

Phenome-wide association studies on a quantitative trait: Application to TPMT enzymatic activity and thiopurine therapy

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INSERM UMR_S 872 eq22

AMIA TBI April, 8th 2014

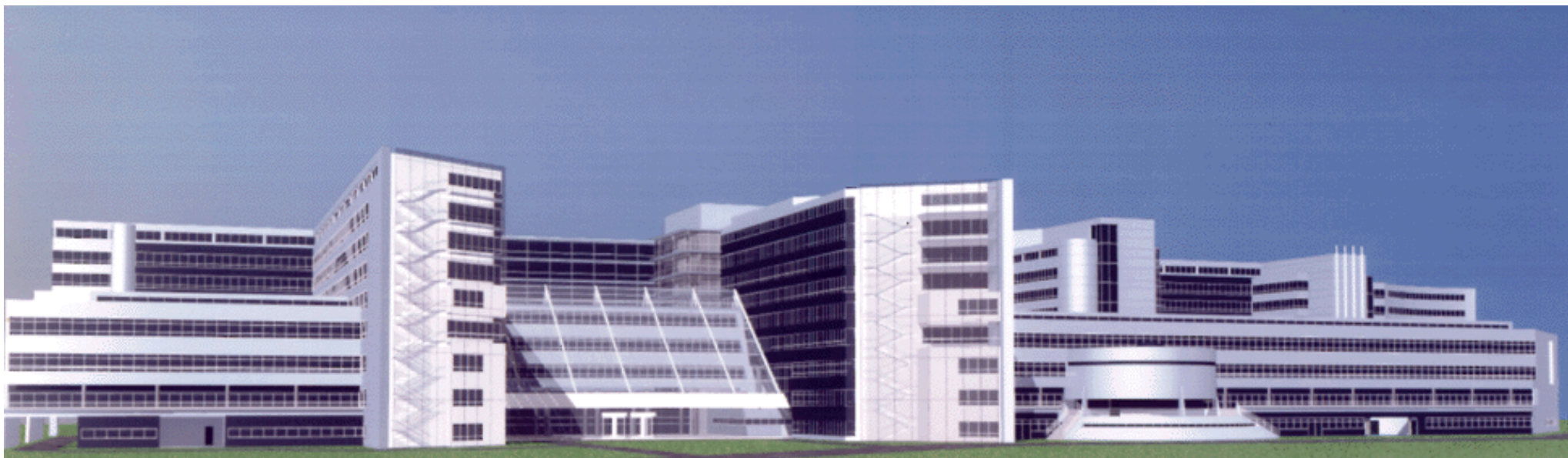


Disclosure

I have no relationships with commercial interests

HEGP background

Opening : July 2000-



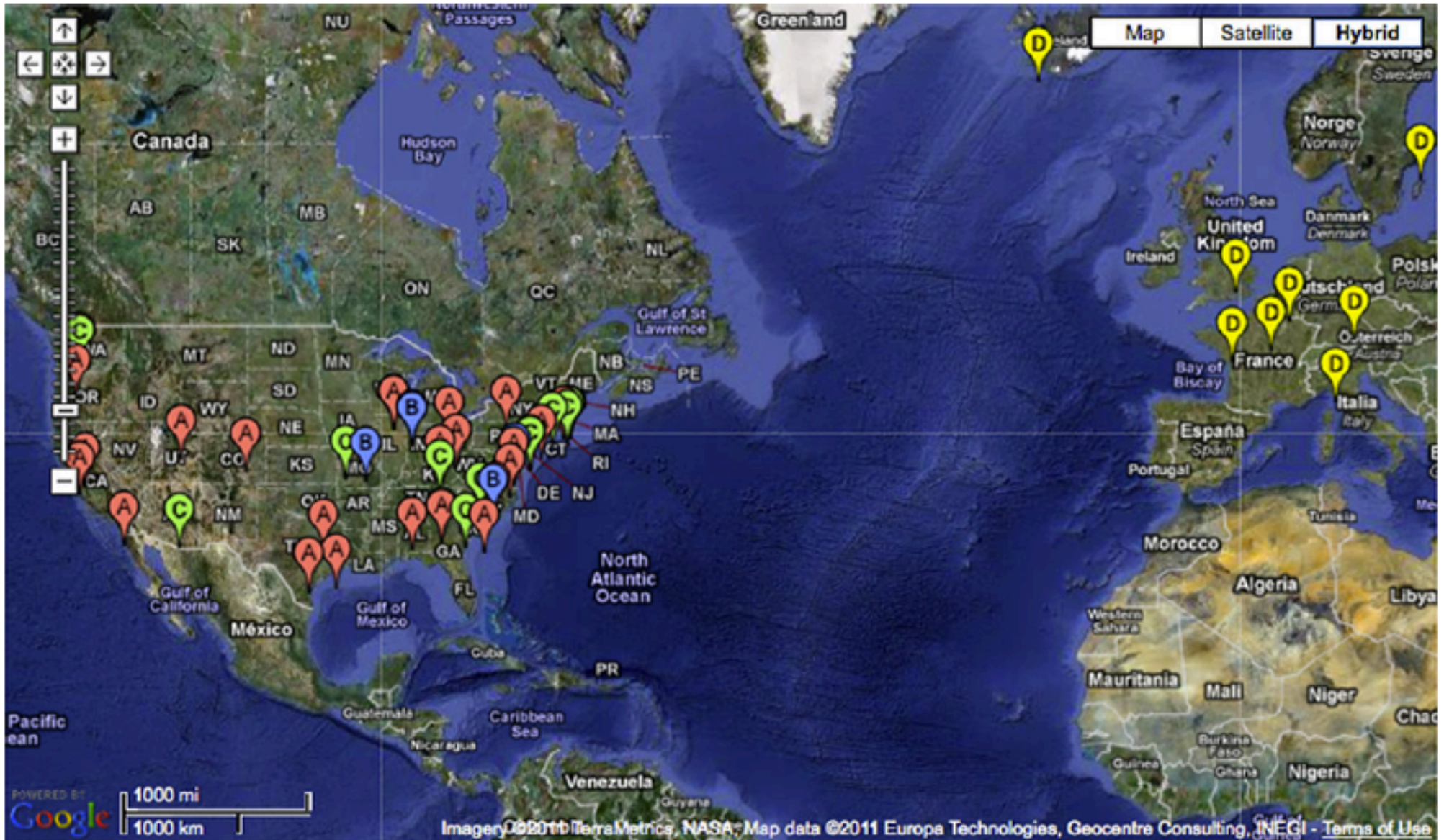
Hôpital Laennec (1634)



Hôpital Boucicaut



Hôpital Broussais



HEGP i2b2



Type of data

	H	OV	Start date	# unique patients	# values
Demographic (age, sex, Hospital vital status)	X	X	1971	606 524	
Vital signs (temperature, blood pressure, weight, ...)	X	X	2000	141 164	14 213 951
Diagnostic codes (DRG ICD10)	X		1995	305 369	2 626 792
Procedures (French CCAM codes)	X		2004	241 482	3 200 482
Clinical data (DxCare questionnaires)	X	X	1971	391 218	46 506 217
Free text reports*: Hospitalization, Surgery, consultations, ...	X	X	2004	289 614	1 961 985
Free text reports**: Imaging and pathology	X	X	2000	-	1 000 000
Pathology codes (ADICAP)	X	X	2000	73 173	-
Biology results (<i>without antibiograms</i>)	X	X	2000	338 068	88 607 301
Antibiograms	X	X	2000	39 040	4 058 842
Drug prescription (<i>without Chemotherapy</i>)	X	X	1988	88 567	2 612 742
Validation of Drug prescription by pharmacists	X		2002	67 151	1 691 137

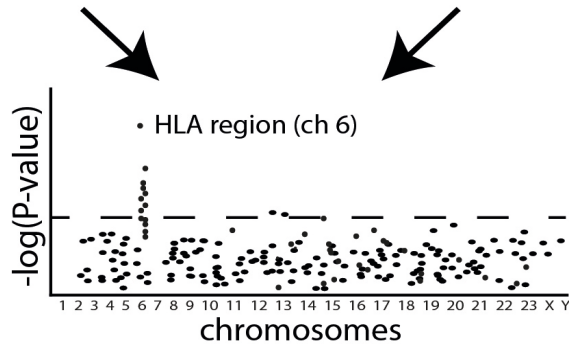
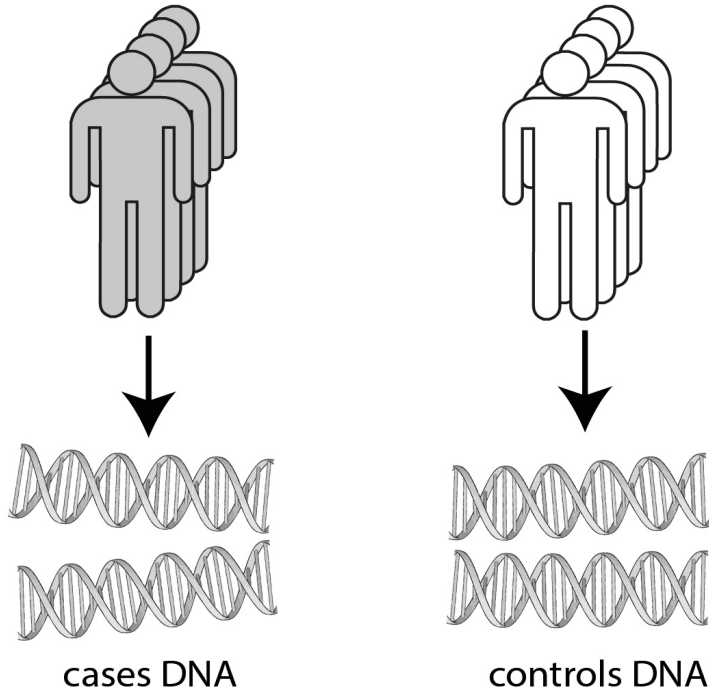
CLINICAL

Genome Wide Association Study

(1 Phenotype compared to ALL SNPs)

cases
(ex: systemic sclerosis)

controls



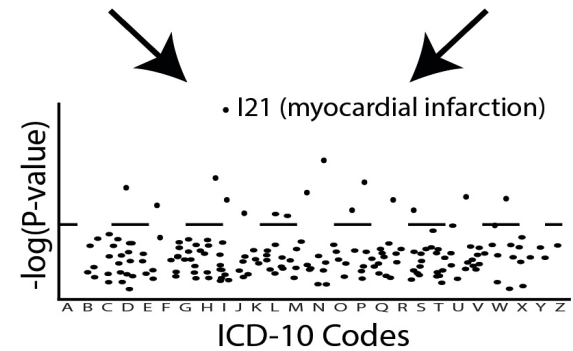
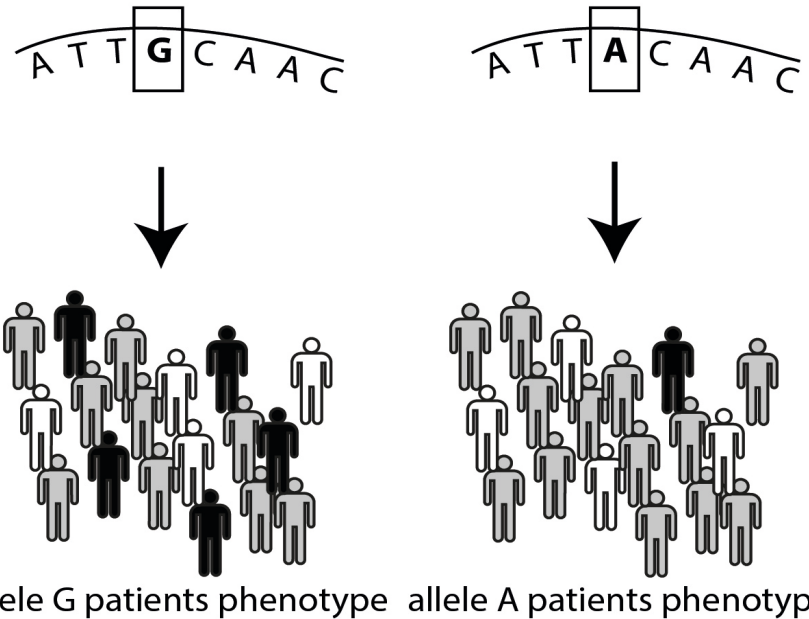
compare ALL SNPs to find differences between cases and controls

Phenome Wide Association Study

(1 SNP compared to ALL Phenotypes)

allele G patients group

allele A patients group



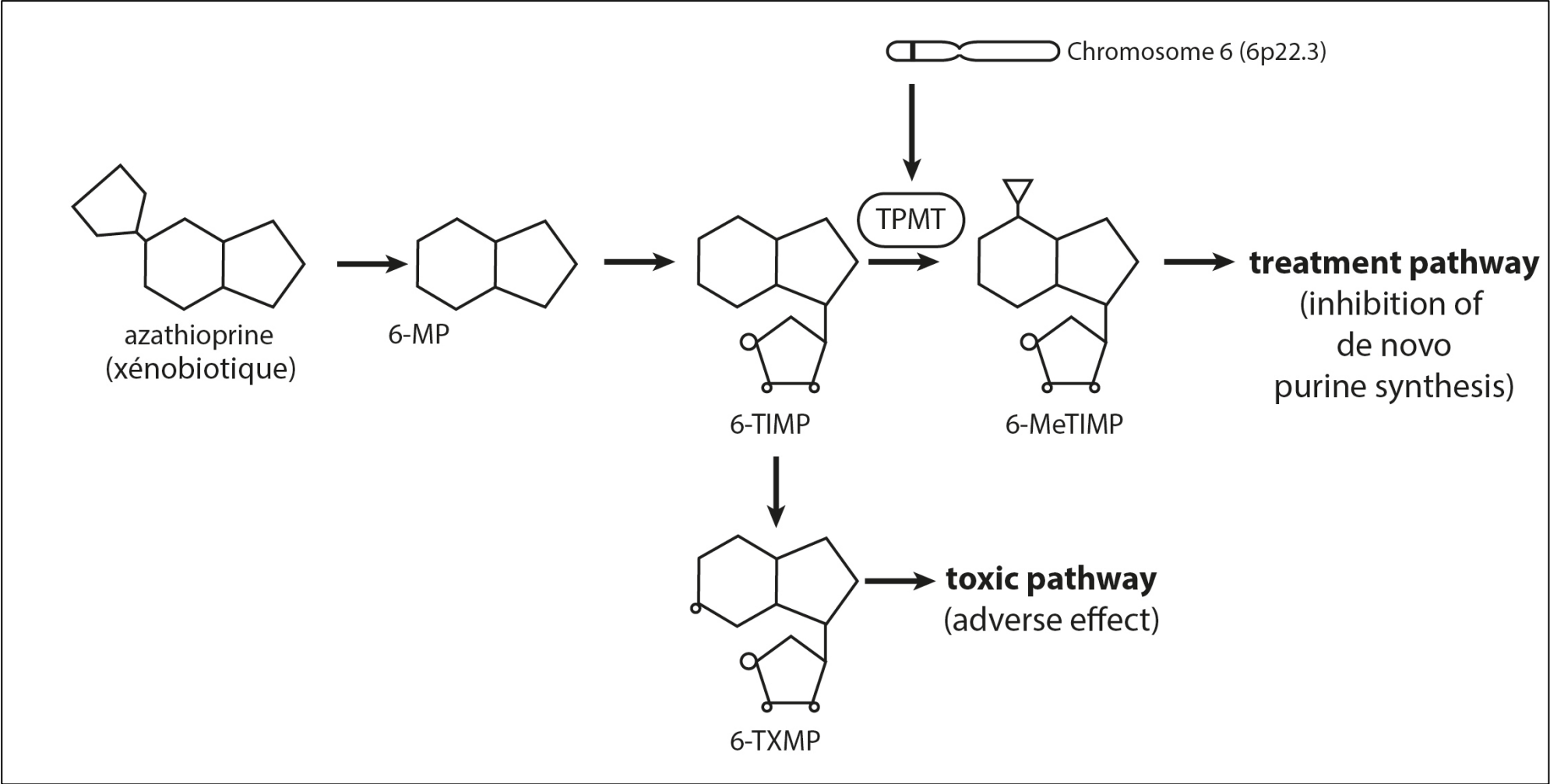
compare ALL DIAGNOSIS to find differences between cases and controls

Phenome-Wide Association Studies on a Quantitative Trait: Application to TPMT Enzyme Activity and Thiopurine Therapy in Pharmacogenomics

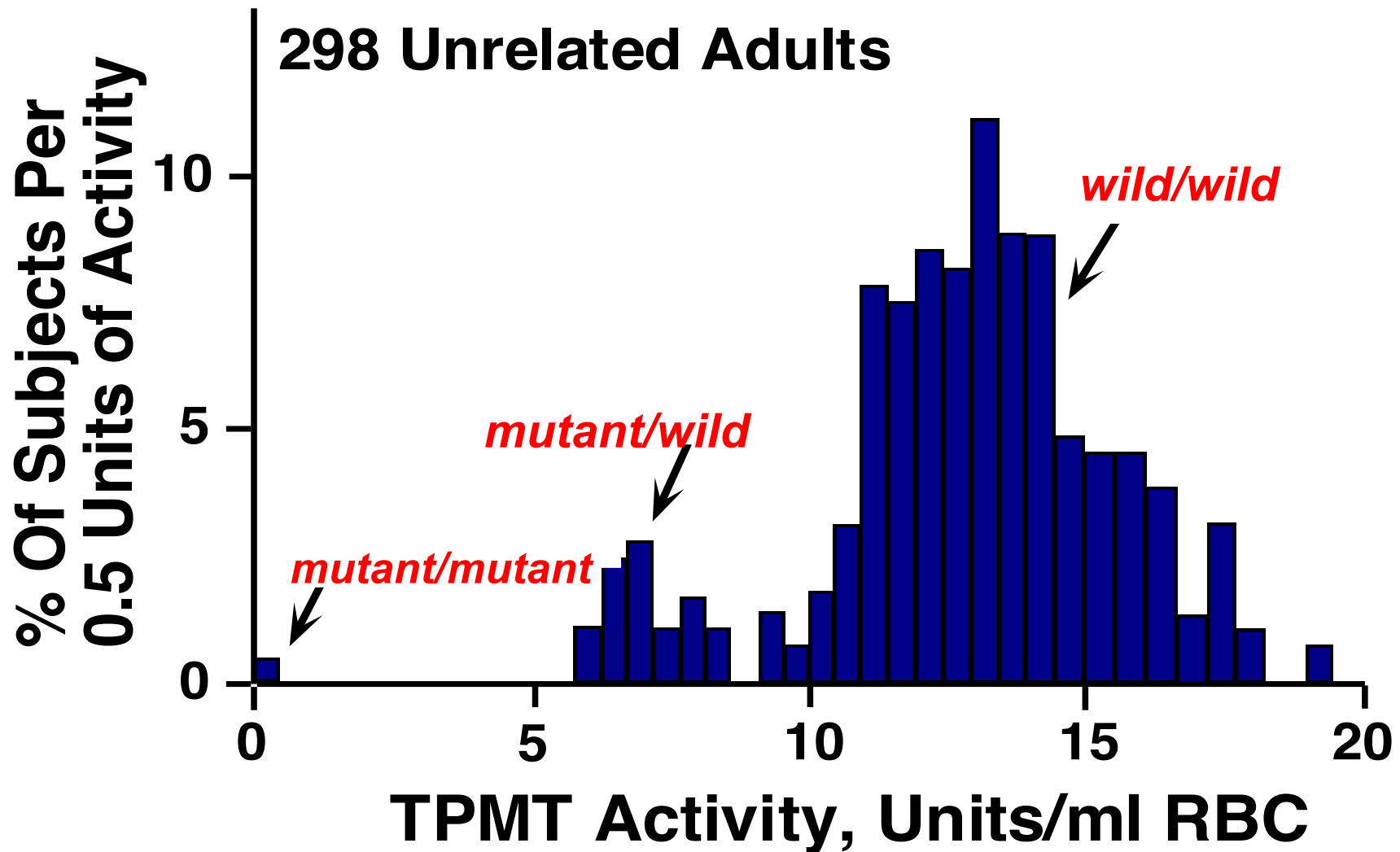
Antoine Neuraz^{1,2}, Laurent Chouchana³, Georgia Malamut⁴, Christine Le Beller⁵, Denis Roche⁶, Philippe Beaune^{3,6}, Patrice Degoulet^{1,2}, Anita Burgun^{1,2}, Marie-Anne Loriot^{3,6}, Paul Avillach^{1,2*}

1 Biomedical Informatics and Public Health Department, University Hospital HEGP, AP-HP, Paris, France, **2** INSERM UMR_S 872 Team 22: Information Sciences to support Personalized Medicine, Université Paris Descartes, Sorbonne Paris Cité, Faculté de Médecine, Paris, France, **3** INSERM UMR-S 775, Université Paris Descartes, Sorbonne Paris Cité, Paris, France, **4** Gastroenterology Department, University Hospital HEGP, AP-HP, Paris, France, **5** Pharmacovigilance Center, University Hospital HEGP, AP-HP, Paris, France, **6** Biochemistry, Pharmacogenetics and Molecular Oncology Unit, University Hospital HEGP, AP-HP, Paris, France

TPMT

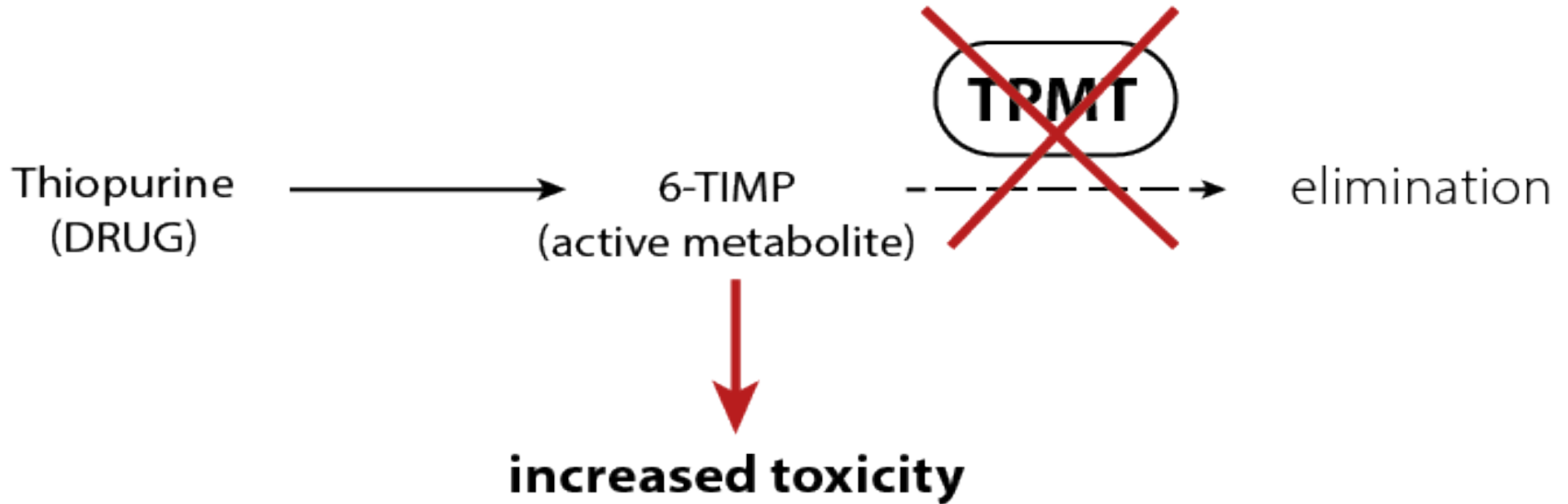


TPMT: activity distribution



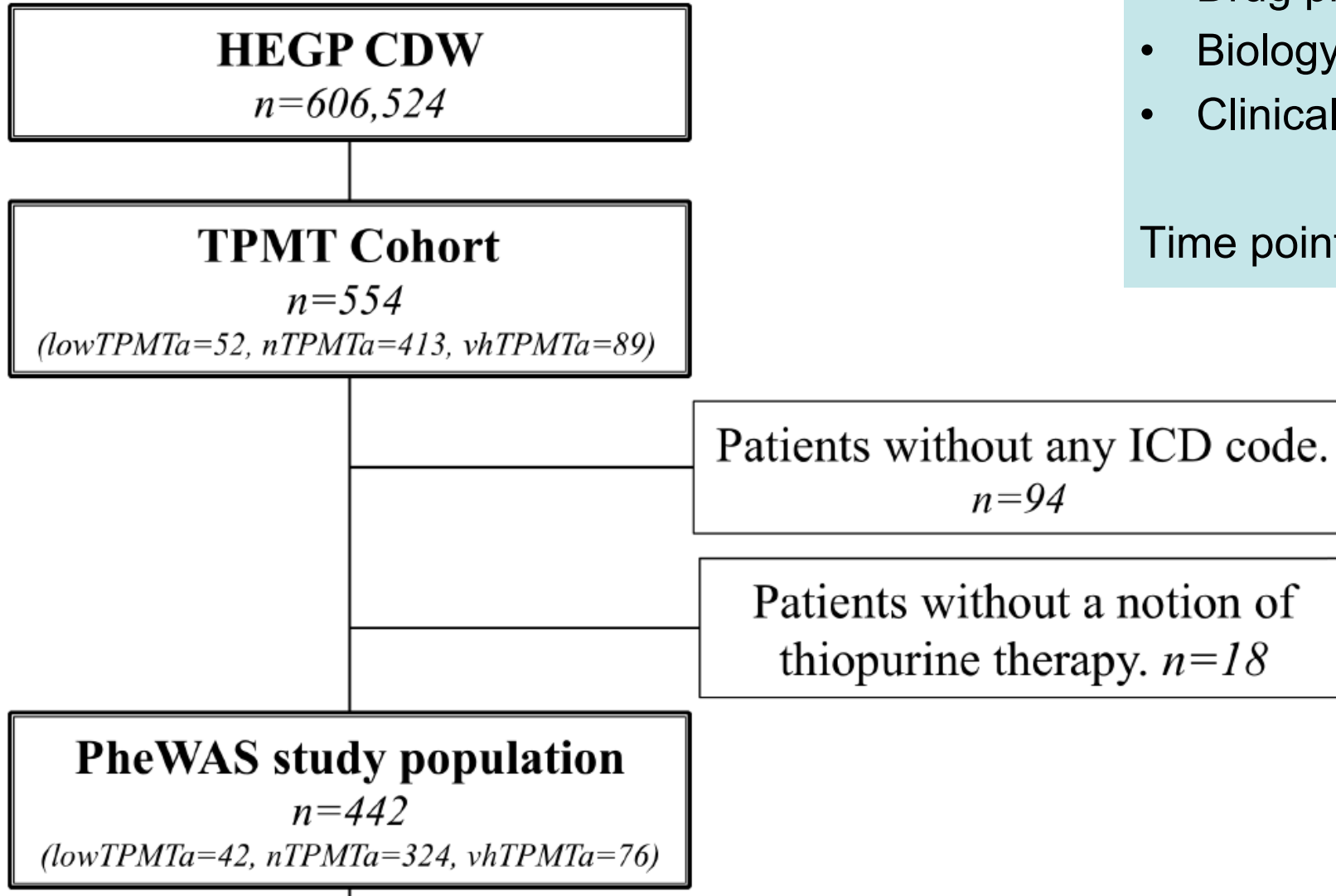
Lennard, Therapeutic drug monitoring of antimetabolic cytothoxic drugs, British journal of Clinical Pharmacology 2001

Methodes: Selection of trait: enzymatic Activity TPMT



FDA & EMA recommendations	Phenotype	Low activity	Intermediate activity	Normal Activity	?
	Thiopurine dose	10 % dose	30 – 70 % dose	100 % dose	

Study design



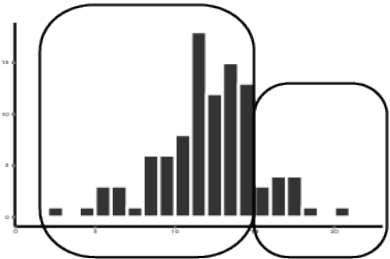
Datatypes:

- ICD10
- Drug prescription
- Biology
- Clinical Notes

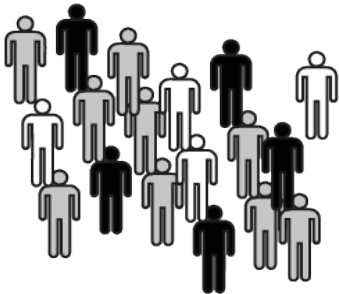
Time points+++

TPMT

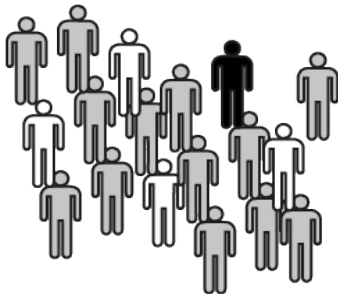
Very High TPMT activity vs others



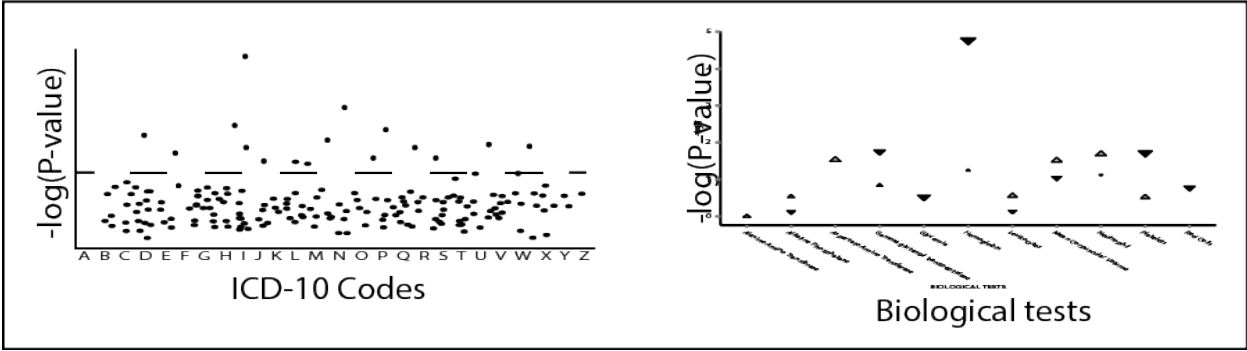
Quantitative trait

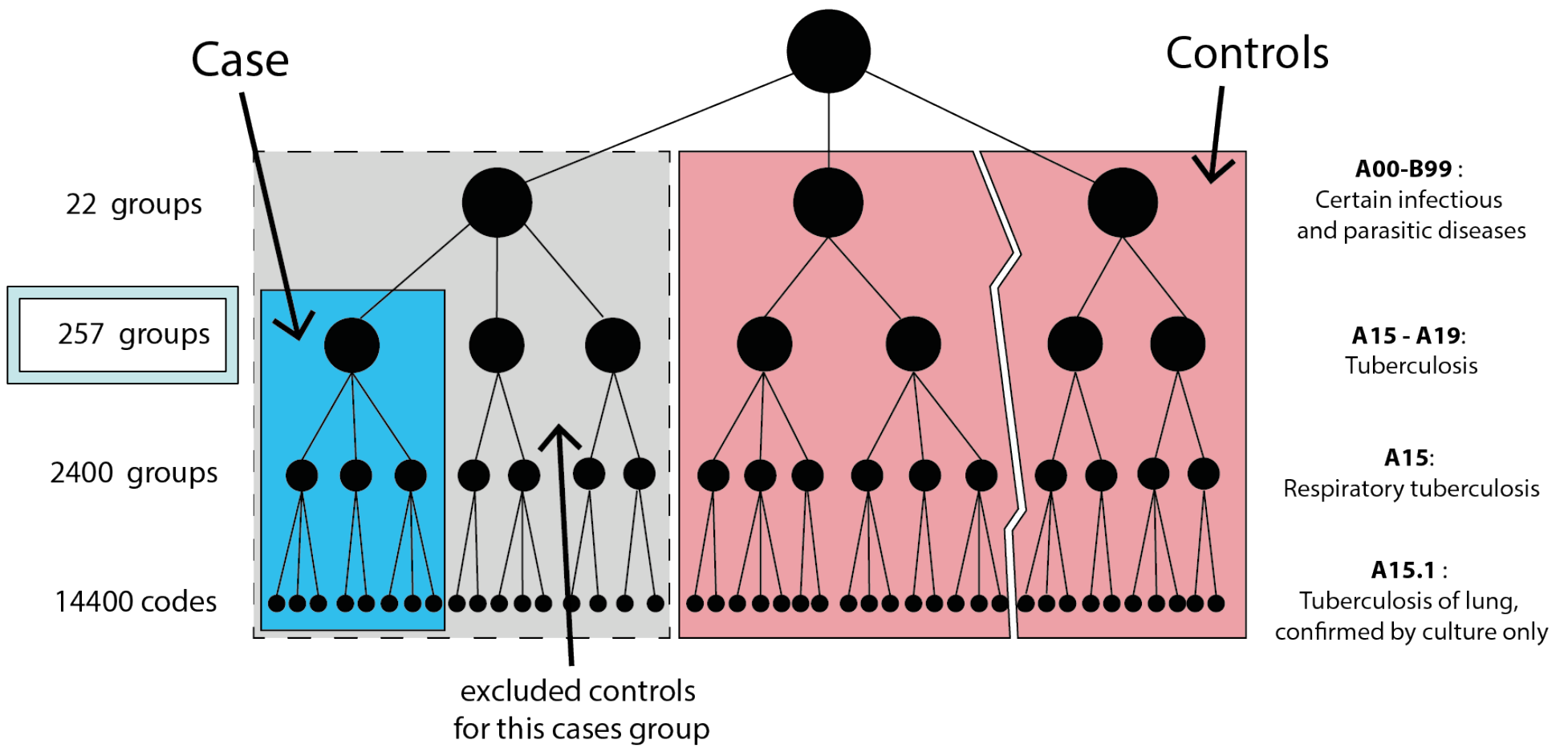


other activity patients
ICD codes/ Biological test results



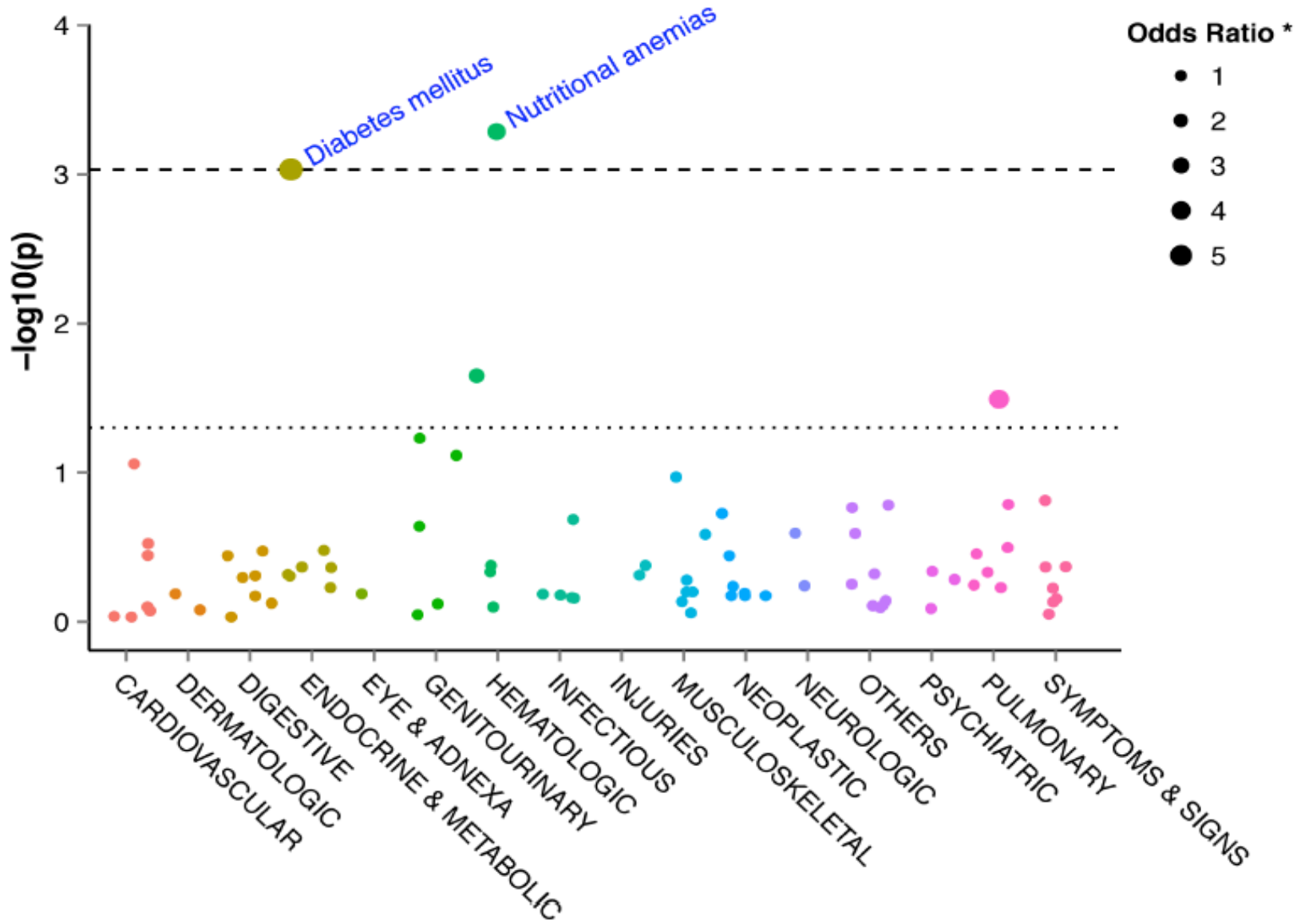
Very High activity patients
ICD Codes / Biological test results



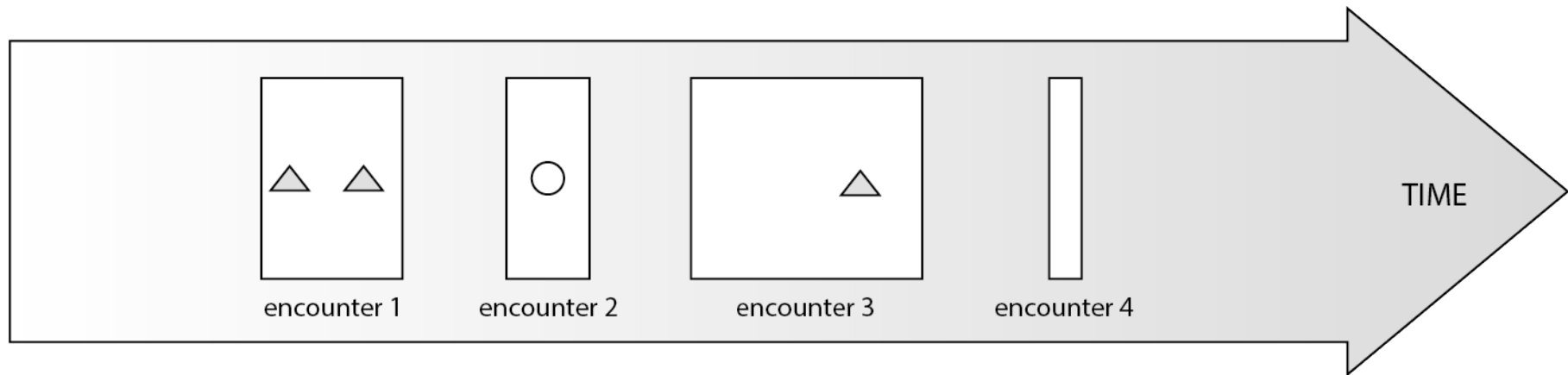


Very High TPMT activity vs others




ICD10

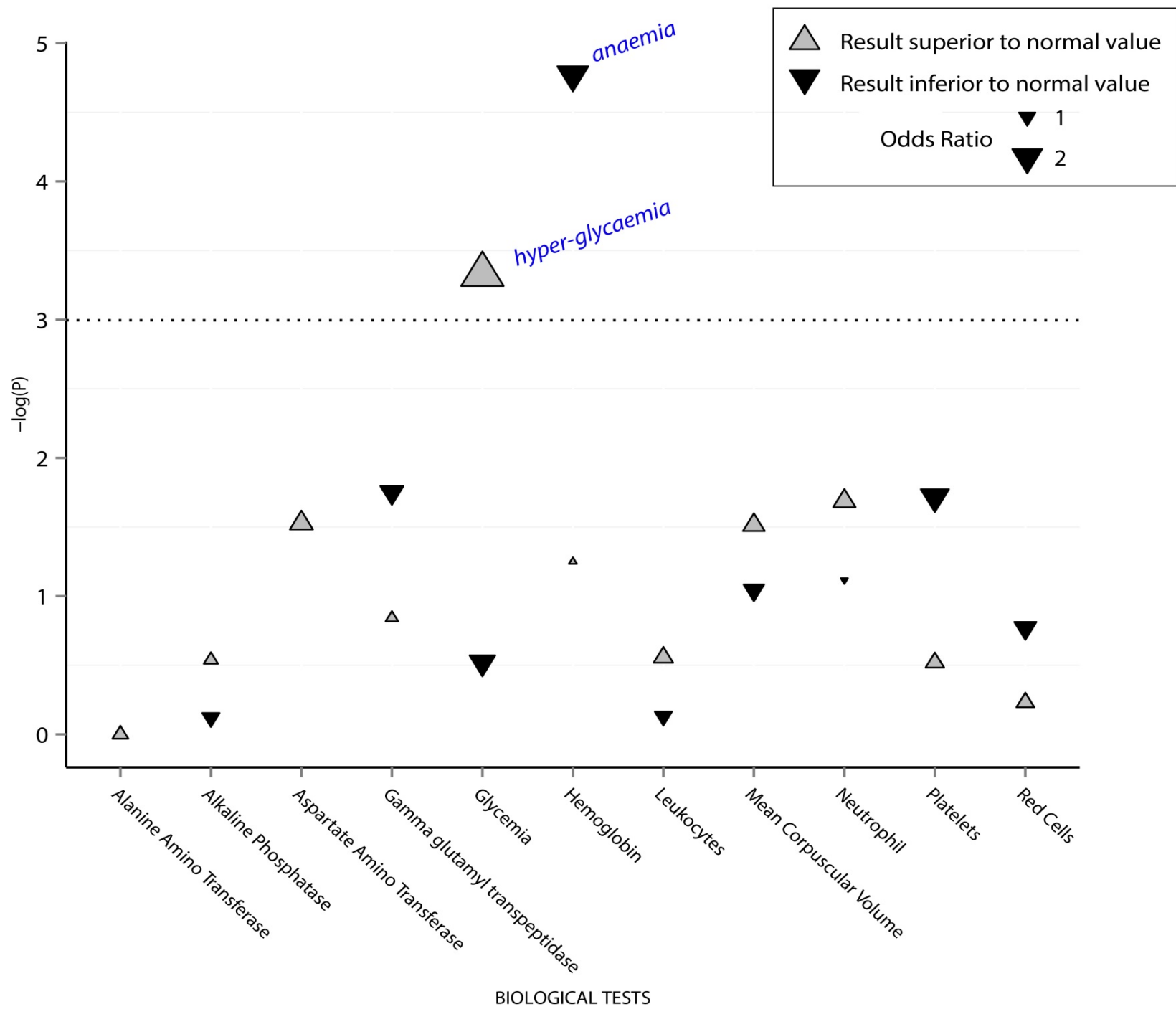


PheWAS on lab values

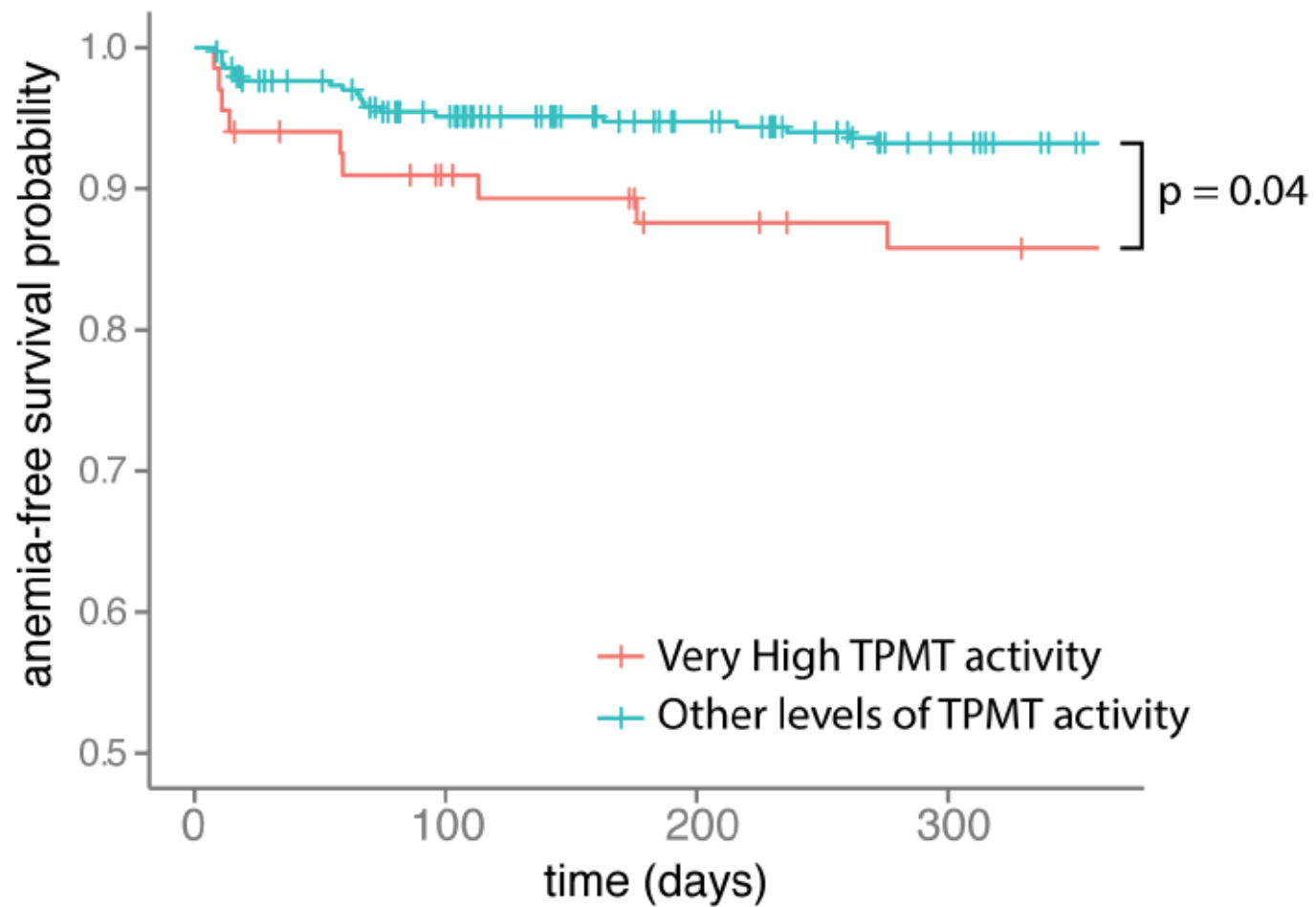


Method A  **1** → high value case = 1
global approach: patient is a case if he has at least one occurrence

Method B  **1**  **1**  → high value frequency = 2/4
frequency approach: frequency of encounters with abnormal results



Survival analysis of the time without anemia AFTER starting thiopurine therapy



Discussion

- PheWAS on a quantitative trait
- 1st PheWAS on ICD10 codes
- ICD codes + biology → cross-validation
- temporality

- TPMT:

Phenotype	Low activity	Intermediate activity	Normal Activity	Very High Activity
Thiopurine dose	10 % dose	30 – 70 % dose	100 % dose	> 100 % Dose ?

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