

Evaluation of ovarian tissue cryopreservation and transplantation based on Edinburgh Selection Criteria

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The 53rd Annual Meeting of the Japan Society of Clinical Oncology
October 29-31, 2015. Kyoto International Conference Center

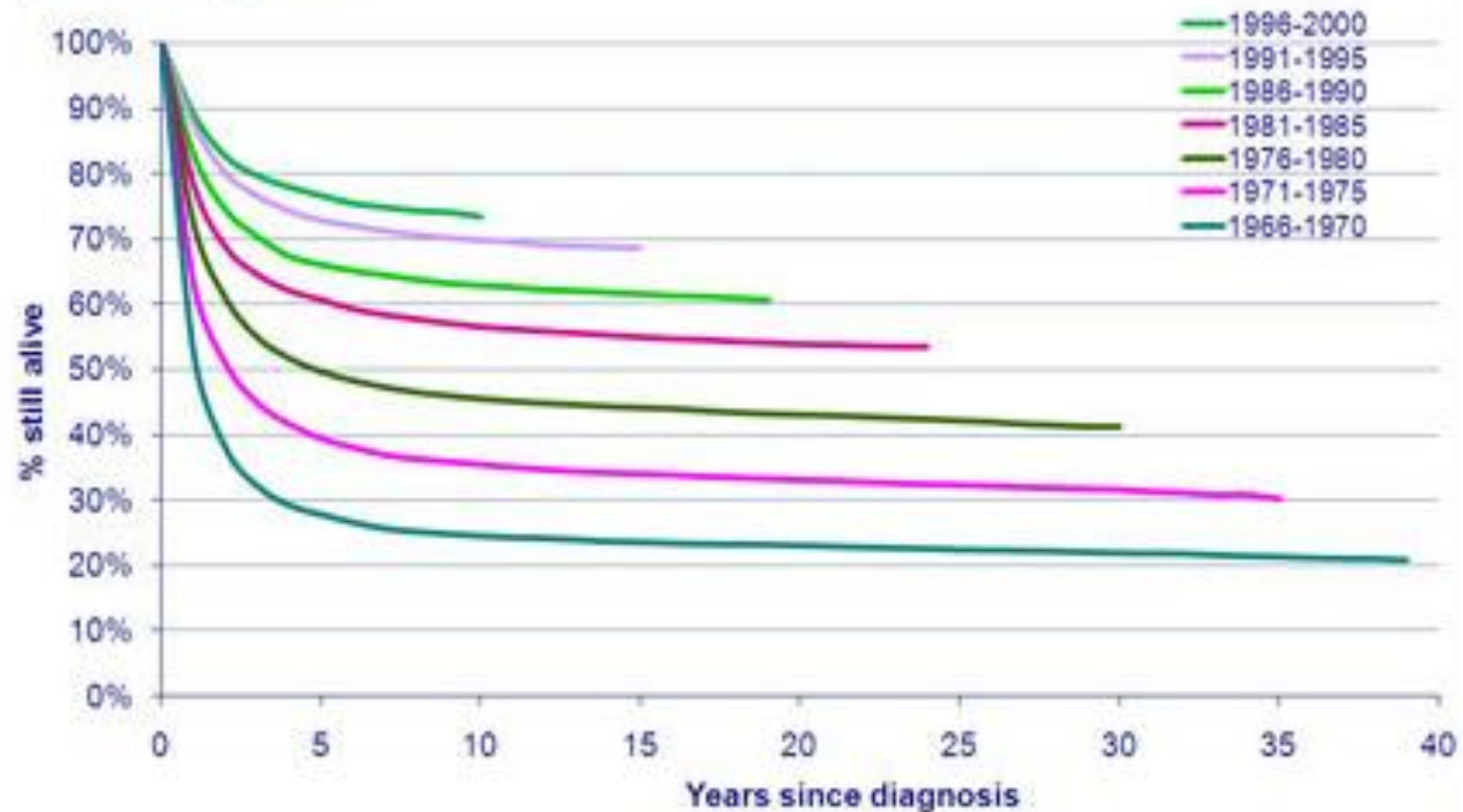
No conflicts of interest to declare



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O maneki itadaki arigatōgozaimasu

Improved Five Year Survival (1966-2000)

Figure 3.1: Survival of childhood cancer patients diagnosed 1966-2000, by period of diagnosis



Panel 1: Intrinsic and extrinsic factors for fertility preservation strategies in children and young adults⁹

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

Risk of infertility

Low risk (<20%)

- Acute lymphoblastic leukaemia
- Soft-tissue sarcoma: stage 1
- Retinoblastoma

- Wilms Tumour
- Germ cell tumours (no radiotherapy)
- Hodgkin lymphoma

Medium risk (20-80%)

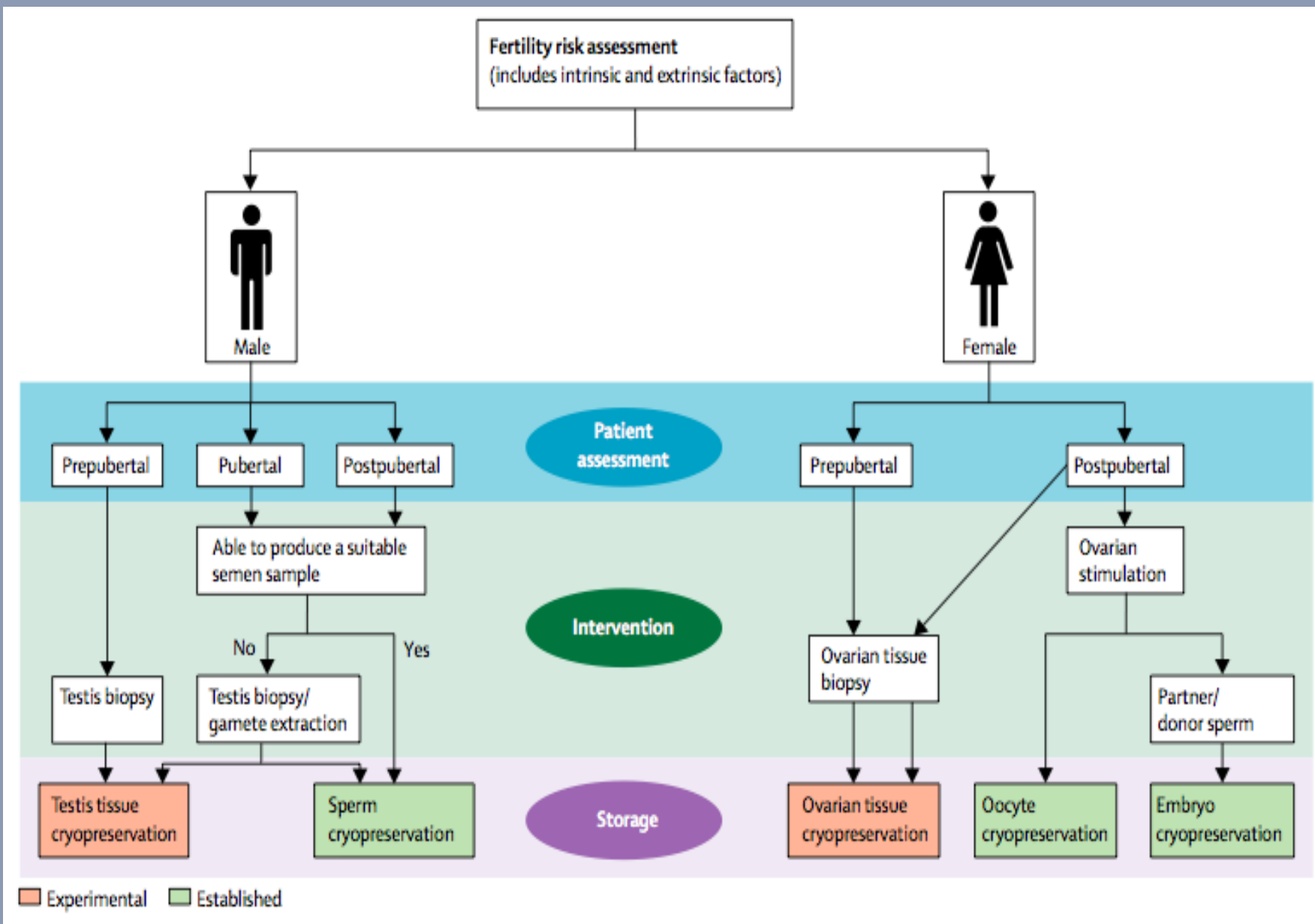
- Acute myeloblastic leukaemia
- Hepatoblastoma
- Osteosarcoma
- Ewing's sarcoma: non metastatic
- Soft tissue sarcoma

- Neuroblastoma
- Non- Hodgkins lymphoma
- Hodgkin lymphoma (Alkylating agents)

High risk (>80%)

- Total body irradiation
- Localised radiotherapy (pelvic/testis)
- Chemotherapy for BMT

- Hodgkin lymphoma (Pelvic RT)
- Soft tissue sarcoma: stage IV (metastatic)
- Ewing's sarcoma: metastatic



Anderson RA...Wallace WH. Lancet Diabetes Endocrinol. 2015

Key features of the 3 options for fertility preservation for women

Technique	Main advantages	Main disadvantages
Embryo cryopreservation	Established technique	May incur delay Sperm required: partner or donor Fixed potential for future fertility
Oocyte cryopreservation	Does not require sperm	May incur delay Not appropriate for pre-pubertal child Limited numbers of eggs can be stored in time available
Ovarian tissue cryopreservation	Minimal delay No lower age limit Allows for spontaneous and repeated conception Greater allowance for future developments	Requires surgical procedure Malignant contamination in some conditions precludes reimplantation In vitro follicle growth unlikely to be available for several years.

Ovarian tissue cryopreservation: World-wide experience

At least 60 pregnancies worldwide after orthotopic reimplantation of frozen-thawed ovarian cortex

Success rate is unclear as the denominator is unknown

No pregnancies reported following the reimplantation of ovarian tissue harvested pre-pubertally

Young children are potentially ideal candidates

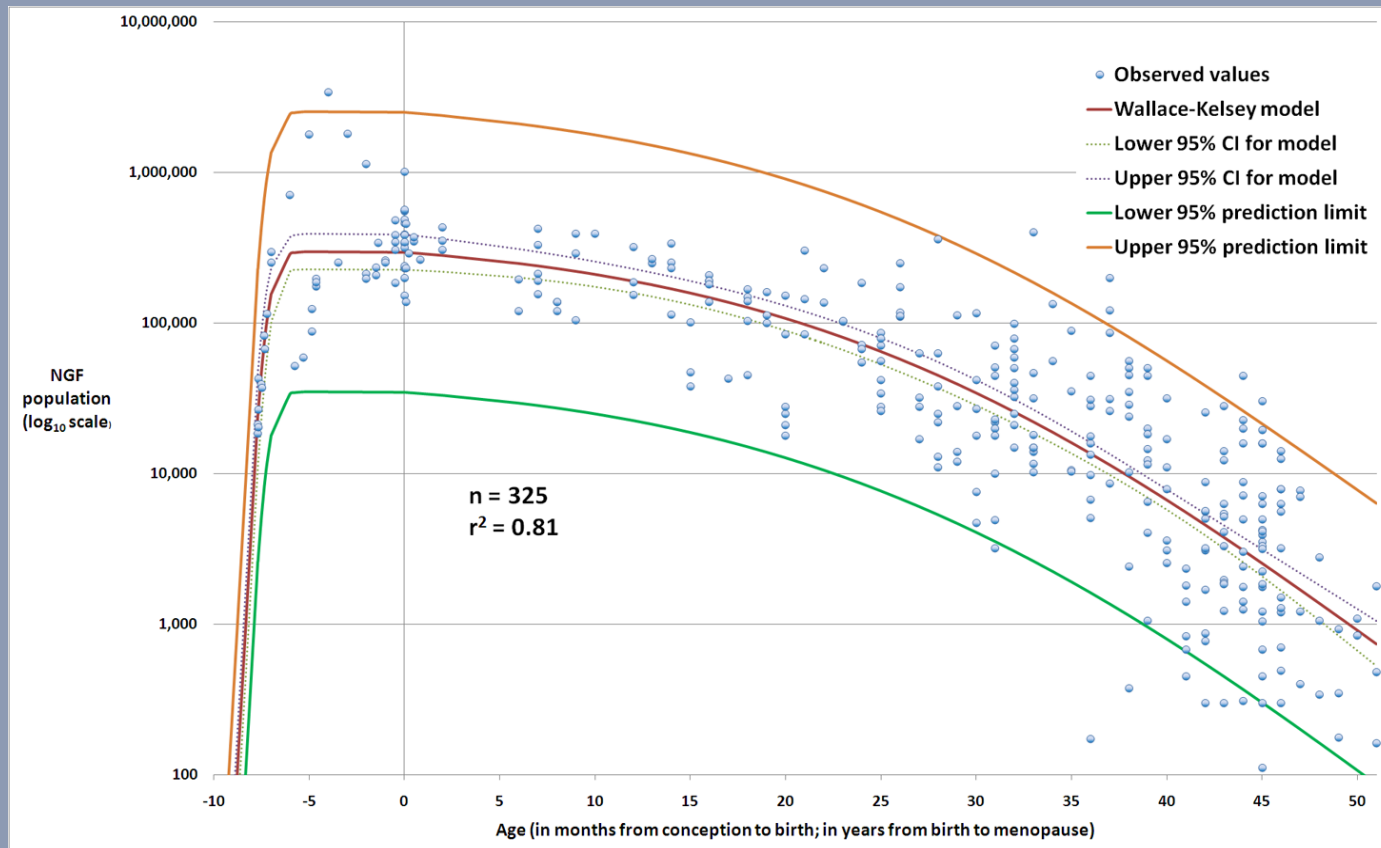


Ovarian Reserve?



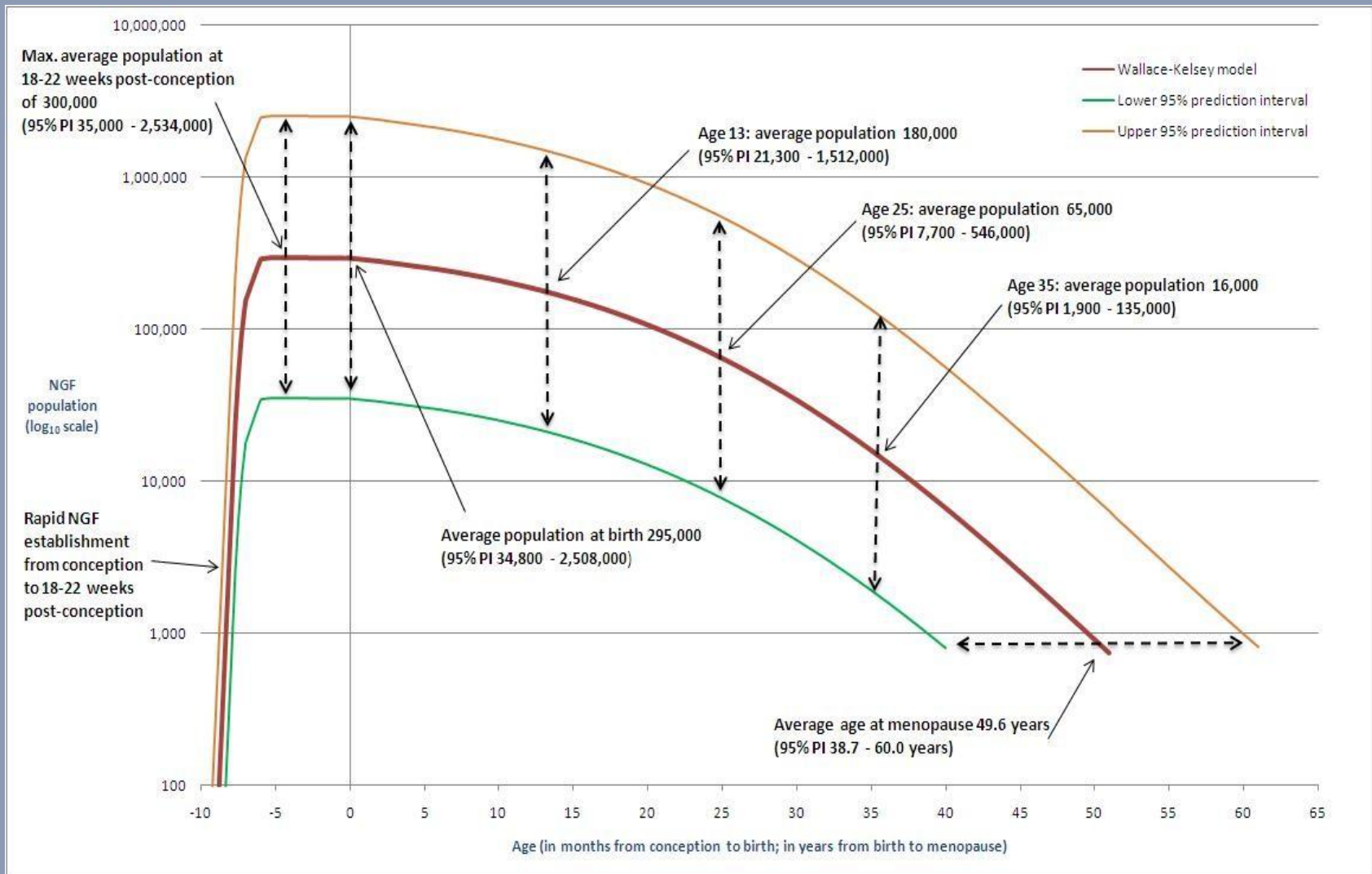
The Wallace-Kelsey Model

(Five parameter asymmetric double-Gaussian cumulative curve)

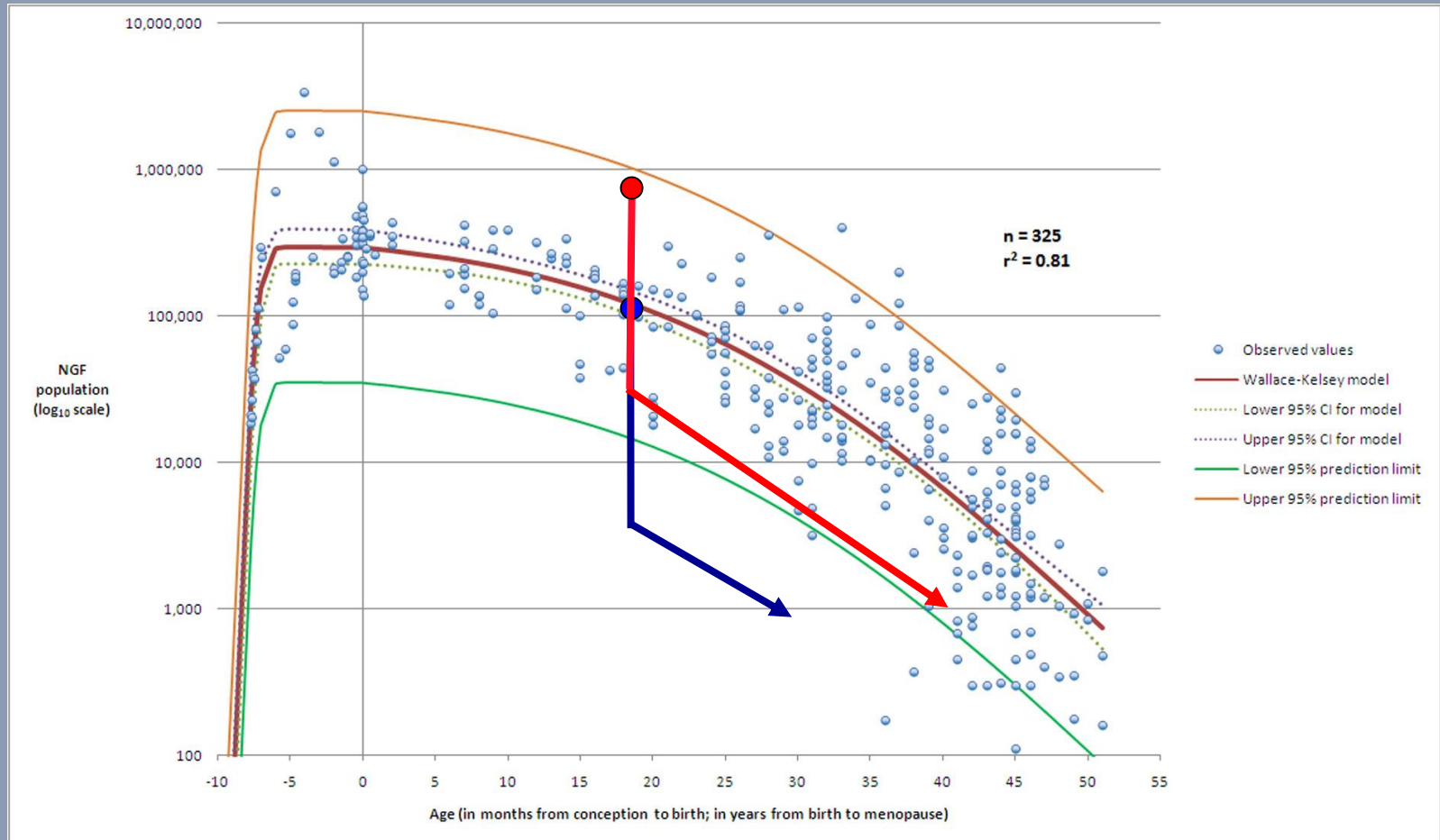


$$\log_{10}(y) = \frac{a}{4} \left[1 + \operatorname{Erf} \left(\frac{x+b+\frac{c}{2}}{d\sqrt{2}} \right) \right] \left[1 - \operatorname{Erf} \left(\frac{x+b-\frac{c}{2}}{e\sqrt{2}} \right) \right]$$

Ovarian reserve: Conception to Menopause



Current model of follicular depletion

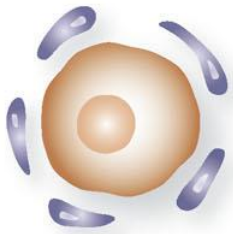


AMH reflects the number of small growing follicles

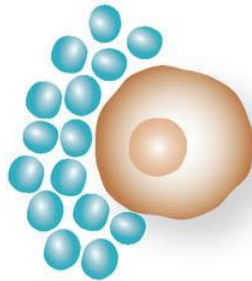
AMH

Inhibin B, estradiol

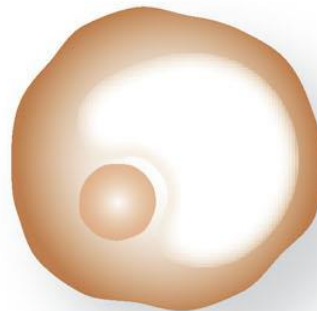
Primordial



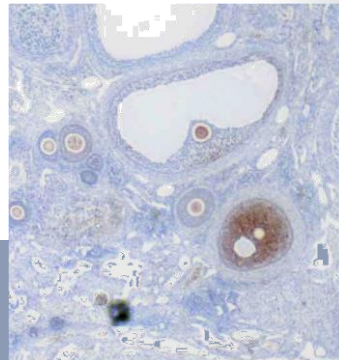
Preantral



Antral



Preovulatory



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

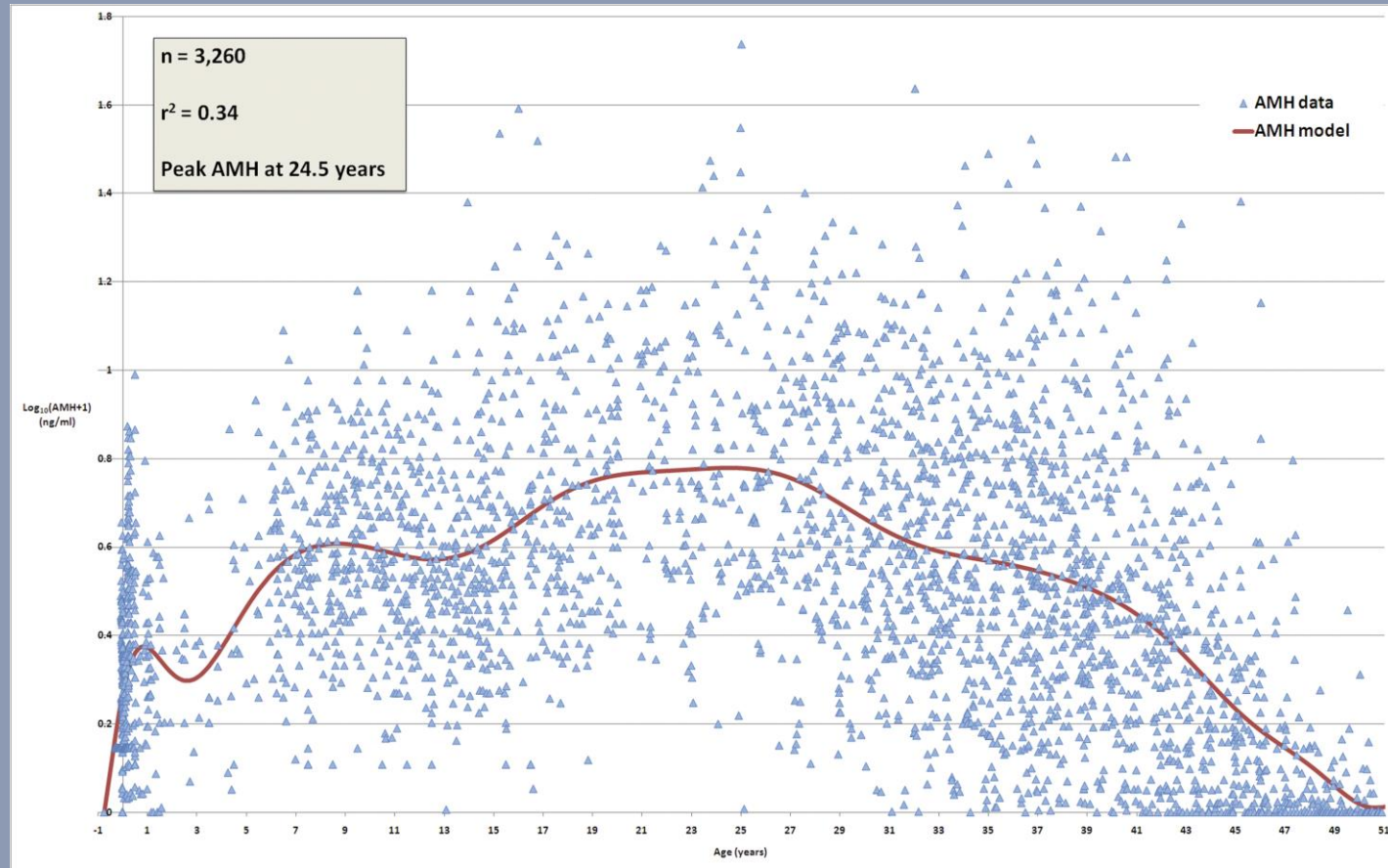
AMH has little variation across and between menstrual cycles

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

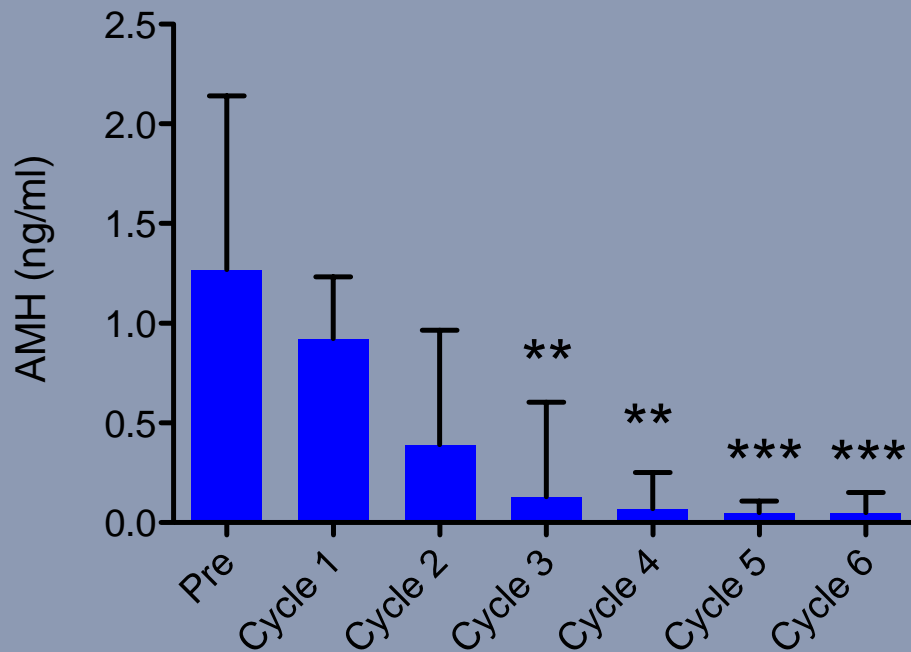
But there was no validated reference model for AMH available

Anderson, Nelson, Wallace (2011) Maturitas

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

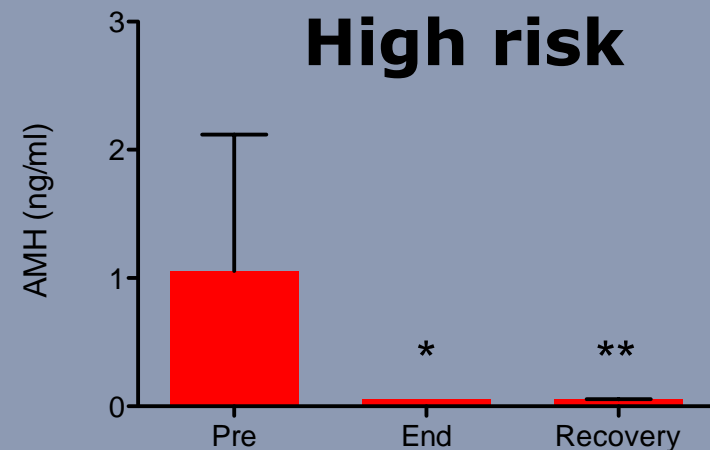
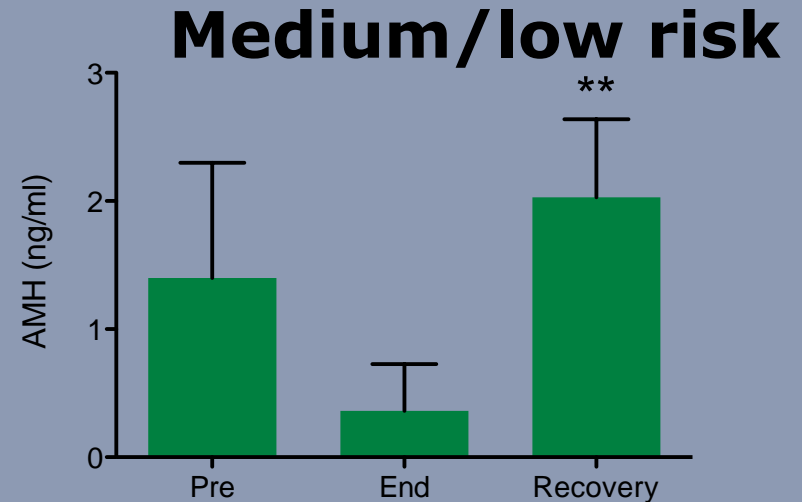


AMH in childhood cancer

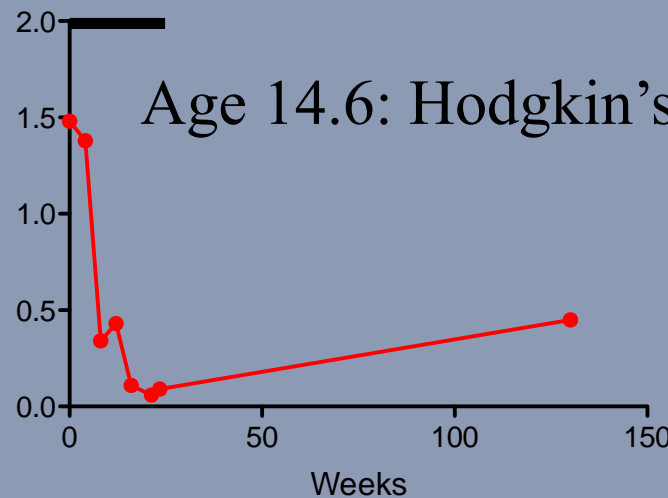
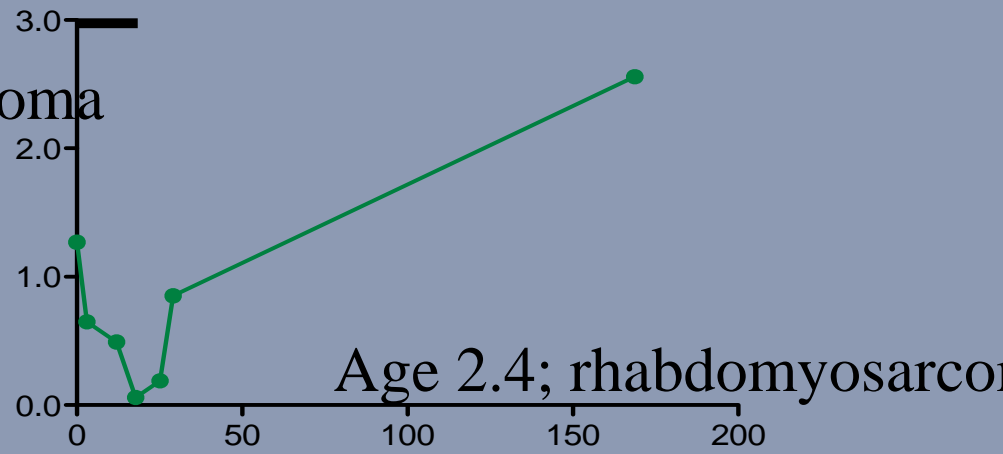
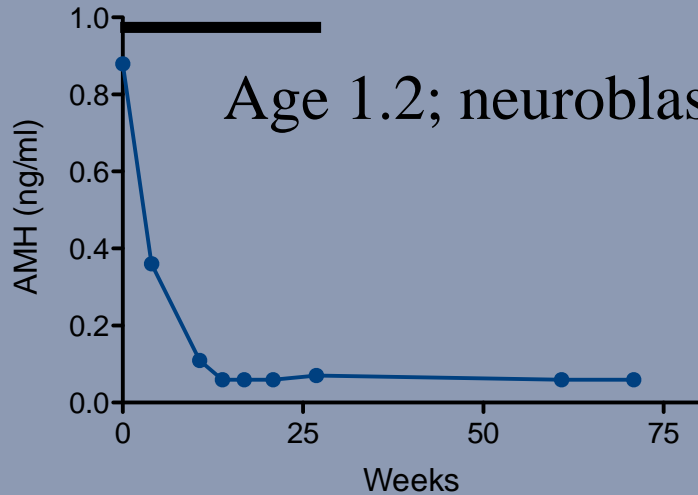


22 girls age 0.3-15yr
17 prepubertal

Brougham et al 2012 JCE&M



AMH in 3 girls with cancer



Summary

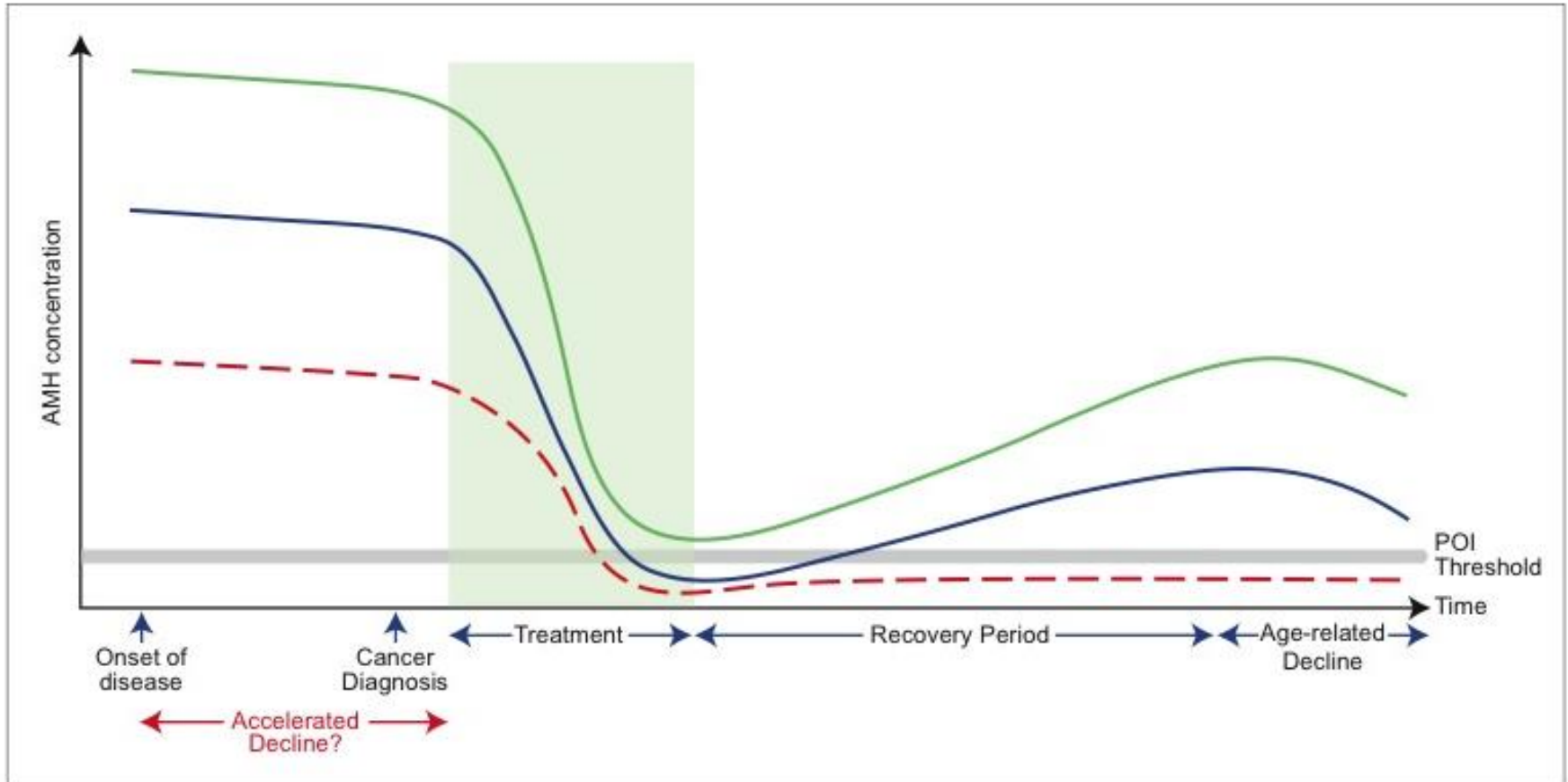
AMH is detectable before puberty

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

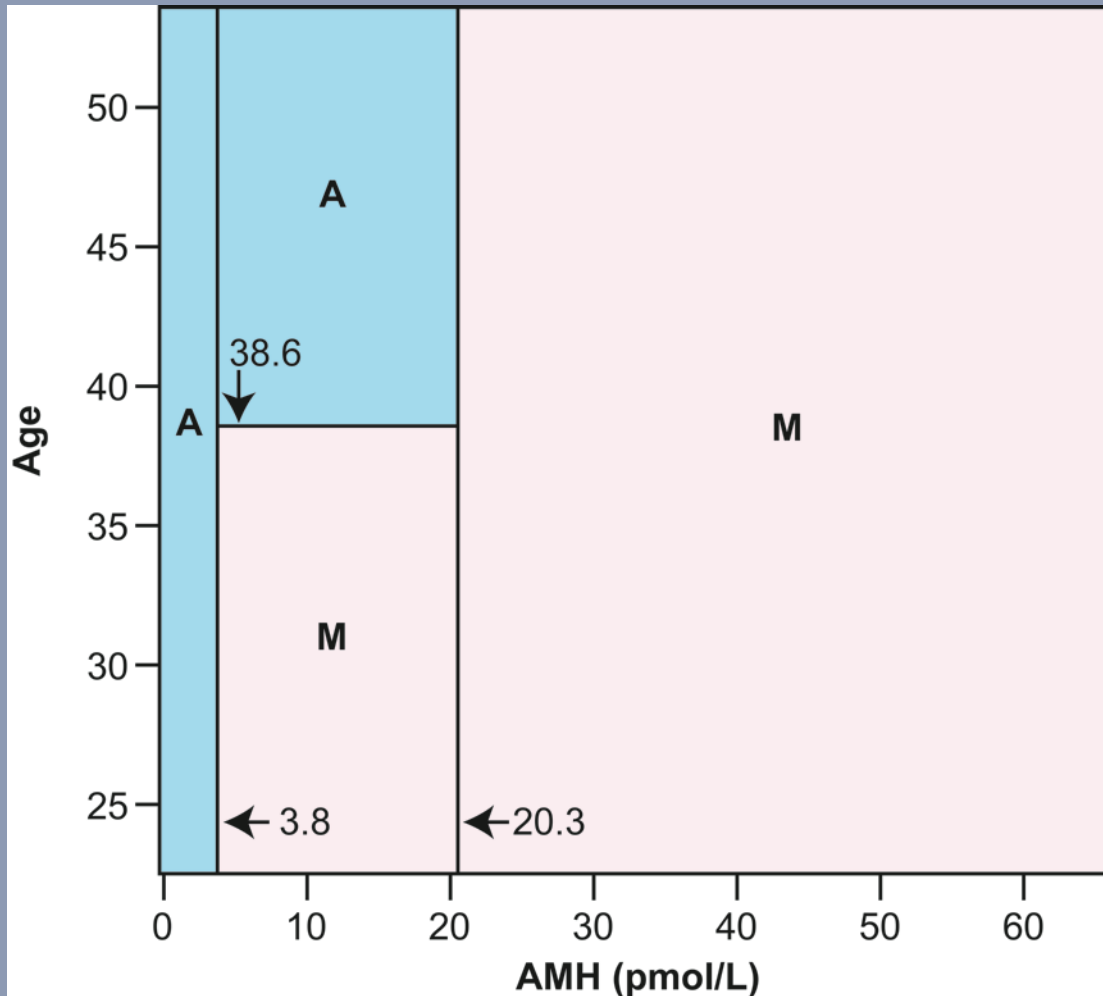
AMH levels recover in those patients at low/medium risk of gonadotoxicity

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

AMH profiles in the oncology patient



Pretreatment anti-Müllerian hormone predicts for loss of ovarian function after chemotherapy for early breast cancer.



sensitivity 98.2%
specificity 80.0%
for correct classification of
amenorrhoea

n=75

Fertility preservation for girls and young women with cancer: population-based validation of criteria for ovarian tissue cryopreservation

W Hamish B Wallace, Alice Grove Smith, Thomas W Kelsey, Angela E Edgar, Richard A Anderson

Lancet Oncol 2014; 15: 1129-36



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 patients¹¹²

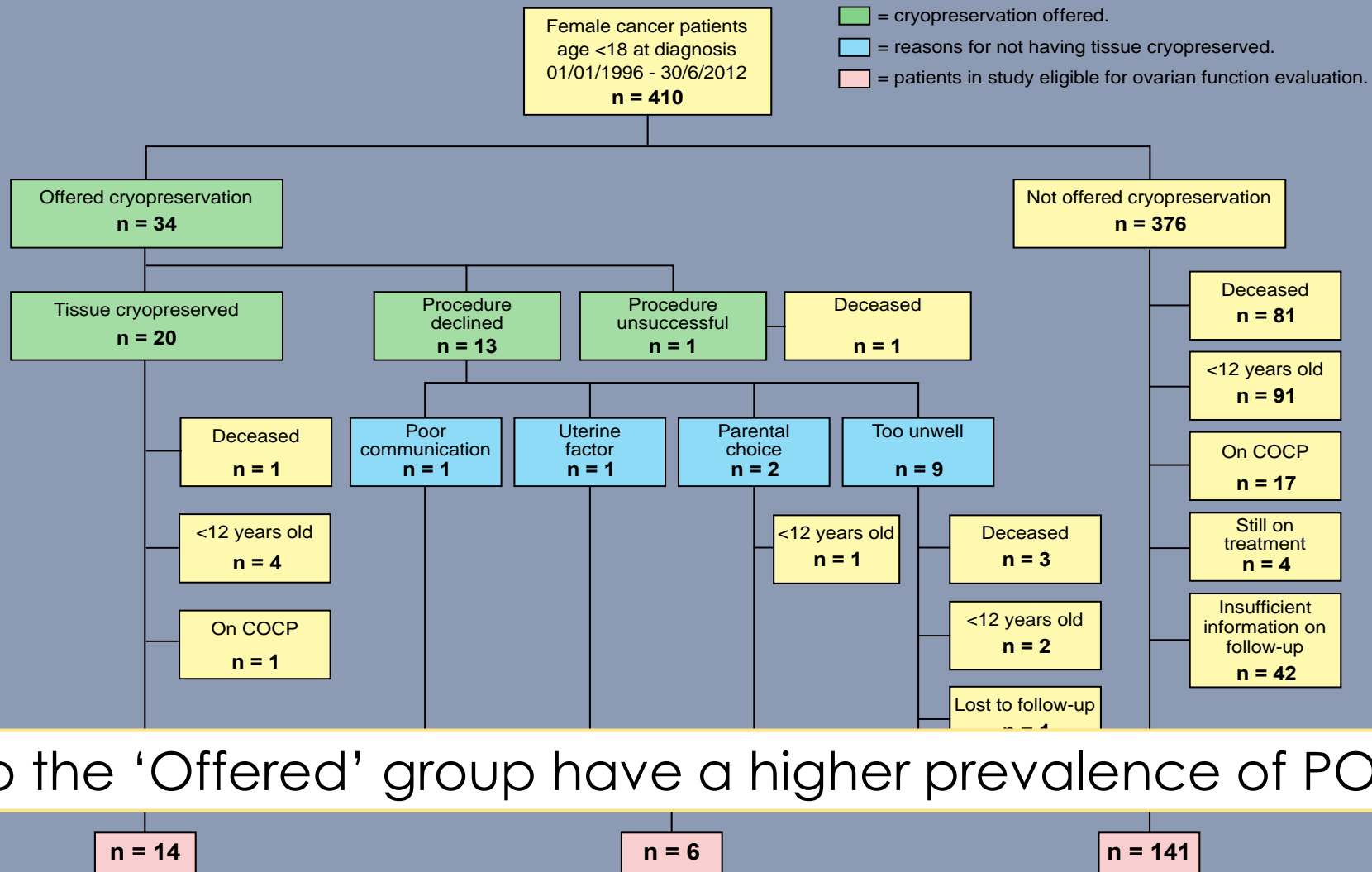
- Age younger than 35 years
- No previous chemotherapy or radiotherapy if aged 15 years or older at diagnosis, but mild, non-gonadotoxic chemotherapy is acceptable if younger than 15 years
- A realistic chance of 5-year survival
- A high risk of premature ovarian insufficiency (>50%)
- Informed consent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

Male patients

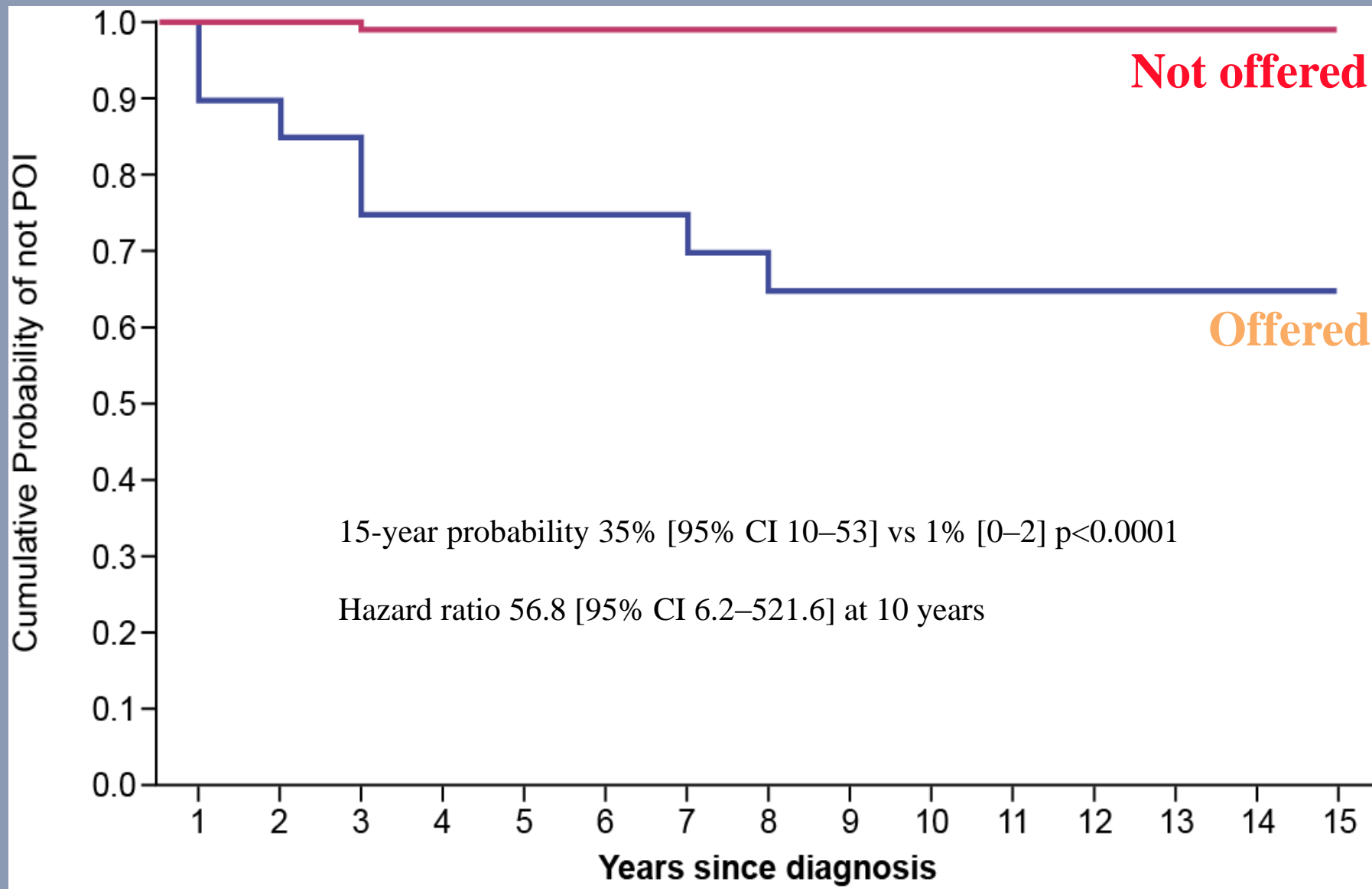
- Age 0–16 years
- A high risk of infertility (>80%)
- Unable to produce a semen sample by masturbation
- No clinically significant pre-existing testicular disease (eg, cryptorchidism)
- Informed consent (parent and, when possible, patient)
- Negative HIV, syphilis, and hepatitis serology

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 ^f	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 ^g	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 ^f	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 ^f	None	1.0	13.4	Not POI
20	Wilms' Tumour	1.2	Oophorectomy	None	0.6		Not assessed

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



Cumulative incidence of POI



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

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

Edinburgh Fertility Preservation



www.ed.ac.uk/Edinburgh-fertility-preservation



@edinfertility

Acknowledgements



Richard Anderson

David T Baird

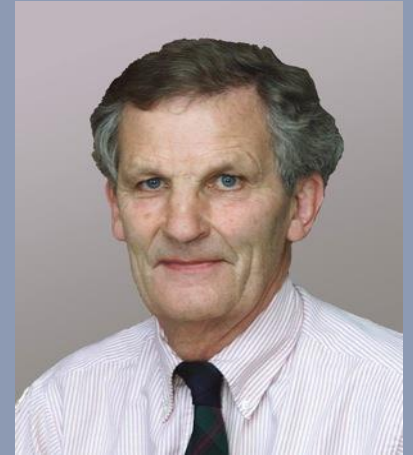
Tom Kelsey

Evelyn Telfer

Marie McLaughlan

Alice Grove Smith

George Galea



Rod Mitchell

Louise Bath

Chris Kelnar

Angela Edgar

Mark Brougham

Fraser Munro



どうもありがとうございます
Domo arigatou gozaimasu

