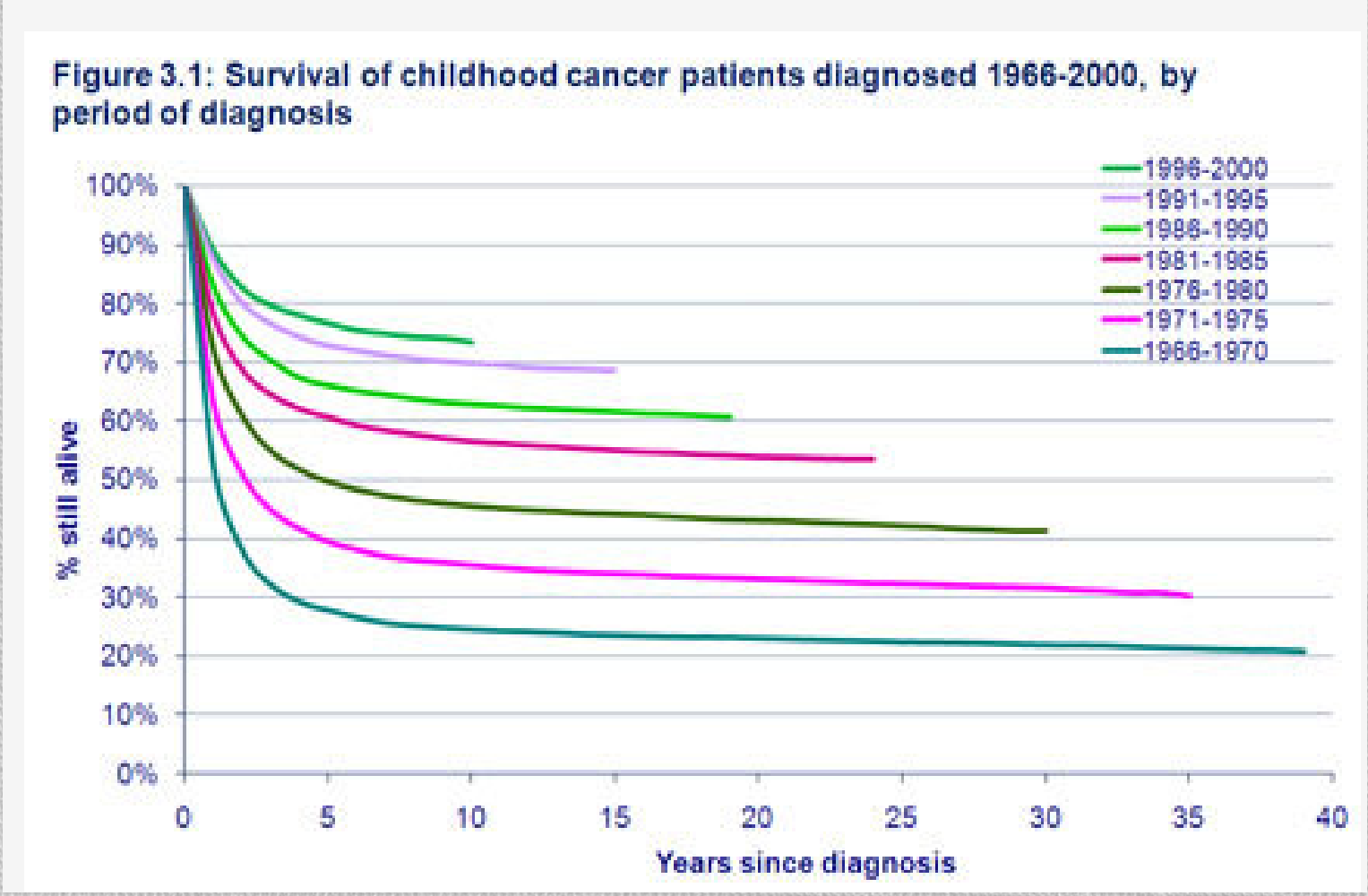
Fertility: Its Biology and preservation

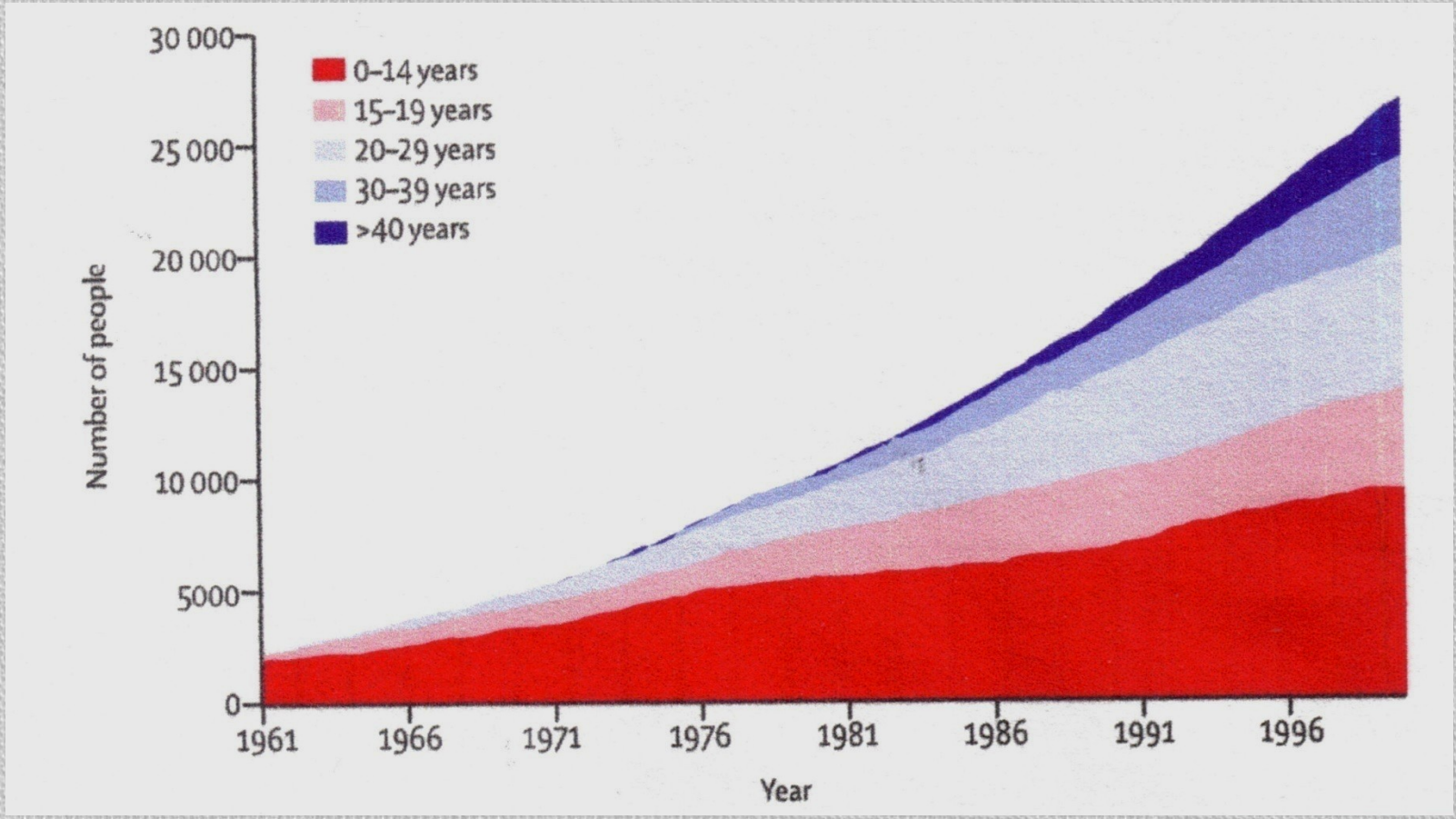
Professor W Hamish B Wallace

Dr Thomas W Kelsey

Improved Five Year Survival (1966-2000)



Increasing numbers of five year UK survivors by current age



Skinner et al, Lancet Oncology, 2006

Cure at a cost

Sustain survival rates

Minimise late effects

Risk assessment for fertility preservation

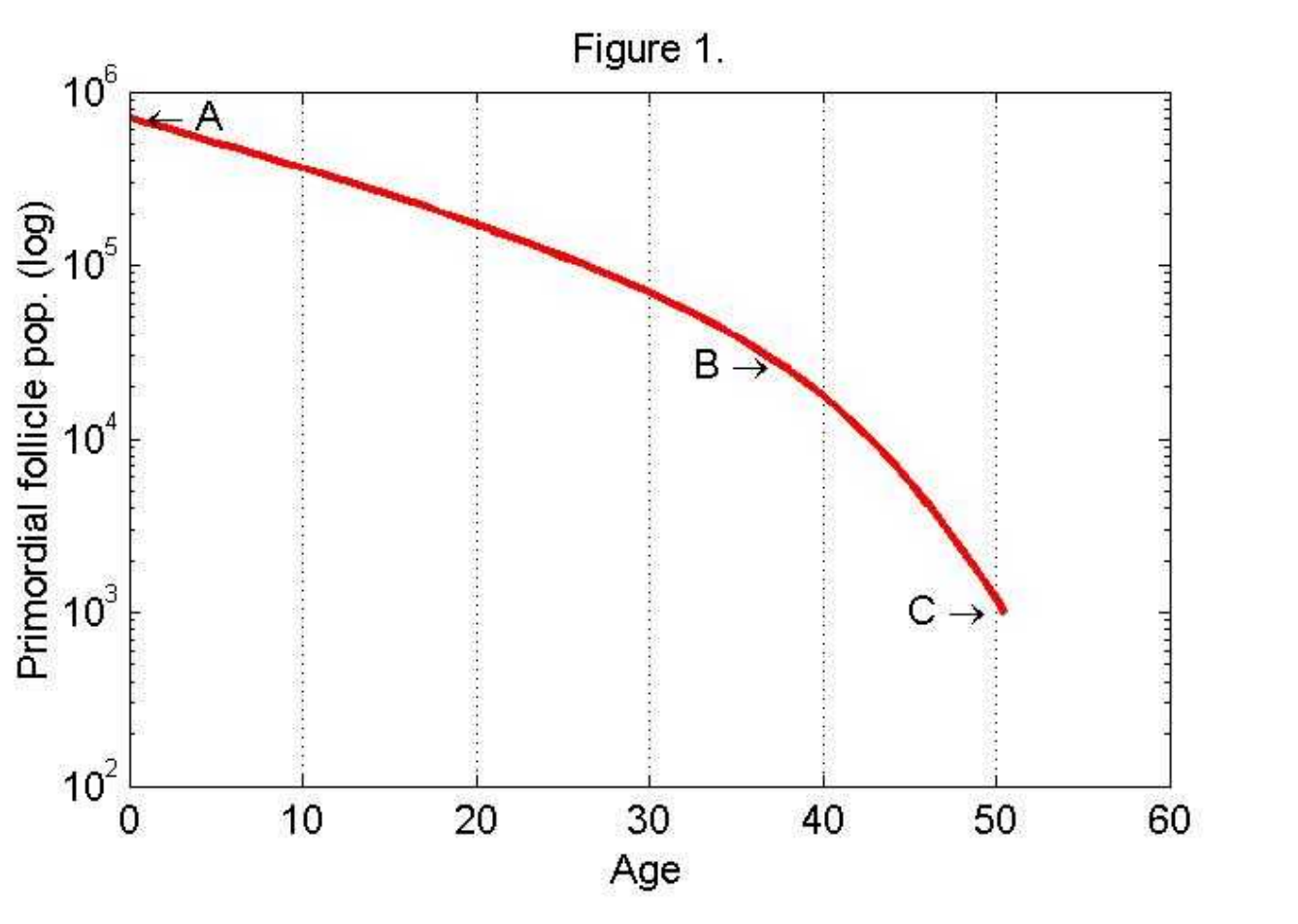
- Intrinsic factors
  - Health status of patient
  - Consent (Patient/Parent)
  - Assessment of ovarian reserve
- Extrinsic factors
  - Nature of predicted treatment
    - High/Medium/Low/Uncertain Risk
  - Time available
  - Expertise available

Wallace WH et al. JCO, 2012

Risk of infertility

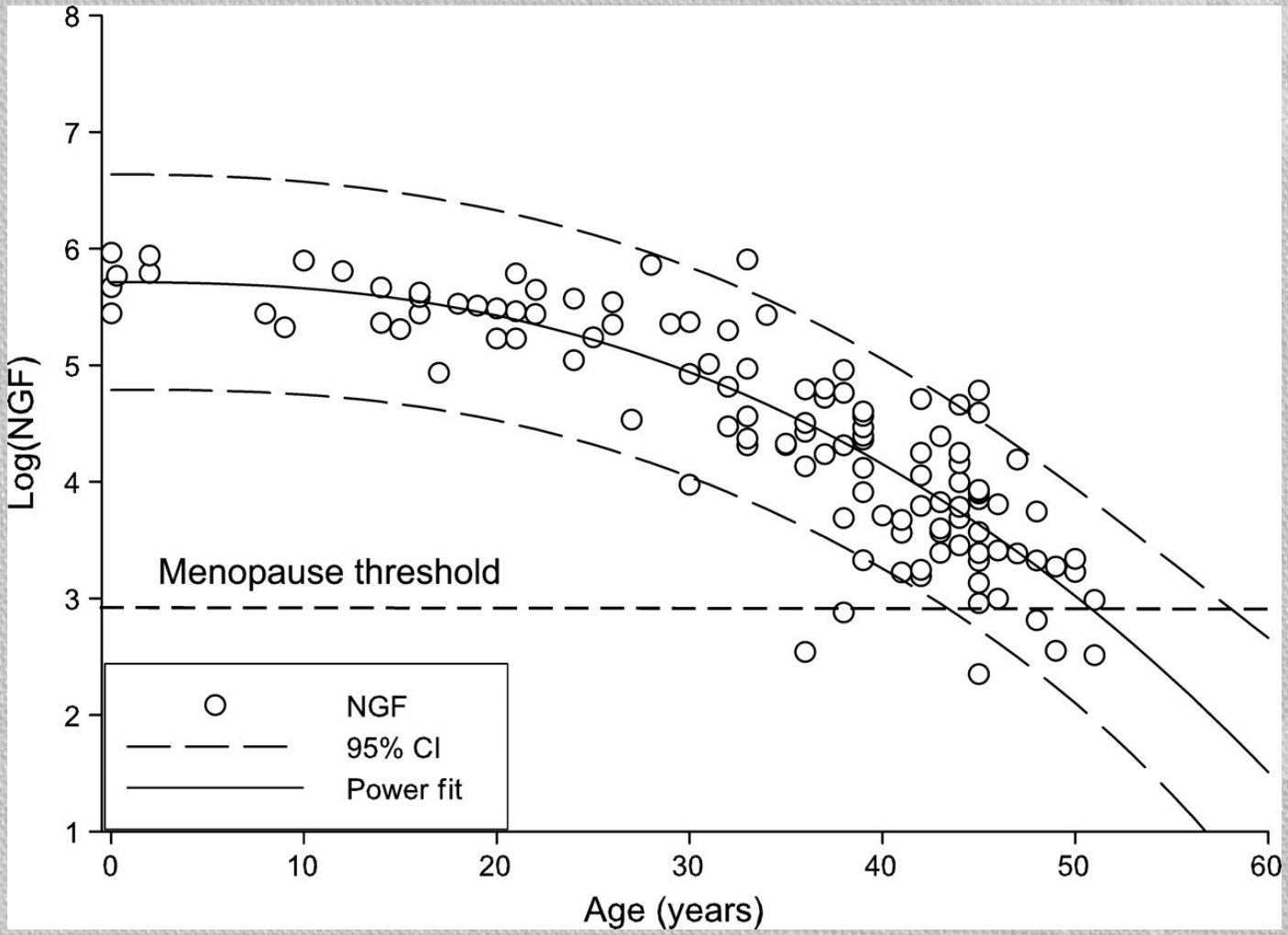
Low risk (<20%)	Medium risk	High risk (>80%)
ALL Wilms' tumour Brain tumour Sx, RT < 24Gy Soft tissue sarcoma (stage1) Hodgkin's Lymphoma HL(Low stage)	AML Osteosarcoma Ewing's sarcoma STS: stage II/III Neuroblastoma NHL Brain tumour RT>24Gy HL (High Stage)	Total Body Irradiation Pelvic/testes RT Chemo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

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

Methodology

- D

ata aggregation

- Systematic search for data sources from the literature
  - Tables, charts, descriptive statistics
- Our own data – if available

- D

ata selection to create data set

- Exclusion & Inclusion criteria (e.g. exclude infertile)
- Homogeneous data set that approximates the healthy population for a wide range of ages.

Methodology

omparative analysis of biologically plausable models

- goodness of fit (coefficient of determination: r^2)
- minimise overfitting
  - too accurate to generalise to unseen data
  - too many peaks and troughs
- minimise underfitting
  - not accurate enough
  - too few peaks and troughs

Methodology

- M

odel validation is important

- the highest-ranked candidate could be a result of serendipity
- small changes in the data could promote other candidates

- T

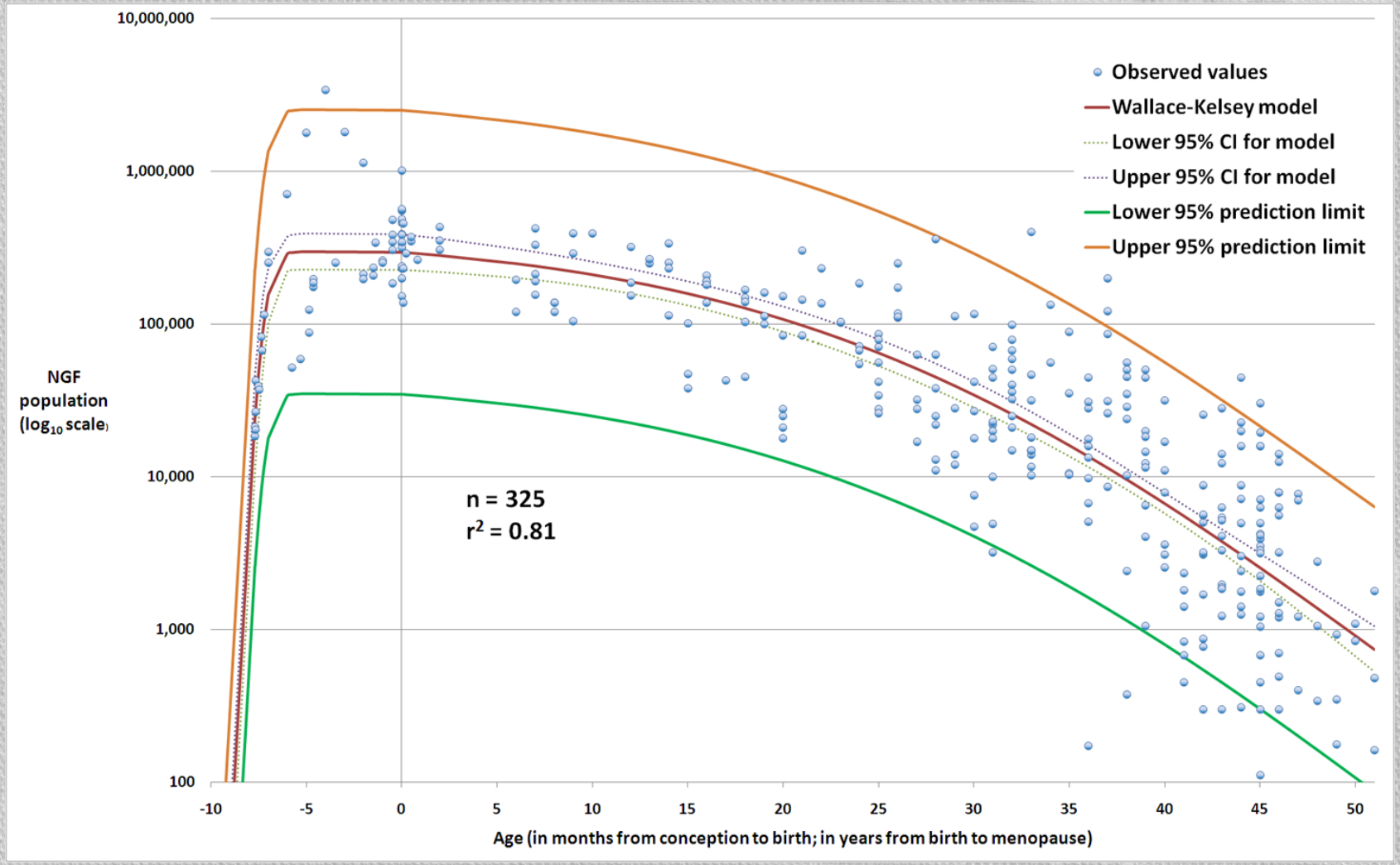
here are various techniques

- k-fold: split the data into 10 equal subsets
- train on 90%, test using 10%, for each choice of 10%
- model validated if the prediction error is similar each time

Data set:
Eight quantitative histological studies

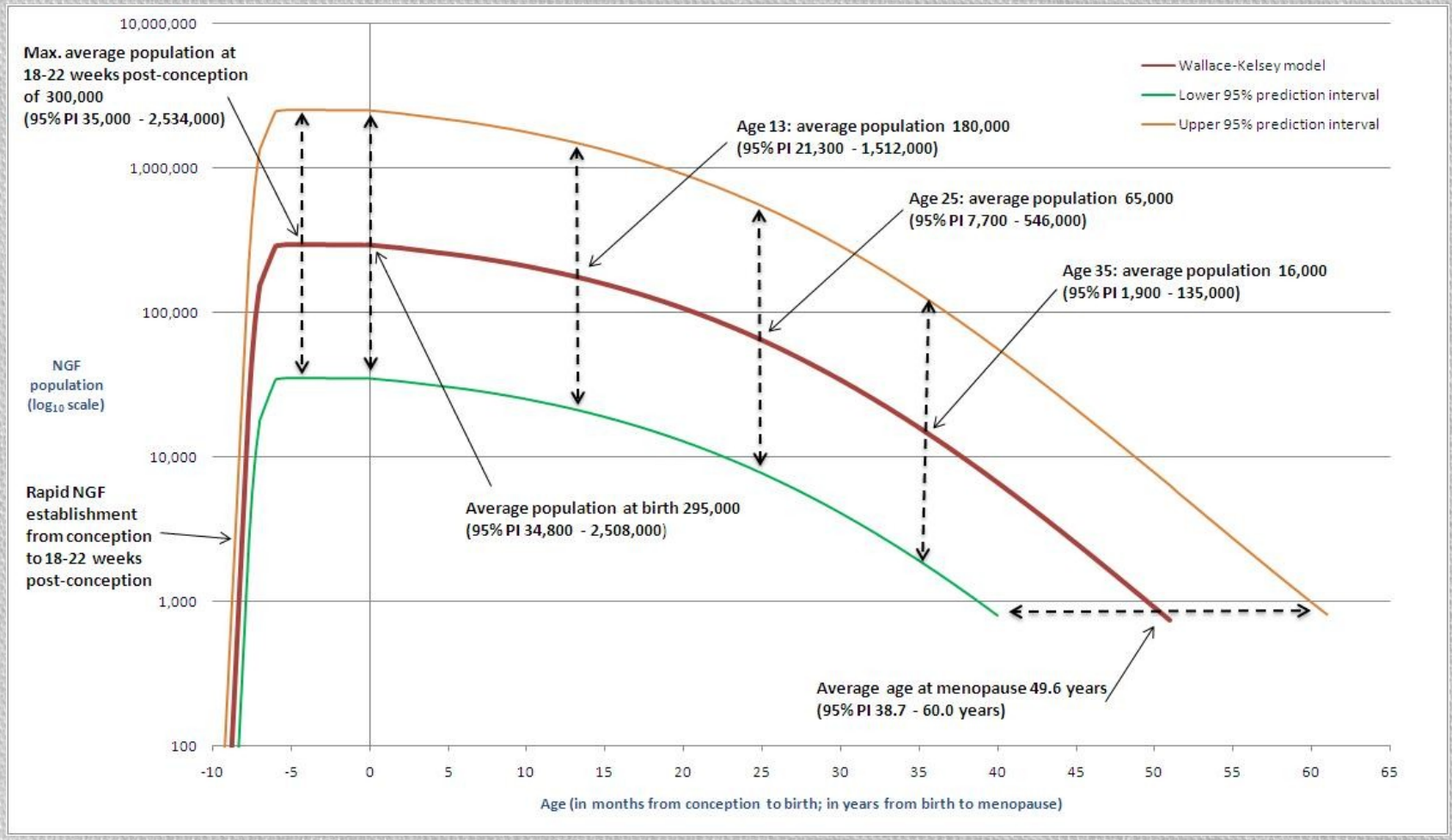
Study			Statistics			
Number	First author	Year	No. ovaries	Min. age	Max. age	Median age
1	Bendsen	2006	11	−0.6	−0.6	−0.6
2	Baker	1963	11	−0.6	7.0	−0.2
3	Forabosco	2007	15	−0.5	0.5	−0.3
4	Block	1953	19	−0.2	0.0	0.0
5	Hansen	2008	122	0.1	51.0	38.0
6	Block	1951	86	6.0	44.0	28.0
7	Gougeon	1987	52	25.0	46.0	39.5
8	Richardson	1987	9	45.0	51.0	46.0
Overall			325	−0.6	51.0	32.0

The Wallace-Kelsey NGF Model



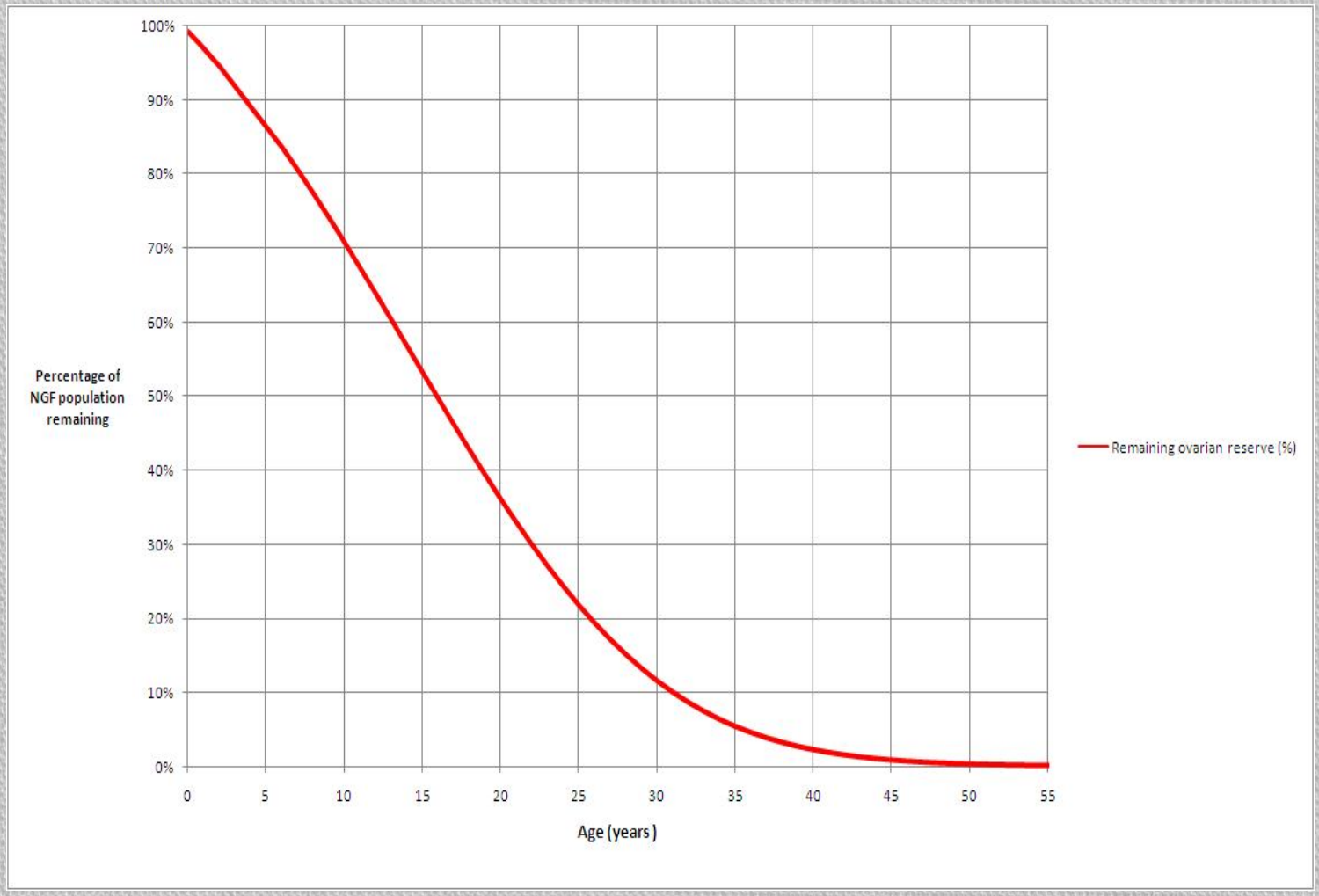
Wallace & Kelsey (2010) PloS ONE

Ovarian reserve: Conception to Menopause



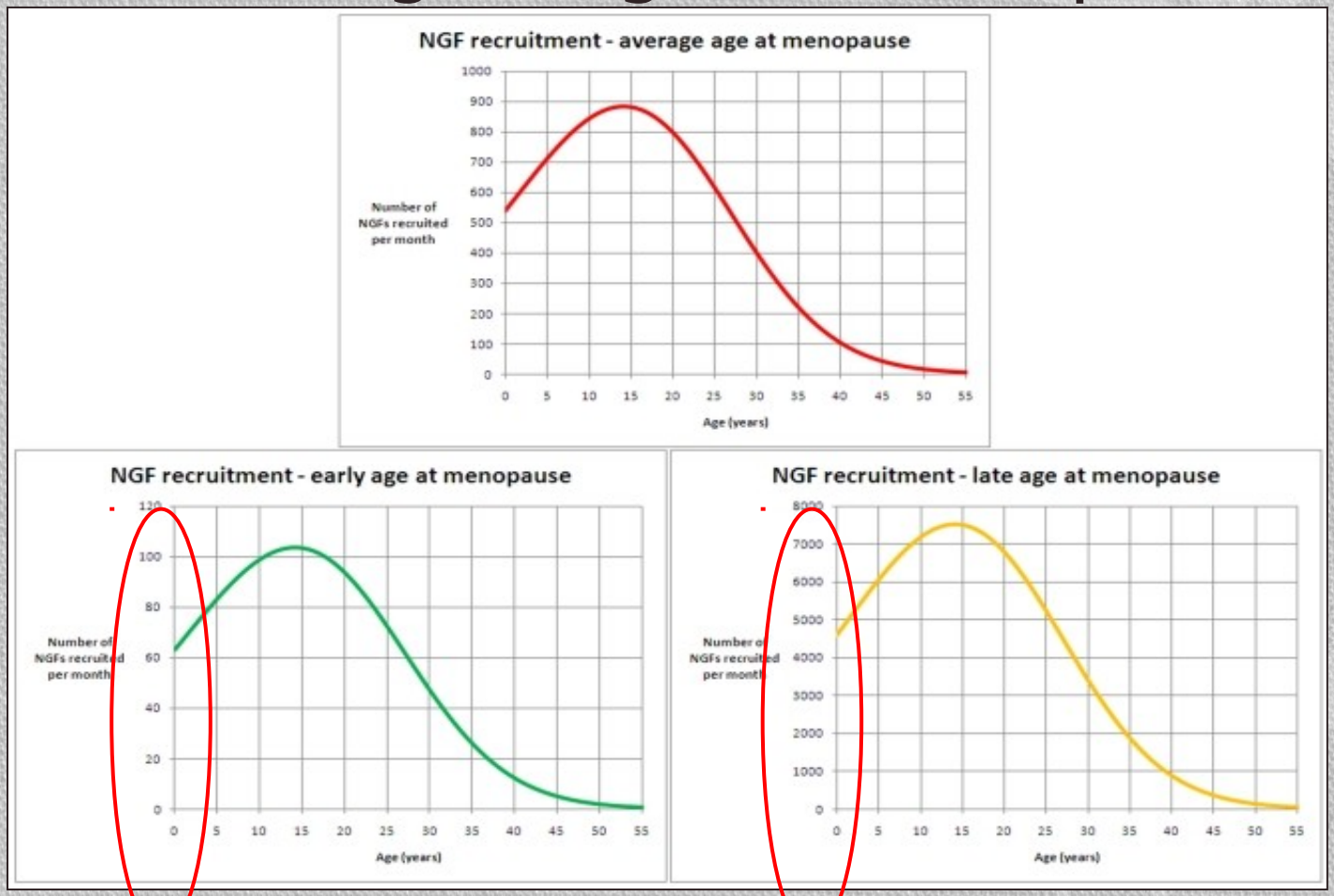
Wallace & Kelsey (2010) PloS ONE

Percentage of NGF population remaining with increasing age



Wallace & Kelsey (2010) PloS ONE

Follicular Recruitment from the Pool according to age of menopause



There is close to 100 fold difference in recruitment between the early and late menopause groups

Wallace & Kelsey, 201

External Validation

- Using our model and the distribution of menopausal ages derived from the population based Prospect-EPIC cohort (n = 4,037)
- We obtain linked models for both age at menopause and declining NGF count with increasing age
- The distributions of observed age at natural menopause and predicted age at natural menopause show close conformity

- This gives us increased confidence:

A) that our model correctly describes something that is impossible to measure *in vivo*

B) that a larger than average NGF pool means later than average menopause (and *vice versa*)

Depmann, Faddy et al. JCEM 2015

Indirect measures of ovarian reserve

- Anti Mullerian Hormone (AMH) is 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

- Ovarian Volume (OV)
- Decreases later in life
- In line with the decrease in NGF population
- Hypothesis: a large ovary contains a large number of NGFs

- Antral Follicle Counts (AFC)
- Not covered in this talk

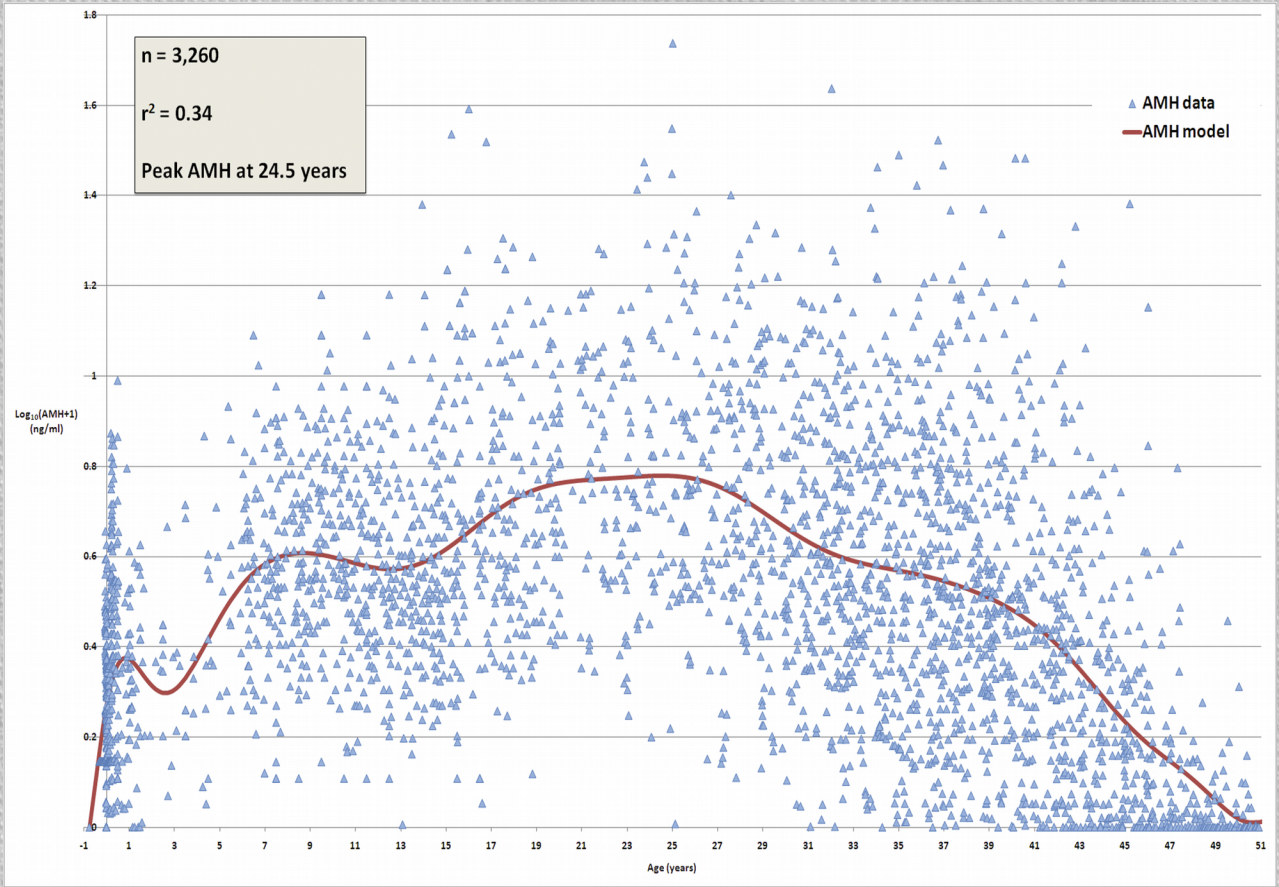
Kelsey, Anderson et al. Molecular Human Reproduction 2012

AMH Data set

Ref.	1st Author	Data	Assay	n	Average age	Age range	Det. lim.	Intra CV	Inter CV
[35]	Soto	Graph	IBC	58	30.3 (mean)	±8.7 SD	0.10	5.3	8.7
[38]	Guibourdenche	Graph	IBC	192	NS	−0.3–1.0	0.30	5.3	8.7
[39]	Hudecova	Graph	IBC	64	46.3 (mean)	±6.4 SD	0.70	12.3	12.3
[40]	Mulders	Graph	IBC	82	29.9	19.6–35.6	NS	5.0	8.0
[41]	Pastor	Graph	IBC	42	NS	18.0–50.0	0.10	5.3	7.8
[42]	Piltonen	Graph	IBC	44	31.6 (mean)	21.0–44.0	NS	5.1	6.6
[20]	van Rooij	Graph	IBC	162	NS	25.0–46.0	0.05	5.0	8.0
[43]	Laven	Graph	IBC	41	NS	20.0–36.0	0.05	5.0	8.0
[19]	de Vet	Graph	IBC	82	29.0	±4.0 SD	0.05	5.0	8.0
[44]	Knauf	Graph	IBC	83	34.2 (mean)	±3.4 SD	0.03	11.0	11.0
[45]	Lee	Graph	IBC	225	NS	0.0–51.0	0.50	9.0	15.0
[36]	La Marca	Graph	IBC	24	44.0 (mean)	±2.8 SD	0.24	5.0	8.0
[29]	Hagen	Graph	IBC	891	NS	0.0–68.0	0.03	7.8	11.6
[46]	van Beek	Graph	DSL	82	29.0	20.0–35.0	NS	5.0	15.0
[47]	Sanders	Graph	DSL	43	24.1 (mean)	0.1–51.0	0.01	NS	11.4
[34]	van Disseldorp	Graph	DSL	144	37.9 (mean)	25.0–46.0	0.03	11.0	11.0
[48]	Tehrani	Graph	DSL	267	27.1	16.0–44.0	0.01	5.2	9.1
[49]	Dorgan	Graph	DSL	204	44.7 (mean)	33.3–54.7	0.06	8.0	8.0
[30]	Ahmed	Raw	DSL	128	8.5	0.5–16.5	0.50	8.0	8.0
[25]	Nelson	Raw	DSL	441	36.1	21.9–47.8	0.03	3.4	8.6
	Total IBC			1,990	15.8	−0.3–68.0			
	Total DSL			1,309	35.4	0.2–54.7			
	Total *n*			3,299	34.0	−0.3–68.0			
	Censored total n			**3,260**	**28.3**	**−0.3–54.3**			

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

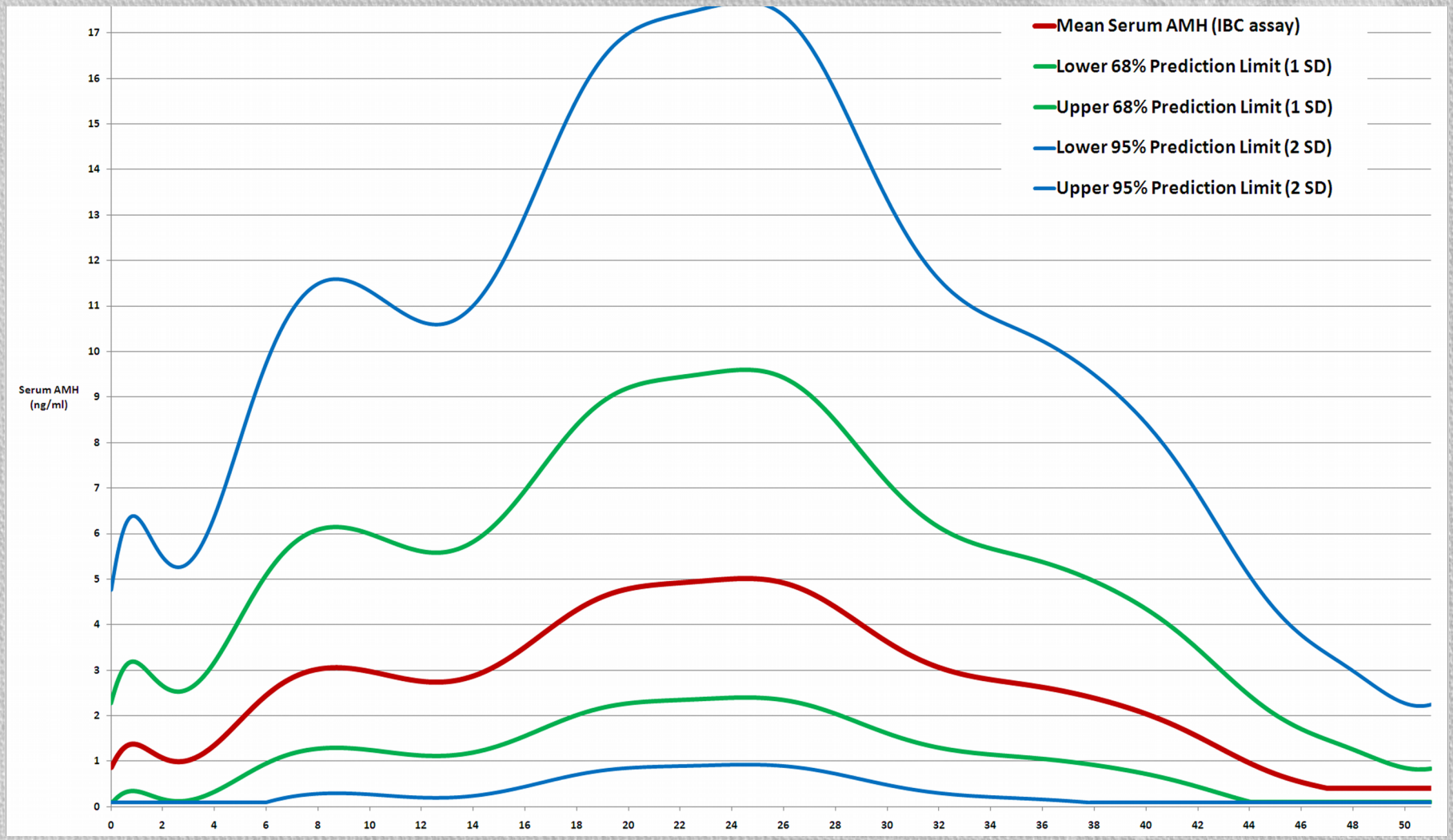
(a single data set of healthy females (n=3260) from twenty different sources)



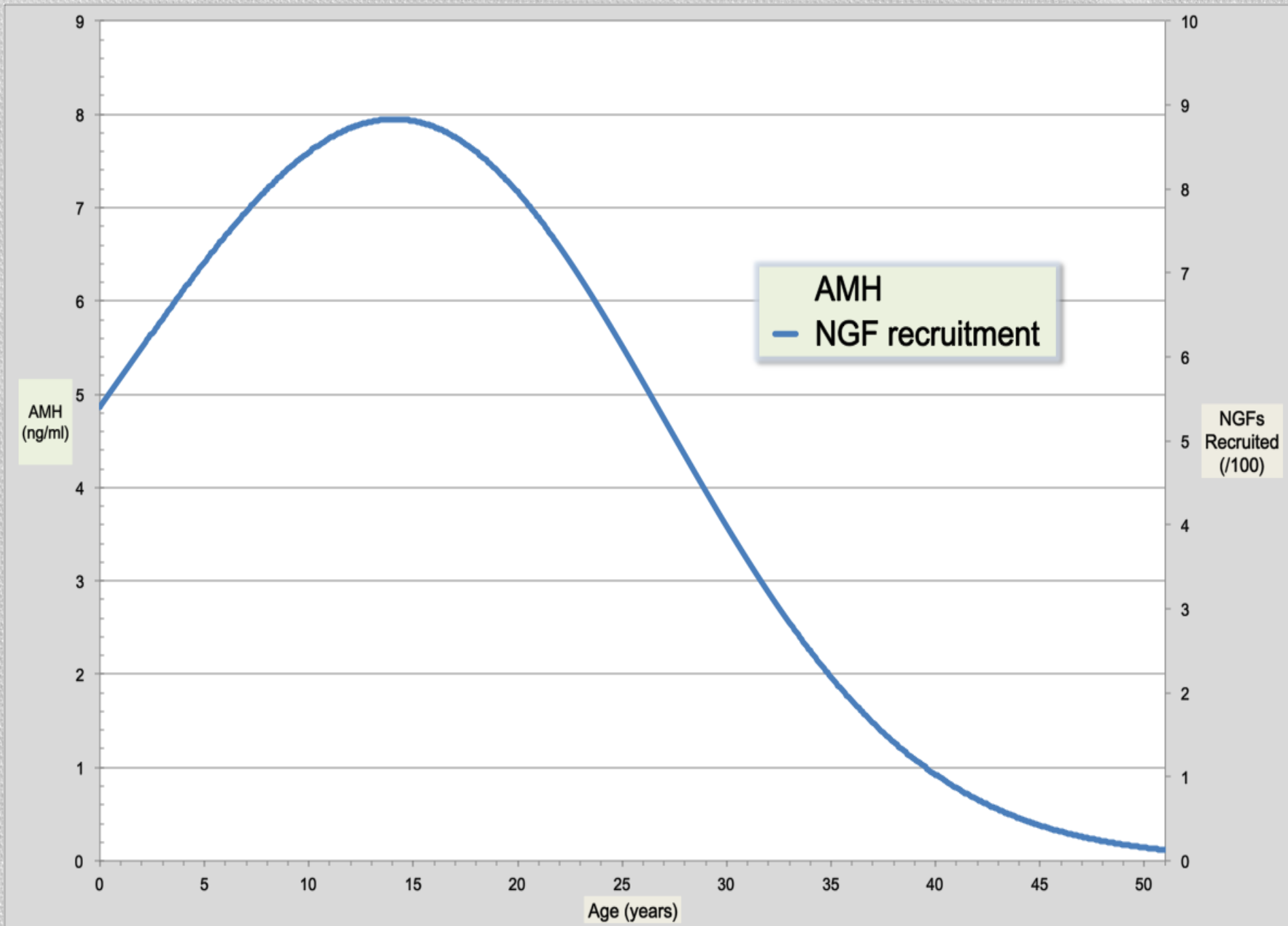
Kelsey et al. PLoS ONE 2011

AMH: Normogram from birth to menopause

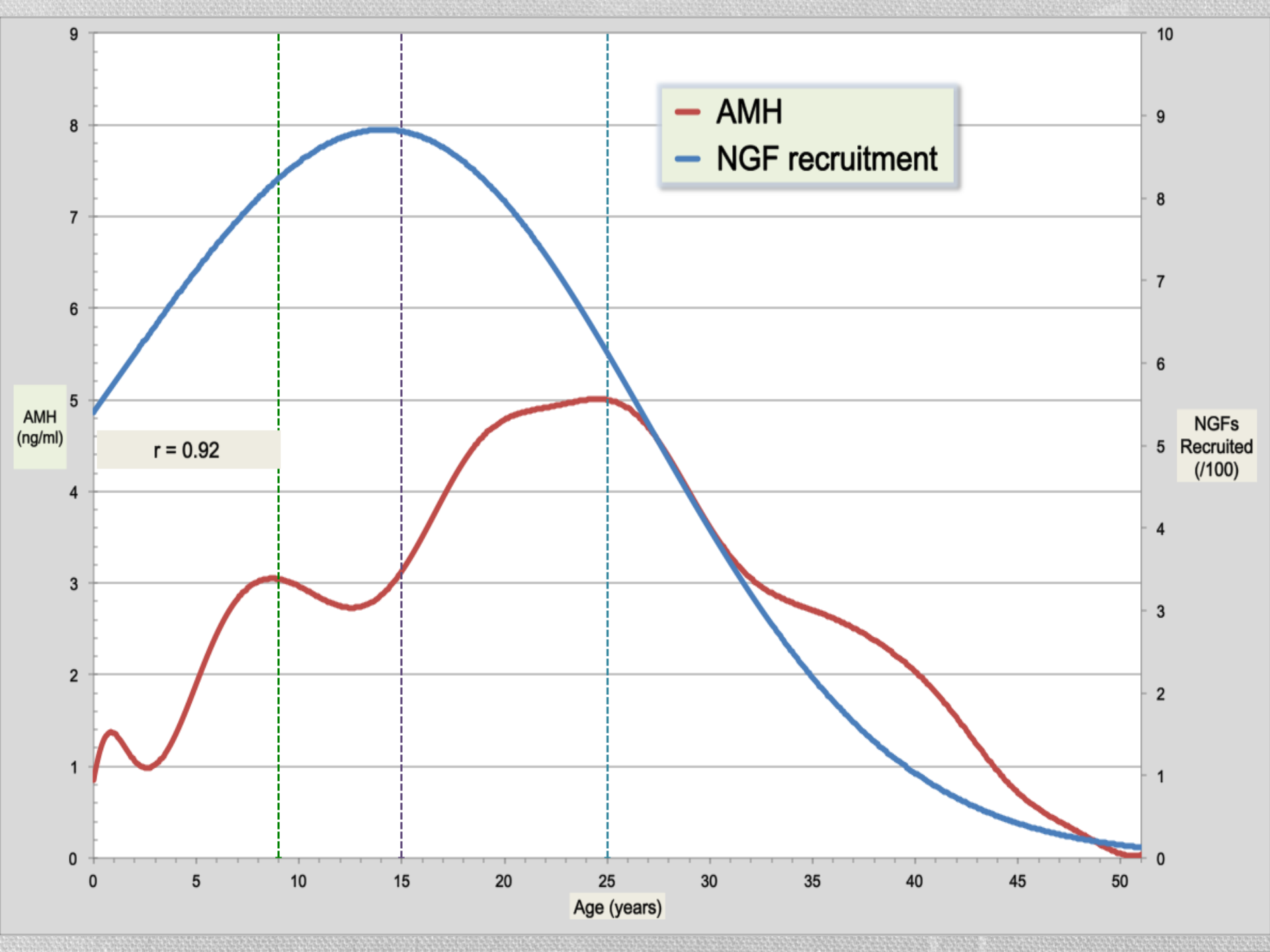
The green and blue lines are the 68% and 95% prediction limits for the model

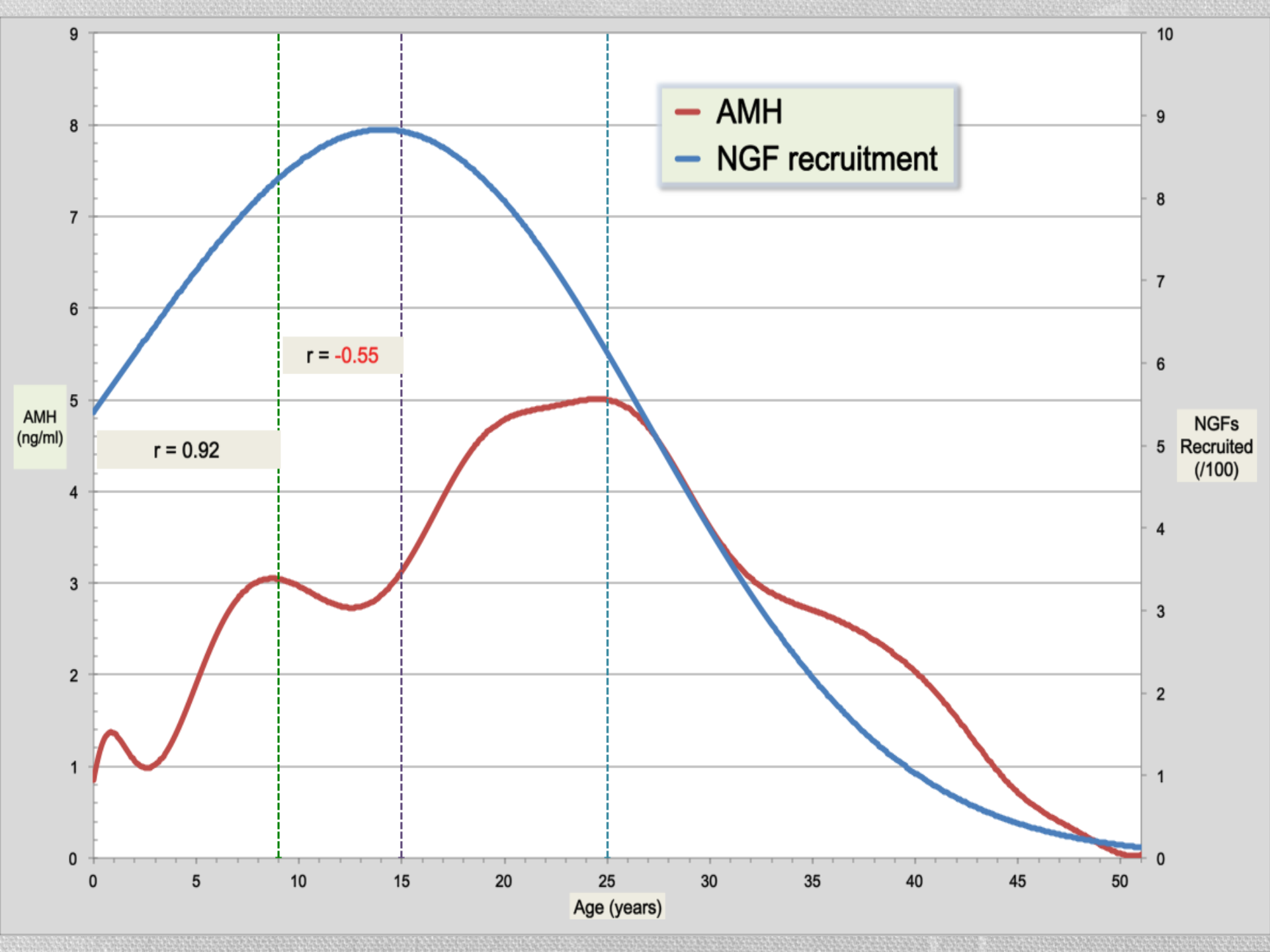


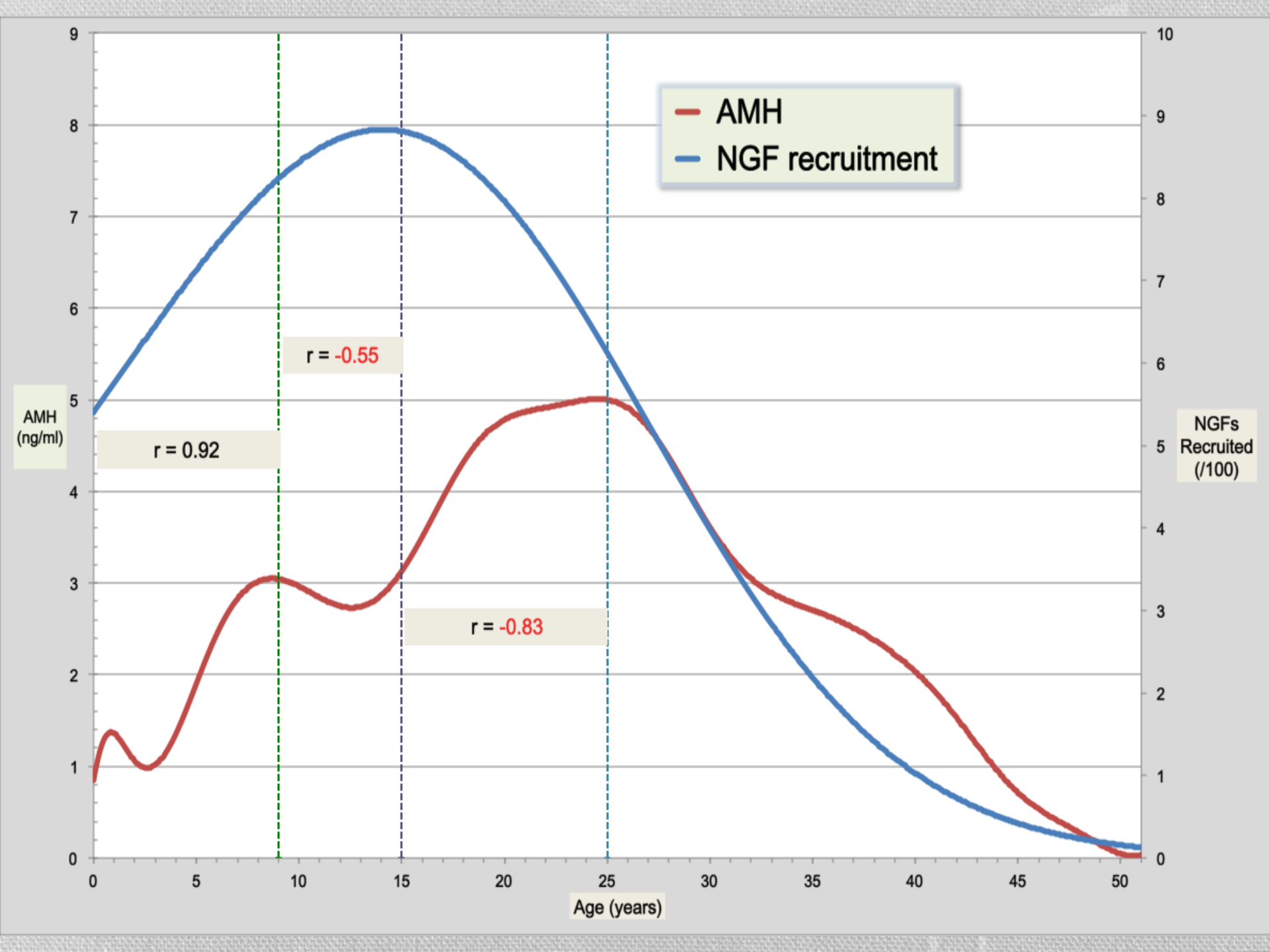
Kelsey et al. PLoS ONE 2011

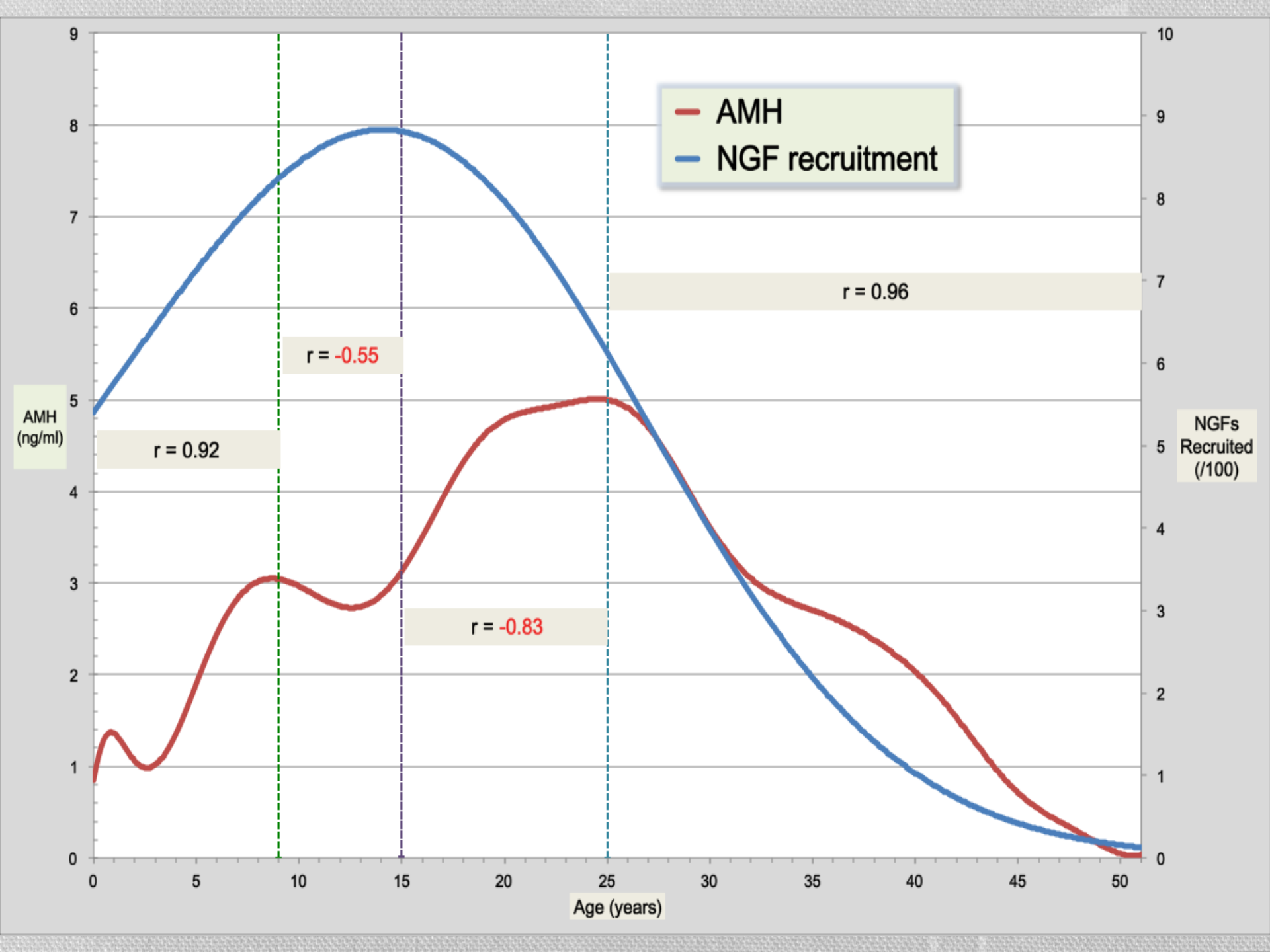

AMH
NGF recruitment
AMH (ng/ml)
NGFs Recruited (/100)
Age (years)
0
1
2
3
4
5
6
7
8
9
10
0
5
10
15
20
25
30
35
40
45
50


AMH
NGF recruitment
AMH (ng/ml)
NGFs Recruited (/100)
Age (years)
0
1
2
3
4
5
6
7
8
9
10
0
5
10
15
20
25
30
35
40
45
50


AMH
NGF recruitment
r = 0.92
AMH (ng/ml)
NGFs Recruited (/100)
Age (years)
0
1
2
3
4
5
6
7
8
9
10
0
5
10
15
20
25
30
35
40
45
50


AMH
NGF recruitment
r = -0.55
r = 0.92
AMH (ng/ml)
NGFs Recruited (/100)
Age (years)
0
1
2
3
4
5
6
7
8
9
10
0
5
10
15
20
25
30
35
40
45
50


AMH
NGF recruitment
r = -0.55
r = 0.92
r = -0.83
AMH (ng/ml)
NGFs Recruited (/100)
Age (years)
0
5
10
15
20
25
30
35
40
45
50
0
1
2
3
4
5
6
7
8
9
10


AMH
NGF recruitment
r = 0.92
r = -0.55
r = -0.83
r = 0.96
AMH (ng/ml)
NGFs Recruited (/100)
Age (years)
0
5
10
15
20
25
30
35
40
45
50
0
1
2
3
4
5
6
7
8
9
10

Relationship between AMH and Follicular recruitment

- P

re-puberty: Strong positive correlation (r = 0.92). AMH and follicular recruitment increasing

- P

ubertal: Moderate negative correlation (r = -0.55). AMH falls as follicular recruitment continues to rise (Transition Phase)

- P

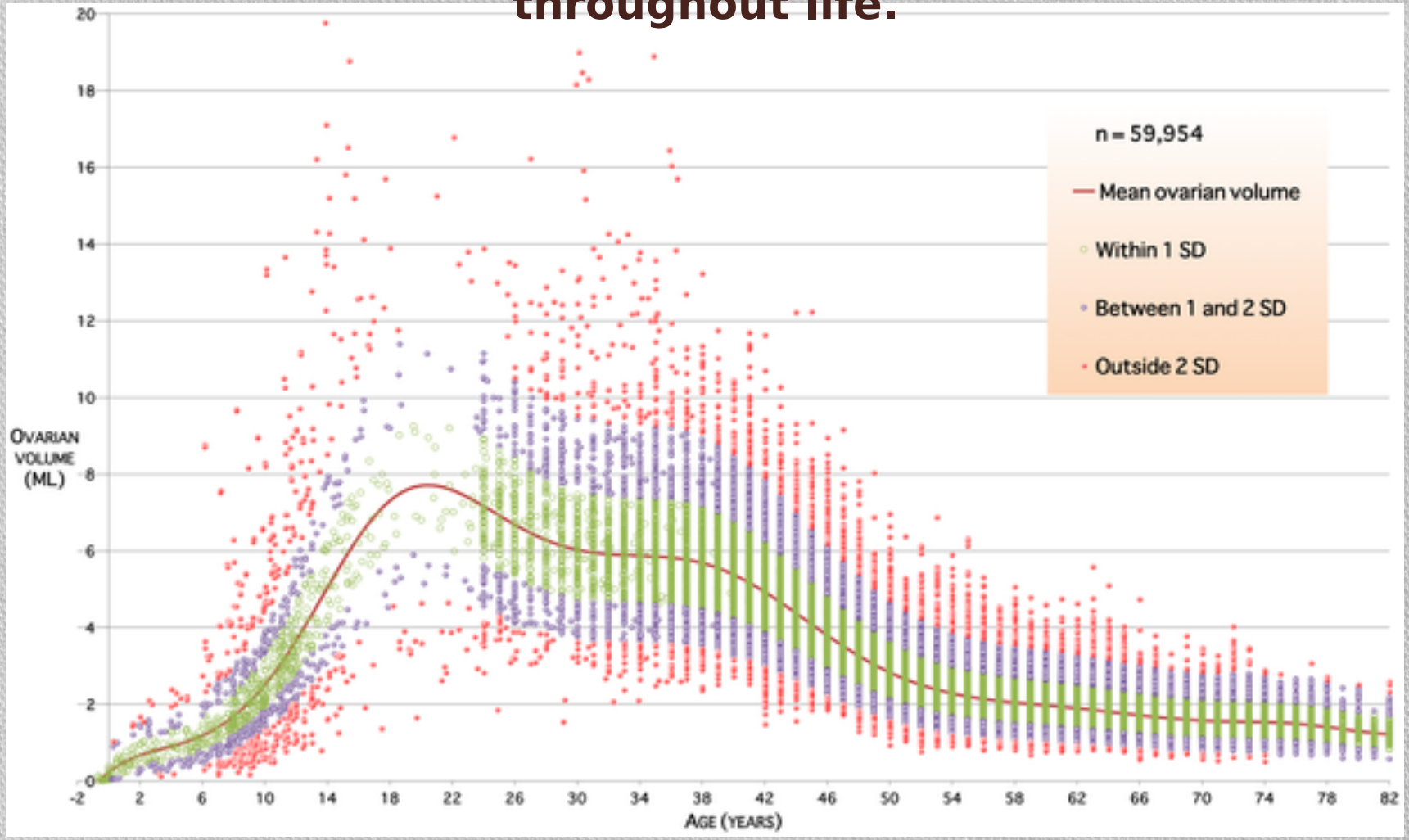
ost–pubertal (15 - 25): Strong negative correlation (r= -0.83). AMH rises as Follicular recruitment falls.

- P

ost Age 25 years: Very Strong positive correlation (r=0.96). AMH level is a good surrogate marker of declining ovarian reserve

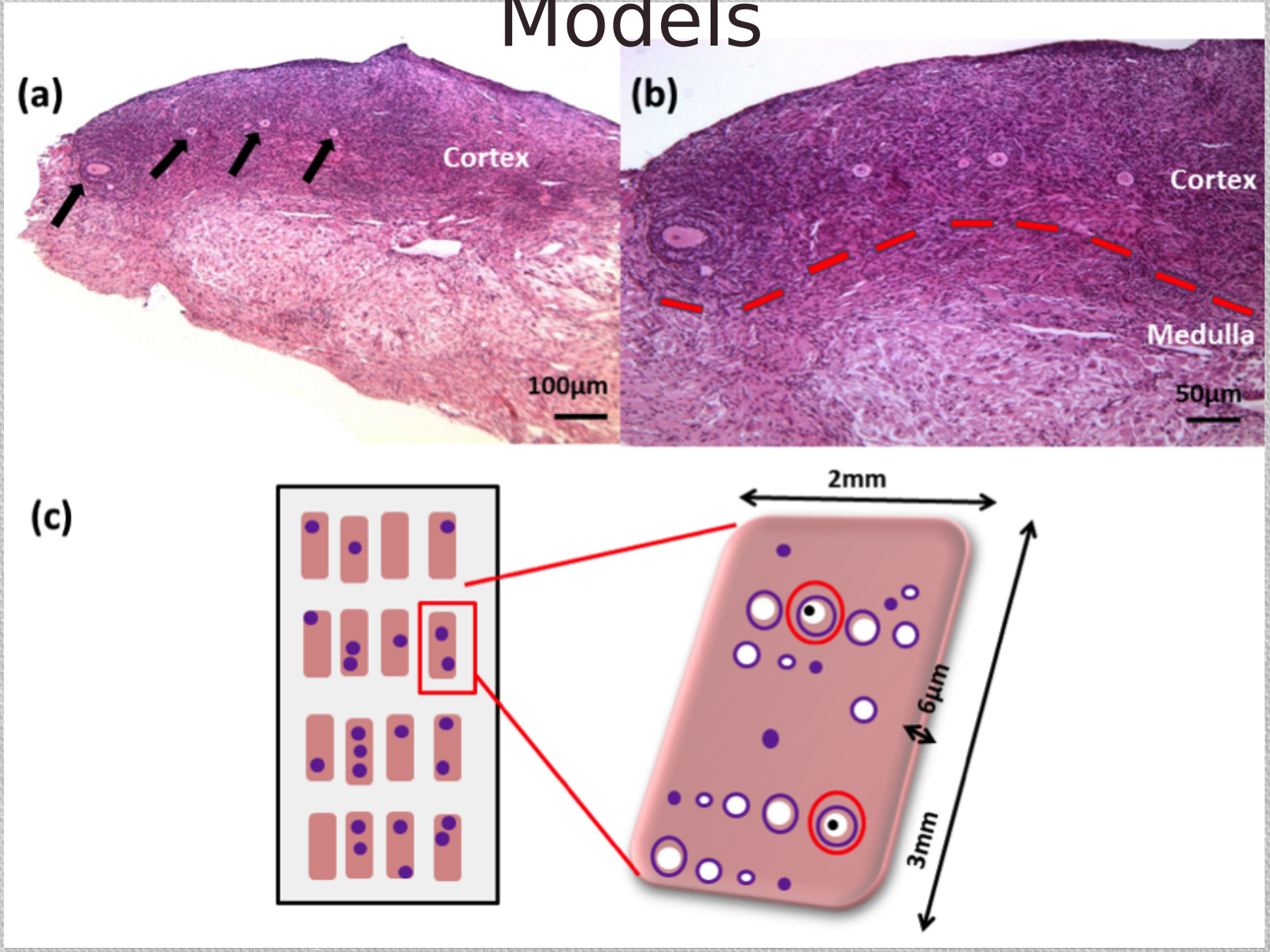
Fleming, Kelsey et al. Fertility & Sterility 2012

The normative validated model of ovarian volume throughout life.

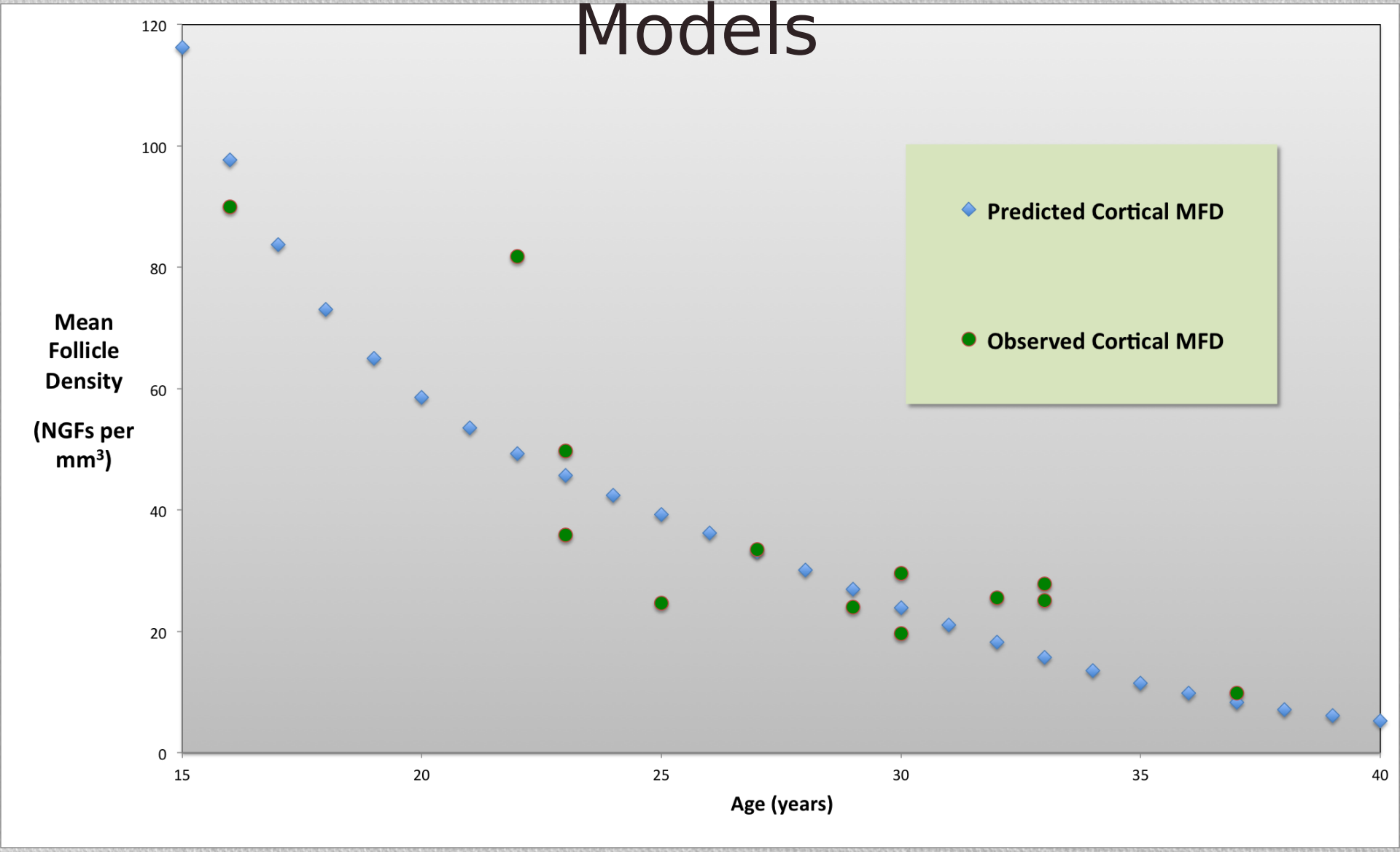


Kelsey TW, Dodwell SK, Wilkinson AG, Greve T, Andersen CY, et al. (2013) Ovarian Volume throughout Life: A Validated Normative Model. PLoS ONE 8(9): e71465

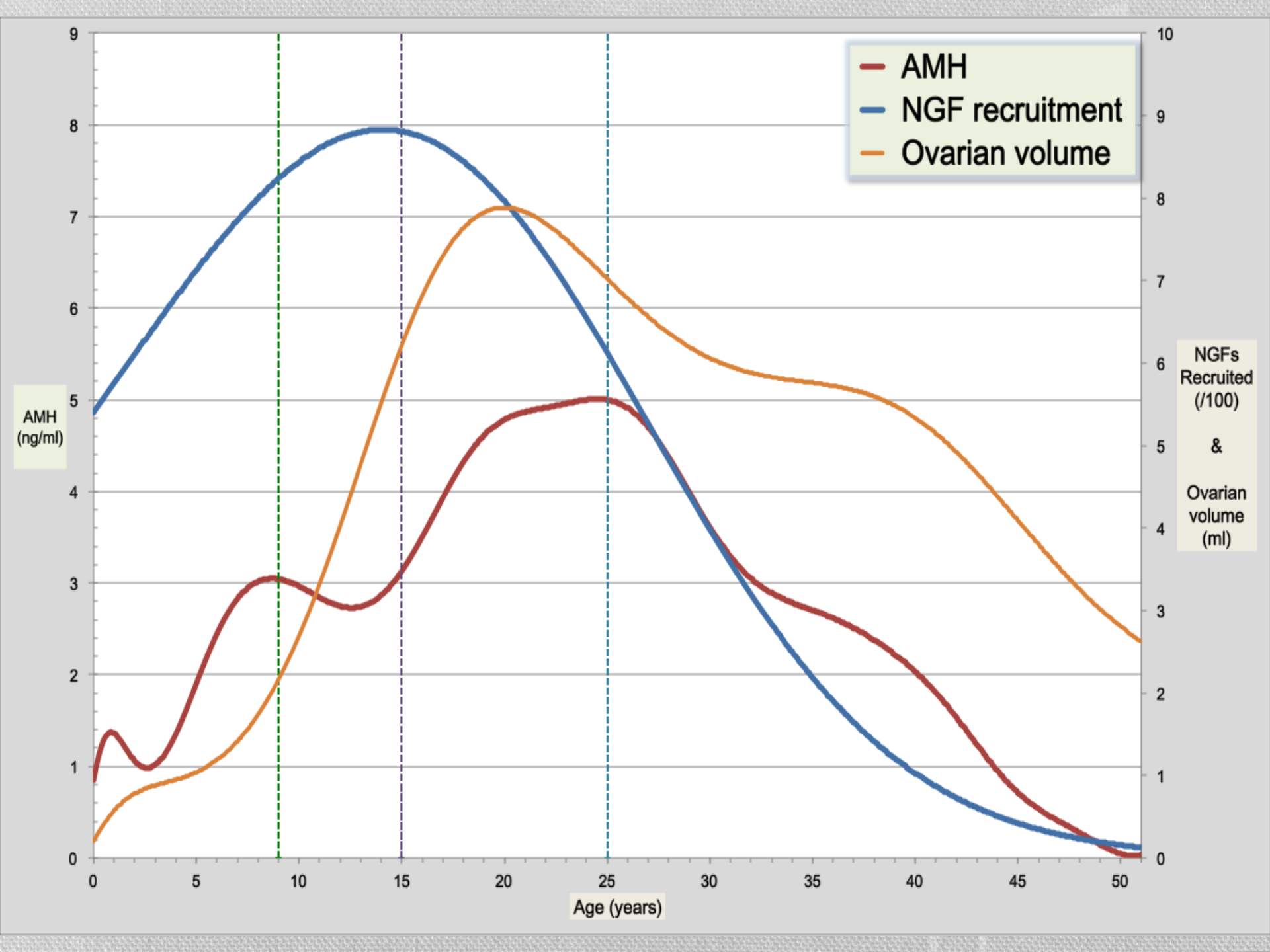
External Validation of NGF and OV Models



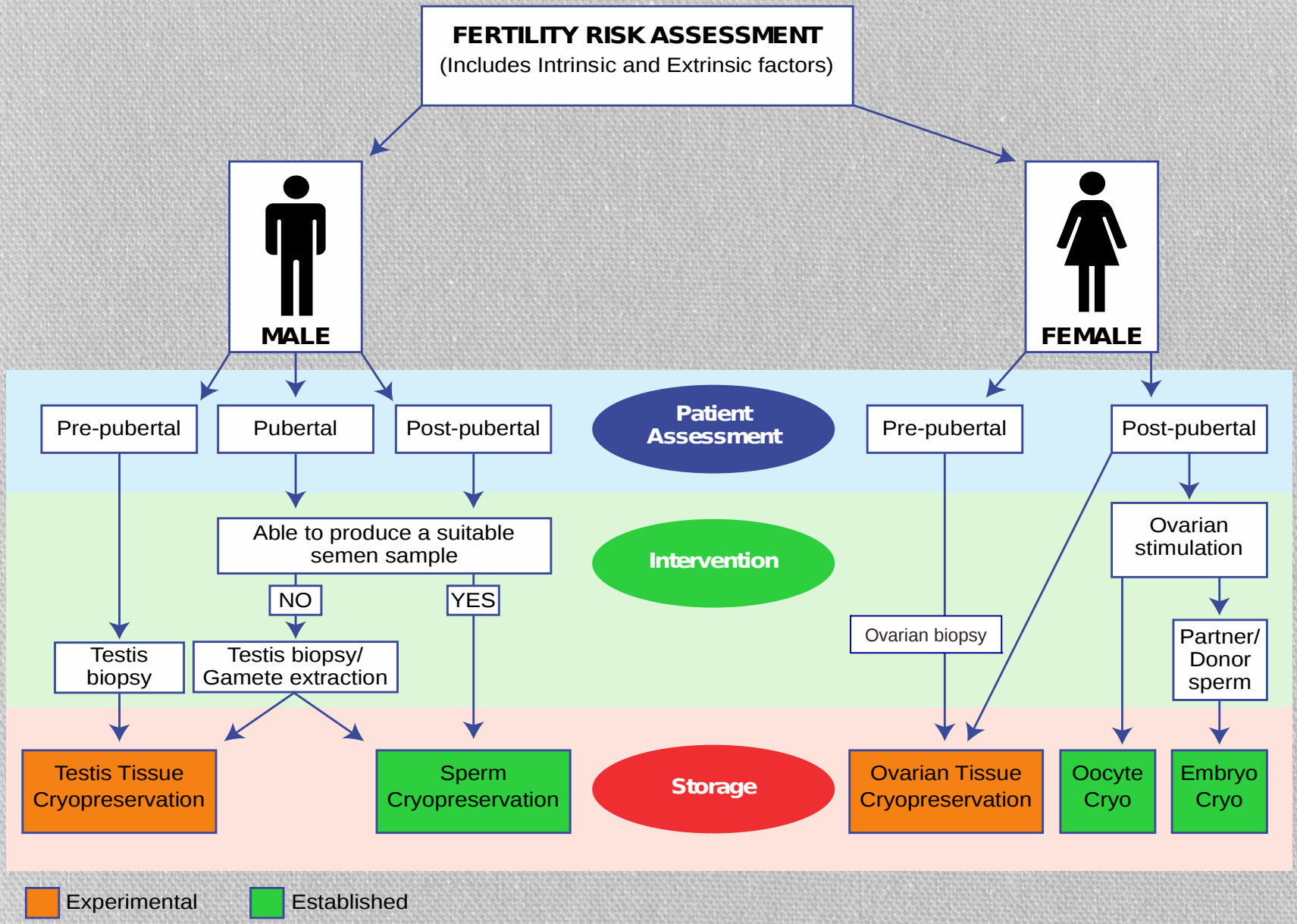
External Validation of NGF and OV Models



McGloughlin, Kelsey et al. JARG 2015 (under review)


AMH
NGF recruitment
Ovarian volume
AMH (ng/ml)
NGFs Recruited (/100) & Ovarian volume (ml)
Age (years)
0
1
2
3
4
5
6
7
8
9
10
0
5
10
15
20
25
30
35
40
45
50

Fertility preservation options: established and experimental


FERTILITY RISK ASSESSMENT
(Includes Intrinsic and Extrinsic factors)
MALE
FEMALE
Pre-pubertal
Pubertal
Post-pubertal
Patient Assessment
Pre-pubertal
Post-pubertal
Able to produce a suitable semen sample
Intervention
Ovarian stimulation
NO
YES
Ovarian biopsy
Partner/ Donor sperm
Testis biopsy
Testis biopsy/ Gamete extraction
Testis Tissue Cryopreservation
Sperm Cryopreservation
Storage
Ovarian Tissue Cryopreservation
Oocyte Cryo
Embryo Cryo
Experimental
Established

Key features of the 3 options for fertility preservation for women

mbryo cryopreservation

- Established but require time and a partner

ocyte cryopreservation

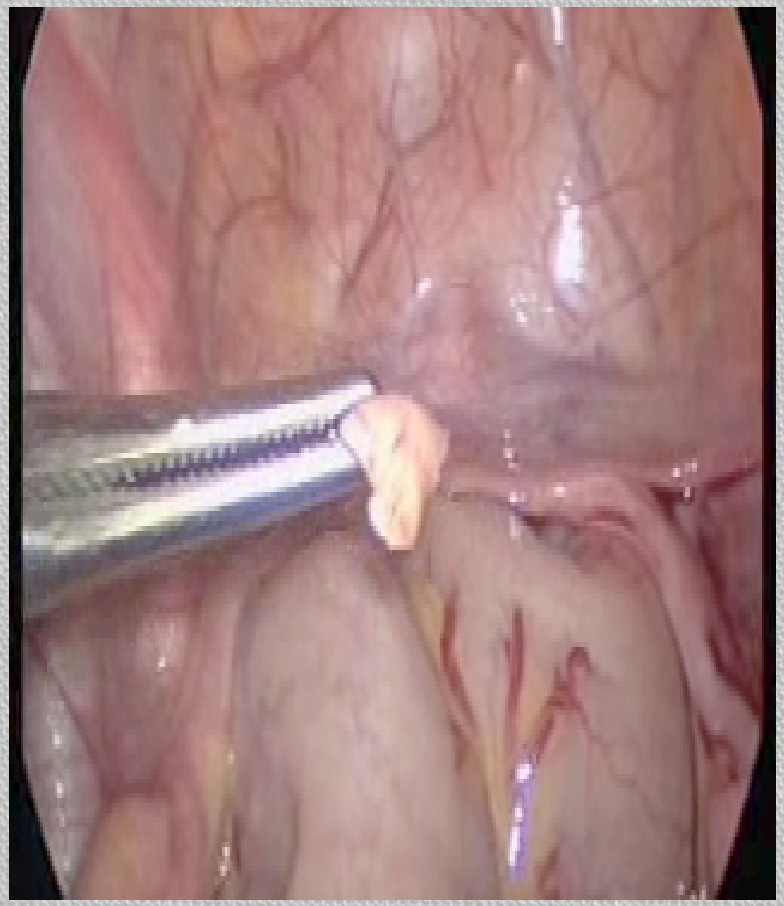
- Established but require time and hormone stimulation (success rate per oocyte low)

varian tissue cryopreservation

- Minimal delay
- No lower age limit
- Surgical procedure
- Allows for future developments

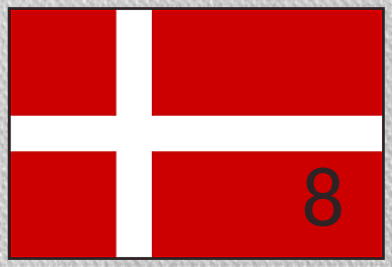
Ovarian tissue cryopreservation: World-wide experience

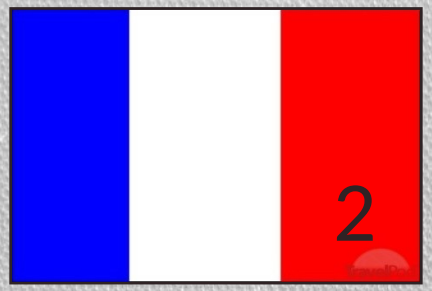
- At least 40 pregnancies worldwide after othotopic reimplantation of frozen–thawed ovarian cortex
- Success rate is unclear as the denominator is unknown
- No pregnancies reported following the reimplantation of ovarian tissue harvested pre-pubertally
- Young children are potentially ideal candidates



Donnez, J. & Dolmans, M.-M. *Nat. Rev. Endocrinol.* 9, 735–749 (2013)

Children born from transplantation of frozen/thawed ovarian tissue





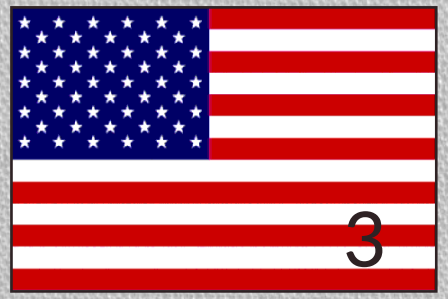
All Normal Babies

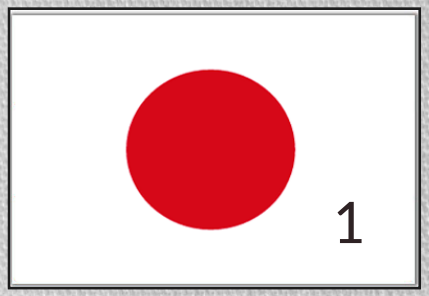
weight and duration

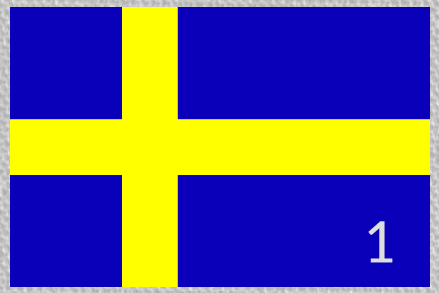
Orthotopic >> heterotopic

All except for one is a result of a slow-freezing protocol

An estimated excess of 150 transplantations have been performed







Cryopreservation: European experience

- T
- 6
- O
- S
- R
- T

hree centres (Denmark, Spain and Belgium)

0 cases of orthotopic reimplantation.

f these women, 11 (21%) became pregnant

ix have delivered 12 healthy babies.

estoration of ovarian activity was observed in 93% of the patients between 3.5 months and 6.5 months after grafting

he mean duration of ovarian function after trans- plantation is ~4–5 years but can persist for up to 7 years.

Donnez, J. *et al.* *Fertil. Steril.* 99, 1503–1513 (2013).

Ovarian Cryopreservation & Ovarian Function

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

Cryopreservation of ovarian cortical tissue – Edinburgh criteria

S

election criteria (1995, modified 2000)

- A
- N
- M
- A
- A
- I
- N
- N

ge < 35 years

o previous chemotherapy/radiotherapy if age >15 years

ild, non gonadotoxic chemotherapy if < 15 years

realistic chance of surviving five years

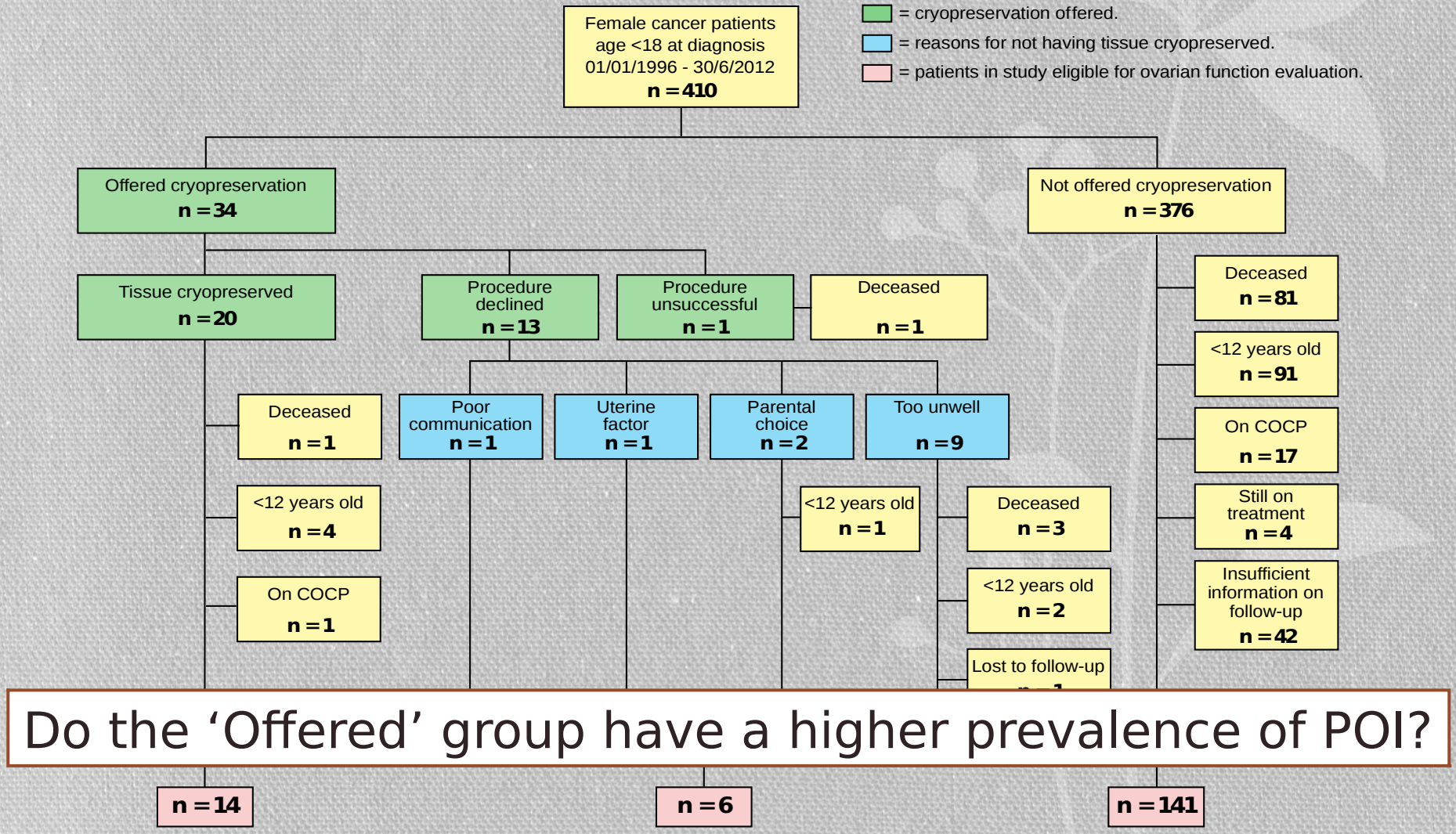
high risk of ovarian failure

nformed consent (parent and where possible patient)

egative HIV and Hepatitis serology

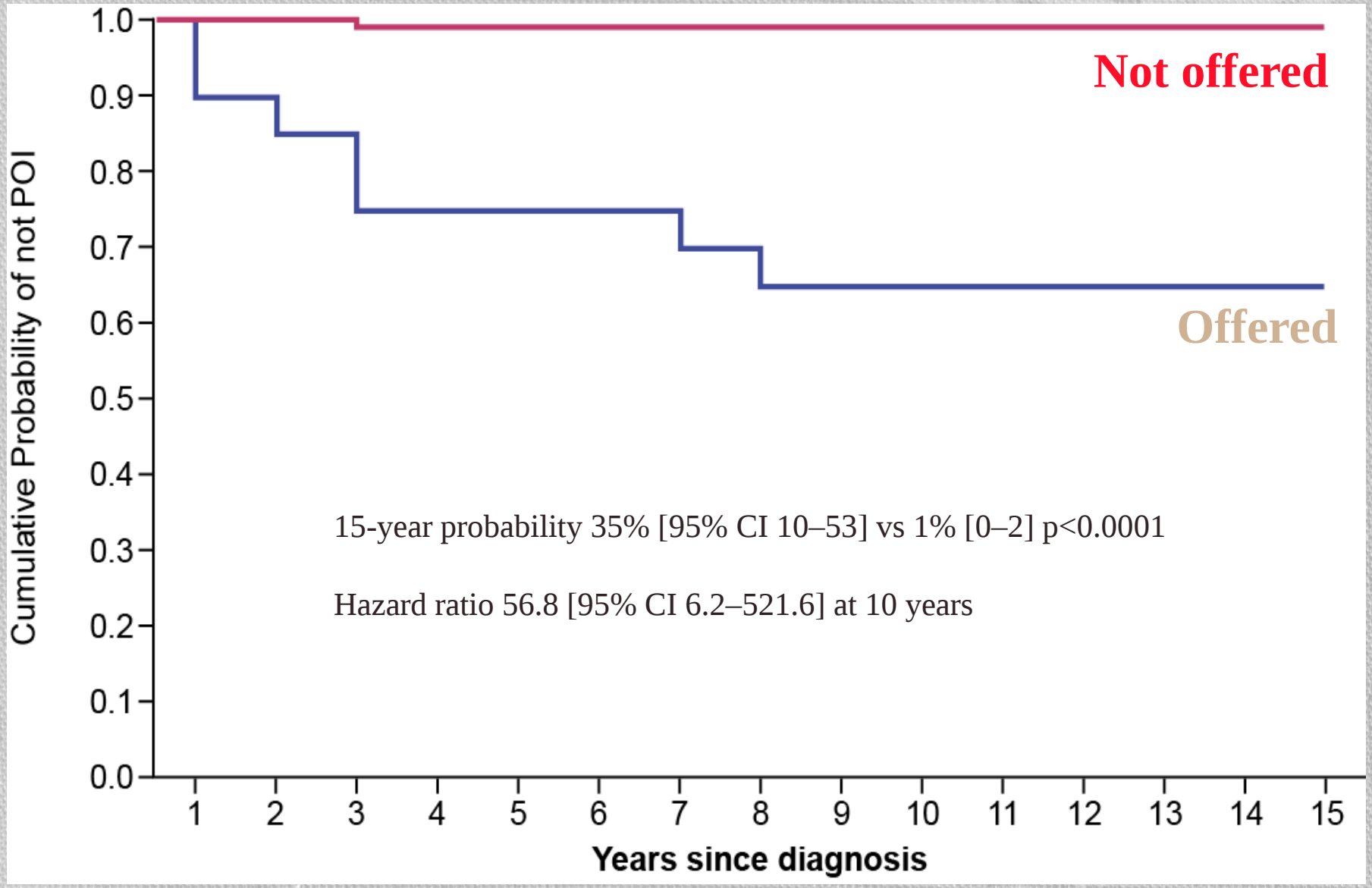
o existing children

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



Walllace WH et al. 2014 Lancet Oncology

Cumulative incidence of POI



Walllace…..and Anderson 2014 Lancet Oncology

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 one patient

- T

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

Wallace WH…..and Anderson 2014 Lancet Oncology

Reimplantation?

- I

t 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

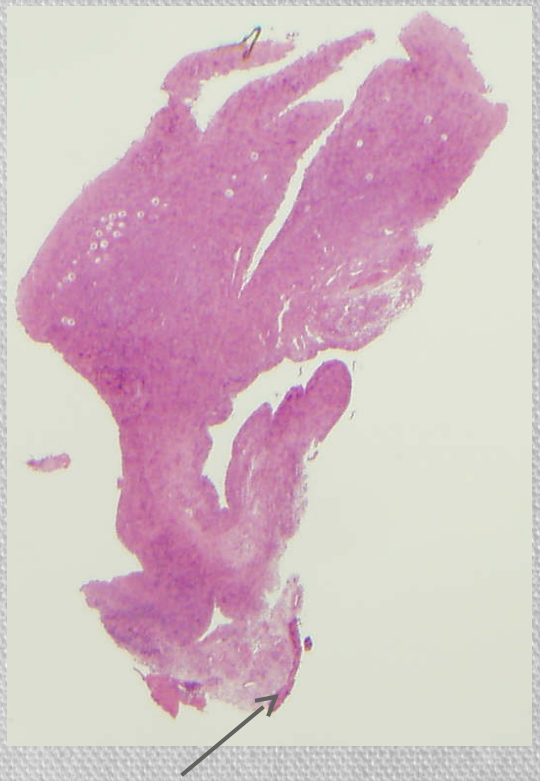
- C

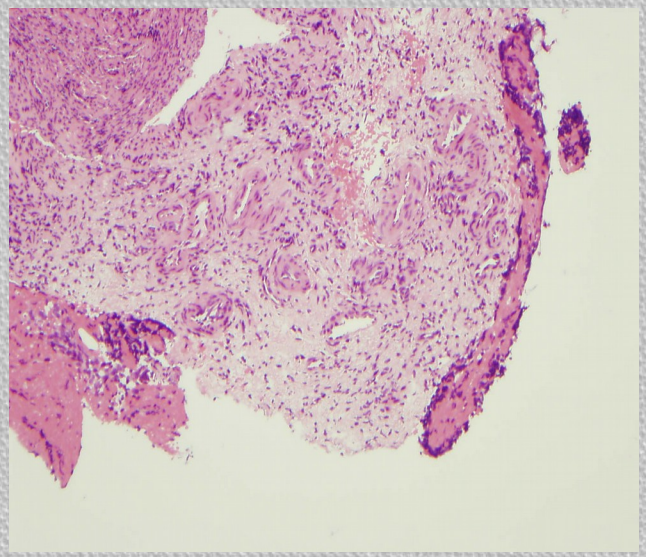
onsent for harvesting ovarian tissue from children often will have been obtained from their parents

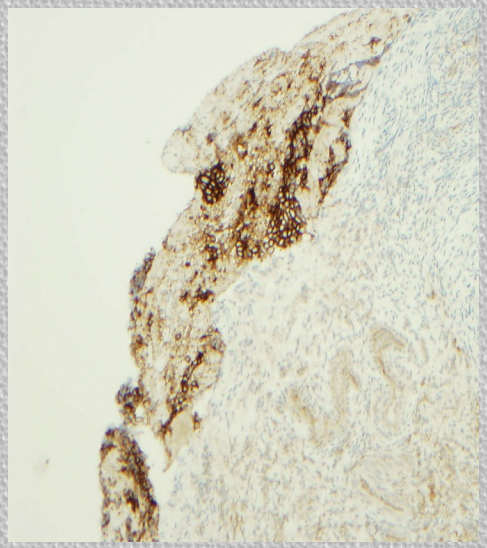
- I

nformed 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







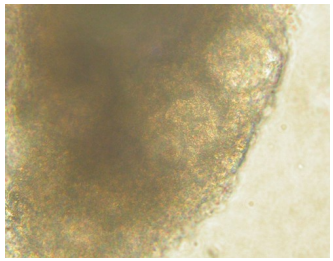
CD99

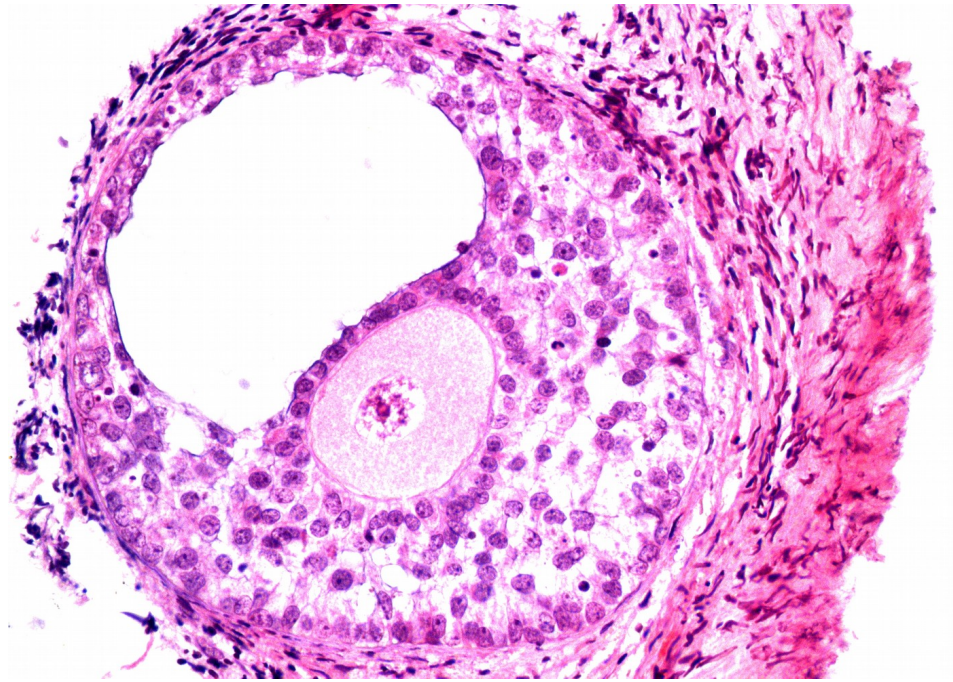
Re-implantation or IVG and maturation?

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

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

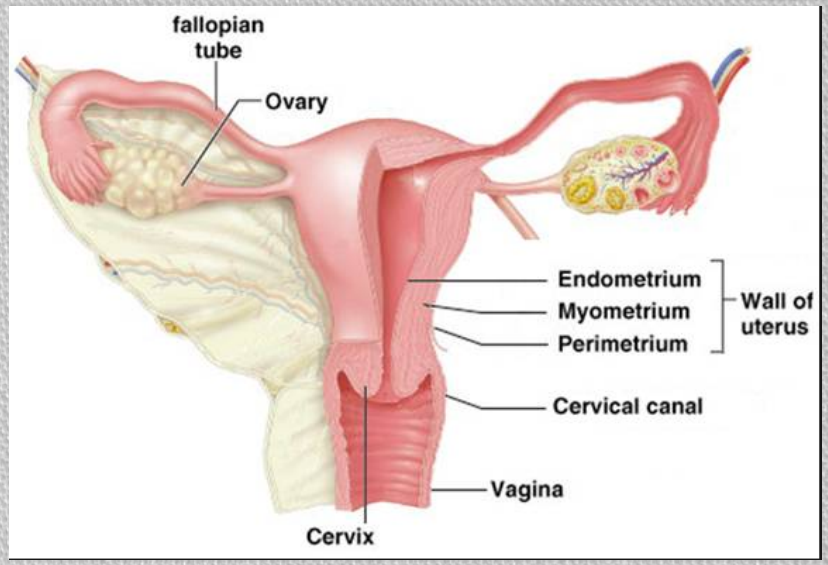
Antral development from *in vitro* grown human primordial follicles within 10 days

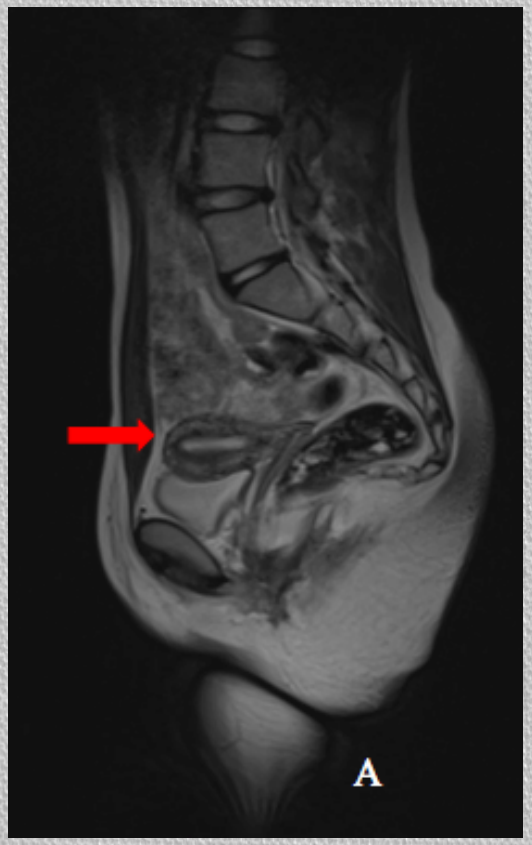




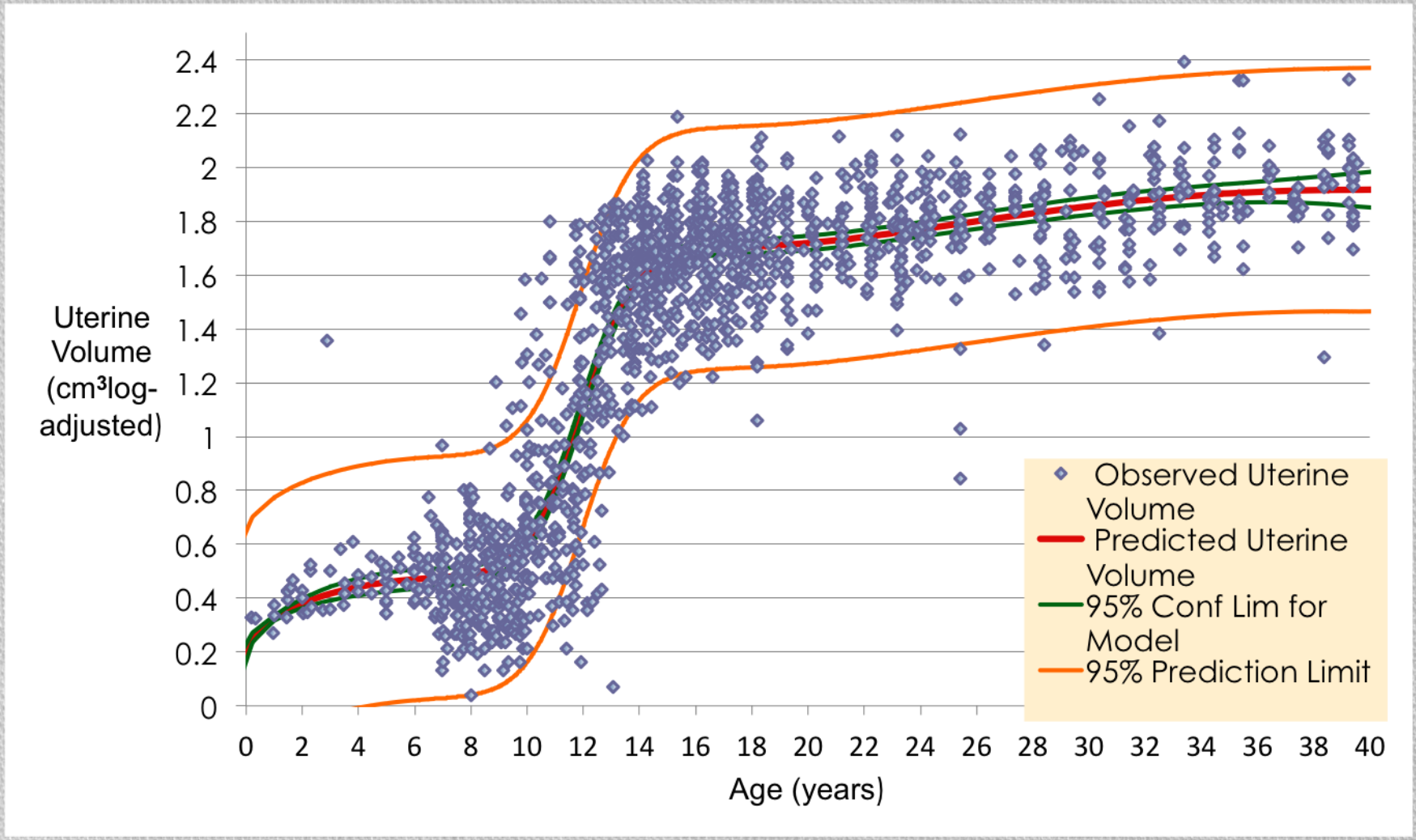
Telfer et al., 2008: A two step serum free culture system supports development of human oocytes from primordial follicles in the presence of activin. **Human Reproduction** 23: 1151-1158

The Uterus


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

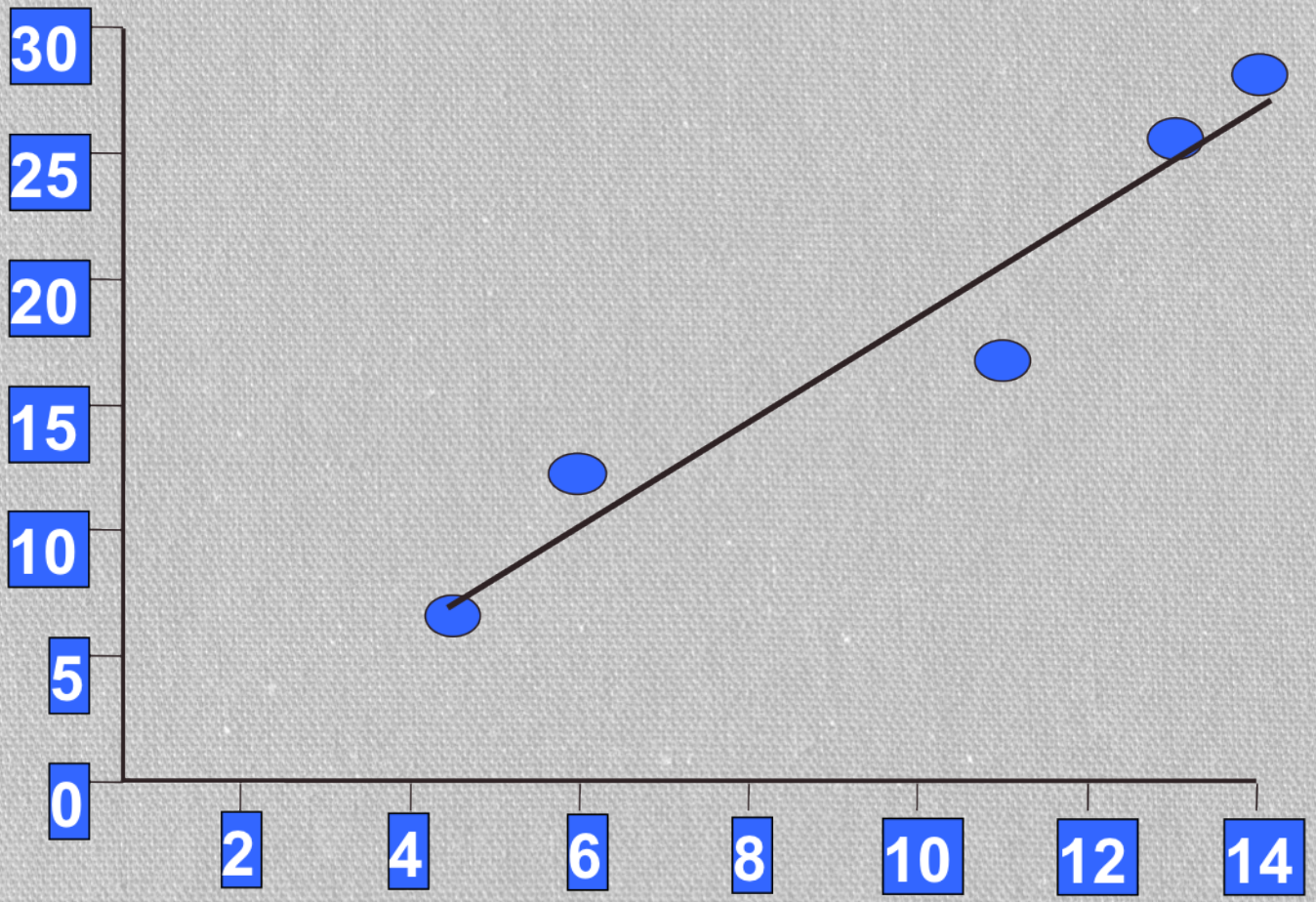

A

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

o reports of uterine damage due to chemotherapy

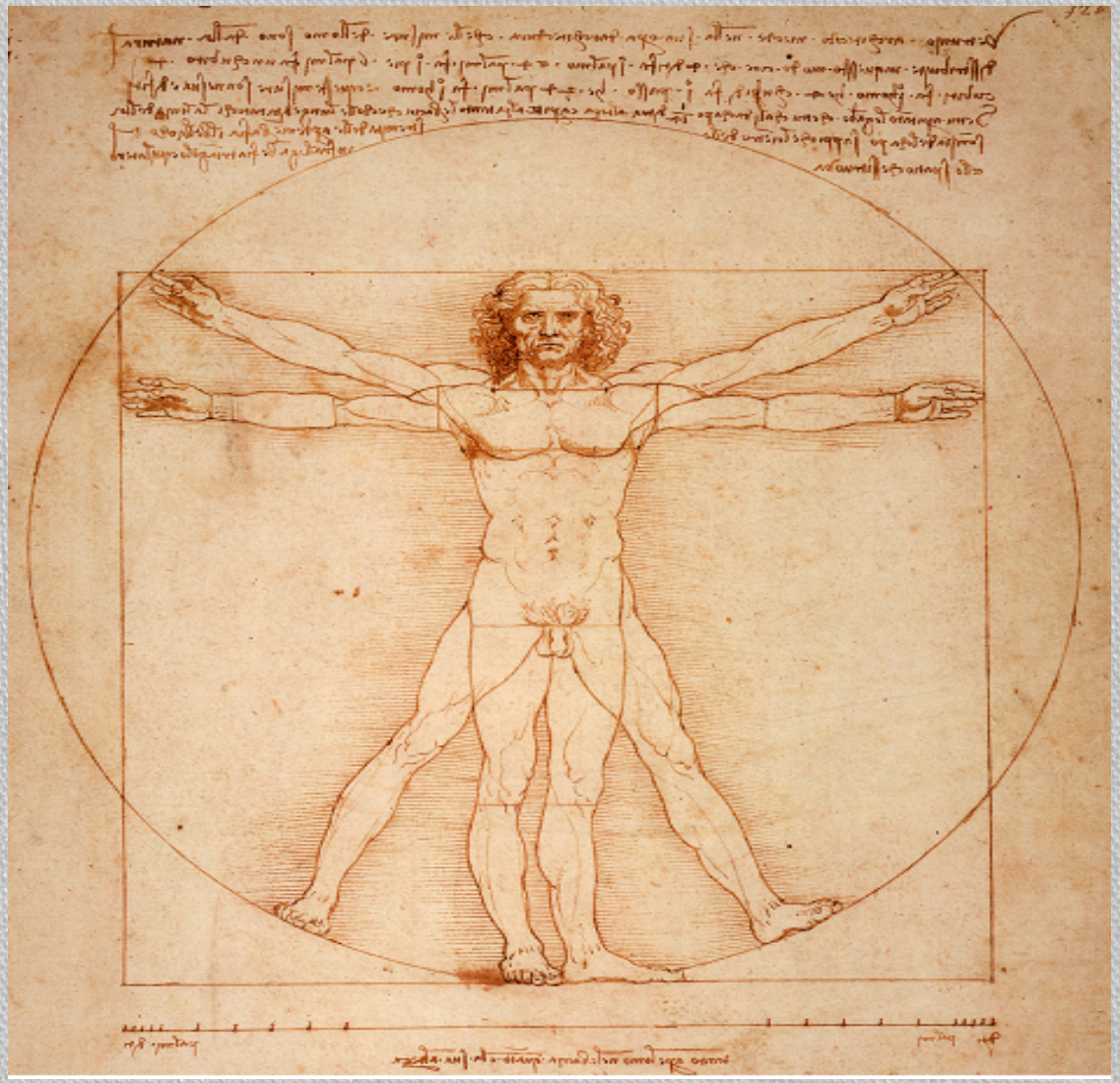
adiotherapy:

terine damage, manifest by impaired growth and blood flow.

Uterine volume correlates with age at irradiation.

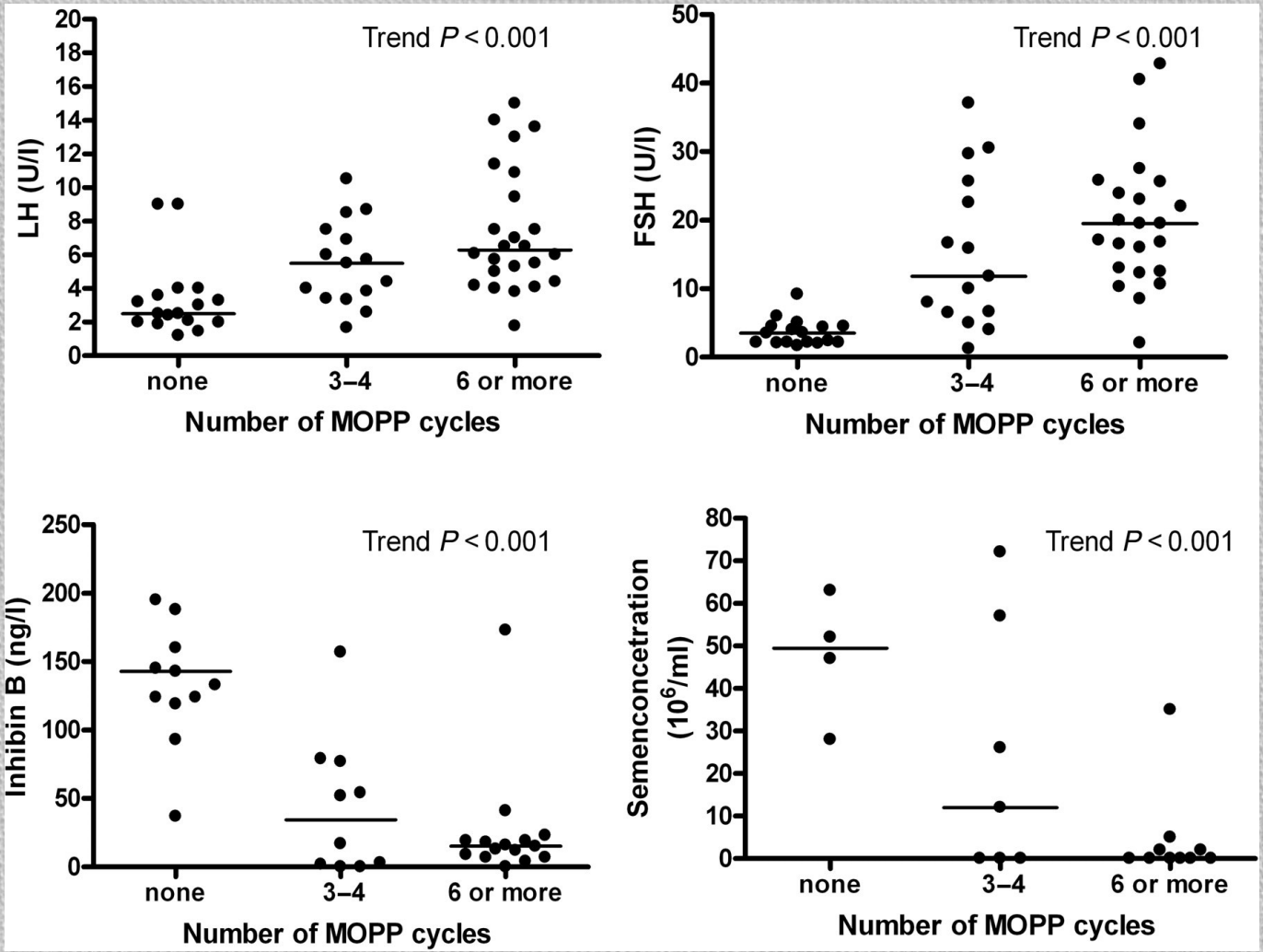
Exposure of the pelvis to radiation is associated with an increased risk of miscarriage, mid-trimester pregnancy loss, PPH, pre-term birth and low birth weight.

Vitruvian man



Leonardo da Vinci 1490

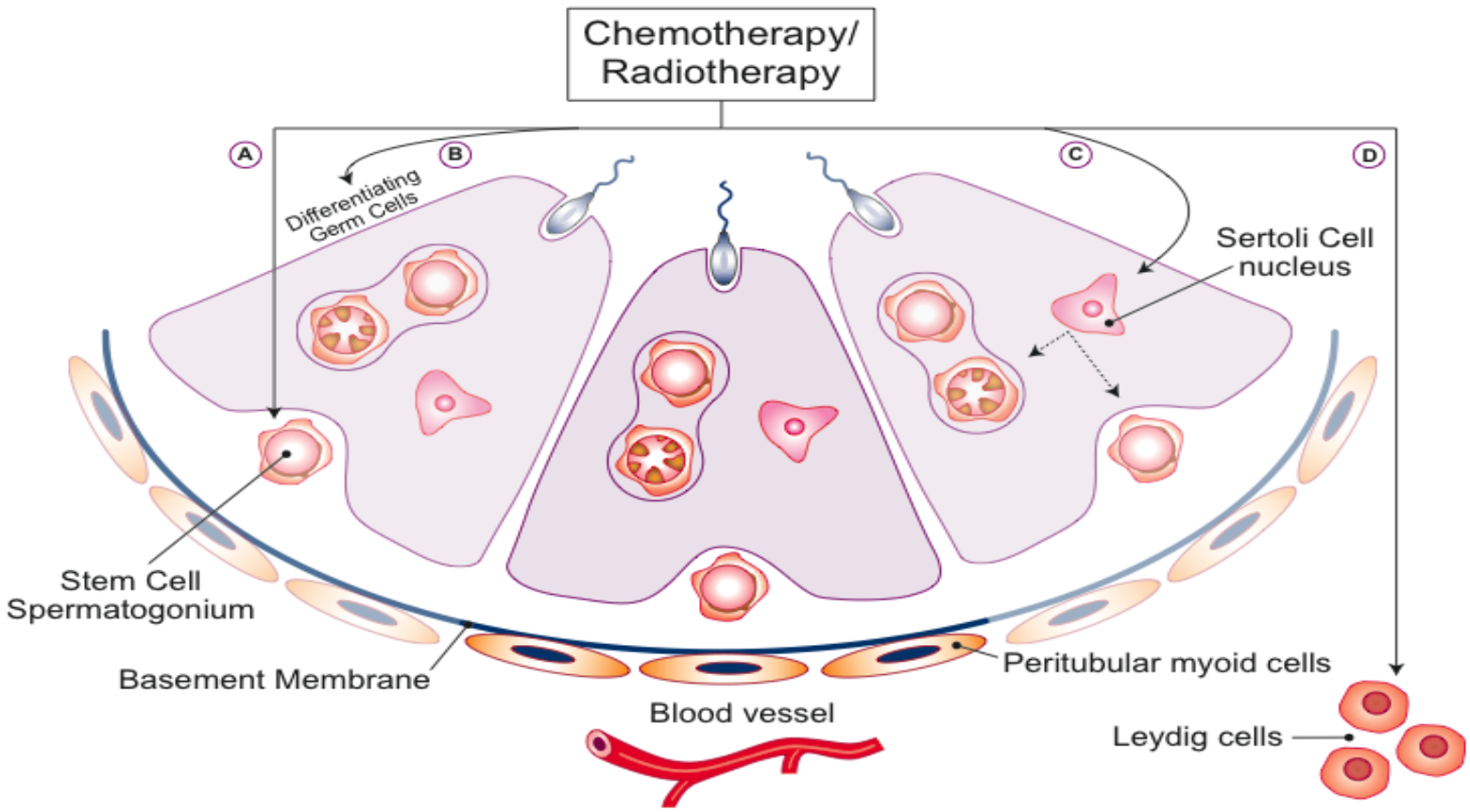
Hormone levels and semen concentration in relation to the number of MOPP cycles in male long-term survivors of childhood Hodgkin's.



van Beek R D et al. Hum. Reprod. 2007;22:3215-3222

human reproduction

Sertoli Cell

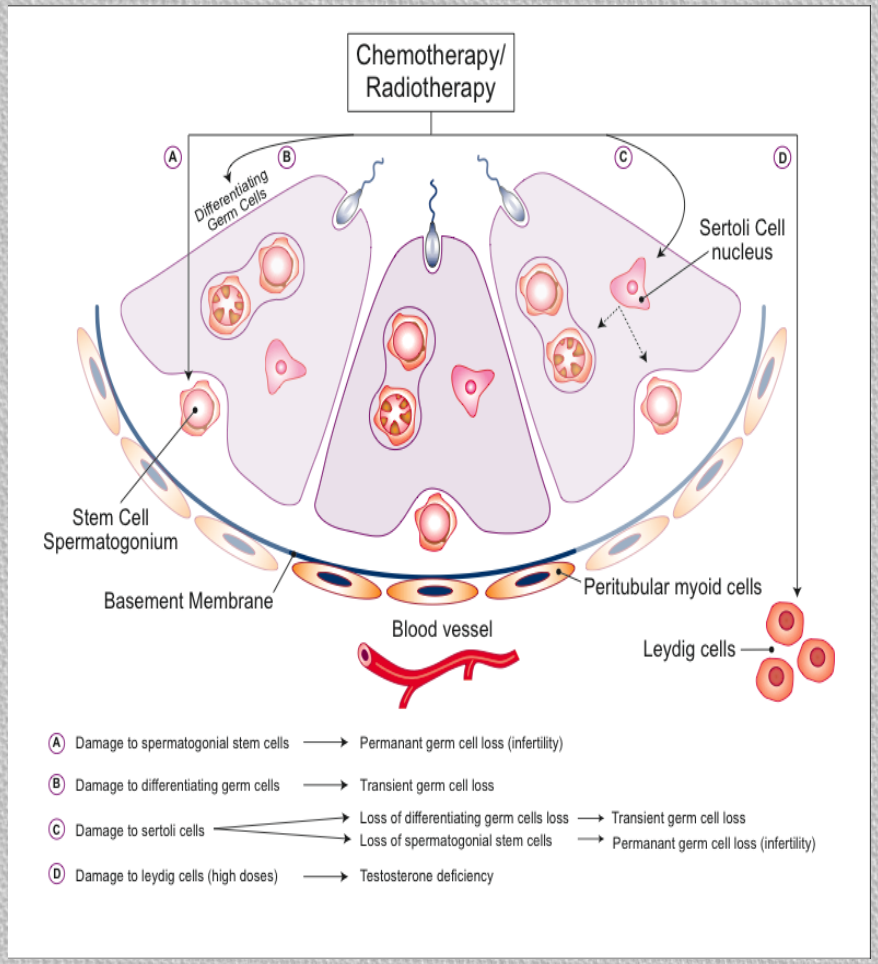


- (A) Damage to spermatogonial stem cells → Permanant germ cell loss (infertility)
- (B) Damage to differentiating germ cells → Transient germ cell loss
- (C) Damage to sertoli cells → Loss of differentiating germ cells loss → Transient germ cell loss
  - Damage to sertoli cells → Loss of spermatogonial stem cells → Permanant germ cell loss (infertility)
- (D) Damage to leydig cells (high doses) → Testosterone deficiency

Radiation-induced testicular damage

Germinal epithelium

>1.2Gy azoospermia



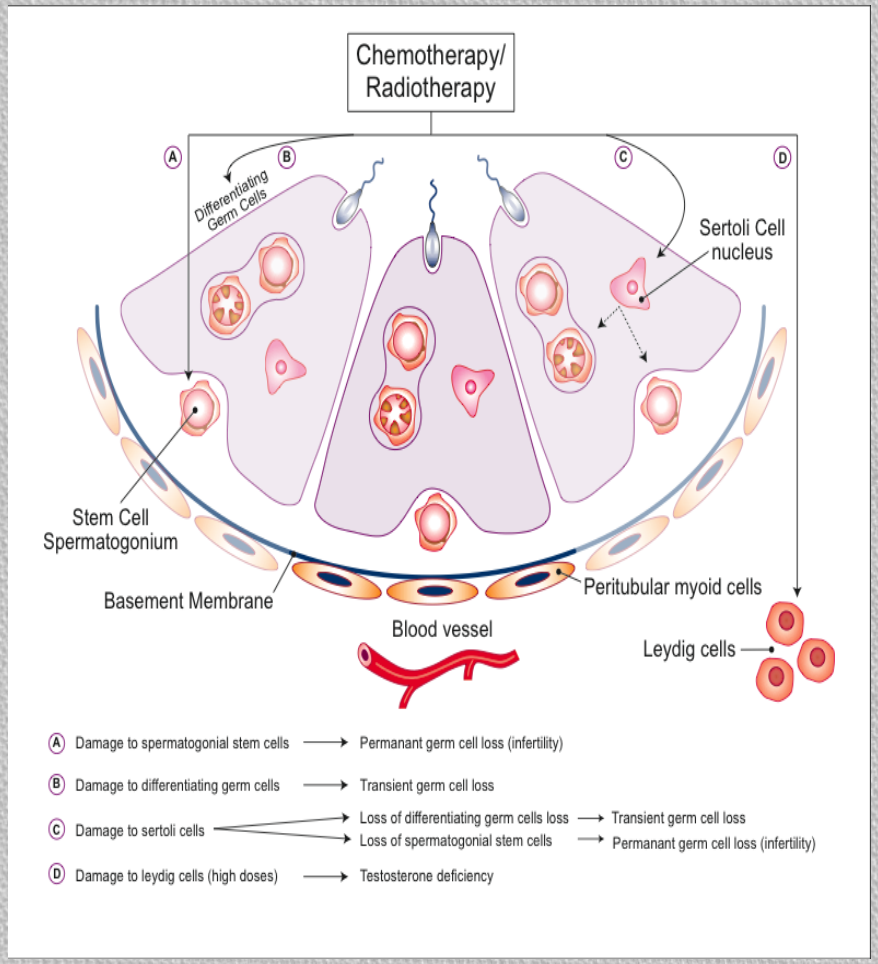
Radiation-induced testicular damage

Leydig cell function

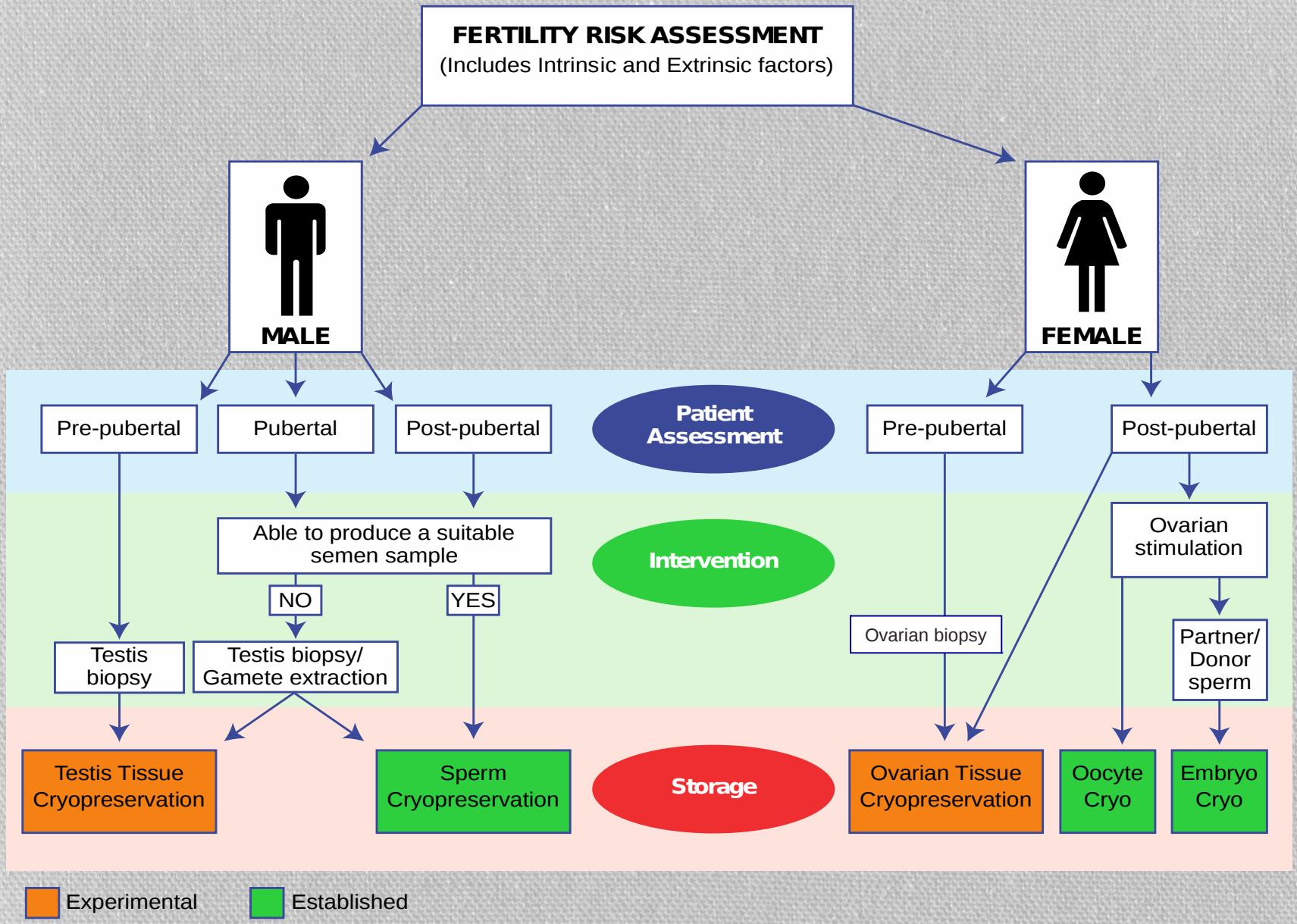
ose received by testis P <0.05

ime Interval after radiotherapy P <0.05

ge at treatment NS



Li, Kelsey, Wallace (unpublished data)

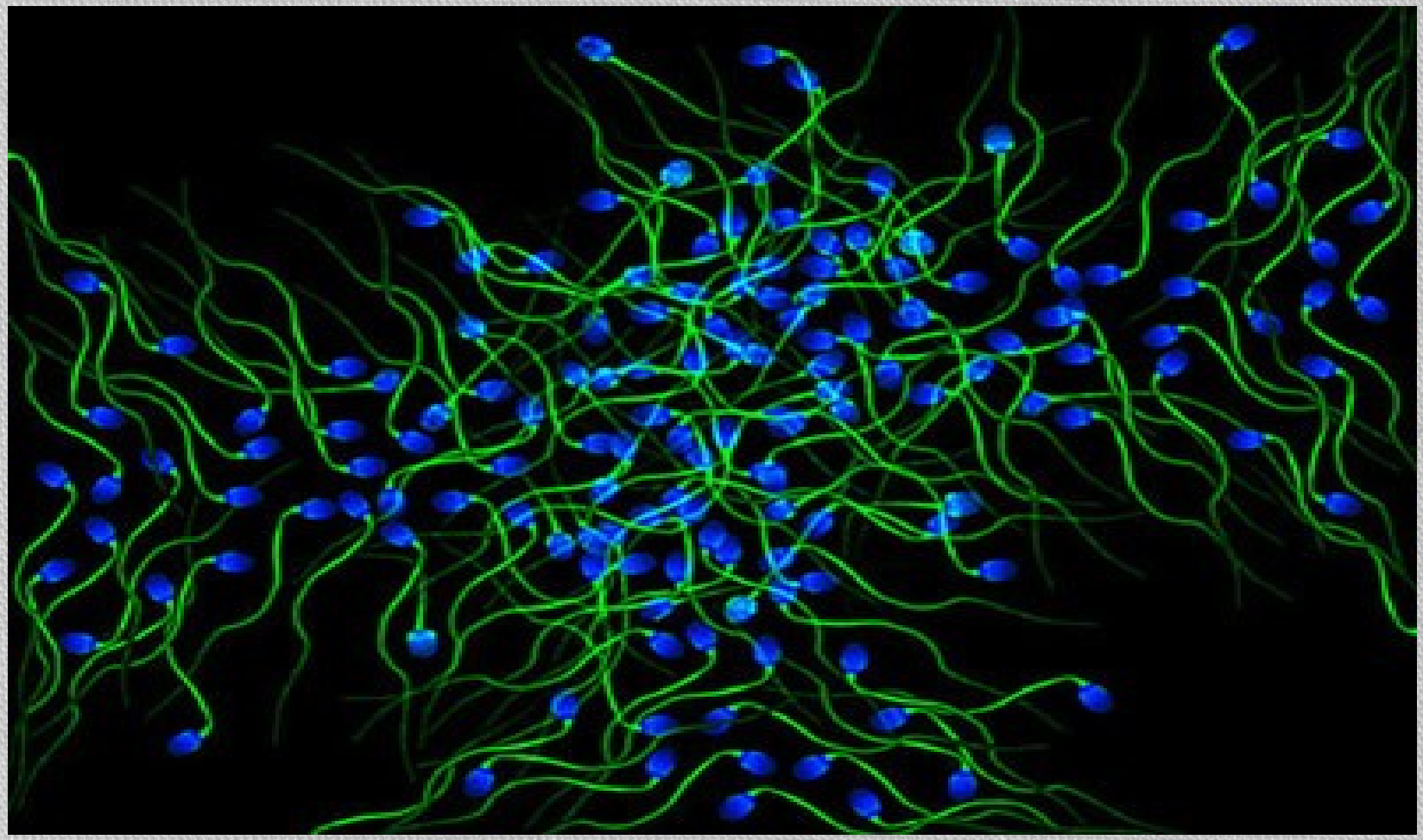

FERTILITY RISK ASSESSMENT
(Includes Intrinsic and Extrinsic factors)
MALE
FEMALE
Pre-pubertal
Pubertal
Post-pubertal
Patient Assessment
Pre-pubertal
Post-pubertal
Able to produce a suitable semen sample
Intervention
Ovarian stimulation
NO
YES
Ovarian biopsy
Partner/ Donor sperm
Testis biopsy
Testis biopsy/ Gamete extraction
Testis Tissue Cryopreservation
Sperm Cryopreservation
Storage
Ovarian Tissue Cryopreservation
Oocyte Cryo
Embryo Cryo
Experimental
Established

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 established option to preserve fertility in the pre-pubertal boy….

Isolated human sperm cells (1500x)

Albert Tousson – Nikon Small world



Cryopreservation of pre-pubertal testis tissue prior to cancer treatment

ys undergoing cancer treatment with >80% risk of infertility

opsy to be taken with routine procedure

orage by Tissue Services according to ‘mature’ or ‘immature’ protocol

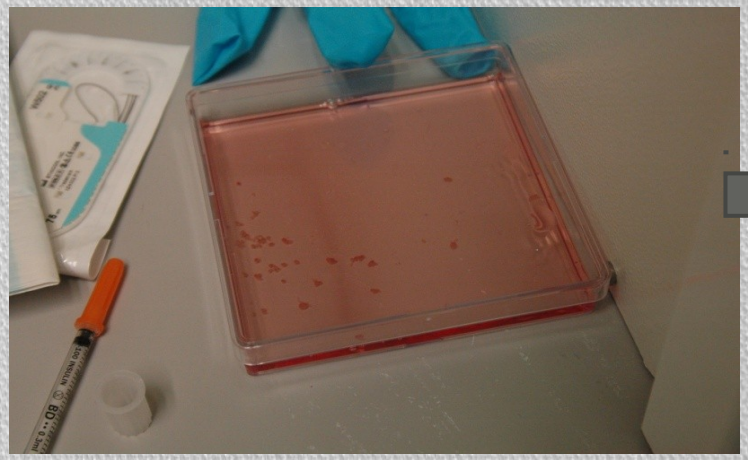
mall piece of tissue to be used for research

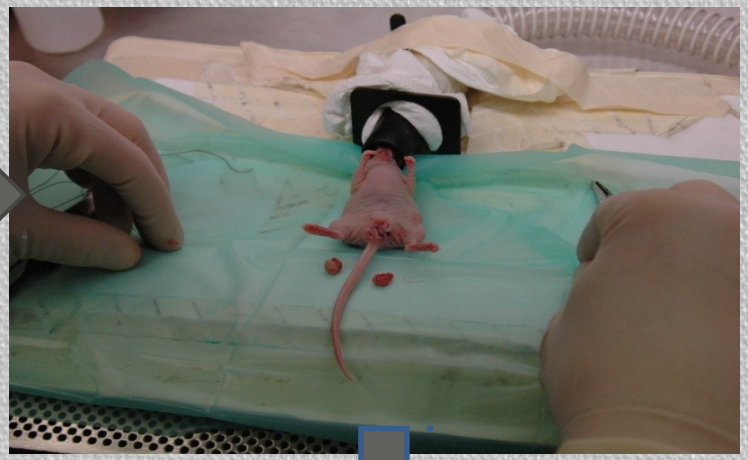
hical Approval Granted – September 2013

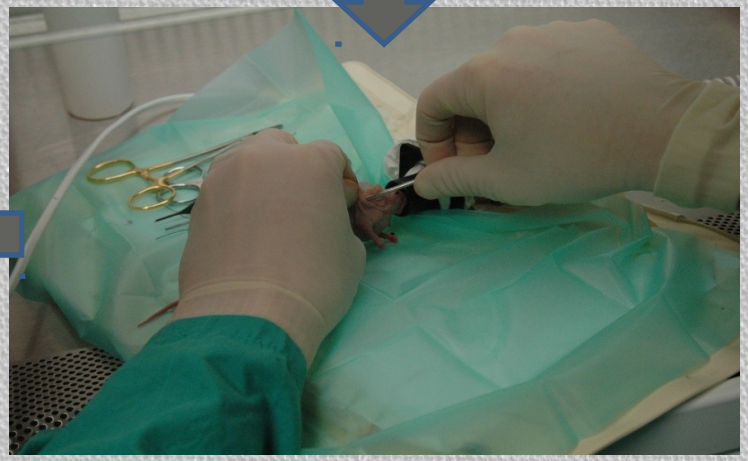
- Bo
- Bi
- St
- S

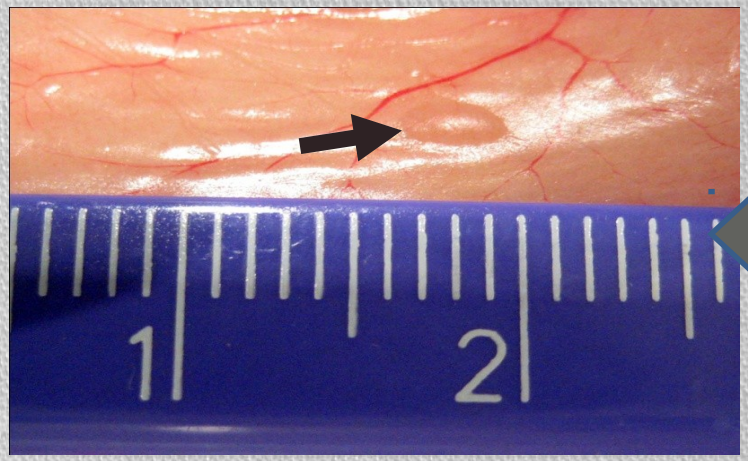
Et

Human Testis Xenografting









Challenges

rovide fertility counseling to all young patients with cancer

ryopreserve ovarian tissue from the right (high risk) patients

efine the success rate of the procedures

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

Acknowledgements

ichard Anderson

velyn Telfer

arie McLaughlin

lice Grove Smith

hoebe Wright

eorge Galea

arah Dodwell

ouise Bath

hris Kelnar

ngela Edgar

ark Brougham

raser Munro

cott Nelson

ichard Fleming

- R
- E
- M
- A
- P
- G
- S

Thank You

nowledgements

ichard Anderson

avid T Baird

om Kelsey

velyn Telfer

arie McLaughlan

lice Grove Smith

eorge Galea

od Mitchell

ouise Bath

hris Kelnar

ngela Edgar

ark Brougham

raser Munro

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

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

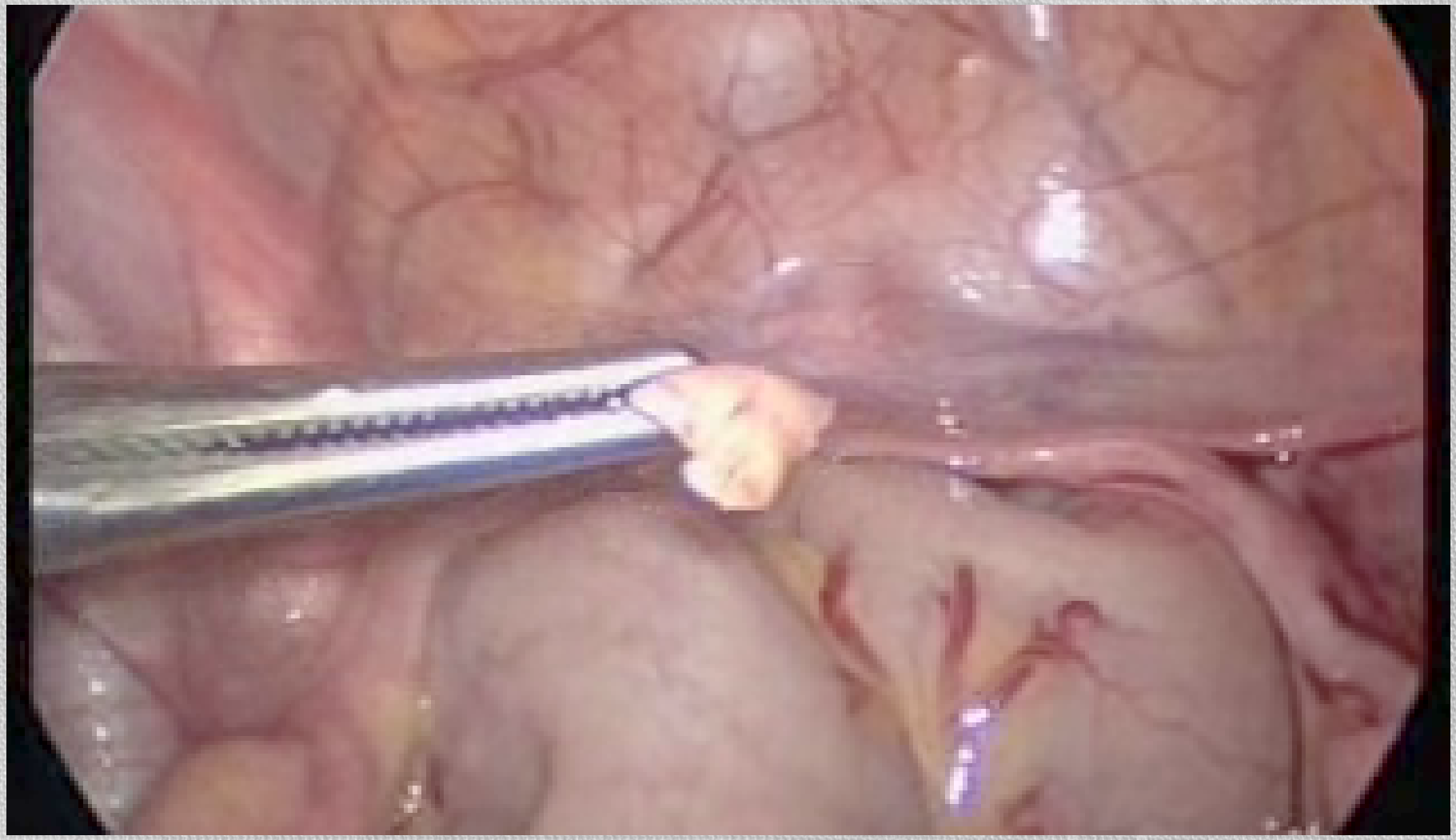
urvive cryopreservation

echnique validated in sheep

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 biopsy at laparoscopy



Cryopreservation: World-wide experience

- At least 20 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

Ovarian transplantation: World-wide experience

- Silber et al. have also extensively reported their experience of successful fresh ovarian transplantation in identical twins discordant for premature ovarian failure
- 12 pregnancies and eight healthy babies have been reported from nine homozygotic transplants

Silber et al. MHR 2012

Cryopreservation: World-wide experience

ecent report of three women who have experienced long-term (> 7 years) duration of function of ovarian cortical tissue grafts.

irth of eight healthy babies in total following a single graft per patient.

Andersen et al. 2012 RBMonline

Ethical issues

thical considerations for children are different and more challenging from those involving adults

- who are assumed to be competent

nterventions in children can only be ethical if they can be considered to be therapeutic and in the best interests of the minor

HRT and pubertal induction

- An intriguing question remains: Should ovarian tissue that has been harvested and frozen be reimplanted to provide HRT?
- or even pubertal induction in the young patient with premature ovarian failure?
  - Poirot et al., Lancet 2012
- Ovarian grafts will survive for up to 7 years
  - Andersen et al ., 2012
- Several groups have reimplanted ovarian tissue once the initial graft has failed
  - Silber et al., 2008
- Our view is that this precious tissue should only be reimplanted if fertility is requested

Technology or evidence led?

n the field of fertility preservation there is a dearth of well-designed studies to fully evaluate exciting new techniques

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 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

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 trial

he ASCO guideline recommends that ovarian cryopreservation and transplantation procedures should only be performed in centres with the necessary expertise under IRB-approved protocols that include follow-up for recurrent cancer

Lee et al. JCO 2006, 24(18):2917-31

Ovarian cryopreservation & ovarian function

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

Cryopreservation of ovarian cortical tissue – Edinburgh criteria

ection criteria (1995,modified 2000)

< 30 years

previous chemotherapy/radiotherapy if age >15 years

, non gonadotoxic chemotherapy if < 15 years

realistic chance of surviving five years

high risk of ovarian failure

rmed consent (Parent and where possible Patient)

ative HIV and Hepatitis serology

existing children

Sel

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

Consent

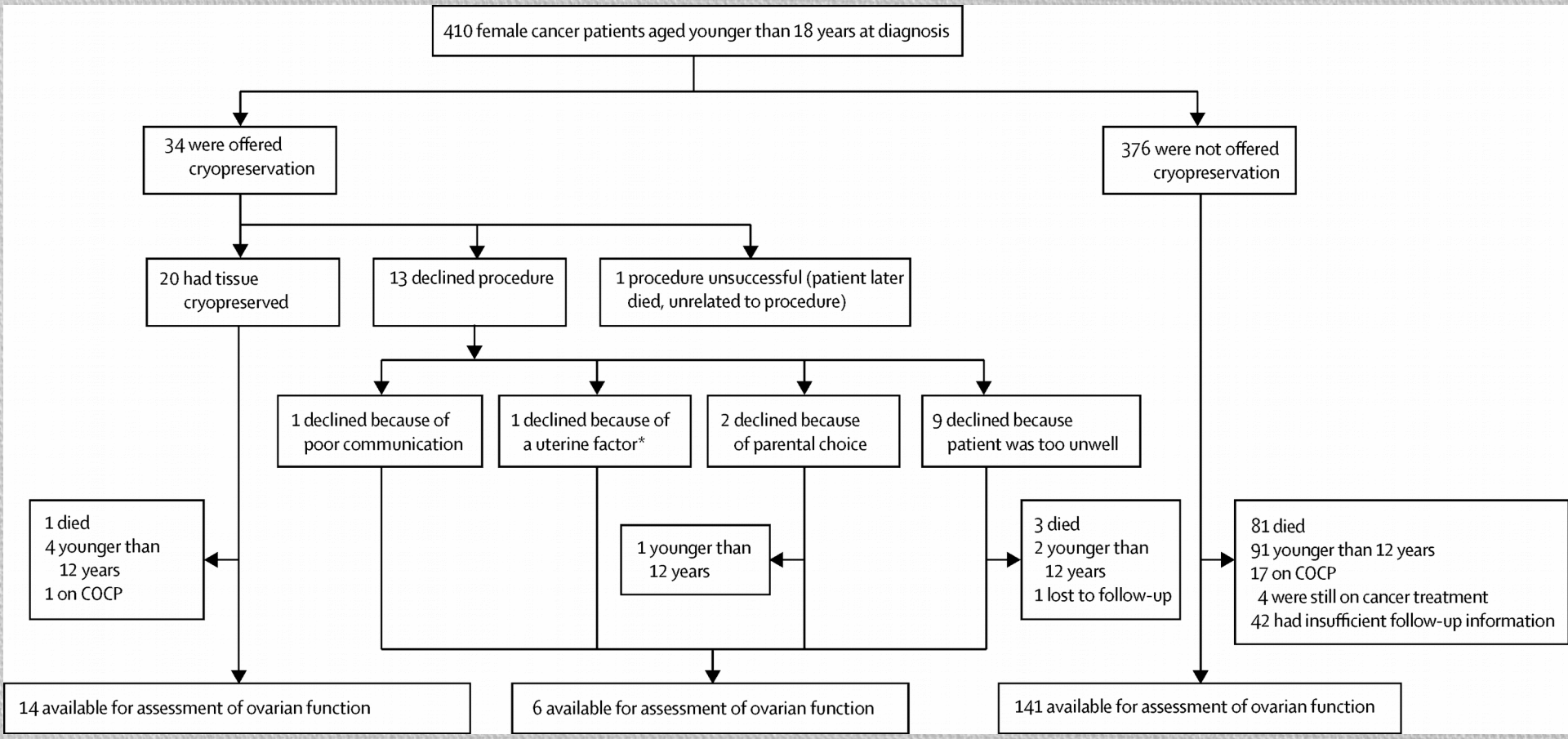
- We emphasize in the information sheet that the procedure is voluntary and experimental, and not part of routine practice
- We obtain informed consent for disposal of ovarian tissue if it is no longer required or the patient dies
- If consent has been obtained, it may be used for ethically approved research studies
- Separately, we ask if an additional small amount can be taken at the time of collection for research studies
- Our practice constitutes research and has been approved by the local institutional review board (IRB)

Edinburgh Paediatric Experience

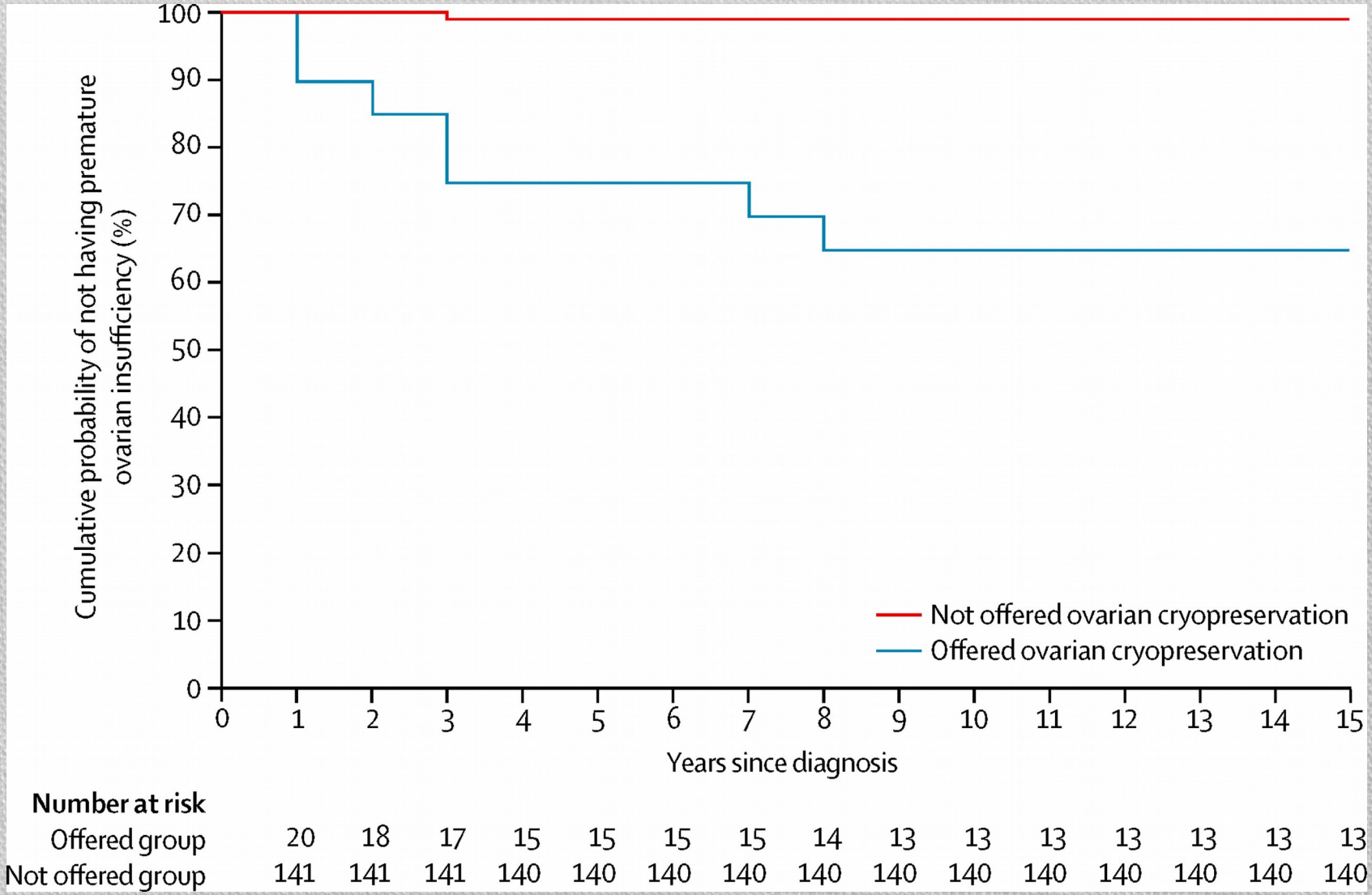
Table 3: Patients that had ovarian tissue cryopreserved

Patient No.	Diagnosis	Age at procedure	Method	Complications
1	Hodgkin's lymphoma¤	14.9	Laproscopic Cortical Strip	None
2	Ewing's sarcoma of pubic bone	14.9	Laproscopic Cortical Strip	None
3	Sacral ependymoma	11.3	Laproscopic Cortical Strip	None
4	Hodgkin's lymphoma	13.7	Laproscopic Cortical Strip	None
5	Hodgkin's lymphoma	11.0	Laproscopic Cortical Strip	None
6	Chronic granulocytic leukaemia	9.9	Laproscopic Cortical Strip	None
7	Rhabdomyosarcoma	5.3	Laproscopic Cortical Strip	None
8	Ewing's sarcoma (pelvic)	9.8	Laproscopic Cortical Strip	None
9	Uterine Cervix Rhabdomyosarcoma*	16.5	Laproscopic Cortical Strip	None
10	Hodgkin's lymphoma°	14.1	Laproscopic Cortical Strip	None
11	Abdominal embryonal Rhabdomyosarcoma	7.9	Laproscopic Cortical Strip	None
12	Ewing's sarcoma	12.1	Laproscopic Cortical Strip†	None
13	Hodgkin's lymphoma	12.7	Laproscopic Cortical Strip	None
14	Metastatic Medulloblastoma	8.1	Laproscopic Cortical Strip	None
15	Hodgkin's lymphoma	15.2	Laproscopic Cortical Strip	None
16	Alveolar Rhabdomyosarcoma	10.5	Laproscopic Cortical Strip	None
17	Embryonal Rhabdomyosarcoma	3.0	Oophorectomy	None
18	Ewing's Sarcoma	12.0	Laproscopic Cortical Strip	None
19	Undifferentiated Sarcoma	12.3	Laproscopic Cortical Strip†	None
20	Wilm's Tumour	1.2	Oophorectomy	None

Cohort Summary



Wallace et al. *The Lancet Oncology* 2014 15, 1129-1136



The cumulative probability of developing premature ovarian insufficiency after treatment was completed was significantly higher for patients who met the criteria for ovarian tissue cryopreservation than for those who did not (15-year probability 35% *vs* 1%; p<0·0001; hazard ratio 56·8 at 10 years).

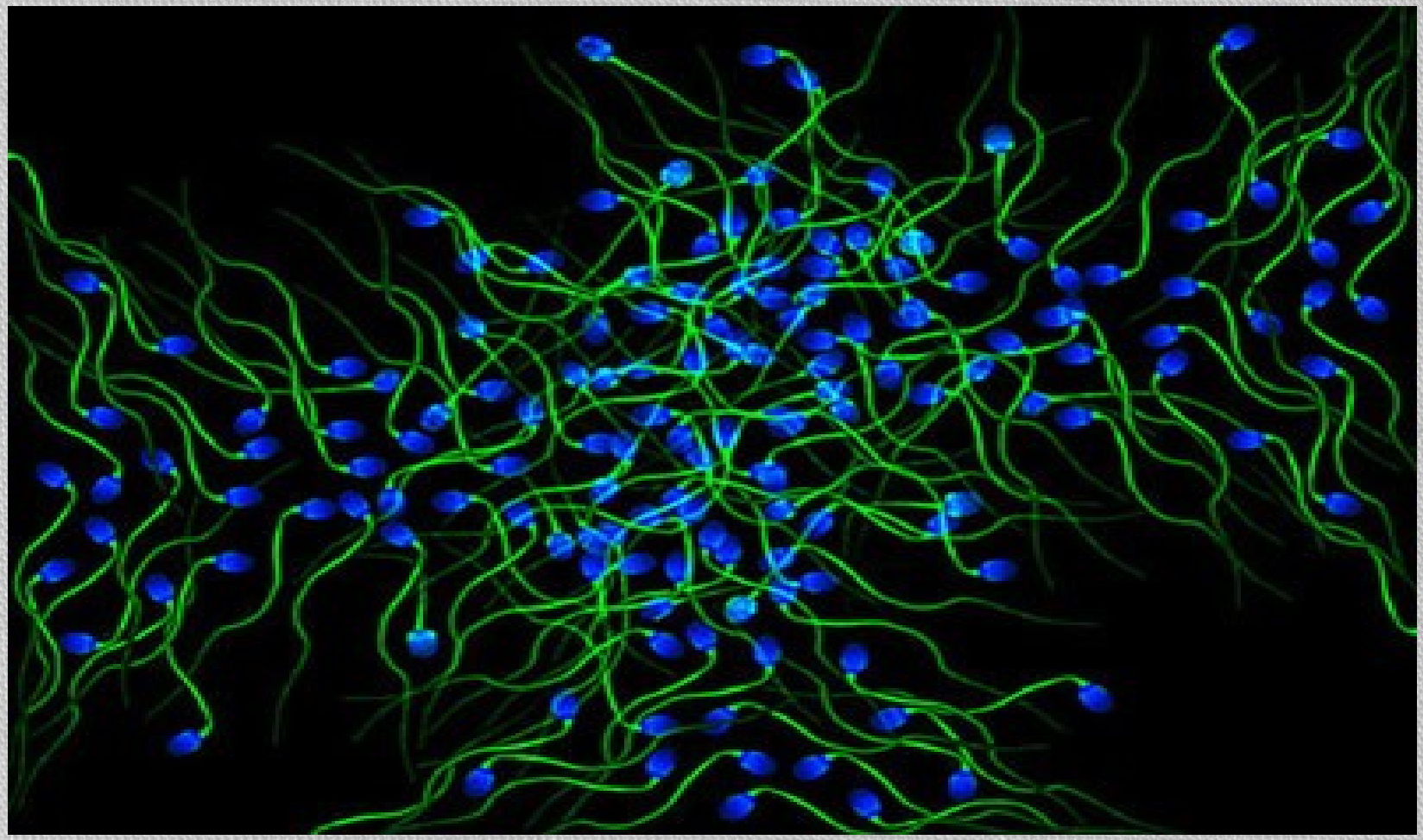
Wallace et al. *The Lancet Oncology* 2014 15, 1129-1136

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 (15.7 [1.3-30.9] yrs)
- All patients who have thus far developed ovarian failure were identified
- The Edinburgh Selection Criteria have proved to be helpful (only one patient not offered cryopreservation who has uncertain ovarian function)

Isolated human sperm cells (1500x)

Albert Tousson – Nikon Small world



Strategies for fertility preservation in males undergoing treatment for cancer

linical practice

- Sperm banking
  - Ejaculation
  - Rectal electrostimulation?
  - Testicular/epididymal aspiration

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 prepubertal boy

Summary

ales

perm banking must be considered in all males before treatment that carries a risk of long-term gonadal damage

here is currently no option to preserve fertility in the pre-pubertal boy (more research required)

Anderson, Mitchell et al. The Lancet Diabetes & Endocrinology 2015

Summary

emales

t remains difficult to predict which patients are at high risk of a premature menopause

ryopreservation of ovarian tissue before treatment is the best option for girls and young women

rthotopic reimplantation works but so far there have been very few live births.

ccelerated IVG of human oocytes is likely to become a realistic possibility.

Anderson, Mitchell et al. The Lancet Diabetes & Endocrinology 2015

Challenges

- Provide fertility counseling to all young patients with cancer
- Cryopreserve ovarian tissue from the right patients
- Define the success rate of the procedure
- Develop IVG/M as a safe alternative to reimplantation