Predicting and preserving Ovarian function for the young female with cancer

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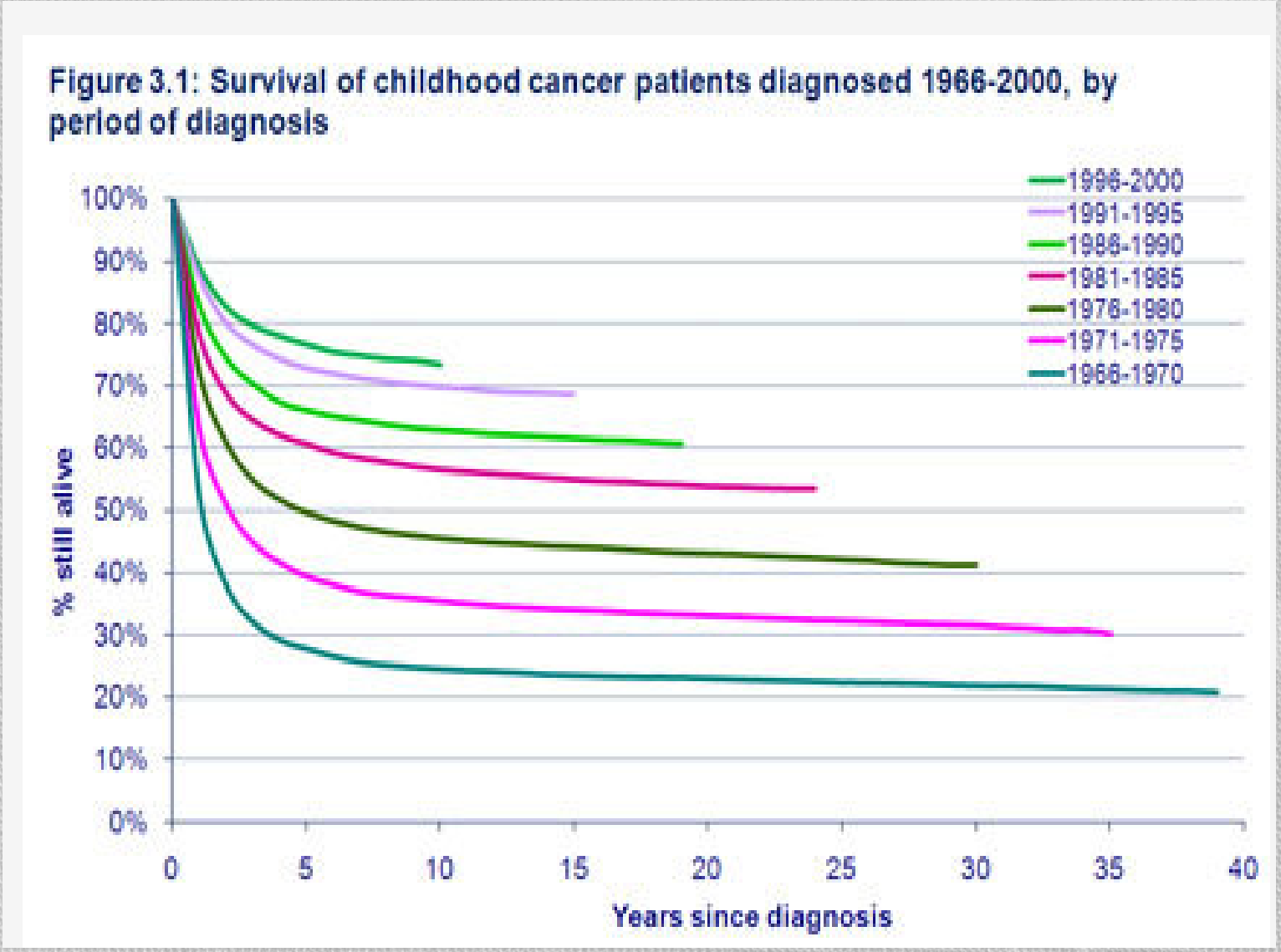
Late Effects in Cancer Survivors
5th Biennial Sheffield meeting
12-13 June 2014

No Conflicts of Interest to Declare

Improved Five Year Survival (1966-2000)



Risk assessment for fertility preservation

- Intrinsic factors
  - Health status of patient
  - Consent (Patient/Parent)
  - Assessment of ovarian reserve (Females)
  - Assessment of pubertal status (Males)
- Extrinsic factors
  - Nature of predicted treatment
    - High/Medium/Low/Uncertain Risk
  - Time available
  - Expertise available

Wallace WH et al. JCO, 2012

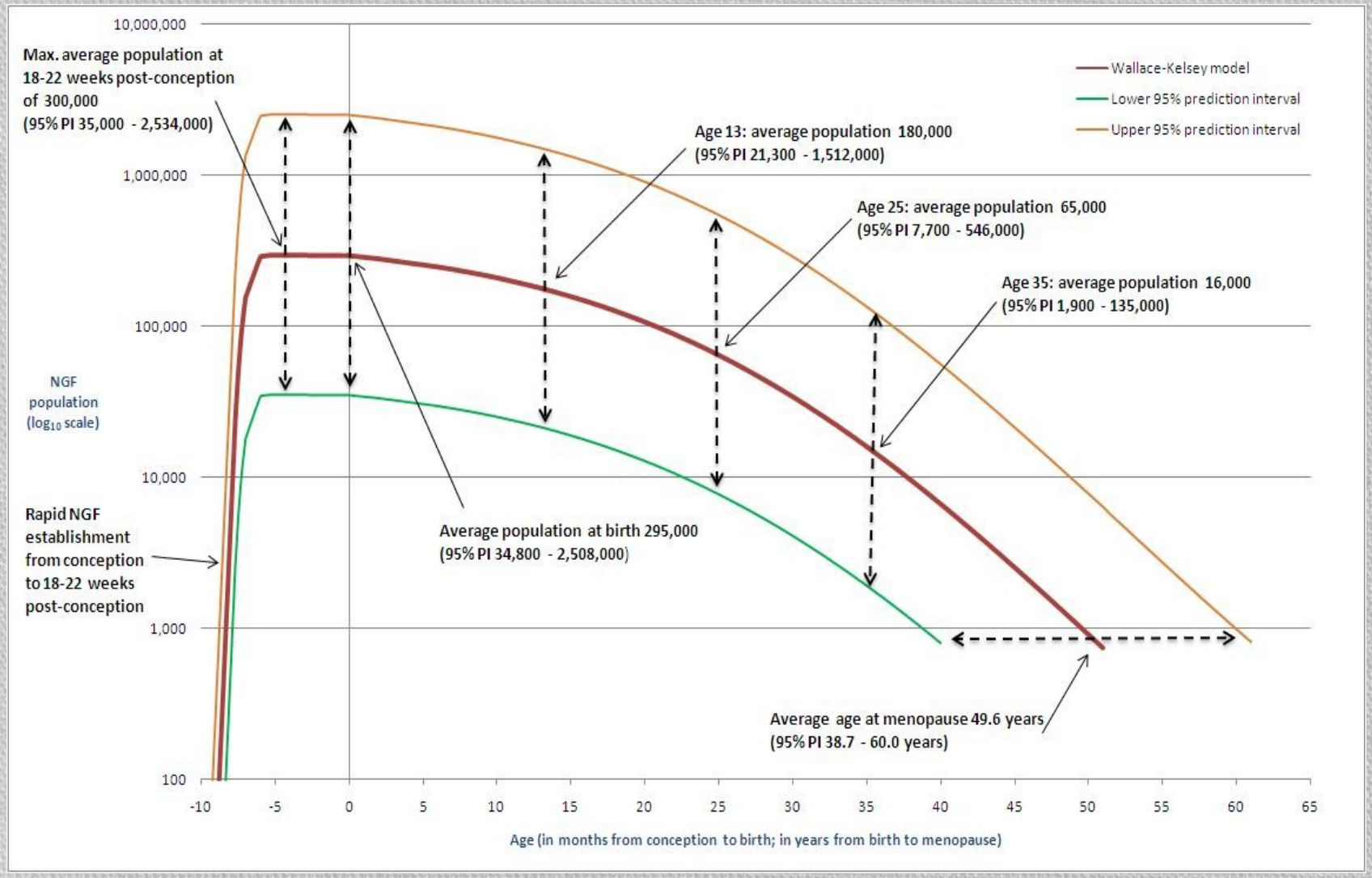
Risk of infertility

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

Wallace et al., The Lancet Oncology, 2005

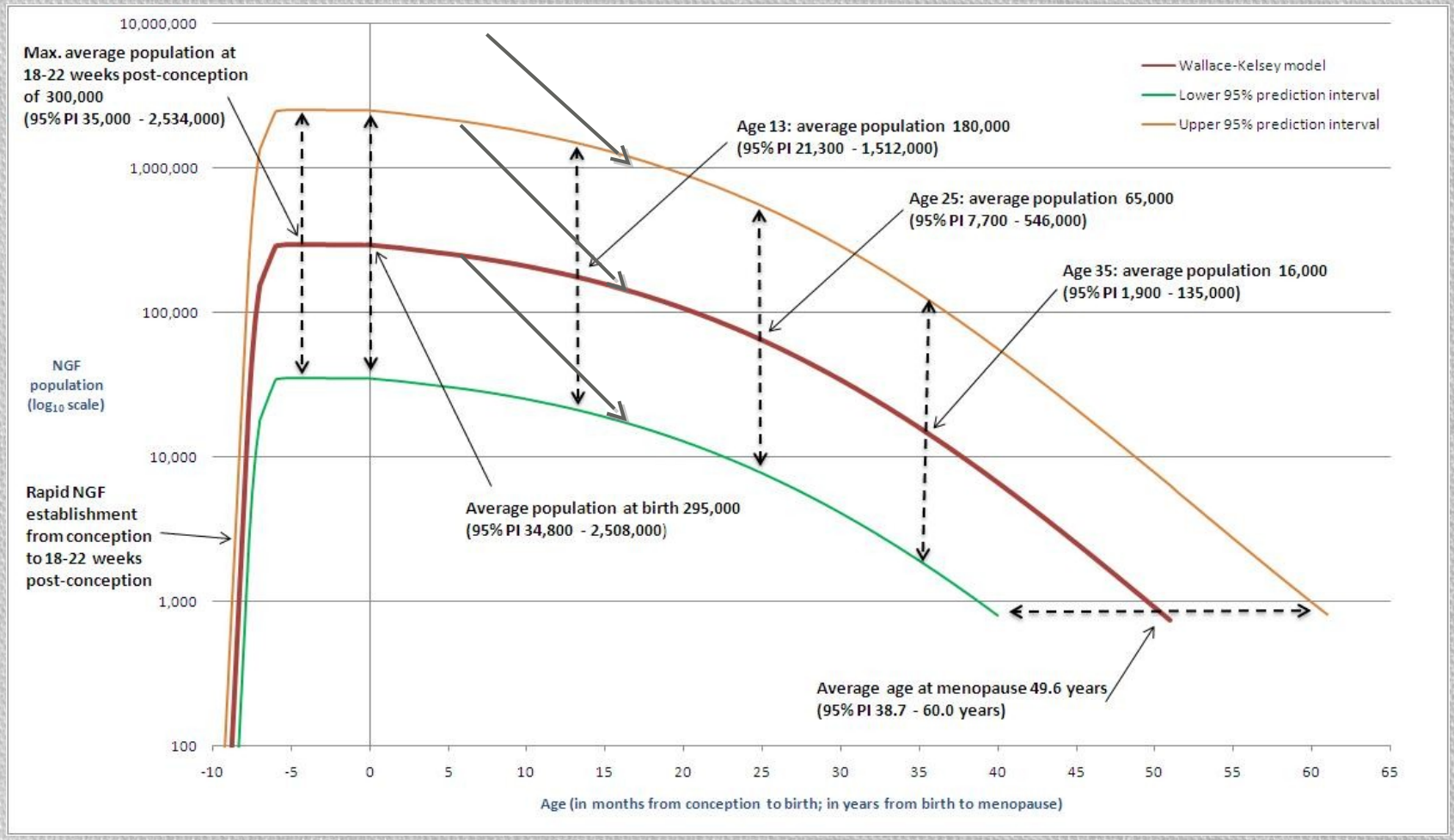
Ovarian Reserve?

Ovarian reserve: Conception to Menopause



Wallace & Kelsey (2010) PloS ONE

Ovarian reserve:
A Validated model from Conception to Menopause (NGF population)



Wallace &Kelsey (2010) PloS ONE

Prediction of Ovarian Reserve (AMH)

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

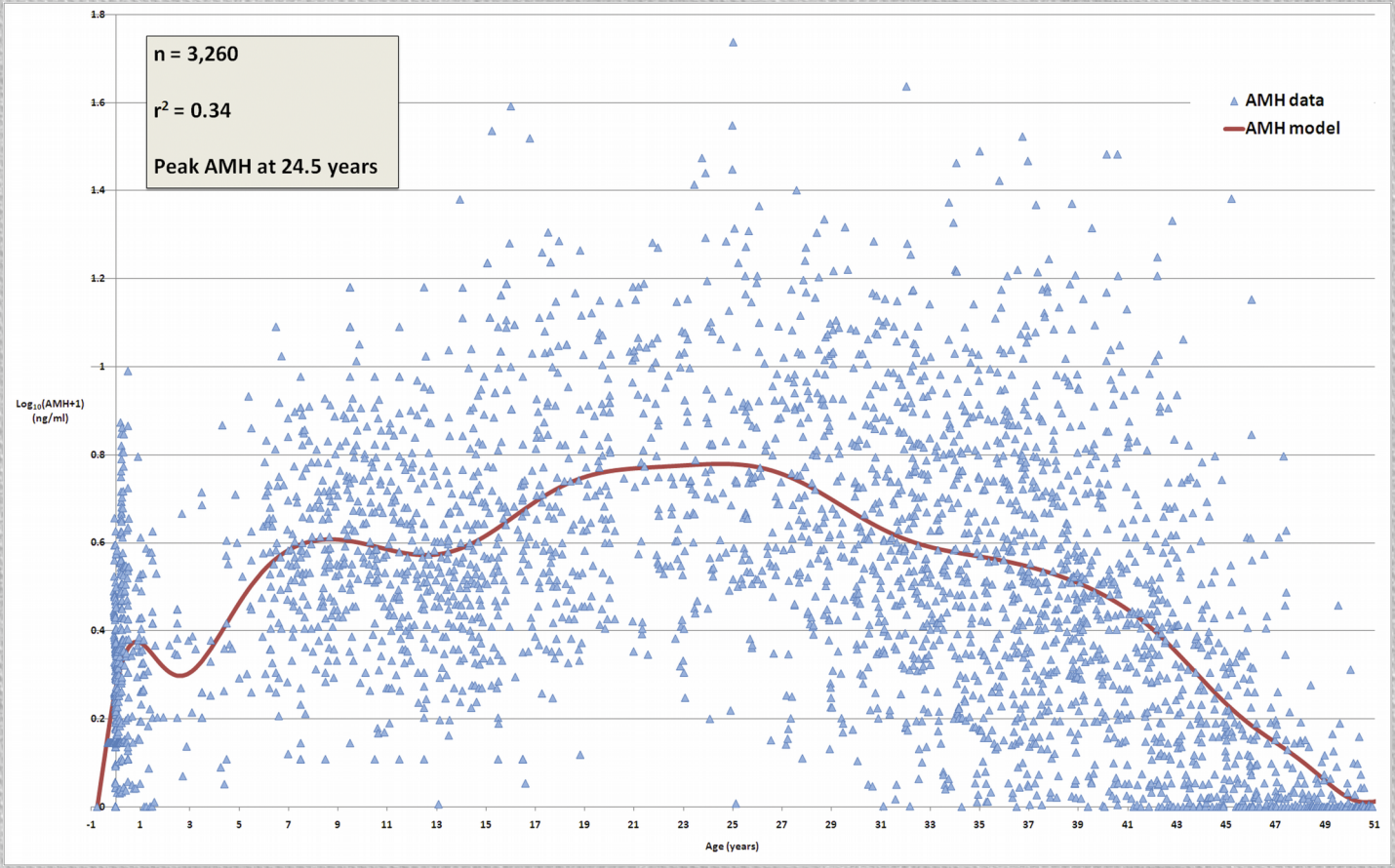
MH has little variation across and between menstrual cycles

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

ut there was no validated reference model for AMH available

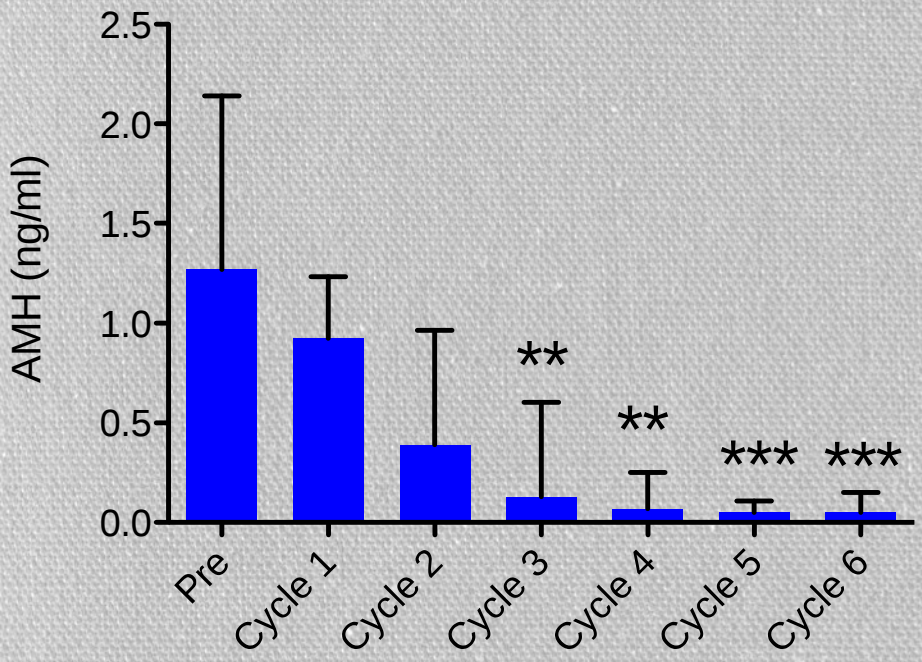
Anderson, Nelson, Wallace (2011) Maturitas

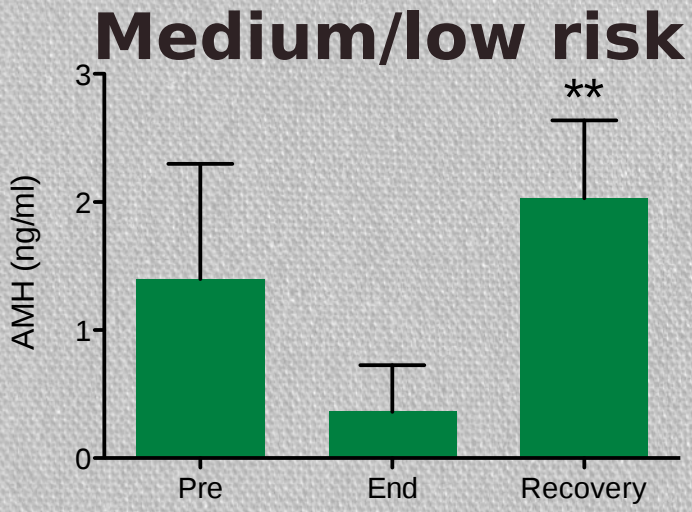
A validated model of serum anti-Mullerian hormone (AMH) from conception to menopause

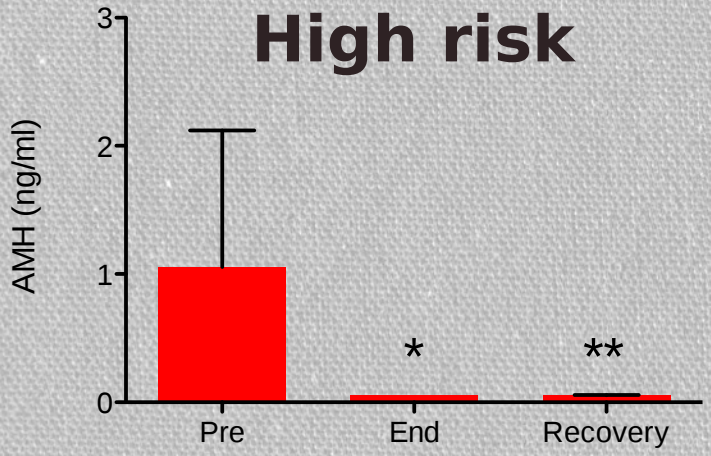


Kelsey et al. PLoS ONE 2011

AMH in childhood cancer



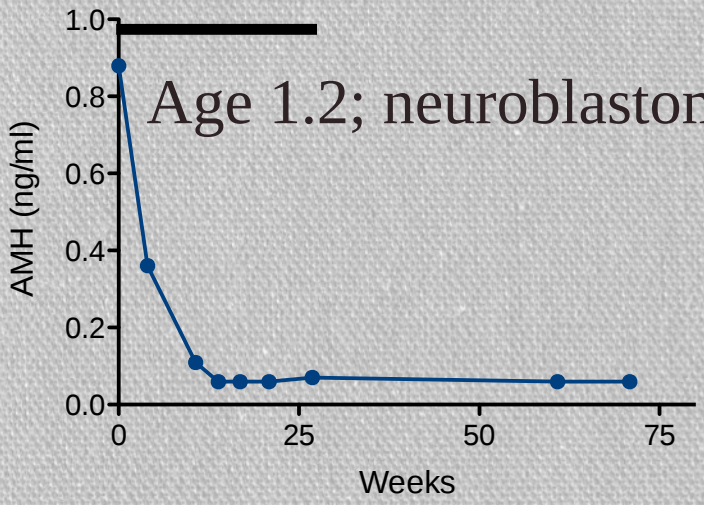


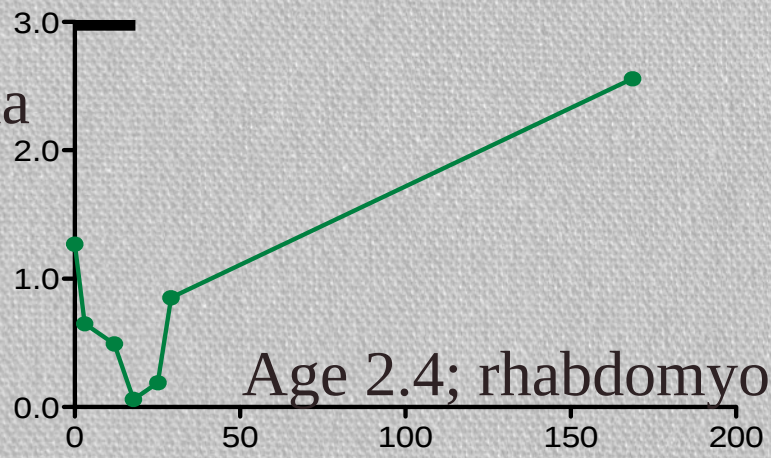


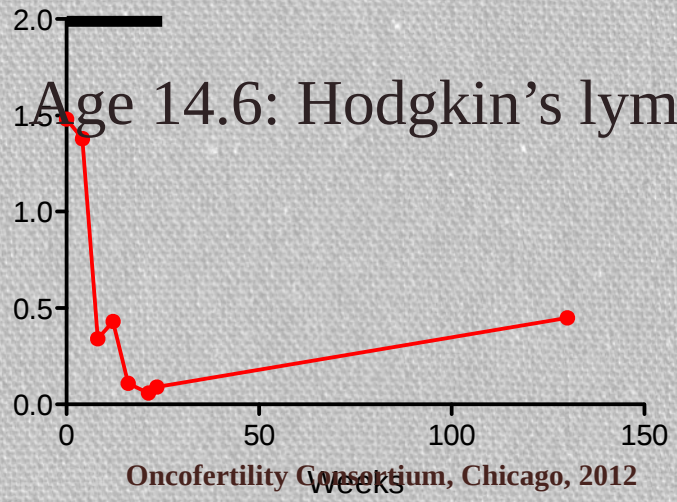
22 girls age 0.3-15yr
17 prepubertal

Brougham et al 2012 JCE&M

AMH in 3 girls with cancer







Brougham et al 2012 JCE&M

Summary

MH is detectable before puberty

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

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

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

Brougham et al 2012 JCE&M

Young females with cancer

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 cortical strips

ich in primordial follicles

urvive cryopreservation

echnique validated in sheep

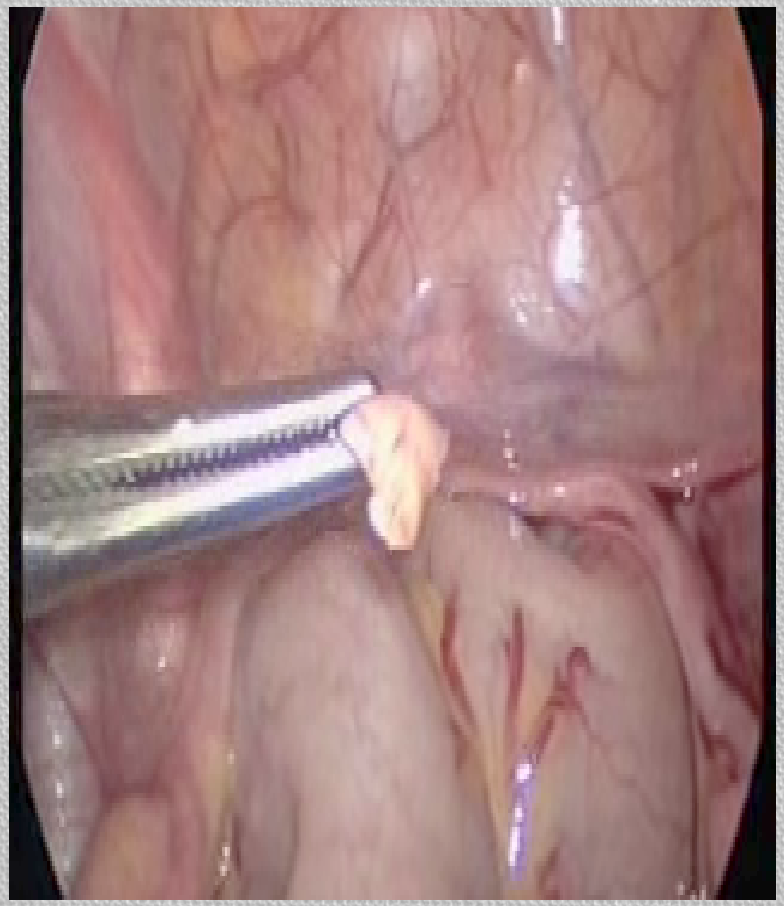
Baird DT et al., Endocrinology (1999)

Live births following cryopreservation of ovarian tissue and transplantation

Diagnosis	Age (yrs)	Surgical method	Reimplantation	Pregnancy	Reference
Hodgkin's Lymphoma	25	Unilateral ovarian biopsy	Orthotopic	Spontaneous, live birth	Donnez, 2004
Non-Hodgkin's Lymphoma	28	Unilateral ovarian biopsy (after 1st course chemo)	Orthotopic (Both ovaries)	IVF, live birth	Meirow 2005; 2007
Hodgkin's Lymphoma	31	Unilateral ovarian biopsy (after 1st course chemo)	Ortho and heterotopic	Spontaneous, miscarriage then livebirth	Demeestere 2007
Hodgkin's lymphoma	27	Whole ovary	Orthotopic	Livebirth male Week 37 B.Wt 2.6 Kg	Andersen et al 2008
Ewings Sarcoma	36	Whole ovary	Orthotopic	Livebirth Female Term B Wt 3.2 Kg	Andersen et al 2008

Ovarian tissue cryopreservation: World-wide experience

- At least 30 pregnancies worldwide after othotopic 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



Technology or evidence led?

- hen there is uncertainty about a new experimental procedure, it is important for it to be evaluated in IRB-approved clinical trials

- nlikely to be feasible or ethical to perform an RCT in a well characterized group of young women to test laparoscopic collection of ovarian cortex versus versus either dummy laparoscopy or no intervention

- t is highly unlikely that IRBs would pass such a study, or that such a randomized study would be able to recruit sufficient patients

Fertility Preservation ASCO Guidelines (2006) and update (2013)

- T

o develop guidance to practicing oncologists about available fertility preservation methods and related issues in people treated for cancer

- E

xpert Panel

- T

he questions to be addressed by the guideline were determined by the Panel

- S

ystematic review of the available literature

Lee et al. JCO 2006
Loren et al. JCO 2013

Fertility Preservation ASCO Guidelines (2006) and update (2013): General

- Discuss fertility preservation with **all** patients of reproductive age (and with parents or guardians of children and adolescents) if infertility is a potential risk of therapy
- Refer patients who express an interest in fertility preservation to reproductive specialists
- Address fertility preservation as early as possible, before treatment starts
- Document fertility preservation discussions in the medical record
- Encourage patients to participate in registries and clinical studies

Lee et al. JCO 2006
Loren et al. JCO 2013

Fertility Preservation ASCO Guidelines update (2013) (Females)

mbryo (2006) and oocyte cryopreservation (2013) should be considered as **established** fertility preservation methods

here is insufficient evidence of the effectiveness of ovarian suppression (gonadotropin-releasing hormone analogs) as a fertility preservation method

ther methods (e.g., ovarian tissue cryopreservation) are still **experimental**

Lee et al. JCO 2006
Loren et al. JCO 2013

Ovarian cryopreservation & ovarian function

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

Cryopreservation of ovarian cortical tissue – Edinburgh criteria

ection criteria (1995,modified 2000)

< 35 years

previous chemotherapy/radiotherapy if age >15 years

, non gonadotoxic chemotherapy if < 15 years

realistic chance of surviving five years

high risk of premature ovarian insufficiency

rmed consent (Parent and where possible Patient)

ative HIV and Hepatitis serology

existing children

Sel

- Age
- No
- Mild
- A
- A
- Info
- Neg
- No

Table 2: Patient characteristics and ovarian function in those patients where ovarian tissue was cryopreserved

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[0]	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

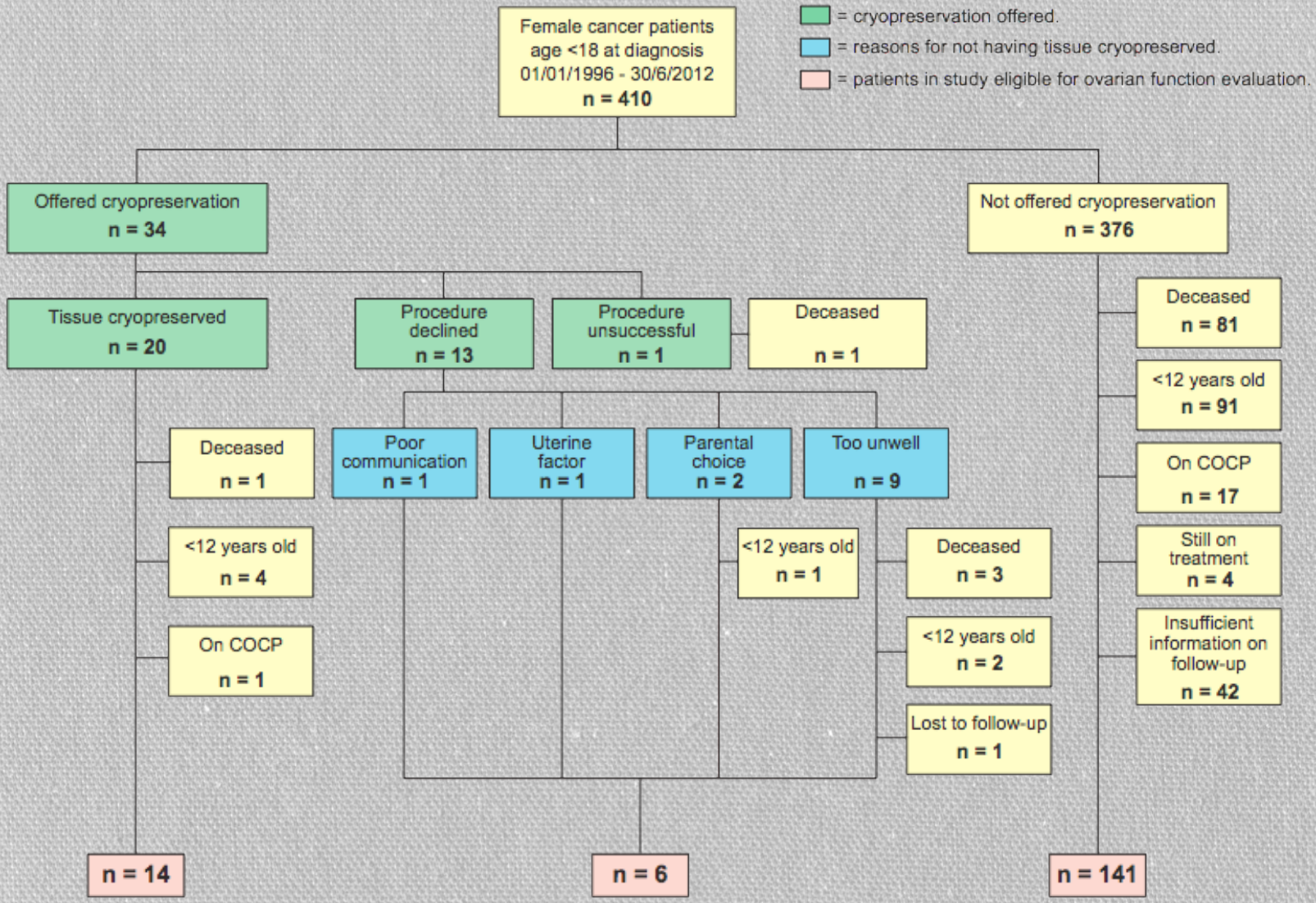
All tissue collected before chemotherapy/radiotherapy administered (except patients 1 and 10). Ovarian function was not assessed in those patients who were under the age of 12 years at the time of the study.

[◊] tissue collected after relapse of disease 21 months post initial radiotherapy

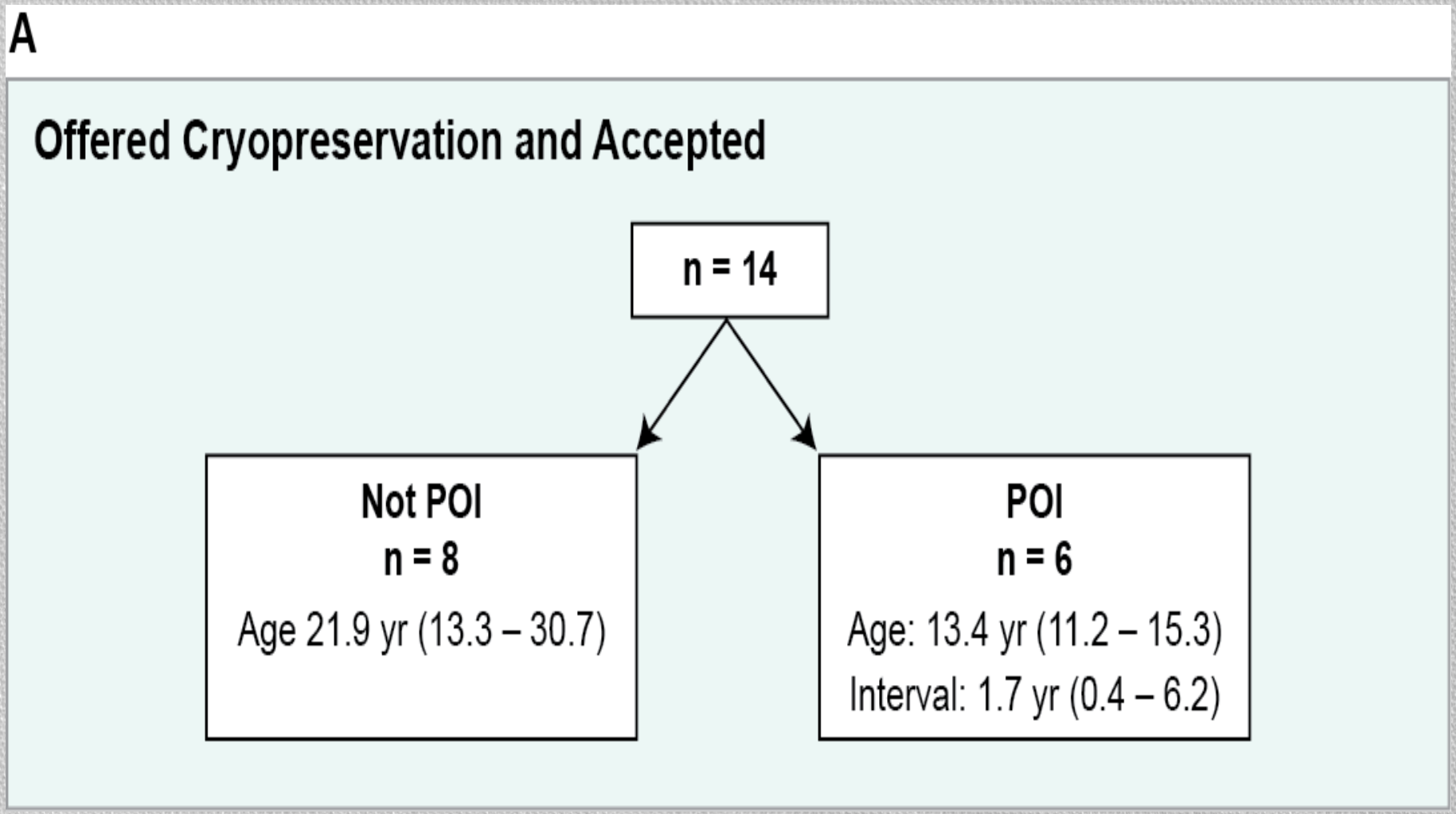
[0] tissue collected after relapse of disease 7 months post initial radiotherapy

• diagnosis changed to Mullerian Adenosarcoma shortly after tissue cryopreserved

† metastatic deposits found on cortical strip

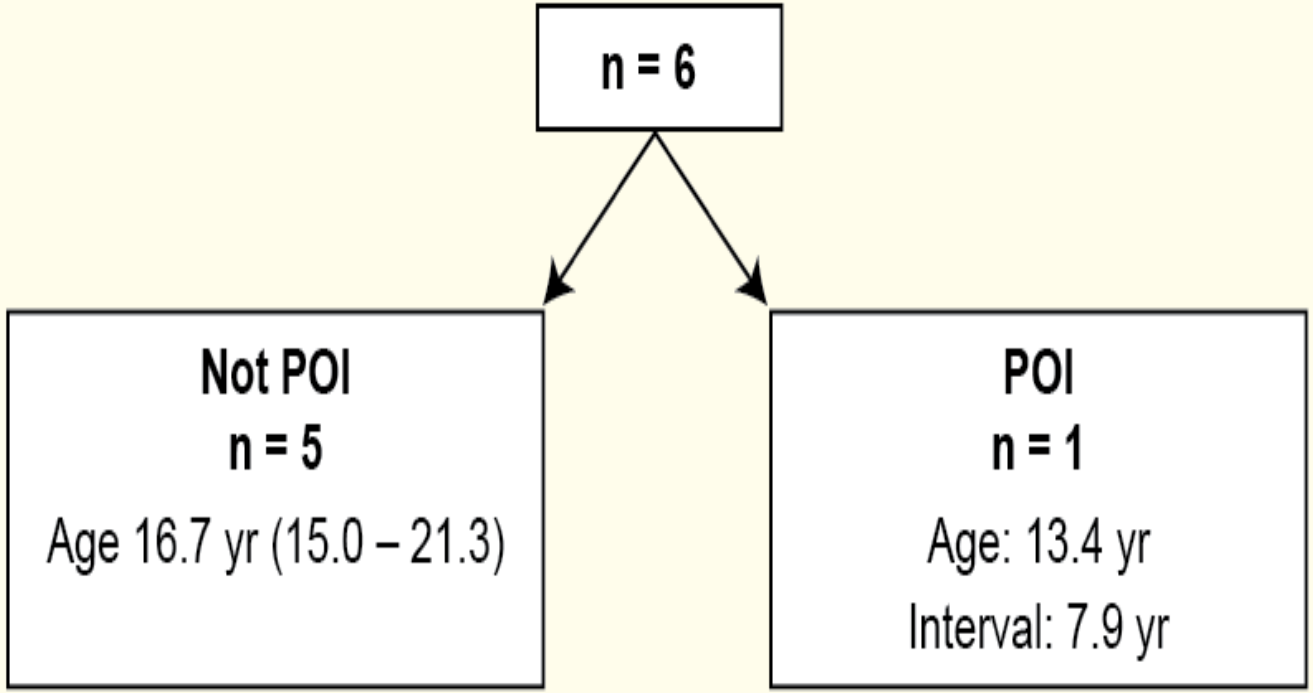

= cryopreservation offered.
= reasons for not having tissue cryopreserved.
= patients in study eligible for ovarian function evaluation.
Female cancer patients age <18 at diagnosis 01/01/1996 - 30/6/2012 n = 410
Offered cryopreservation n = 34
Not offered cryopreservation n = 376
Tissue cryopreserved n = 20
Procedure declined n = 13
Procedure unsuccessful n = 1
Deceased n = 1
Deceased n = 1
<12 years old n = 4
On COCP n = 1
Poor communication n = 1
Uterine factor n = 1
Parental choice n = 2
Too unwell n = 9
<12 years old n = 1
Deceased n = 3
<12 years old n = 2
Lost to follow-up n = 1
Deceased n = 81
<12 years old n = 91
On COCP n = 17
Still on treatment n = 4
Insufficient information on follow-up n = 42
n = 14
n = 6
n = 141

A


Offered Cryopreservation and Accepted
n = 14
Not POI
n = 8
Age 21.9 yr (13.3 – 30.7)
POI
n = 6
Age: 13.4 yr (11.2 – 15.3)
Interval: 1.7 yr (0.4 – 6.2)

B

Offered Cryopreservation - procedure declined



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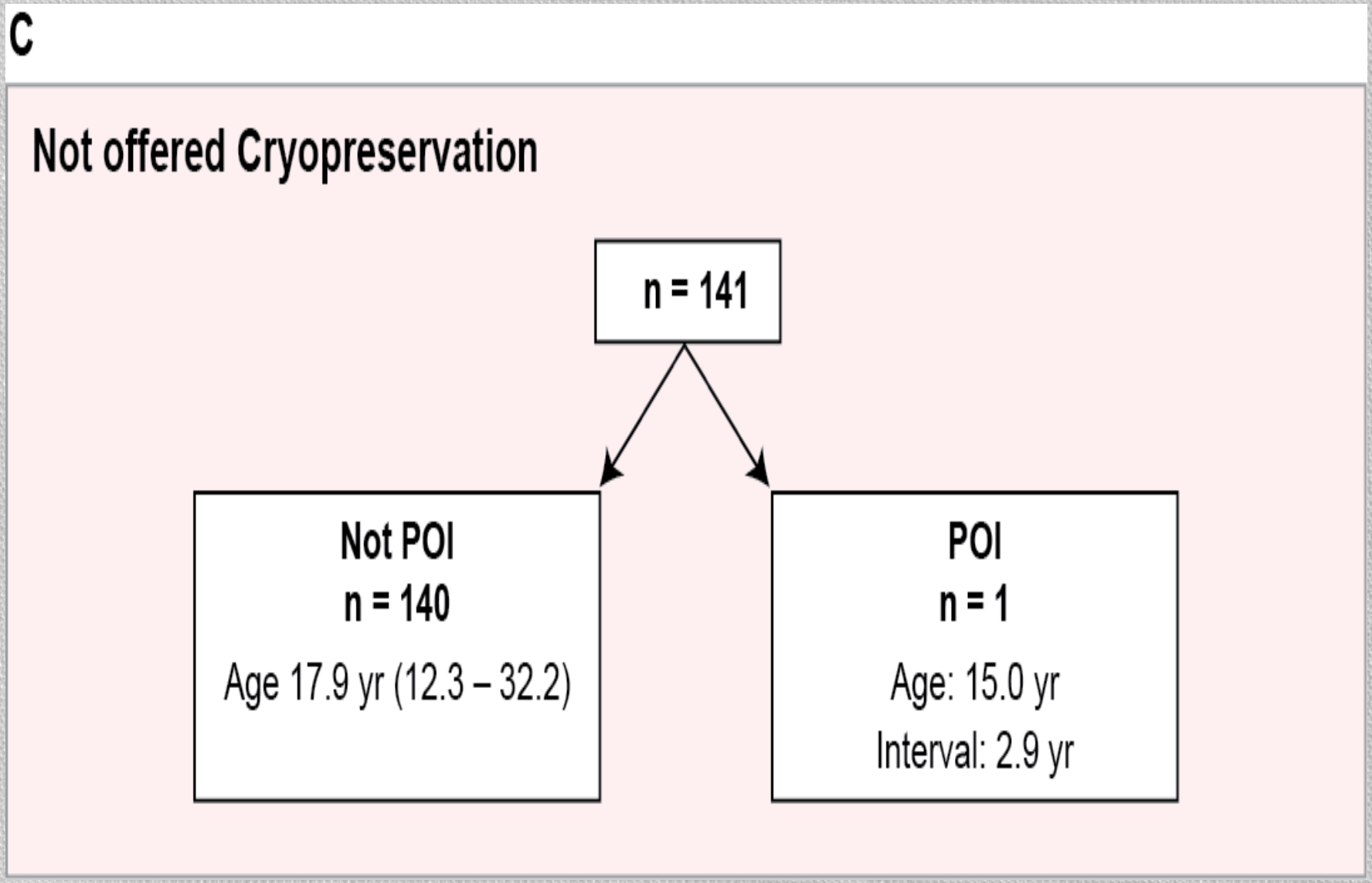
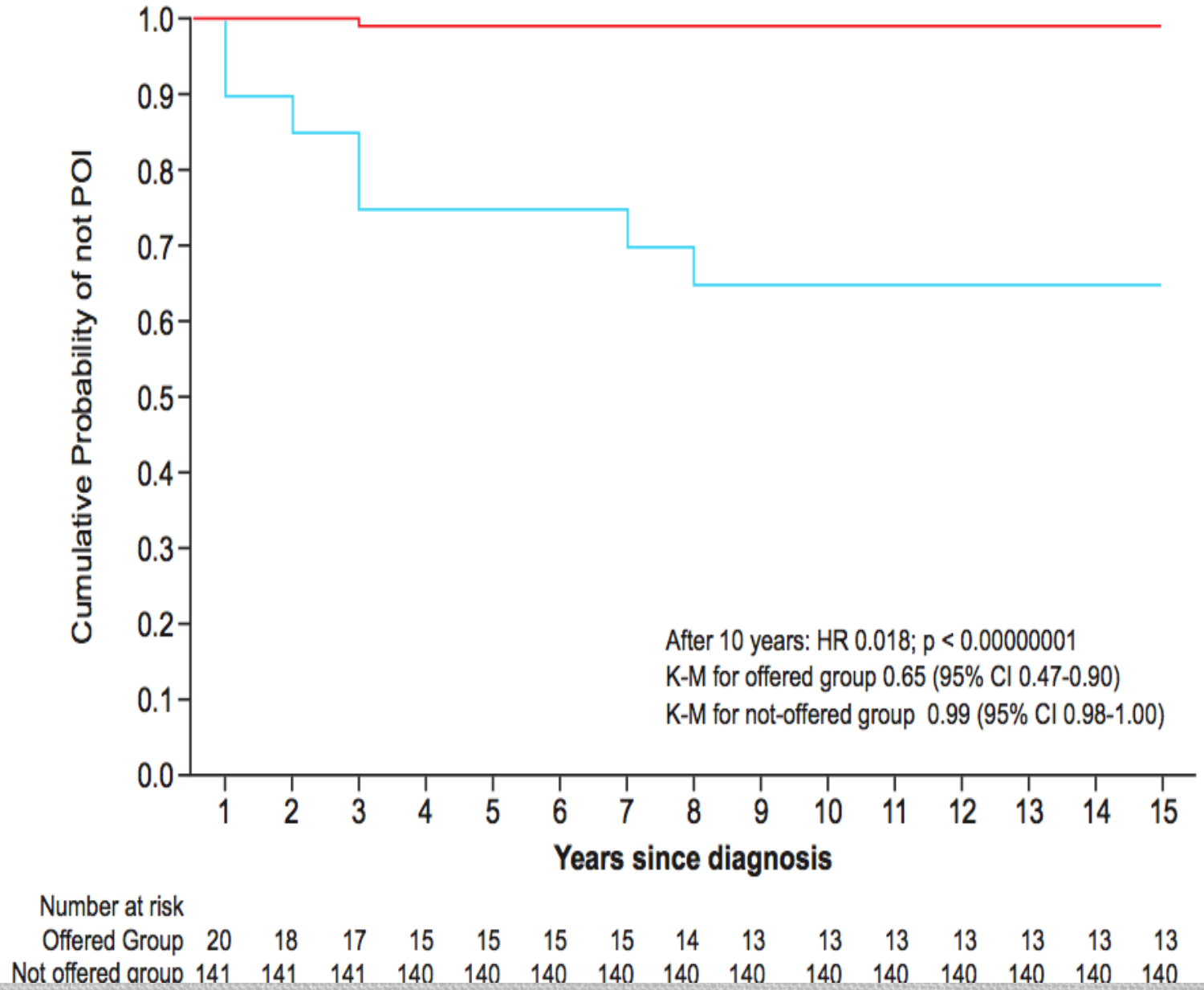

Not offered Cryopreservation
n = 141
Not POI
n = 140
Age 17.9 yr (12.3 – 32.2)
POI
n = 1
Age: 15.0 yr
Interval: 2.9 yr


Cumulative Probability of not POI
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
After 10 years: HR 0.018; p < 0.00000001
K-M for offered group 0.65 (95% CI 0.47-0.90)
K-M for not-offered group 0.99 (95% CI 0.98-1.00)
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Years since diagnosis
Number at risk
Offered Group 20 18 17 15 15 15 15 14 13 13 13 13 13 13 13
Not offered group 141 141 141 140 140 140 140 140 140 140 140 140 140 140 140

Conclusion

- O

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

- T

he procedure was safe and without complications

- N

o patients have asked for re-implantation of their tissue – to date

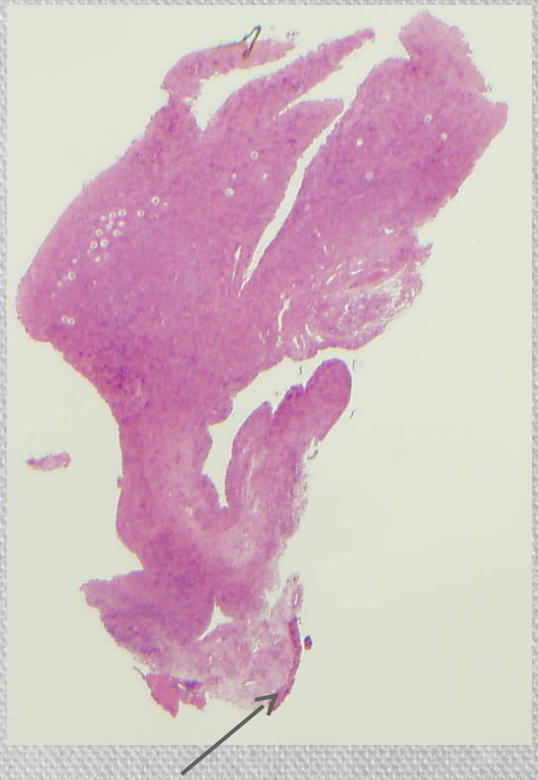
- A

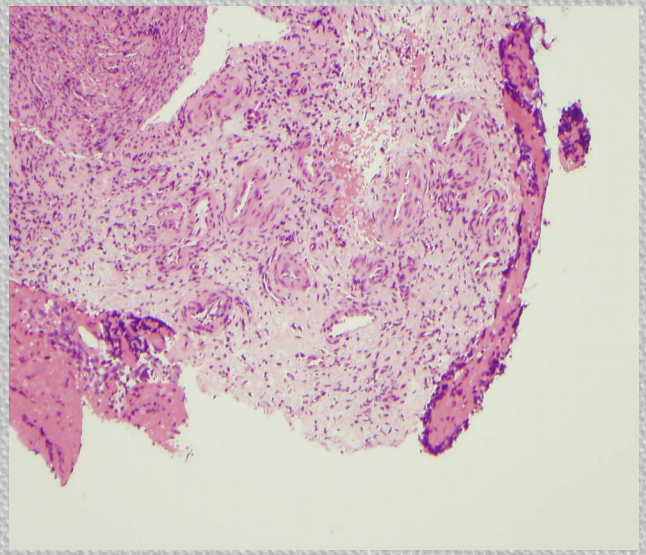
ll patients who have thus far developed premature ovarian insufficiency were identified except onepatient

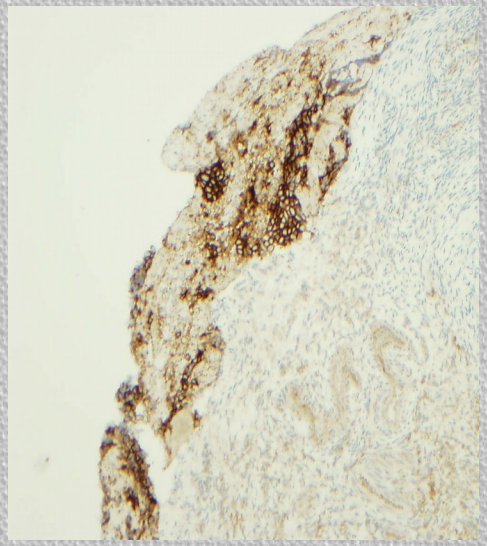
- T

he Edinburgh Selection Criteria have proved to be helpful (only one patient not offered cryopreservation who has uncertain ovarian function)

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





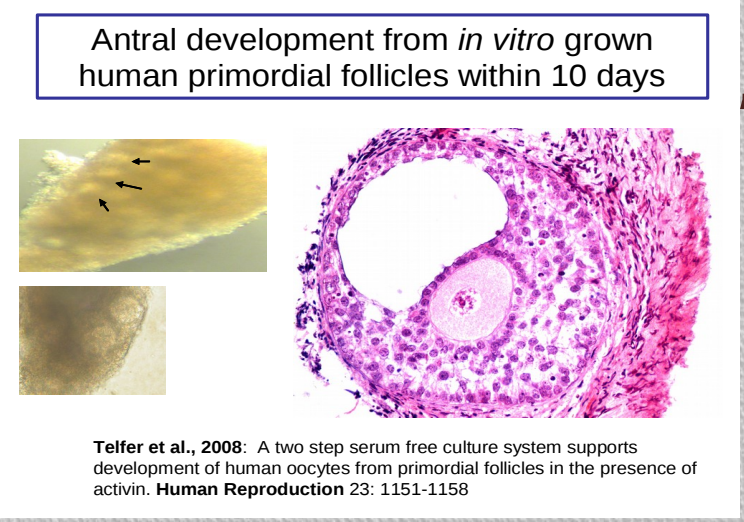


CD99

Re-implantation or IVG and maturation?

ontamination 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

oc , followed by IVF, would el



Telfer et al. (2008) Human Reproduction

Acknowledgements

om Kelsey

ichard Anderson

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arie McLaughlan

lice Grove Smith

eorge Galea

od Mitchell

ouise Bath

hris Kelnar

ngela Edgar

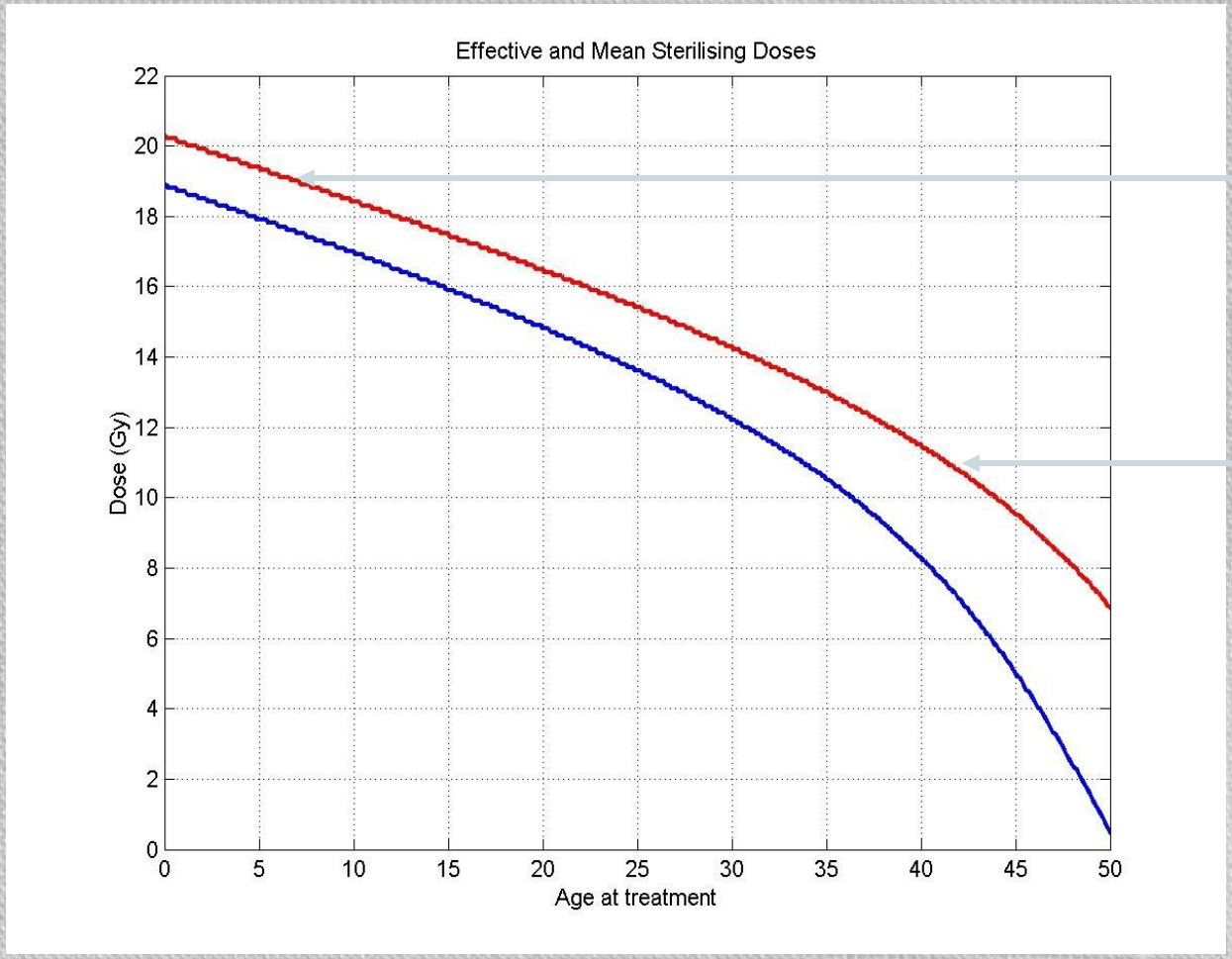
ark Brougham

raser Munro

- T
- R
- E
- M
- A
- G

Thank You

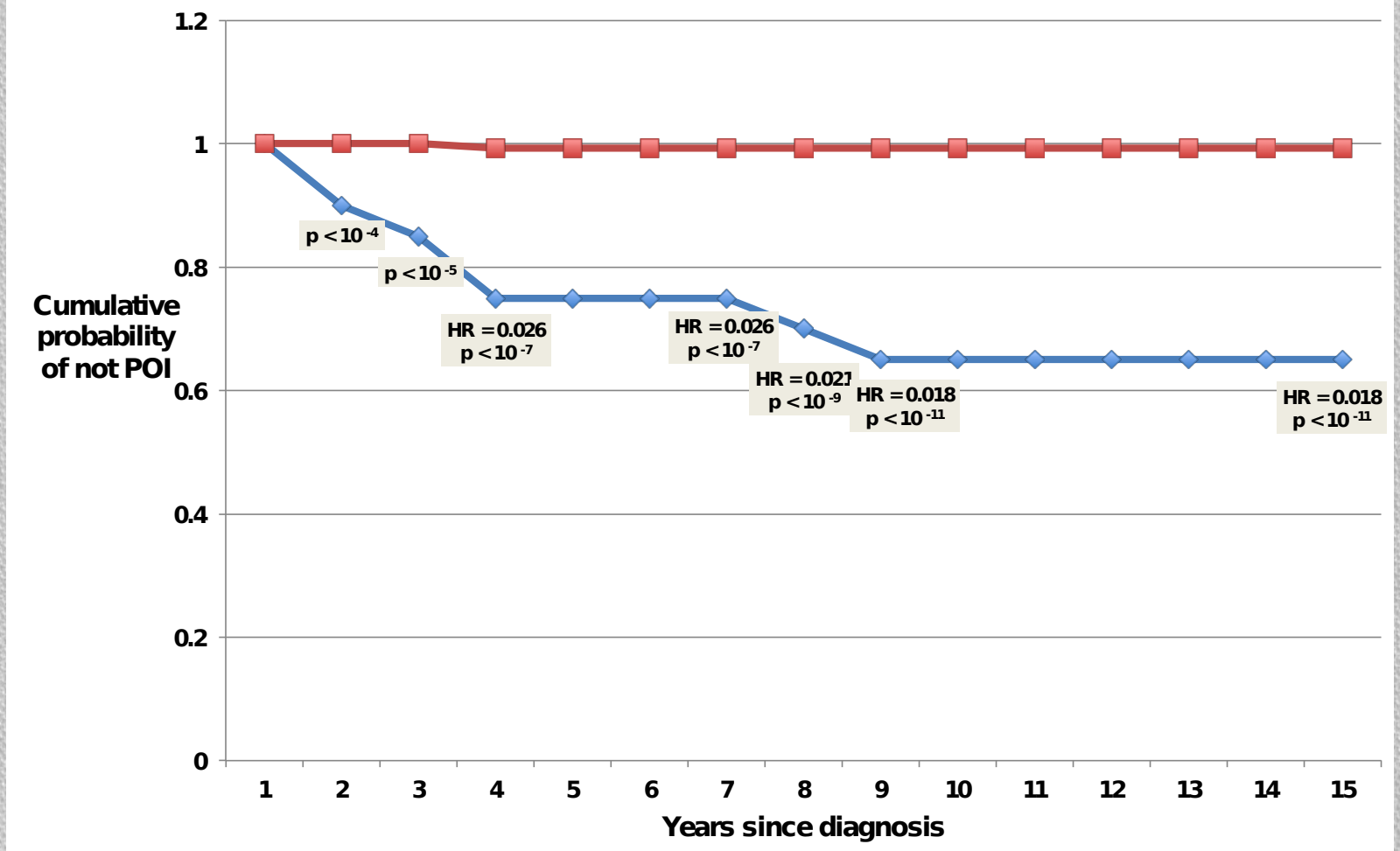
Effective and mean ovarian sterilizing doses of radiotherapy at increasing age



19 Gy will sterilize at 7 years

11 Gy will sterilize at 42 years

allace WH et al. IJRBP (2005)


1.2
1
0.8
0.6
0.4
0.2
0
Cumulative probability of not POI
p < 10 -4
p < 10 -5
HR = 0.026
p < 10 -7
HR = 0.026
p < 10 -7
HR = 0.021
p < 10 -9
HR = 0.018
p < 10 -11
HR = 0.018
p < 10 -11
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
Years since diagnosis