How Do We Assess the Value of Genetic Information in Predicting Disease

?

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Common variation in three genes, including a noncoding variant in *CFH*, strongly influences risk of age-related macular degeneration

Julian Maller[1,3],
Johanna M Sedd

Genetic Prediction of Future Type 2 Diabetes

Inflammatory Gene Polymorphisms and Risk of Postoperative Myocardial Infarction After Cardiac Surgery

M.V. Podgoreanu, MD;
M. Stafford-Smith, MI
M.
Perioperative Genetics a

Cumulative Association of Five Genetic Variants with Prostate Cancer

Polymorphisms Associated with Cholesterol and Risk of Cardiovascular Events

Sekar Kathiresan, M.D., Olle Melander, M.D., Ph.D., Dragi Anevski, Ph.D., Candace Guiducci, B.S., Noël P. Burtt, B.S., Charlotta Roos, M.Sc.,

th, M.S.,
D.,
h.D.,
Ph.D.,
D.,

Review: Janssens & van Duijn. *Hum Mol Genet* 2008

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Why do people want genetic tests?

- Because they want to know their risks of disease

  - Why?
    - Just to know
    - To act upon with interventions that may reduce their risks

  - When will they adopt interventions?
    - If their risk of disease is higher than average?
    - If their risk of disease is not zero?

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What do people need to know?

- Their risk of disease

- Presented against a reference risk, often average risk

- Information on available interventions

What should people want to know?

- The accuracy of the risk estimate (calibration)

- The disease risks of others (risk distribution)

- The risk change compared to prediction without the test result (e.g. risk difference and reclassification)

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Criteria for evaluation (short list)

0.   Genetic associations   → Janssens et al. *AJHG* 2008

1.   Clinical validity : (is it a worthy test?)

   - Calibration and validation

   - Risk distribution / discriminative accuracy

2.   Clinical utility : (is it worth testing?)

   - Benefits available (intervention or knowledge)

   - Change (clinical) decision → e.g risk difference and reclassification

3.   Cost-effectiveness, etc

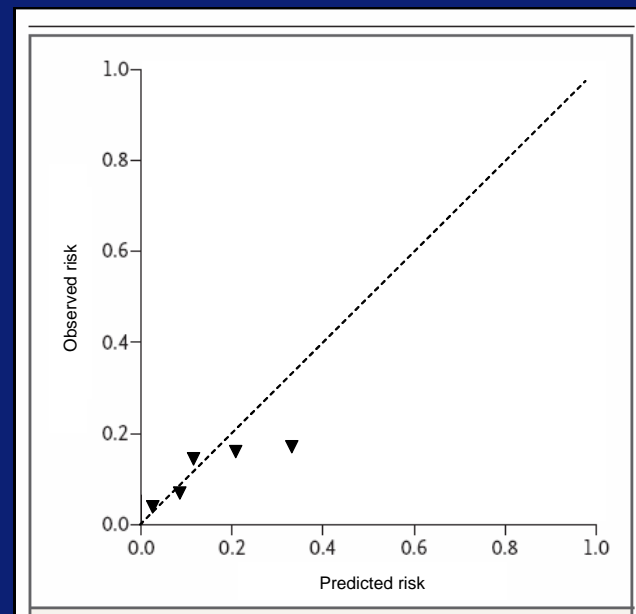4.   Feasibility, lab quality, counseling, etc.

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Calibration

Are the predicted risks correct?

- Calibration = agreement between predicted and observed risks
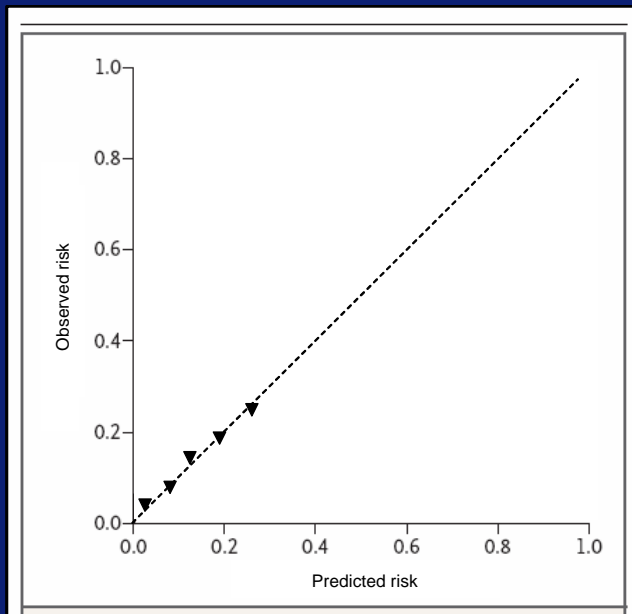
Well-calibrated

High risks overestimated

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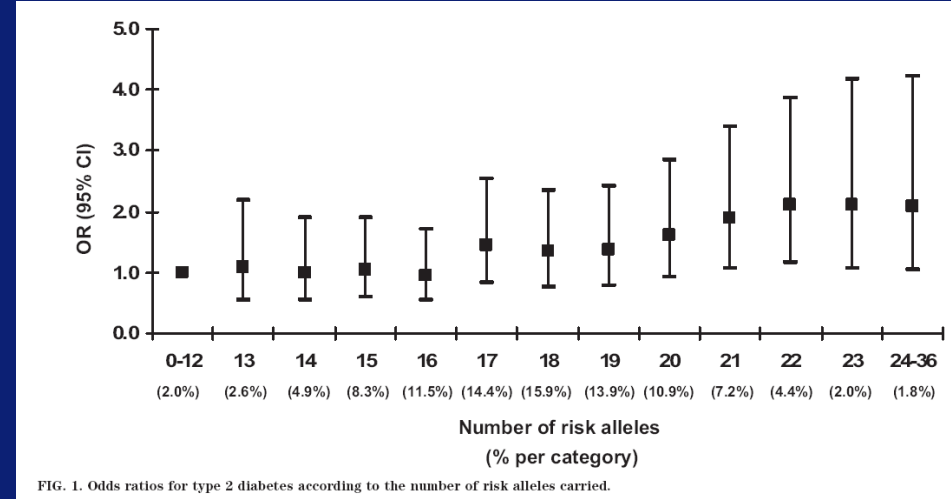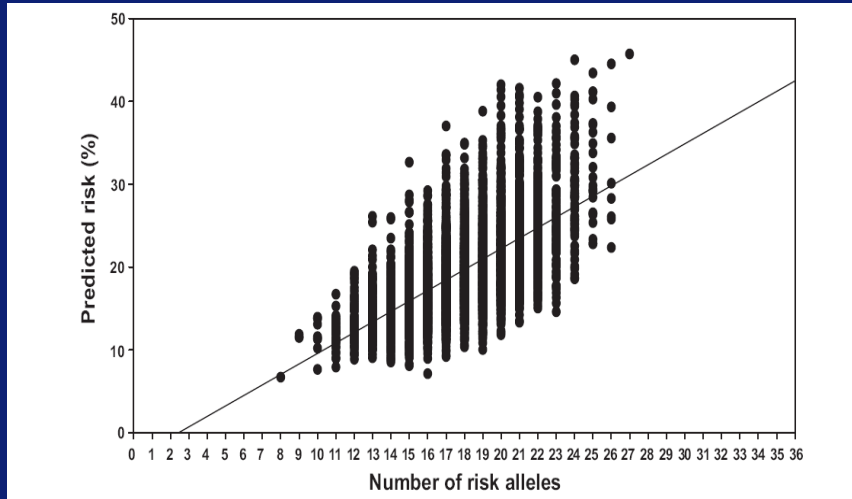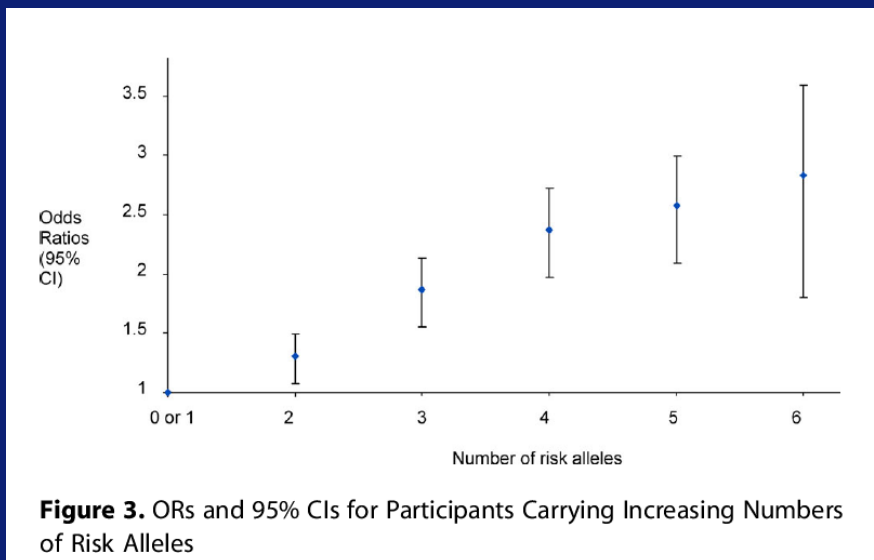
'Calibration' in recent empirical studies

FIG. 1. Odds ratios for type 2 diabetes according to the number of risk alleles carried.

Van Hoek et al. *Diabetes* 2008

Figure 3. ORs and 95% CIs for Participants Carrying Increasing Numbers of Risk Alleles

Weedon et al. *PLoS Med* 2005

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Calibration

Always important, but particularly when predictions are based on models:

- Is multiplicative model right assumption?

- Are effects independent?

- Do effect sizes (odds ratios) obtained from various studies apply to the population tested? (particularly when ORs are obtained from hyperselected case-control series, rather than prospective population-based studies)
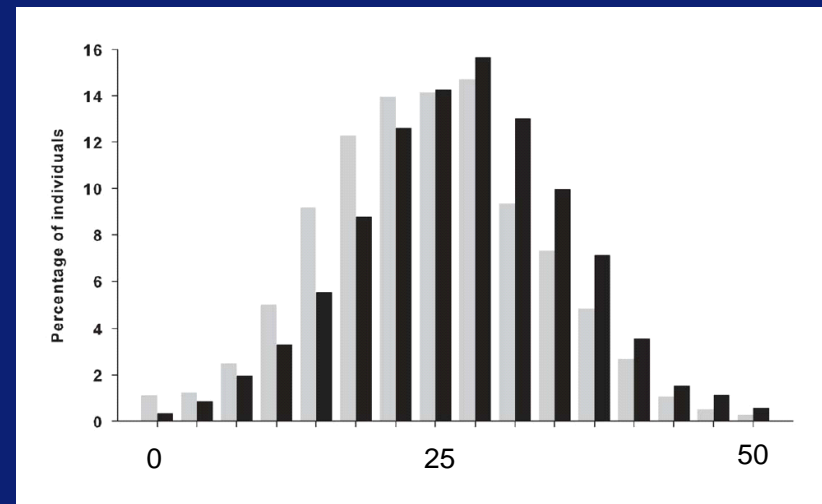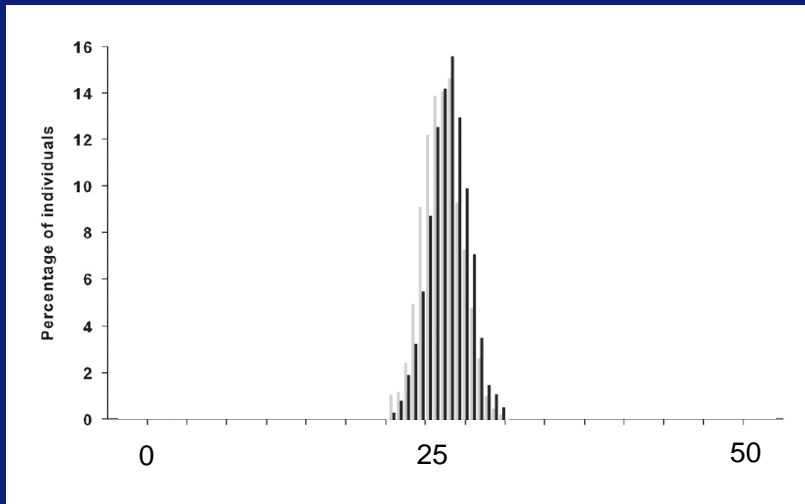
Validation

Investigating the predictive value in an independent dataset

Always important, but less when risk estimates are obtained from other studies (then calibration = validation)

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Risk distribution

- How useful is it to know one's risk of disease also depends on the risks of others

- If all predicted risks are around average, then the test is not useful

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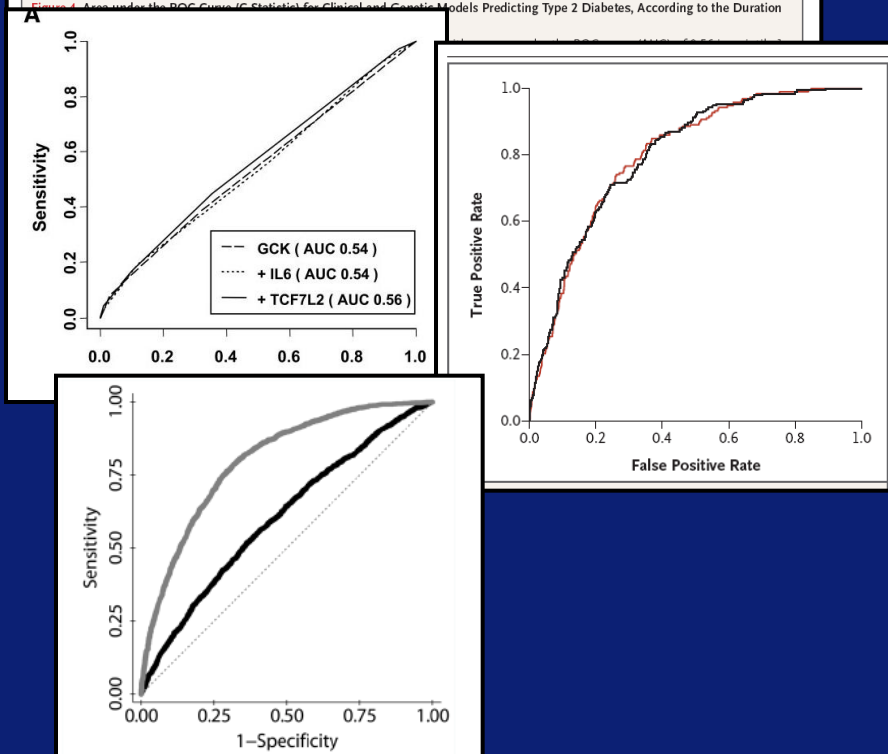
From risk distribution to discrimination

- If all predicted risks are around the average, than risk distributions for those who will develop the disease and for those who will not, largely overlap

- Overlapping distributions: limited/no discrimination

- Discriminative value (AUC) is good summary measure for risk distribution
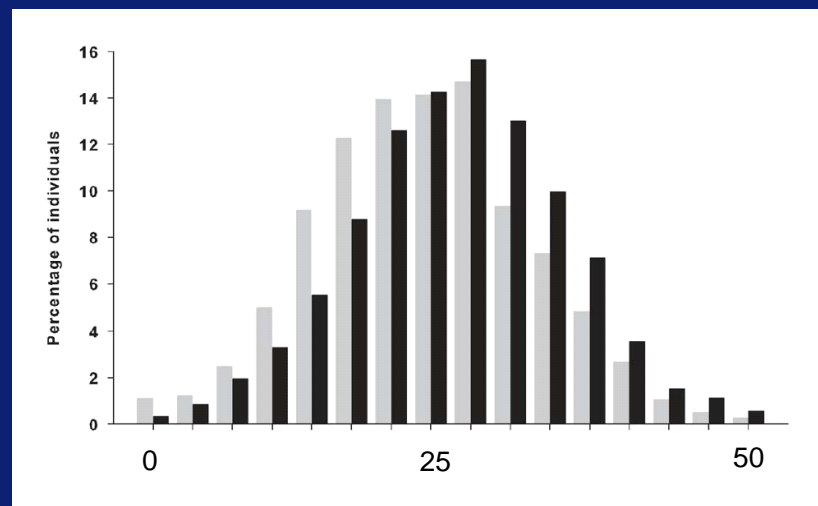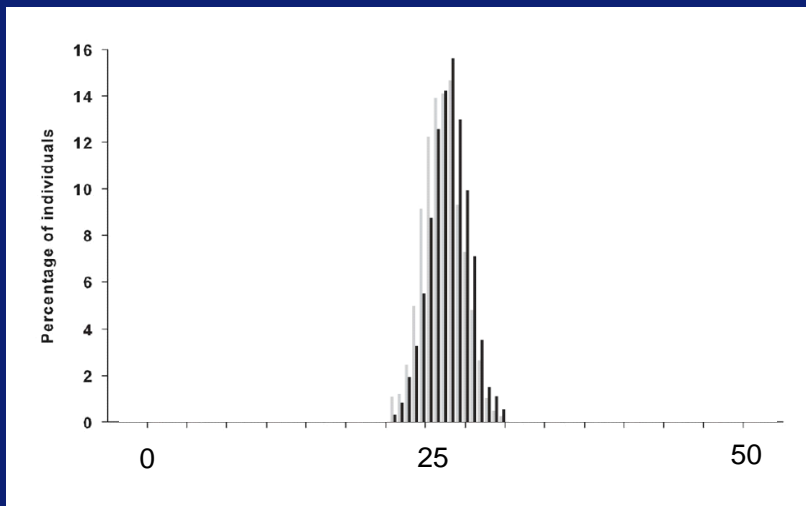
Discriminative accuracy: AUC
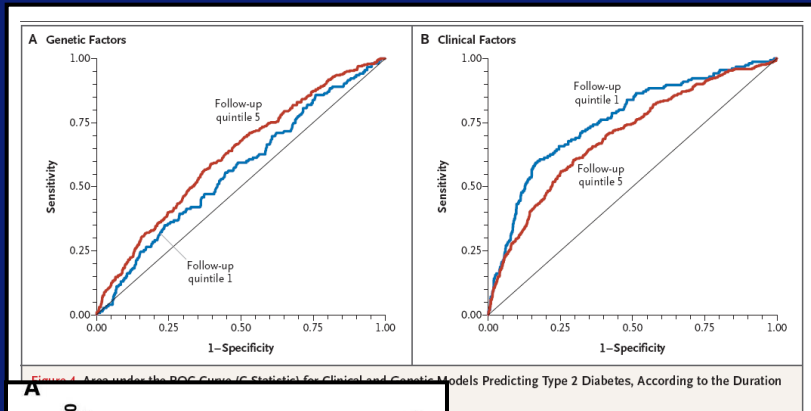
AUC = Plot of all sensitivity-specificity combinations for ALL possible cut-off values of the predicted risks

ROC curves of prediction models: typically have rounded shape

→ Higher AUC

= better discrimination

= better prediction

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Reclassification

In clinical practice: risk distributions often transformed in categories to make clinical decisions (e.g. treat / don't treat)

Reclassification = percentage of individuals that change between risk categories when prediction models are updated

E.g. comparing:

1. Model based on traditional risk factors versus

   traditional risk factors + genetic variants

2. Model based on genetic variants versus model on more variants

Rationale: if people do not change between categories, updating of prediction model is not useful

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TABLE 3. Comparison of Observed and Predicted Risks Among Women in the Women's Health Study*

Model Without HDL 10-Year Risk (%)	Model With HDL 10-Year Risk (%)				% Reclassified
	0 to <5%	5 to <10%	10 to <20%	20%+	
0% to <5%					
Total, n	22655	696	6	0	...
%†	97.0	3.0	0.0	0.0	3.0
Observed 10-year risk (%)‡	1.5	5.9	0.0	...	...
5% to <10%					
Total, n	593	1712	291	0	...
%	22.8	66.0	11.2	0.0	34.0
Observed 10-year risk (%)	3.7	7.6	14.7	...	...
10% to <20%					
Total, n	3	214	512	76	...
%	0.4	26.6	63.6	9.4	36.4
Observed 10-year risk (%)	0.0	7.5	10.7	23.3	...
20%+					
Total, n	0	0	41	102	...
%	0.0	0.0	28.7	71.3	28.7
Observed 10-year risk (%)	...	...	15.8	32.5	...

*This comparison uses models that include Framingham risk factors with and without HDL. All estimated and

Cook. *Circulation* 2007

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Reclassification

Critical note:

reclassification is often used to compensate for the disappointing results from AUC analyses. Yet:

AUC ↑   Reclassification ↑   : prediction better

AUC -   Reclassification ↑   : different errors

can easily be explained by less than perfect calibration

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Risk updating and reclassification

Example: prediction of type 2 diabetes based on 18 polymorphisms in Rotterdam study

Model 1: TCF7L2

Model 2: 18 polymorphisms

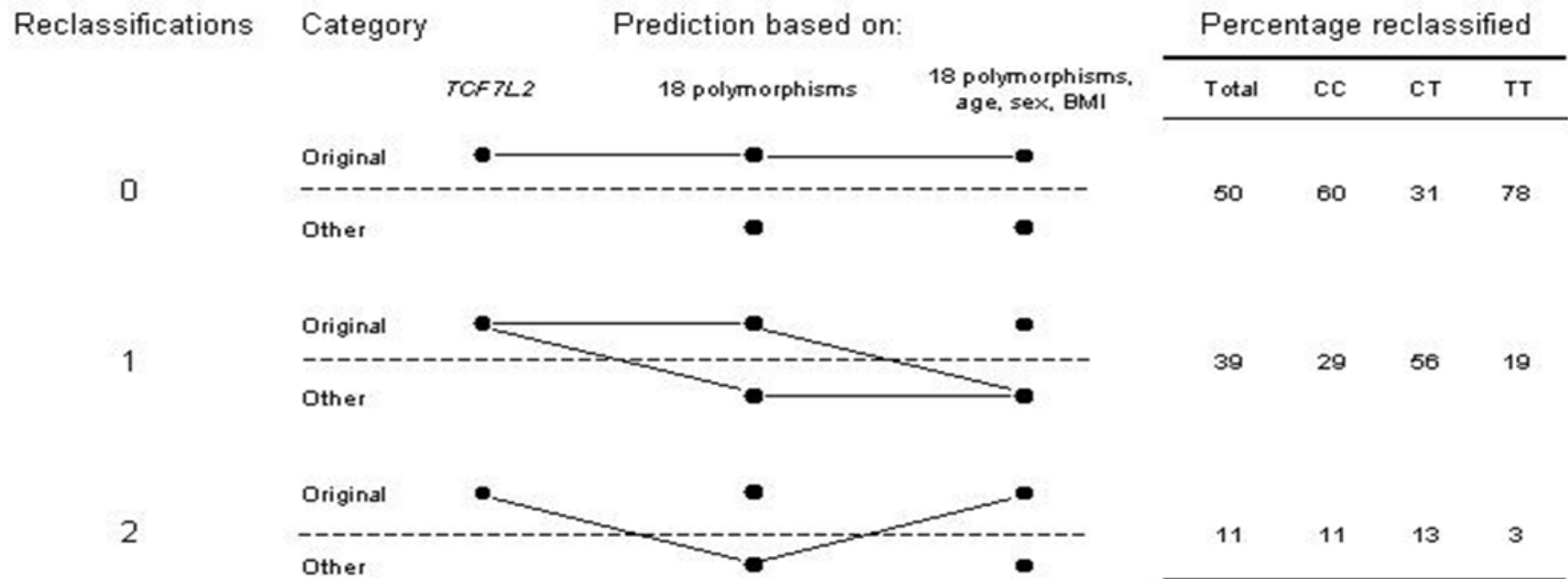Model 3: + age, sex and body mass index

	Model 1	Model 2	Model 3
AUC	0.55	0.60	0.66
Reclassification	32%*	28%	

* 50% if reclassification was evaluated after every single polymorphism

Mihaescu et al. *Submitted*

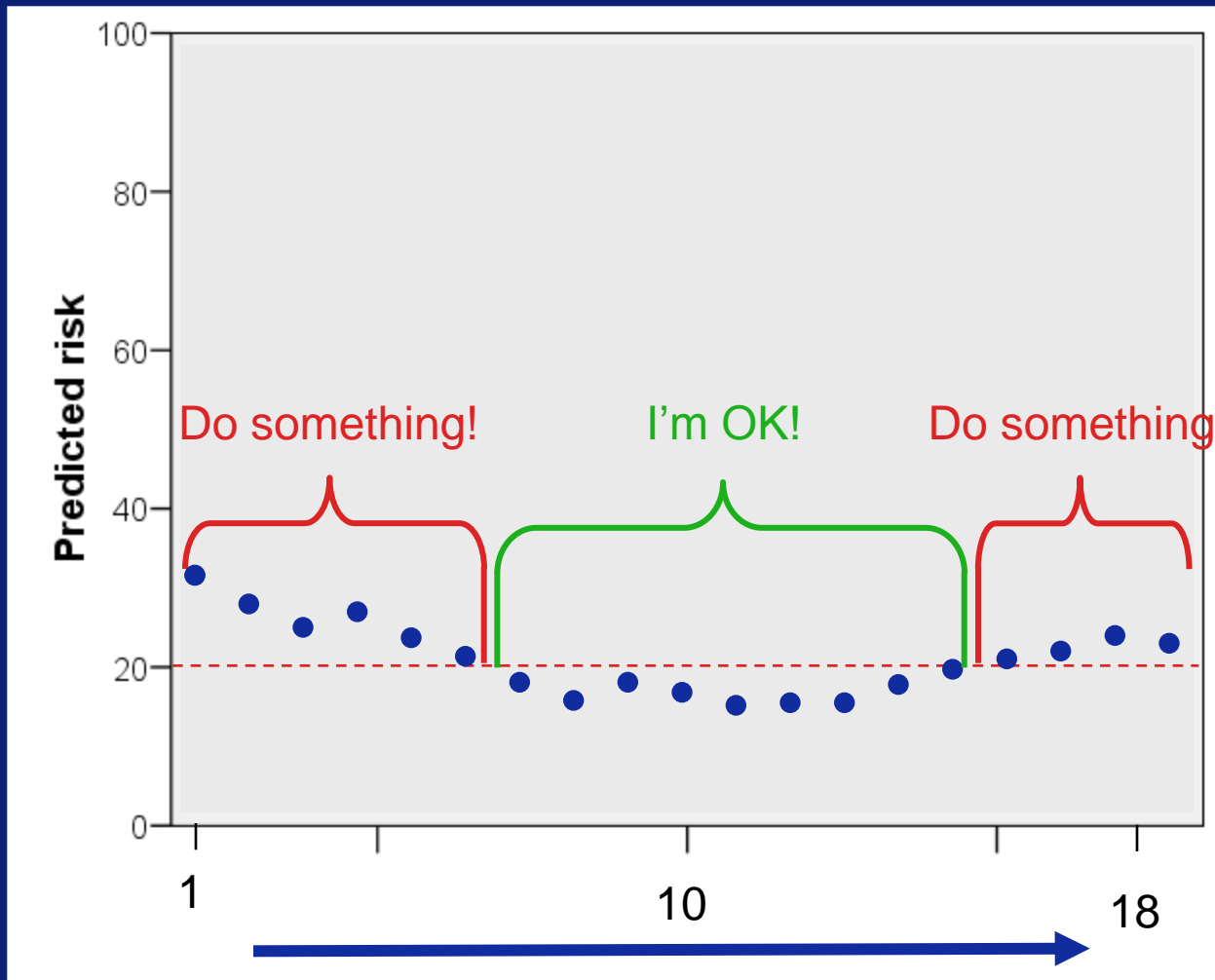Figure 3. Patterns of reclassification that result from updating risk predictions

Mihaescu et al. *Submitted*

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Risk updating and reclassification

How useful is it to learn about every risk update?

Conclusion

Top 3 assessments

      1. Calibration

      2. Discrimination (risk distribution)

      3. Reclassification

New challenge:

- Assessing the impact of updating risk predictions

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