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Artificial intelligence and datamining with biological data.

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Overview

- Case studies: Biological data science for late effects research
  - Original model
  - Validation
  - Application(s)
  - The future
- Common themes
- Techniques
- External validation
- Implications

Methodology

- Data aggregation
  - Systematic search for data sources from the literature
  - Tables, charts, descriptive statistics
  - Our own data – if available
- Data selection to create data set with minimal bias
  - Exclusion & inclusion criteria (e.g. exclude infertile)
- Homogeneous data set that approximates the healthy population for a wide range of ages
- Identify model with good fit to the data and low generalisation error
  - Accurate when used to predict unseen examples

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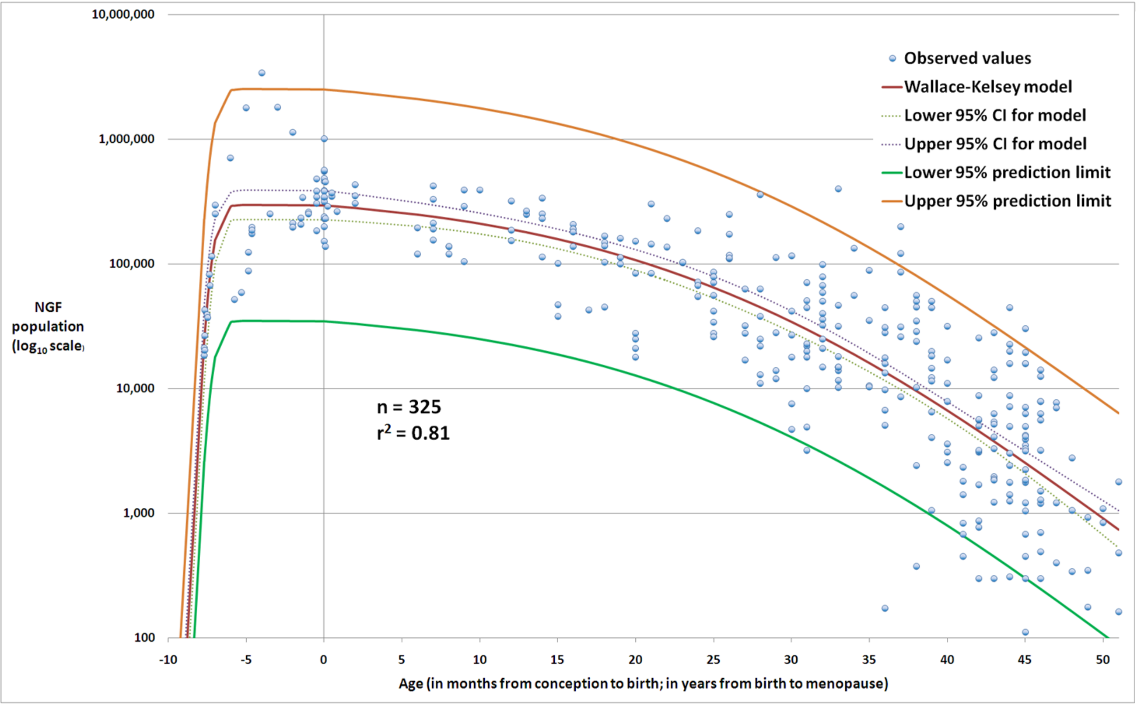
Observational data model - external validation

Number of potential eggs (NGFs) in the human ovary



Predictions compared to later observations from a population-based cohort

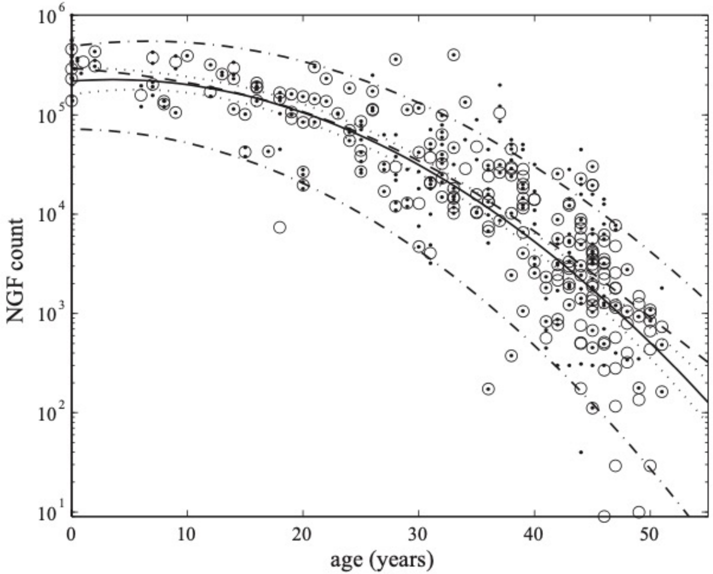


Figure 1. NGF counts (circles) from the 2015 data and (dots) from the 2010 data. The quadratic regression (solid line) fitted to the 2015 data with 95% confidence intervals (dotted lines) and 90% prediction intervals (dash-dotted lines). The Wallace-Kelsey model as fitted to the 2010 data is also depicted (dashed line).

Wallace & Kelsey, PLoS ONE 2010; Depmann *et al.*, JCEM 2015

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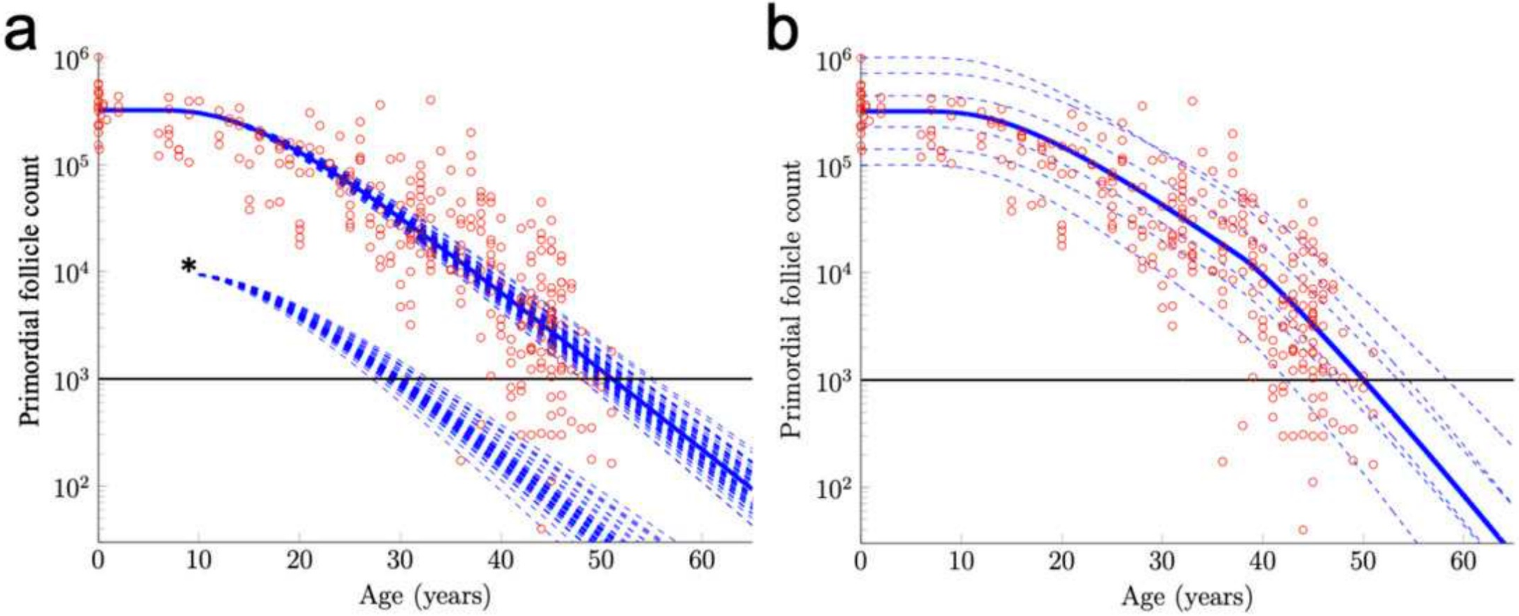
Random walk approach

Number of potential eggs (NGFs) in the human ovary



J. Johnson, JW. Emerson, SD. Lawley; https://doi.org/10.1101/2022.05.31.494088

Random walk approach

- Same data
- Good agreement with Wallace-Kelsey
  - In particular, accurate prediction of ages at menopause
- More modern technique (arguably)
  - Machine learning/AI method to remember or forget elements to optimise results
  - Stochastic gradient descent
- Can be used to test two important assumtions made by Wallace-Kelsey
  - High/low population at birth means late/early menopause
  - Radio- and/or chemotherapy moves a patient to an older age in terms of fertility, and decline is at the rate for the older healthy woman

J. Johnson, JW. Emerson, SD. Lawley; https://doi.org/10.1101/2022.05.31.494088

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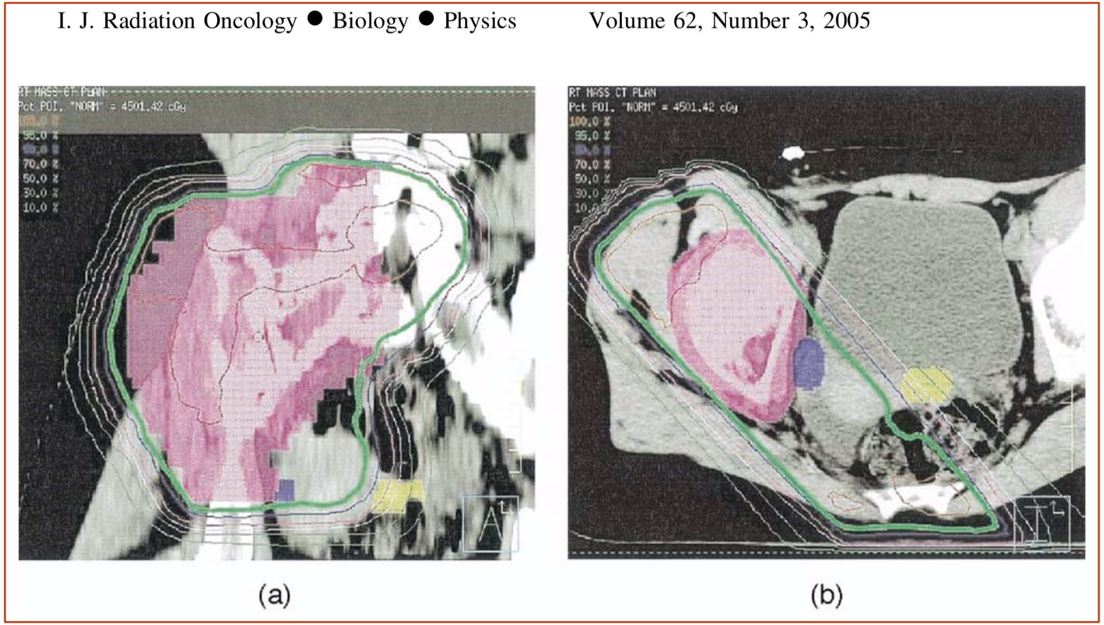
Fertility after Radiotherapy



I. J. Radiation Oncology ● Biology ● Physics Volume 62, Number 3, 2005

- Estimate LD_{50} for the human oocyte
- Use to plan conformal RXT to optimise dose to the least-affected ovary
- Calculate window of opportunity for fertility
- Calculate the age-related effective sterilising dose
- Use to inform fertility preservation decision making

- Minimise the long-term effects of radiotherapy on healthy tissue
- Whilst maintaining cure rates

Wallace *et al.*, 2003; Anderson *et al.*, Lancet Diabetes Endocrinol. 2015

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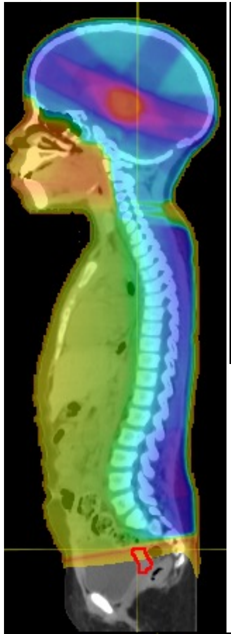
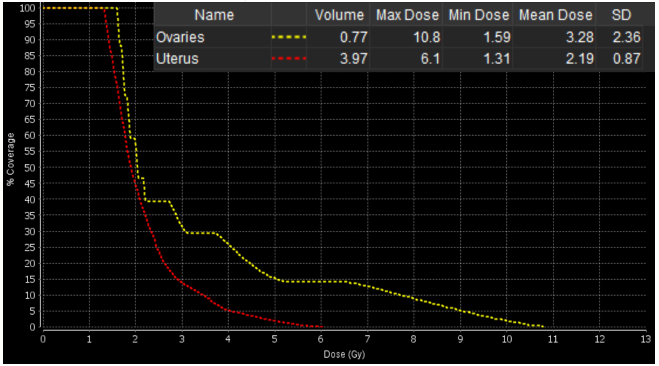
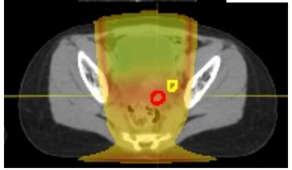
Fertility after Radiotherapy



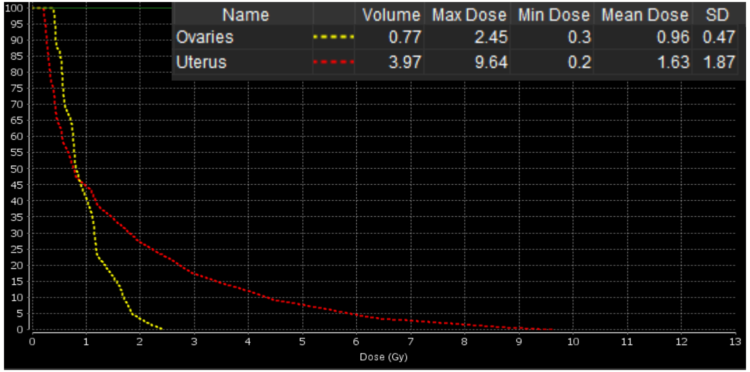


Name		Volume	Max Dose	Min Dose	Mean Dose	SD
Ovaries	- - - - -	0.77	10.8	1.59	3.28	2.36
Uterus	- - - - -	3.97	6.1	1.31	2.19	0.87

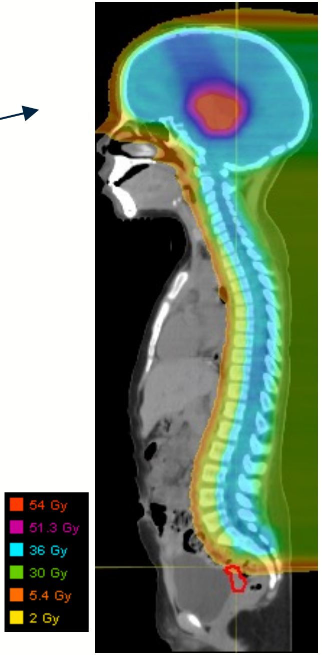
Photon Plan

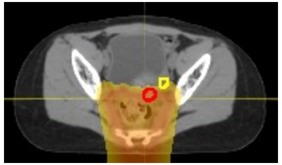


Proton Plan



Name		Volume	Max Dose	Min Dose	Mean Dose	SD
Ovaries	- - - - -	0.77	2.45	0.3	0.96	0.47
Uterus	- - - - -	3.97	9.64	0.2	1.63	1.87





Source: Danny Indelicato, MD - University of Florida Proton Therapy Institute

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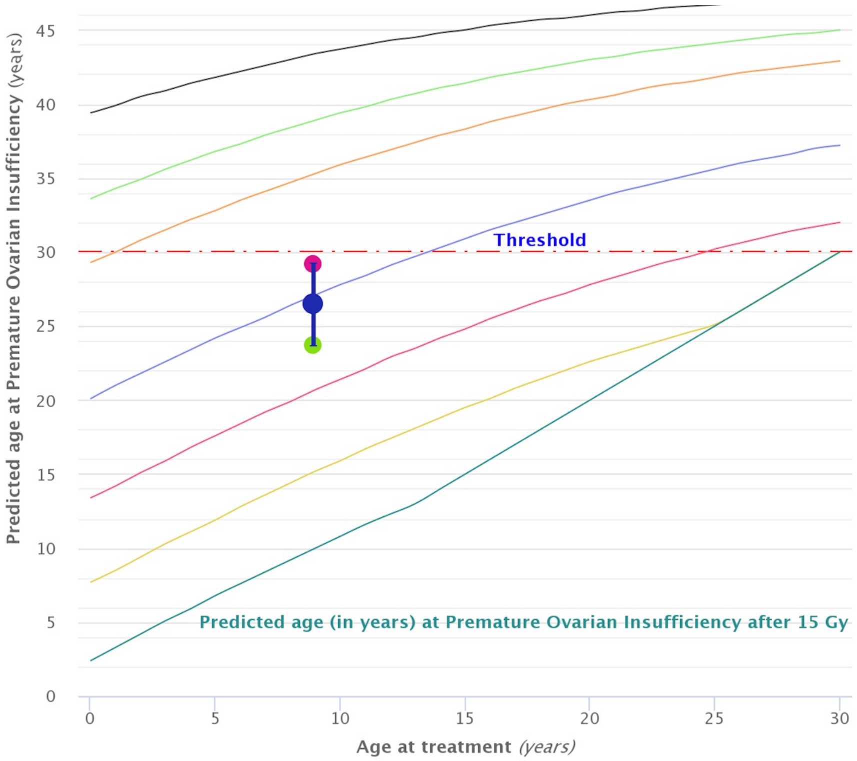
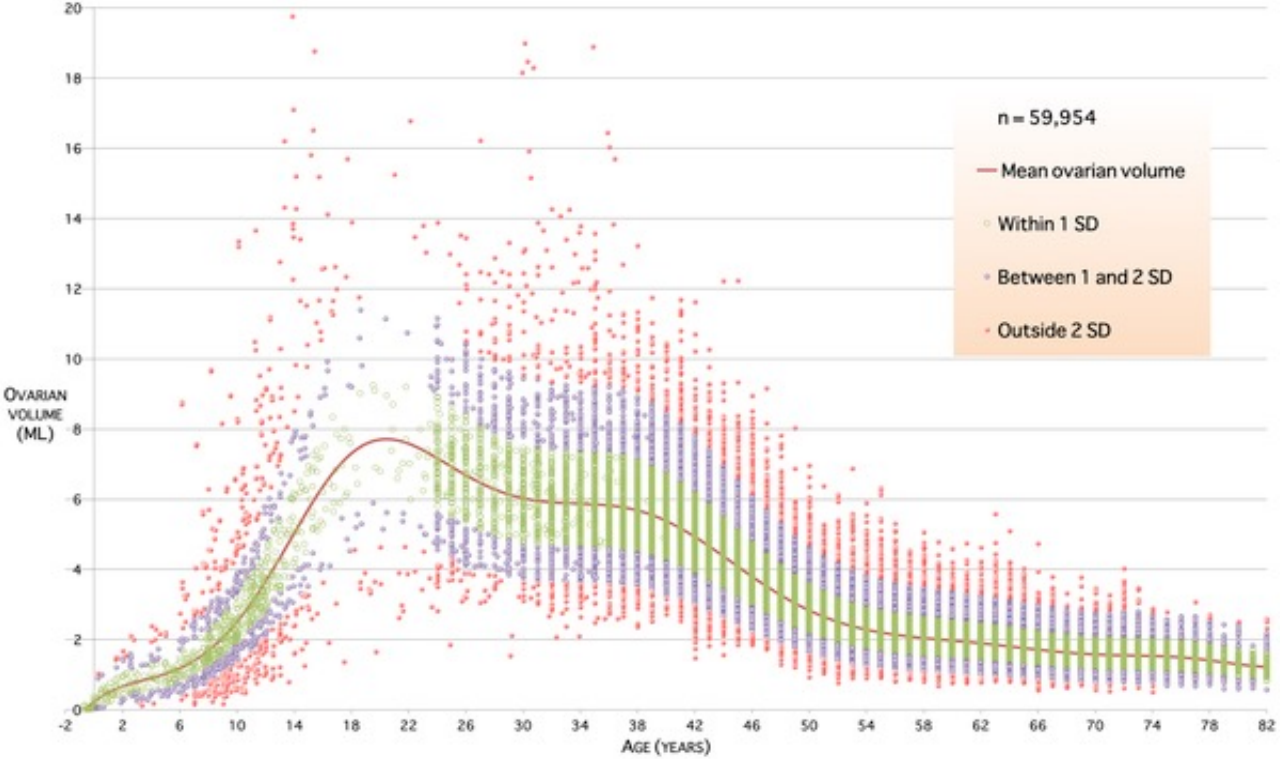
Fertility after Radiotherapy

- 8.9 year old patient (say)
- CSI plan for Ewing sarcoma treatment with calculated min, max and mean dose to the least affected ovary
- Revised radiosensitivity modelling using externally validated model of ovarian reserve and best current estimate of LD_{50}
- Estimate range of ages at premature ovarian insufficiency
- Useful for treatment planning
- Also an illustrative tool informing fertility preservation discussions



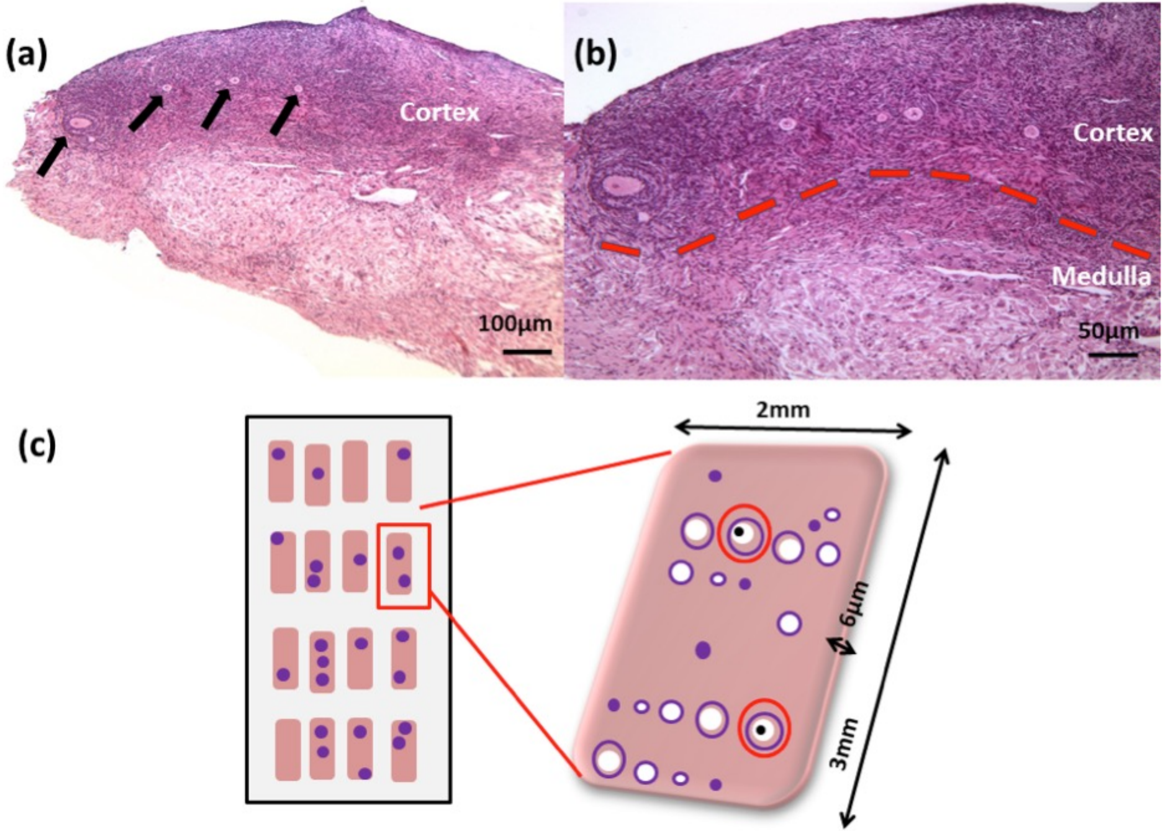
Kelsey *et al.*, 2022 PLOS ONE (under review)

Observational data model – ovarian volume



Kelsey TW et al. (2013) PLoS ONE 8(9): e71465

Follicle density



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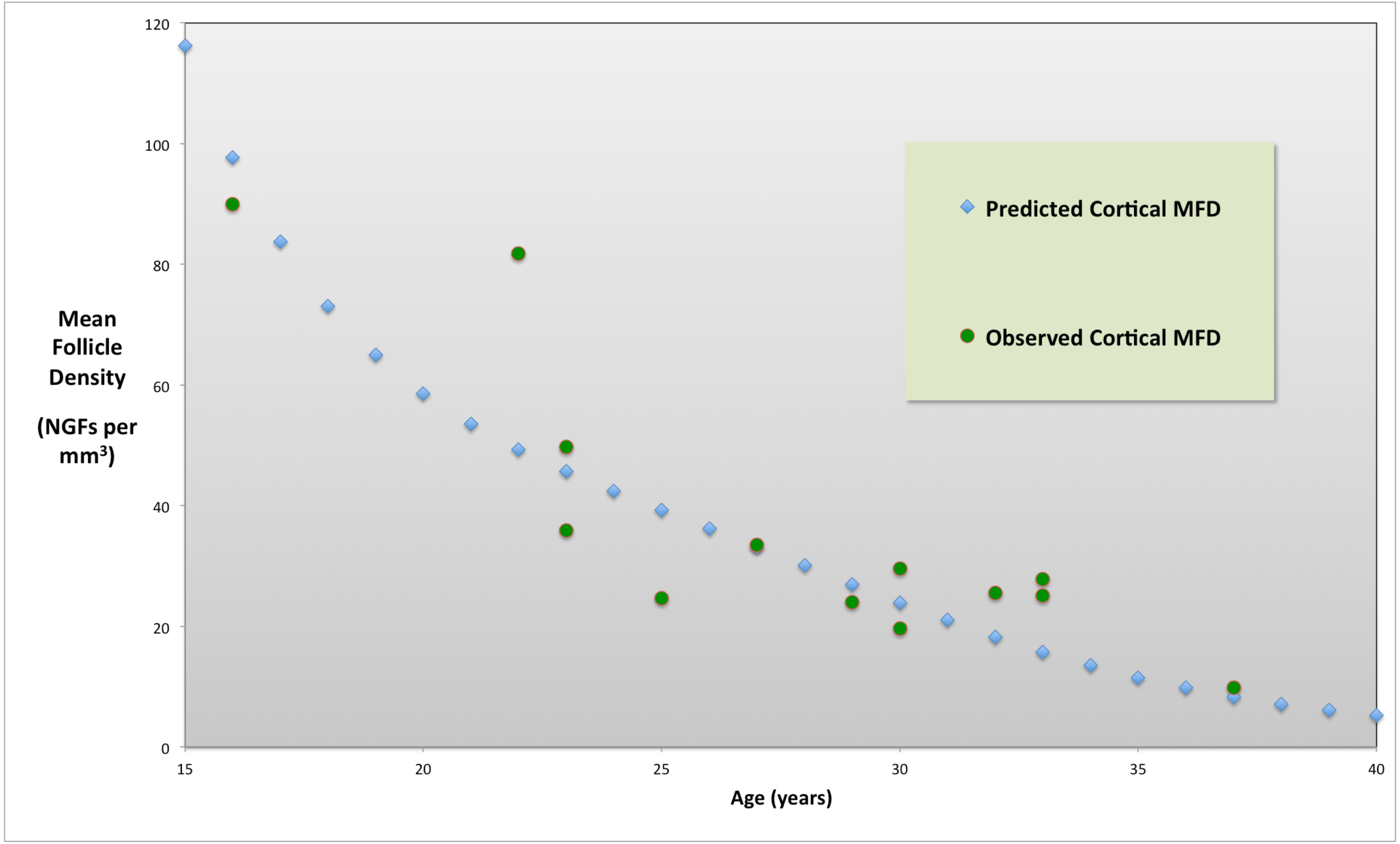
A model to predict Mean Follicle Density for healthy females aged 15 – 37 years

- Assumption: a large ovary contains more eggs than a small one
- NGFs: use the Wallace-Kelsey model to estimate NGF population, giving NGF(age)
- Volume: use our model to estimate the ovarian volume, giving Volume(age)
- Predicted MFD(age) is then NGF(age) divided by Volume(age)
- (We have to adjust for the proportion of a typical ovary that consists of cortical tissue)
- Simple arithmetic – no AI, no advanced statistics
- Sophisticated and modern techniques are not always required

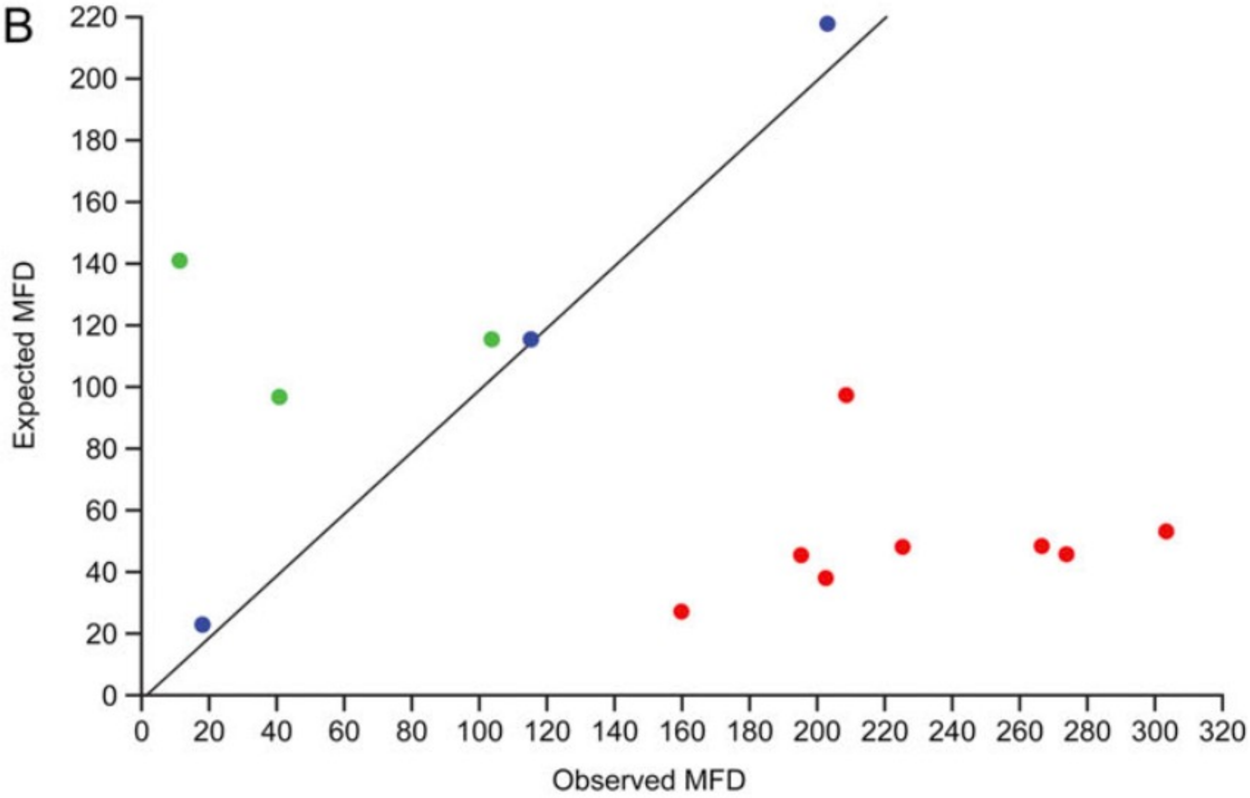
Fleming, Kelsey et al. Fertility & Sterility 2012

External Validation of NGF and OV Models



McGloughlin, Kelsey et al. Journal of Assisted Reproduction and Genetics **32; 2015**

Using the models to assess NGF density after ABVD



McLaughlin, Kelsey et al. Human Reproduction 32(1) 2016

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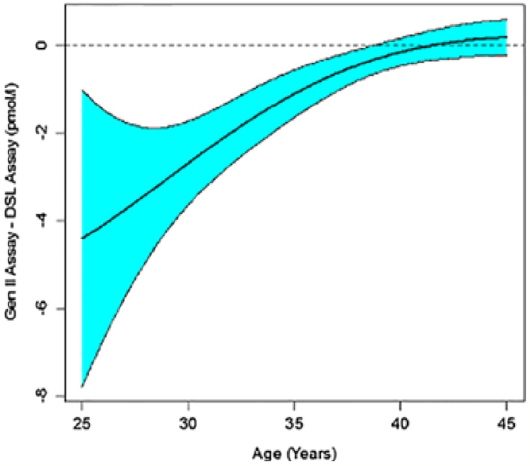
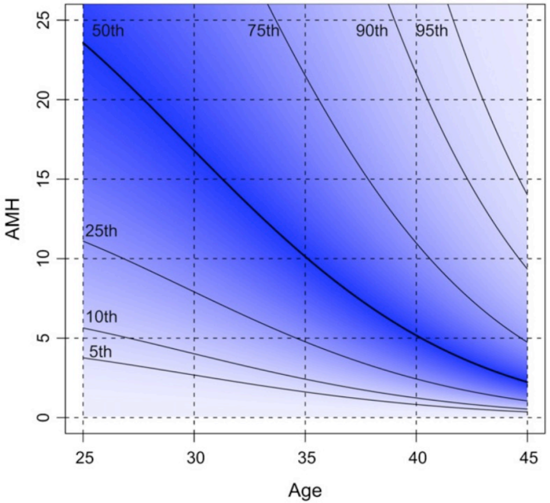
Observational data approaches have been critical to our understanding of AMH and its utility



Derived N = 5,492
Validated N = 5,492
Compared N = 9,601



Derived = 9,601
Validated in N =15,834

- AMH is a product preantral and small antral follicles in women
- As such, AMH is only present in the ovary until menopause
- **Can it be used as a biomarker for remaining ovarian reserve?**
- First studies are promising, but are based on infertile subjects

Nelson *et al* Fertil Steril 2011, Nelson *et al* RBM Online 2011

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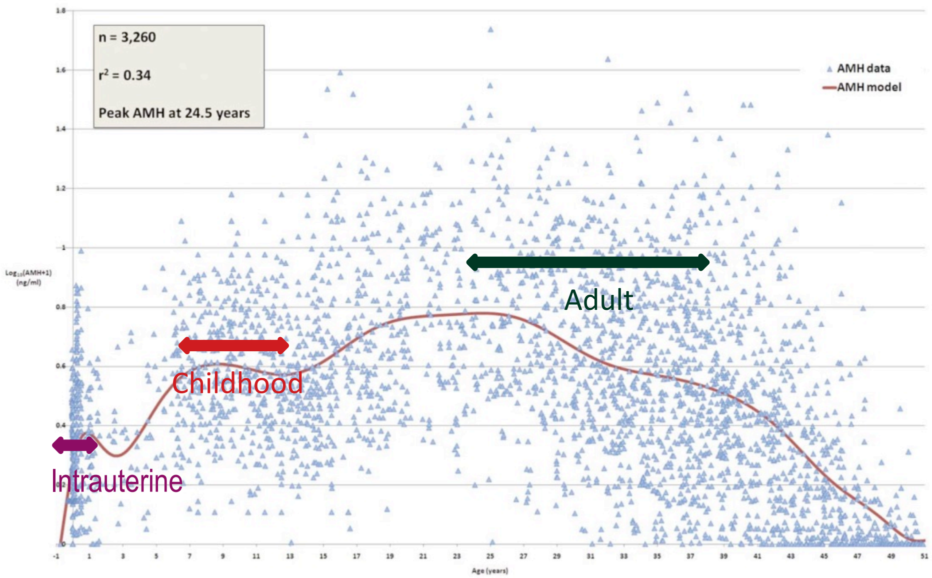
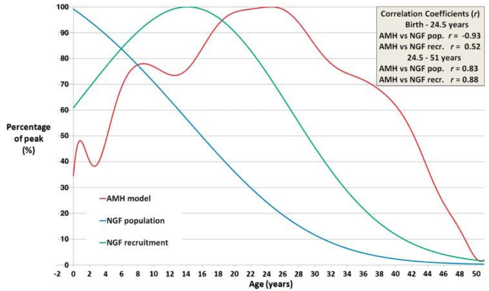
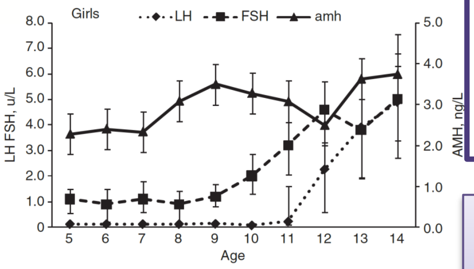
Observational data approaches have been critical to our understanding of AMH and its utility







- AMH model from conception to menopause
- Validated for adult ages
- Validated for childhood/pubertal ages using 10-year longitudinal data

- AMH now accepted as biomarker

Kelsey et al PLOS One 2011, Kelsey et al Mol Hum Reprod 2012; Jeffery et al J Ped Endocrinol Metab 2015

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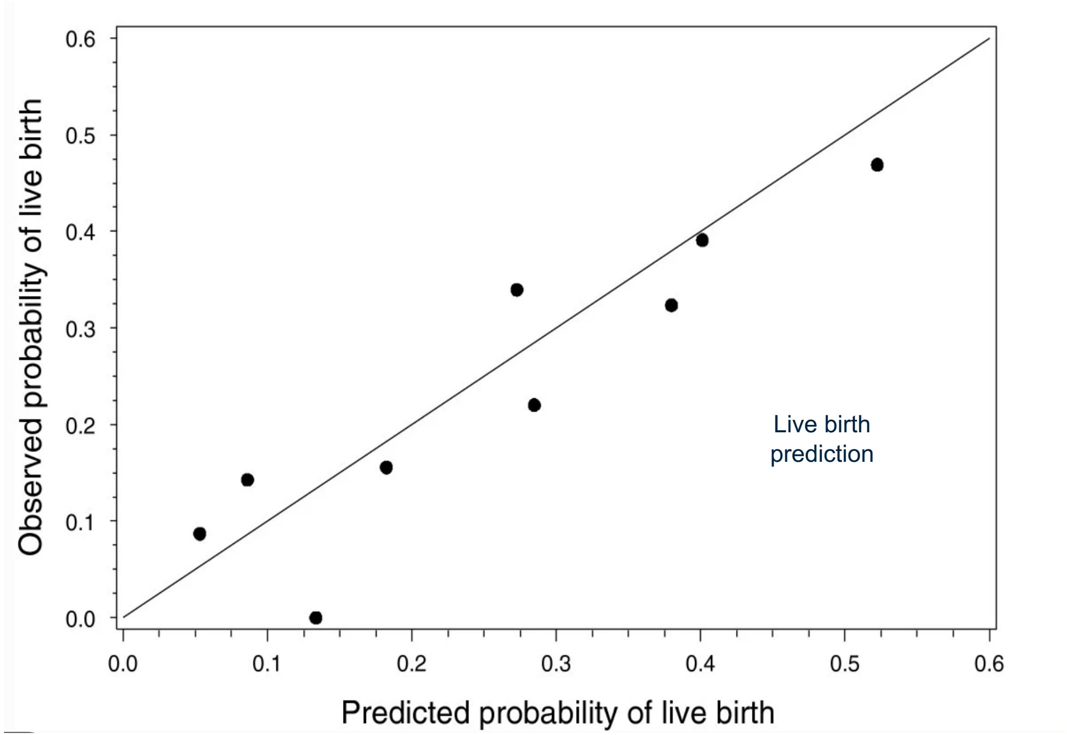
Observational data approaches have been critical to our understanding of AMH and its utility



- "Our findings provide genetic support for the well-established use of AMH as a marker of ovarian reserve"
- AMH now routinely used as adjunct to the 2003 criteria for PCOS diagnosis
- Predicted live births based on AMH match observations

- AMH now used effectively as a biomarker
- Providing further validation of the underlying models

Perry et al,. Hum Mol Genet, 2016; Iliodromiti et al HRU 2014; Khader et al J Ovarian Res 2013

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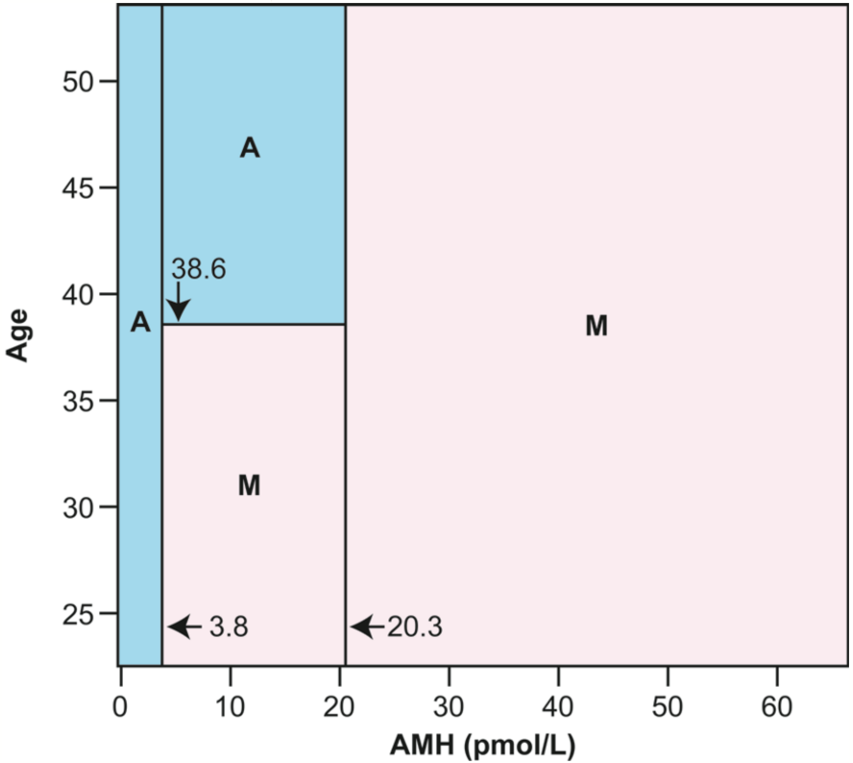
Using AMH to inform fertility preservation for survivors of cancer



Anderson et al 2013 Eur J Cancer; Anderson et al 2020 in prep.

- Pre-treatment AMH predicts for loss of ovarian function after chemotherapy for early breast cancer
- 6-month post-treatment AMH has high PPV for impaired fertility
- Pre- and post-chemo AMH combined with BMI, age, parity and endocrine factors has high diagnostic utility

- We can optimise and personalise post-chemo endocrine therapy

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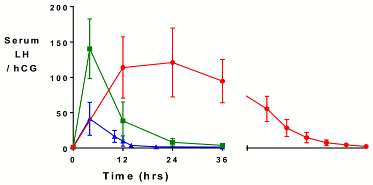
AI as a strategy to improve endocrine therapy after breast cancer

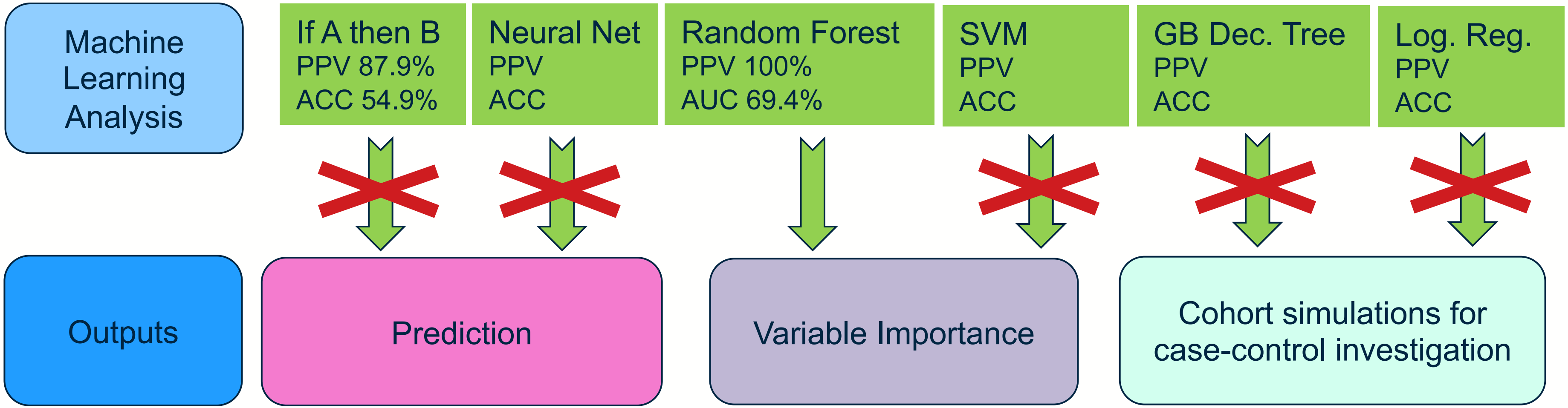
Inputs

Longitudinal endocrine data



Treatment data

Patient phenotype



Machine Learning Analysis

If A then B
PPV 87.9%
ACC 54.9%

Neural Net
PPV
ACC

Random Forest
PPV 100%
AUC 69.4%

SVM
PPV
ACC

GB Dec. Tree
PPV
ACC

Log. Reg.
PPV
ACC

Outputs

Prediction

Variable Importance

Cohort simulations for case-control investigation

Anderson et al Breast Cancer Research and Treatment **192, 2022**

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Where is the modern AI?

- Cohort studies
  - Regression models
  - Multivariable logistic regression
  - Dose-response models
- Oservational data studies
  - Life tables using Kaplan-Meier
  - PK style modelling using ODEs
  - Cox proportional hazards
  - Normative age-related models
- Meta analyses
  - Hierarchical summary ROC curves
  - Fixed & random effects meta-regression

All of these are well-understood statistical and/or optimisation methods

AI methods are slowly and steadily being used to obtain publishable results and new insights

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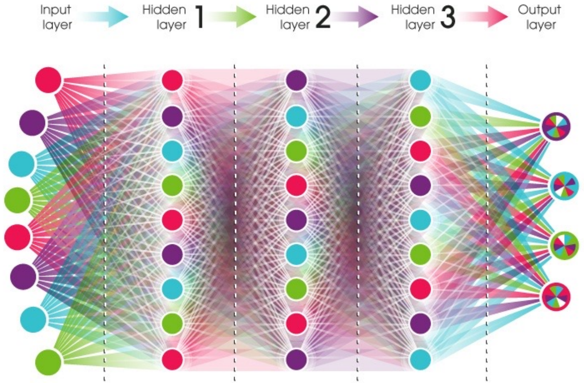
Due process of AI studies still required

Deep neural network



- Publish in accordance with
- existing reporting standards

→

Clinical validation in real-world medicine

- Publish, RCTs showing benefit, Regulatory approval

→

Implementation in healthcare

- Cost of implementation

- how many workflows will be affected?
- Does the model increase the efficiency of existing workflows?
- Is the model being deployed within an existing digital workflow?

Slide taken from Scot Nelson, 2020

Nagendran et al BMJ 2020; Topol Nature Medicine 2019; Morse et al Nature Medicine 2020;

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Conclusions

- Careful identification and analysis of biomedical data can lead to models
  - All of these models are wrong
  - Some of them are useful
- The key measure of utility is **external validation**
  - Predictions match observations for new and/or unseen data
- Many of the techniques used are old and well understood
- AI and machine learning techniques are becoming more prevalent, with notable improvements on existing knowledge
- But the specific method used is less important than validation

Colleagues

- Edinburgh
  - Hamish Wallace, Richard Anderson, Evelyn Telfer, …
- Copenhagen
  - Stine Gry Kristensen, Linn Mamsen, Claus Yding Andersen,…
- Imperial College
  - Ali Abbara, Waljit Dhillo,…
- Glasgow
  - Scott Nelson, Stamiatina Iliodromiti
- St Andrews
  - Gerry Humphris, Frank Sullivan,…

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Thank you