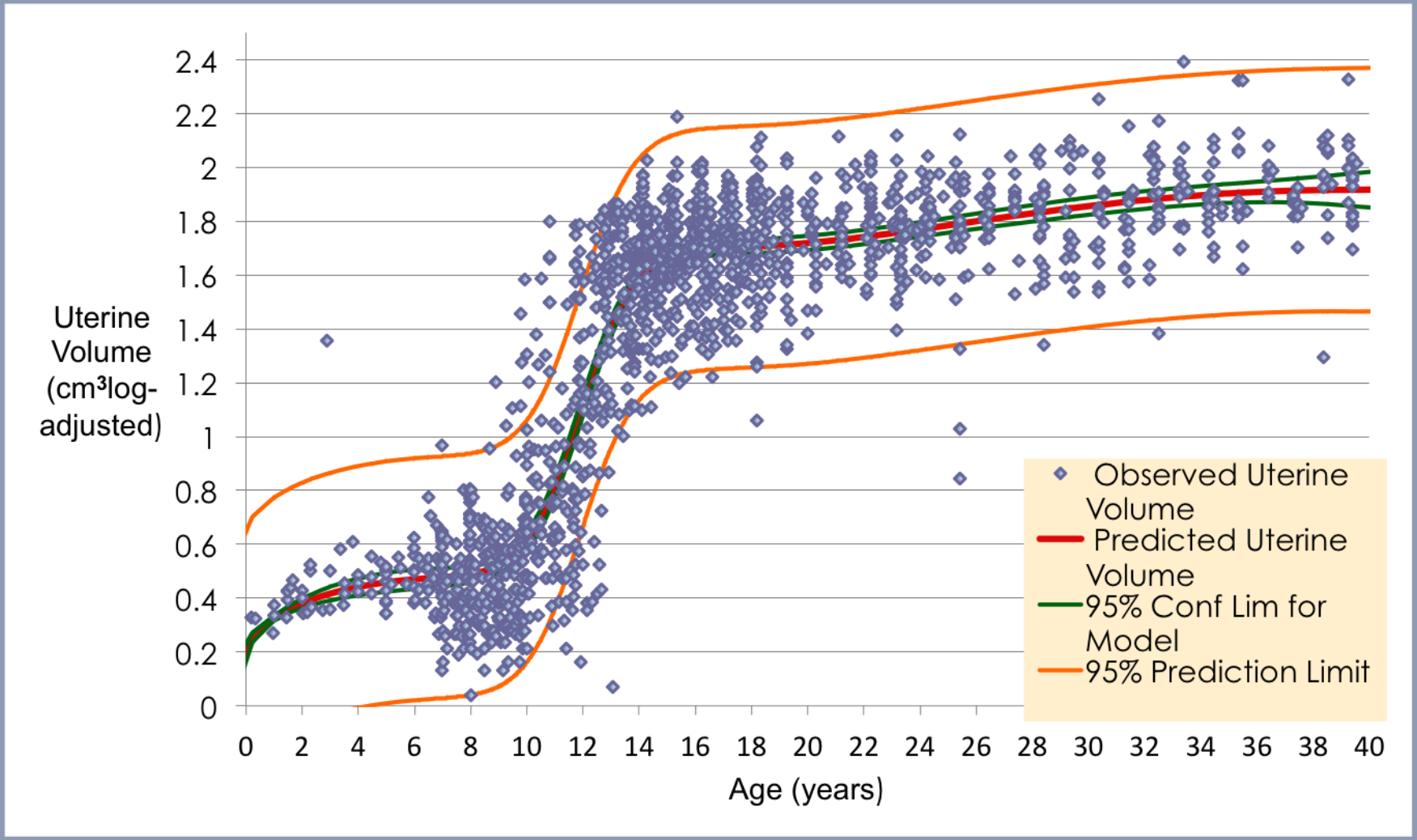
# Thank You

# The Uterus


fallopian tube
Ovary
Endometrium
Myometrium
Perimetrium
Wall of uterus
Cervical canal
Vagina
Cervix

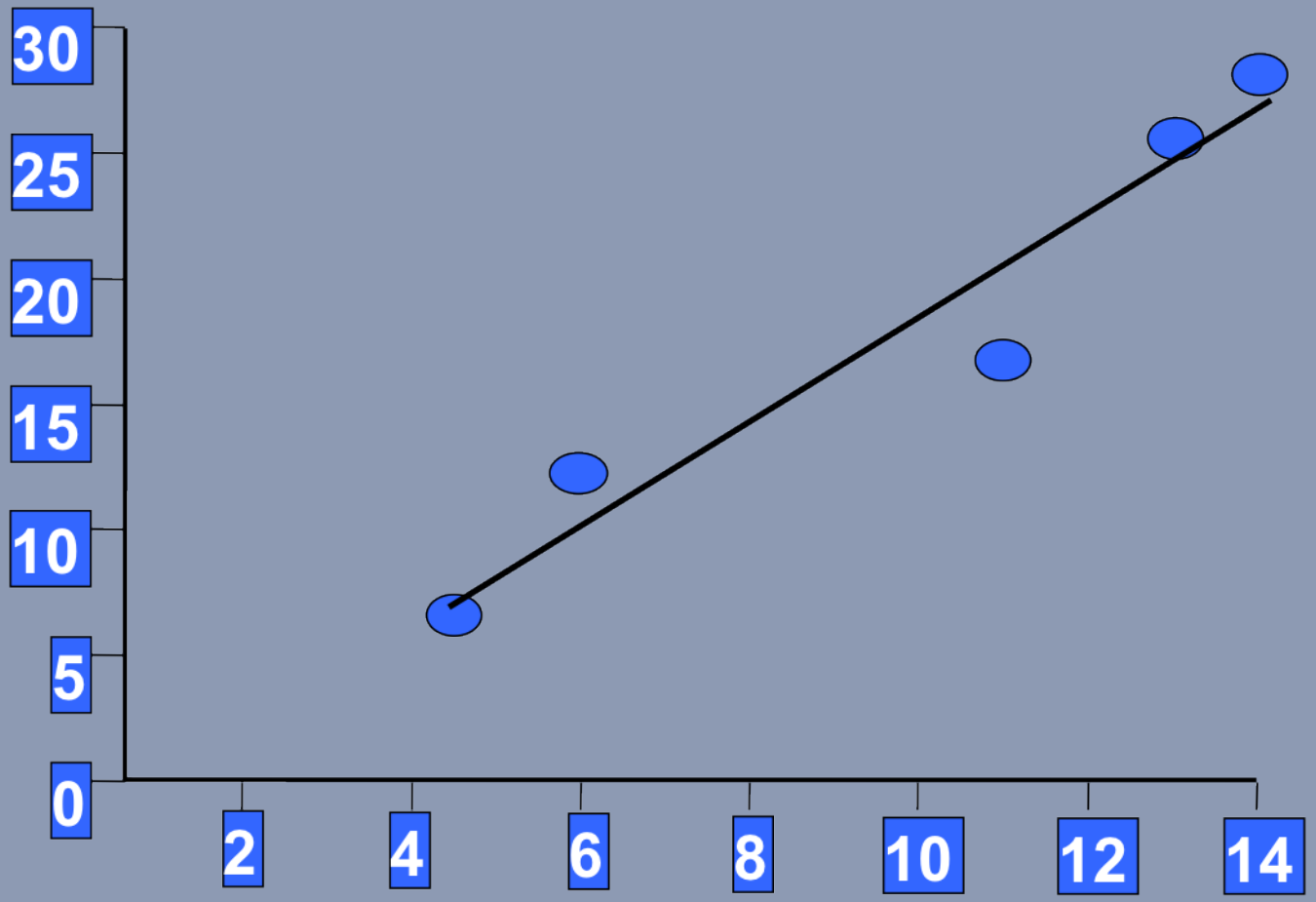

A

# Normative model for uterine volume from birth to 40 years. The $r^2$ is 0.859.




Kelsey et al. unpublished

# Uterine volume and age at irradiation (TBI)




Bath et al. BJOG (1999)

# Uterine function after cancer treatment

No reports of uterine damage due to chemotherapy

Radiotherapy:

Uterine damage, manifest by impaired growth and blood flow.

Uterine volume correlates with age at irradiation.

Exposure of the pelvis to radiation is associated with an increased risk of miscarriage, mid-trimester pregnancy loss, PPH, pre-term birth and low birth weight.

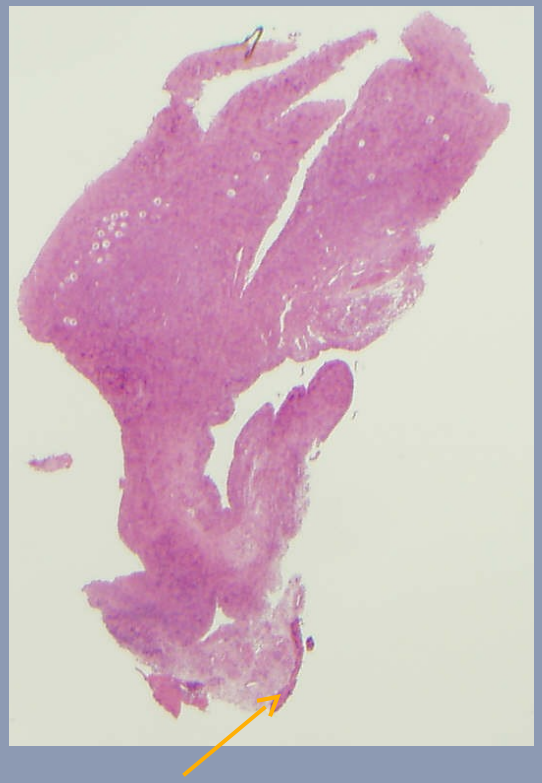
# Reimplantation?

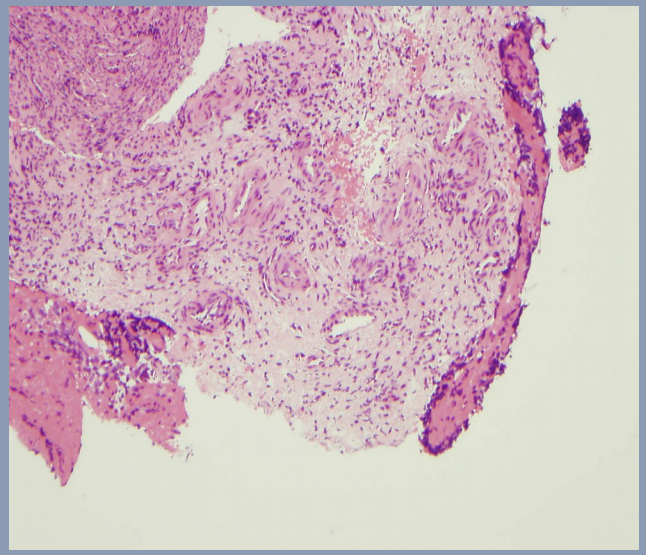
It is important to be aware that reimplantation of ovarian cortical tissue is a separate procedure at a time distant from the treatment of the original cancer

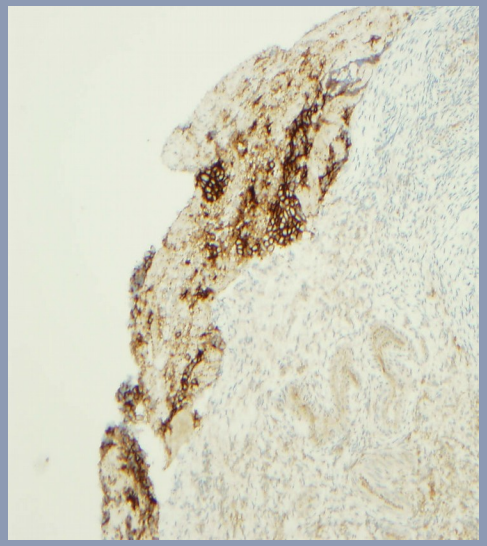
Consent for harvesting ovarian tissue from children often will have been obtained from their parents

Informed consent for reimplantation can be obtained from the patients at a much later date when they are competent to assess the complex issues themselves.

# Ewings sarcoma localised  T 7 Vertebrae (Age 12) – unexpected contamination of ovarian biopsy





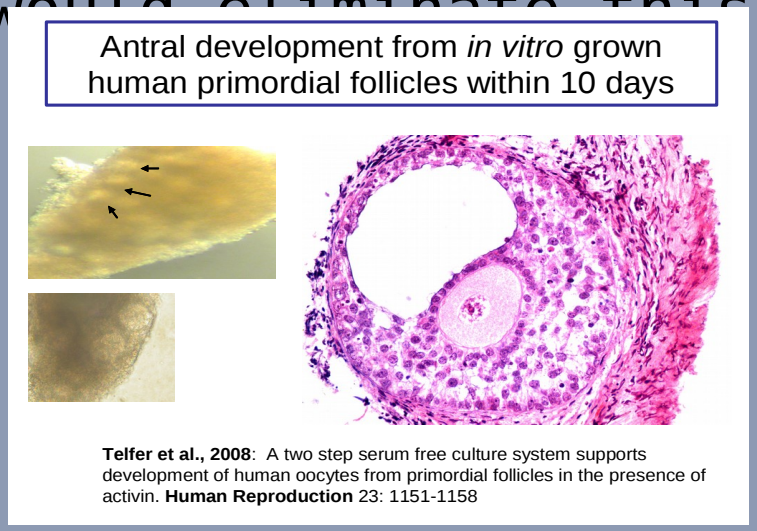


CD99

# Re-implantation or IVG and maturation?

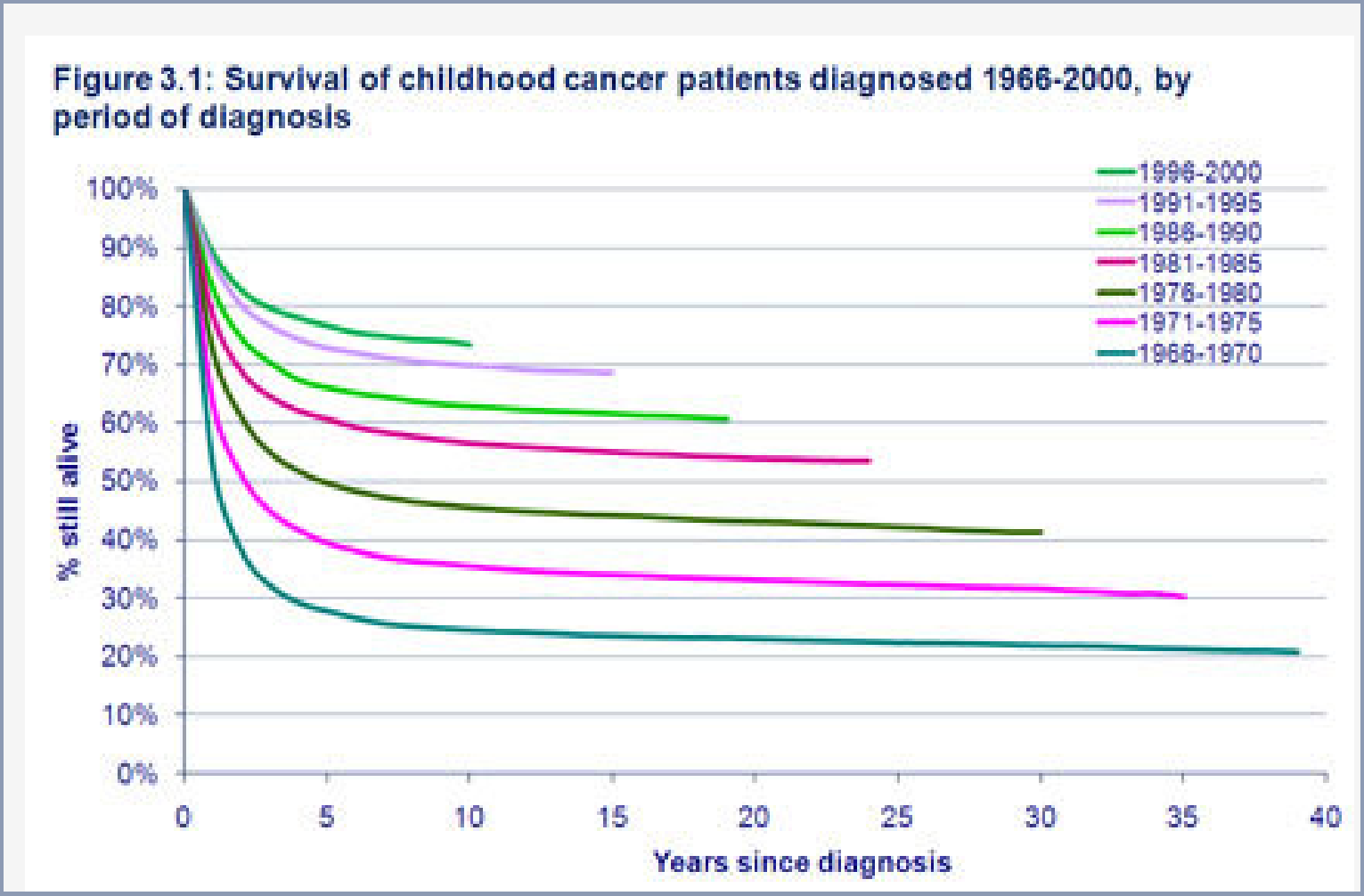
Contamination of the cryopreserved tissue with malignant cells, particularly in haematological malignant disease – shown in a rodent lymphoma model – to cause recrudescence of the original disease

Oocyte maturation in vitro, followed by IVF, would eliminate this risk

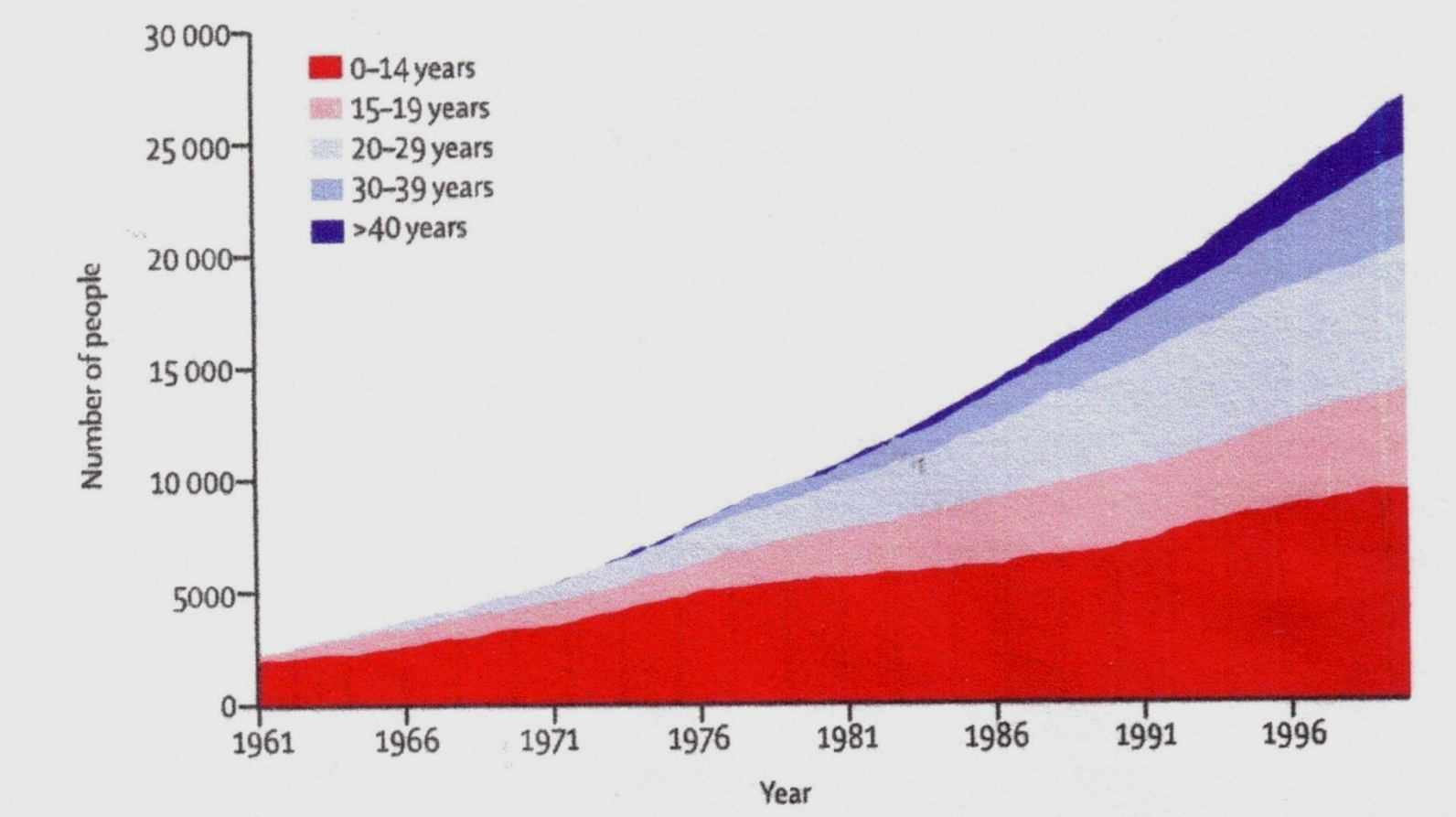



Telfer et al. (2008) Human Reproduction

# Improved Five Year Survival (1966-2000)

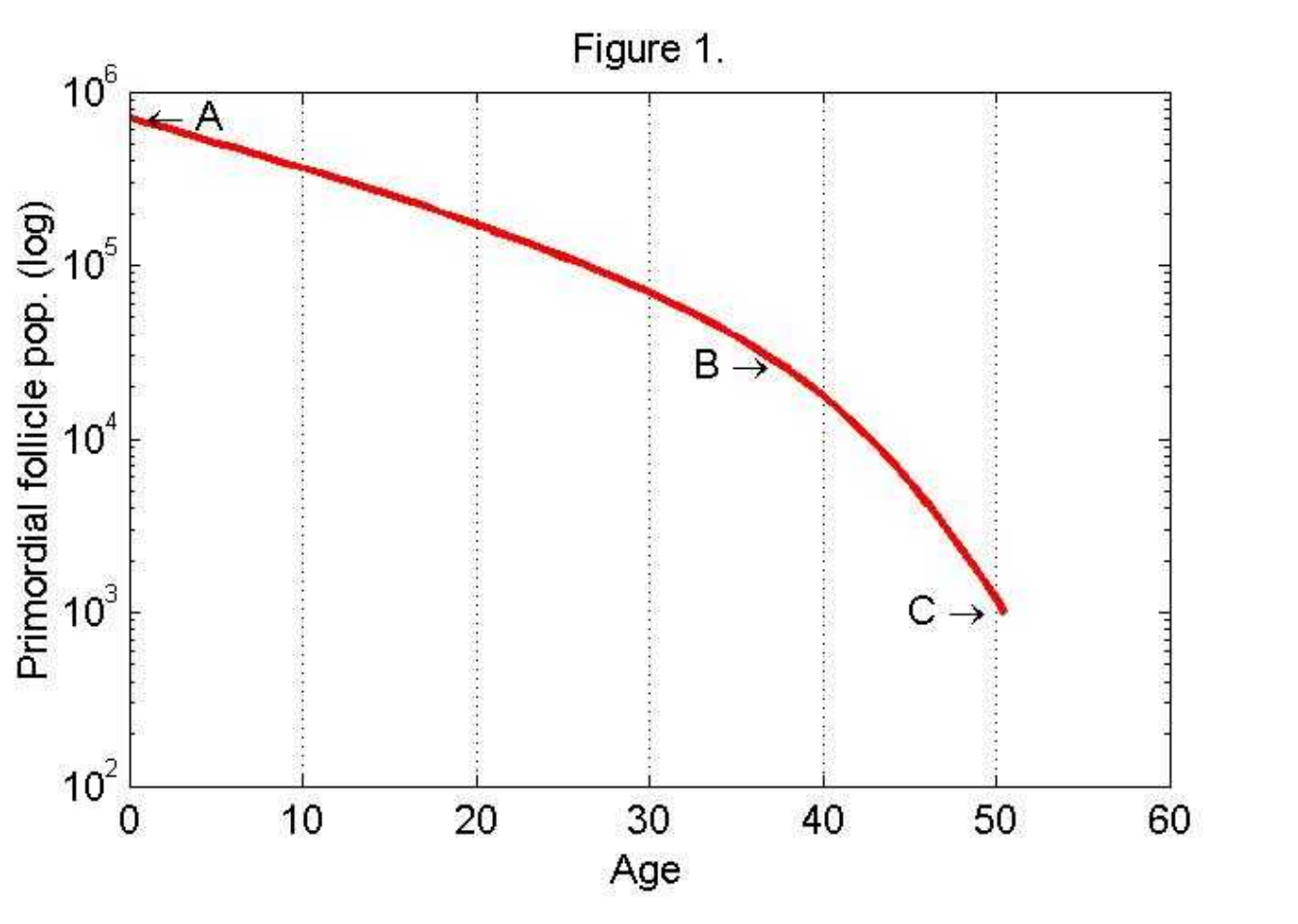


# Increasing numbers of five year UK survivors by current age



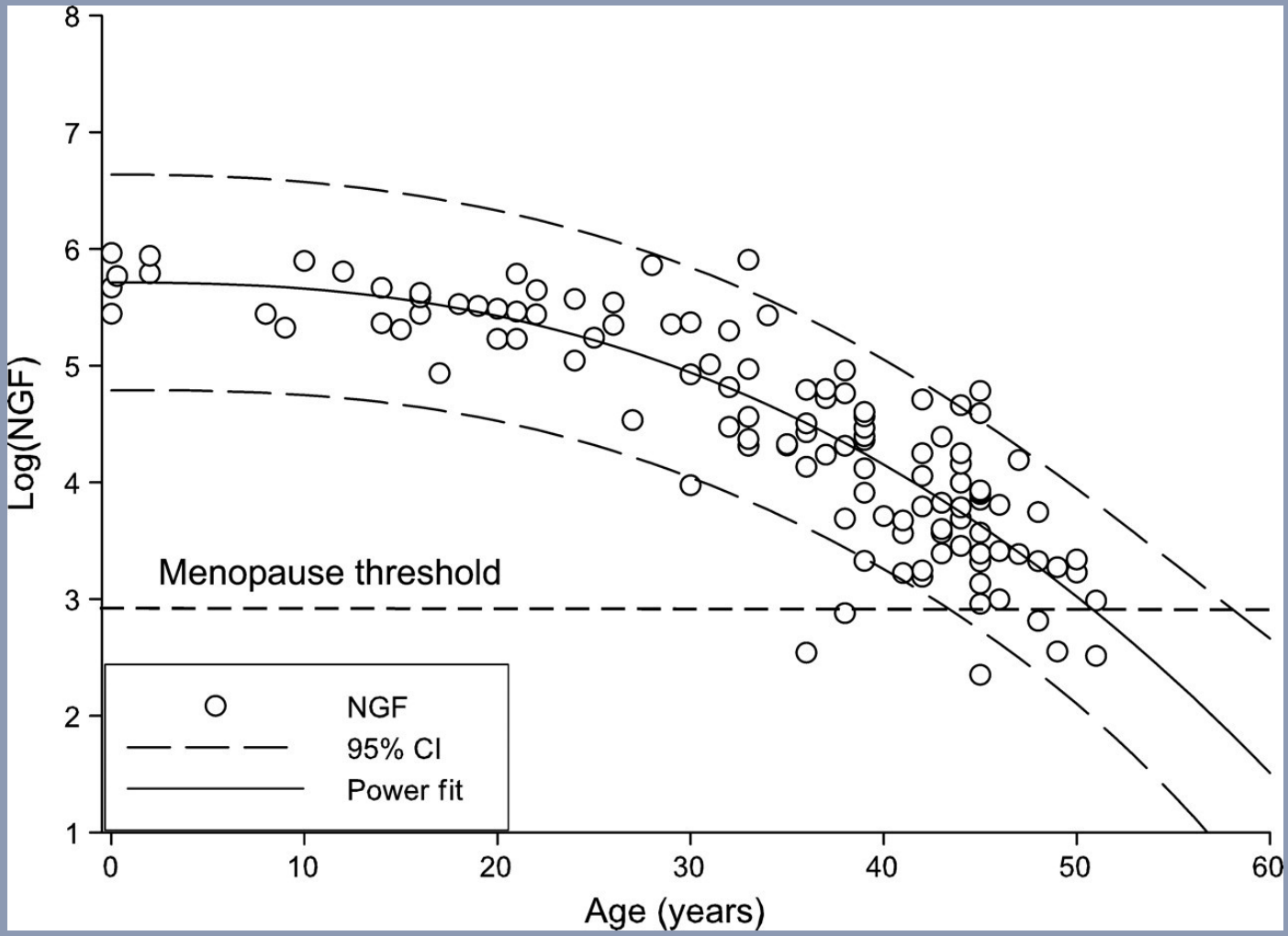

Skinner et al, Lancet Oncology, 2006

# The Faddy-Gosden model of primordial follicle decline (birth-menopause)




Faddy MJ, Gosden RG (1996) A model conforming the decline in follicle numbers to the age of menopause in women. Human Reproduction 11: 1484–1486.

# Power-model of human ovarian NGF decay

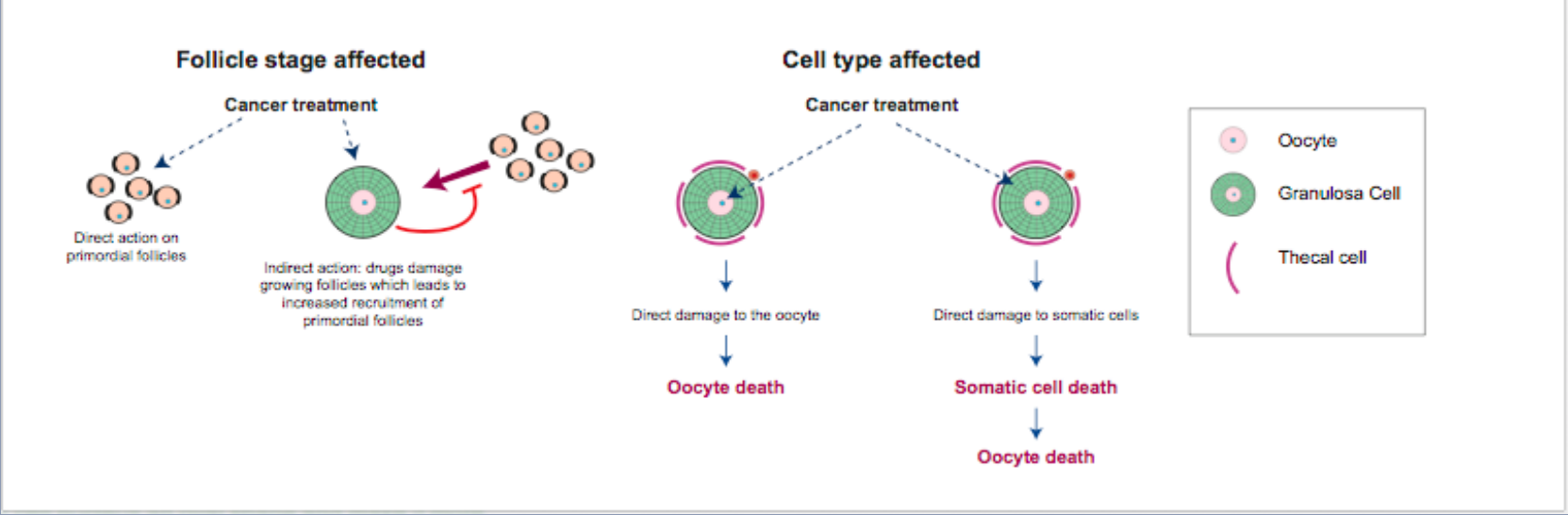



Hansen, K. R. et al. Hum. Reprod. 2008 23:699-708

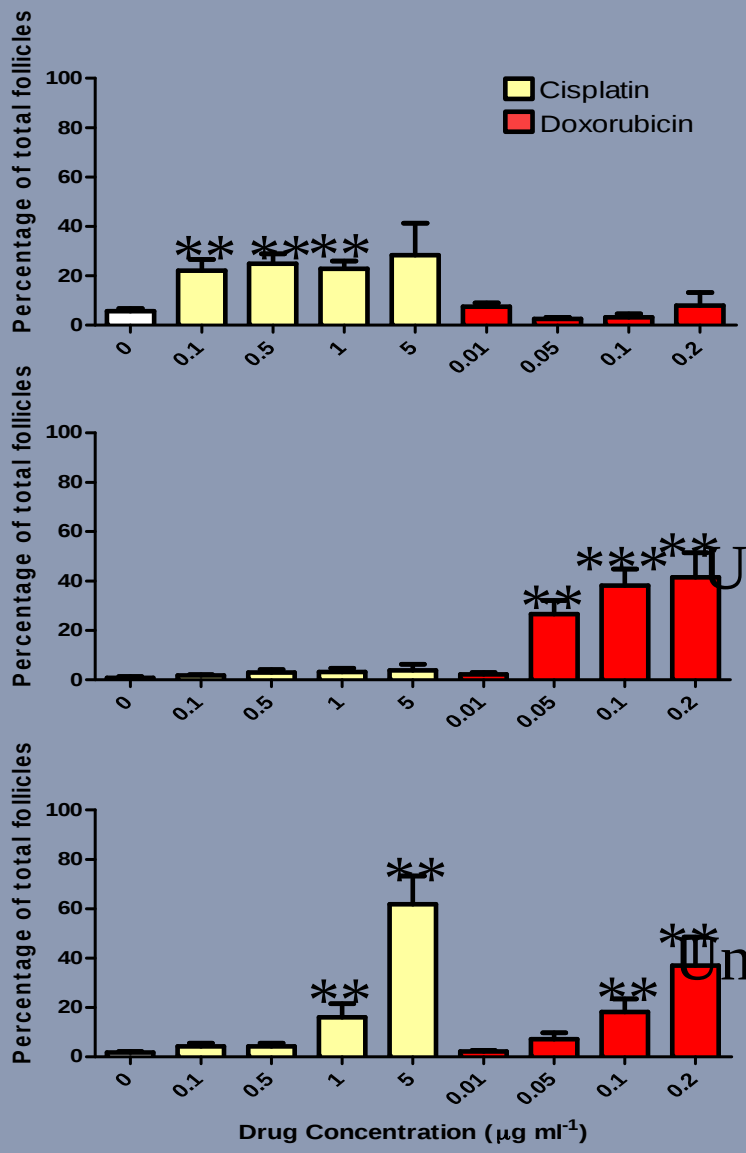
# Oocyte or granulosa cells?

Newborn mouse ovary culture system

Morgan et al. 2013,  PLoS ONE



# Cisplatin and doxorubicin: a mouse ovary culture system




Unhealthy oocytes

Unhealthy granulosa cells

Unhealthy oocytes and granulosa cells

Morgan et al, 2013, PlosOne

# Cisplatin and Doxorubicin (Mouse ovary)

Cisplatin showed oocyte-specific damage

Doxorubicin preferentially caused damage to the granulosa cells

Suggestion:

Imatinib protected the mouse ovary against damage by cisplatin but not doxorubicin

Morgan et al, 2013, PlosOne