

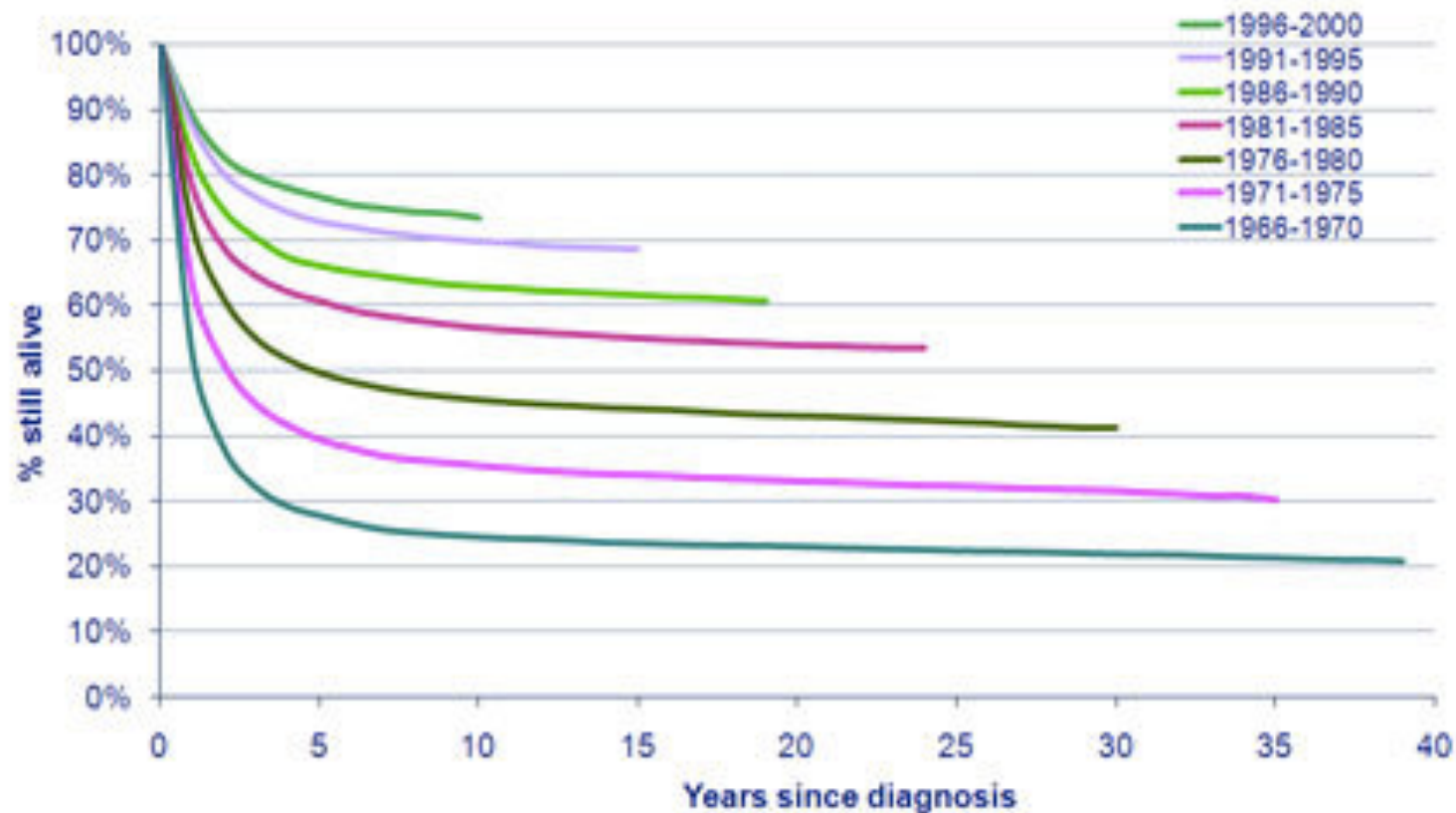
The treatment finishes: what
then?
Empowering yourself to be a
survivor

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Sydney, 16.11.14

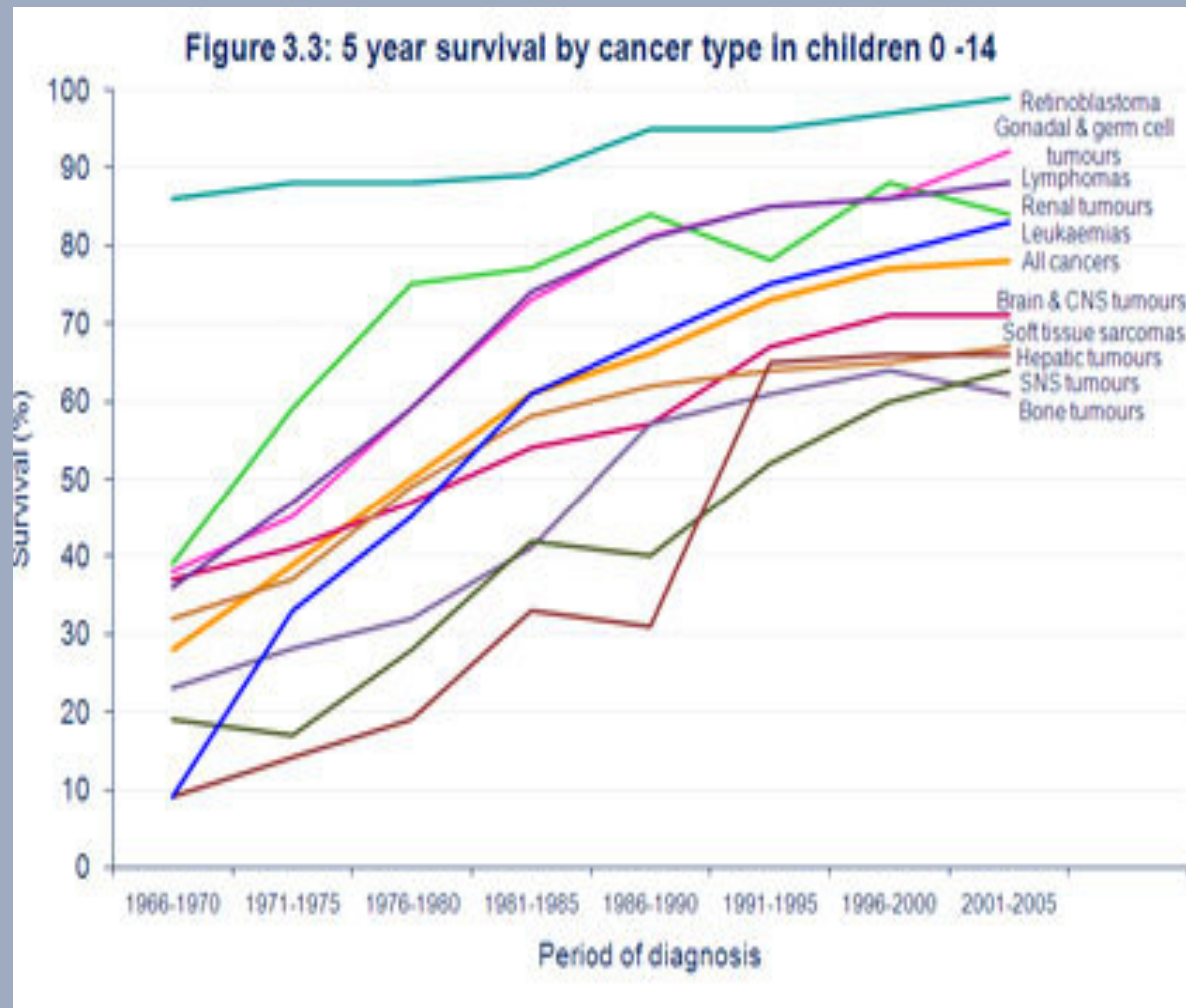
Improved Five Year Survival (1966-2000)

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



Improved survival rates

- * Paediatric oncology units
- * Clinical trials
- * Intensifying treatment
- * Supportive care



Cure at a cost

Sustain
survival
rates



Minimise
late effects

Lucca





LUCCA

- * Learn
- * Understand
- * Contact
- * Communication
- * Achieve

LUCCA

- * Learn about your diagnosis and treatment
- * *It is not the cancer diagnosis that determines the late effects you are at risk of, it is the actual treatment you received...*
- * Surgery
- * Chemotherapy
- * Radiotherapy

LUCCA

* Understand

- * *How your treatment may put you at risk of a late effect*
- * Anthracycline exposure – **Cardiomyopathy**
- * Radiotherapy – **Second primary cancer**
- * Alkylating agents &/or Radiotherapy to the pelvis
- **infertility**

LUCCA

- * Contact
- * *Key worker* (may change as you grow older)
 - * Nurse
 - * Doctor
 - * Oncologist/Haematologist
 - * Primary care Physician

LUCCA

- * Communication

- * Learn and understand your long-term risks
- * Discuss them with your Key Worker
- * Plan your own long-term follow-up

LUCCA

* *Achieve your potential*







Benefits of long-term follow-up

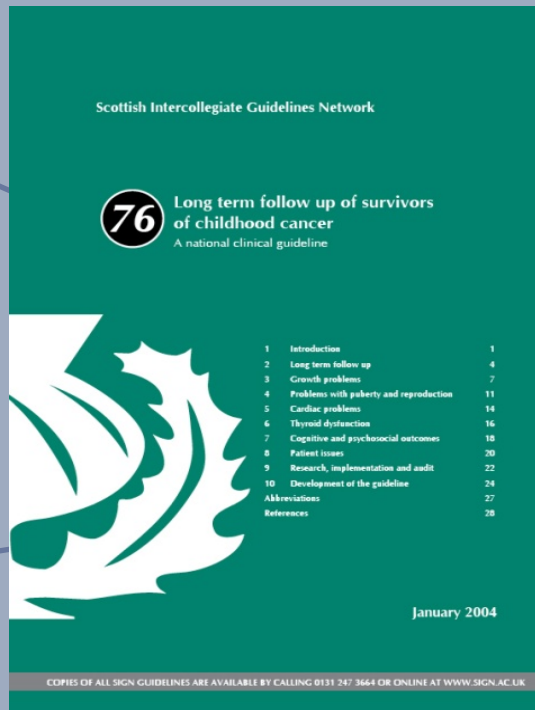
- * Decrease morbidity and mortality by identifying and treating treatment-related late effects
- * Educate survivors
- * Encouragement of health promoting behaviour for improved outcomes
 - * Increased patient satisfaction/quality of life
- * Research
 - * Follow new treatments/treatment regimens over the long-term

Evidence-based guidelines for Young Survivors of Cancer

SIGN 76: long term follow up of survivors of childhood cancer¹

All survivors of childhood cancer should be actively followed up for life

Each survivor of childhood cancer should have access to an appropriate designated key worker to co-ordinate care



At the end of a course of cancer treatment, patients, their parents/carers and GPs should be given a summary of the treatment and a list of signs of late effects to look out for

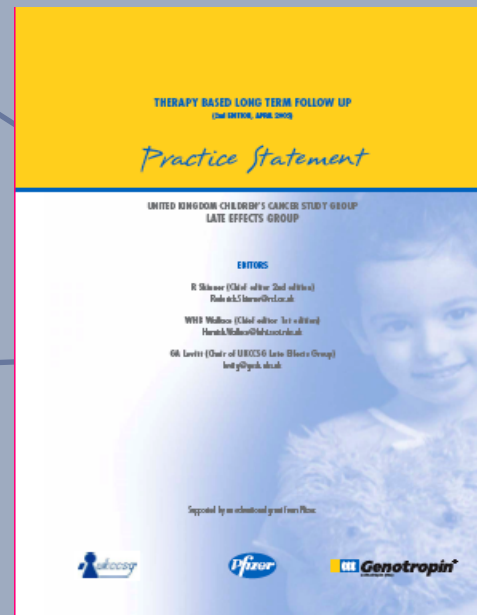
Reference: 1. SIGN 76. Long term follow-up of survivors of childhood cancer, January 2004.

CCLG: Therapy-based long-term follow-up practice statement

Guidance for surveillance of survivors at least 3 years off therapy

Protocols should be used in out-patient clinic

Protocol 1 = impaired quality of life
Protocol 2 = secondary malignancy
Protocol 3 = transfusion-associated complications

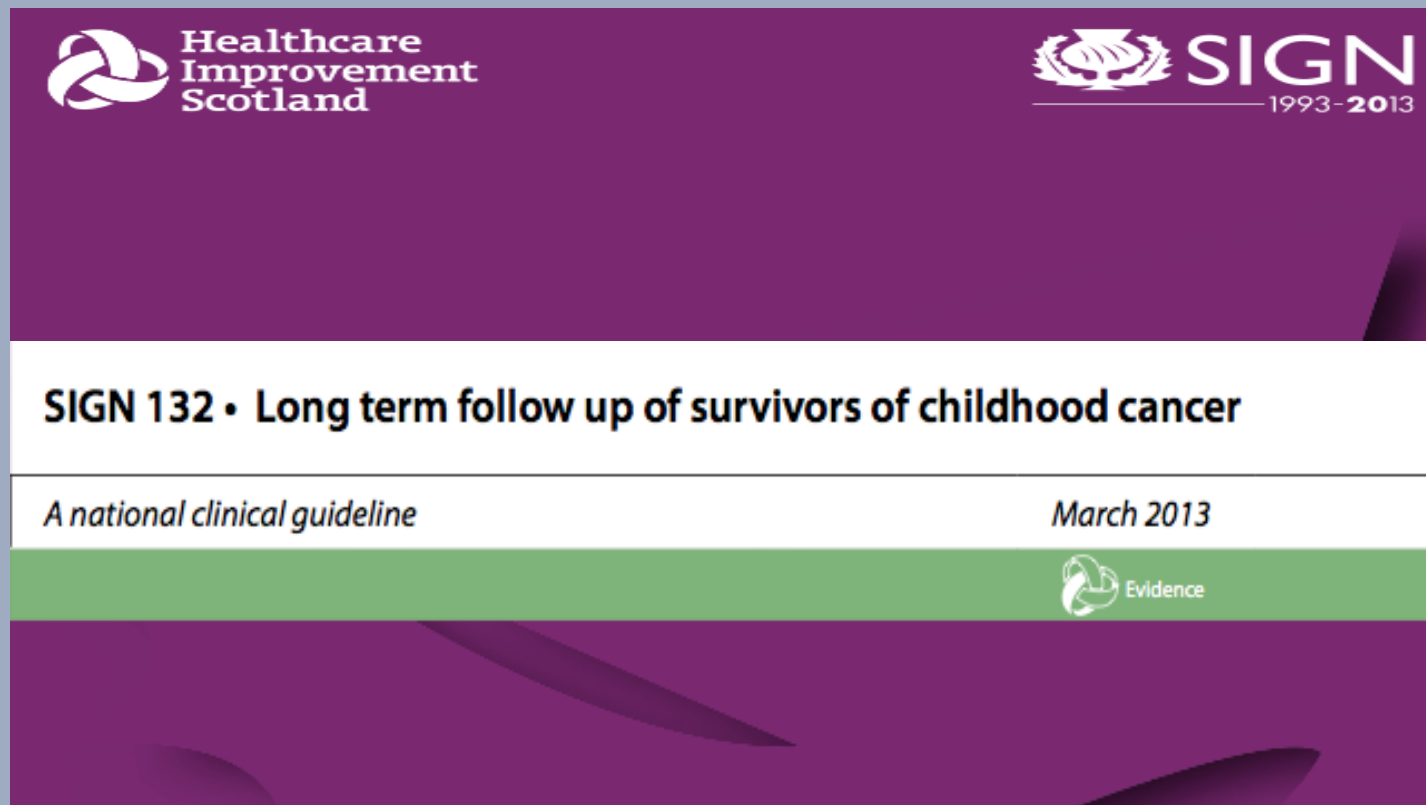


Summarize treatment received under the headings:

- Chemotherapy
- Radiotherapy
- Surgery

Work through “Treatment/Potential late adverse effects” lists and select appropriate follow-up protocol

SIGN 132 updates SIGN 76 (2004)



Wallace, W.H.B., Thompson, L. & Anderson, R.A., 2013 BMJ

International Late Effects of Childhood Cancer Guideline Harmonization Group

IGHG

Worldwide endeavor to collaborate in guideline development



Initiated by

National guideline groups

Cochrane Childhood Cancer Group

In partnership with the PanCareSurFup Consortium

International Late Effects of Childhood Cancer Guideline Harmonization Group

Main goal

To establish a common vision and integrated strategy for the surveillance of late effects in childhood, adolescent and young adult cancer survivors

Aims

- Reduce duplication of effort
- Combine international expertise
- Optimize quality of care
- Improve quality of life

Guideline development

KNOWLEDGE



RECOMMENDATION

Traffic Lights

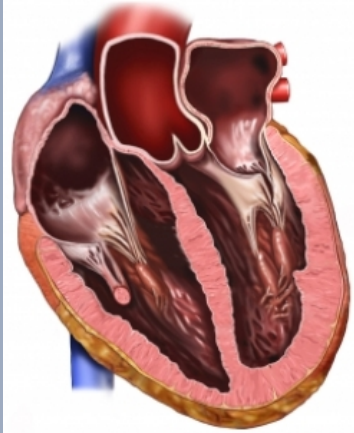


Stop –Don't do it..

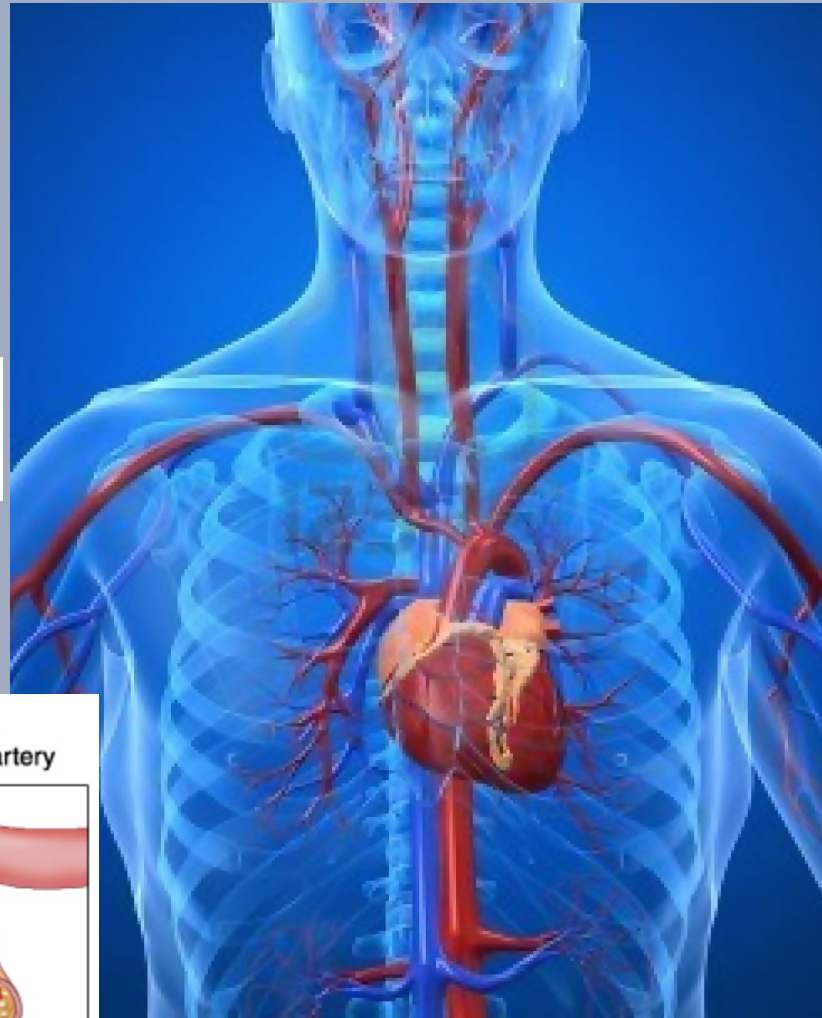
Not sure –More Research
required

Yes, Go do it..

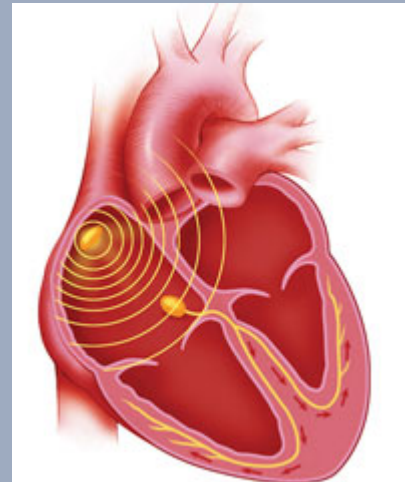
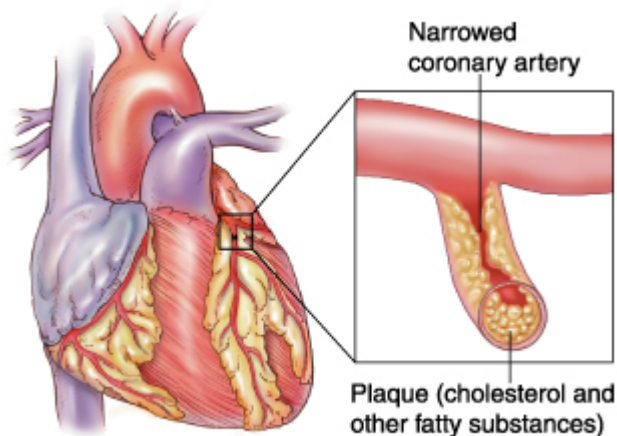
Cardiovascular disease



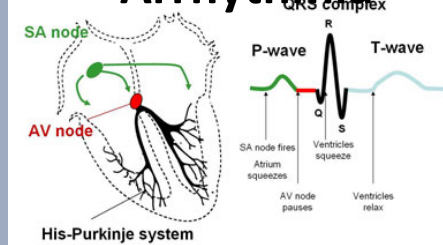
**Cardiac
Dysfunction**



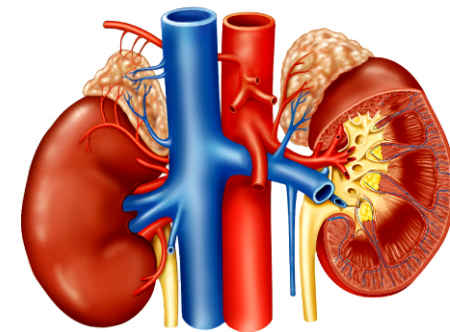
Atherosclerosis



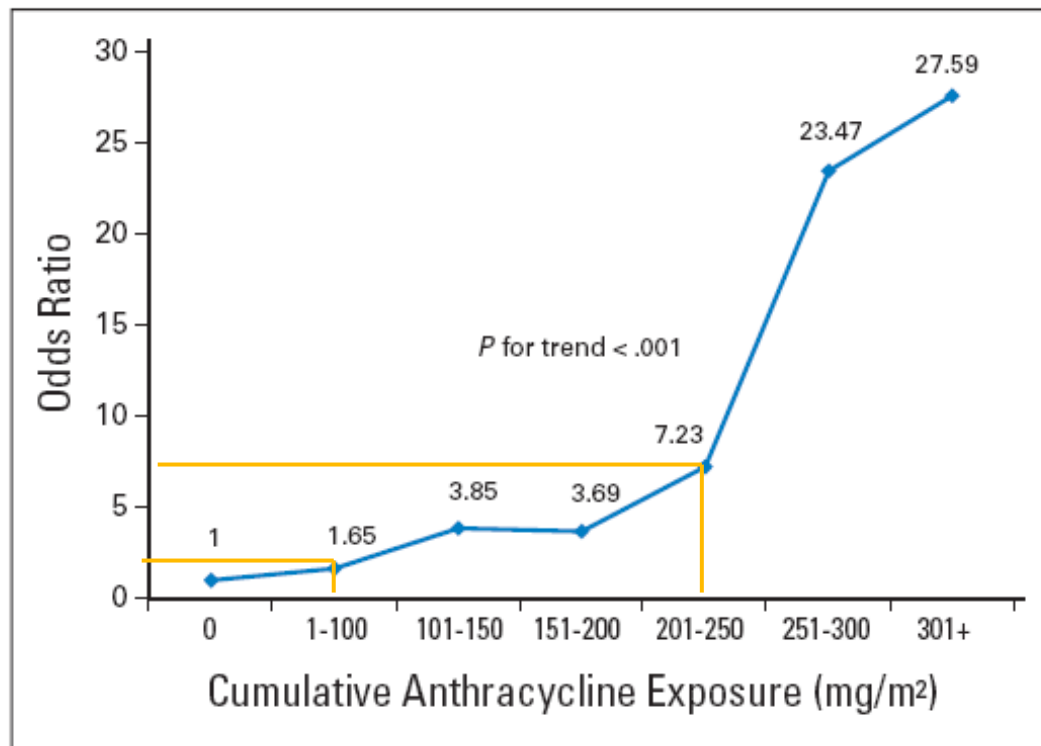
Arrhythmia



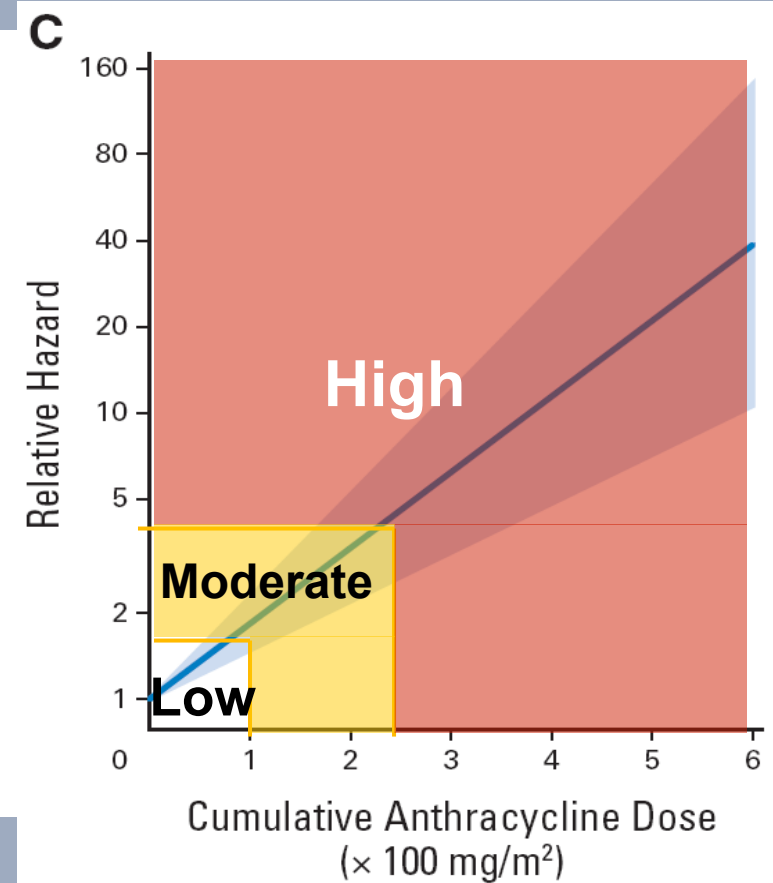
Reno-vascular



HF risk by anthracycline dose



Blanco JG, et al. *J Clin Oncol.* 2012



Van der Pal HJ, et al. *J Clin Oncol.* 2012

General recommendation

Survivors treated with anthracyclines and/or chest radiation and their providers should be aware of the risk of cardiomyopathy.

Who needs surveillance?

Anthracyclines

Cardiomyopathy surveillance is recommended for survivors treated with high dose (≥ 250 mg/m²) anthracyclines.

Cardiomyopathy surveillance is reasonable for survivors treated with moderate dose (≥ 100 to < 250 mg/m²) anthracyclines.

Cardiomyopathy surveillance may be reasonable for survivors treated with low dose (< 100 mg/m²) anthracyclines.

Who needs surveillance?

Chest radiation

Cardiomyopathy surveillance *is recommended* for survivors treated with high dose (≥ 35 Gy) chest radiation.

Cardiomyopathy surveillance *may be reasonable* for survivors treated with moderate dose ($\geq 15 < 35$ Gy) chest radiation.

No recommendation can be formulated for cardiomyopathy surveillance for survivors treated with low dose (< 15 Gy) chest irradiation with conventional fractionation.

Who needs surveillance?

Anthracyclines + Chest radiation

Cardiomyopathy surveillance *is recommended* for survivors treated with moderate-high dose anthracyclines (≥ 100 mg/m²) and moderate-high dose chest radiation (≥ 15 Gy)

No recommendation can be formulated for surveillance:

- Younger (<5 years) age at exposure
- Dexrazoxane
- Different strategies by anthracycline analogue

WG2: What surveillance modality should be used?

Echocardiography *is recommended* as the primary cardiomyopathy surveillance modality for assessment of cardiac function in survivors treated with anthracyclines and/or chest radiation

WG3: At what frequency should surveillance be performed?

High Risk survivors

Cardiomyopathy surveillance is recommended for High Risk survivors to begin no later than 2 years after completion of cardiotoxic therapy, repeated at 5 years after diagnosis and continued every 5 years thereafter.

More frequent cardiomyopathy surveillance is reasonable for High Risk survivors.

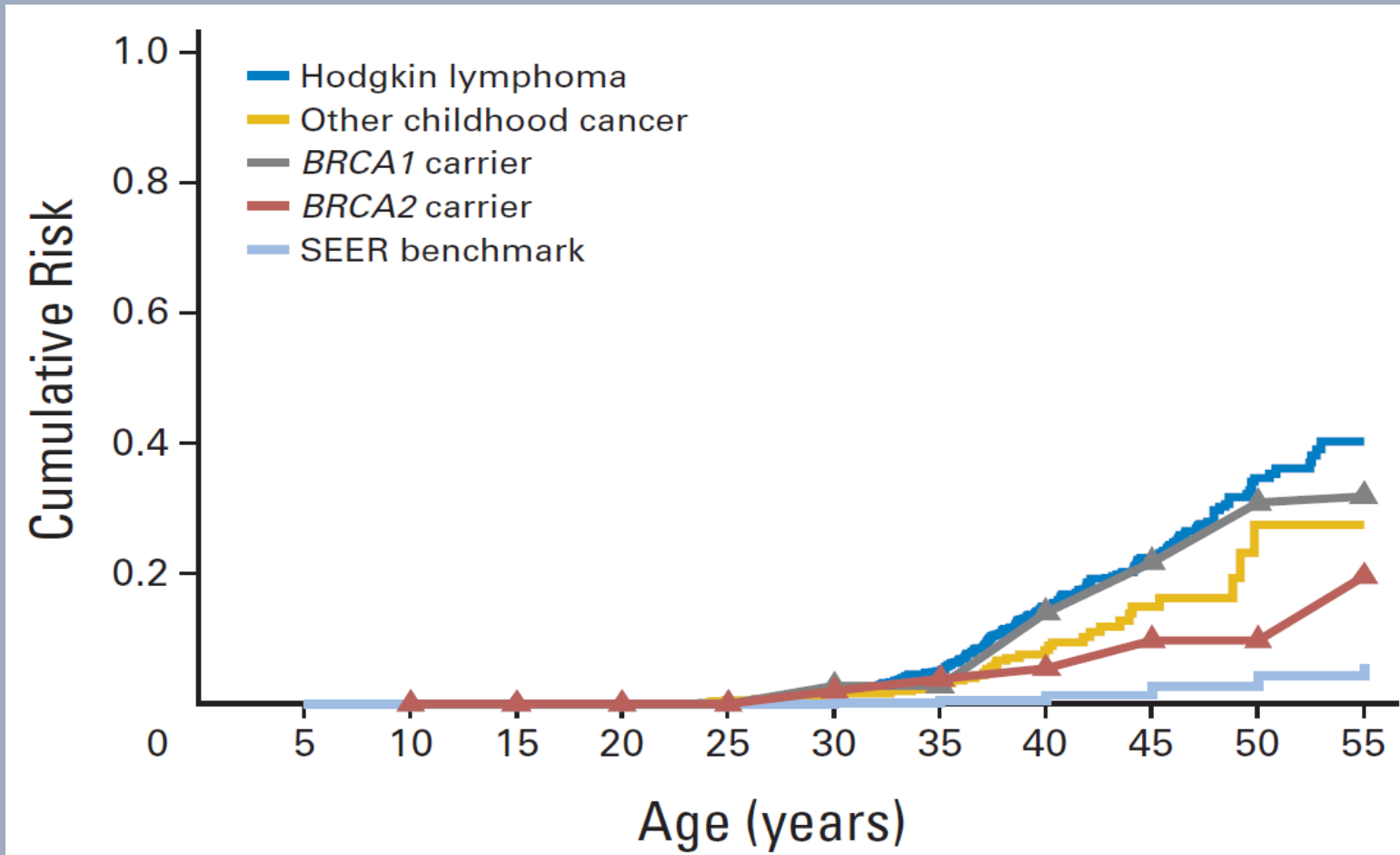
Lifelong cardiomyopathy surveillance may be reasonable for High Risk survivors.

Breast cancer surveillance recommendations

THE LANCET *Oncology* 2013; 14: e621-29

Mulder RL, Kremer LCM, Hudson MM, Bhatia S, Landier W, Levitt G, Constine LS, Wallace WH, van Leeuwen FE, Ronckers CM, Henderson TO, Dwyer M, Skinner R, Oeffinger KC

Breast cancer risk



Moskowitz et al. J Clin Oncol 2014

General recommendation

Female childhood, adolescent and young adult cancer survivors treated with chest radiation and their providers should be aware of the breast cancer risk.

Breast cancer risk by radiation dose

High-dose chest RT (≥ 20 Gy)

High level evidence for increased risk

Low- to moderate-dose chest RT (1-19 Gy)

Insufficient evidence

Linear dose response

Lack of consideration of volume

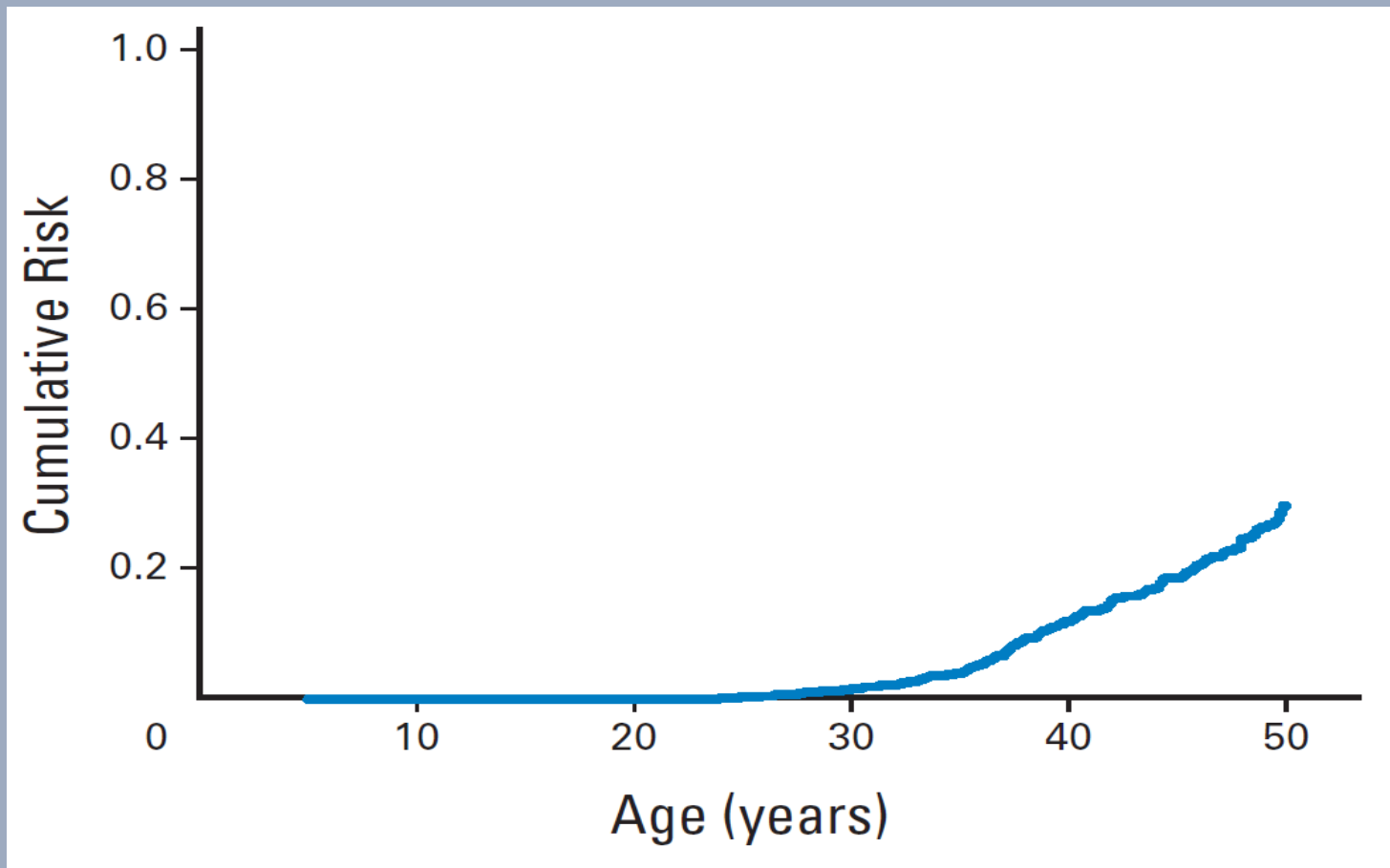
Who needs breast cancer surveillance?

Breast cancer surveillance is recommended for female childhood, adolescent and young adult cancer survivors treated with ≥ 20 Gy chest radiation.

Breast cancer surveillance is reasonable for female childhood, adolescent and young adult cancer survivors treated with 10-19 Gy chest radiation based on clinical judgment and considering additional risk factors.

Breast cancer surveillance may be reasonable for female childhood, adolescent and young adult cancer survivors treated with 1-9 Gy chest radiation based on clinical judgment and considering additional risk factors.

At what age should breast cancer surveillance be initiated?



Moskowitz et al. J Clin Oncol 2014

At what age should breast cancer surveillance be initiated?

Initiation of breast cancer surveillance *is recommended* at age 25 years or ≥ 8 years from radiation (whichever occurs last) for female childhood, adolescent and young adult cancer survivors treated with ≥ 20 Gy chest radiation.

At what frequency should breast cancer surveillance be performed?

Annual breast cancer surveillance *is recommended* for female childhood, adolescent and young adult cancer survivors treated with ≥ 20 Gy chest radiation for at least up to 50 years of age.

What surveillance modality should be used?

Mammography and MRI

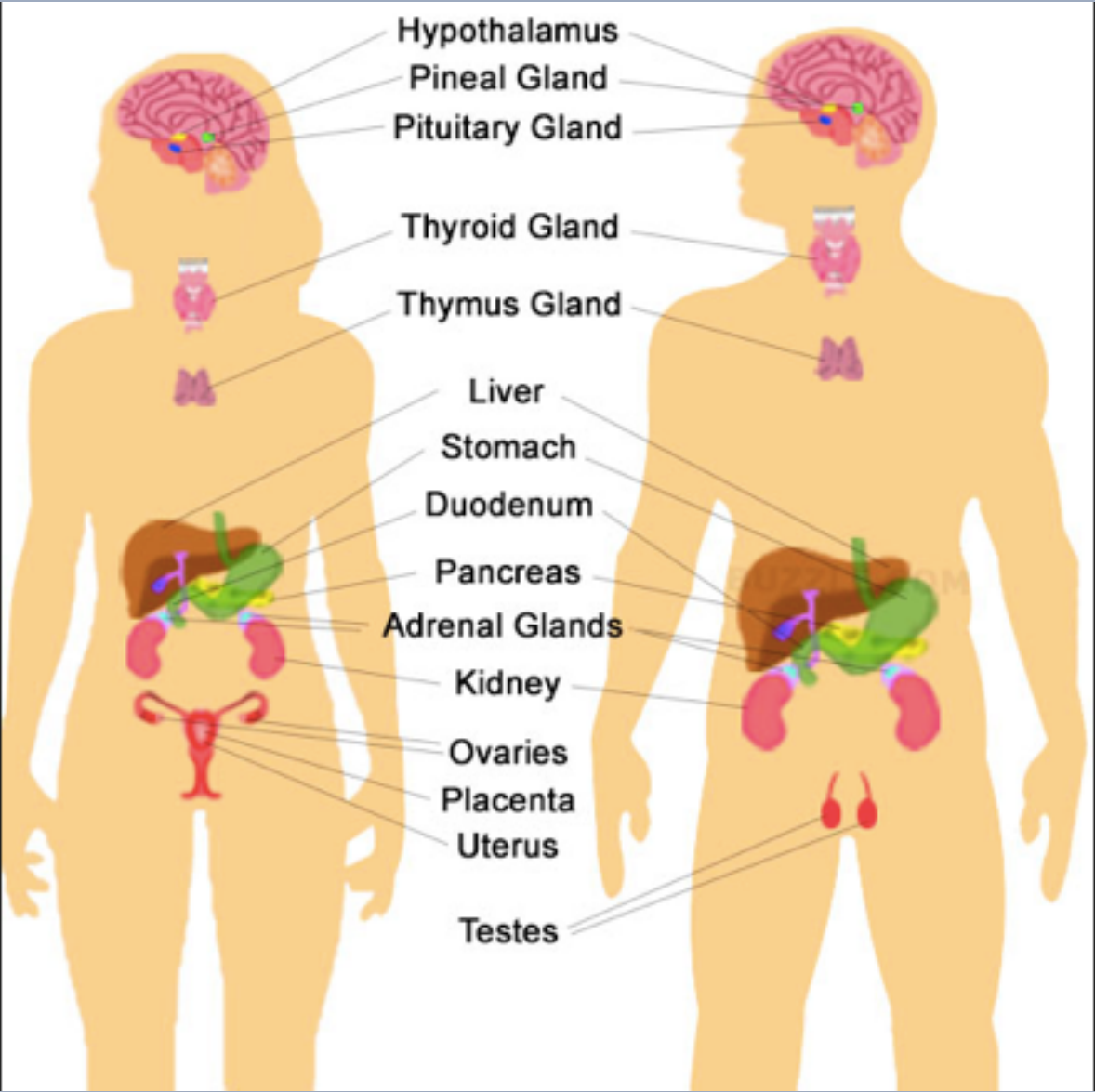
Combination superior to either test alone

Evidence insufficient to recommend ideal imaging modality

Uncertainty balance benefits versus harms

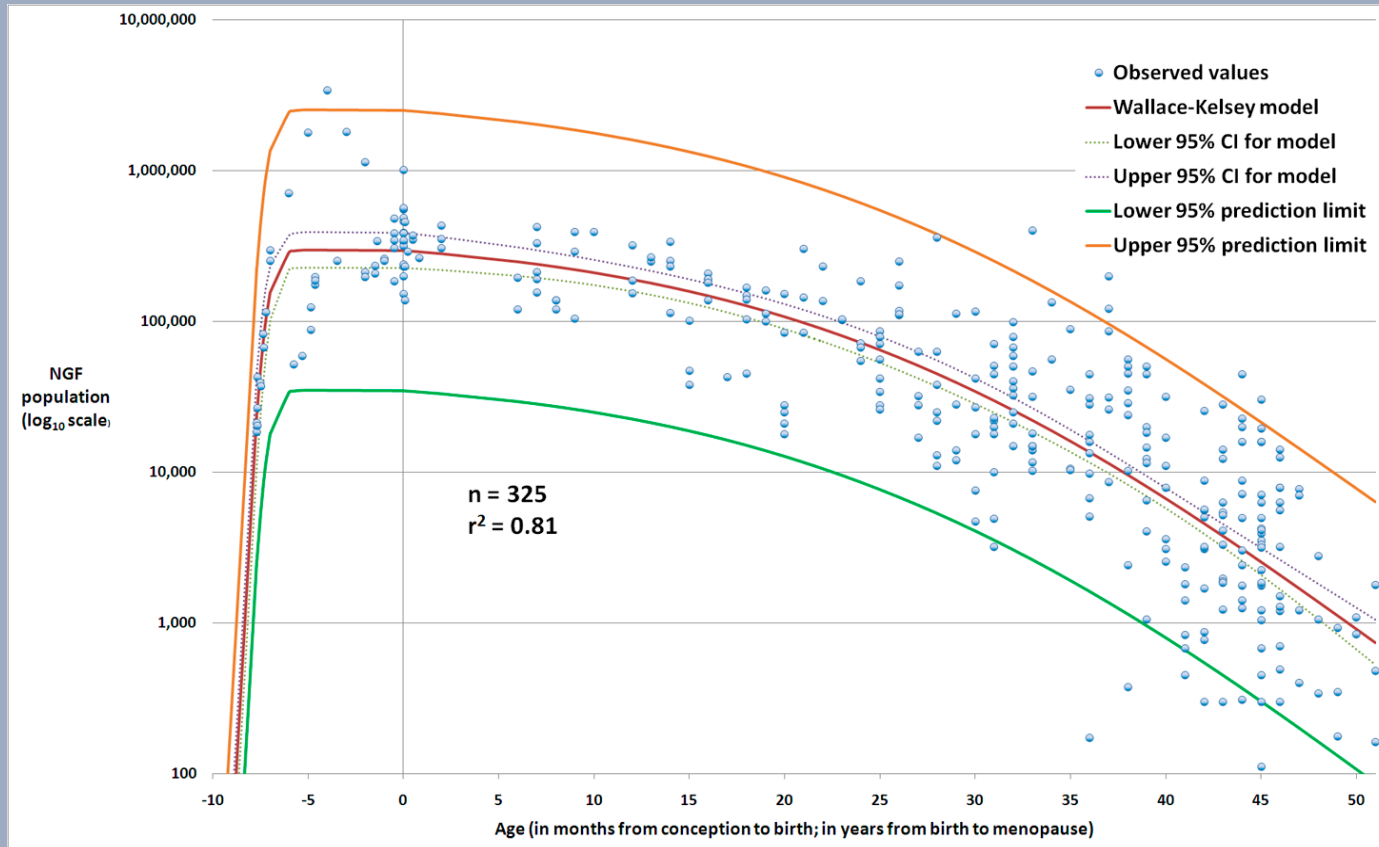
What surveillance modality should be used?

Mammography or breast MRI or a combination of mammography and breast MRI *is recommended* for female childhood, adolescent and young adult cancer survivors treated with chest radiation.



The Wallace-Kelsey Model

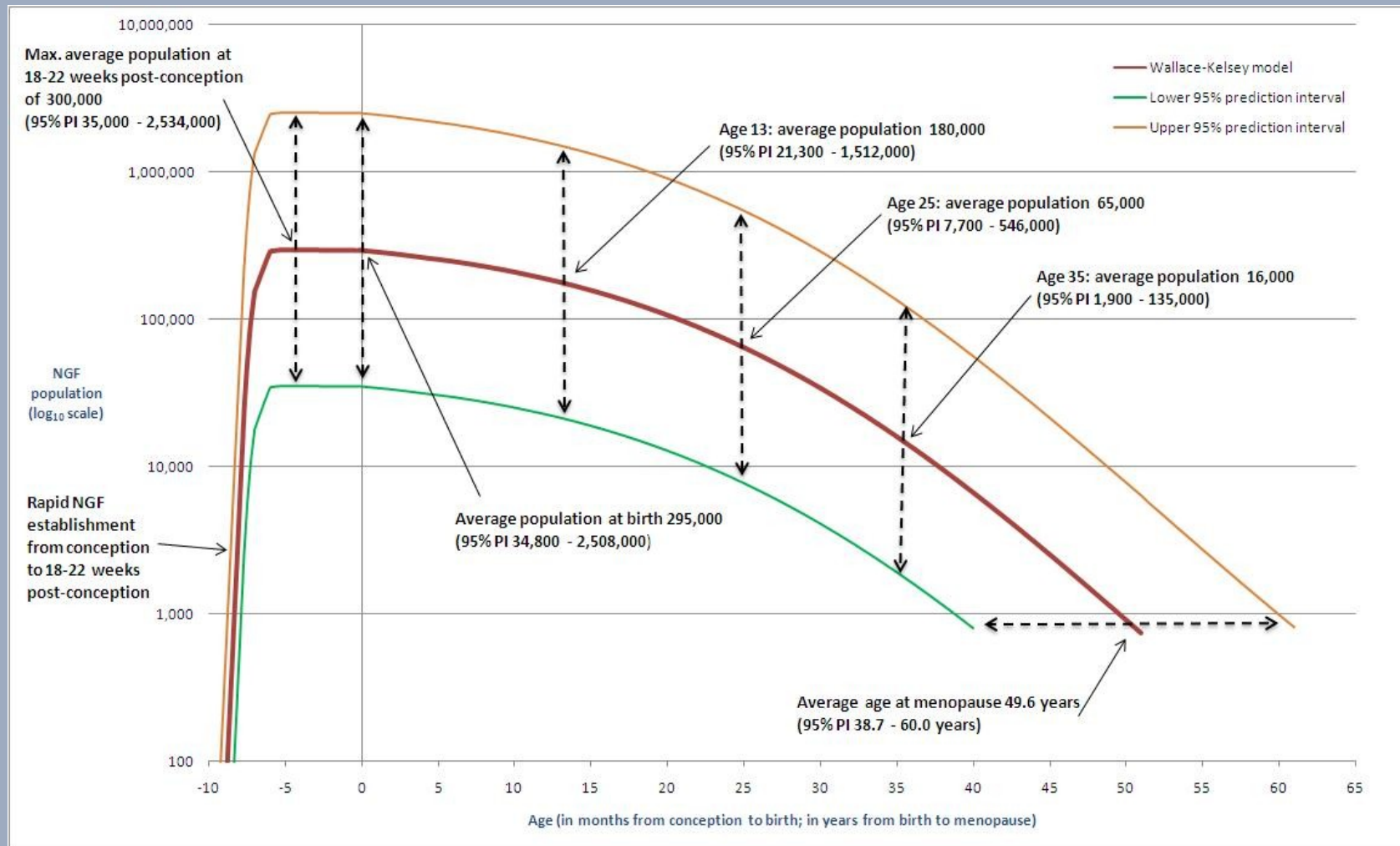
(Five parameter asymmetric double-Gaussian cumulative curve)



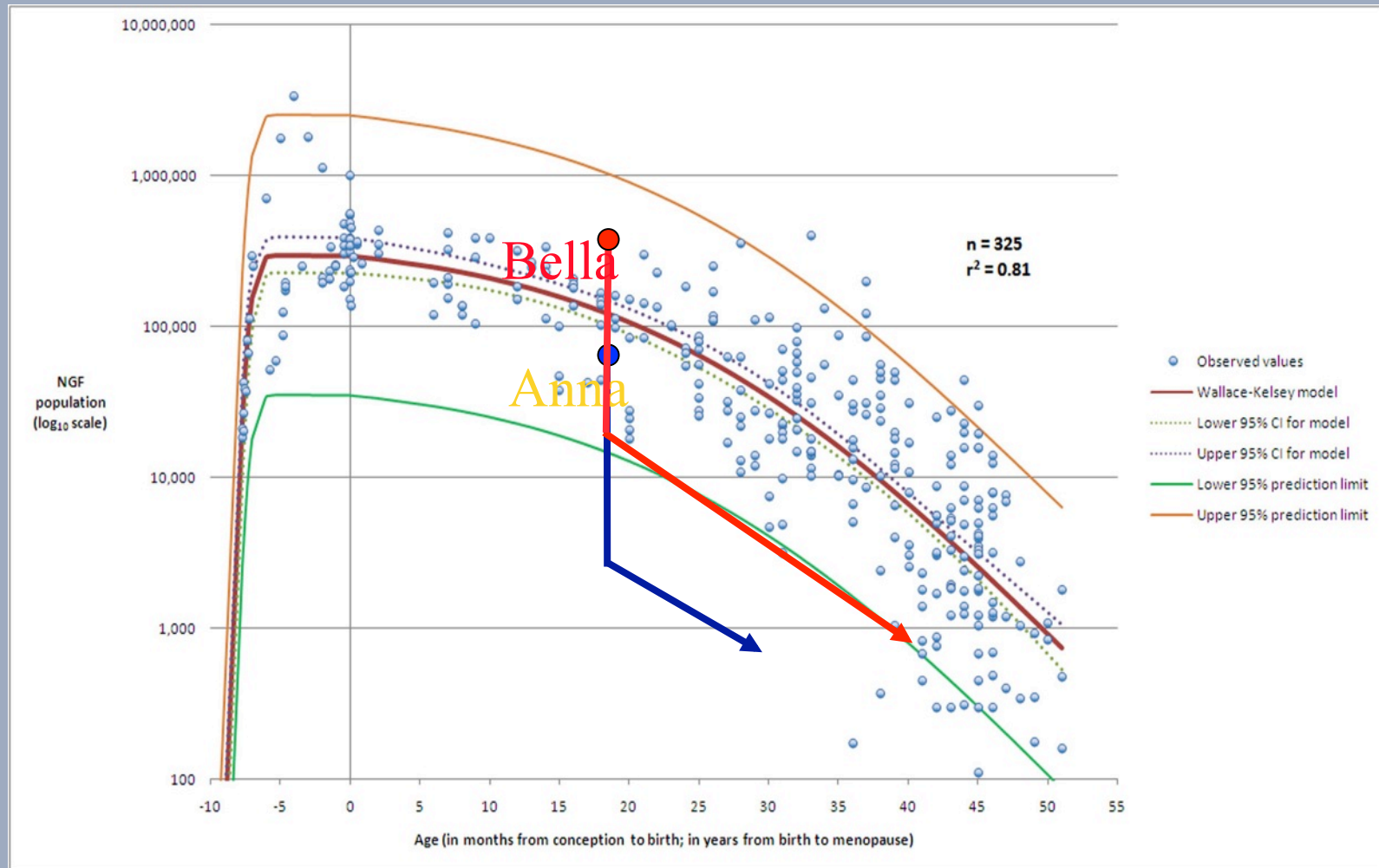
$$\log_{10}(y) = \frac{a}{4} \left[1 + \operatorname{Erf} \left(\frac{x+b+\frac{c}{2}}{d\sqrt{2}} \right) \right] \left[1 - \operatorname{Erf} \left(\frac{x+b-\frac{c}{2}}{e\sqrt{2}} \right) \right]$$

Wallace & Kelsey (2010) PloS ONE

Ovarian reserve: Conception to Menopause



Ovarian reserve: Conception to Menopause



Sertoli Cell

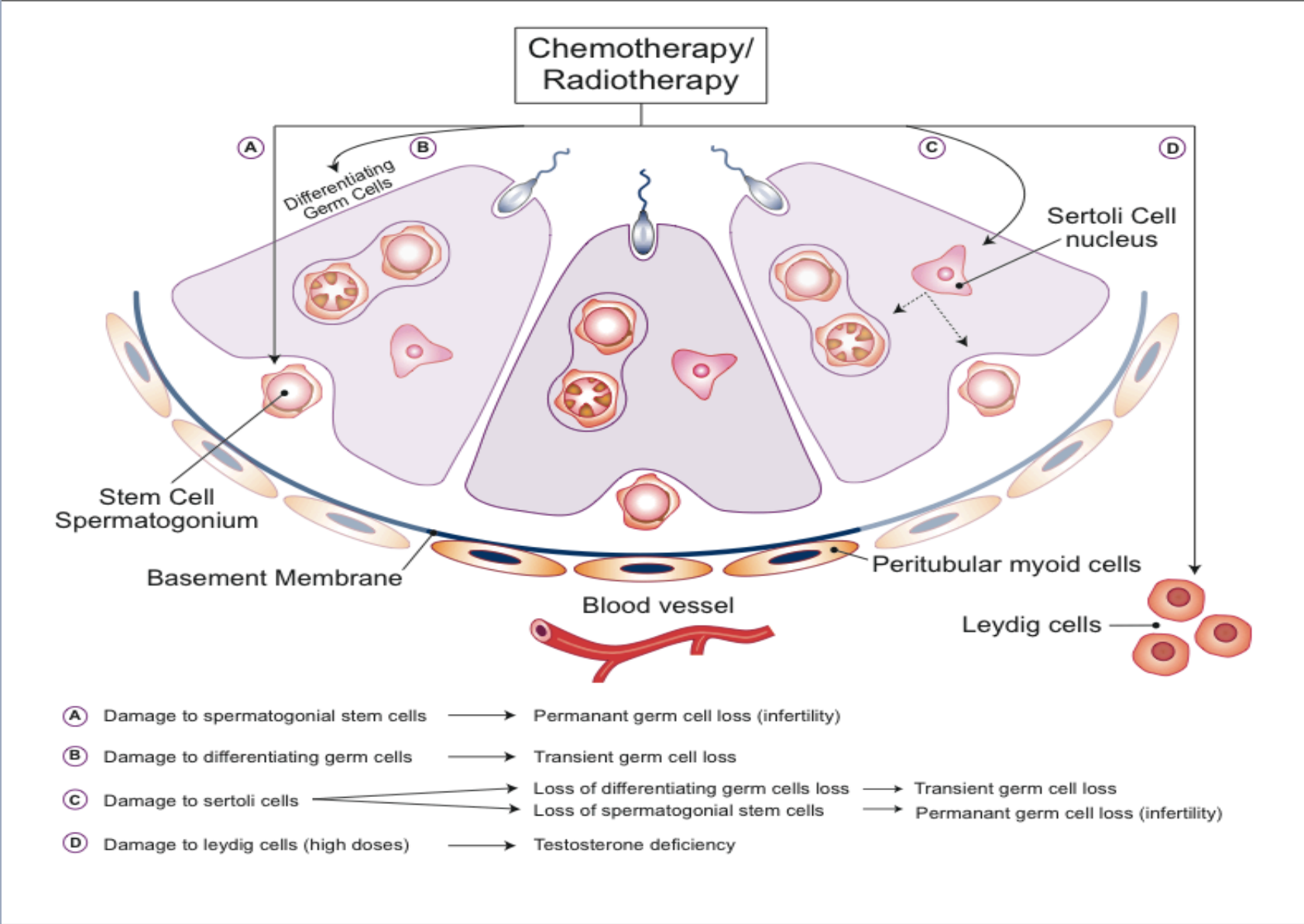
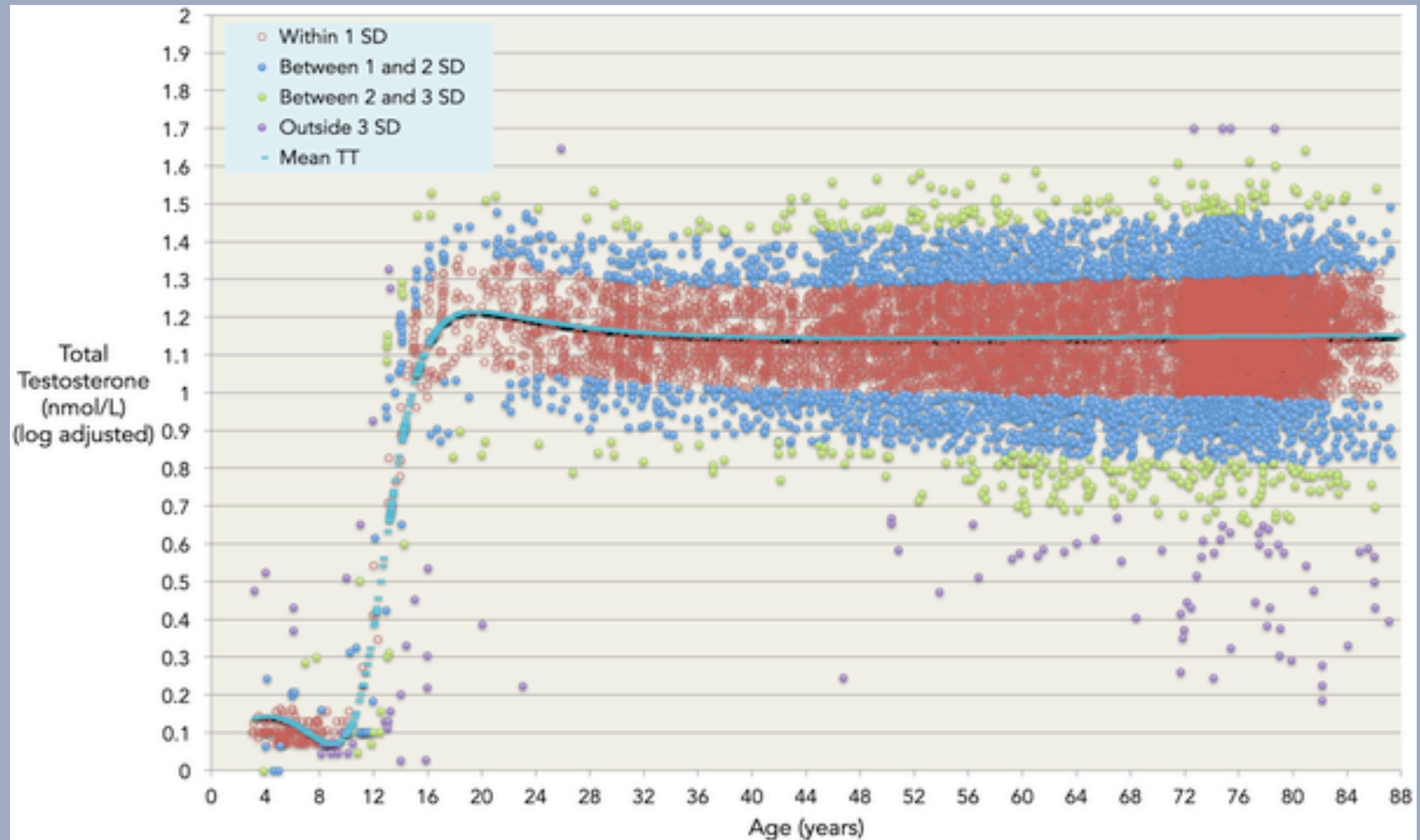
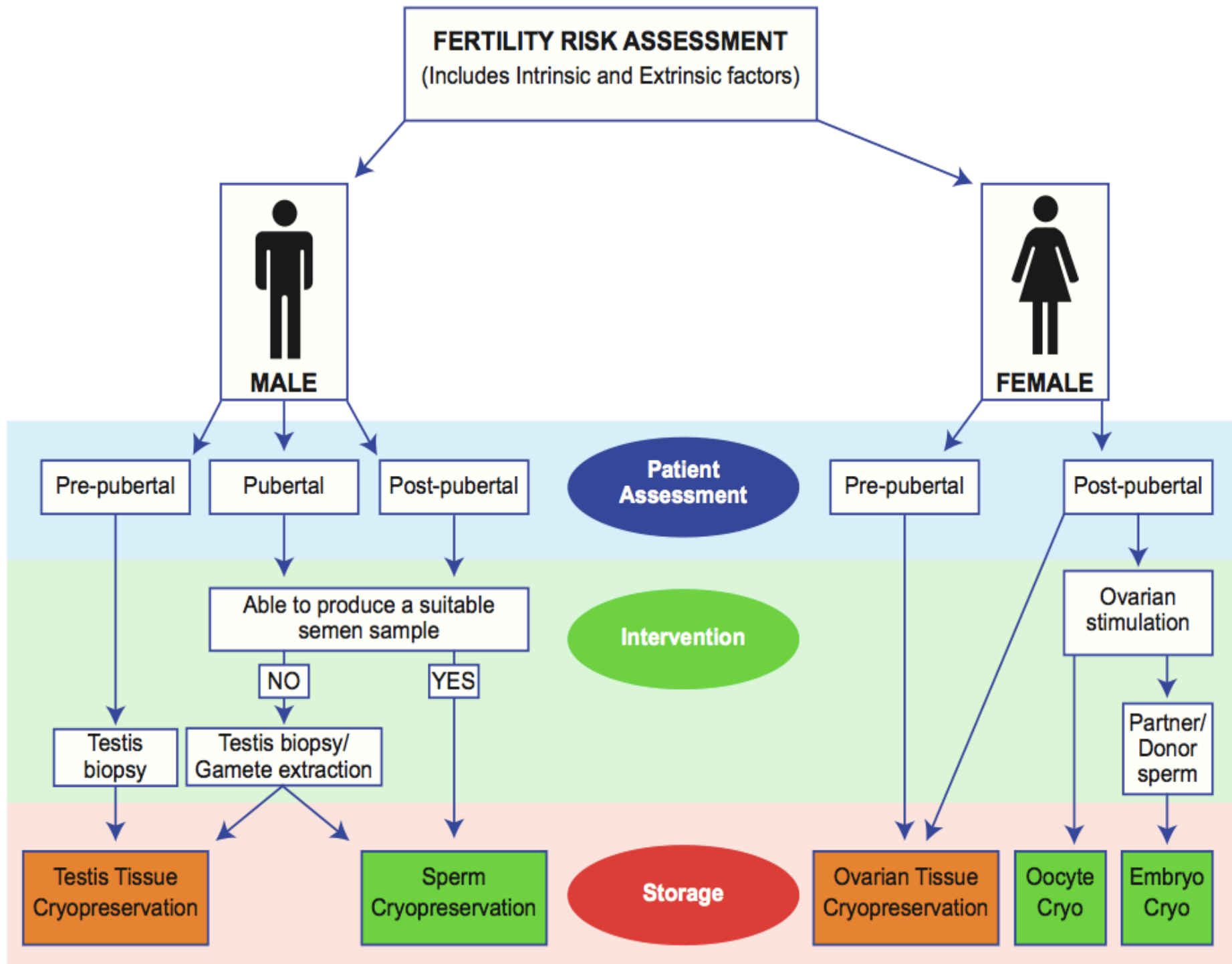


Figure 1. The validated model, log-adjusted testosterone values.



Kelsey TW, Li LQ, Mitchell RT, Whelan A, et al. (2014) A Validated Age-Related Normative Model for Male Total Testosterone Shows Increasing Variance but No Decline after Age 40 Years. PLoS ONE 9(10): e109346. doi:10.1371/journal.pone.0109346

<http://www.plosone.org/article/info:doi/10.1371/journal.pone.0109346>

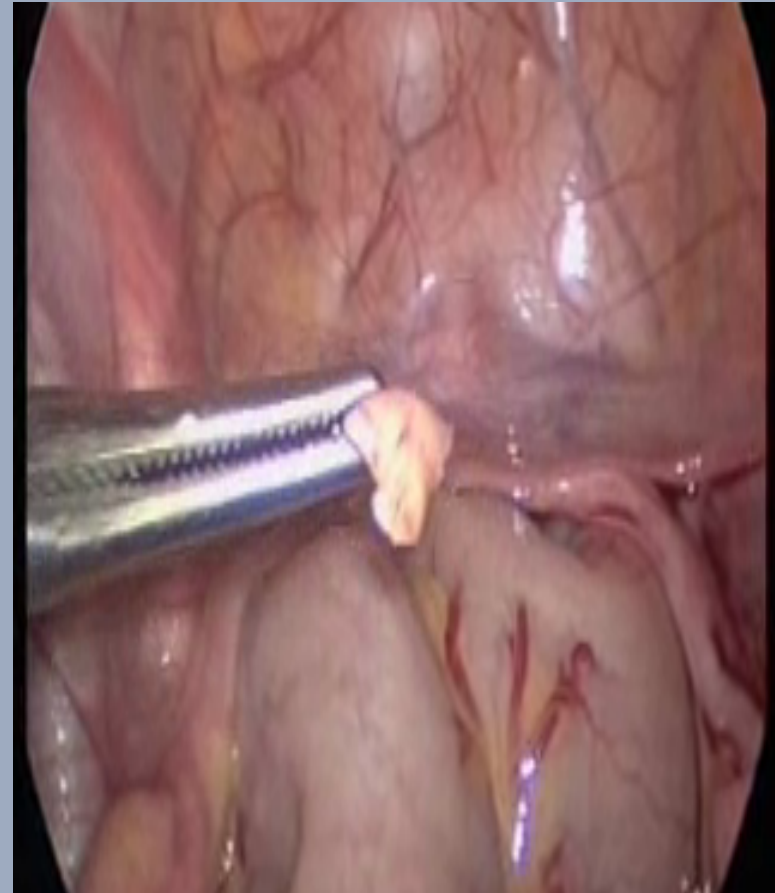


Key features of the 3 options for fertility preservation for women

- * Embryo cryopreservation
 - * Established but require time and a partner
- * Oocyte cryopreservation
 - * Established but require time and hormone stimulation (success rate per oocyte low)
- * Ovarian tissue cryopreservation
 - * Minimal delay
 - * No lower age limit
 - * Surgical procedure
 - * Allows for future developments

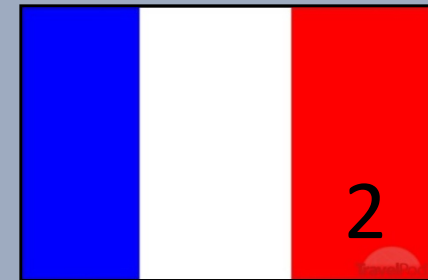
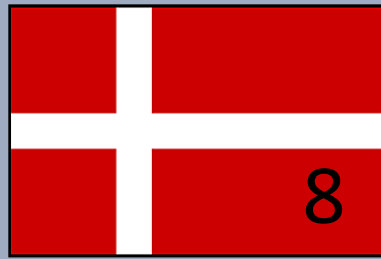
Ovarian tissue cryopreservation: World-wide experience

- * At least 39 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



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

Children born from transplantation of frozen/thawed ovarian tissue

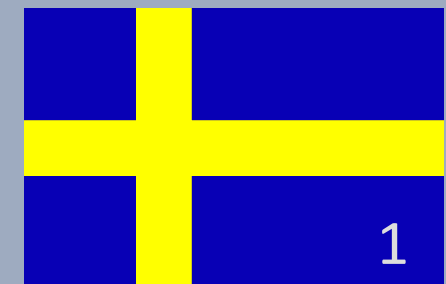
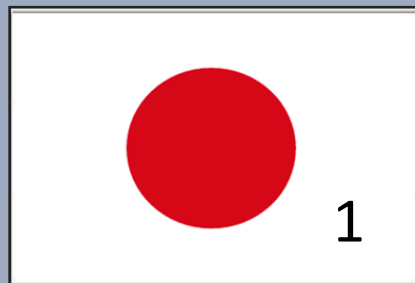
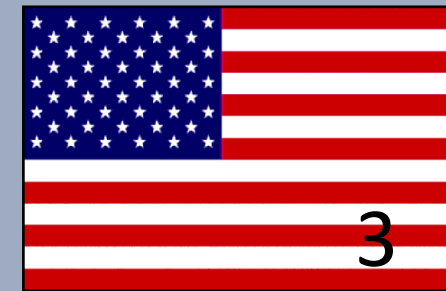


All Normal Babies
weight and duration
Orthotopic >> heterotopic



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

An estimated excess of 150
transplantations have been performed



Thank You



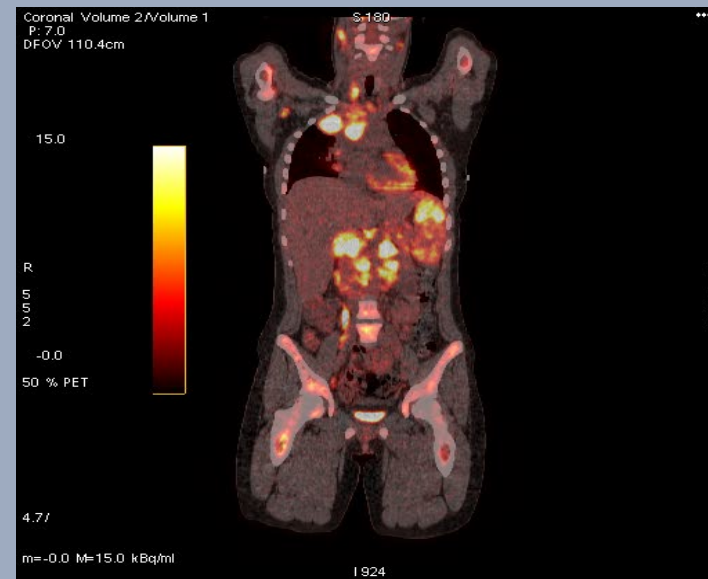
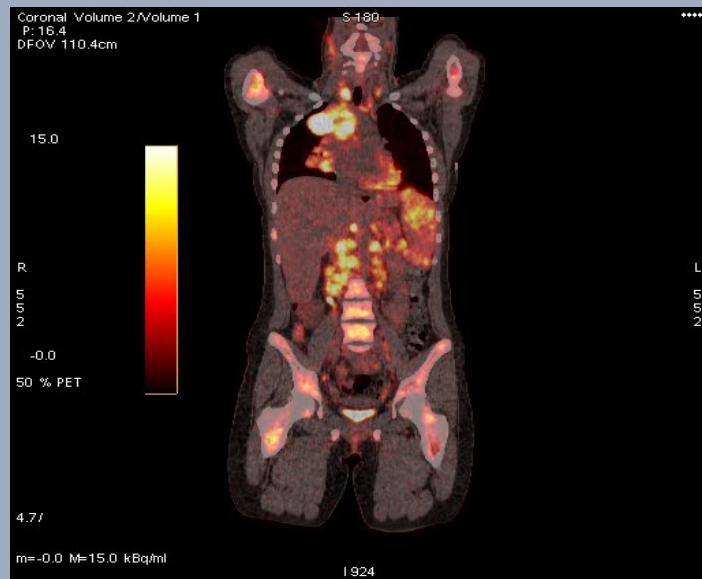
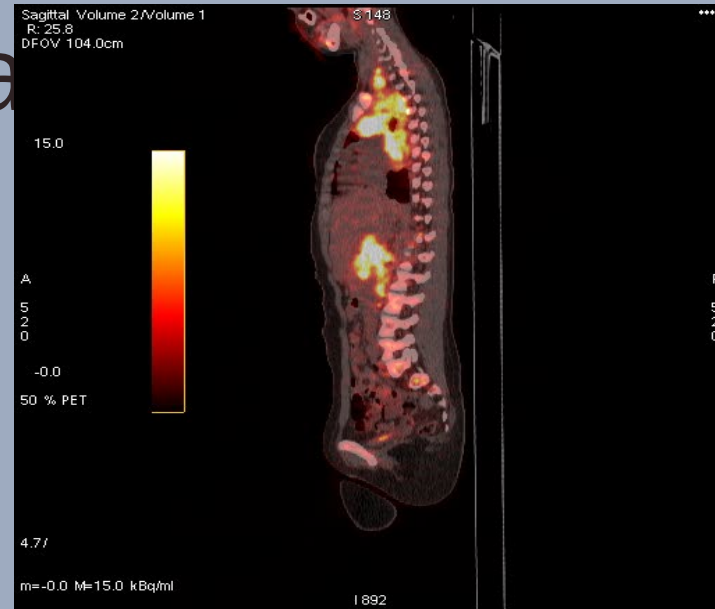
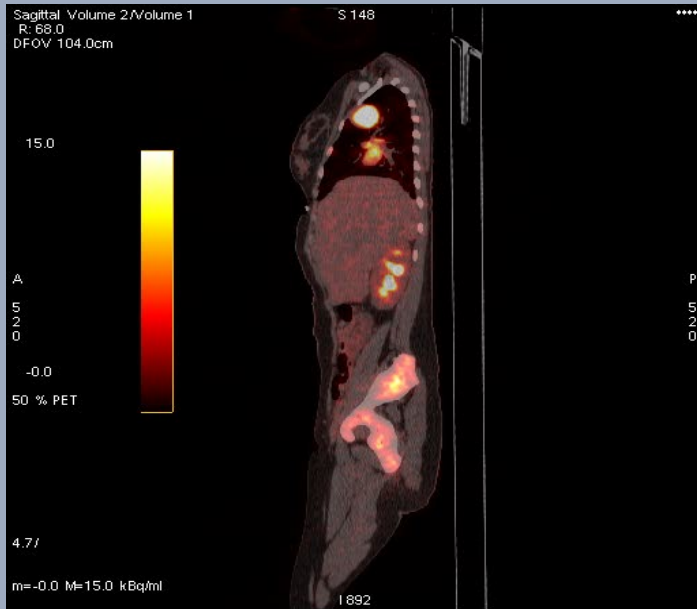
A Patient



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

enta



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, Critchley HOD & Anderson RA. JCO, 2012

Diagnosis and Staging

- Mediastinal lymph node biopsy
 - * Hodgkin's lymphoma
- Insertion of double lumen portacath

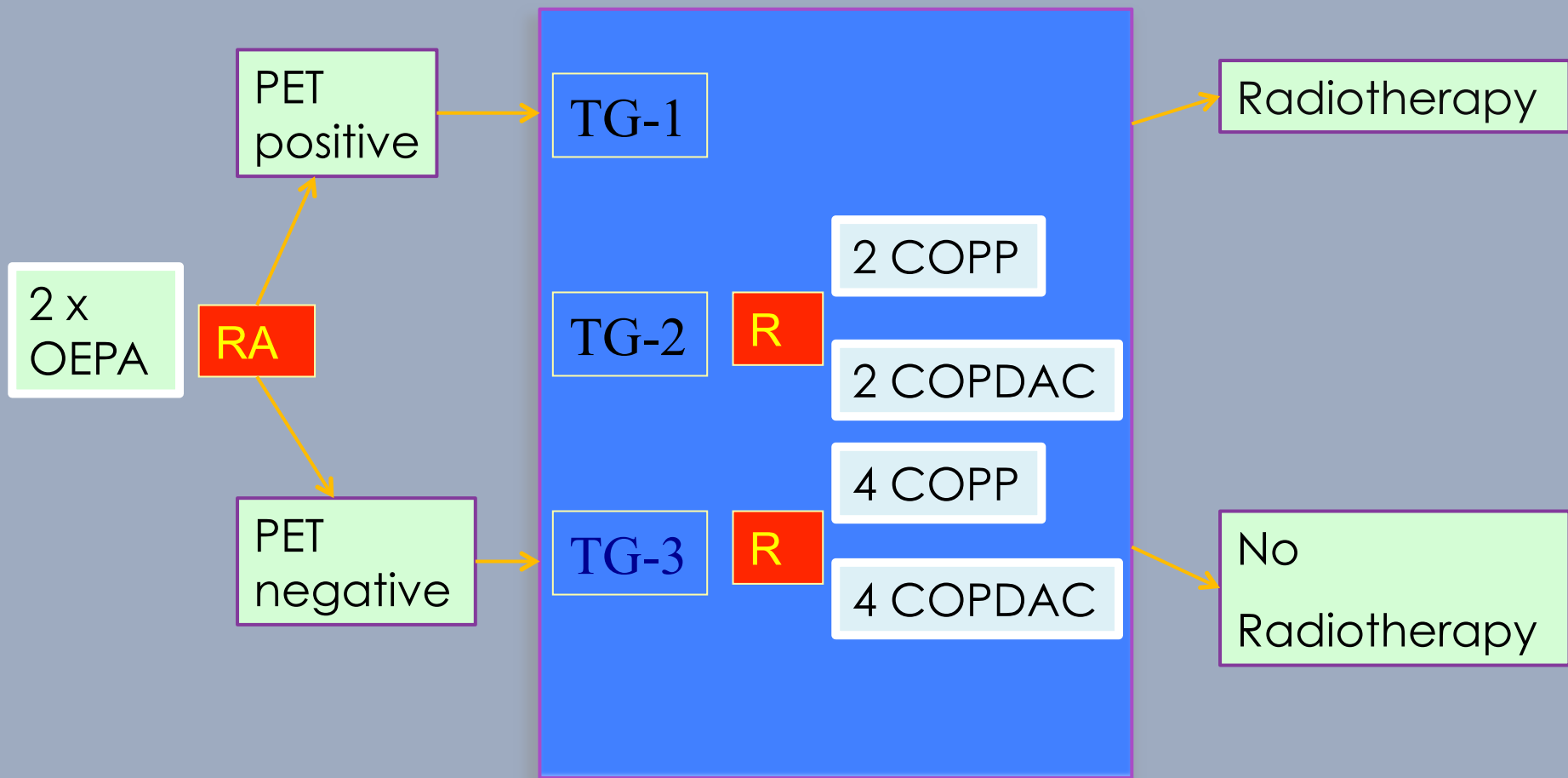
Laparoscopic ovarian biopsy and cryopreservation of ovarian cortical strips



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

Multidisciplinary team (MDT)

NICE guidelines recommend that the late effects MDT should include¹

Lead clinical (oncologist with expertise in late effects)

Key worker

Specialist nurse

Endocrinologist

Appropriate allied health professional

Psychological services professional

SIGN guidelines recommend that the MDT may include:²

Adult oncologist

Clinical psychologist

GP

Paediatric endocrinologist

Paediatric neurologist

Dentist

Paediatric neurosurgeon

Paediatric oncologist

Radiation oncologist

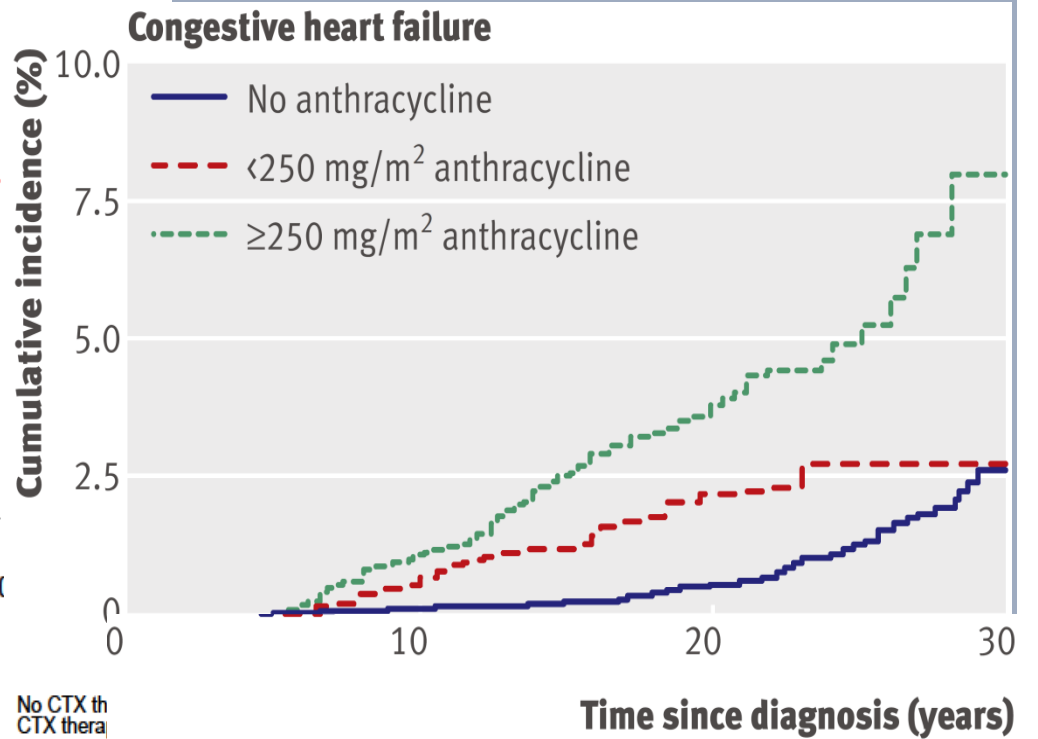
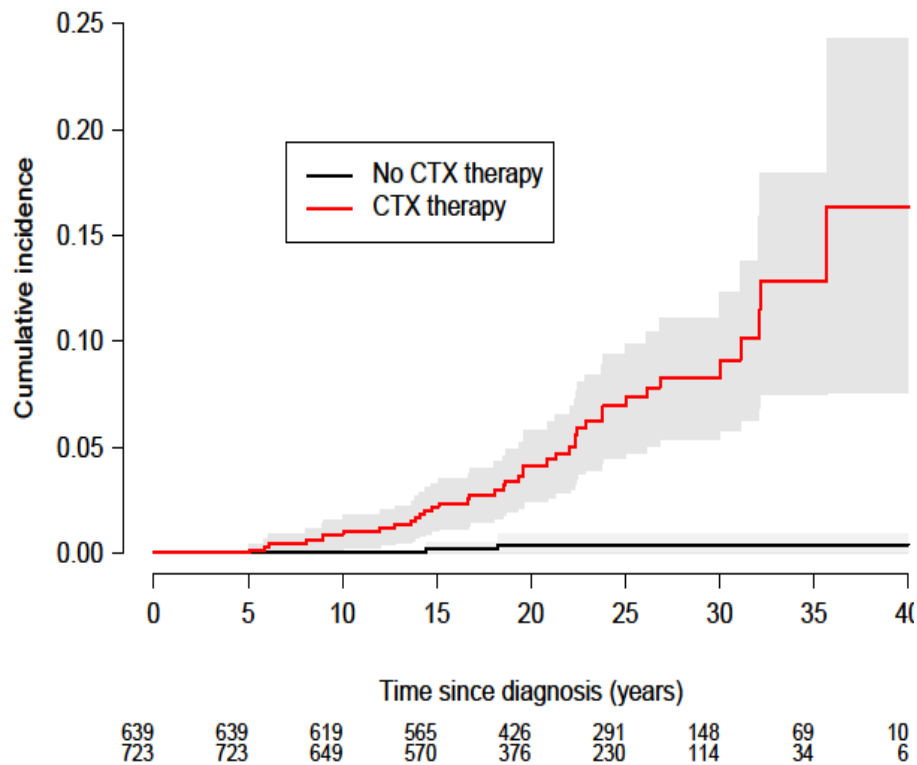
Social worker

Specialist nurse/nurse practitioner

Optician



Risk increases over time



Van der Pal HJ, et al. *J Clin Oncol*. 2012

Mulrooney, et al. *BMJ*. 2009;