Manuscript published in CPT:PSP

Immunogenicity Publication Bias and Its Consequences for Predictive Models

A Call for Transparent Reporting

Sophie Tascedda[3,4], Hans Peter Grimm[1], Zicheng Hu[2], Linnea C. Frannsen[1]

[1] **Roche Pharma Research & Early Development (pRED)**, Pharmaceutical Sciences, Roche Innovation Center Basel

[2] **Genentech Research & Early Development (gRED),** Department of Translational PKPD, Genentech Inc, South San Francisco, California, USA

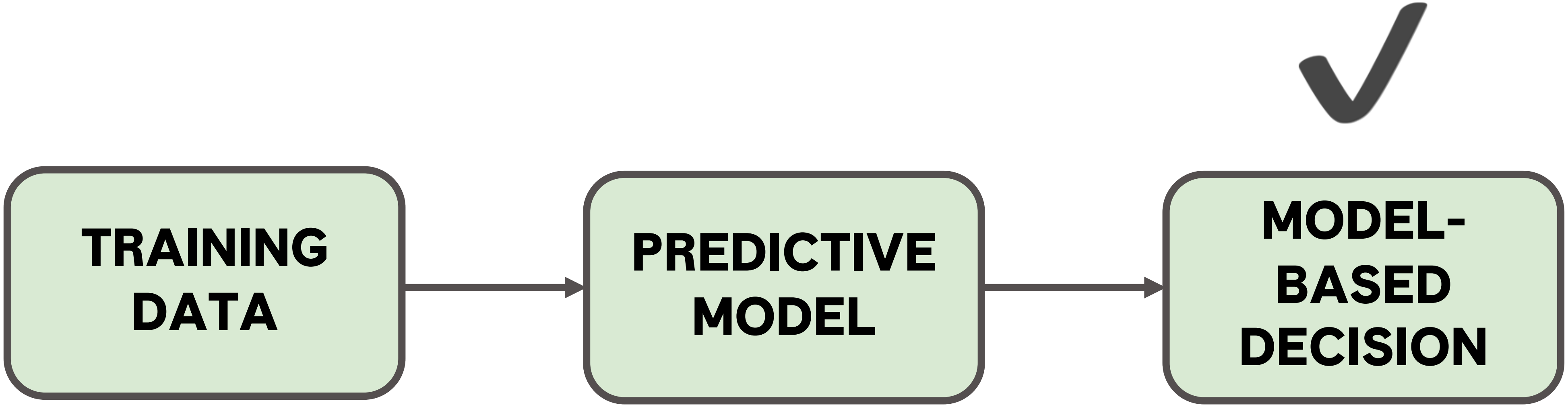
[3] **Research Center for Clinical Neuroimmunology and Neuroscience Basel (RC2NB),** University Hospital Basel and University of Basel, Basel, Switzerland

[4] **Department of Biomedical Engineering,** Faculty of Medicine, University Hospital Basel and University of Basel, Basel, Switzerland

EIP, 18 March 2026

Predictive models have potential to derisk immunogenicity early

But do we give them the chance to reflect the reality of early-phase development?



Guides:

- Candidate selection and ranking
- Protein engineering
- Trial design ...

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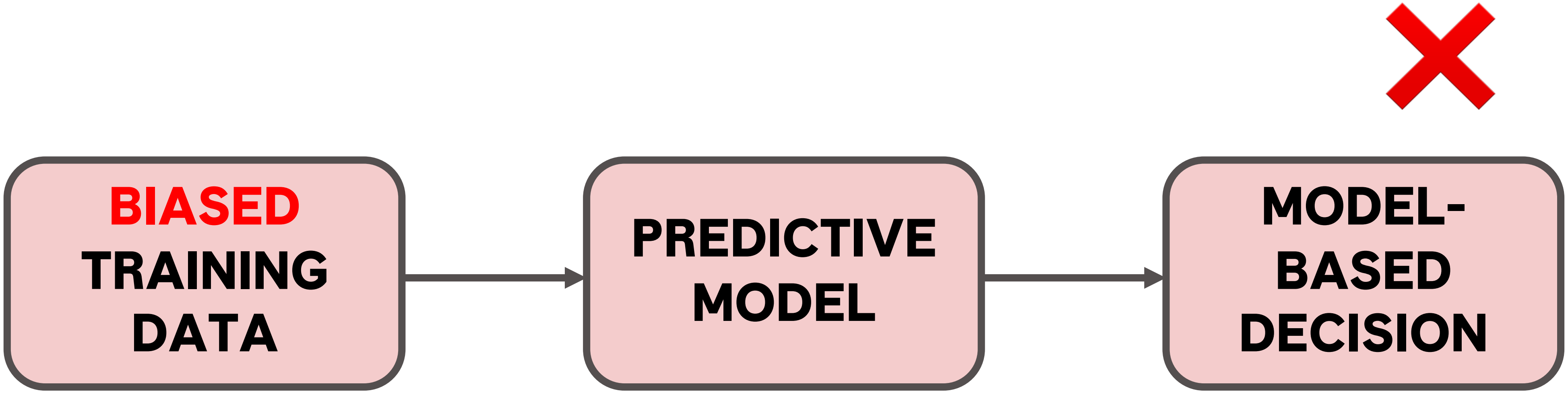

Misguides:

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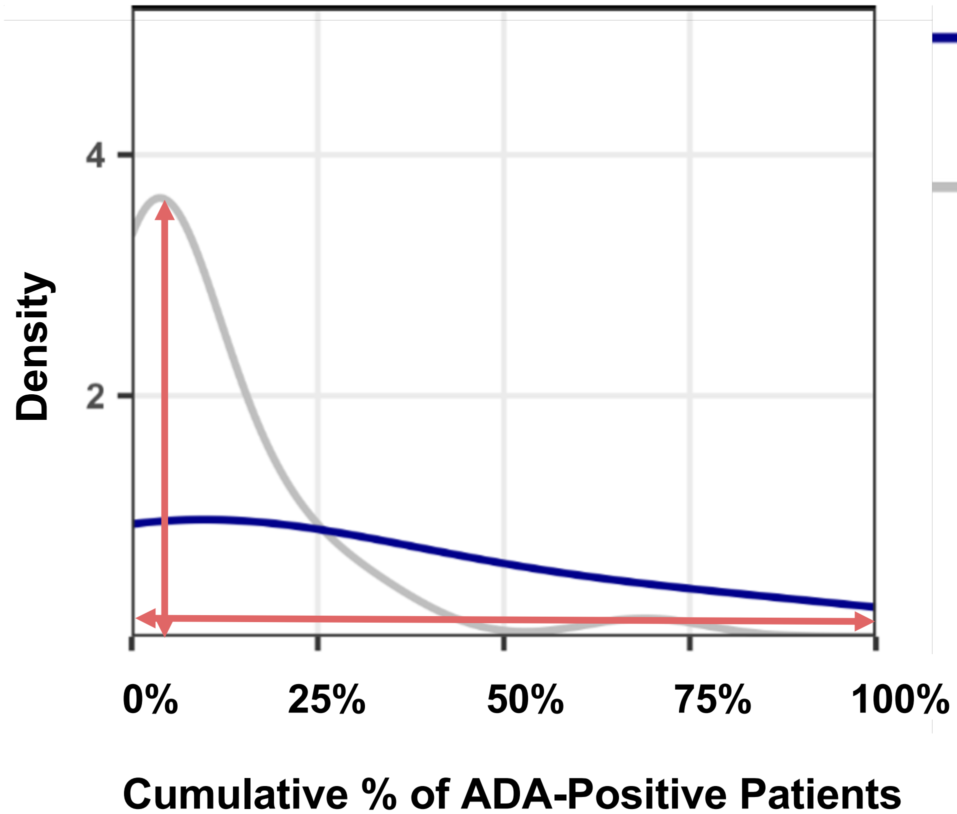
Published Anti-Drug Antibody (ADA) Data vs. Phase I Reality

A clear mismatch in the ADA risk profile - and yet, we want to use models for early-phase prediction



Phase I Roche monoclonal antibody (mAb) studies completed 2014-2024

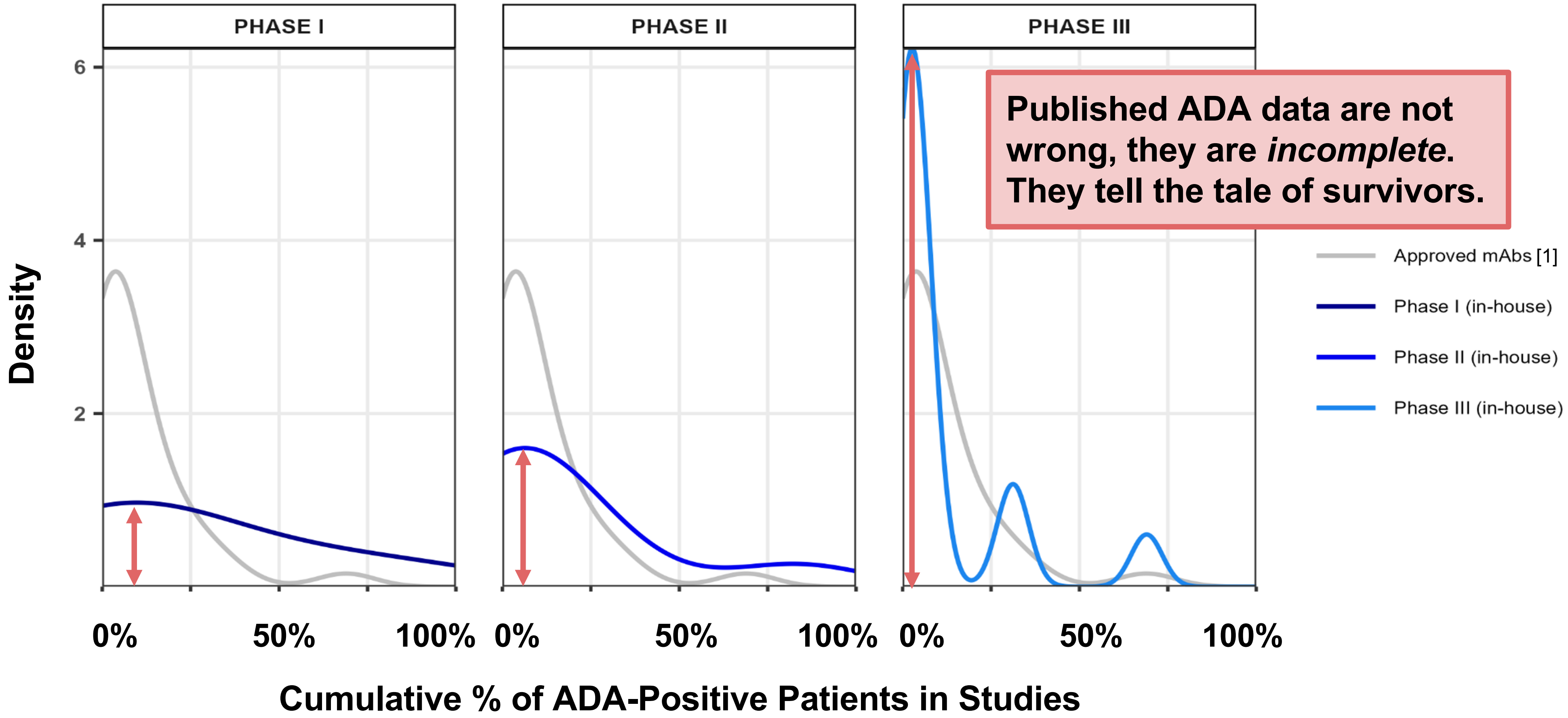
65 mAbs approved 1997–2020 by the FDA [1]

Typical published ADA rates do not represent <u>early</u> clinical ADA rates

[1] Vaisman-Mentesh *et al. Front Immunol.* 2020;11:1951.

Explaining the Gap: "Survival of the Fittest"

Attrition of high ADA risk compounds & lack of publishing of their ADA data drives publication bias



Simulate ADA Time-Course

Empirical ADA Incidence Time Course Model, Closed Solution to 2 State Markov Model

$$y = y_{\max} - (y_{\max} - b) \cdot exp\left(-\frac{k_{\mathrm{np}}}{y_{\max}} \cdot (t - t_{\mathrm{lag}})\right)$$

Structural Time-Course Parameters:

t_{lag} = onset time
k_{np} = transition rate
b = baseline positivity

Learned from NHP data

Peak ADA Incidence:

y_{max} = maximum cumulative ADA incidence

Calibrated on the 2 in-Human datasets

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10000 simulations

Each represents a compound

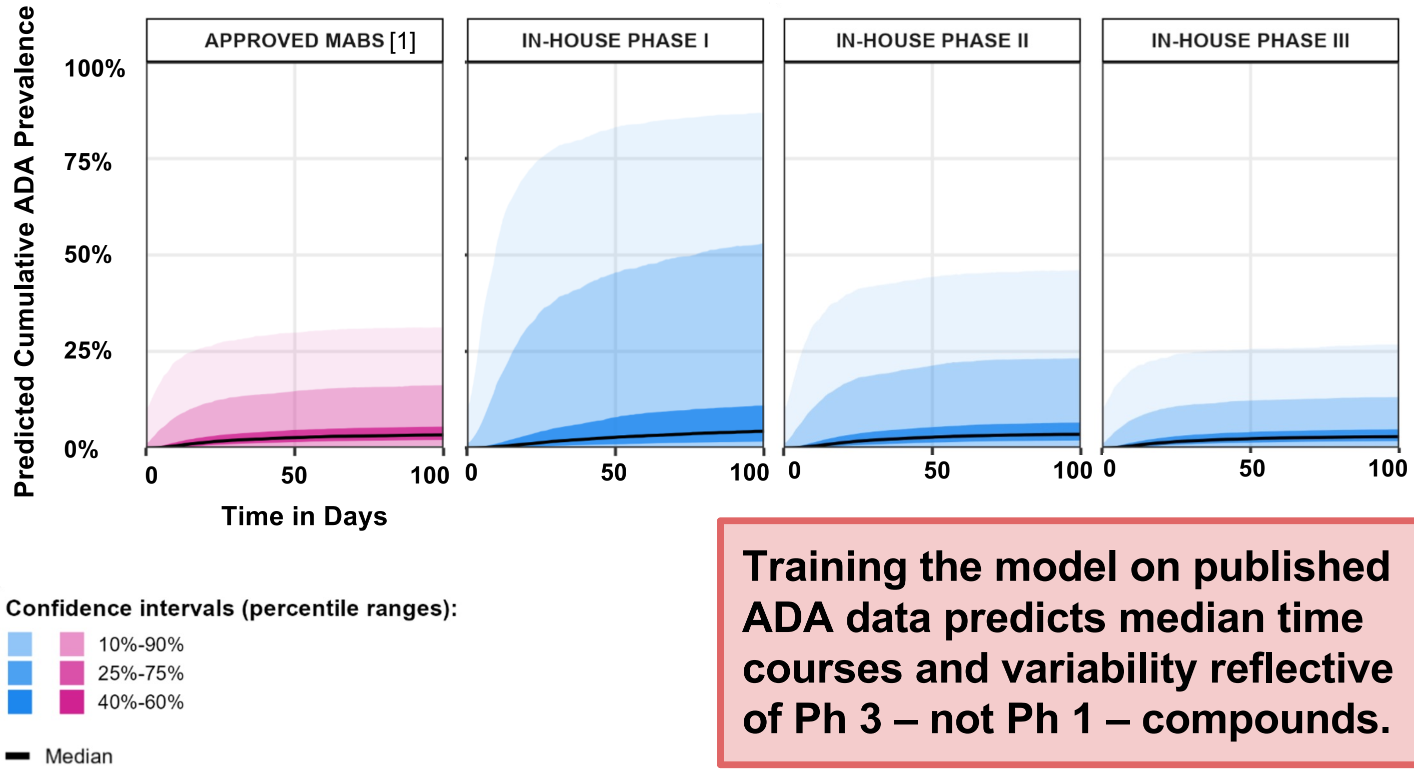
Compare predicted IG dynamics

Biased ADA Data Produce Biased Immunogenicity Predictions

We underpredict early-phase ADA risk if we rely on typical published ADA resources

Our Empirical Model

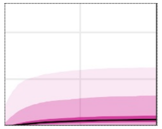
…predicts



Training the model on published ADA data predicts median time courses and variability reflective of Ph 3 – not Ph 1 – compounds.

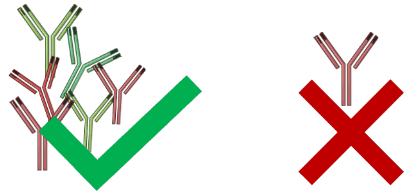
A Simple Thought Experiment:

Imagine early research decisions are informed by predicted ADA incidence.

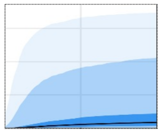


Model trained on public ADA data

- Only Low ADA incidence
- Narrow range

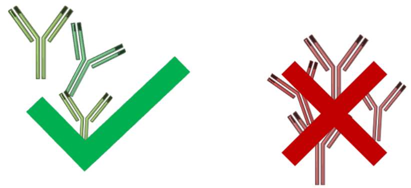


HIGH-RISK COMPOUNDS NOT FLAGGED EARLY



Model trained on representative development data

- Higher ADA incidence
- Realistic Uncertainty



HIGH IMMUNOGENICITY RISK BECOMES VISIBLE EARLIER

! Not as standalone decision rule

Combined with PK, assay, and safety data

Call to Action

Two commitments to improve predictive immunogenicity models

Critically Evaluate Model Training Data

Are the training data representative of the model's context of use?

Demand transparency on data sources and limitations.

Remember: public datasets mainly reflect surviving compounds

Share IG Data, Including Early Phase

Include: Publish data from *terminated programs*.

Beyond Incidence, include:

- detailed **assay data** (cut-points, validation),
- **ADA impact** on PK and safety
- Relevant **covariates**

Support cross-industry data sharing (e.g. ABIRISK [2]).

Acknowledgements

Roche Pharma Research & Early Development (pRED)

Pharmaceutical Sciences

Timothy Hickling
Nicolas Frances
Stephen Fowlers
Jerome Egli

Data & Analytics

Dragomir Dragonov
Guido Steiner

Citations

[1] Vaisman-Mentesh A, Gutierrez-Gonzalez M, DeKosky BJ, Wine Y. *The molecular mechanisms that underlie the immune biology of anti-drug antibody formation following treatment with monoclonal antibodies*. Front Immunol. 2020;11:1951.

[2] Hassler S, Bachelet D, Duhaze J, et al. *Clinicogenomic factors of biotherapy immunogenicity in autoimmune disease: A prospective multicohort study of the ABIRISK consortium.* PLoS Med. 2020;17(10):e1003348.

Doing now what patients need next