Gene+environment risk models: whys and hows

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- Genes are important
- The environment is important
- Risk models that include both can be useful

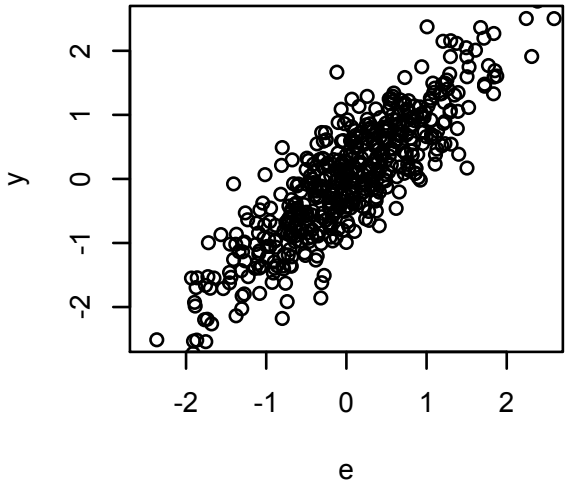
Risk models using E

- Framingham risk model (CVD)
- Breast cancer risk assessment tool
- Chronic and acute risk of VTE

Risk models using E

- Framingham risk model (CVD)
- Breast cancer risk assessment tool
- Chronic and acute risk of VTE
- Prostate cancer

Does adding G help?


y
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1
2
-2
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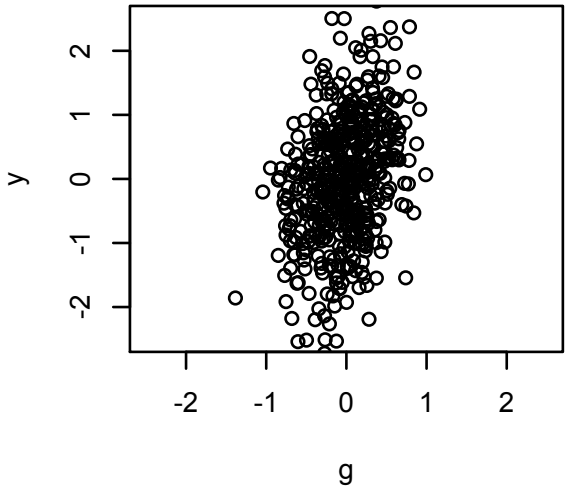
0
1
2
e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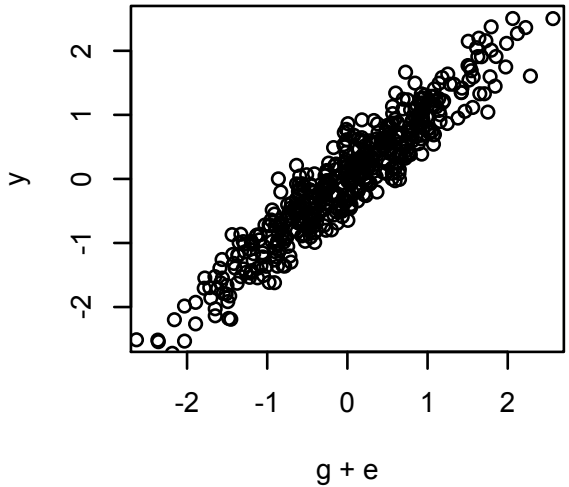
g


y
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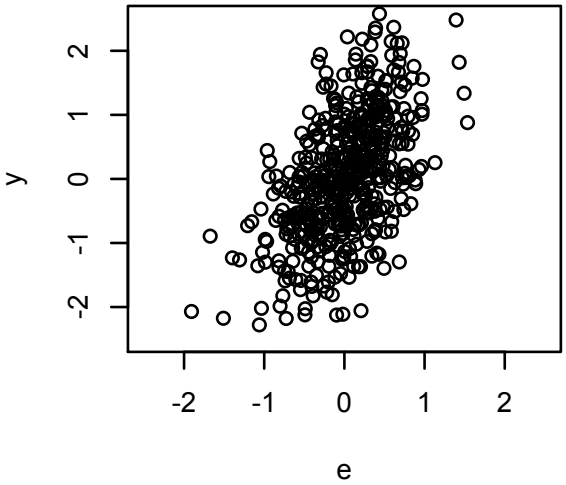
g + e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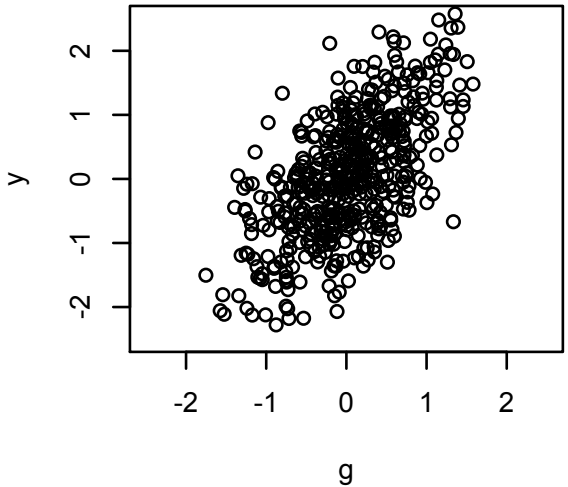
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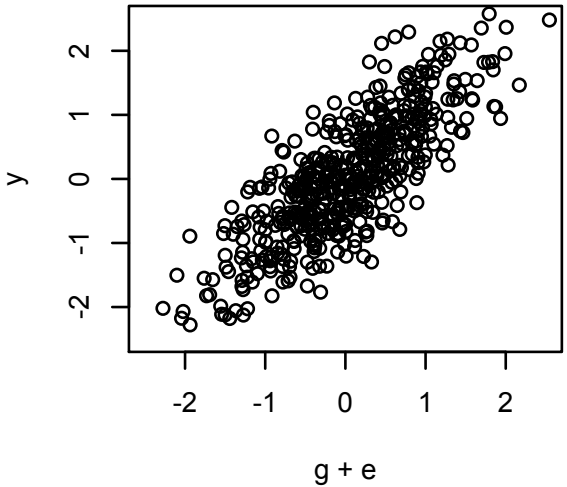

y
-2
-1
0
1
2
-2
-1
0
1
2
g + e

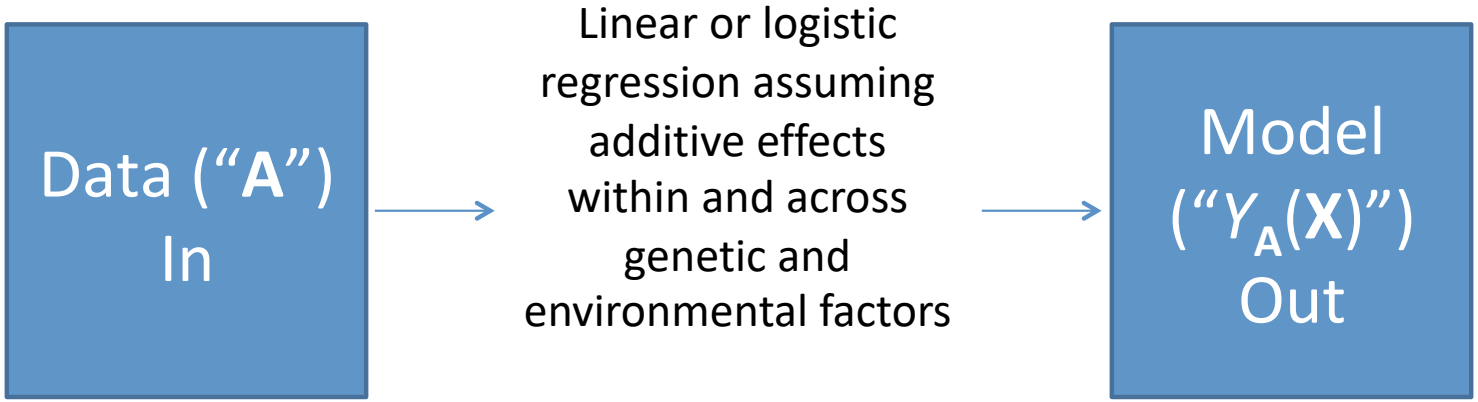
Training Models Including G & E

What functional form should the model have? What variables should be included? How should they be coded?

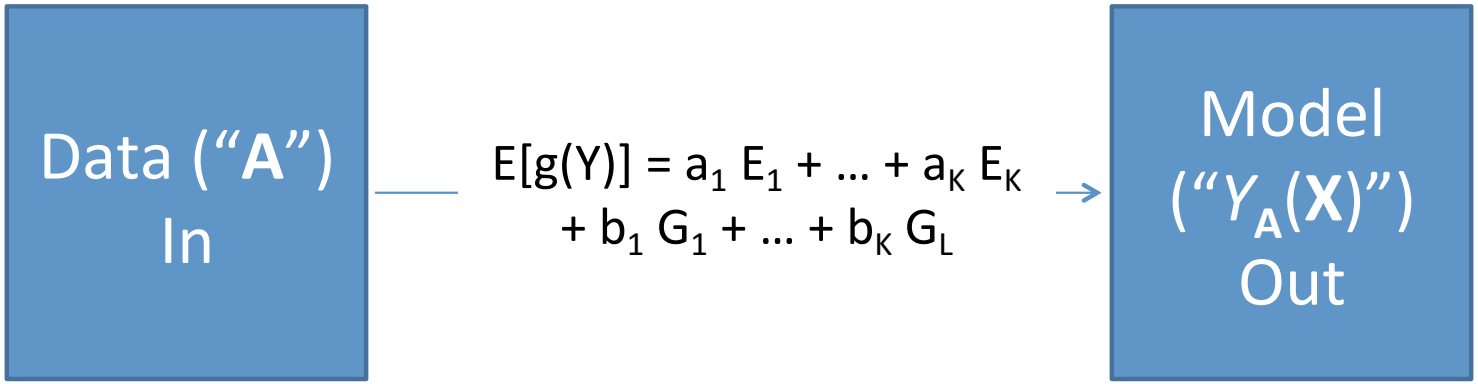
Data ("**A**") In

Model ("$Y_A(\mathbf{X})$") Out

Training Models Including G & E



Training Models Including G & E



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What about non-linear effects (aka interactions)?
School of hard knocks: linear terms pick up most of the signal, potential gains from including non-linear terms swamped by degrees of freedom.

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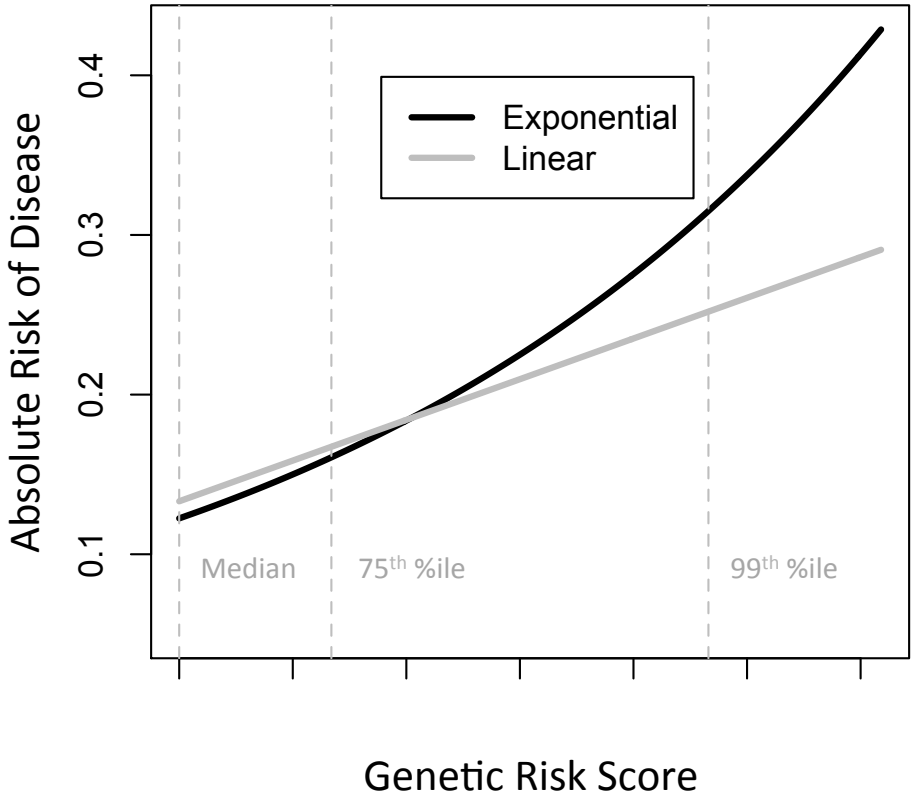
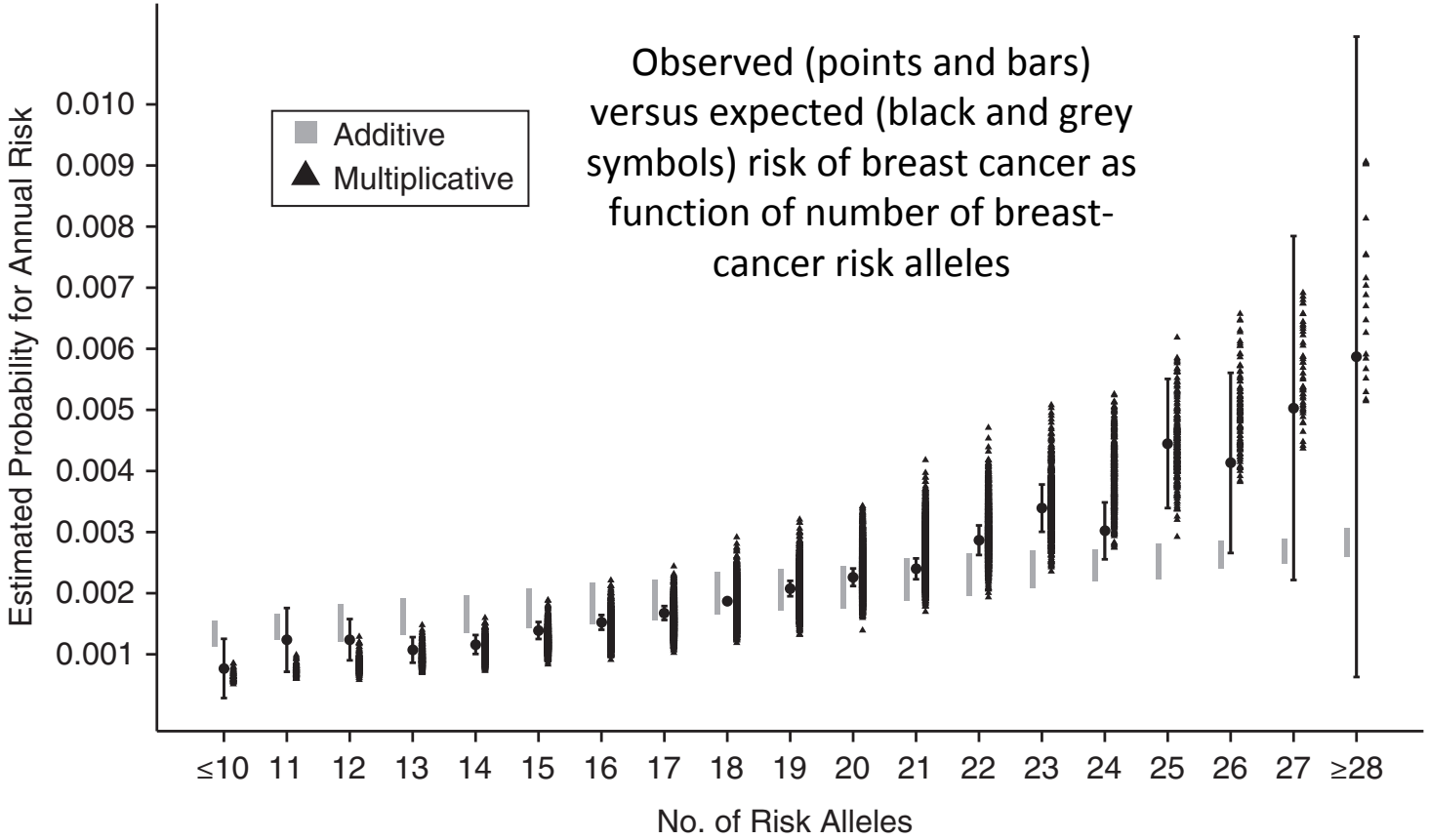
This model choice has implications for *extrapolated* risks in the tails.



The *assumed* log-additive relative risk model has notable implications for individuals in the tails of the genetic risk distribution,

More work is needed to verify that this model is a good fit *in the tails*.

Kraft (2017) *J Clin Oncol*



Joshi (2014) *Am J Hum Genet*

Testing calibration of risk models at extremes of disease risk

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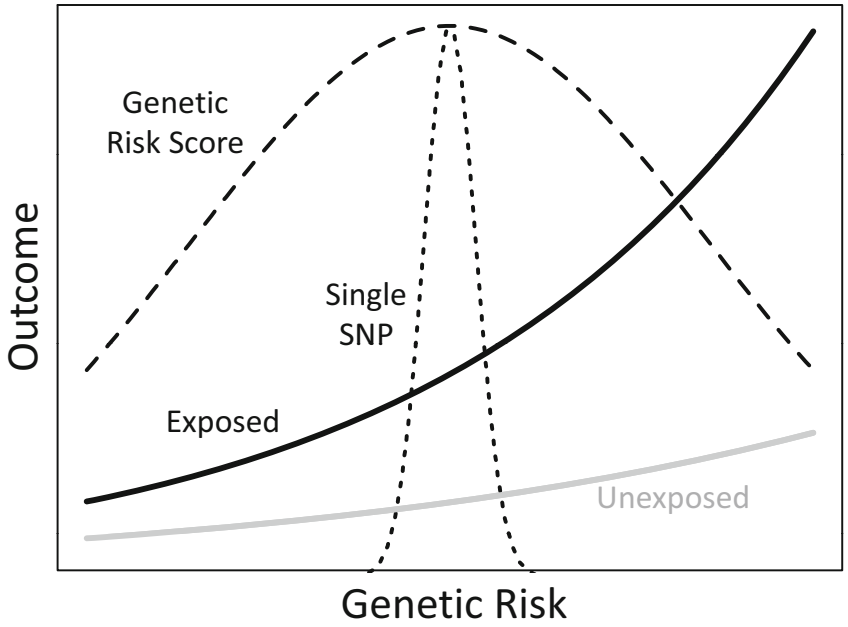
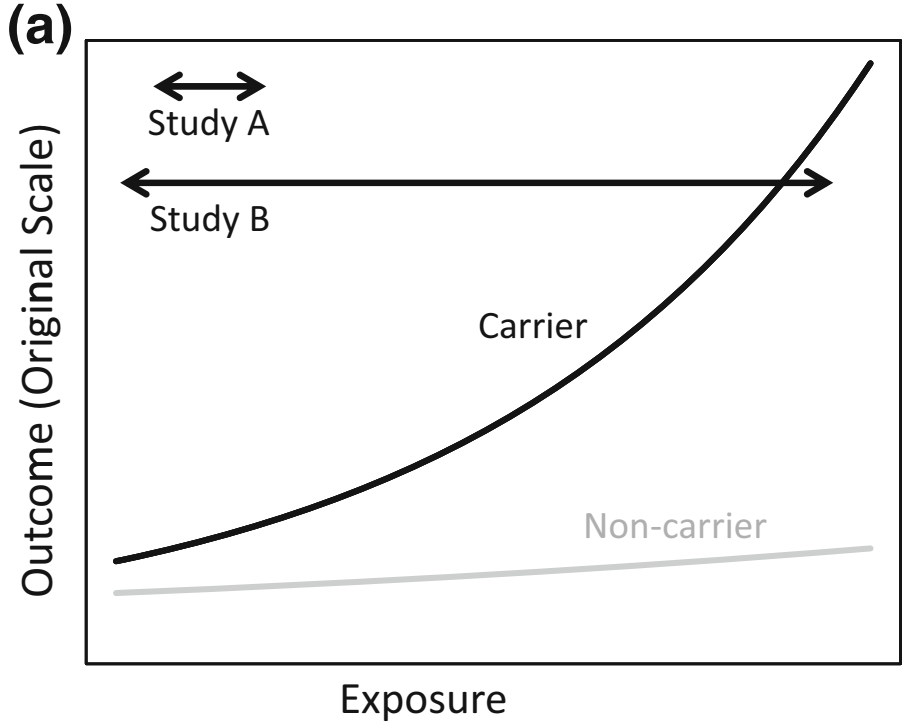
Biostatistics (2015)

Training Models Including G & E

What about non-linear effects (aka interactions)?
School of hard knocks: linear terms pick up most of the signal, potential gains from including non-linear terms swamped by degrees of freedom.

Constraining GxE effects may improve model fit
(assuming SNP-E interactions are mostly in the same direction).
Increasing exposure variance may as well.


Genetic
Risk Score
Single
SNP
Exposed
Unexposed
Outcome
Genetic Risk


(a)
Study A
Study B
Carrier
Non-carrier
Outcome (Original Scale)
Exposure

What if G is Mediated thru E?

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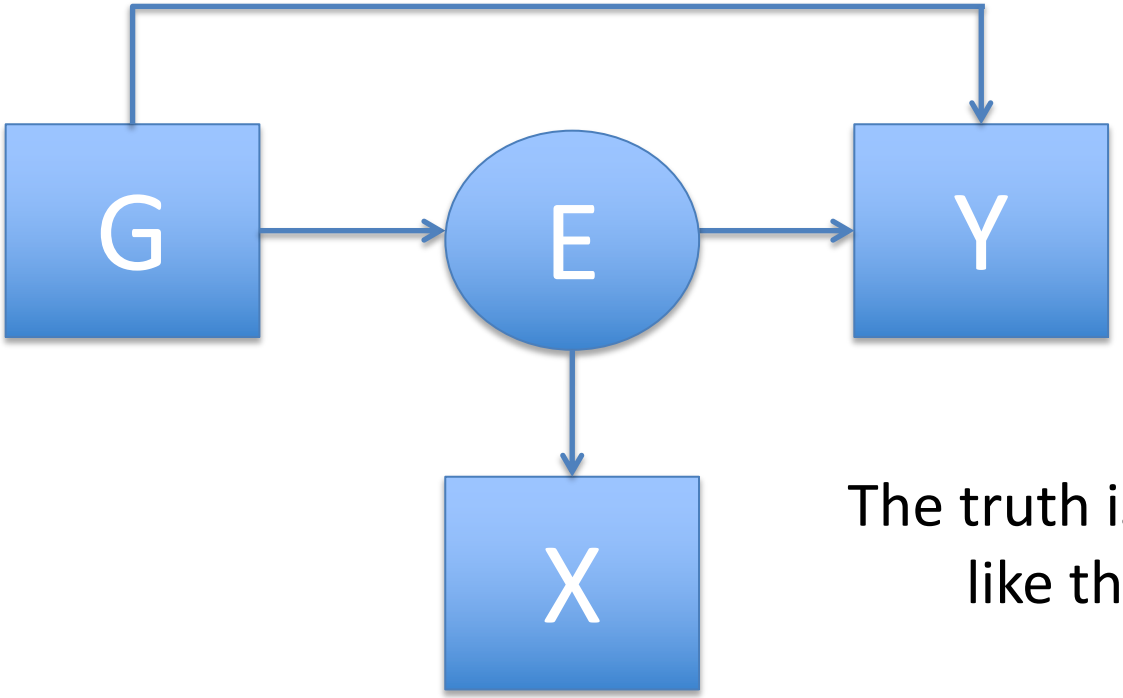
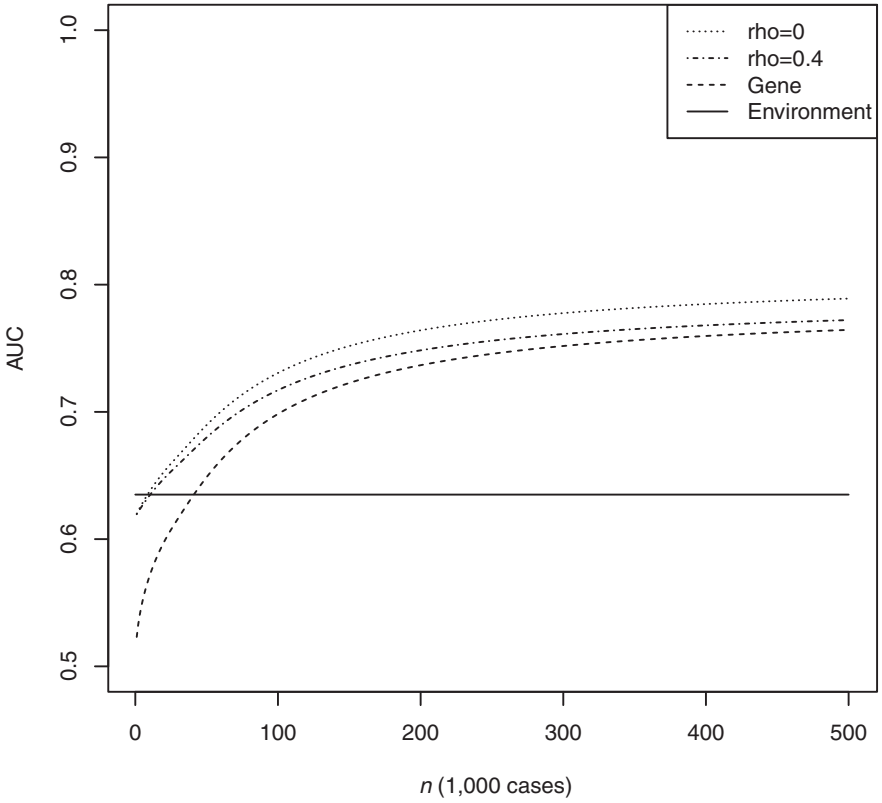
If *all* of G's effect is mediated thru E and we've measured E *without error*, then genetic terms $b_1,\ldots,b_K$ go to 0.

What if G is Mediated thru E?

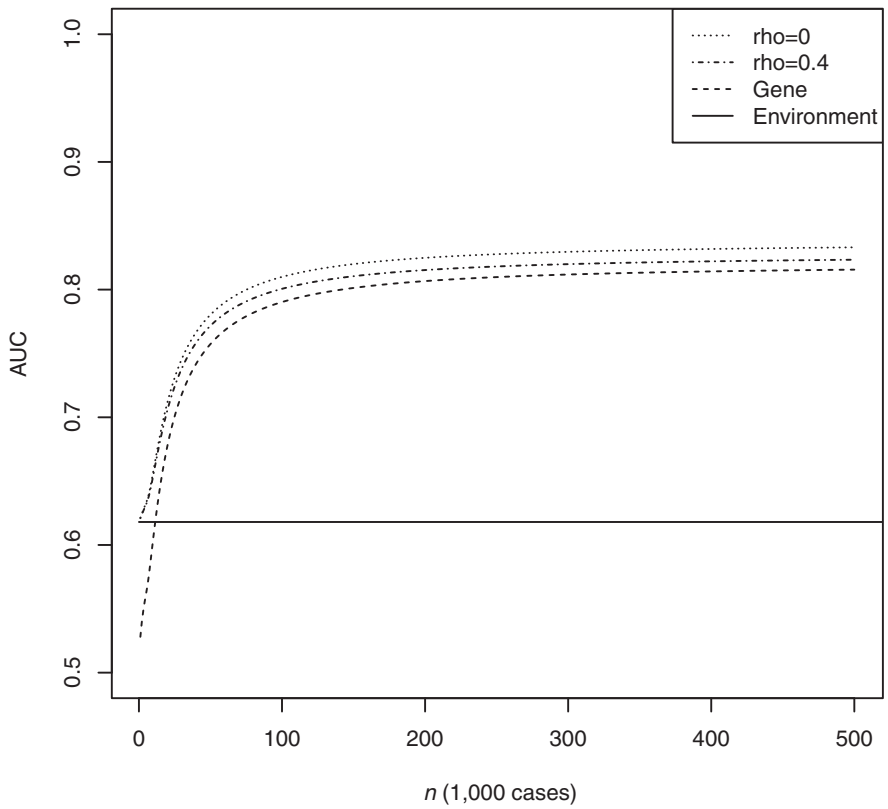


The truth is more like this.

CVD



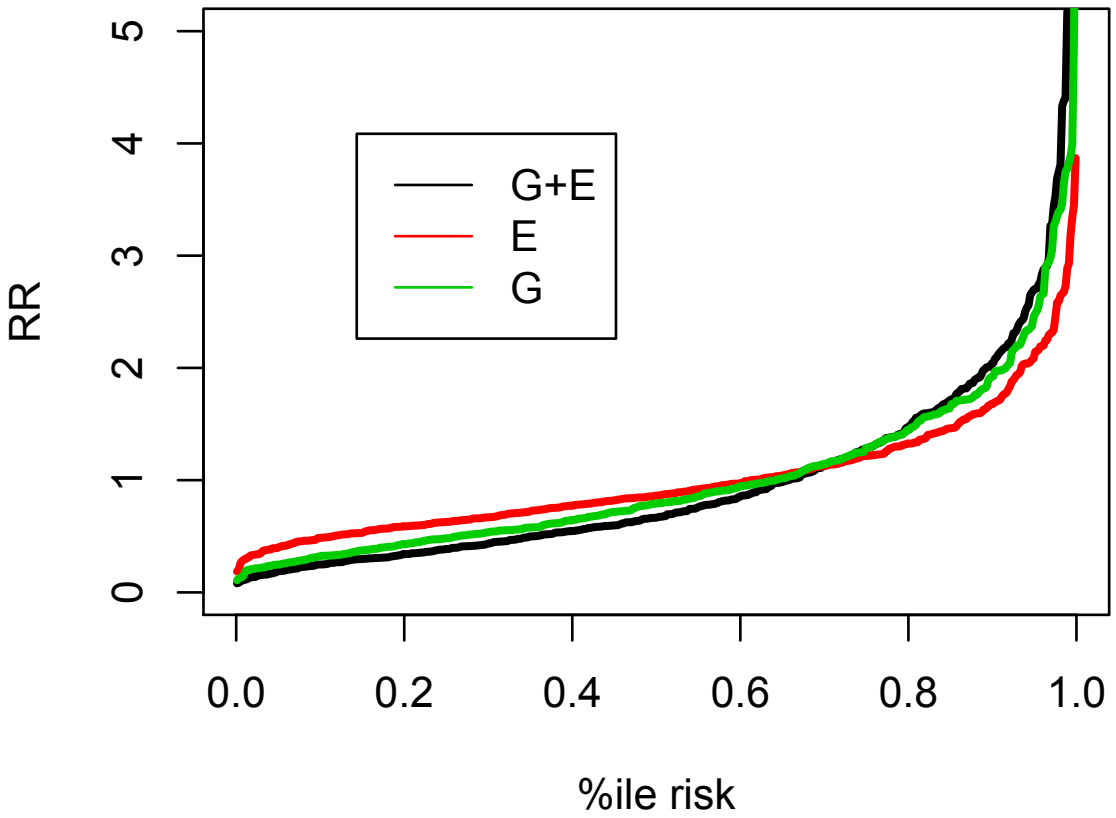
Breast Cancer



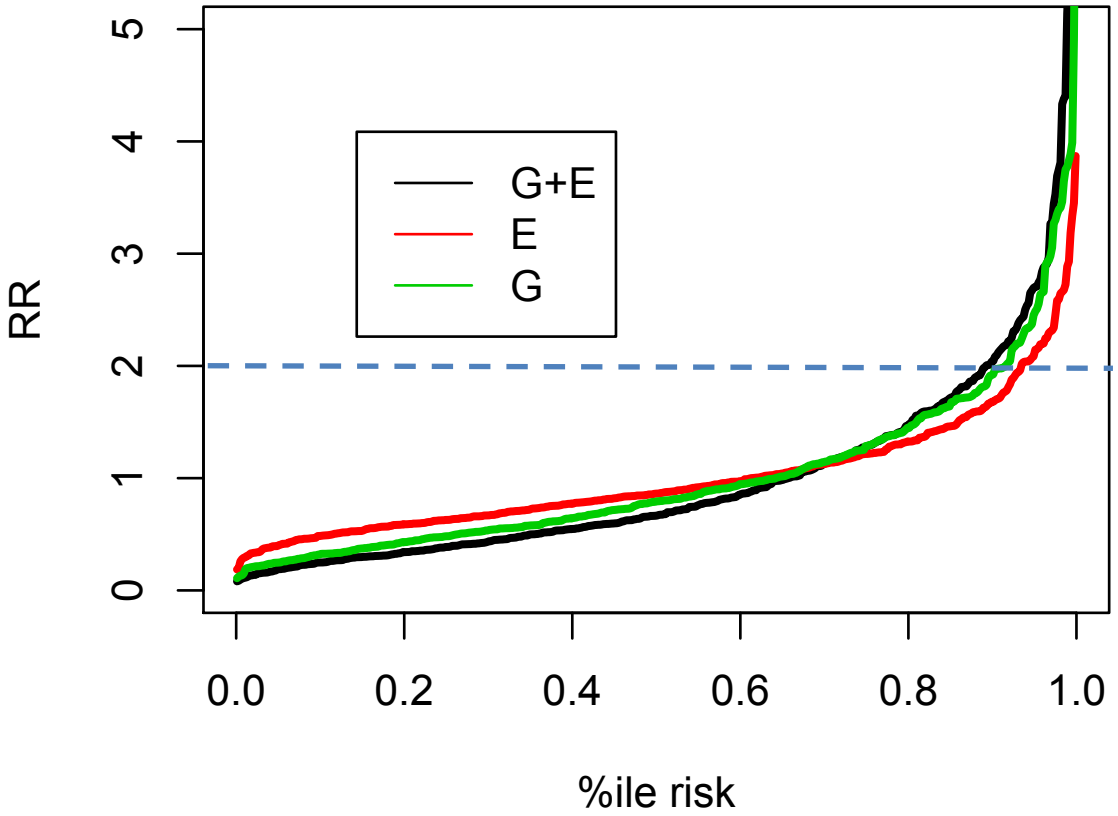
Dudbridge (2018) *Genet Epidemiol*

So, is it useful?

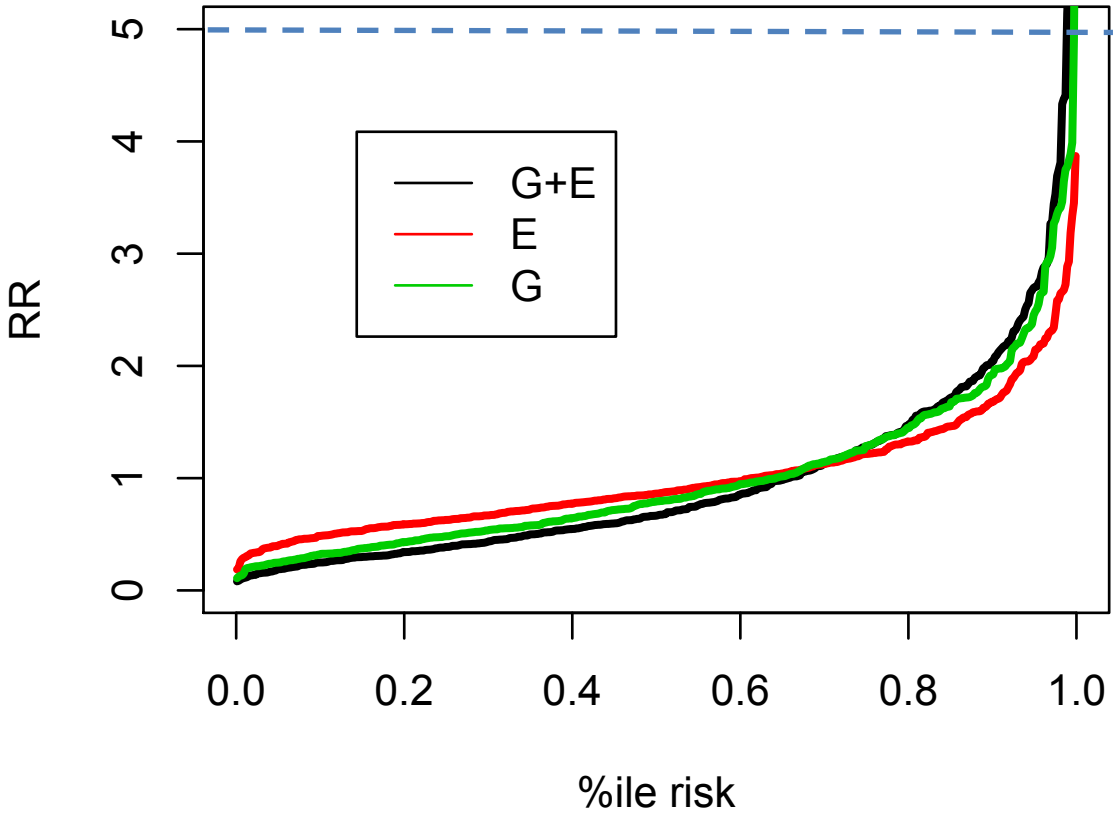
- Spreading risk distribution
- Identifying subgroups where G is actionable



Can increase the gradient of predicted risks by including G, but utility will depend on context—e.g. on the "action threshold" where expected benefits of intervention outweigh risks.



Adding G can identify 2x as many folks with RR>2



Adding G can identify
>10x as many folks
with RR>2

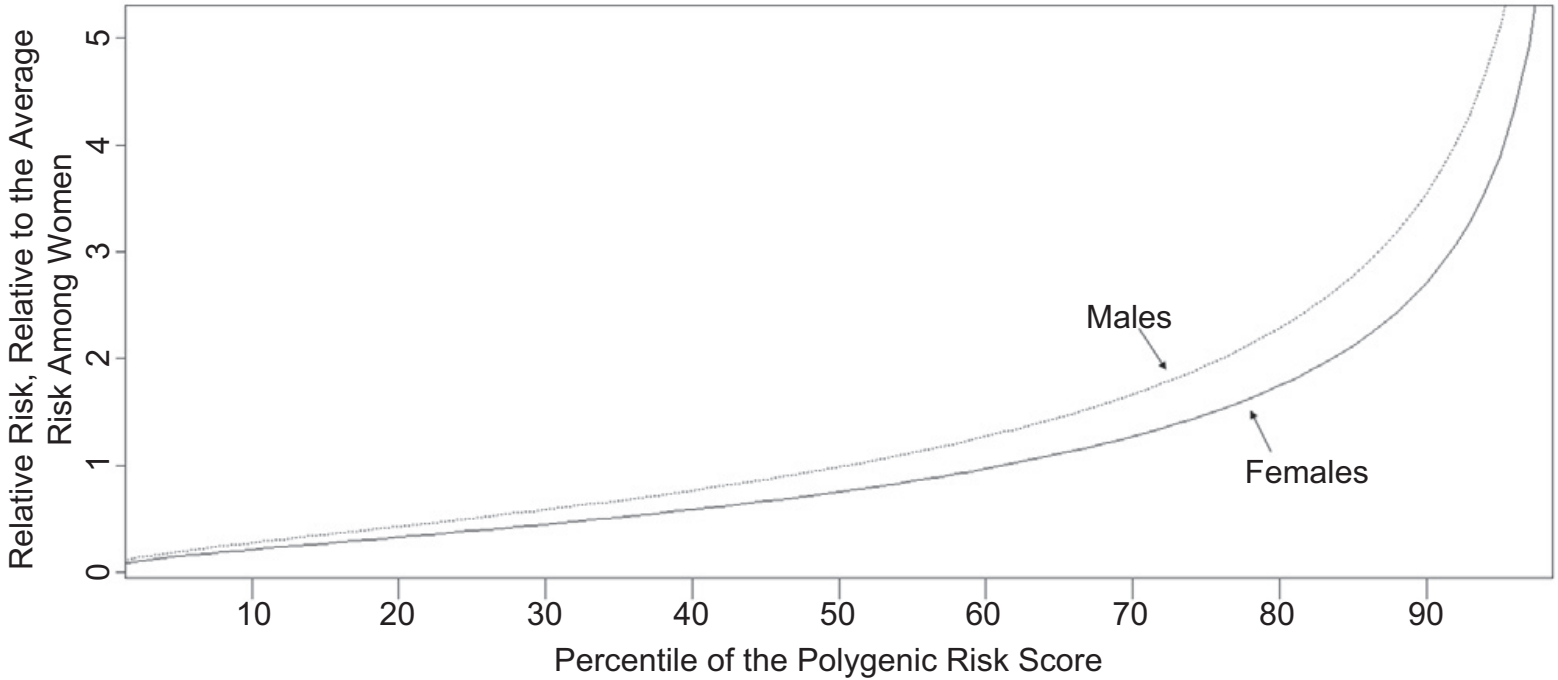
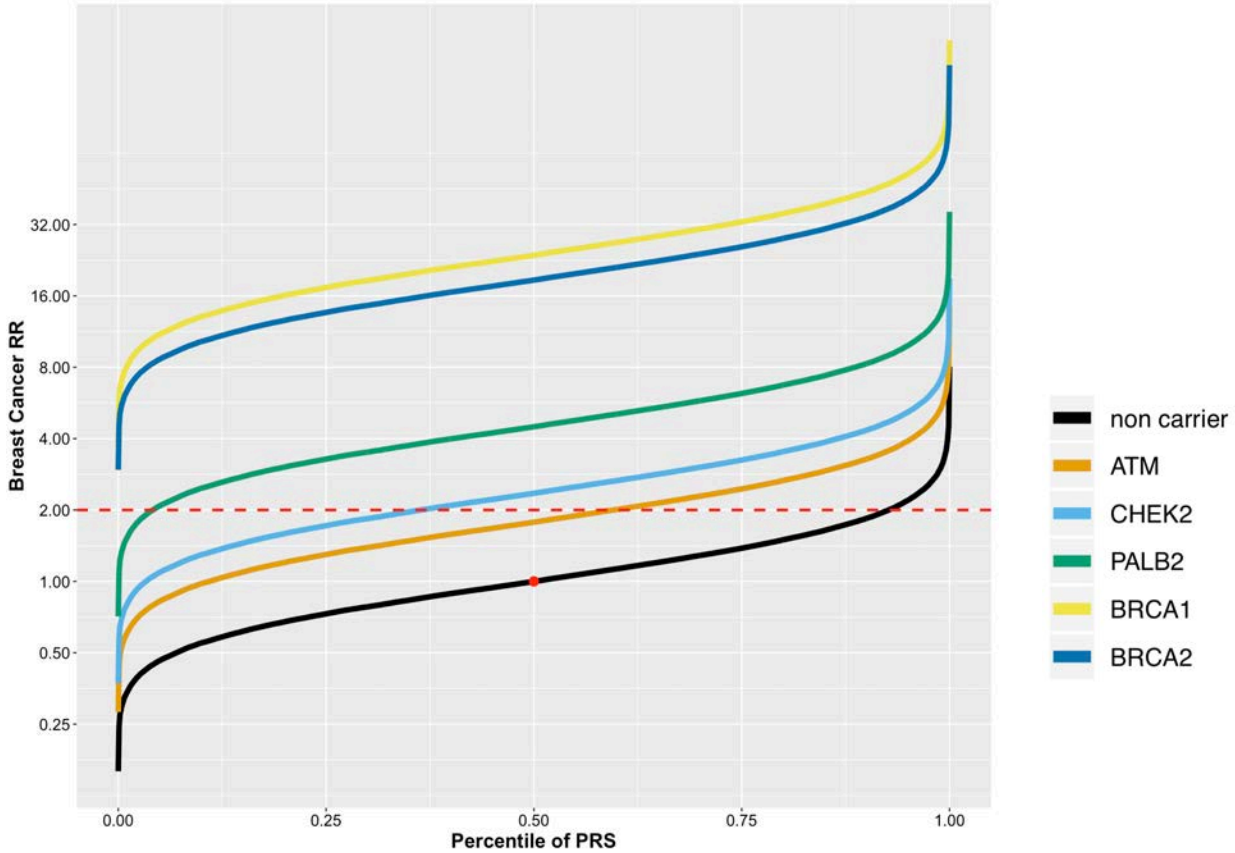


Figure 1. Cutaneous squamous cell carcinoma risk with increasing Polygenic Risk Score.

Women < 40 years old



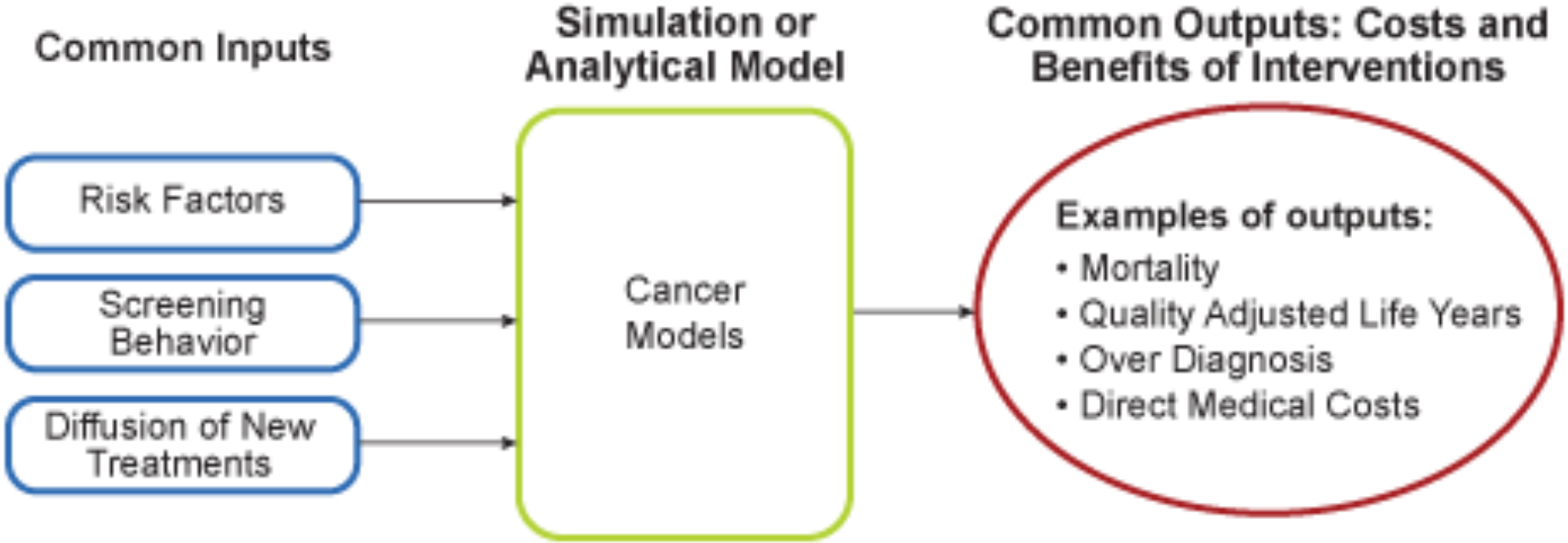
Preliminary results from CARRIERS consortium, presented at AACR 2019

Gao, Couch, Goldgar, Nathanson, Couch, Kraft et. al.

Determining clinical utility

- RCTs
- In the absence of large, expensive, and time consuming RCTs, we can simulate effectiveness using a model of disease natural history w/ or w/o intervention

Determining clinical utility

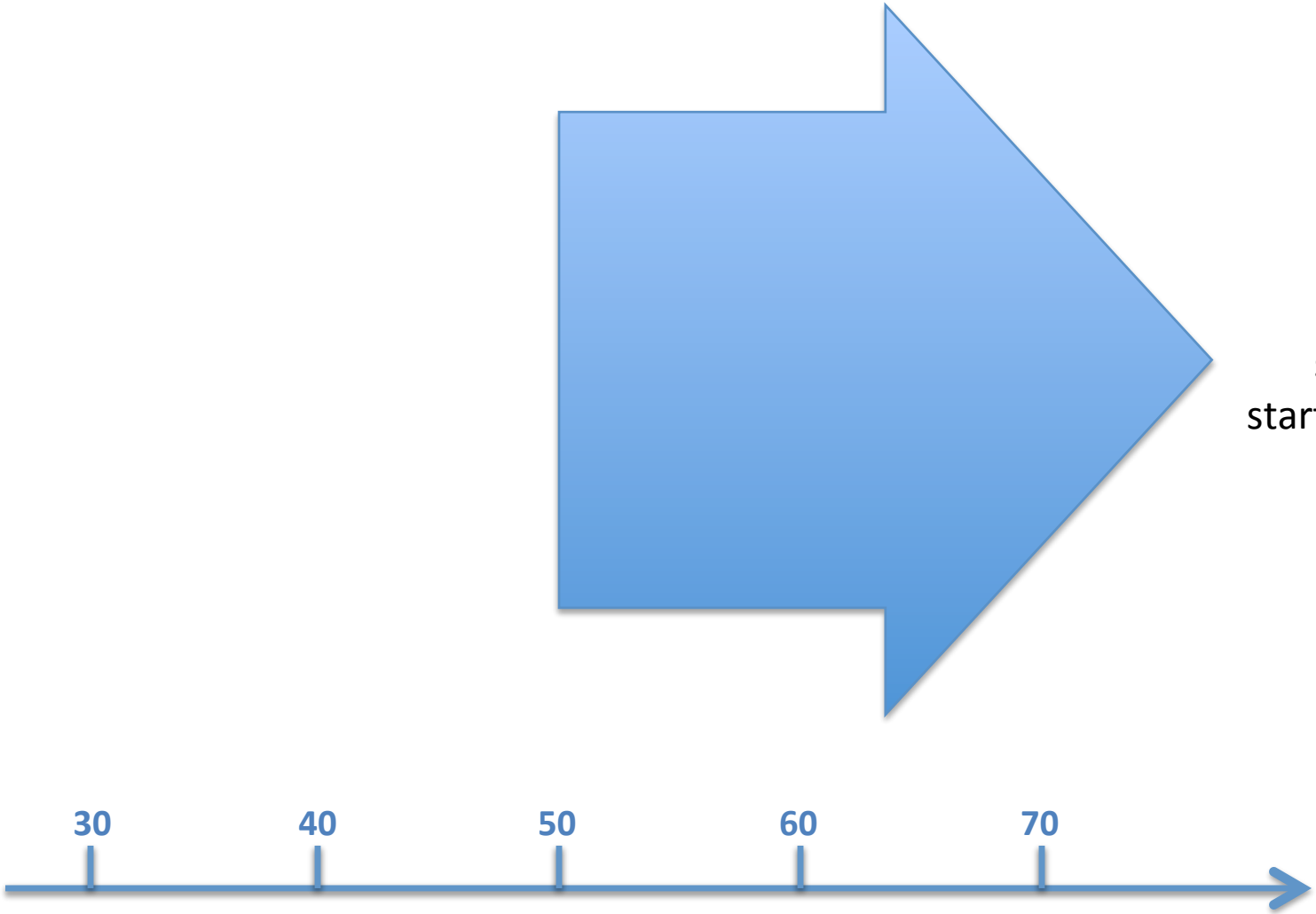


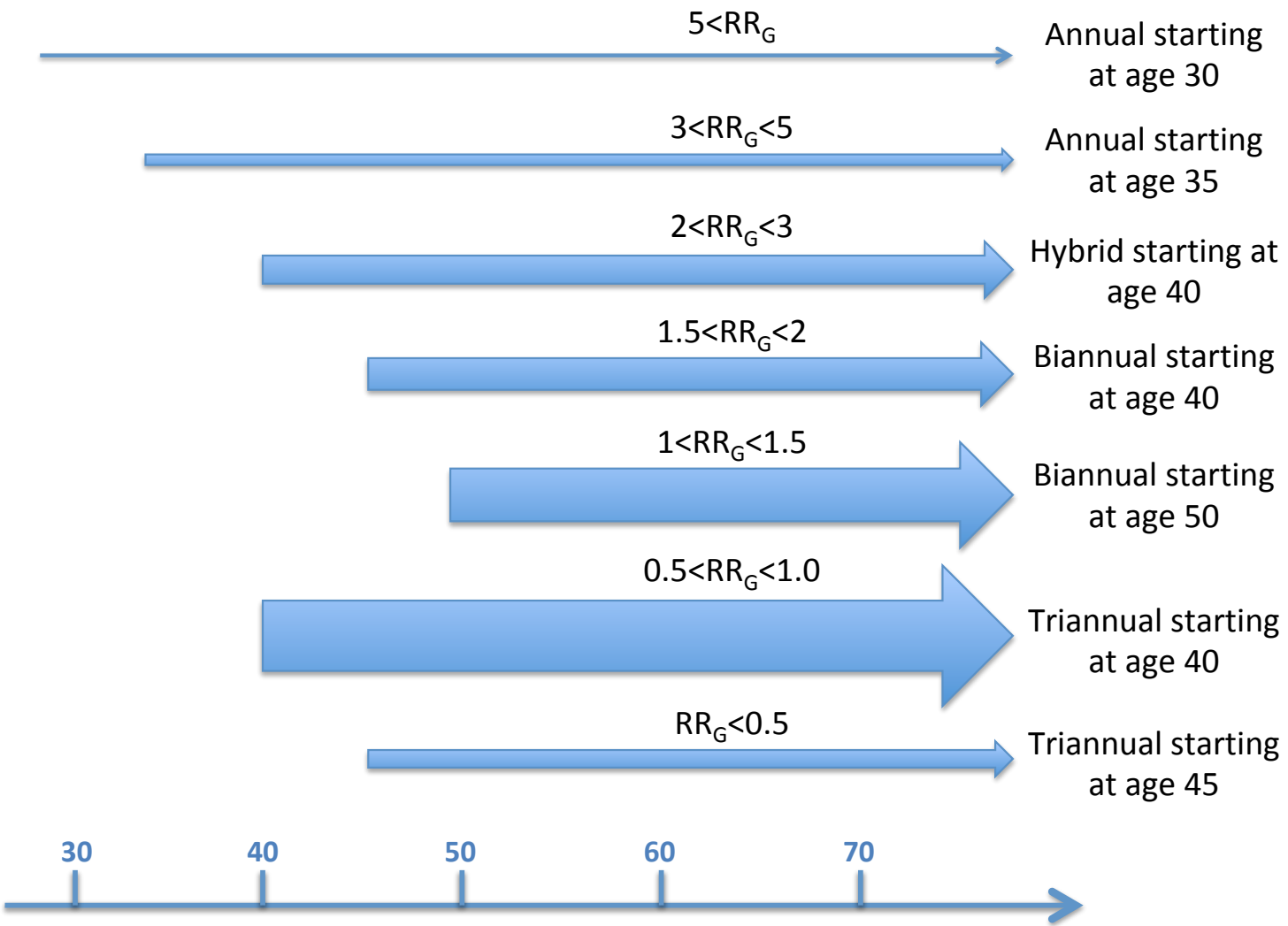
https://cisnet.cancer.gov/modeling/

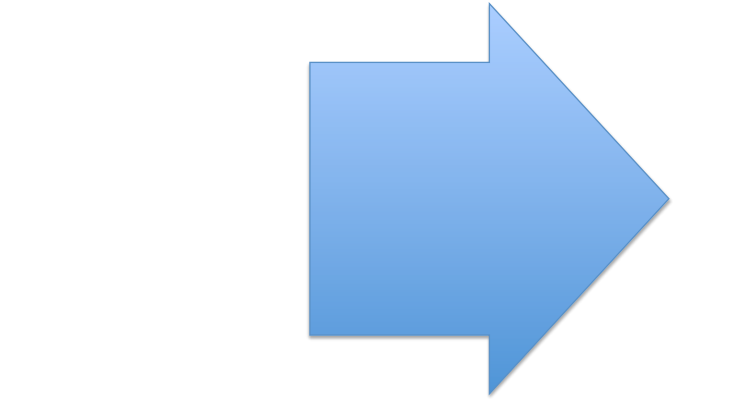
Determining clinical utility

Example: stratified breast cancer screening

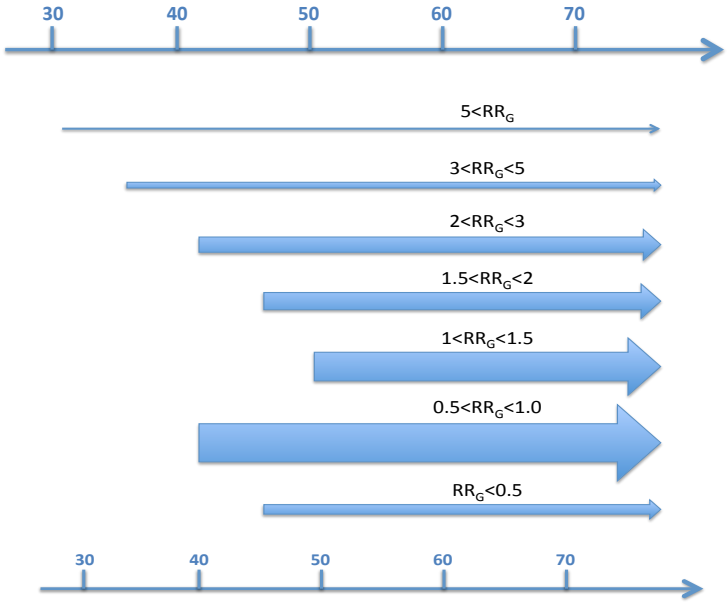
(preliminary work from CISNET breast cancer working group
—van den Broek et al.)


Bi-annual
screening
starting at age 50
30
40
50
60
70


5<RR_G
Annual starting at age 30
3<RR_G<5
Annual starting at age 35
2<RR_G<3
Hybrid starting at age 40
1.5<RR_G<2
Biannual starting at age 40
1<RR_G<1.5
Biannual starting at age 50
0.5<RR_G<1.0
Triannual starting at age 40
RR_G<0.5
Triannual starting at age 45
30
40
50
60
70

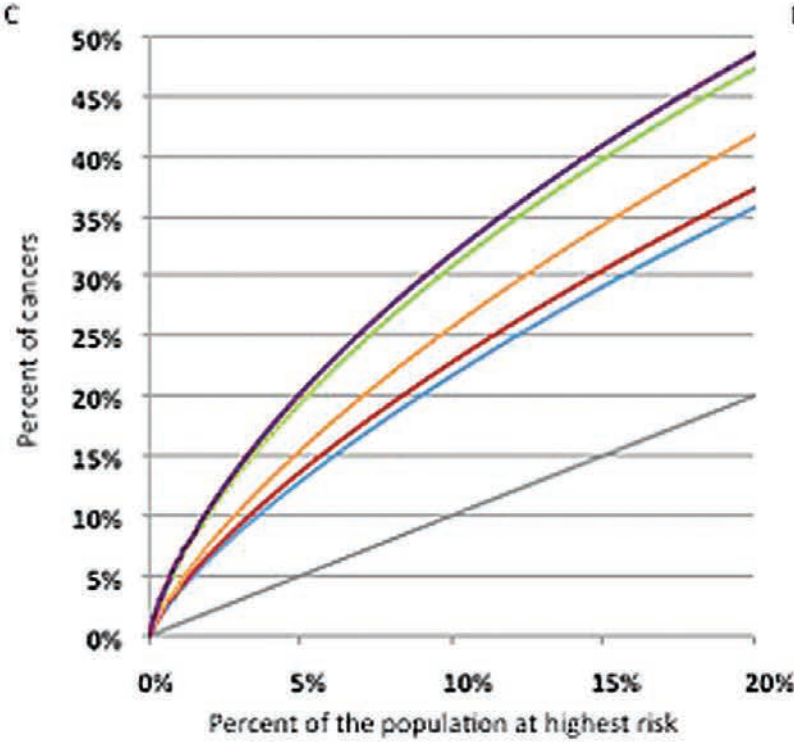


Life years gained: 118
Breast cancer deaths averted: 6.7



Life years gained: 196
Breast cancer deaths averted: 9.7

More can be better

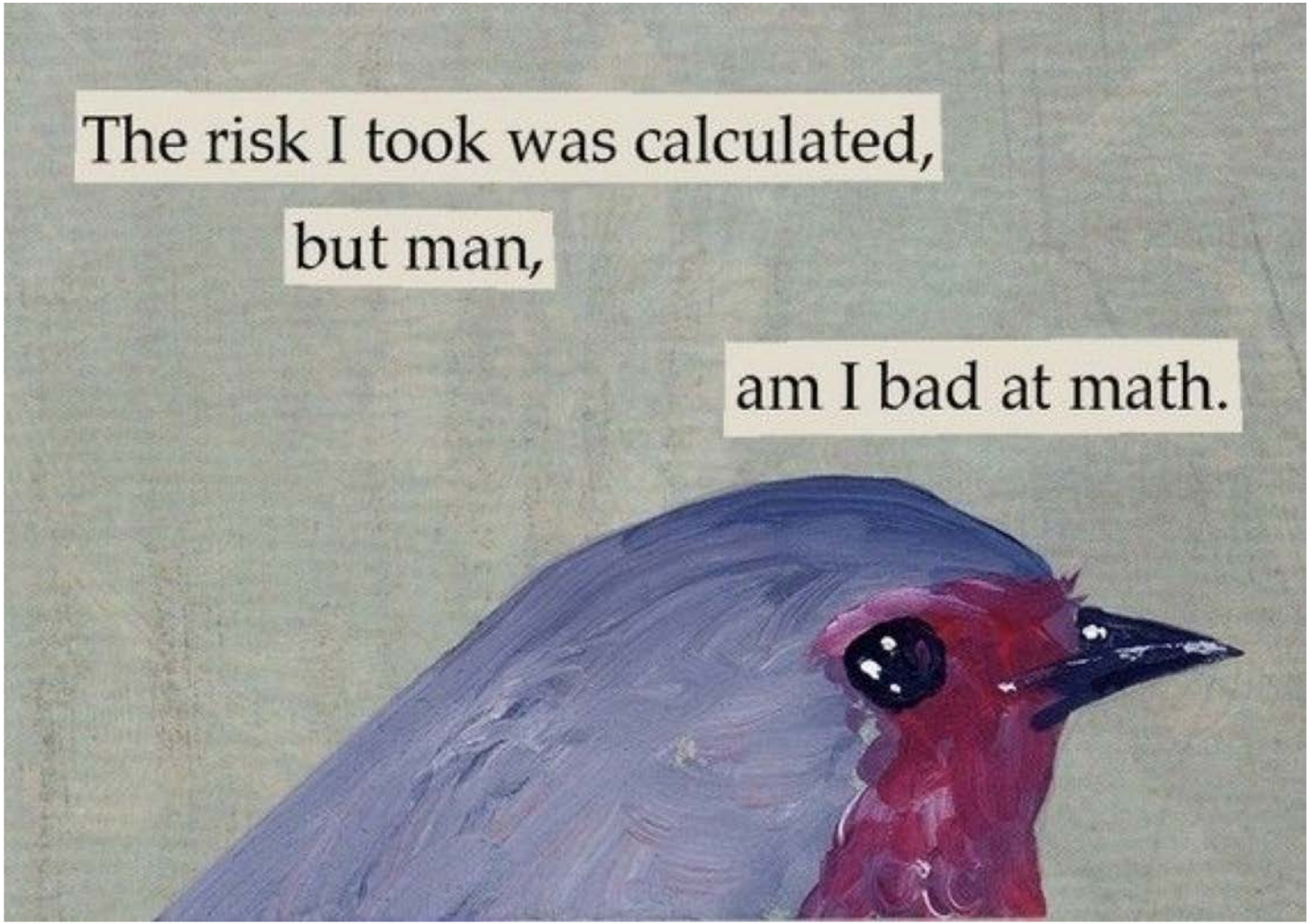


- Qx risk factors
- Mammographic density
- PRS
- Emerging biomarkers

Garcia-Closas (2014) JNCI

Misc Issues

- Implementing “complicated” E models
  —good locally, maybe not globally
- Including biology in risk models


The risk I took was calculated,
but man,
am I bad at math.