
LUCID

House Keeping

Fire Alarms
There are no planned fire alarms; if there is an alarm, please follow the instructions given by venue staff. Fire assembly point is directly outside the front of the hotel.

Mobile Phones
Please turn mobile phones to silent. Filming or photography during the sessions is not permitted.

Food and Drink
Catering points are in the exhibition hall and Ballroom Foyer; seating areas are around the balcony area near registration.

Toilets
Toilets are in the ballroom foyer and opposite the breakout session rooms.

LUCID Conference App

How to Download

- Search for ‘LUCID 2019’ in the app store
- Your user name and password has been emailed to you
- See the registration desk with any queries

Live Q&A

- Use the Live Q&A icon to post questions during sessions


LUCID

Cancer Treatment in 2020 and Beyond

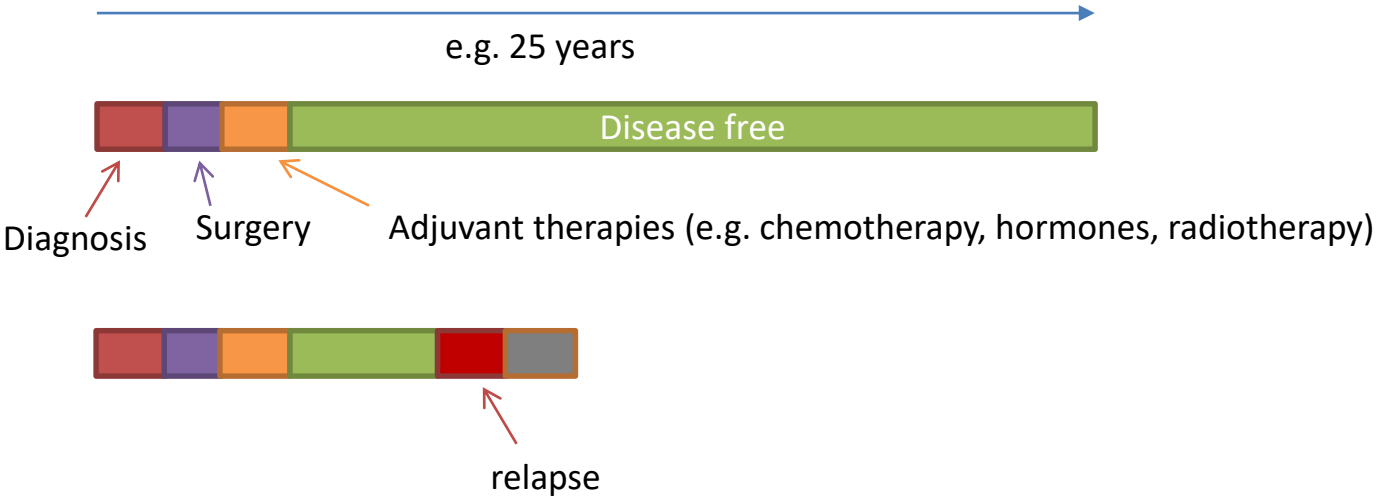
Peter Hall

Edinburgh Cancer Centre

Outline

- Decision making for marginal treatments
- Real World Evidence for decision making
- Rapid adoption of new technologies

Early Cancer

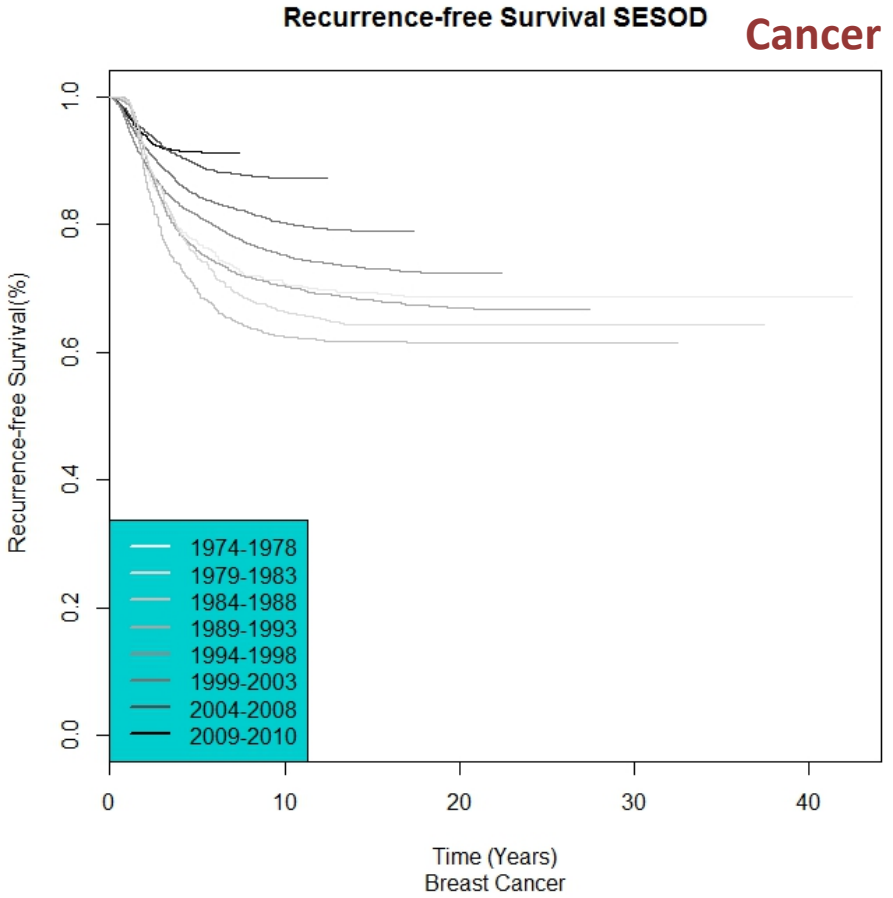


Edinburgh
Cancer Centre

Improving outcomes

Breast Cancer over the last 40 years

- Improved surgical technique
- Early diagnosis
  - Education
  - Screening
- Adjuvant therapies



Adjuvant treatments

Hormones

Immunotherapy

Chemotherapy

Targeted small molecules

Biological therapy

Bisphosphonates

Antibody-drug conjugates

Ruth

59yrs

Diagnosis: Breast cancer

Stage T2(42mm) N0 M0

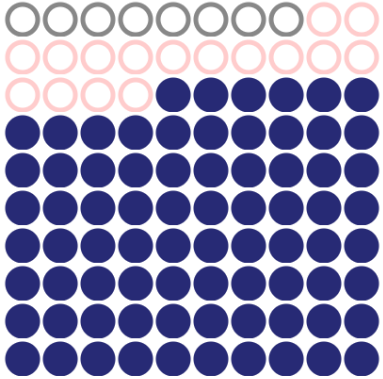
Grade 2

Oestrogen receptor (ER) positive

HER2 receptor negative

Surgery

- Mastectomy and Lymph node biopsy



8 deaths due to other causes

16 breast cancer related deaths

76 survivors with surgery alone

Adjuvant treatments?

Hormones

Immunotherapy

Chemotherapy

Biological therapy

Targeted small molecules

Bisphosphonates

Antibody-drug conjugates

Precision medicine

…to the rescue

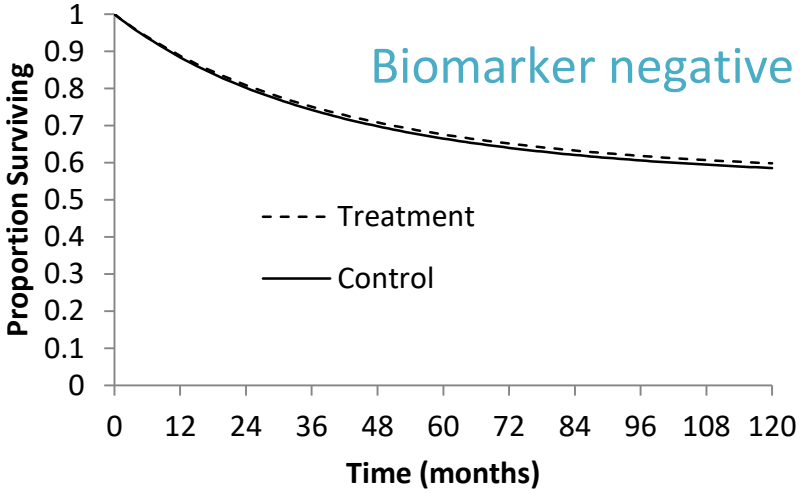
= stratified medicine
= personalised medicine

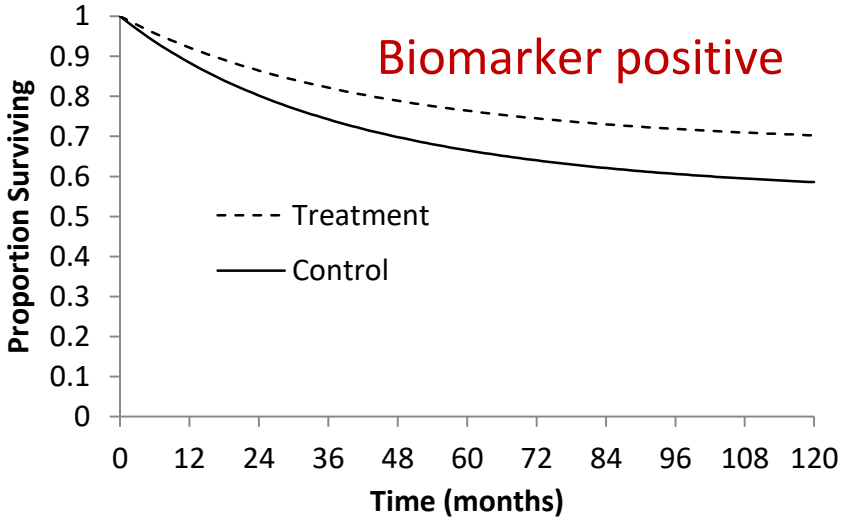
Use of biomarkers to:

1. Predict benefit from specific treatments
2. Magnitude of benefit vs
3. Risk of harm

Biomarker = "a characteristic by which a biological process can be identified"

Predictive Biomarkers





HORMONE THERAPY?

Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

Summary

Background As trials of 5 years of tamoxifen in early breast cancer mature, the relevance of hormone receptor measurements (and other patient characteristics) to long-term outcome can be assessed increasingly reliably. We report updated meta-analyses of the trials of 5 years of adjuvant tamoxifen.

Methods We undertook a collaborative meta-analysis of individual patient data from 20 trials (n=21 457) in early breast cancer of about 5 years of tamoxifen versus no adjuvant tamoxifen, with about 80% compliance. Recurrence and death rate ratios (RRs) were from log-rank analyses by allocated treatment.

Findings In oestrogen receptor (ER)-positive disease (n=10 645), allocation to about 5 years of tamoxifen substantially reduced recurrence rates throughout the first 10 years (RR 0·53 [SE 0·03] during years 0–4 and RR 0·68 [0·06] during years 5–9 [both 2p<0·00001]; but RR 0·97 [0·10] during years 10–14, suggesting no further gain or loss after year 10). Even in marginally ER-positive disease (10–19 fmol/mg cytosol protein) the recurrence reduction was substantial (RR 0·67 [0·08]). In ER-positive disease, the RR was approximately independent of progesterone receptor status (or level), age, nodal status, or use of chemotherapy. Breast cancer mortality was

Lancet 2011; 378: 771–84

Published Online
July 29, 2011
DOI:10.1016/S0140-6736(11)60993-8

See Comment page 747

*Collaborators listed at end of report

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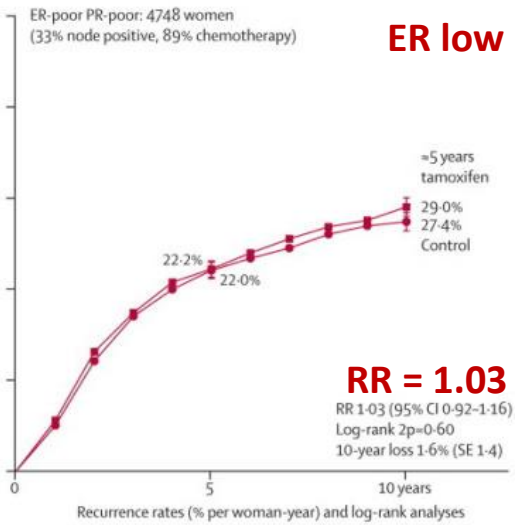
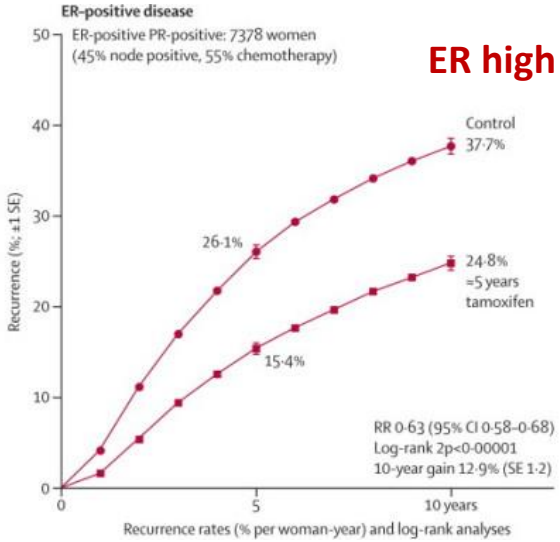
ER status and tamoxifen benefit





RR = 0.63

Lancet. 2011; 378(9793): 771–784.

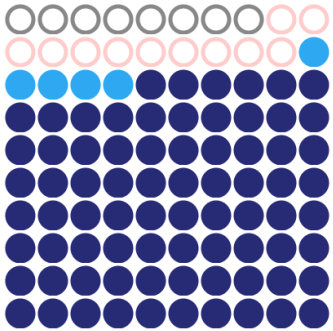
Hormone therapy?

Oestrogen receptor positive

→ Tamoxifen, 10 years

Side effects:

- Menopausal symptoms
- (Thrombosis)
- (Endometrial cancer)



○ 8 deaths due to other causes

○ 11 breast cancer related deaths

● 5 extra survivors due to hormone therapy

● 76 survivors with surgery alone

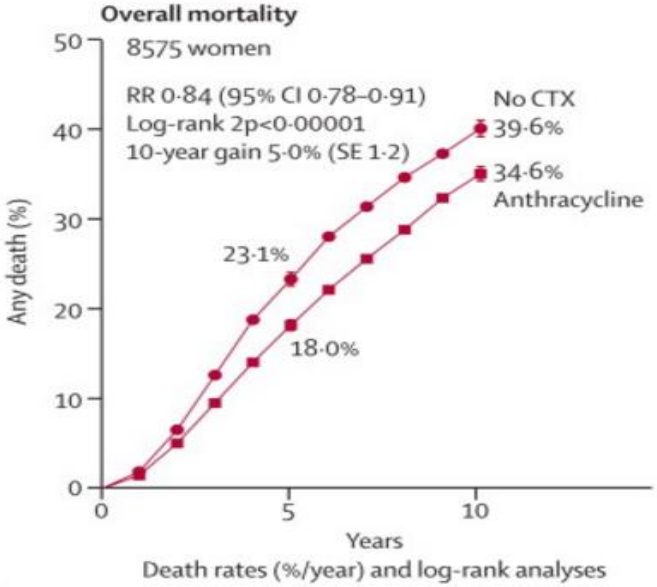
Biological therapy?

Anti-HER2 antibodies

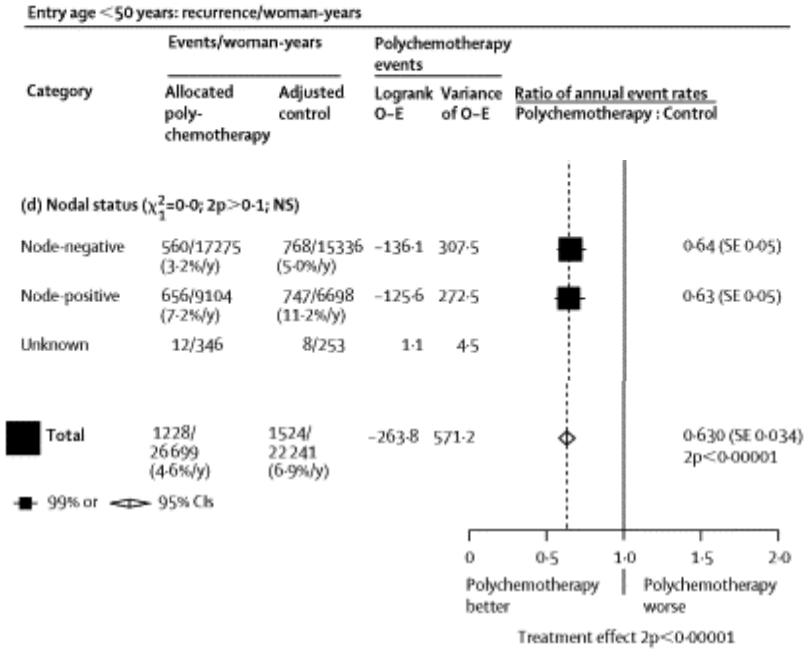
- trastuzumab
- pertuzumab

HER2 negative, therefore no benefit

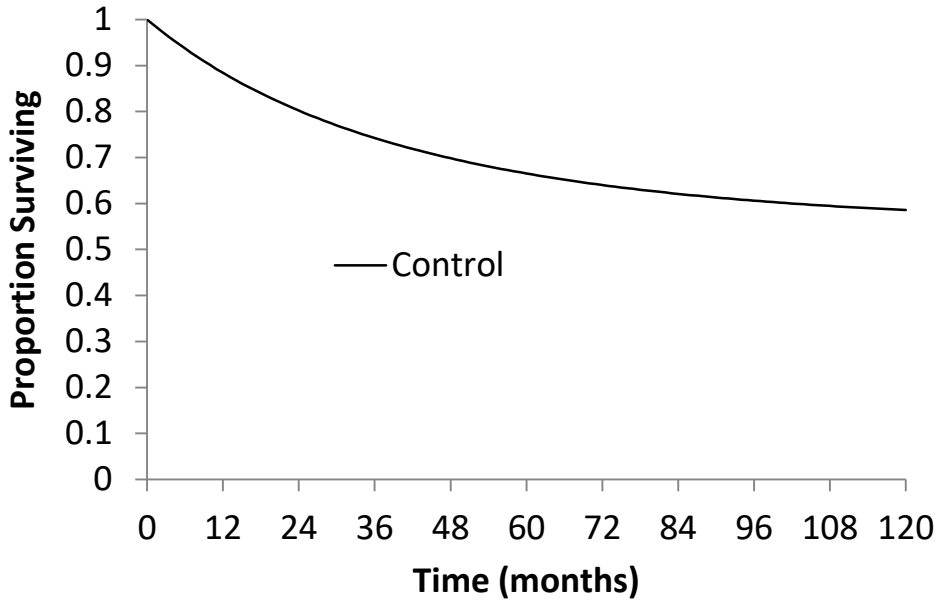
Chemotherapy?



Chemo predictive biomarker?

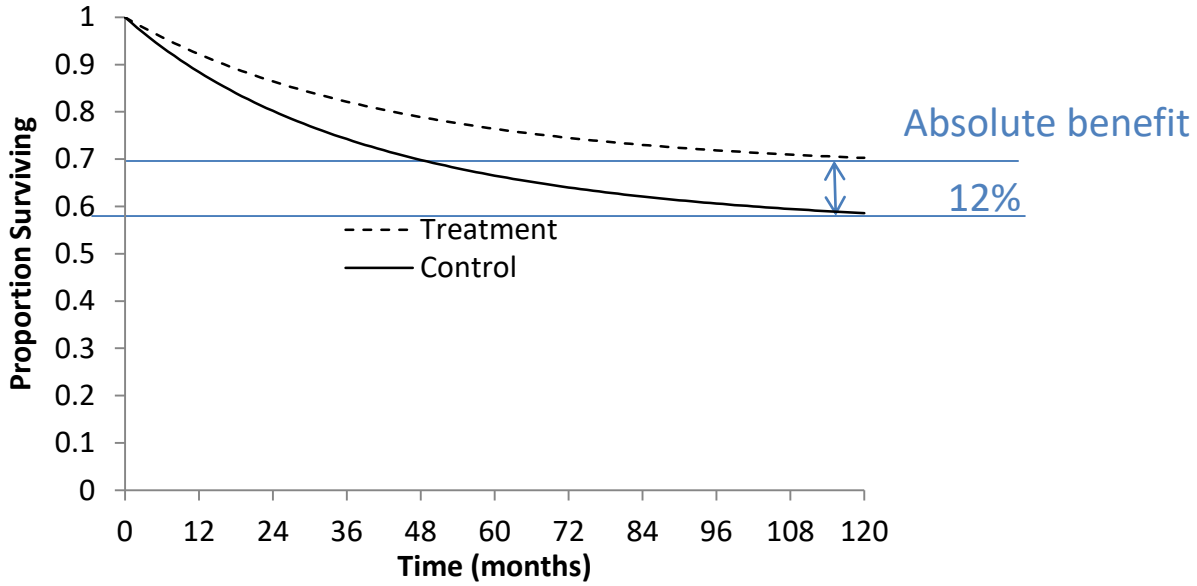


Absolute vs relative benefit

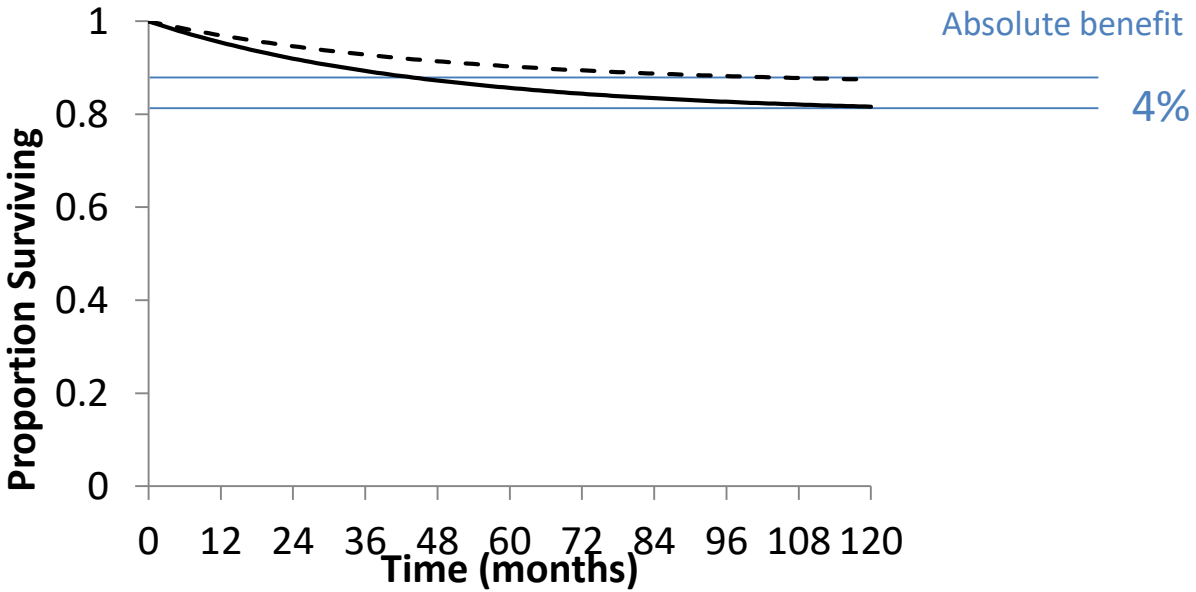


Absolute vs relative benefit

Treatment: Relative reduction in event rate = 0.66 (hazard ratio)



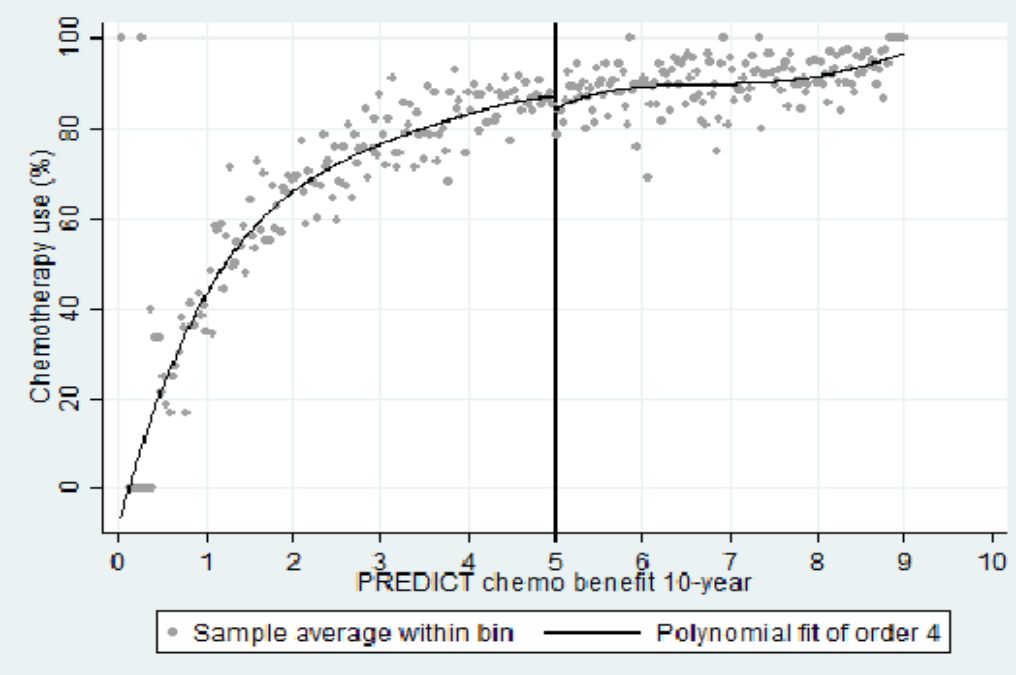
Ruth's prognosis



Worth it?

- 8 deaths due to other causes
- 7 breast cancer related deaths
- 4 extra survivors due to chemotherapy
- 5 extra survivors due to hormone therapy
- 76 survivors with surgery alone

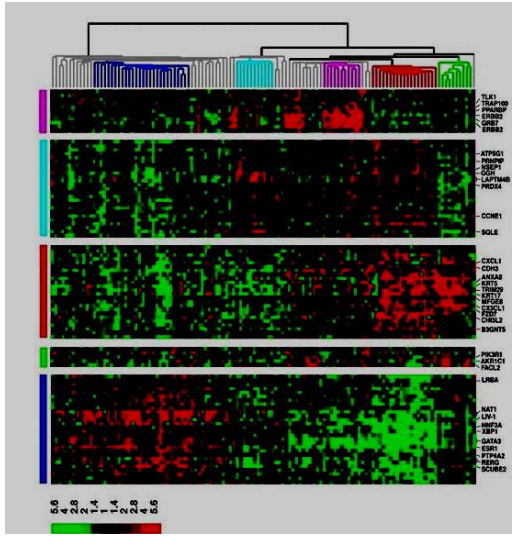
Decisions in Scotland (2001 – 2017)



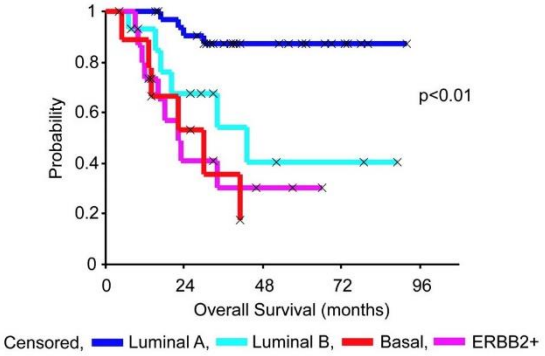
(Clinical trial eligible patients)

Can we do better?

Genomic signatures



4 main biological subtypes of breast cancer with differing prognosis



Perou, Nature 2000; 406:747
Sorlie, PNAS 2001; 98:10869
Sorlie, PNAS 2003; 100:8418

Oncotype DX® 21-Gene Recurrence Score (RS) Assay

16 Cancer and 5 Reference Genes From 3 Studies

PROLIFERATION
Ki-67
STK15
Survivin
Cyclin B1
MYBL2

ESTROGEN
ER
PR
Bcl2
SCUBE2

GSTM1

BAG1

INVASION
Stromelysin 3
Cathepsin L2

CD68

HER2
GRB7
HER2

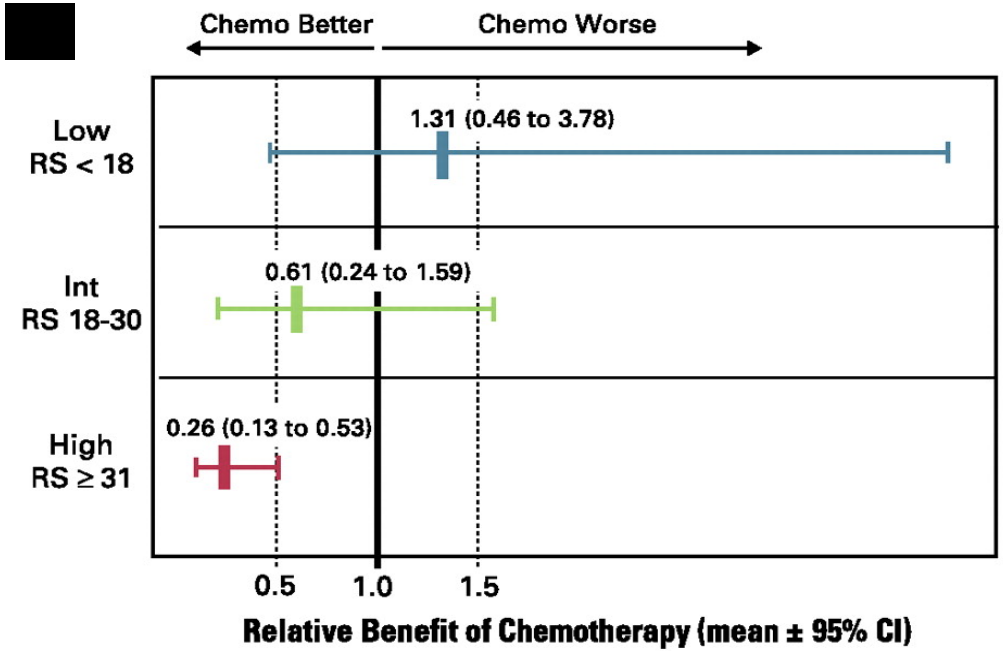
REFERENCE
Beta-actin
GAPDH
RPLPO
GUS
TFRC

RS = + 0.47 x HER2 Group Score
- 0.34 x ER Group Score
+ 1.04 x Proliferation Group Score
+ 0.10 x Invasion Group Score
+ 0.05 x CD68
- 0.08 x GSTM1
- 0.07 x BAG1

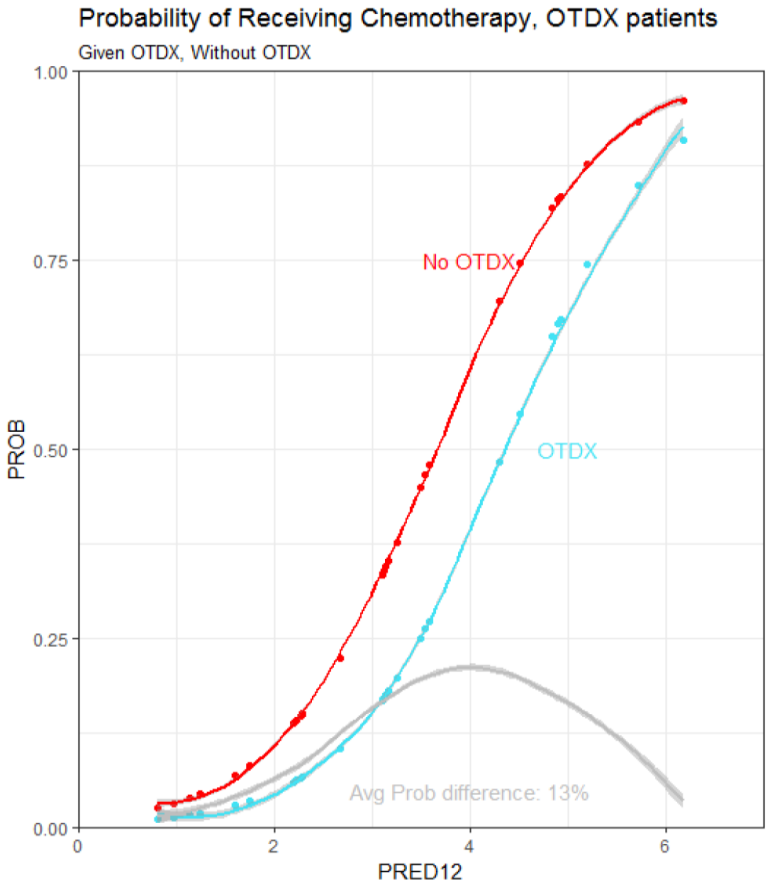
Category	RS (0 -100)
Low risk	RS <18
Int risk	RS 18 - 30
High risk	RS ≥ 31

Paik et al. *N Engl J Med.* 2004;351:2817

Predictive of chemo benefit??



Paik et al. *J Clin Oncol.* 2006.


Probability of Receiving Chemotherapy, OTDX patients
Given OTDX, Without OTDX
1.00
0.75
0.50
0.25
0.00
PROB
No OTDX
OTDX
Avg Prob difference: 13%
0
2
4
6
PRED12

Multi-parameter assays

oncotype DX Breast Cancer Assay	16 (+5) gene RT-PCR performed by GHI	Risk score	low/ (int)/ high
prosigna™ Breast cancer gene signature assay PAM50	50 gene - nCounter performed at OICR	Risk score	low/ int/ high
		Subtyping	Luminal A/B Her2 Enriched, Basal
agendia decoding cancer mammaprint	70 (/80) gene array performed by Agendia	Risk category	low/ high
		Subtyping	Luminal A/B Her2 Enriched, Basal
IHC4	4-gene IHC performed on TMA at OICR	Risk score	low/ int/ high
NexCourse Breast by AQUA Technology	4-gene fluorescent IHC performed on TMA by Genoptix	Risk score	low/ int/ high
MammaTyper STRATIFYER	4-gene RT-PCR performed by Stratifyer	Subtyping	Luminal A/B (int/ hi) Her2 Enriched, Basal

Maureen

75yrs

Diagnosis: Breast cancer

Stage T2(42mm) N2 M0

Grade 2

Oestrogen receptor (ER) positive

HER2 receptor positive

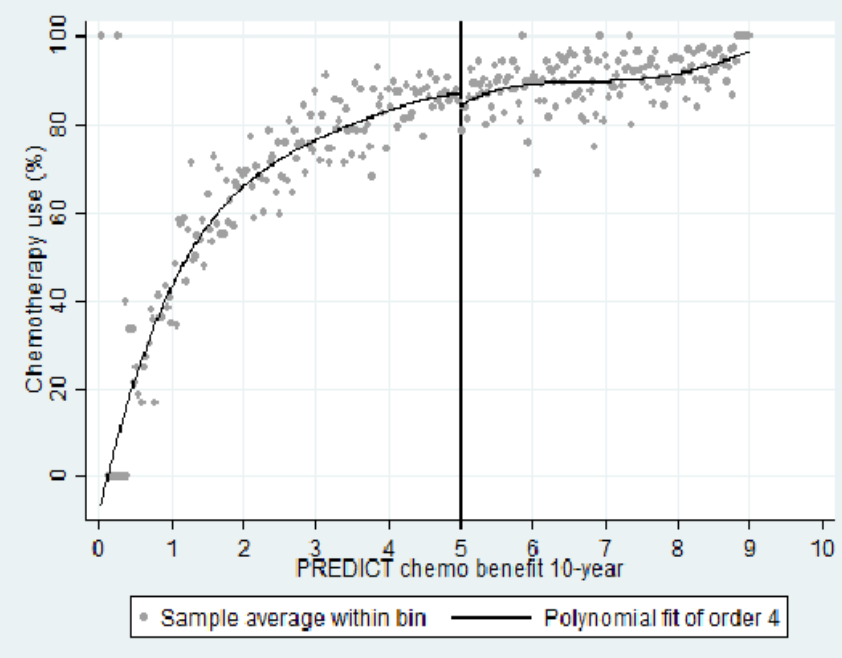
High blood pressure

Diabetes

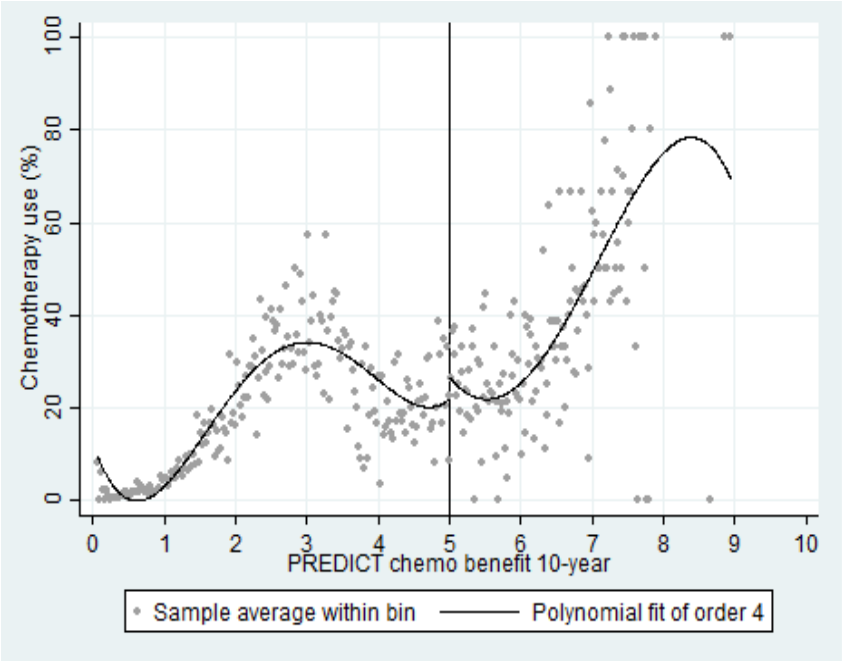
- 31 deaths due to other causes
- 23 breast cancer related deaths
- 7 extra survivors due to trastuzumab
- 11 extra survivors due to chemotherapy
- 28 survivors with surgery alone

Decisions in Scotland (2001 – 2017)

Trial Representative Population



Trial under-representative population



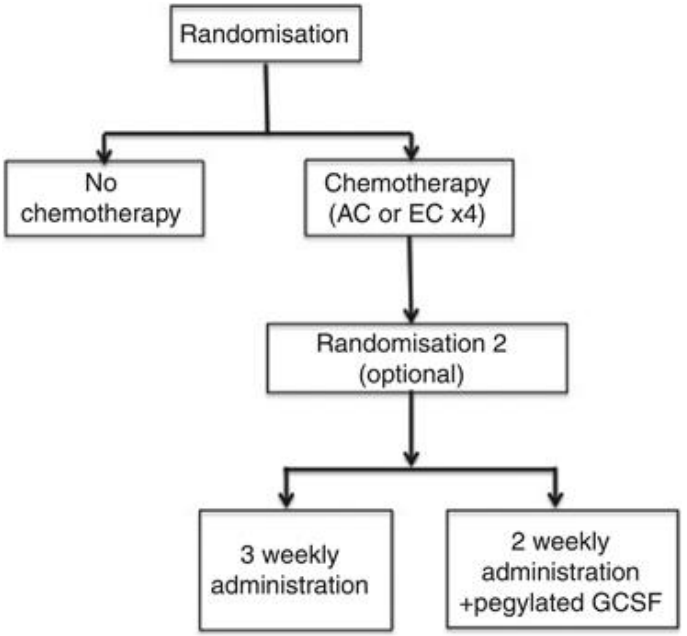
Underlying assumption of RCT effect

Problems with RCTs
- highly selected patient population
- low co-morbidity
- narrow age range
- under-represented groups (socioeconomic status, rurality, ethnicity)
- high risk cancers

Is treatment effect generalisable to real-world populations?
How do we measure it?

Adjuvant chemotherapy in older women (ACTION) study

- age >70
- opened in 43 UK centres
- recruited for 10 months
- only 4 patients recruited



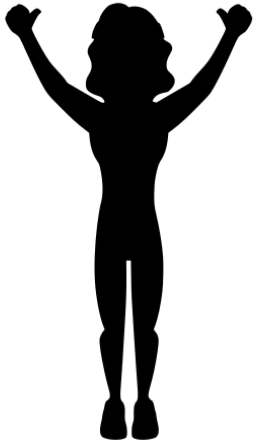
Real world comparison

Chemotherapy

- high cancer risk
- low frailty

= younger

= healthy



No Chemotherapy

- low cancer risk
- high frailty

= older

= comorbid

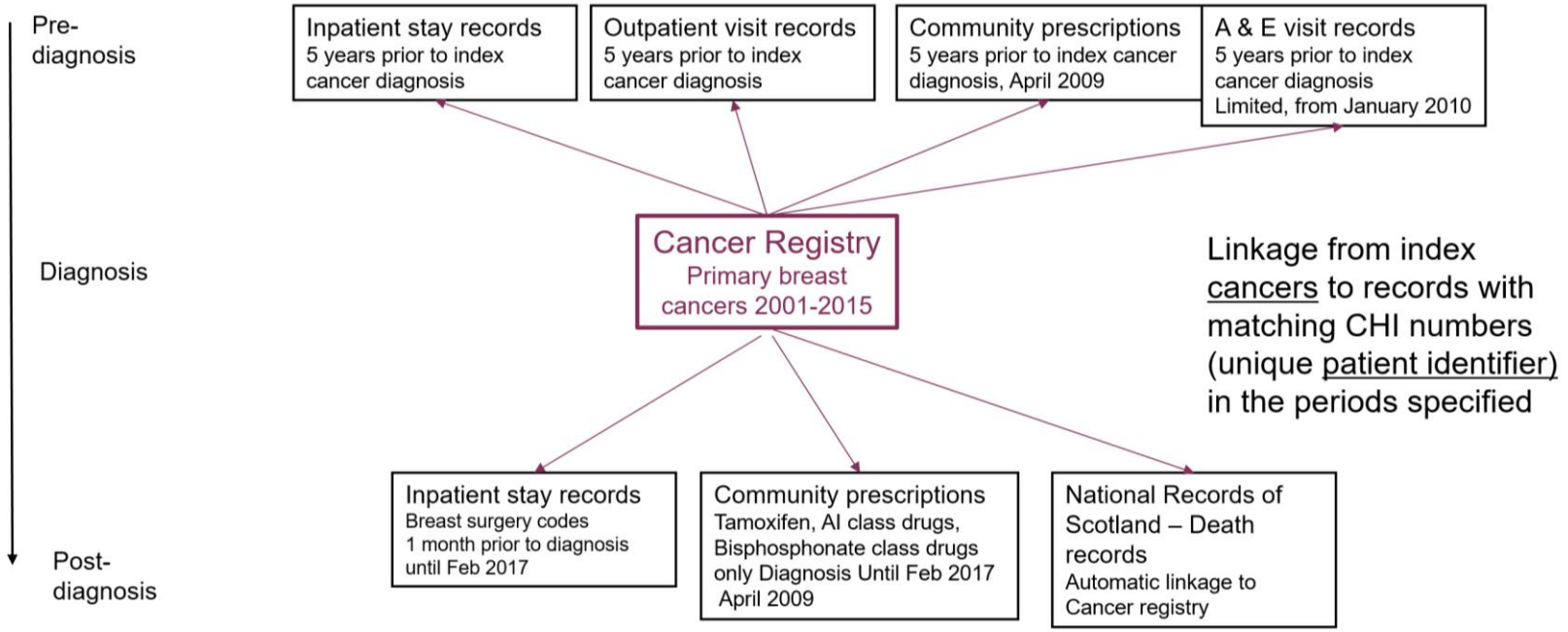
How to compare?

Adjustment for casemix

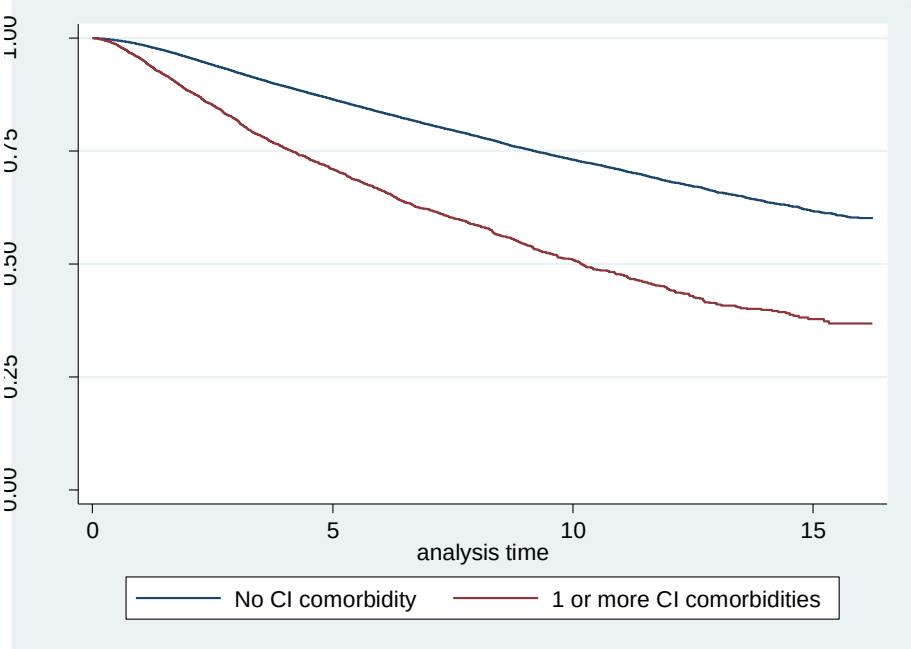
Needs data

Needs methods

Scotland N = 60,000

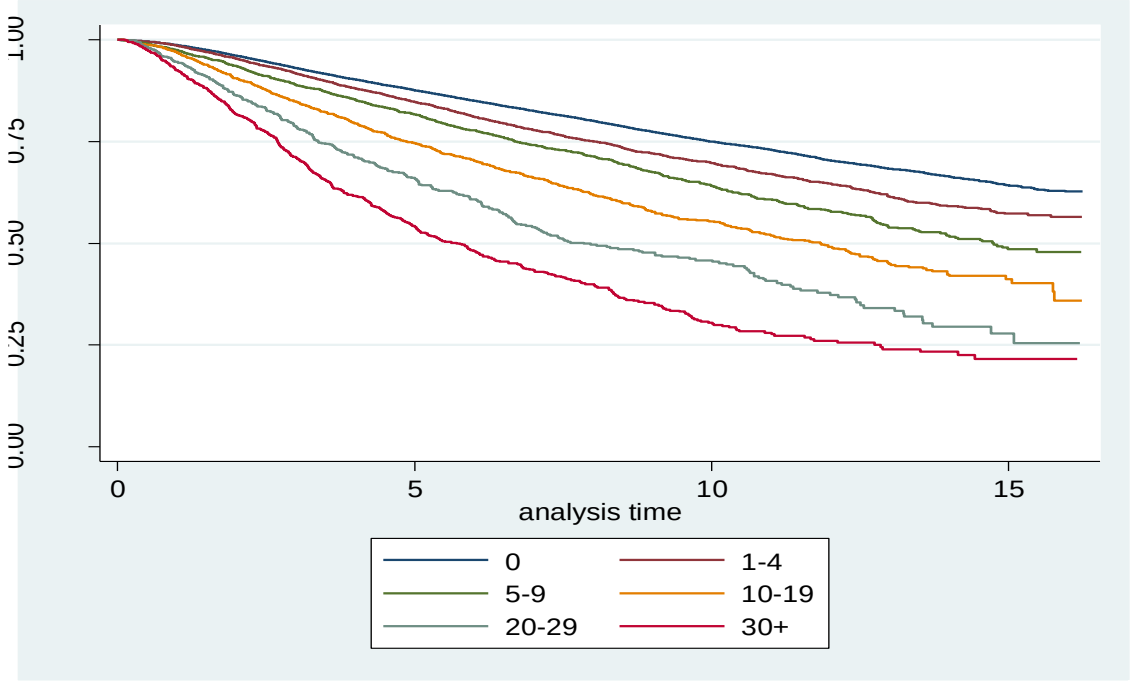


Survival by inpatient diagnoses in prior 5 years (Charlson)

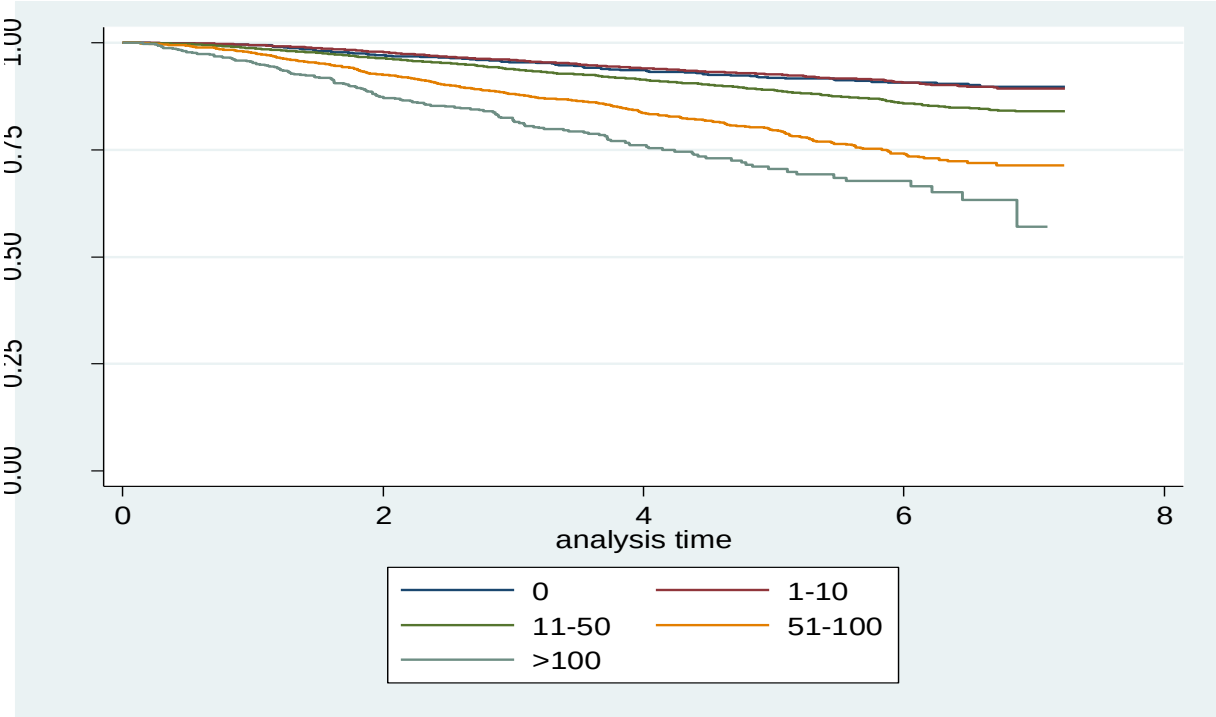


Total number of comorbidities	Proportion of sample (%)
0	94
1	6
2	<1
3	<1
4	<1
	n=49,999

Survival by number of inpatient bed days in previous 5 years



Survival by total medications dispensed in prior year



Candidate methods

Regression with Adjustment for Covariates (RA)

Uses multiple regression based methods to adjust for the imbalance in covariates between treated and untreated cases.

Propensity score matching (PSM)

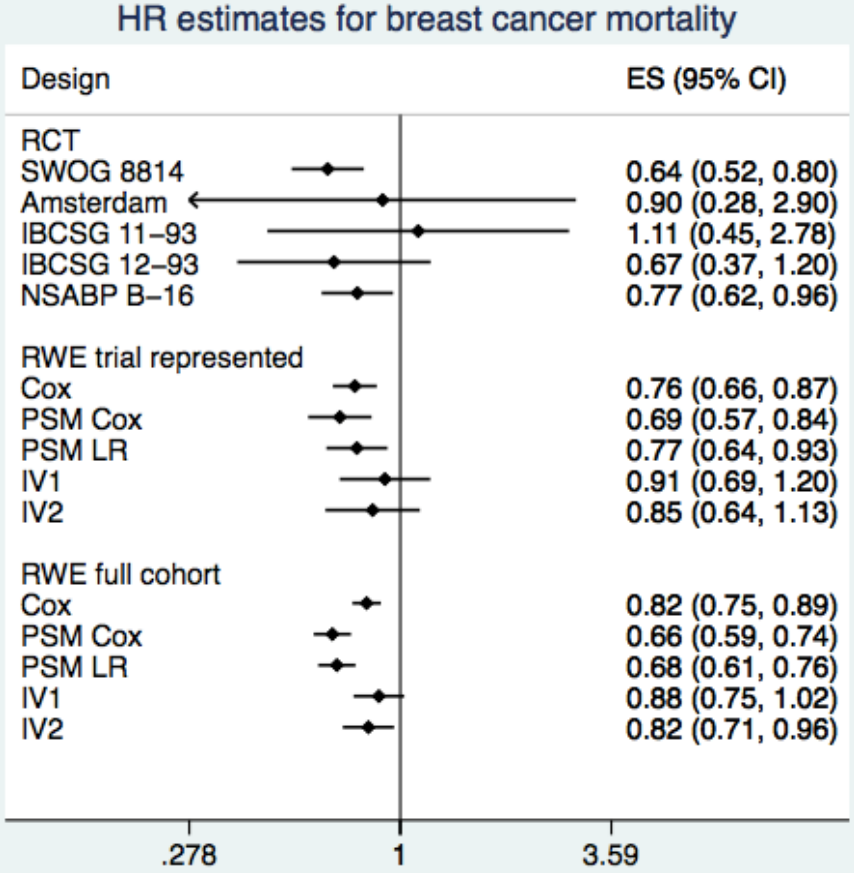
Uses prognostic data to create propensity scores and match treated and untreated cases.

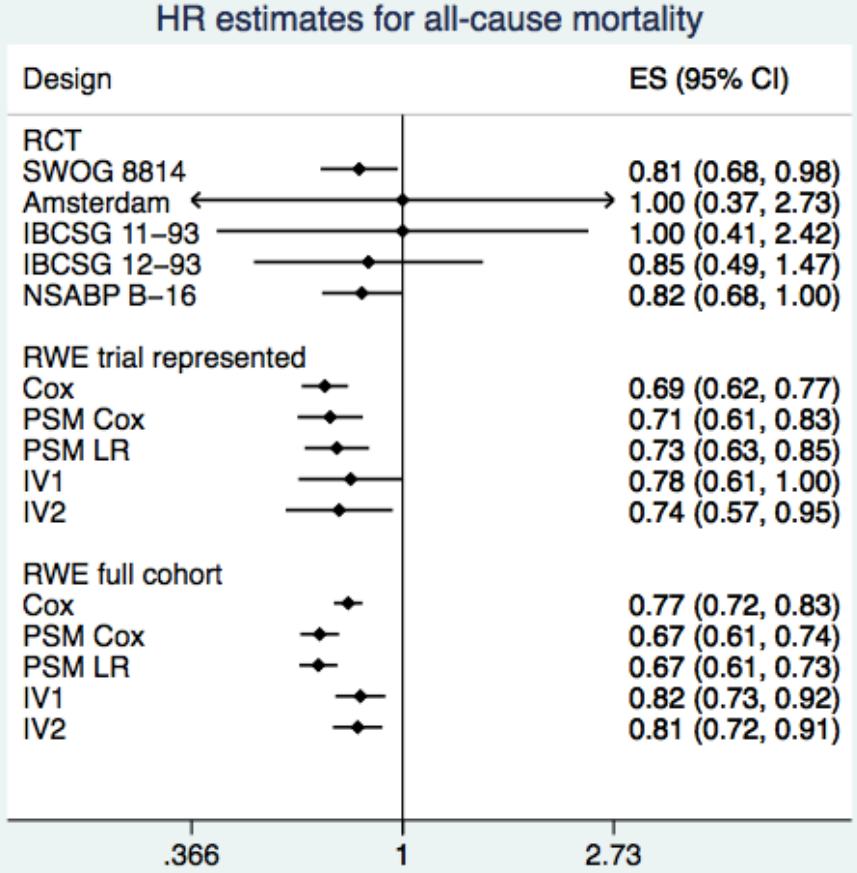
Instrumental variables (IV)

Makes use of variables that are assumed to causally effect the treatment decision but have no effect on outcomes other than indirectly via changing the probability of treatment. [Instrument = NHS Predict score]

Regression discontinuity design (RDD)

Exploiting variation in treatment use created by a treatment guideline based on a threshold level of estimated treatment benefit provided by an online tool.


HR estimates for breast cancer mortality
Design
ES (95% CI)
RCT
SWOG 8814
0.64 (0.52, 0.80)
Amsterdam
0.90 (0.28, 2.90)
IBCSG 11–93
1.11 (0.45, 2.78)
IBCSG 12–93
0.67 (0.37, 1.20)
NSABP B–16
0.77 (0.62, 0.96)
RWE trial represented
Cox
0.76 (0.66, 0.87)
PSM Cox
0.69 (0.57, 0.84)
PSM LR
0.77 (0.64, 0.93)
IV1
0.91 (0.69, 1.20)
IV2
0.85 (0.64, 1.13)
RWE full cohort
Cox
0.82 (0.75, 0.89)
PSM Cox
0.66 (0.59, 0.74)
PSM LR
0.68 (0.61, 0.76)
IV1
0.88 (0.75, 1.02)
IV2
0.82 (0.71, 0.96)
.278
1
3.59


HR estimates for all-cause mortality
Design
ES (95% CI)
RCT
SWOG 8814
0.81 (0.68, 0.98)
Amsterdam
1.00 (0.37, 2.73)
IBCSG 11–93
1.00 (0.41, 2.42)
IBCSG 12–93
0.85 (0.49, 1.47)
NSABP B–16
0.82 (0.68, 1.00)
RWE trial represented
Cox
0.69 (0.62, 0.77)
PSM Cox
0.71 (0.61, 0.83)
PSM LR
0.73 (0.63, 0.85)
IV1
0.78 (0.61, 1.00)
IV2
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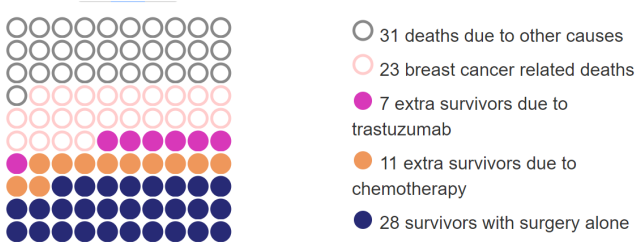
RWE full cohort
Cox
0.77 (0.72, 0.83)
PSM Cox
0.67 (0.61, 0.74)
PSM LR
0.67 (0.61, 0.73)
IV1
0.82 (0.73, 0.92)
IV2
0.81 (0.72, 0.91)
.366
1
2.73

Person-specific evidence for 2020+

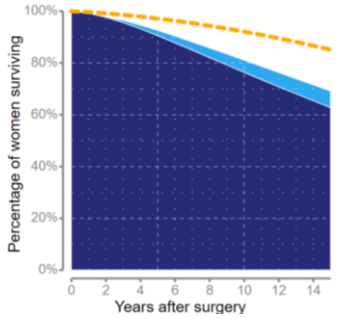
- Real-world patient population (n=60,000)
  - prescribed anti-hypertensives
  - prescribed diabetic medications

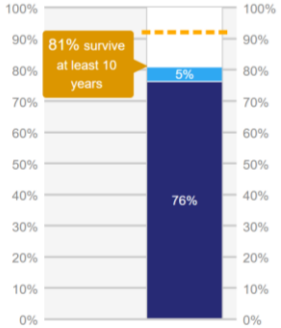
→ Personalised estimate of risk and benefit



Future methods

- Text mining
- AI / Machine learning
- Decision support for shared decision making





Adjuvant treatments

Hormones

Immunotherapy

Chemotherapy

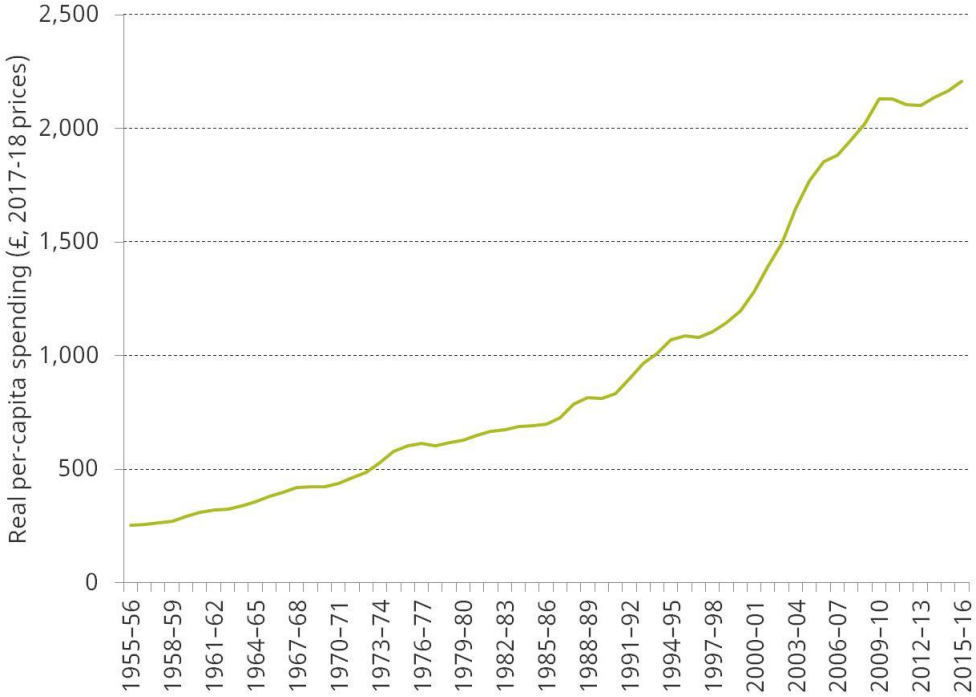
Targeted small molecules

Biological therapy

Bisphosphonates

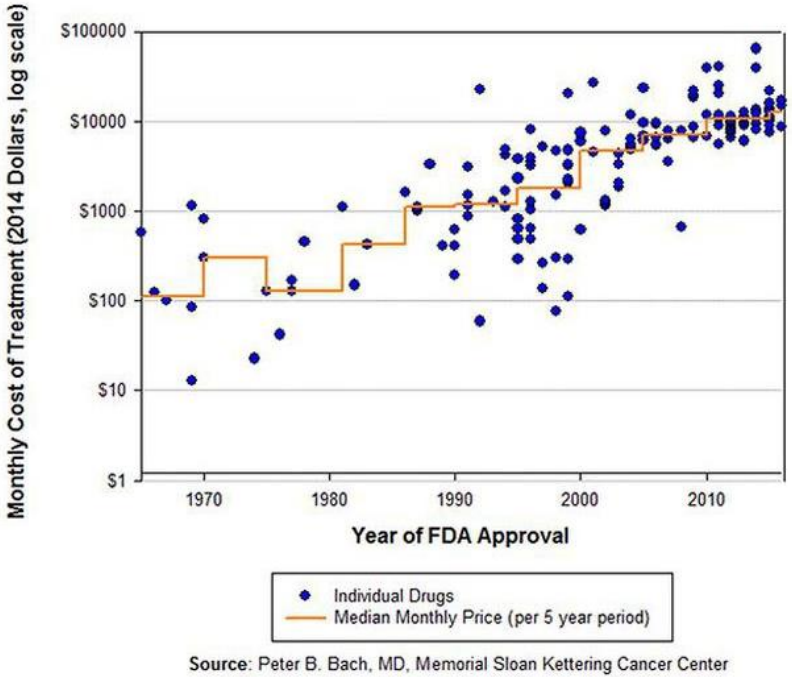
Antibody-drug conjugates

Real-terms NHS expenditure



New technologies

Monthly cost of new cancer drugs - US



Source: Peter B. Bach, MD, Memorial Sloan Kettering Cancer Center

5% above inflation basic rate

Value for money?

- Trastuzumab
- Pertuzumab
+ Chemo

~£100,000

Early marketing authorisation

- Accelerated approvals (FDA / EMA)

- Based on surrogate endpoints
- Small studies
- Molecular subgroups

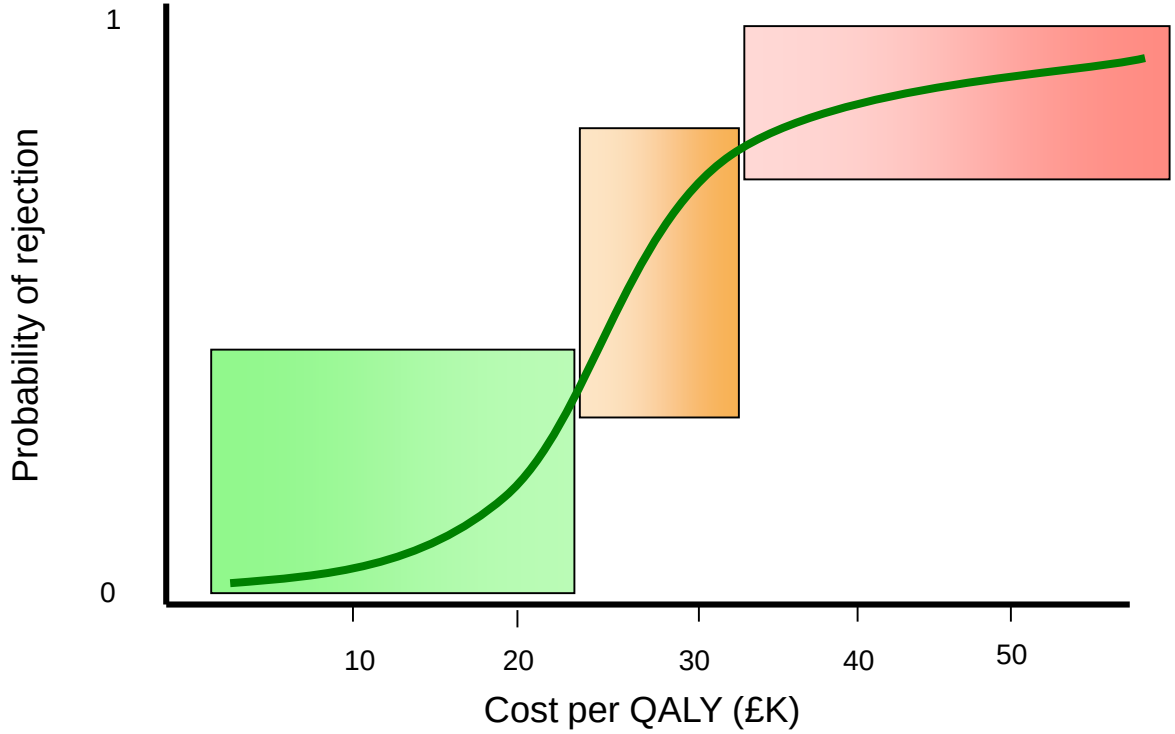
→ Highly uncertain evidence base for NHS adoption

UK Reimbursement decision makers

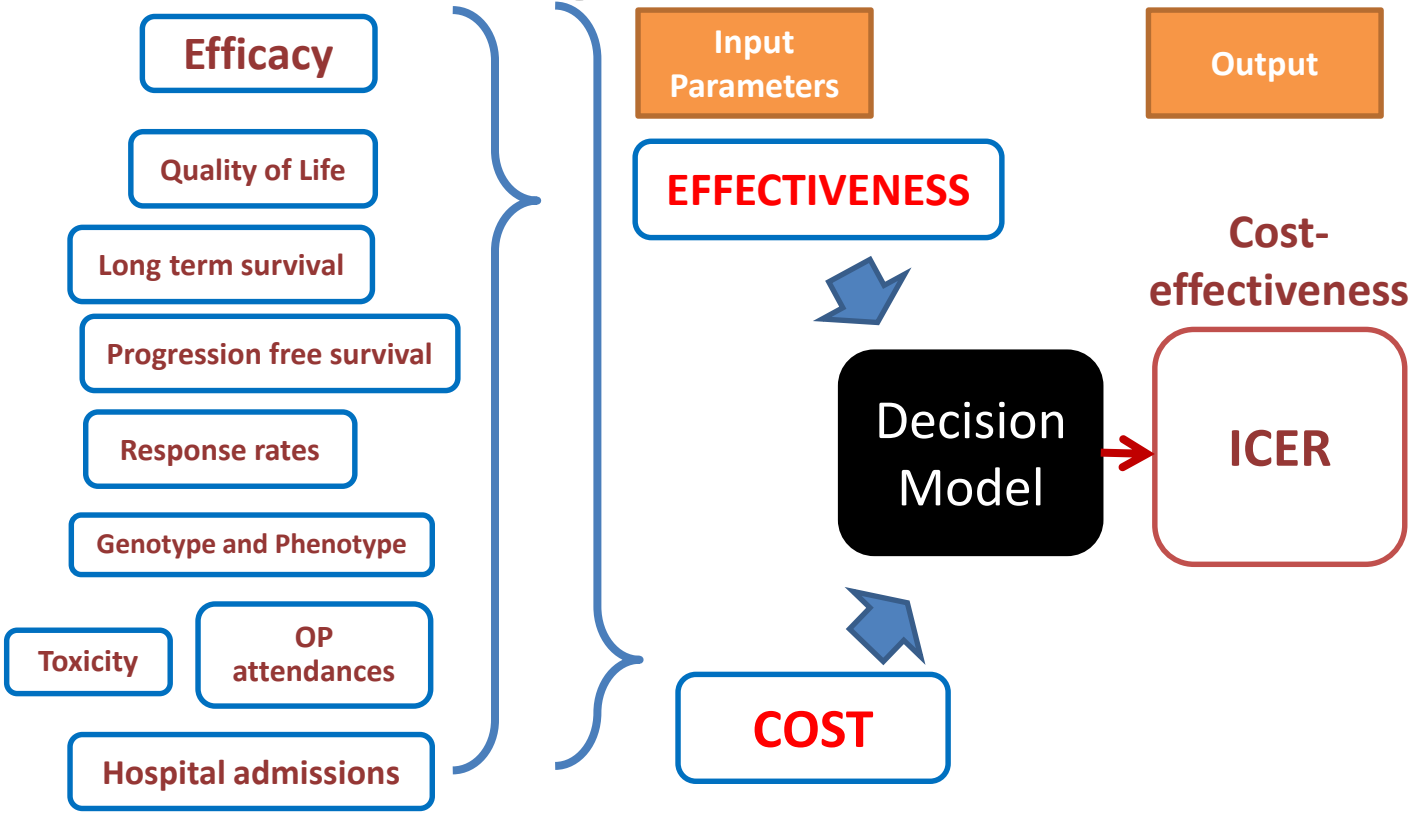
NICE National Institute for Health and Care Excellence

Scottish Medicines Consortium

Cost-effectiveness threshold

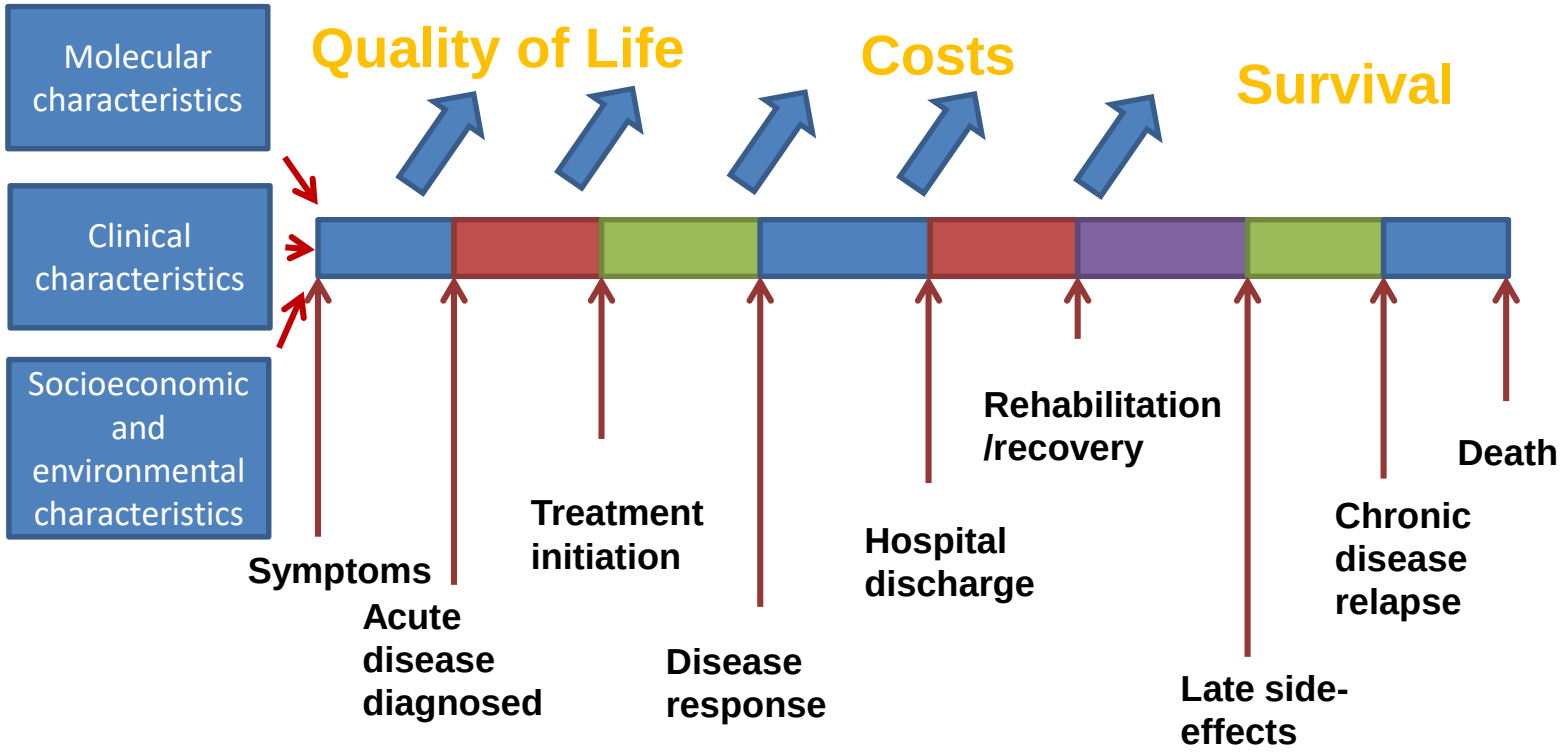


Calculating cost-effectiveness

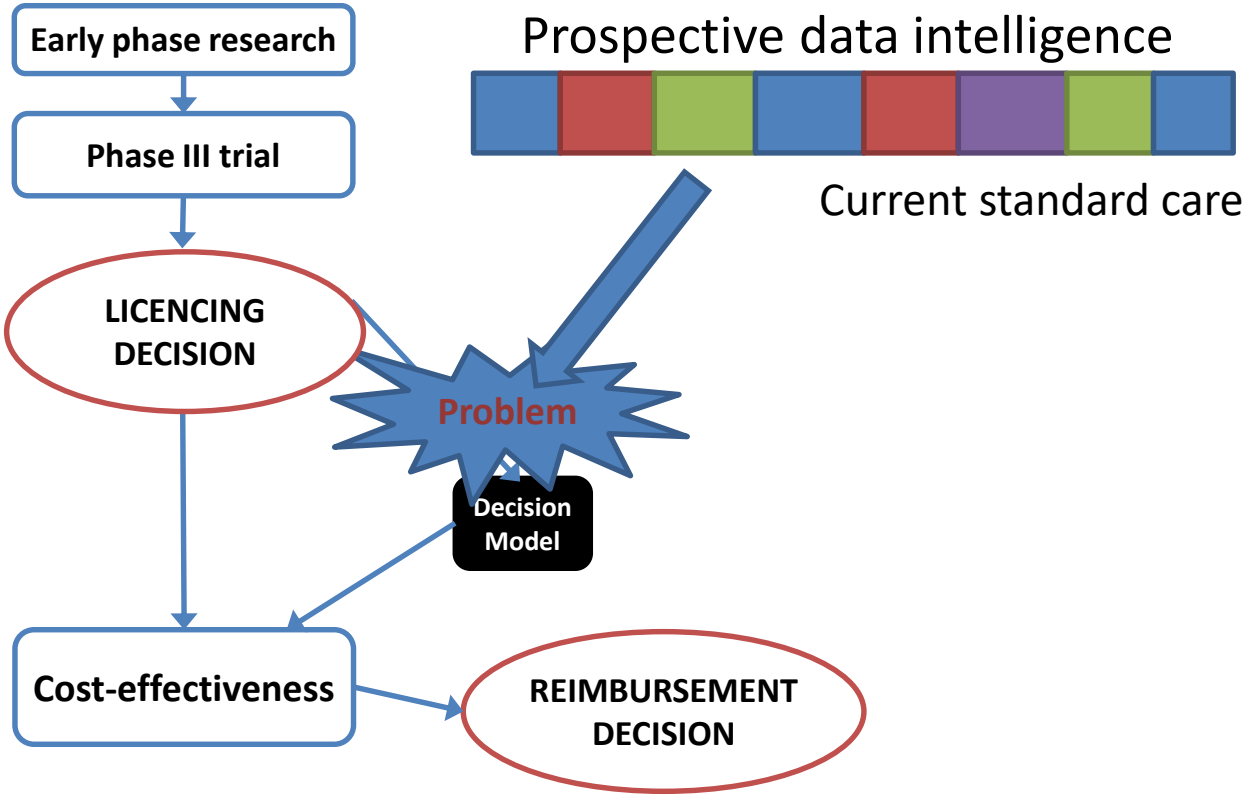


Decision Model

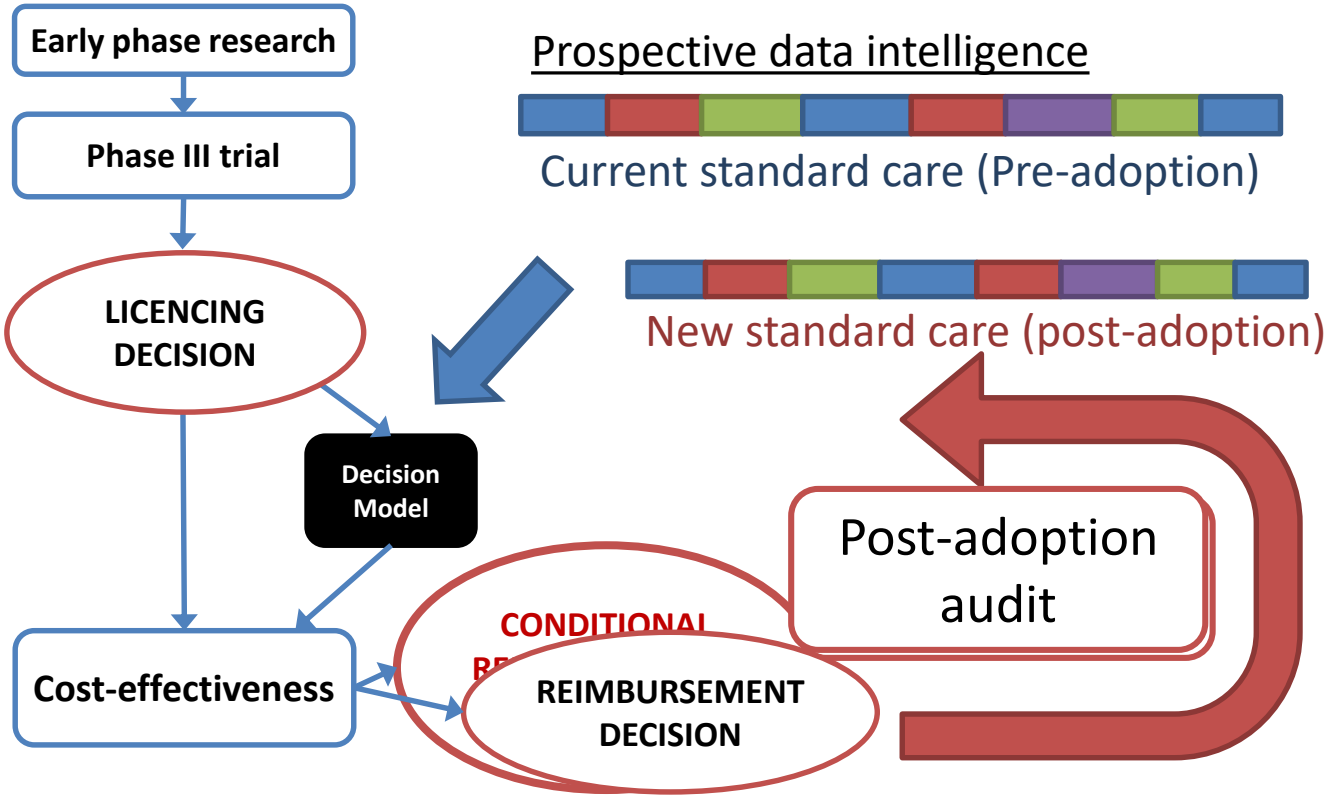
= Clinical care pathway



Health Technology Assessment in the UK



Route to technology adoption?



Summary for 2020+

- Better decision support
  - For individual patients
  - For NHS adoptions decision makers
- Based on Real World Evidence
  - New data opportunities
  - New methods for use