



PENETRANCE AND PLEIOTROPY OF SCHIZOPHRENIA PRS IN 90,000 PATIENTS

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Massachusetts General Hospital*



DISCLOSURES

- ▶ Nothing to disclose.

PREDICTING SCHIZOPHRENIA

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Public Health Burden

- Second most costly disease in the U.S.
- Massive increase in mortality

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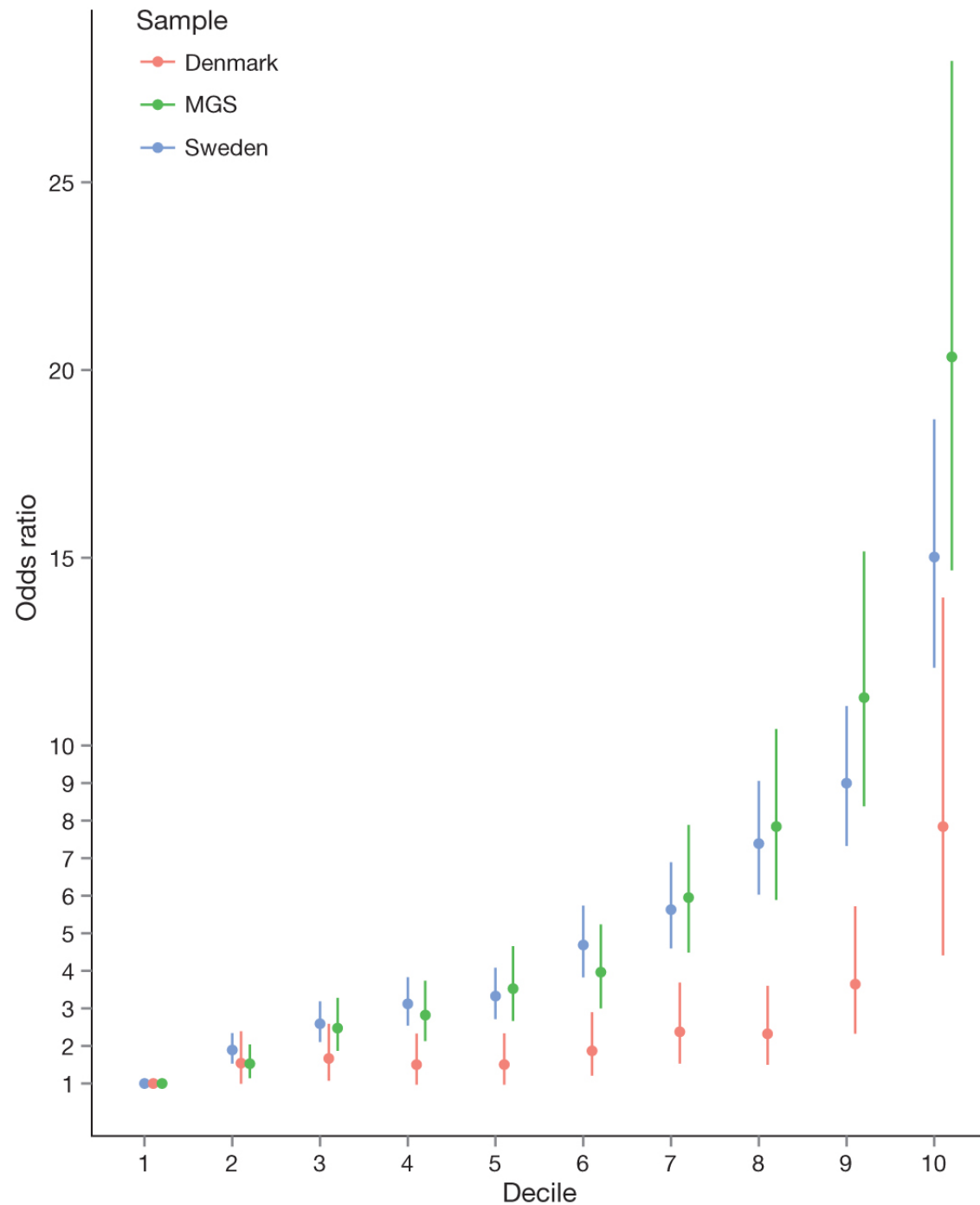
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Poor Risk Detection

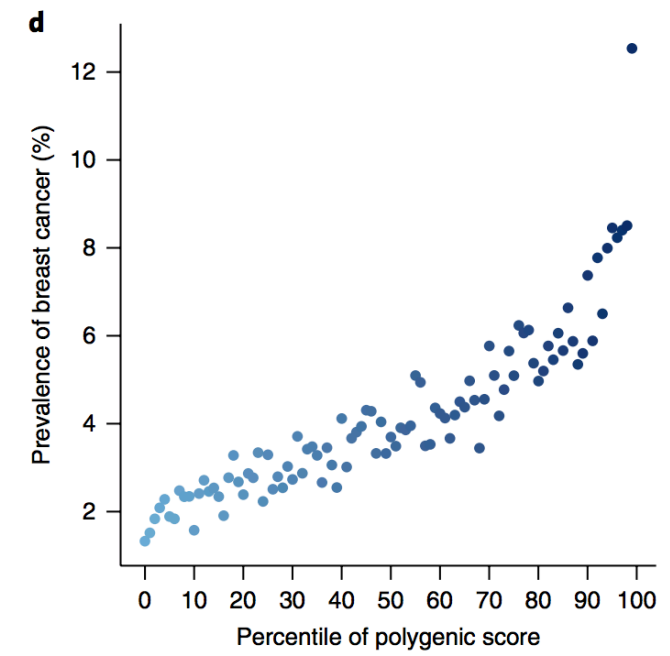
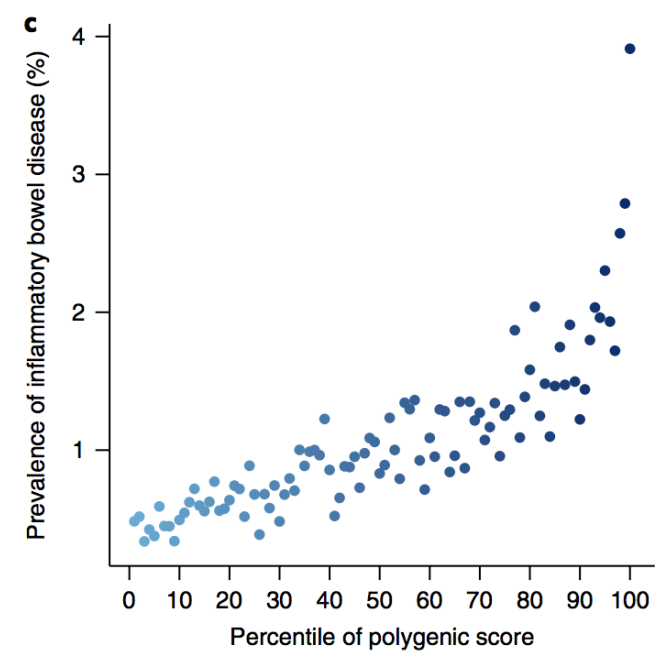
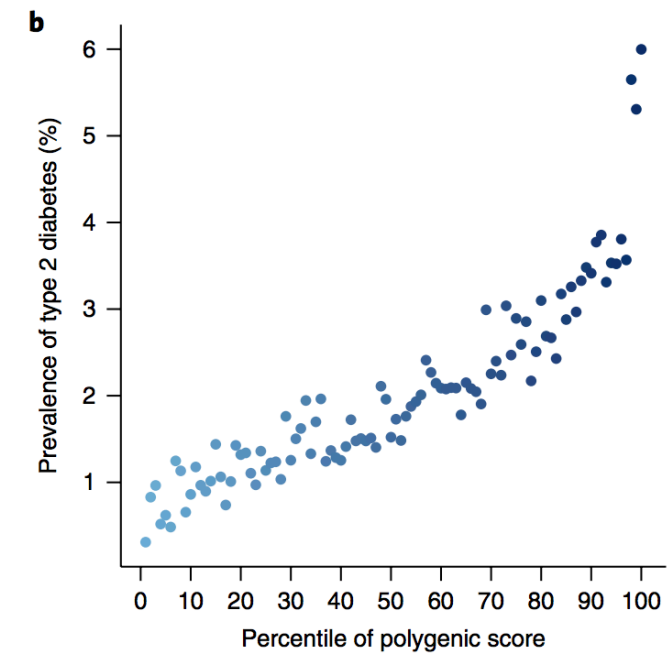
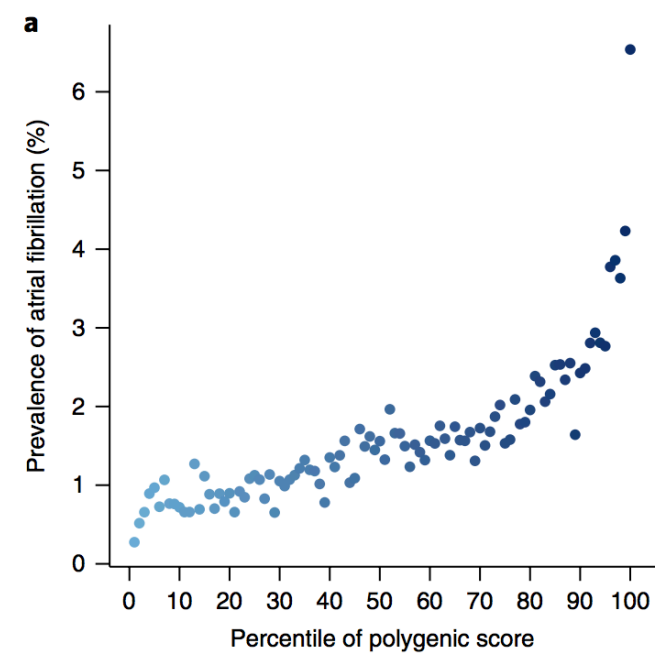
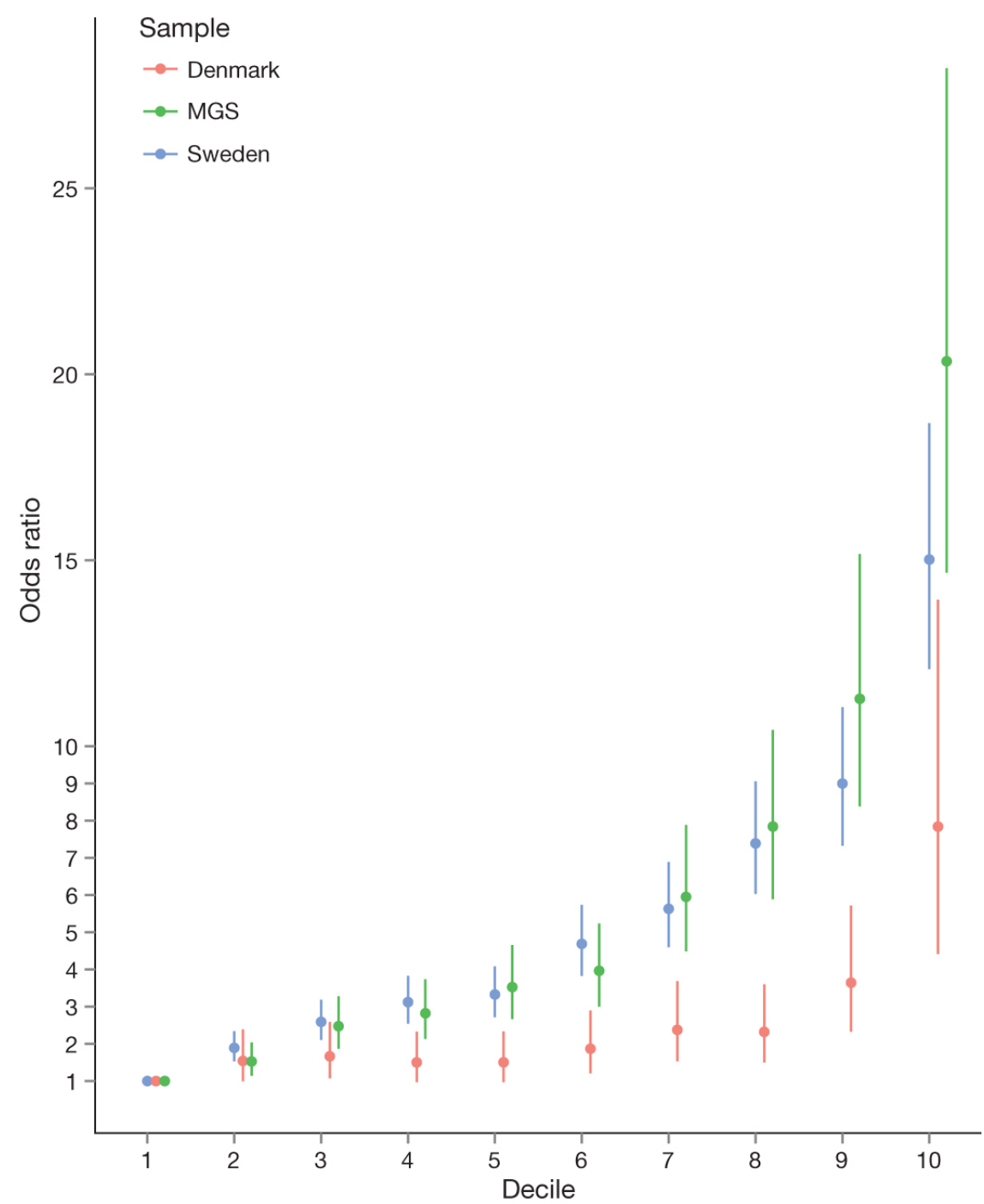
- Most patients already in mental health treatment who later develop psychosis are not detected

GENETIC RISK STRATIFICATION

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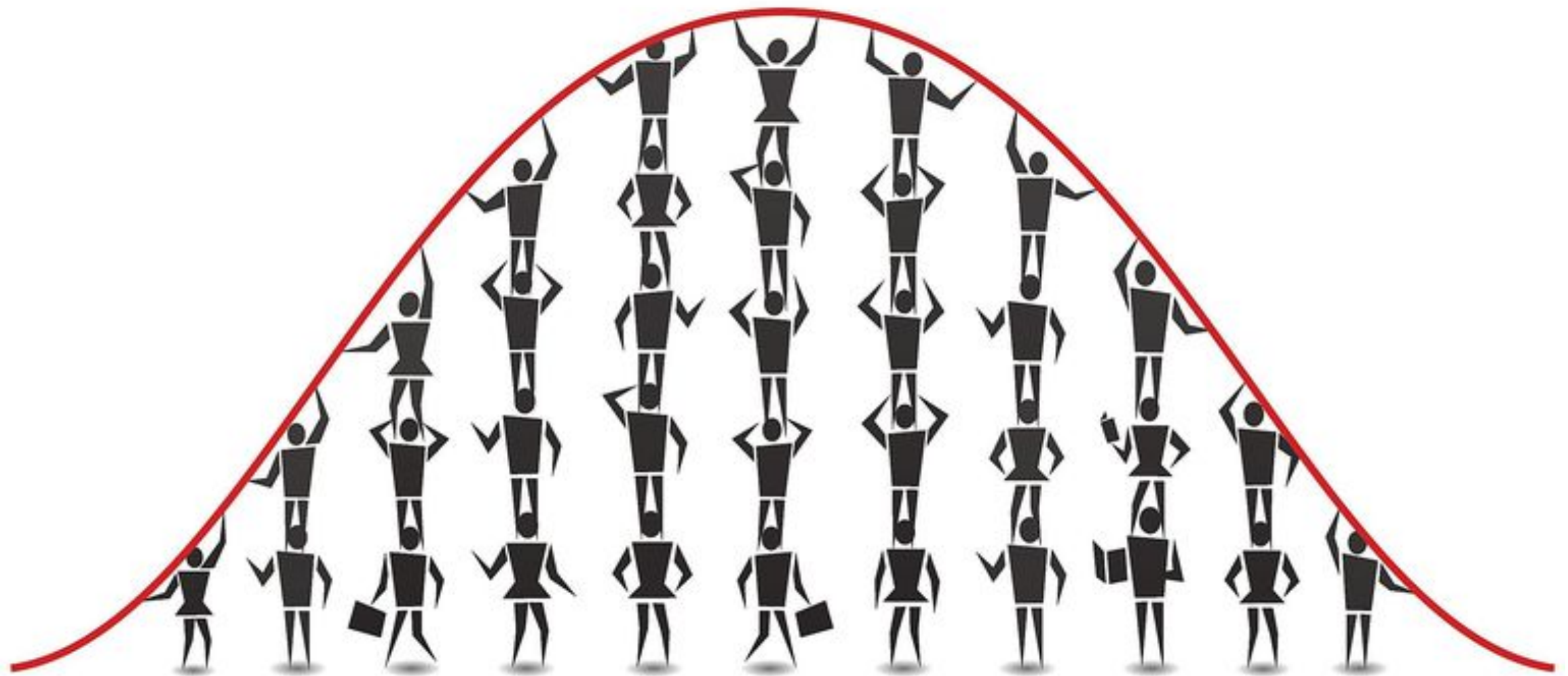


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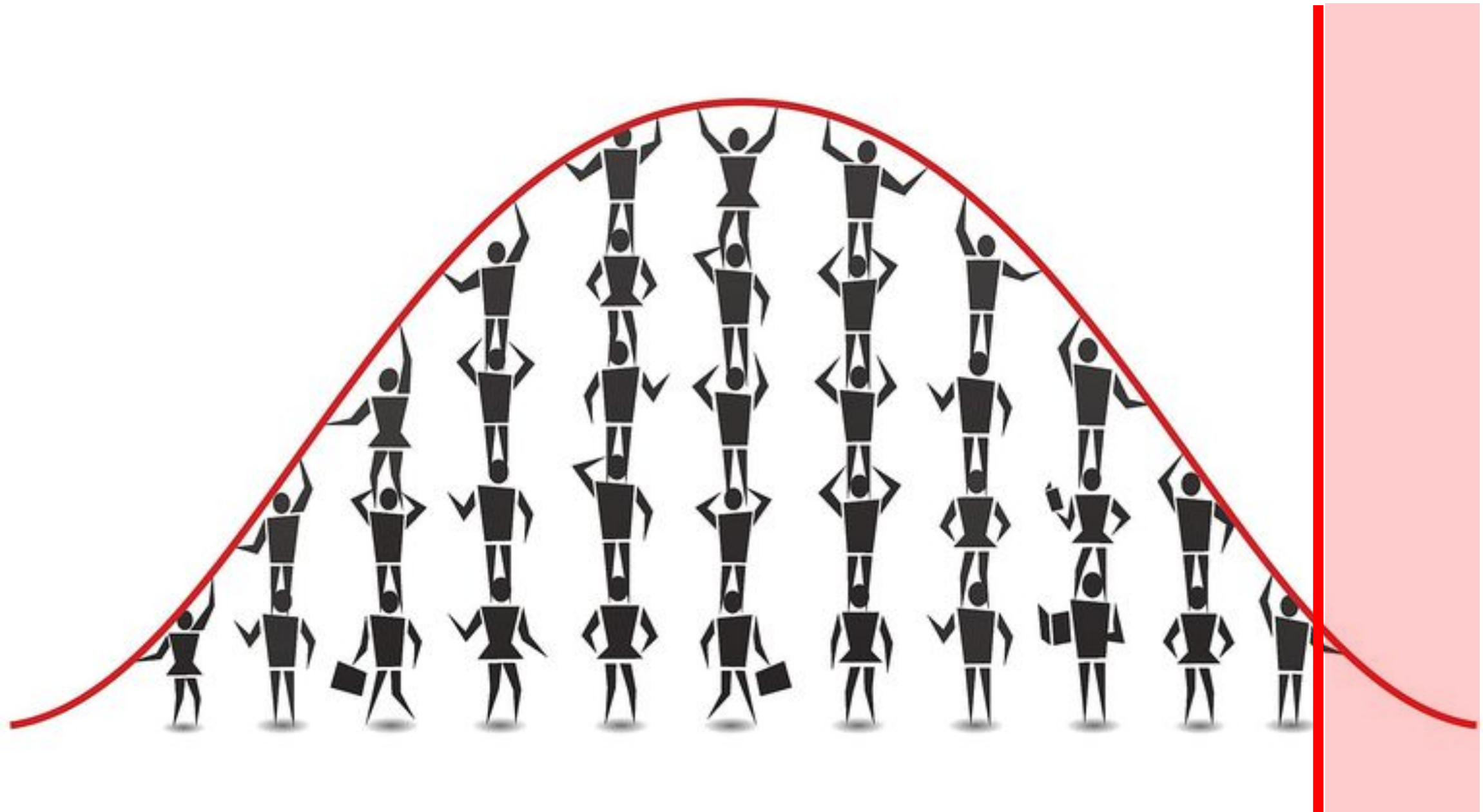


CLINICAL TRANSLATION

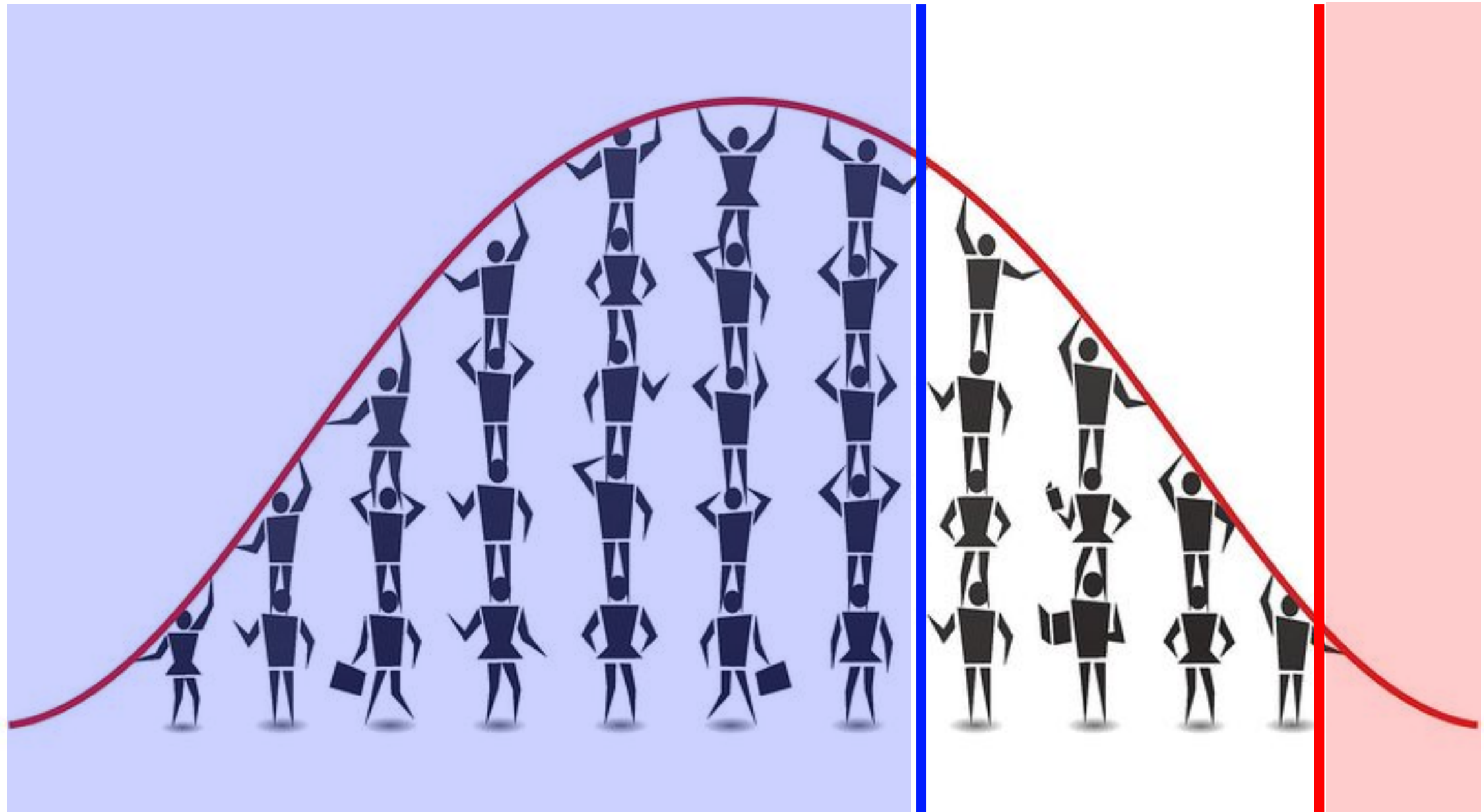
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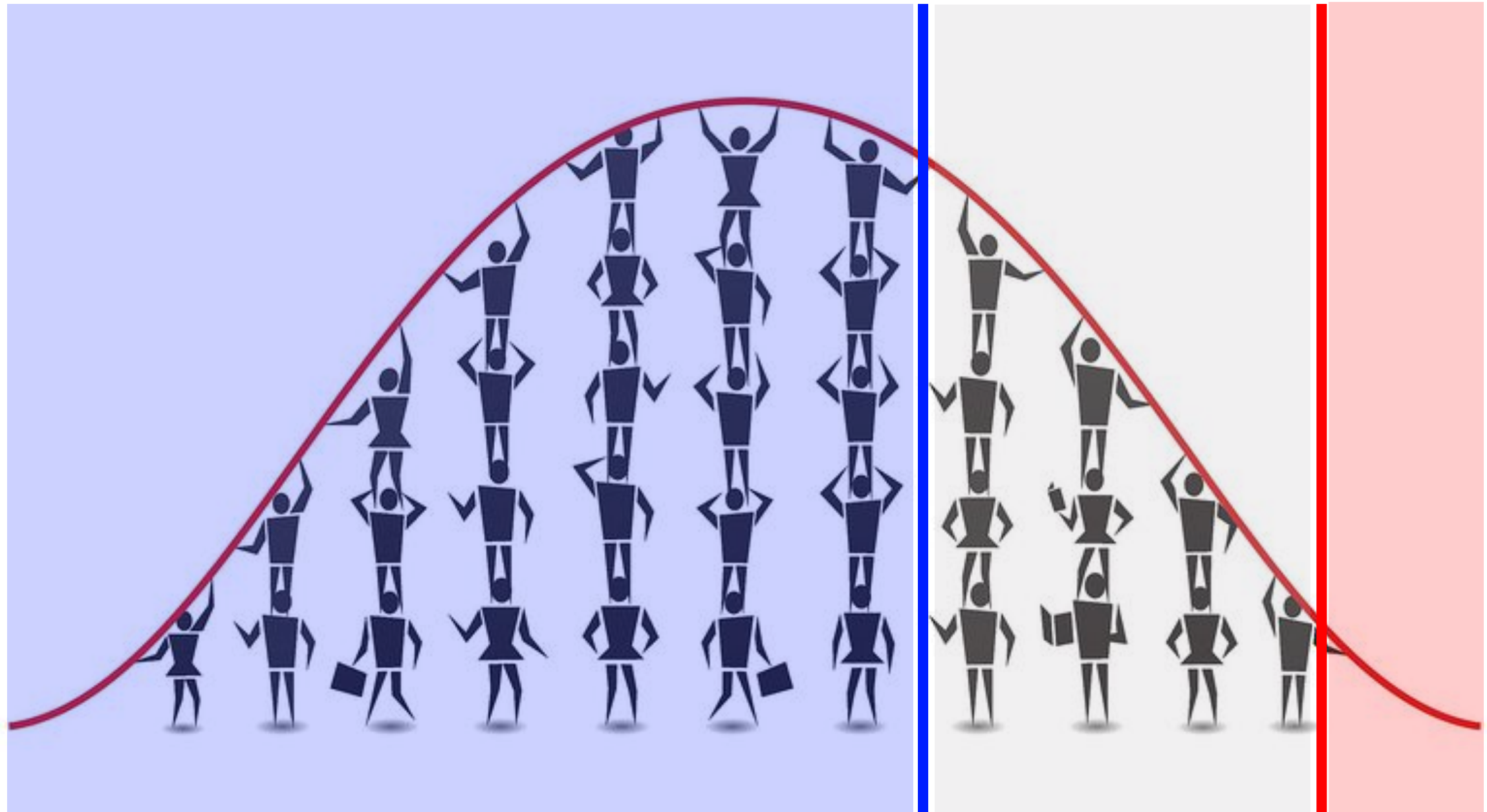
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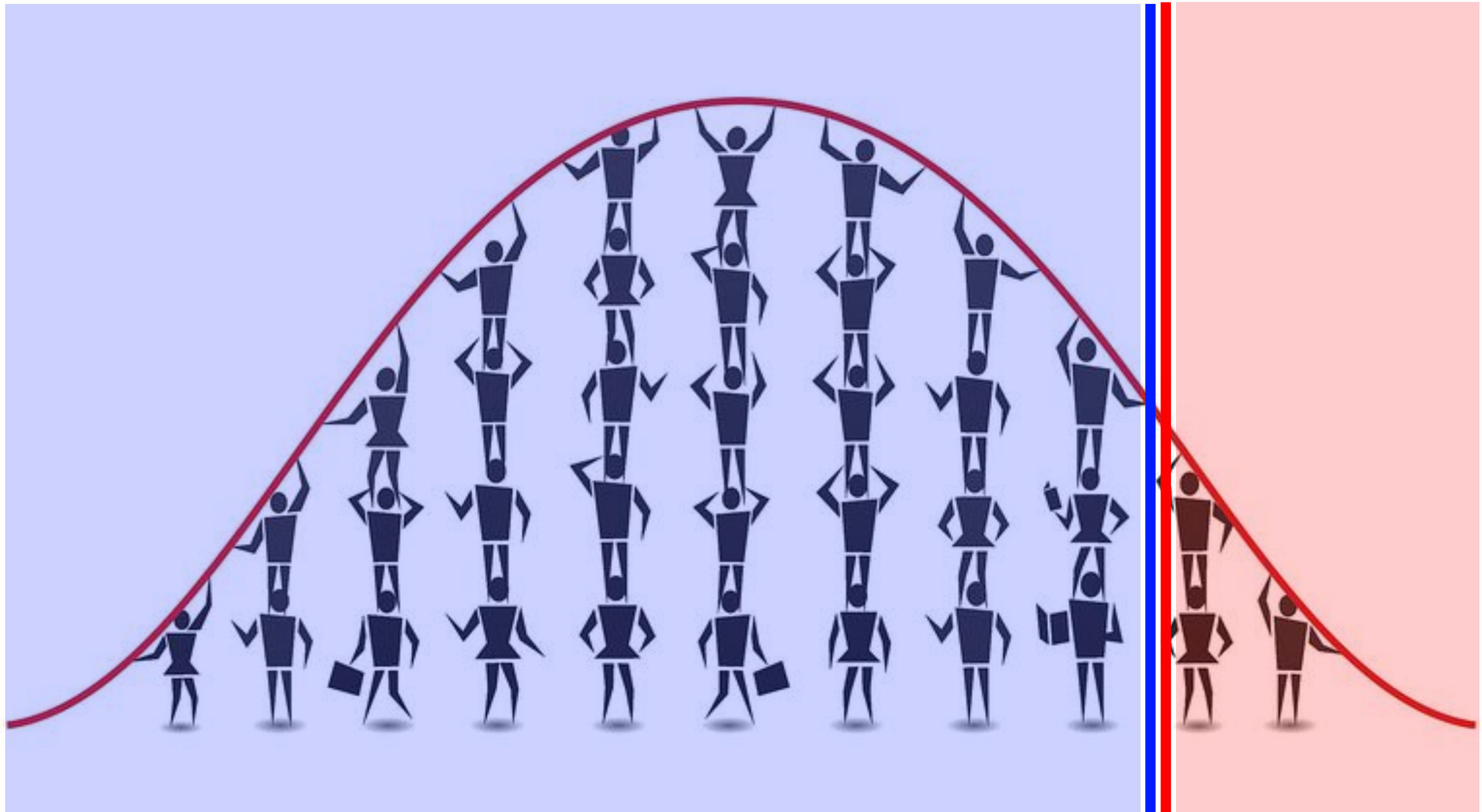
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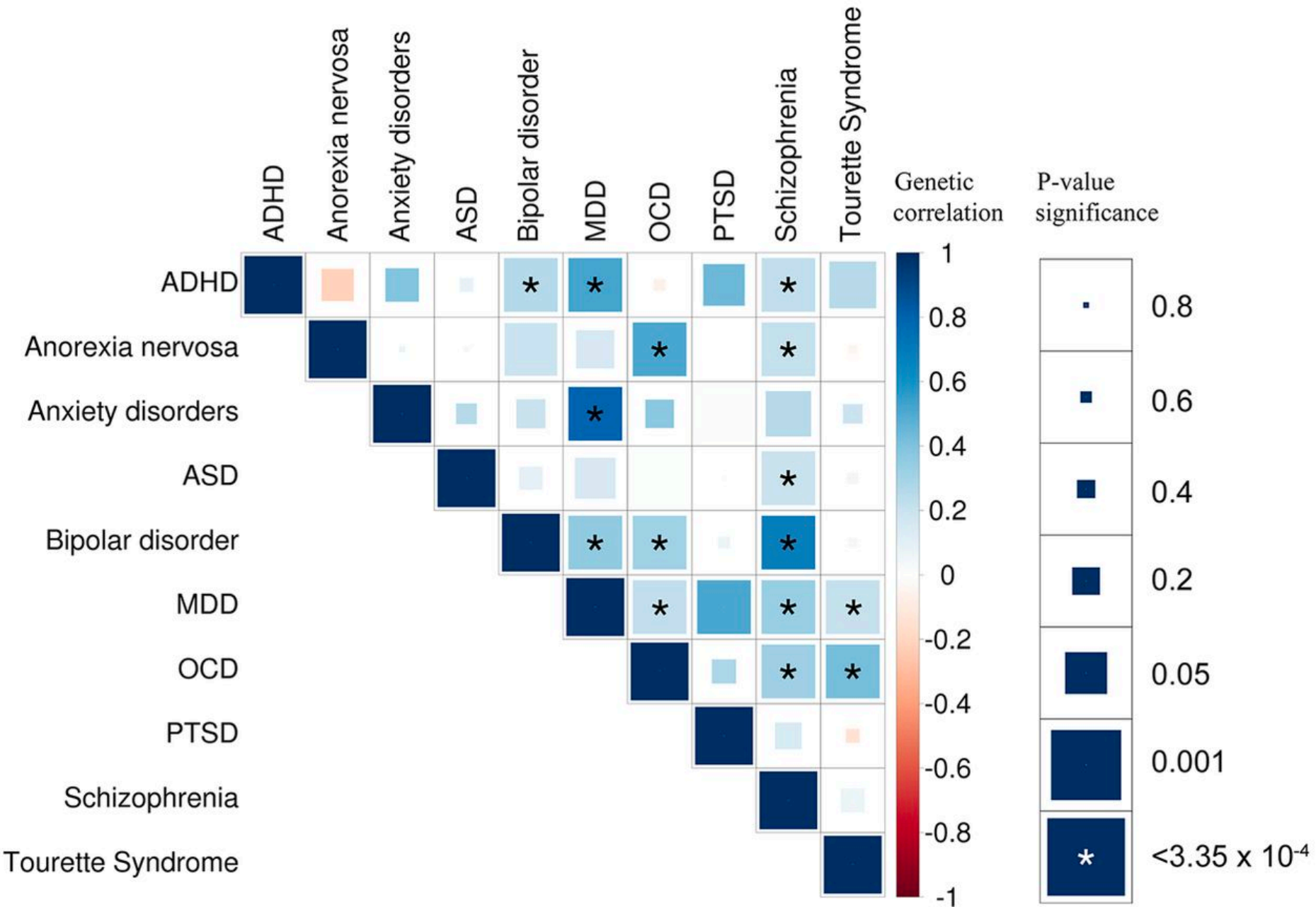


AIMS

- ▶ Establish penetrance of schizophrenia PRS in real-world clinical setting

CONSEQUENCES OF INCREASED RISK?

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- ▶ Identify pleiotropic effects of genetic risk for schizophrenia

CLINICAL VALIDATION



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Geisinger
Health Plan



CLINICAL VALIDATION



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Health Plan



CLINICAL VALIDATION



91,980 PATIENTS

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91,980 PATIENTS

11,289,707 ICD-9 CODES



CLINICAL VALIDATION



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MEDIAN EHR LENGTH: 9-13 YEARS



CLINICAL VALIDATION



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MEDIAN EHR LENGTH: 9-13 YEARS

MEDIAN # OF VISITS: 50-110



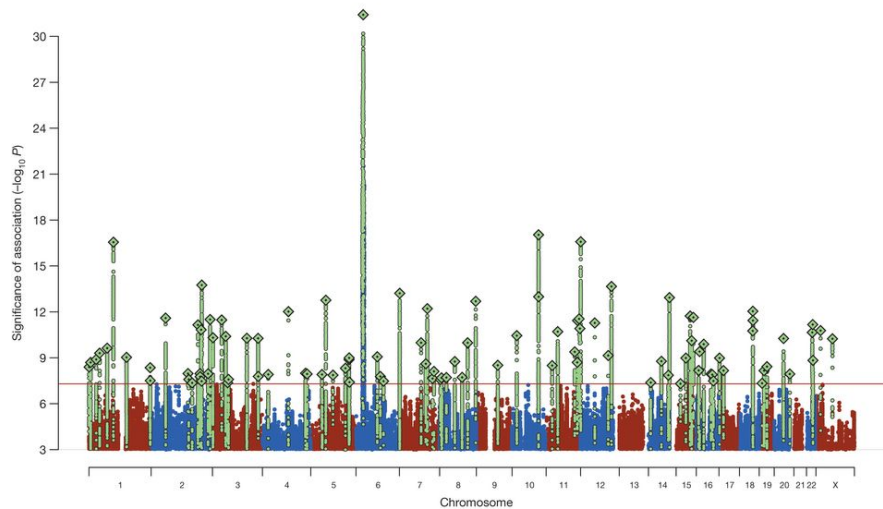
GENOTYPES & PHENOTYPES

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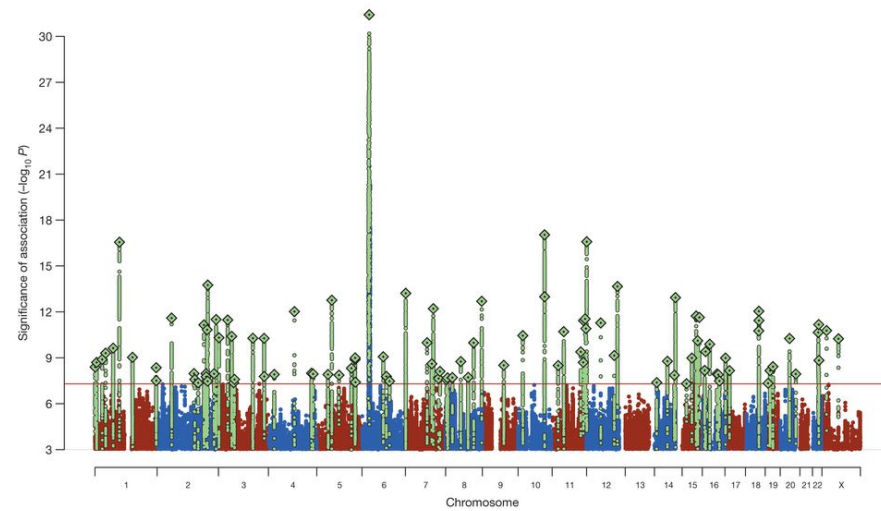
GENOTYPES

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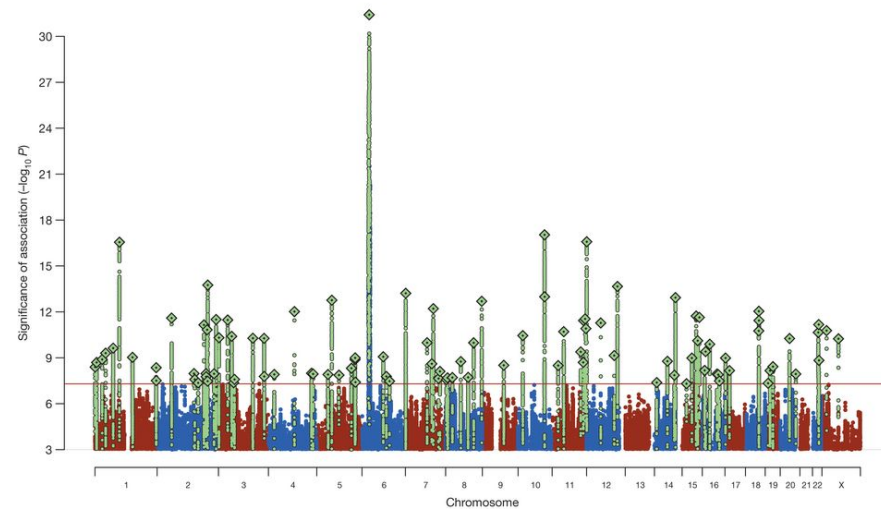


Low risk

High risk

GENOTYPES

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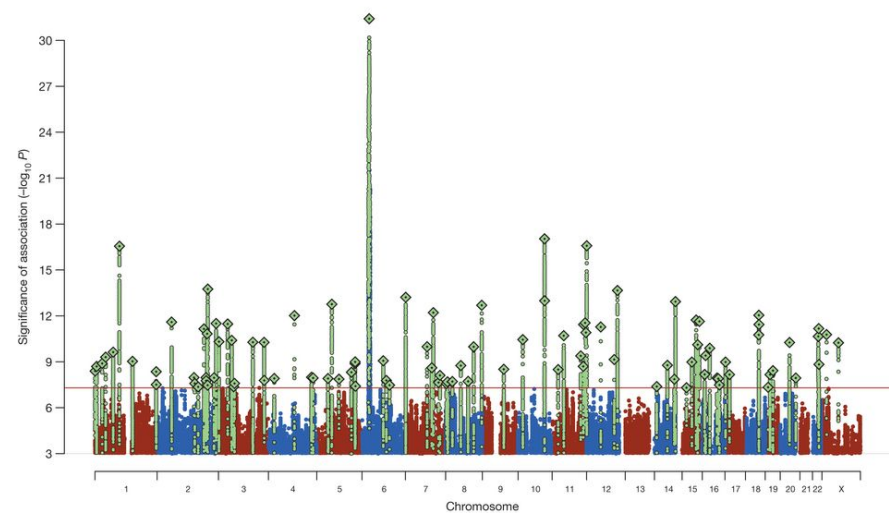
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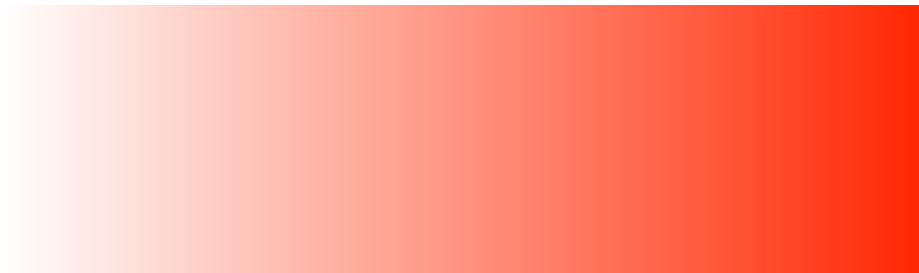
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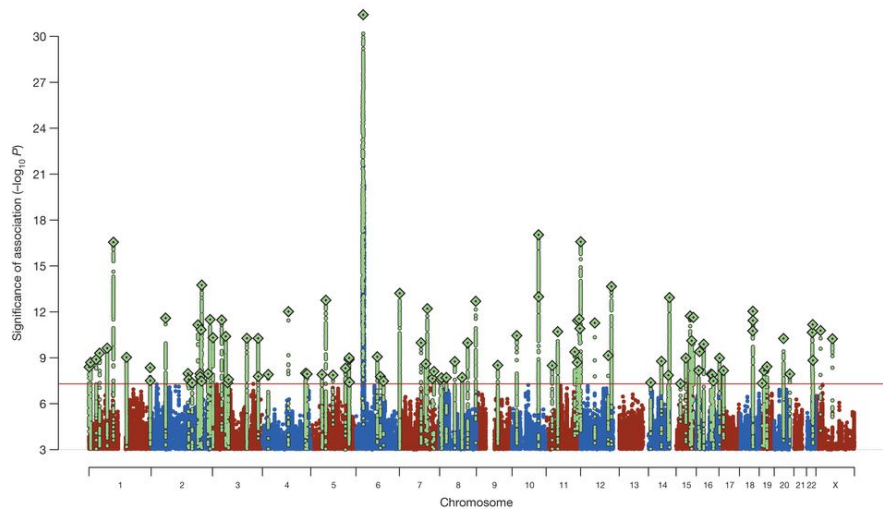
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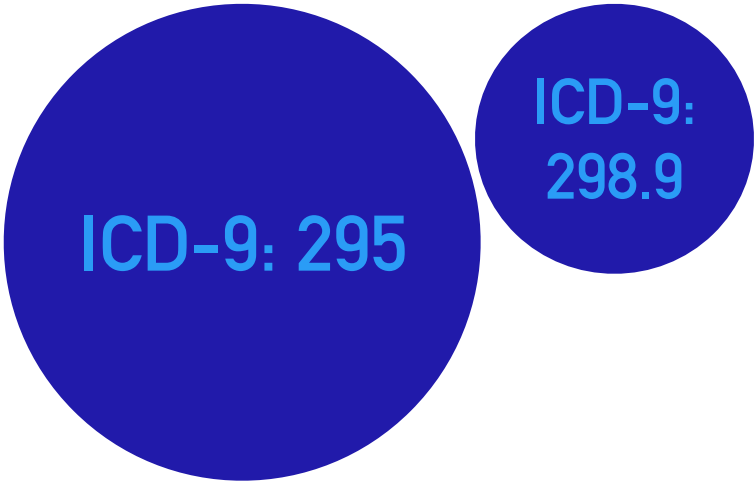
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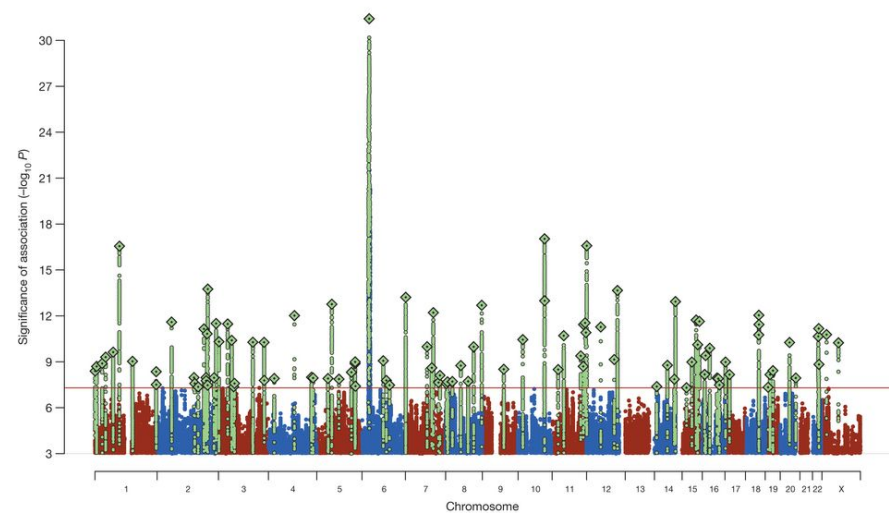
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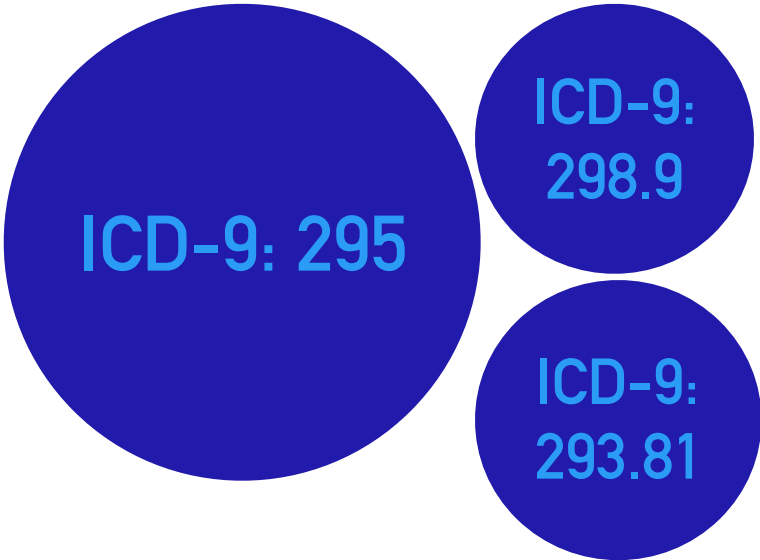
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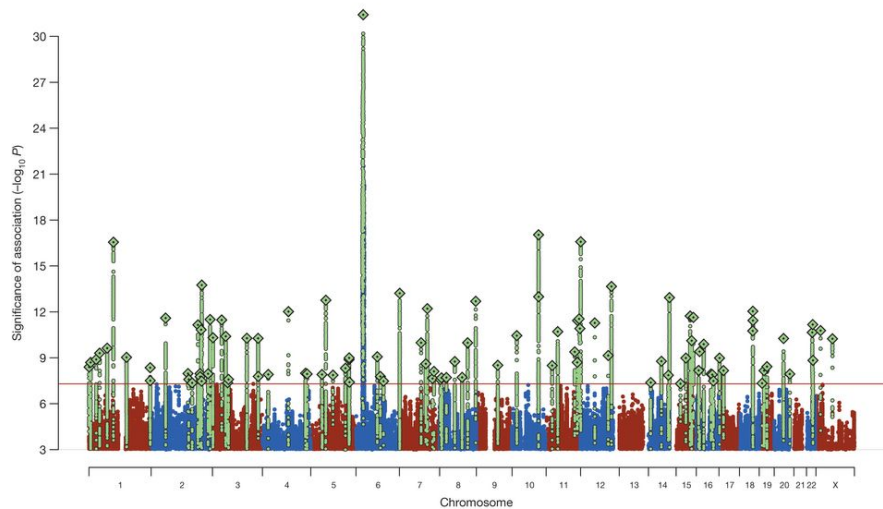
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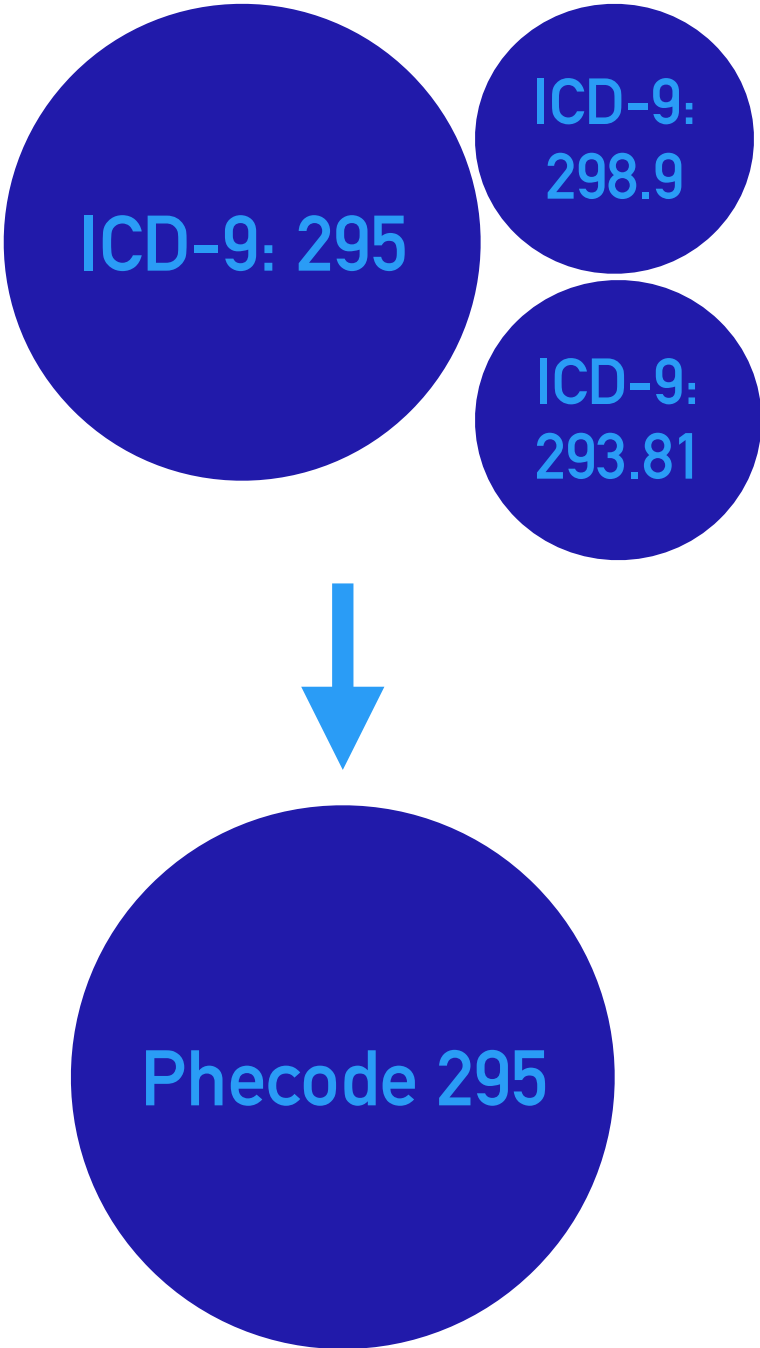
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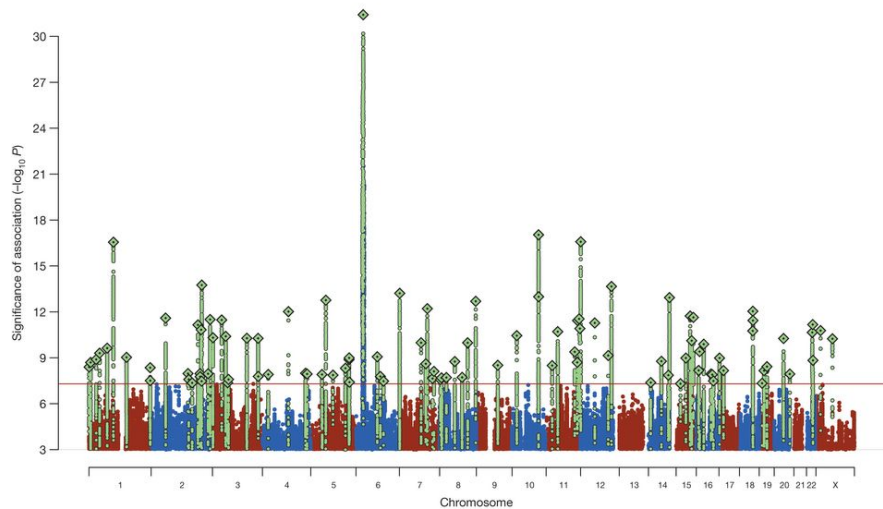
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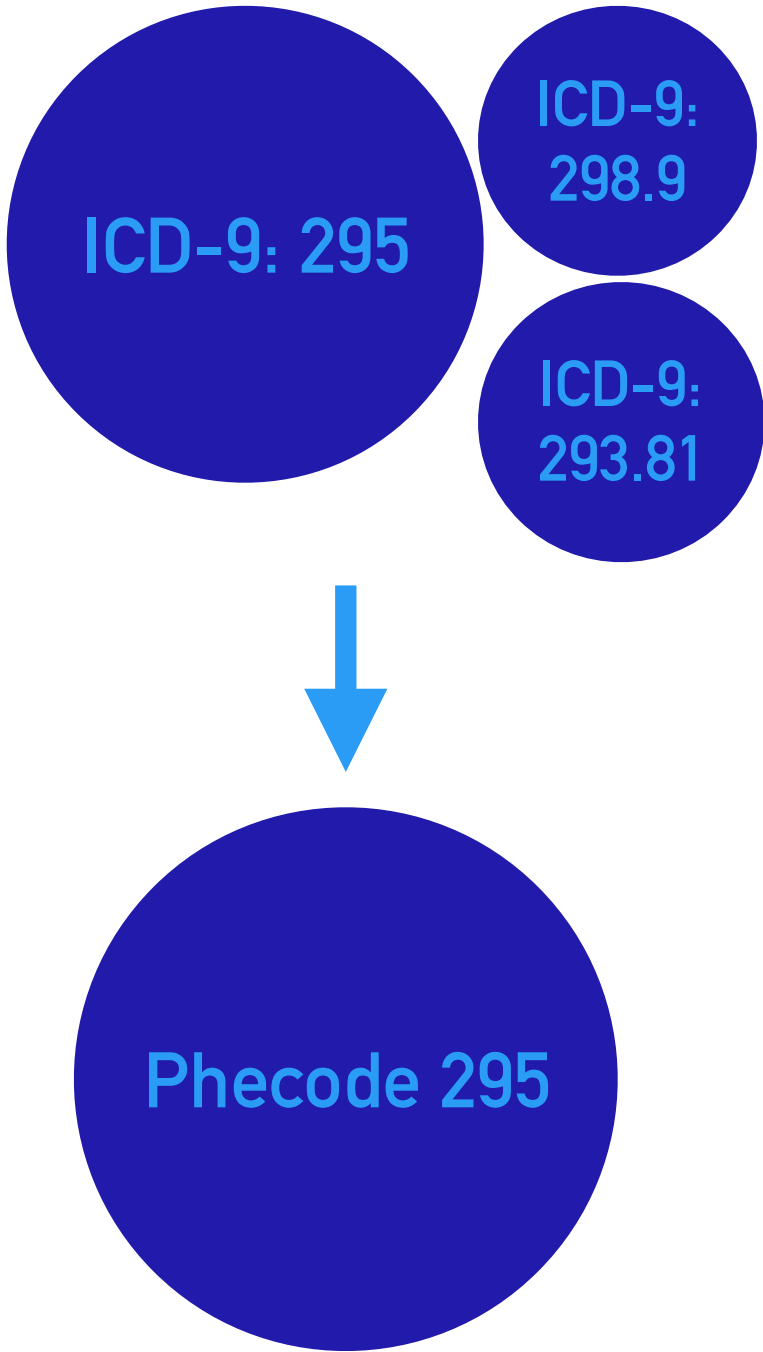
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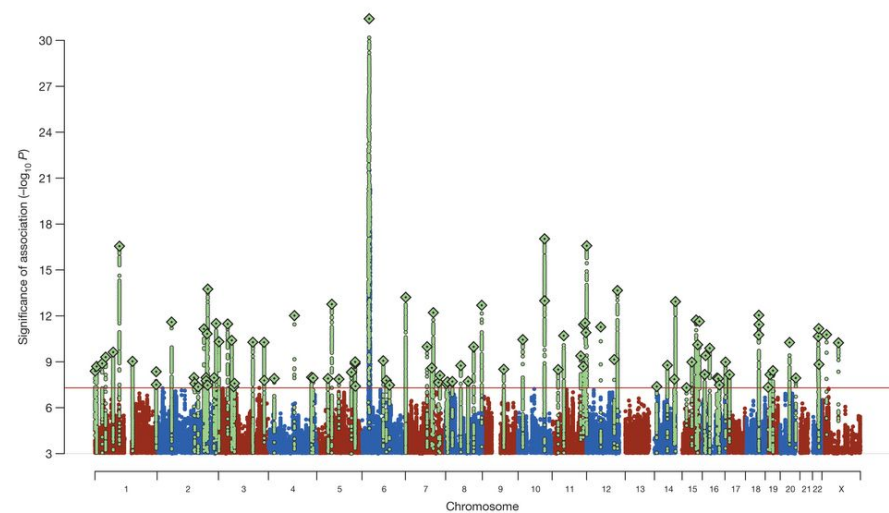
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PHENOTYPES



13,801
ICD-9
codes

GENOTYPES & PHENOTYPES



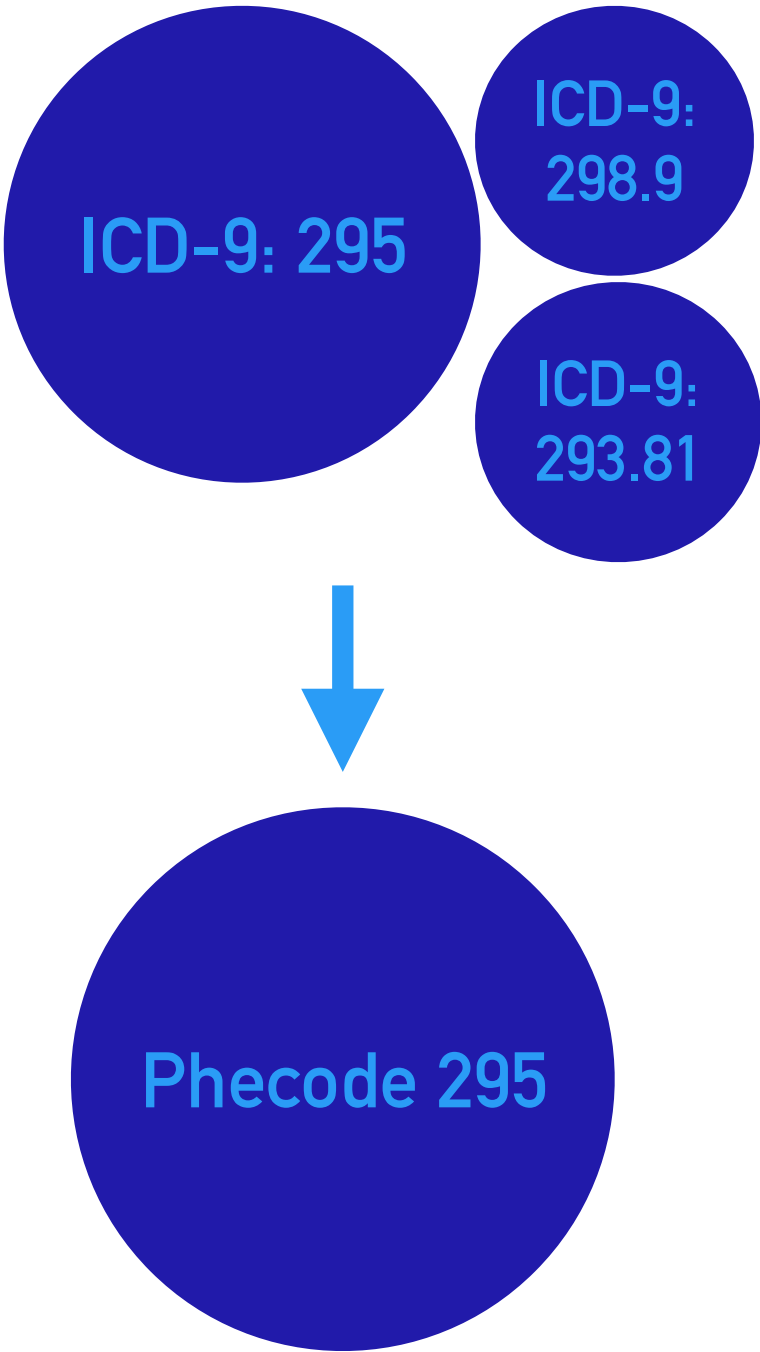
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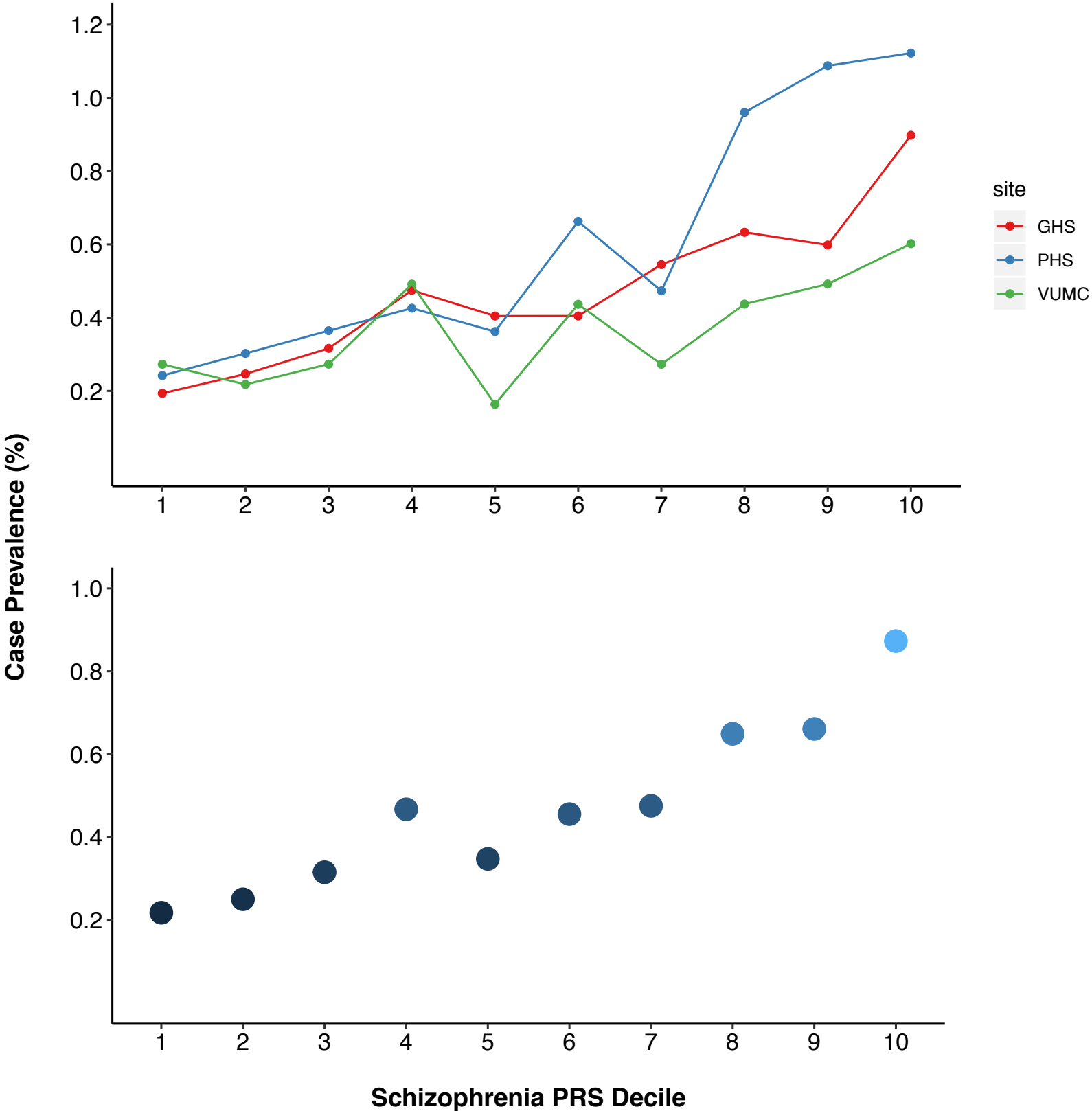
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1338
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PENETRANCE

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OTHER PREDICTORS OF PSYCHOSIS

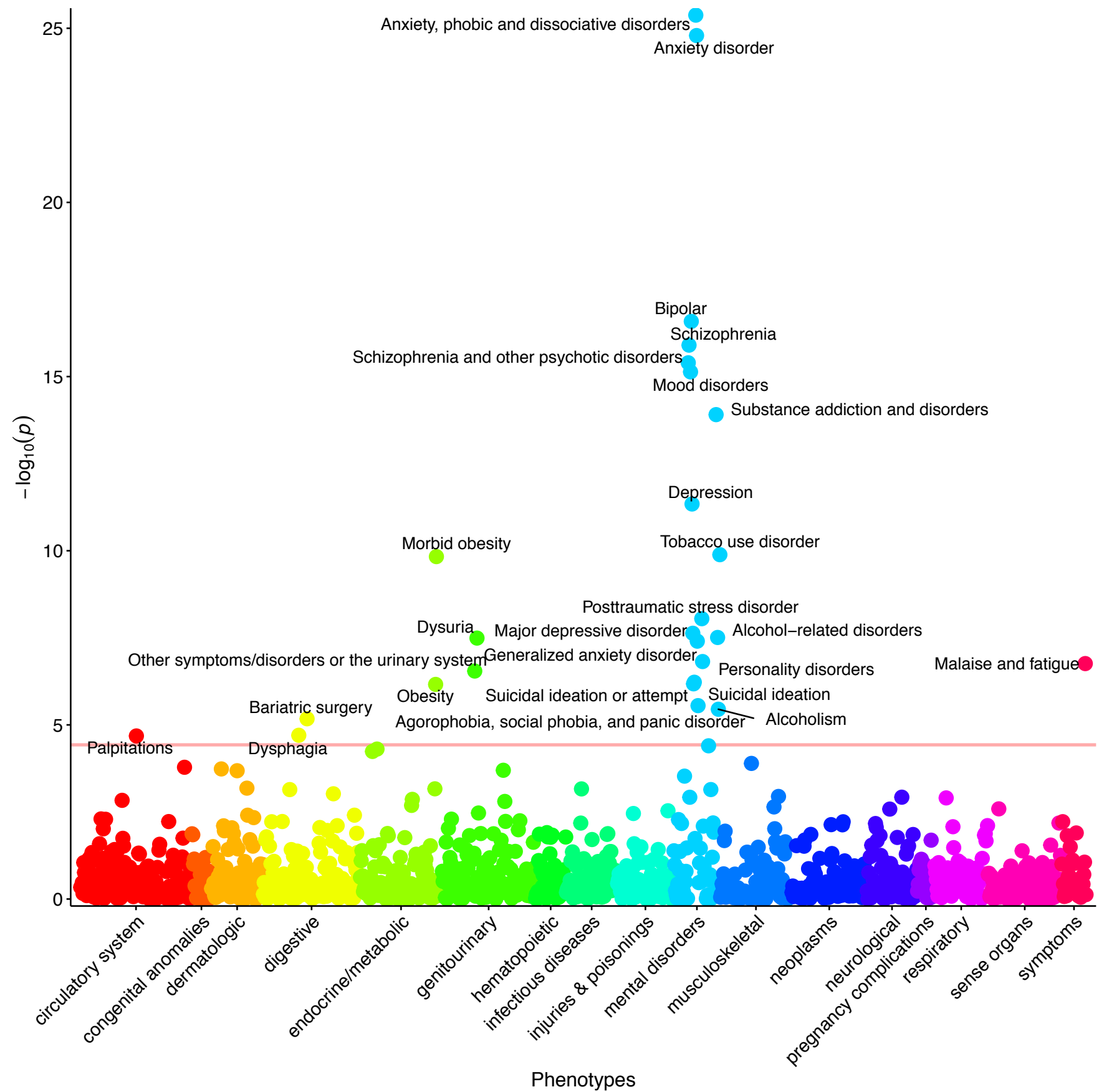
OTHER PREDICTORS OF PSYCHOSIS

Conversion to Psychosis

Predictor	Multivariate Model		
	Hazard Ratio	95% CI	p
Modified SIPS items P1 + P2	2.1	1.6–2.7	<0.001
Decline in social functioning (Global Functioning: Social scale)	1.3	1.1–1.5	0.01
Hopkins Verbal Learning Test–Revised, trials 1–3 summed	0.8	0.6–0.9	0.05
BACS symbol coding, raw score (number completed)	0.8	0.5–1.1	0.10
Age	0.7	0.5–1.1	0.09
Stressful life events	1.2	0.9–1.6	0.21
Family history of psychosis	1.2	0.7–2.1	0.55
Traumas	1.0	0.8–1.3	0.99

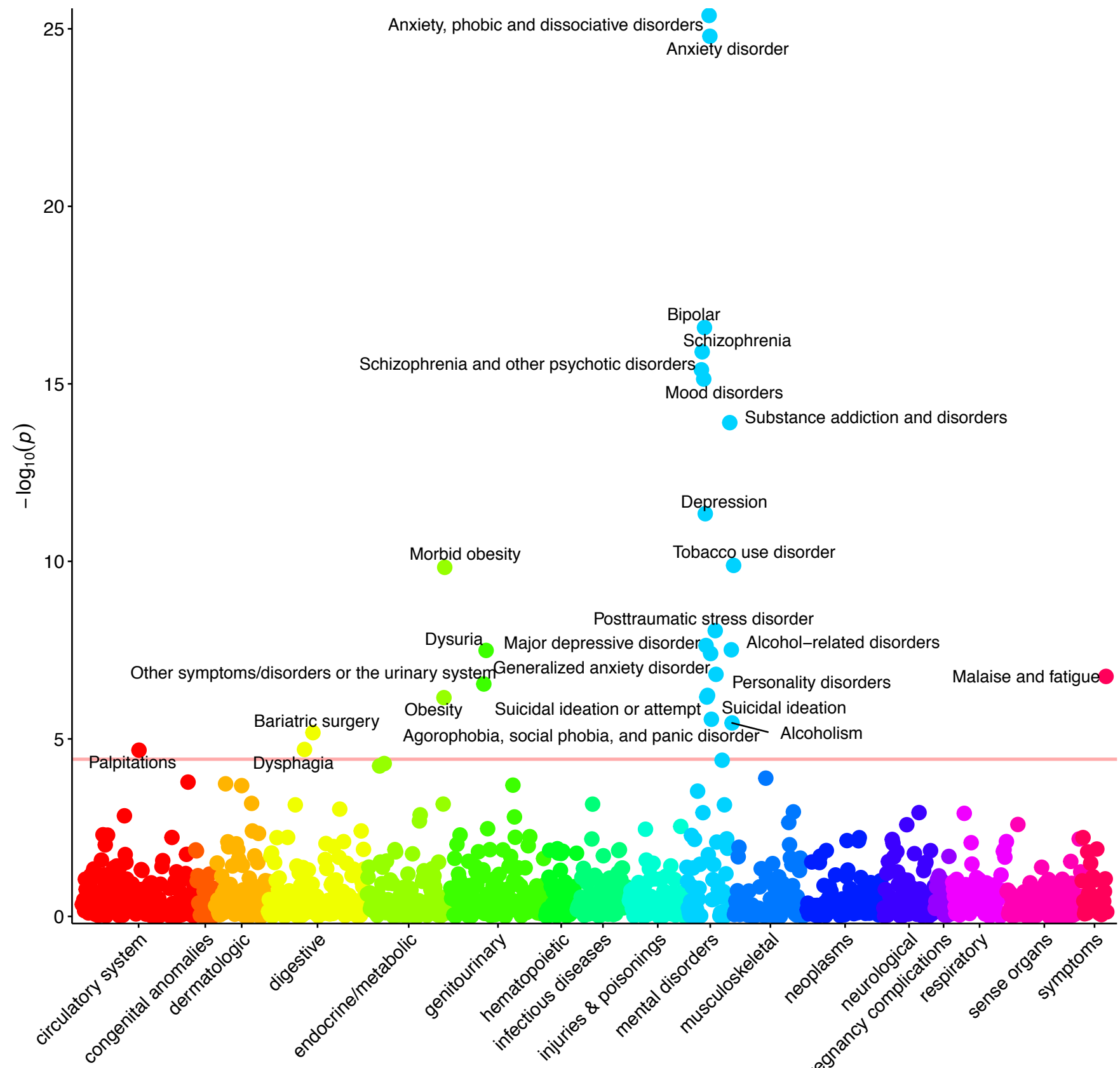
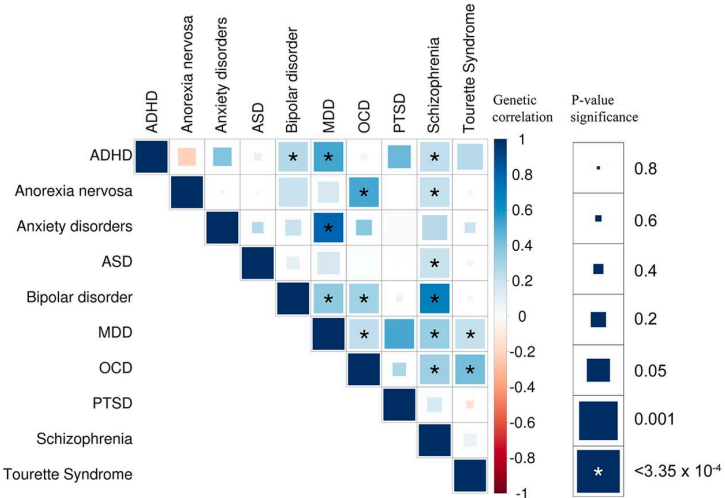
PLEIOTROPY

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RESULTS

PLEIOTROPY



CONCLUSIONS

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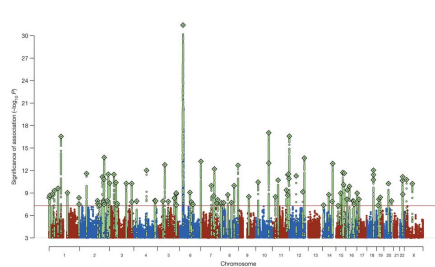
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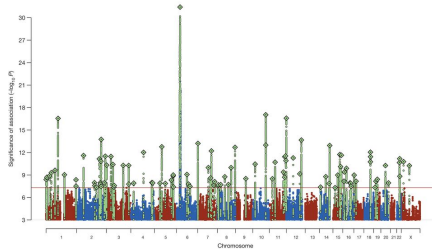


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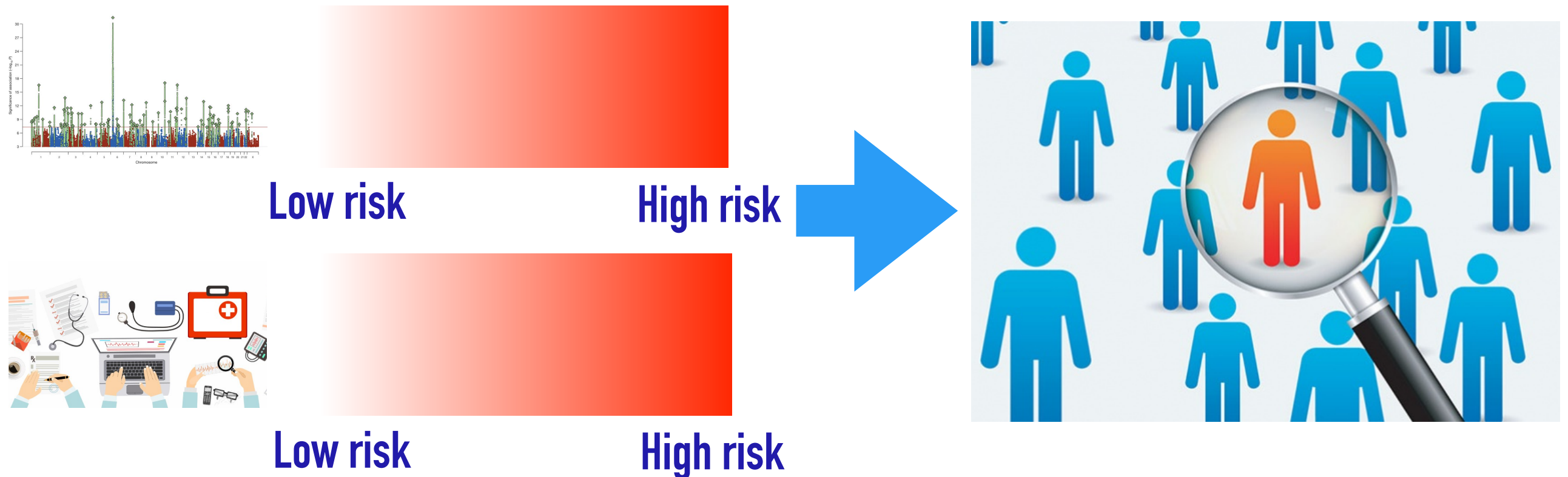


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THANK YOU!

Penetrance and pleiotropy of polygenic risk scores for schizophrenia in 90,000 patients across three healthcare systems

Amanda B Zheutlin, Jessica Dennis, Nicole Restrepo, Peter Straub, Douglas Ruderfer, Victor M Castro, Chia-Yen Chen, H Lester Kirchner, Christopher F Chabris, Lea K Davis, Jordan W Smoller

doi: <https://doi.org/10.1101/421164>

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