FERTILITY PRESERVATION IN THE (YOUNG) CANCER PATIENT

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ESMO
Madrid
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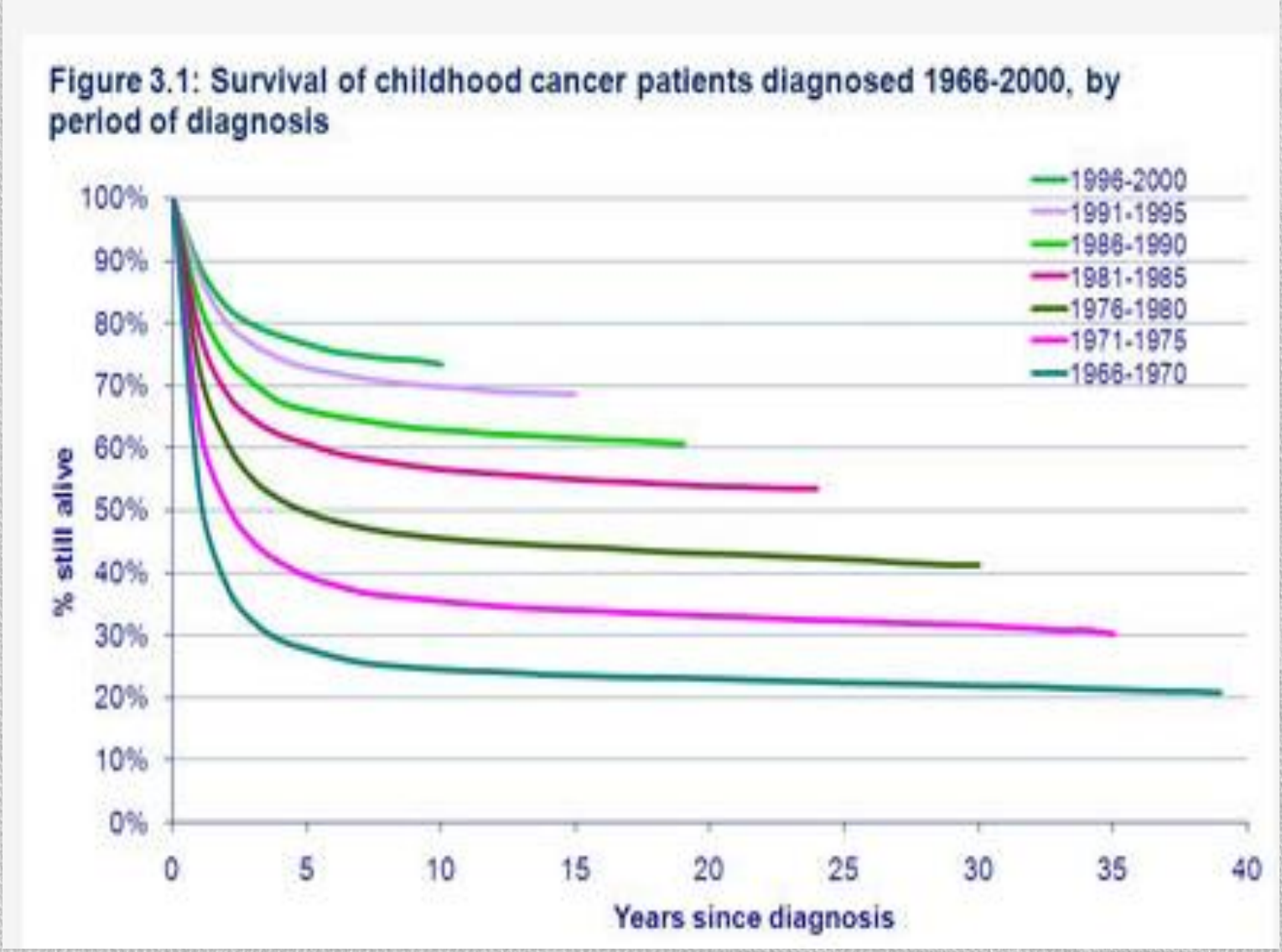
No Conflicts of Interest to Declare

Improved Five Year Survival (1966-2000)



Risk assessment for fertility preservation

- **Intrinsic factors**
  - Health status of patient
  - Consent (patient/parent)
  - Age
  - Assessment of ovarian reserve
- **Extrinsic factors**
  - Nature of predicted treatment
    - (high/medium/low/uncertain risk)
  - Expertise/options available

After Wallace WH, Critchley HO and Anderson RA
Optimizing reproductive outcome in children and young people with cancer.
J Clin Oncol 2012; **30**: 3-5.

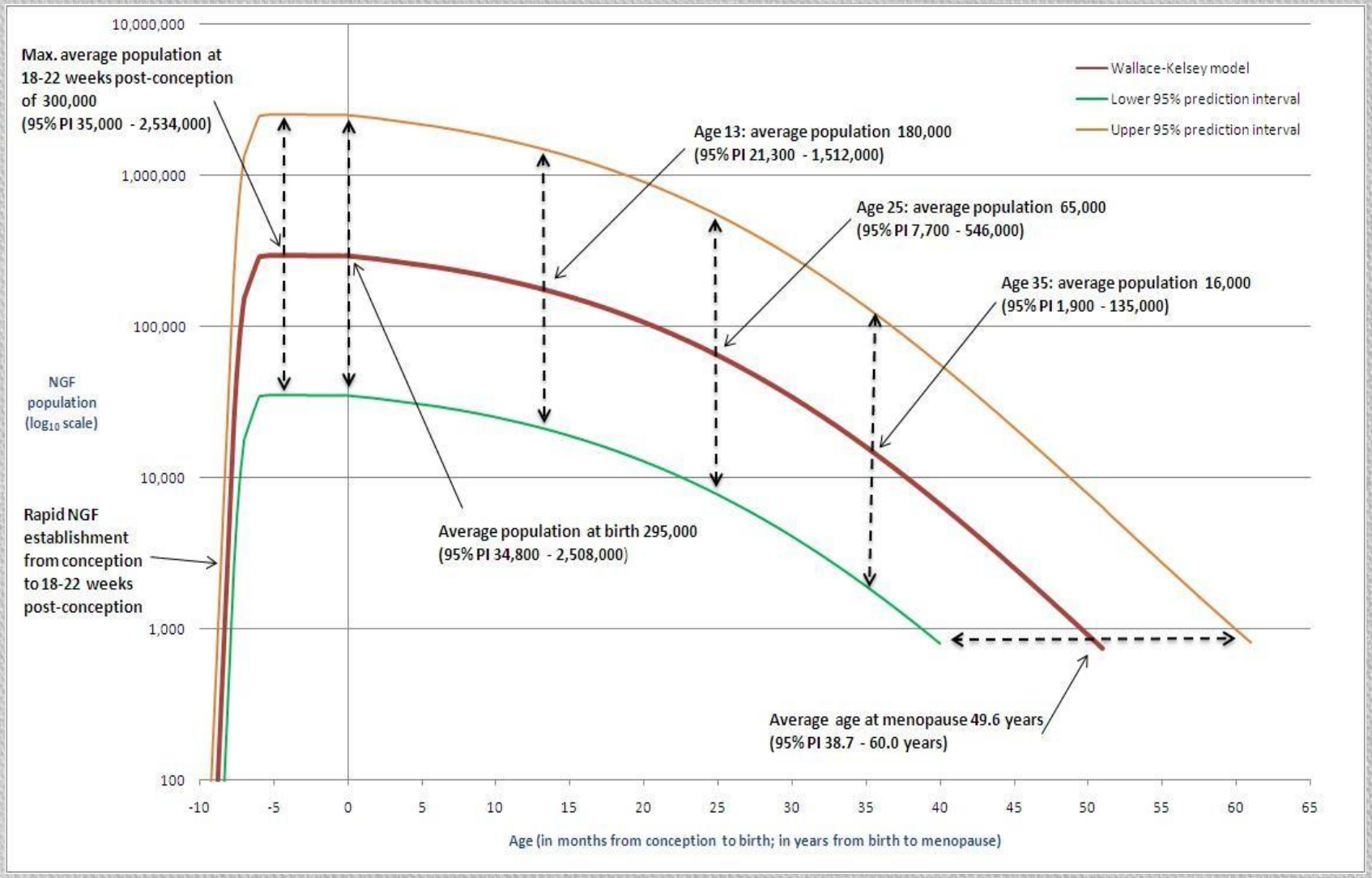
Risk of infertility

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

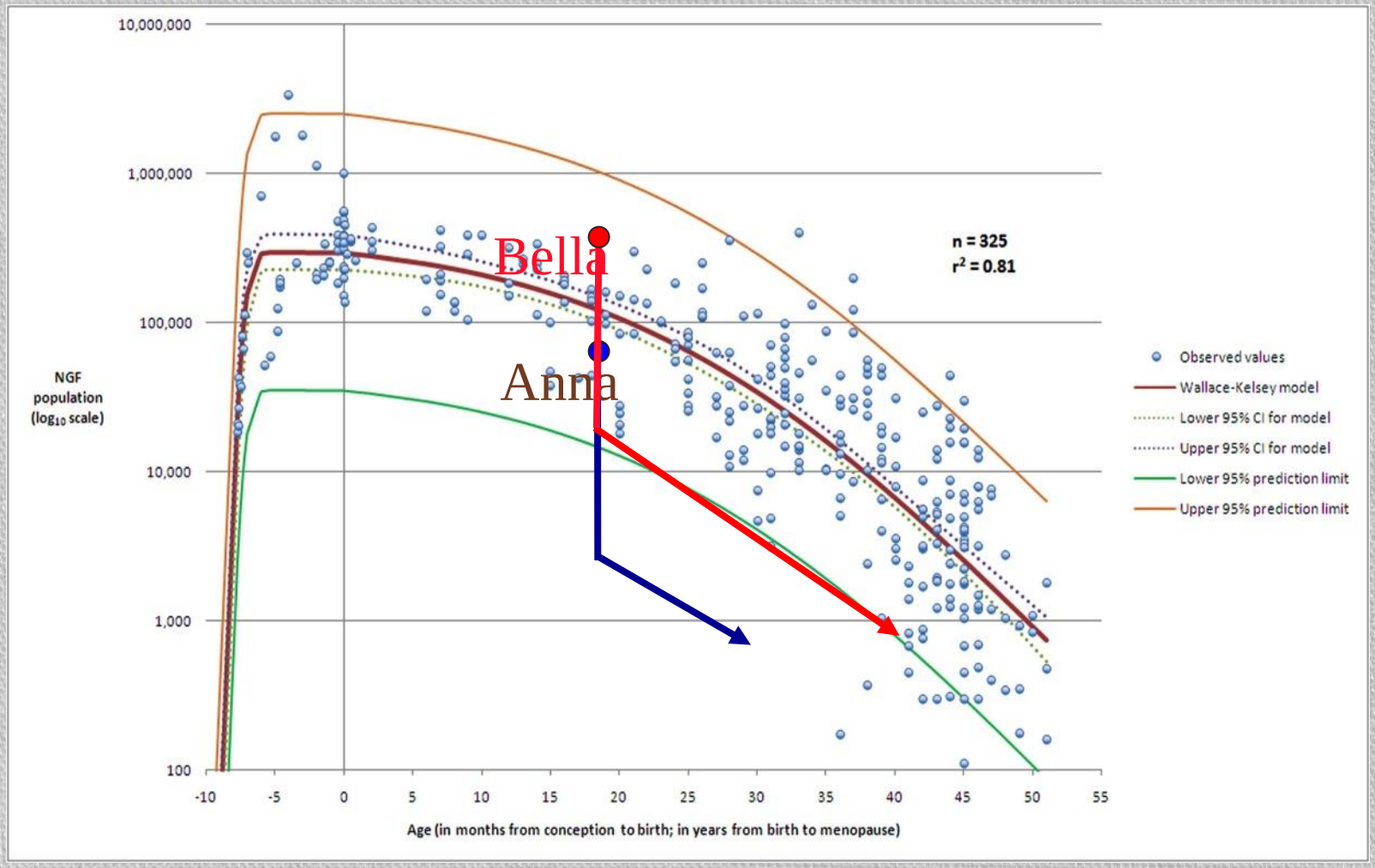
Young females with cancer

Ovarian reserve: Conception to Menopause



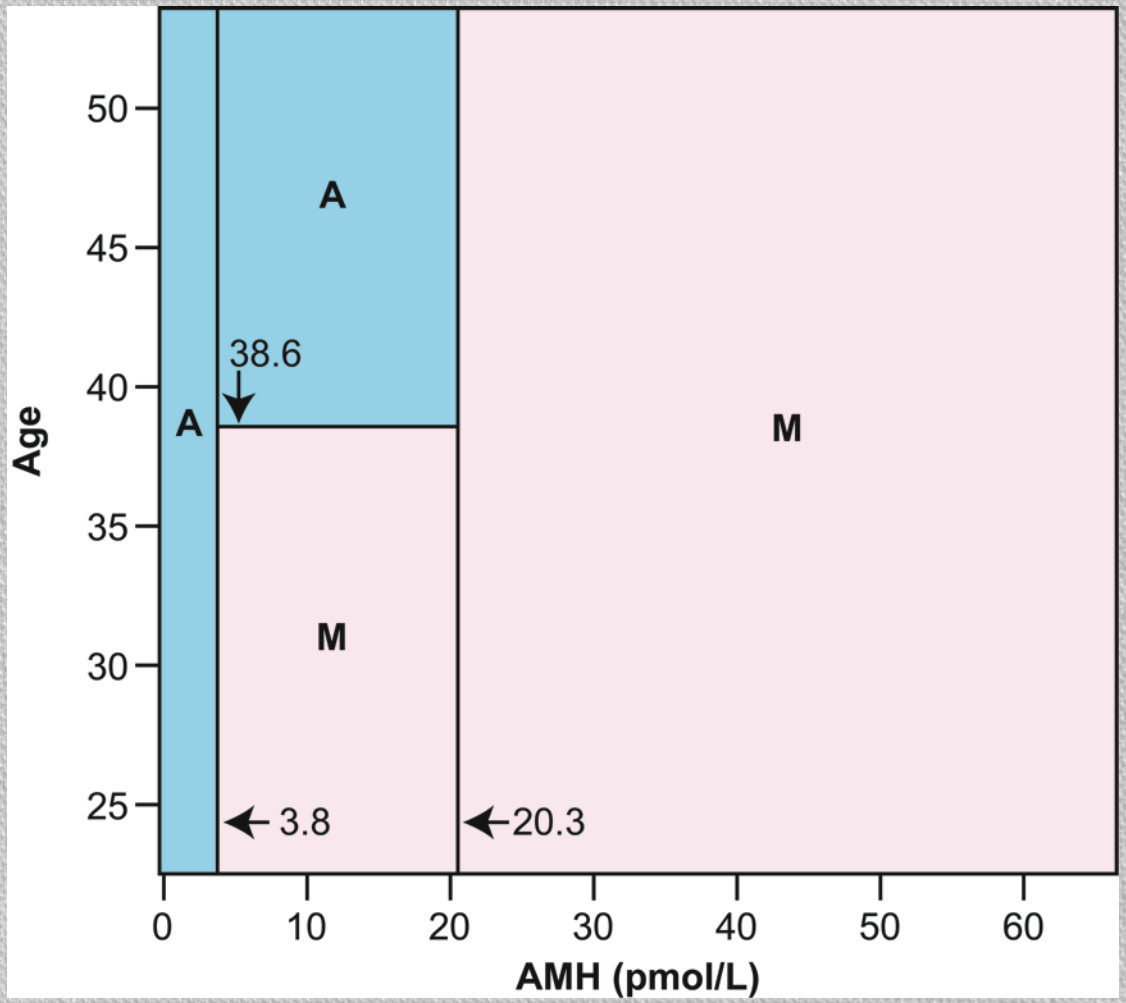
Wallace & Kelsey (2010) PloS ONE

Ovarian reserve: Conception to Menopause



Wallace and Kelsey 2010 PLoS One 5; e8772

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

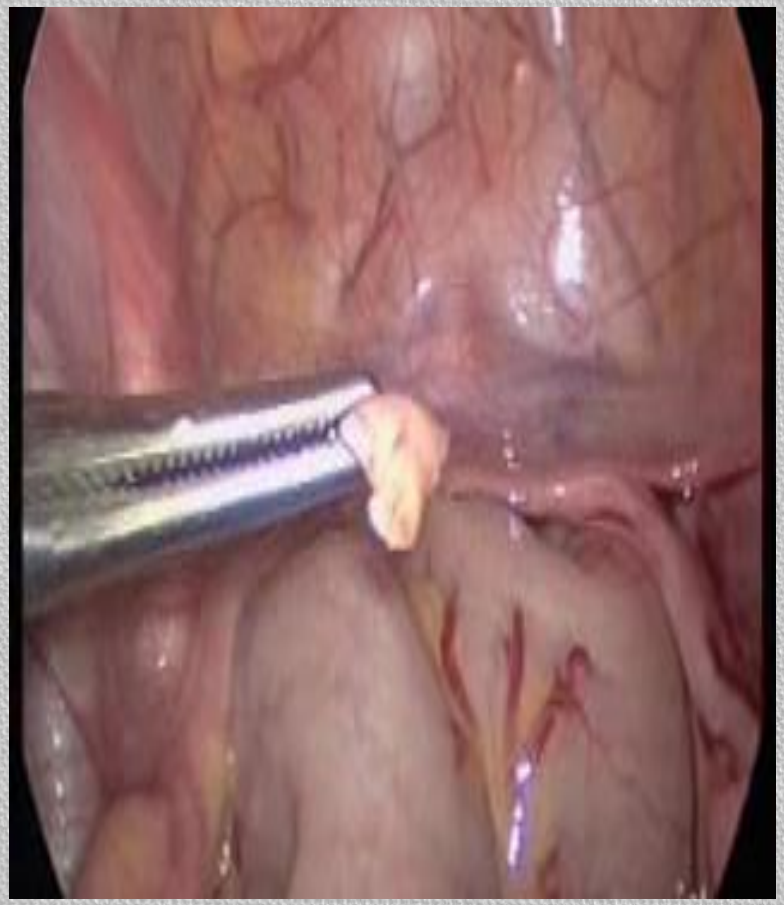
Anderson and Cameron 2011 JCE&M
Anderson et al 2013 Eur J Cancer

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 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



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

- To develop guidance to practicing oncologists about available fertility preservation methods and related issues in people treated for cancer
- Expert Panel
- The questions to be addressed by the guideline were determined by the Panel
- Systematic 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)

- Embryo (2006) and oocyte cryopreservation (2013) should be considered as **established** fertility preservation methods
- There is insufficient evidence of the effectiveness of ovarian suppression (gonadotropin-releasing hormone analogs) as a fertility preservation method
- Other 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

Can we develop useful criteria for fertility preservation in children and adolescents?

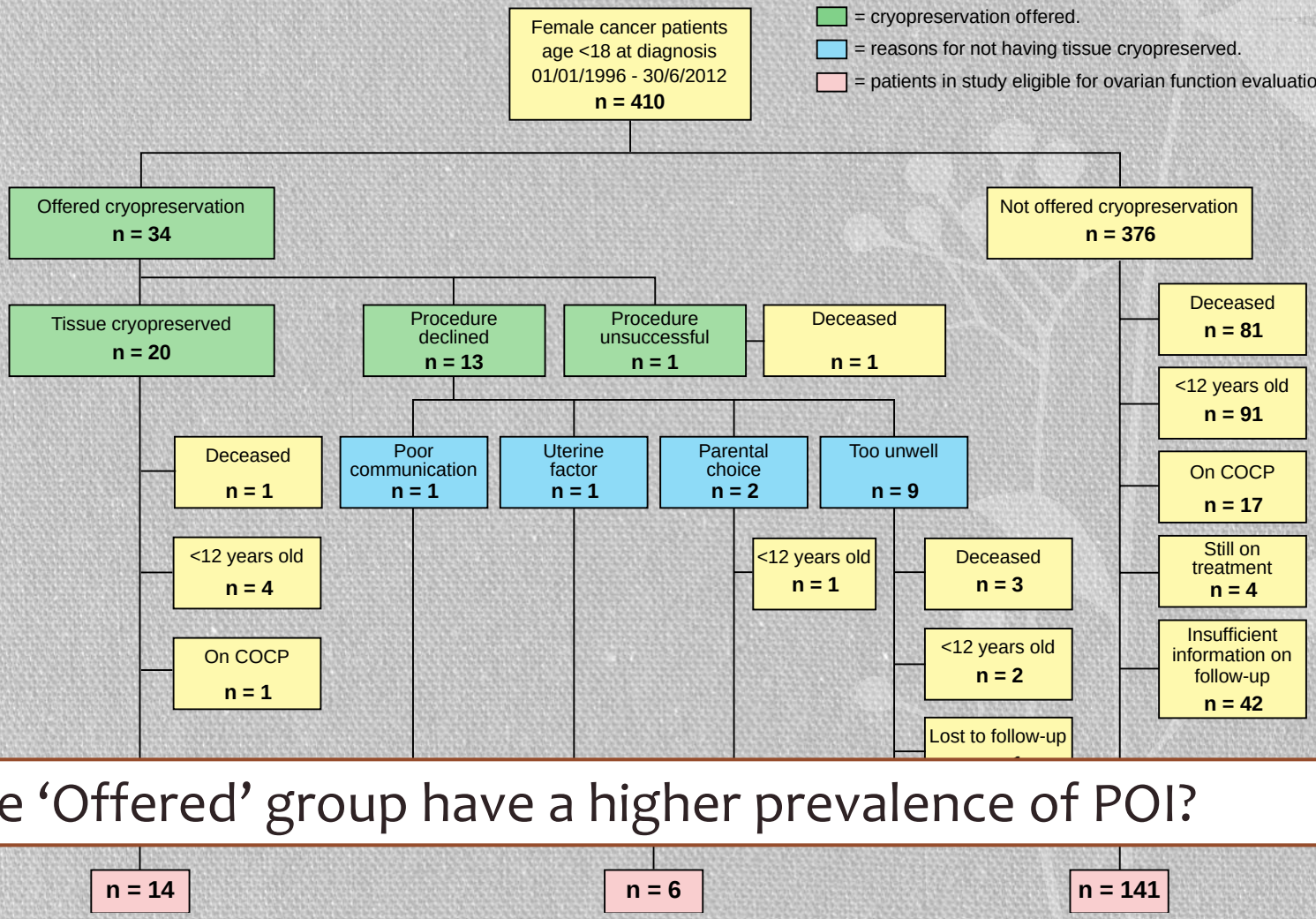
Development of 'Edinburgh criteria' since 1996

- Age <35 years
- No previous chemotherapy (or low risk)
- High (>50%) risk of ovarian failure
  - High dose alkylating agents
  - Radiotherapy to pelvis
- Good (>50%) chance of survival

Can this predict those at high risk of POI?

Anderson Wallace and Baird 2008 Reproduction 131, 681
Walllace..and Anderson 2014 Lancet Oncology

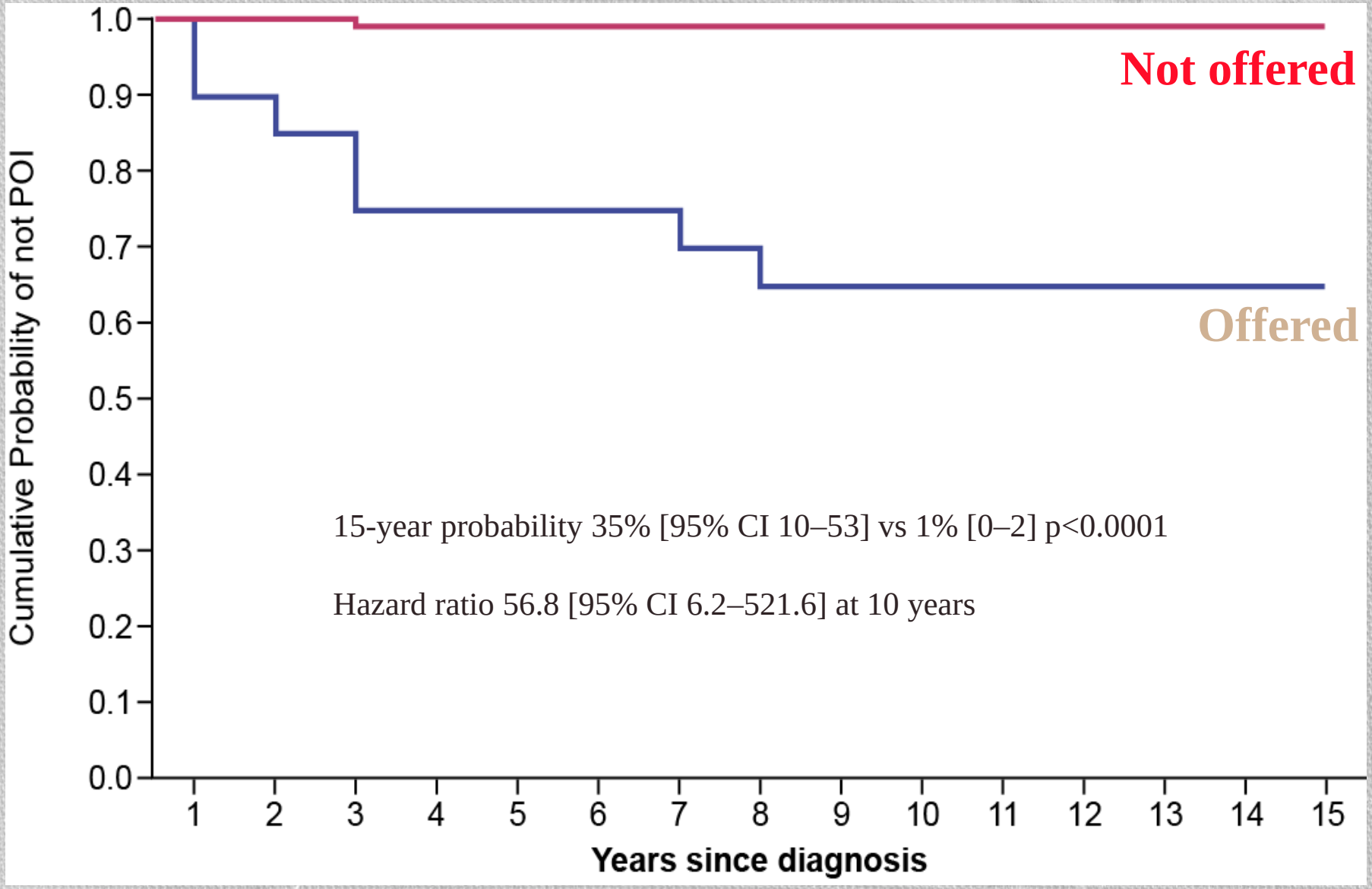
15 year, population-based analysis of criteria for ovarian cryopreservation



Do the 'Offered' group have a higher prevalence of POI?

Walllace…..and Anderson 2014 Lancet Oncology

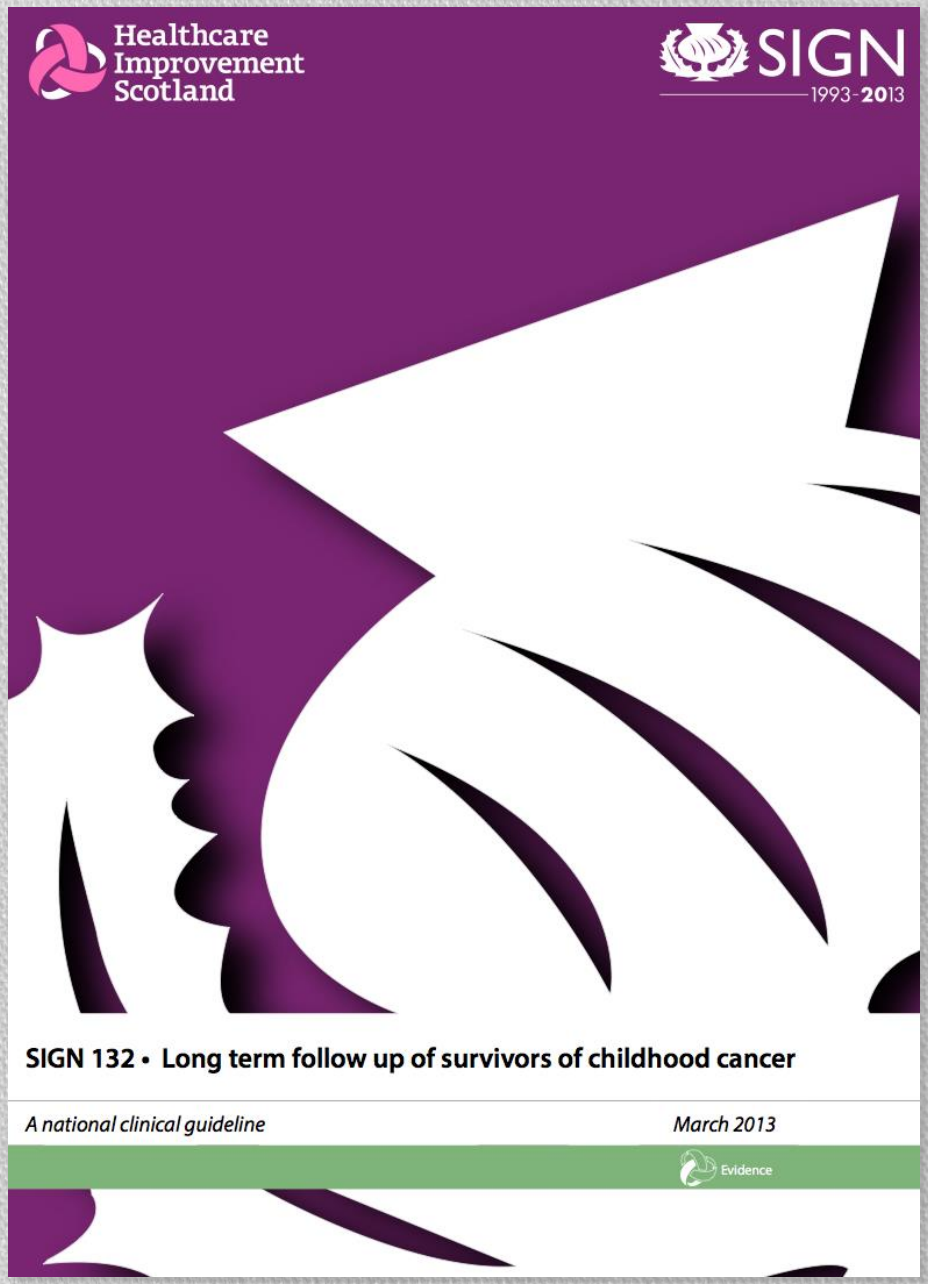
Cumulative incidence of POI



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



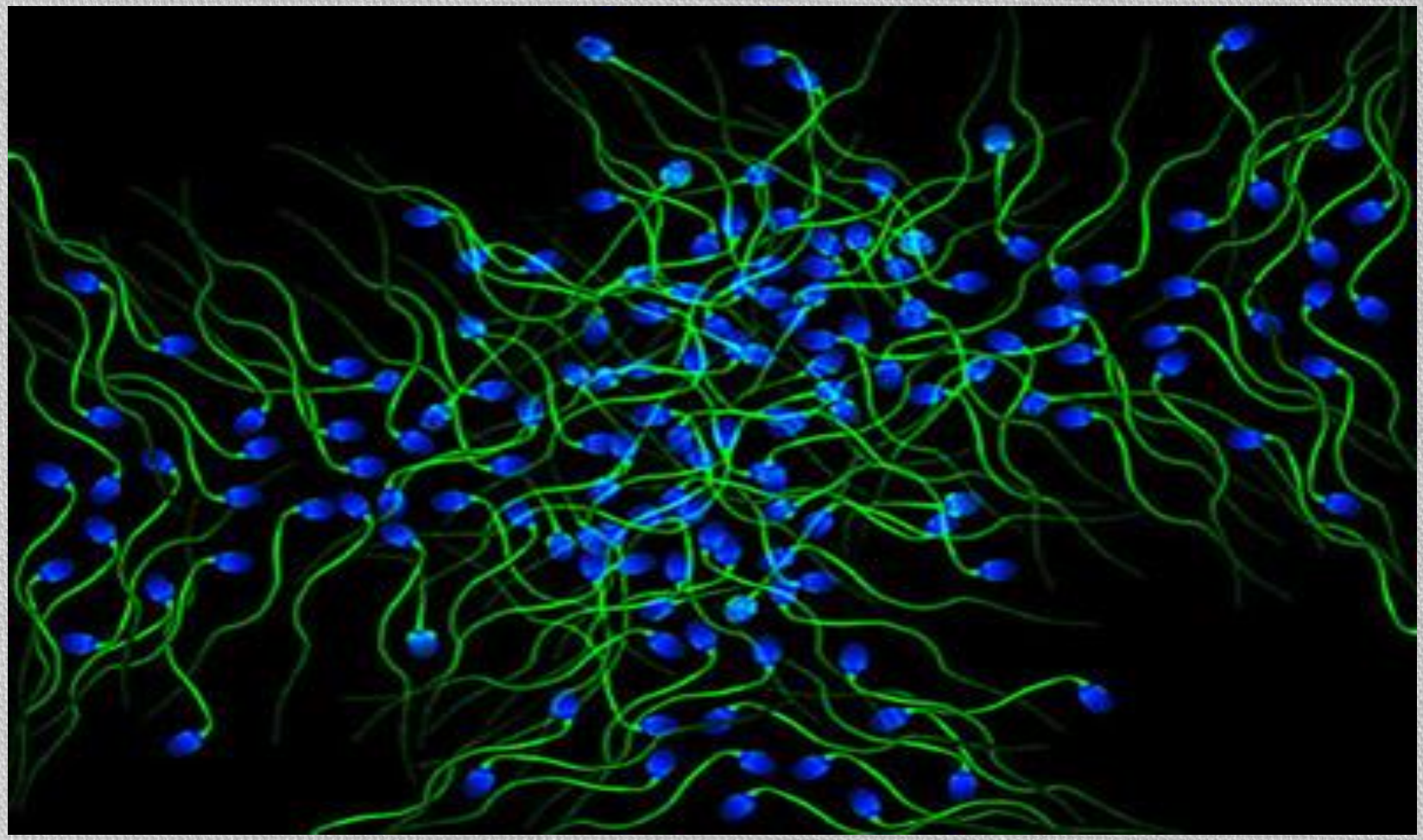
Fertility:
Good links are required between paediatric oncology units and fertility services

Consider ovarian tissue cryopreservation (within the context of a clinical trial) in girls at high risk of premature ovarian insufficiency (D)

Wallace WH, Thompson L, Anderson RA Long term follow-up of survivors of childhood cancer: summary of updated SIGN guidance. *BMJ* 2013; **346**: f1190.

Isolated human sperm cells (1500x)

Albert Tousson – Nikon Small world



Males: Fertility preservation

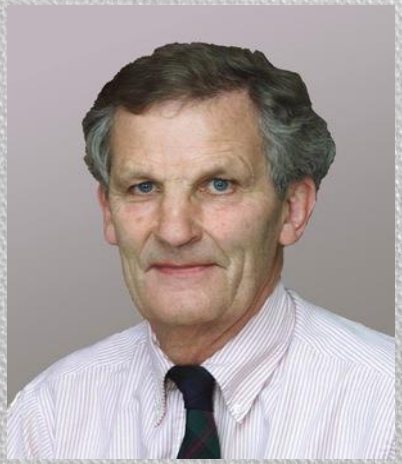
- Young men who can produce semen should have the opportunity of sperm banking before treatment begins
- Sperm retrieval should be considered if the chances of infertility are high and the testes are >10mls
  - Storage of gametes is governed by the HFE act 1990
  - Written informed consent from a competent male is required
- There is currently no option to preserve fertility in the pre-pubertal boy

Fertility Preservation ASCO Guidelines update (2013) (Males)

- Present sperm cryopreservation (sperm banking) as the only established fertility preservation method
- Do not recommend hormonal therapy in men; it is not successful in preserving fertility
- Inform patients that other methods (eg, testicular tissue cryopreservation) are experimental
- Advise men of a potentially higher risk of genetic damage in sperm collected after initiation of chemotherapy

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

Acknowledgements



- Richard Anderson
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THANK YOU

Ovarian cortical strips

- rich in primordial follicles
- survive cryopreservation
- technique 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

Technology or evidence led?

- When there is uncertainty about a new experimental procedure, it is important for it to be evaluated in IRB-approved clinical trials
- Unlikely 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
- It is highly unlikely that IRBs would pass such a study, or that such a randomized study would be able to recruit sufficient patients

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

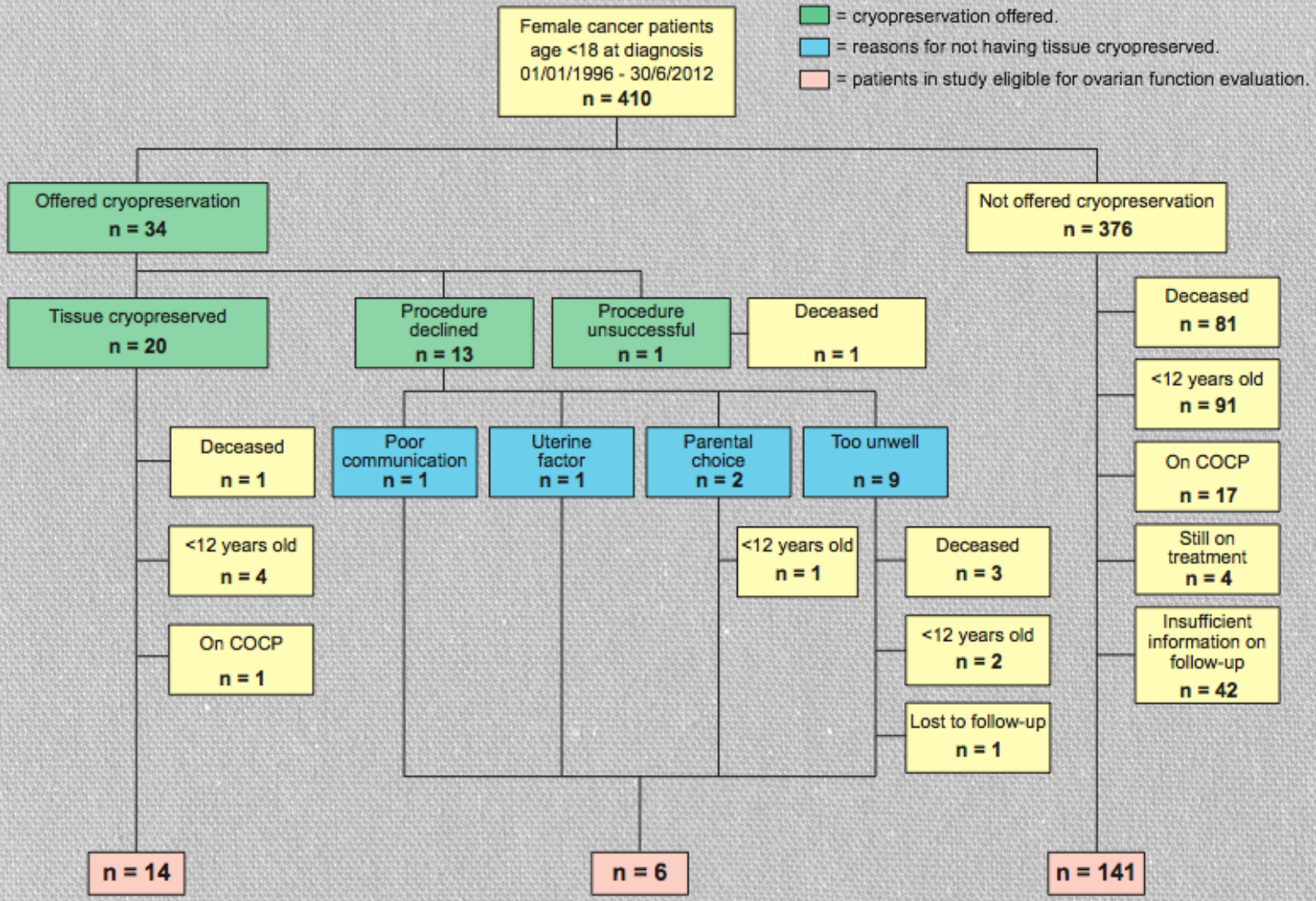
All tissue collected before chemotherapy/radiotherapy administered (except patients 1 and 10). Ovarian function was not assessed in those patients who were under the age of 12 years at the time of the study.

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

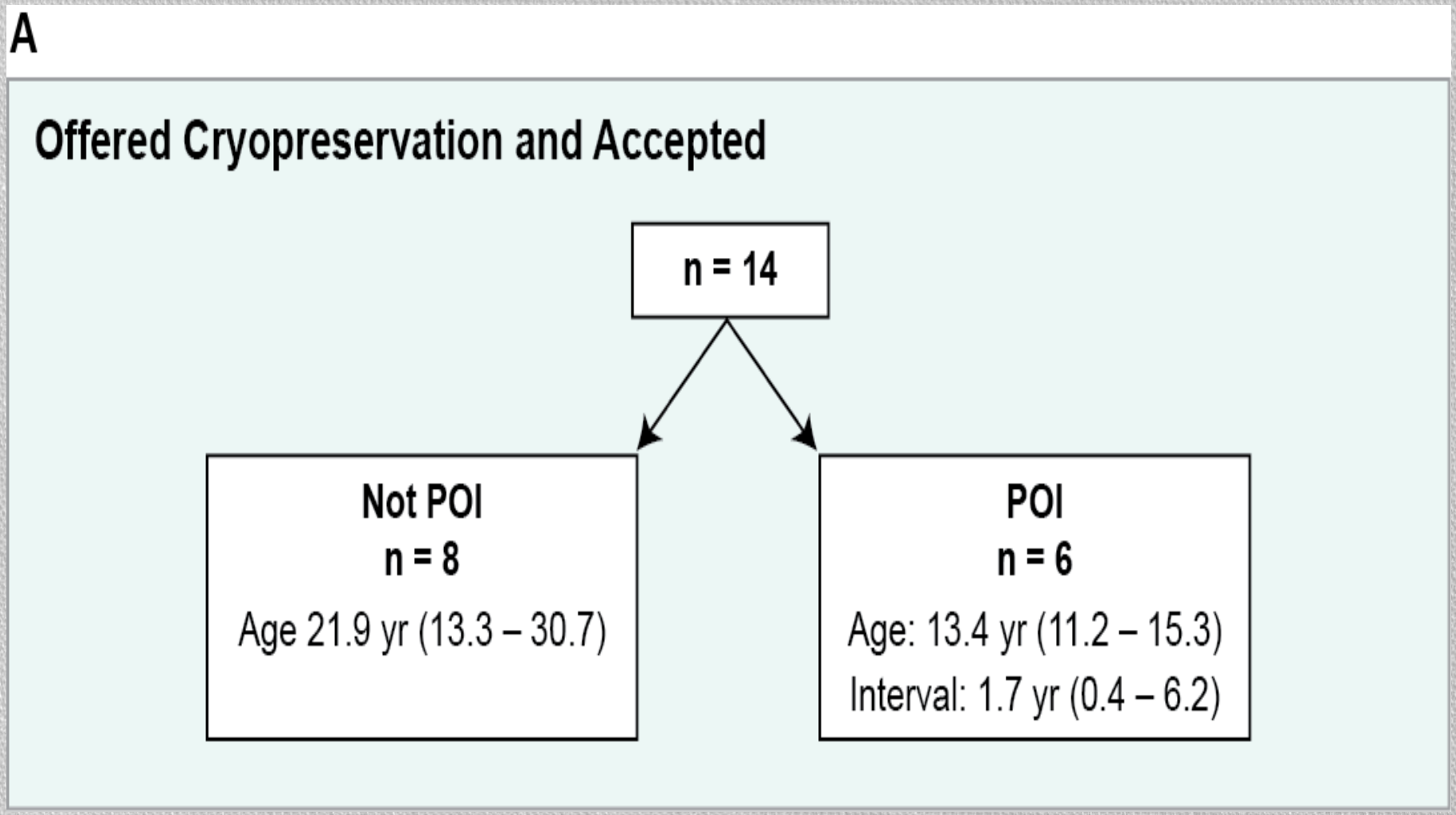
[0] tissue collected after relapse of disease 7 months post initial radiotherapy

• diagnosis changed to Mullerian Adenosarcoma shortly after tissue cryopreserved

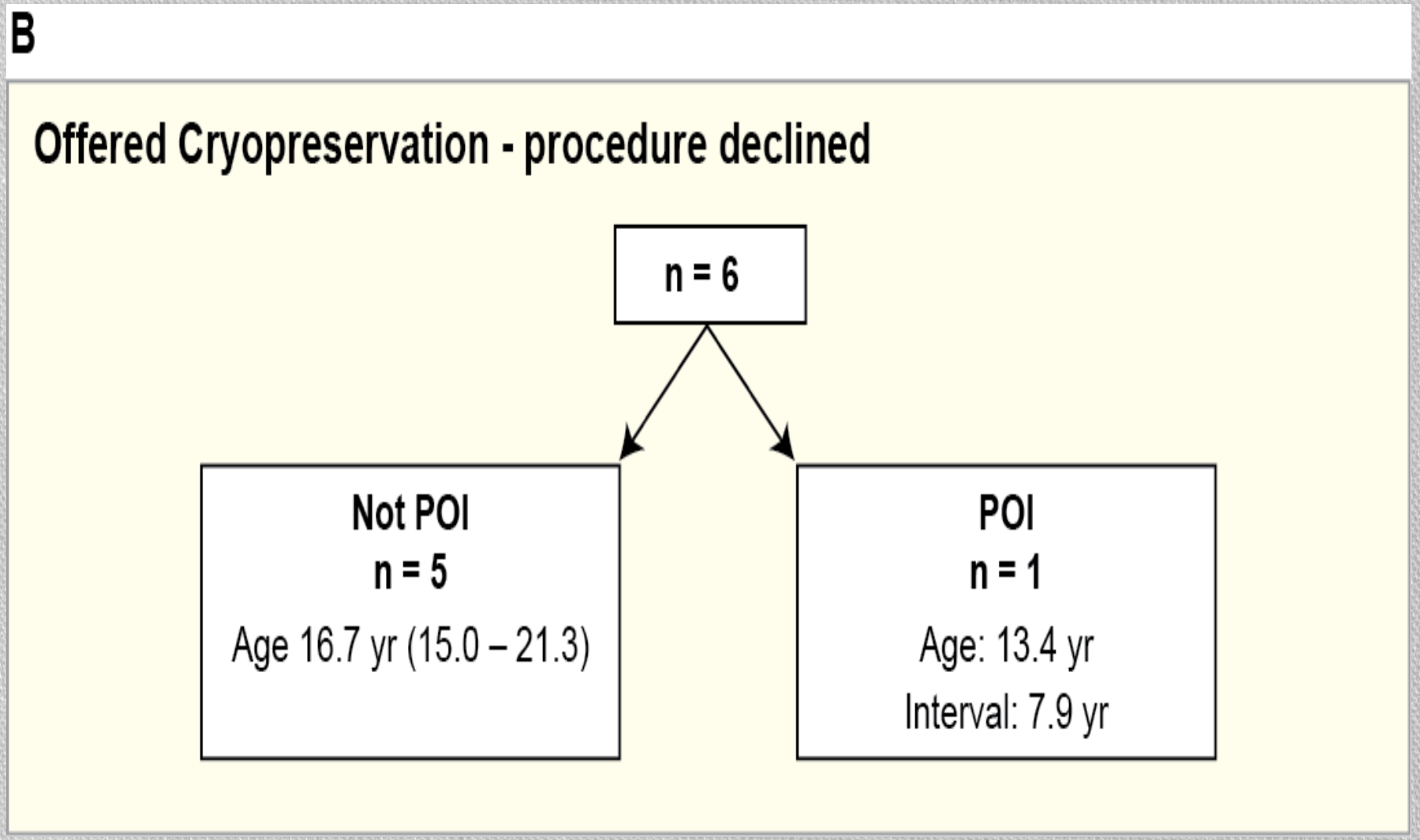
† metastatic deposits found on cortical strip


= 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

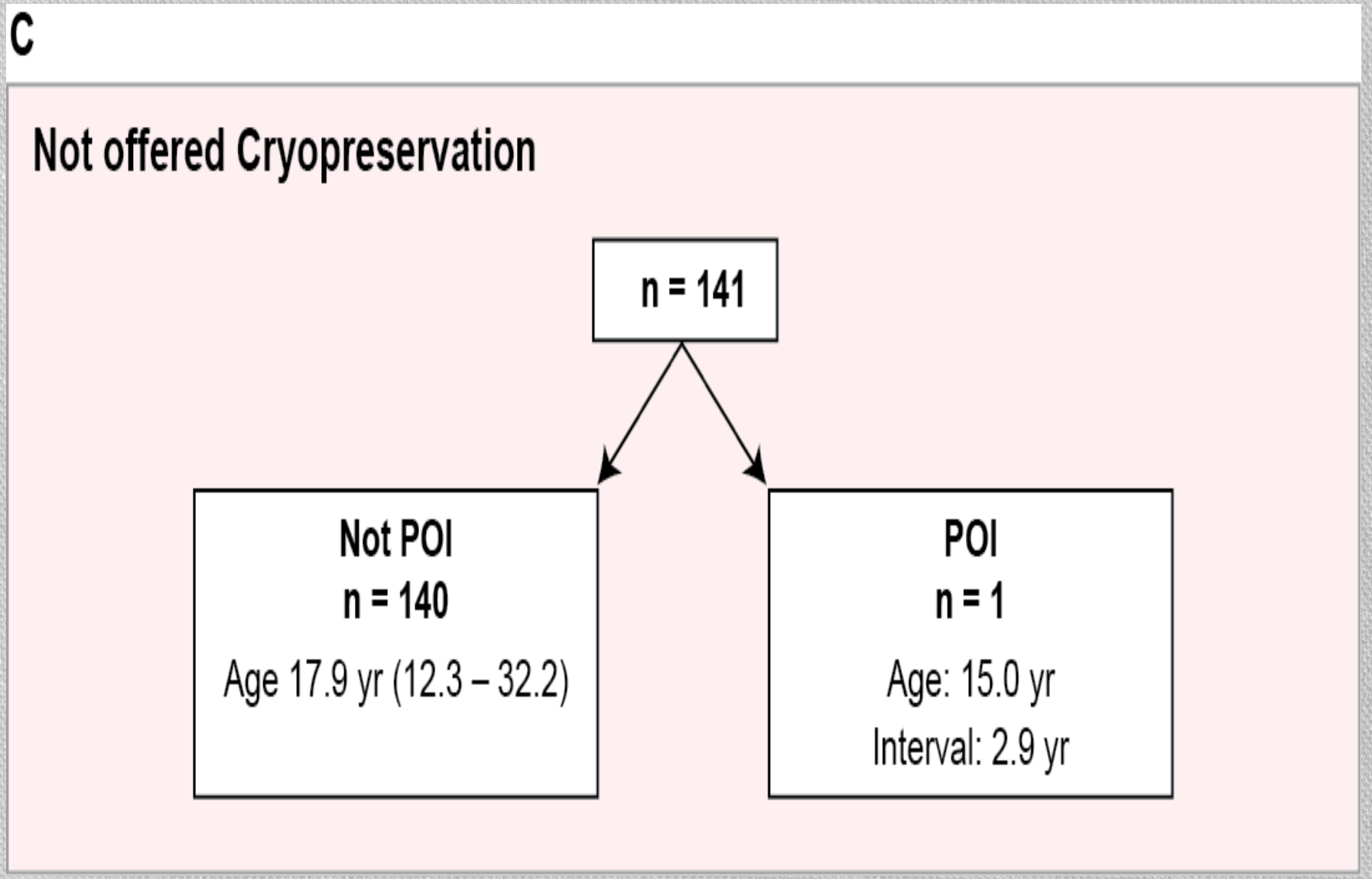
A

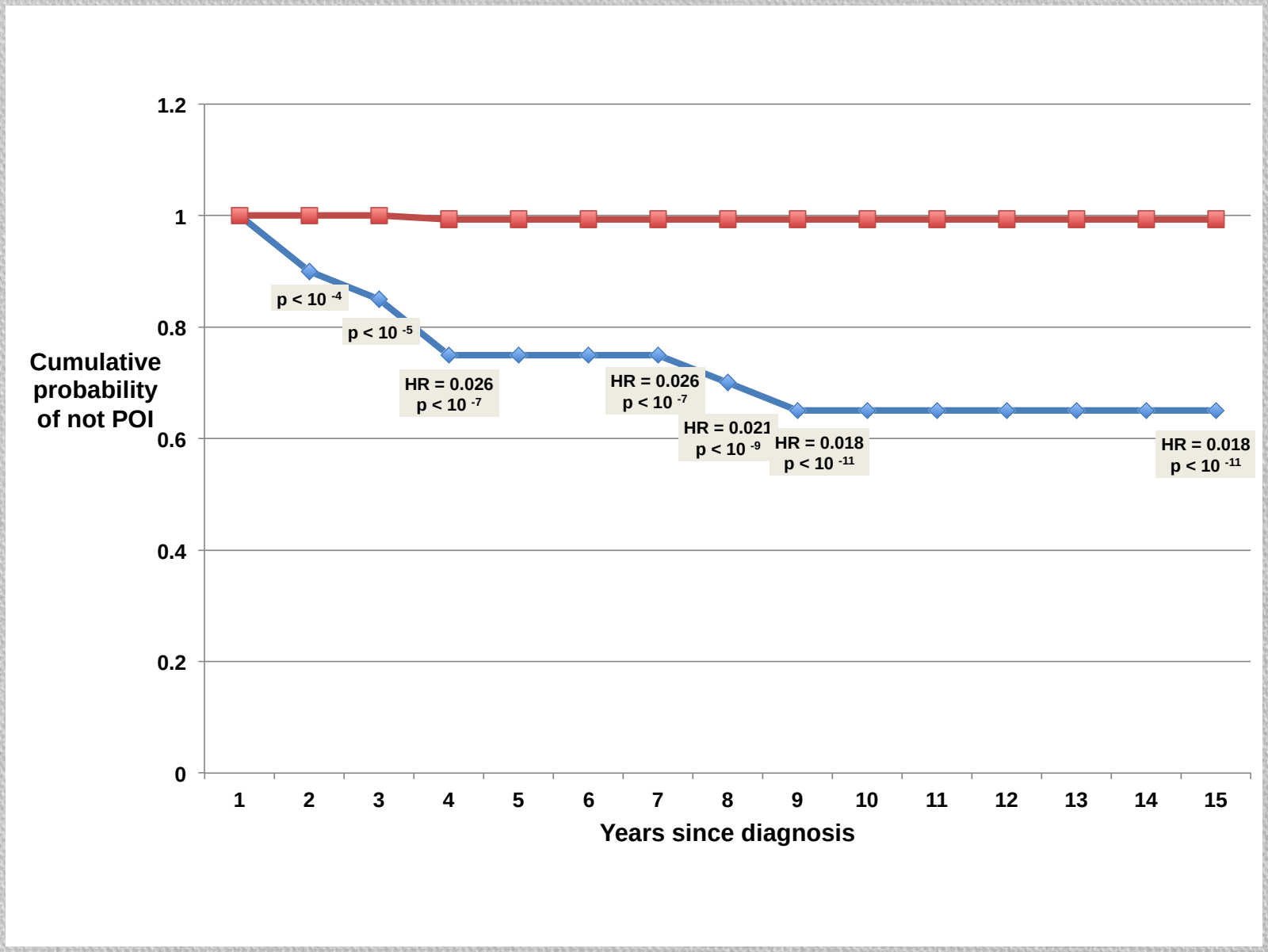

Offered Cryopreservation and Accepted
n = 14
Not POI
n = 8
Age 21.9 yr (13.3 – 30.7)
POI
n = 6
Age: 13.4 yr (11.2 – 15.3)
Interval: 1.7 yr (0.4 – 6.2)

B


Offered Cryopreservation - procedure declined
n = 6
Not POI
n = 5
Age 16.7 yr (15.0 – 21.3)
POI
n = 1
Age: 13.4 yr
Interval: 7.9 yr

C


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

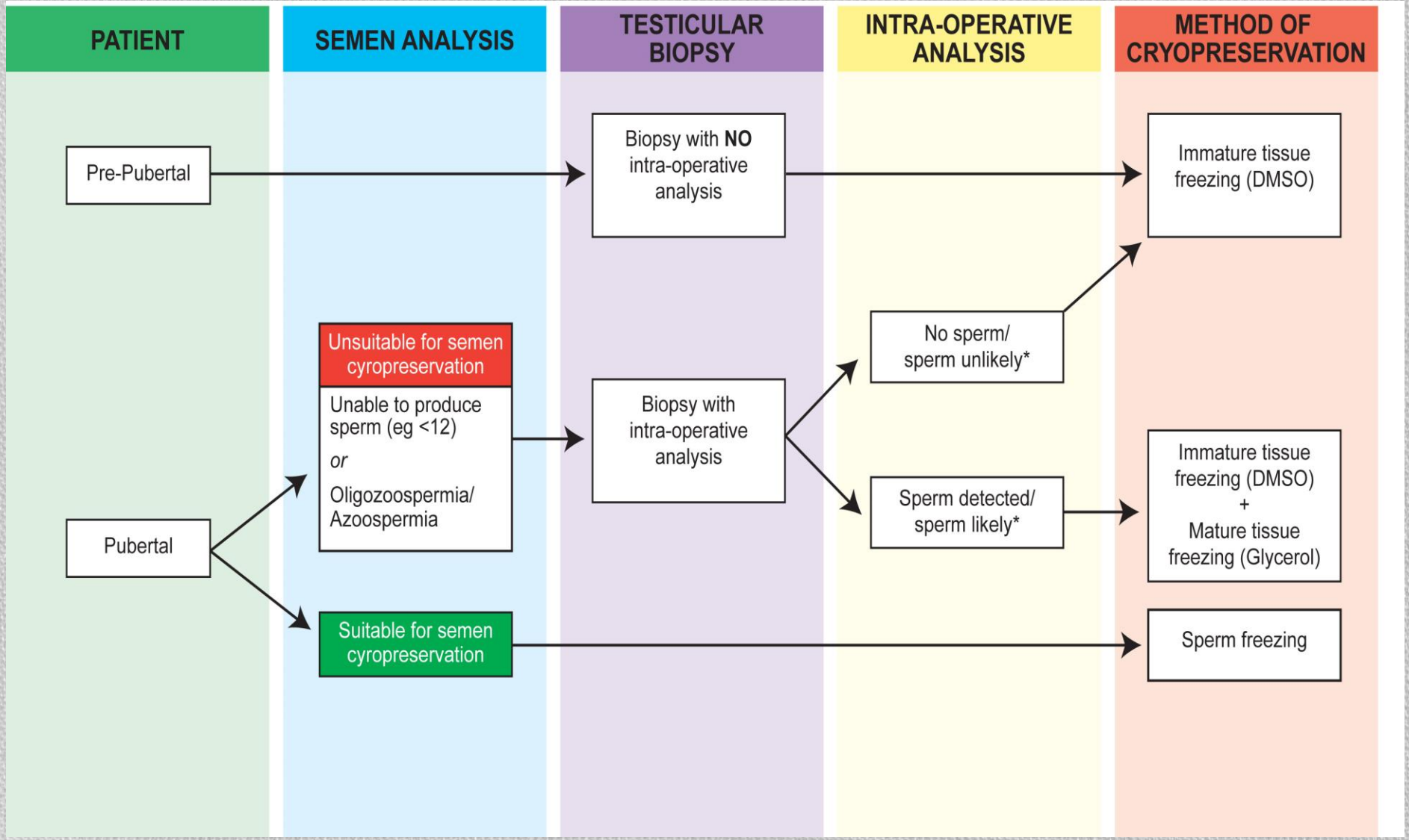

1.2
1
0.8
0.6
0.4
0.2
0
Cumulative probability of not POI
p < 10 -4
p < 10 -5
HR = 0.026
p < 10 -7
HR = 0.026
p < 10 -7
HR = 0.021
p < 10 -9
HR = 0.018
p < 10 -11
HR = 0.018
p < 10 -11
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
Years since diagnosis

Cryopreservation of ovarian cortical tissue – Edinburgh criteria

Selection criteria (1995,modified 2000)

- Age < 35 years
- No previous chemotherapy/radiotherapy if age >15 years
- Mild, non gonadotoxic chemotherapy if < 15 years
- A realistic chance of surviving five years
- A high risk of premature ovarian insufficiency
- Informed consent (Parent and where possible Patient)
- Negative HIV and Hepatitis serology
- No existing children

Algorithm for Tissue Cryopreservation



Cryopreservation of pre-pubertal testis tissue prior to cancer treatment

- Boys undergoing cancer treatment with >80% risk of infertility
- Biopsy to be taken with routine procedure
- Storage by Tissue Services according to ‘mature’ or ‘immature’ protocol
- Small piece of tissue to be used for research

Ethical Approval Granted – September 2013

Human Testis Xenografting