From multiomic discovery

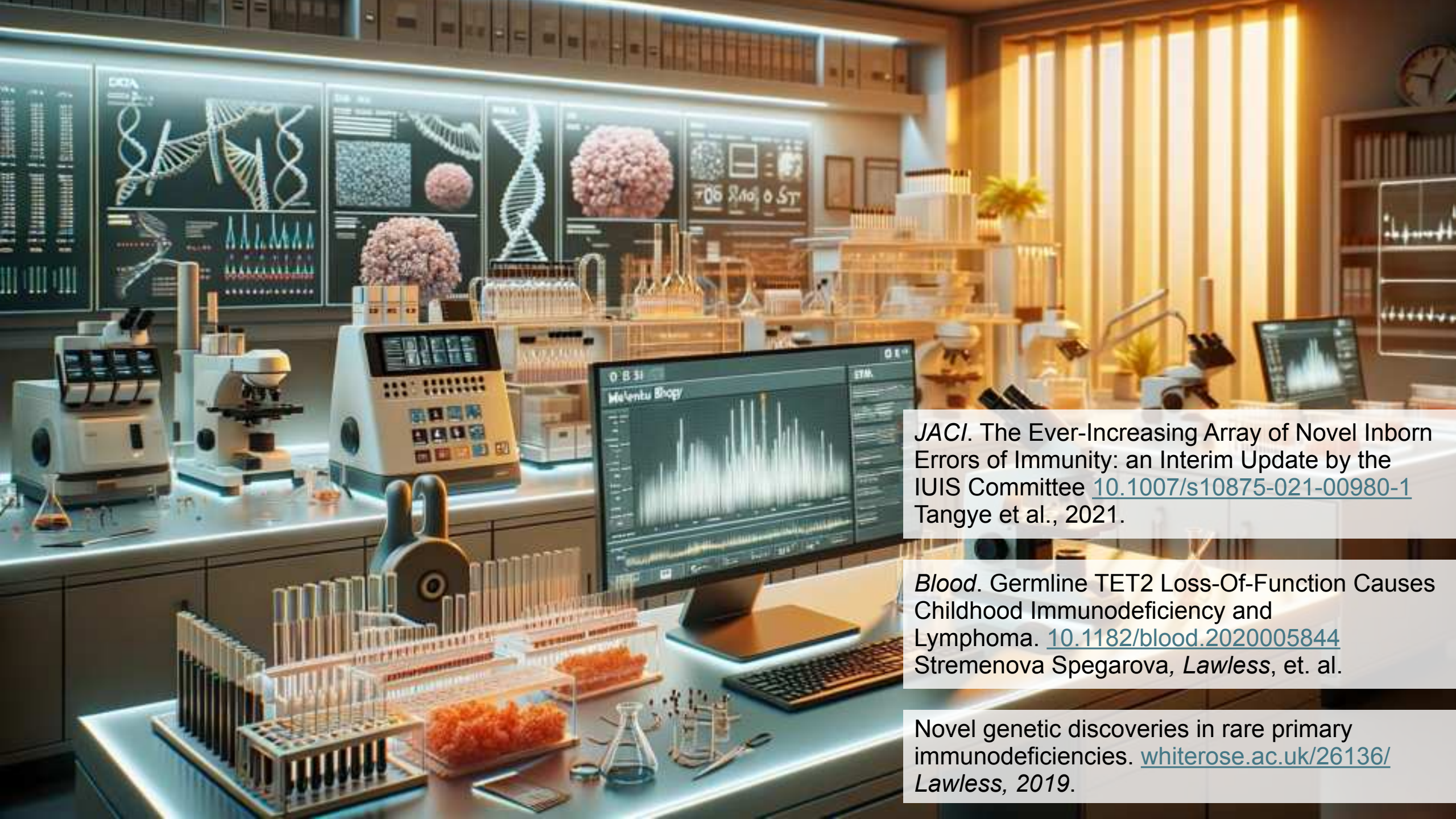
to real-time rapid diagnostics

Lawless, *et al*.

Phases 0-3

Phase 0.0

Birth

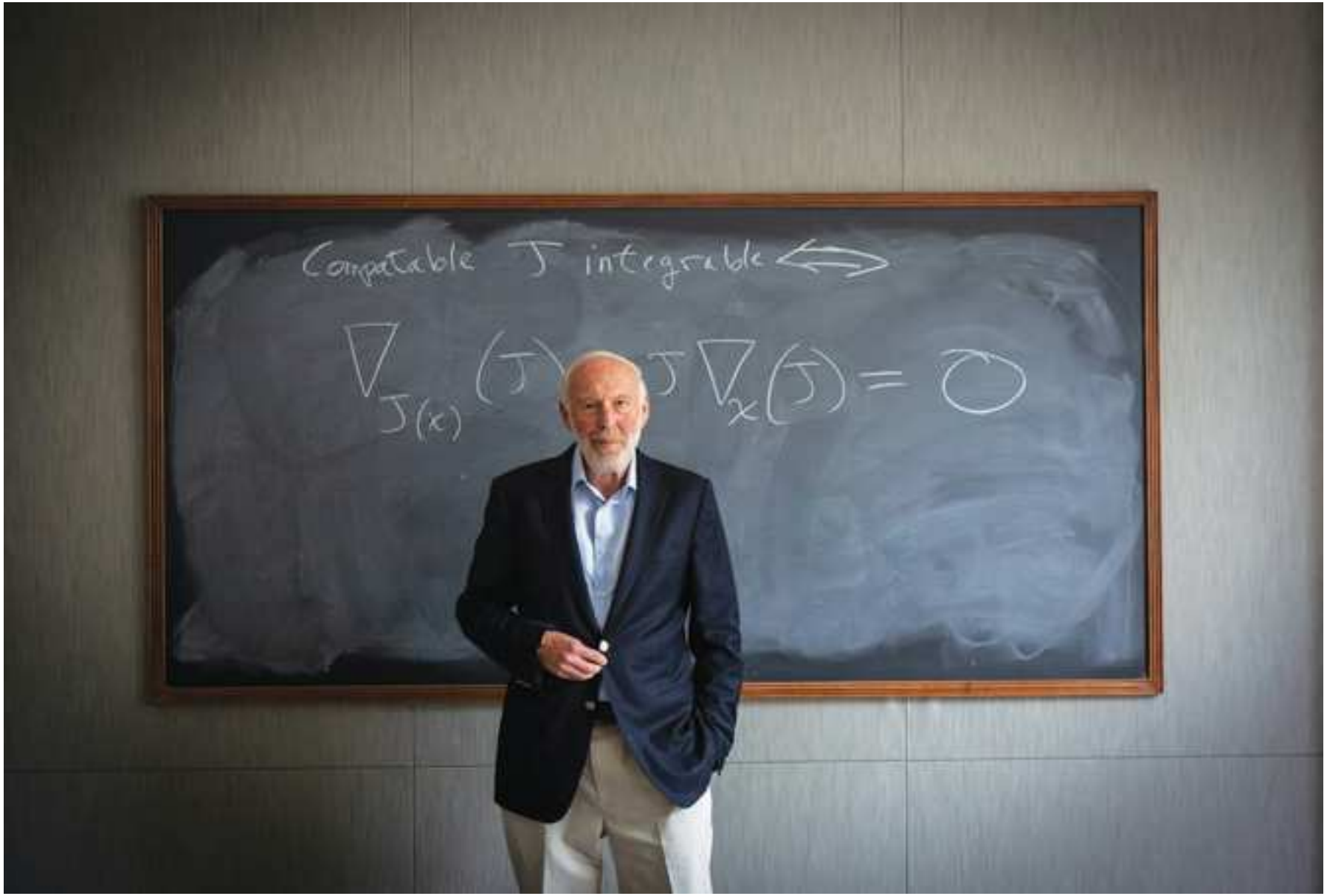


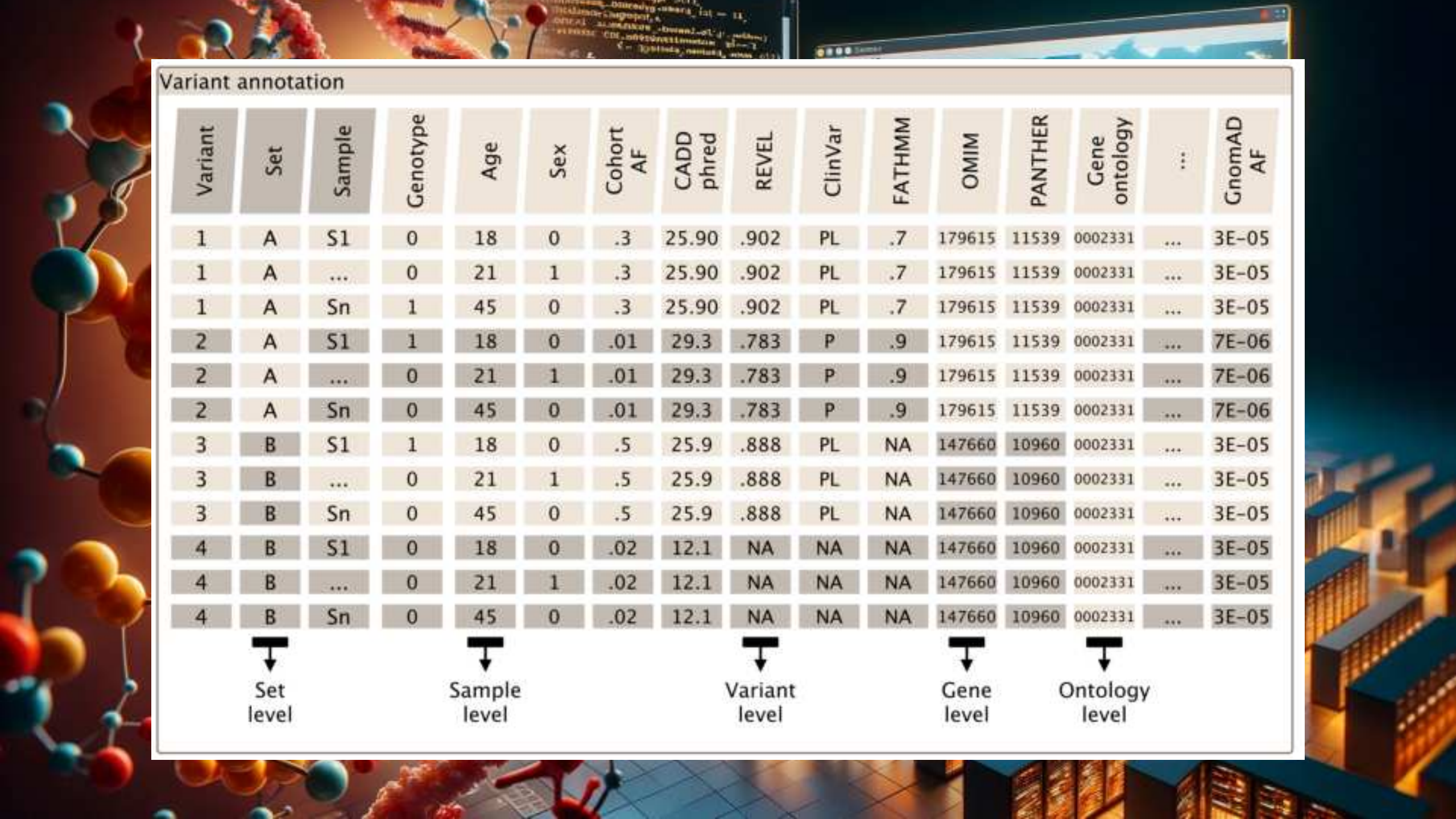
JACI. The Ever-Increasing Array of Novel Inborn Errors of Immunity: an Interim Update by the IUIS Committee 10.1007/s10875-021-00980-1 Tangye et al., 2021.

Blood. Germline TET2 Loss-Of-Function Causes Childhood Immunodeficiency and Lymphoma. 10.1182/blood.2020005844 Stremenova Spegarova, *Lawless*, et. al.

Novel genetic discoveries in rare primary immunodeficiencies. whiterose.ac.uk/26136/ *Lawless, 2019*.

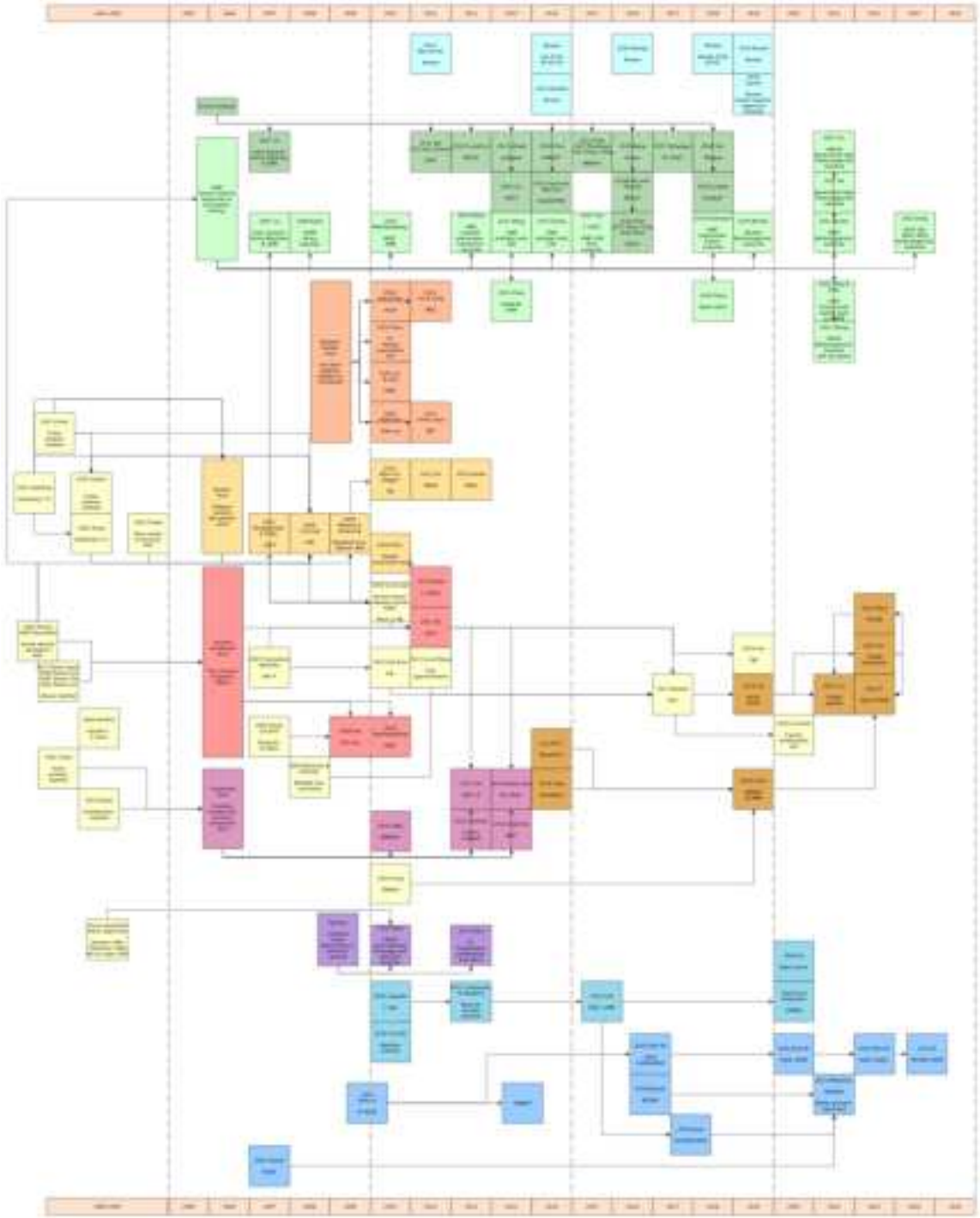
Phase 1.0
Technical foundation

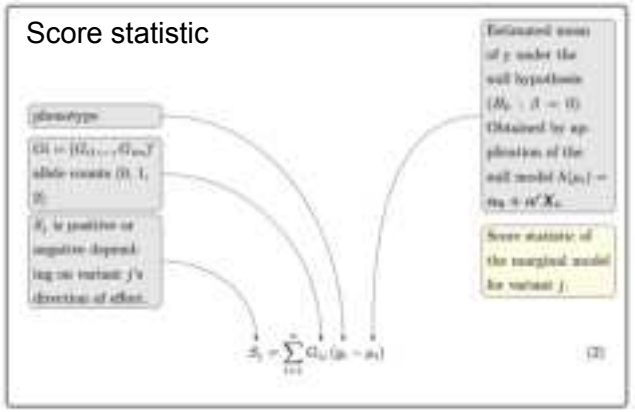

Compatable J integrable ⟺
$\nabla_{J(x)}(J) \cdot J \nabla_x(J) = 0$

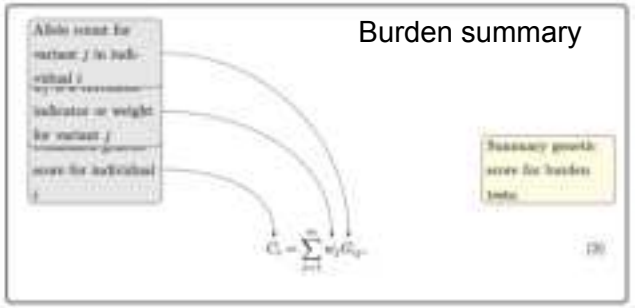

Variant annotation
Variant
Set
Sample
Genotype
Age
Sex
Cohort AF
CADD phred
REVEL
ClinVar
FATHMM
OMIM
PANTHER
Gene ontology
...
GnomAD AF
1 A S1 0 18 0 .3 25.90 .902 PL .7 179615 11539 0002331 ... 3E-05
1 A ... 0 21 1 .3 25.90 .902 PL .7 179615 11539 0002331 ... 3E-05
1 A Sn 1 45 0 .3 25.90 .902 PL .7 179615 11539 0002331 ... 3E-05
2 A S1 1 18 0 .01 29.3 .783 P .9 179615 11539 0002331 ... 7E-06
2 A ... 0 21 1 .01 29.3 .783 P .9 179615 11539 0002331 ... 7E-06
2 A Sn 0 45 0 .01 29.3 .783 P .9 179615 11539 0002331 ... 7E-06
3 B S1 1 18 0 .5 25.9 .888 PL NA 147660 10960 0002331 ... 3E-05
3 B ... 0 21 1 .5 25.9 .888 PL NA 147660 10960 0002331 ... 3E-05
3 B Sn 0 45 0 .5 25.9 .888 PL NA 147660 10960 0002331 ... 3E-05
4 B S1 0 18 0 .02 12.1 NA NA NA 147660 10960 0002331 ... 3E-05
4 B ... 0 21 1 .02 12.1 NA NA NA 147660 10960 0002331 ... 3E-05
4 B Sn 0 45 0 .02 12.1 NA NA NA 147660 10960 0002331 ... 3E-05
Set level
Sample level
Variant level
Gene level
Ontology level

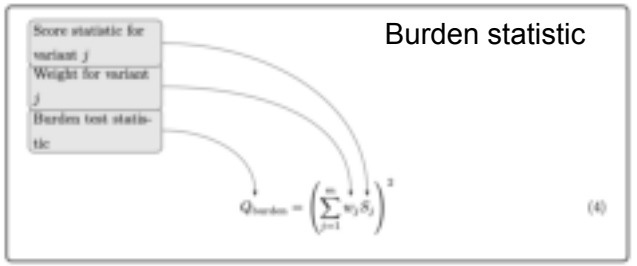
Phase 1.5

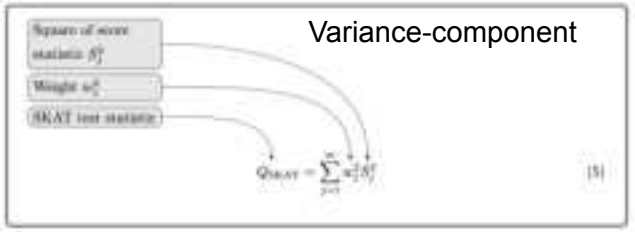
Tools

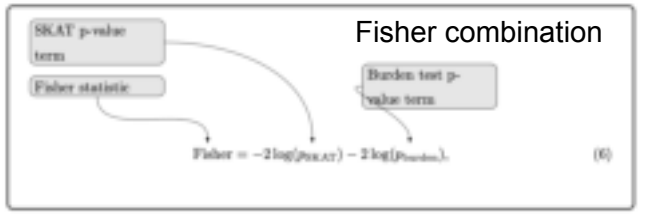


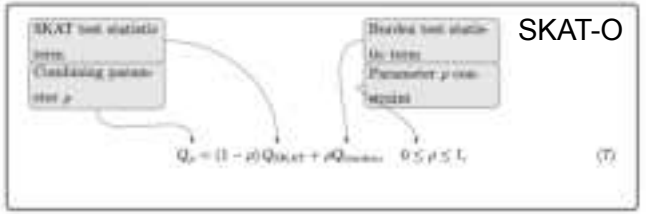

Score statistic
phenotype
Estimated mean of y under the null hypothesis ($H_0 : \beta = 0$). Obtained by application of the null model $h(\mu_i) = \alpha_0 + \alpha' X_i$.
Score statistic of the marginal model for variant j.
$S_j = \sum_{i=1}^{n} G_{ij}(y_i - \mu_i)$
(2)

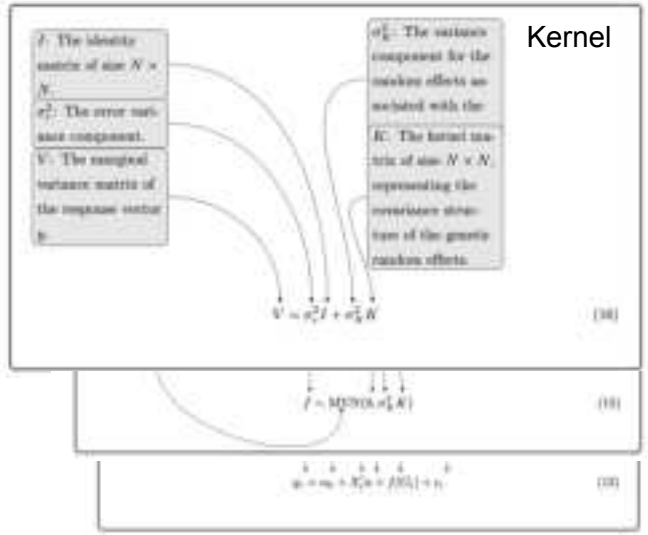

Burden summary
Allele count for variant j in individual i
indicator or weight for variant j
score for individual i
Summary genetic score for burden tests
$C_i = \sum_{j=1}^{m} w_j G_{ij}$
(3)

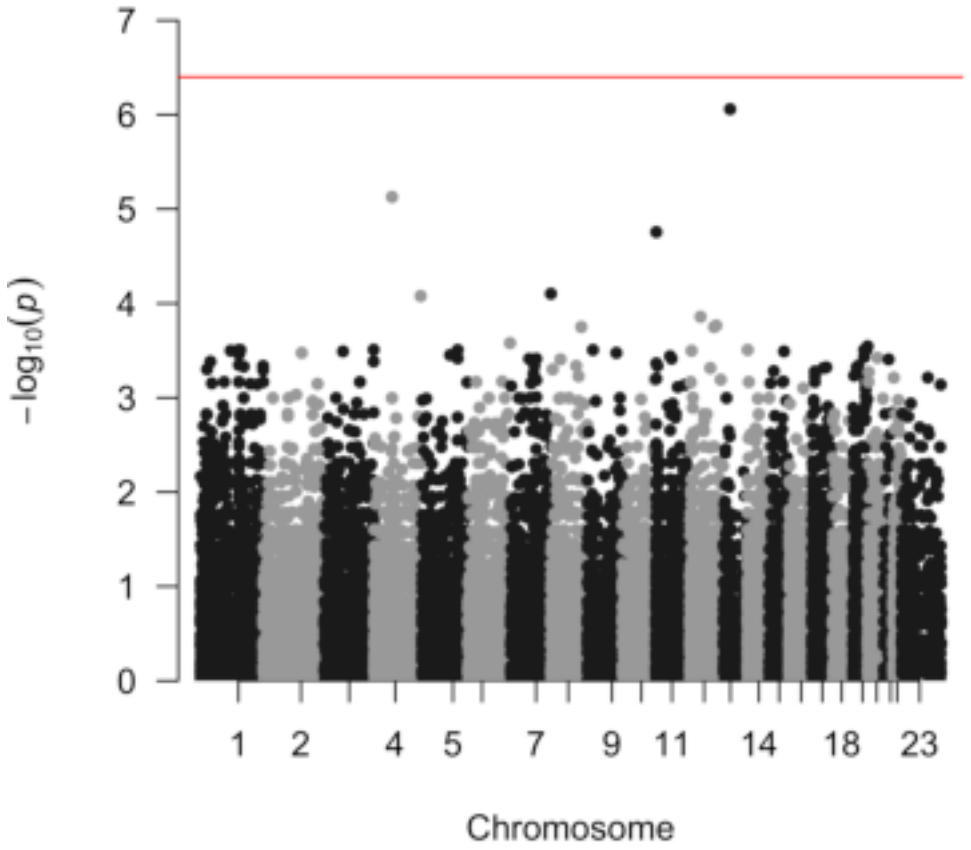

Burden statistic
Score statistic for variant j
Weight for variant j
Burden test statistic
$Q_{\text{burden}} = \left(\sum_{j=1}^{m} w_j S_j\right)^2$
(4)

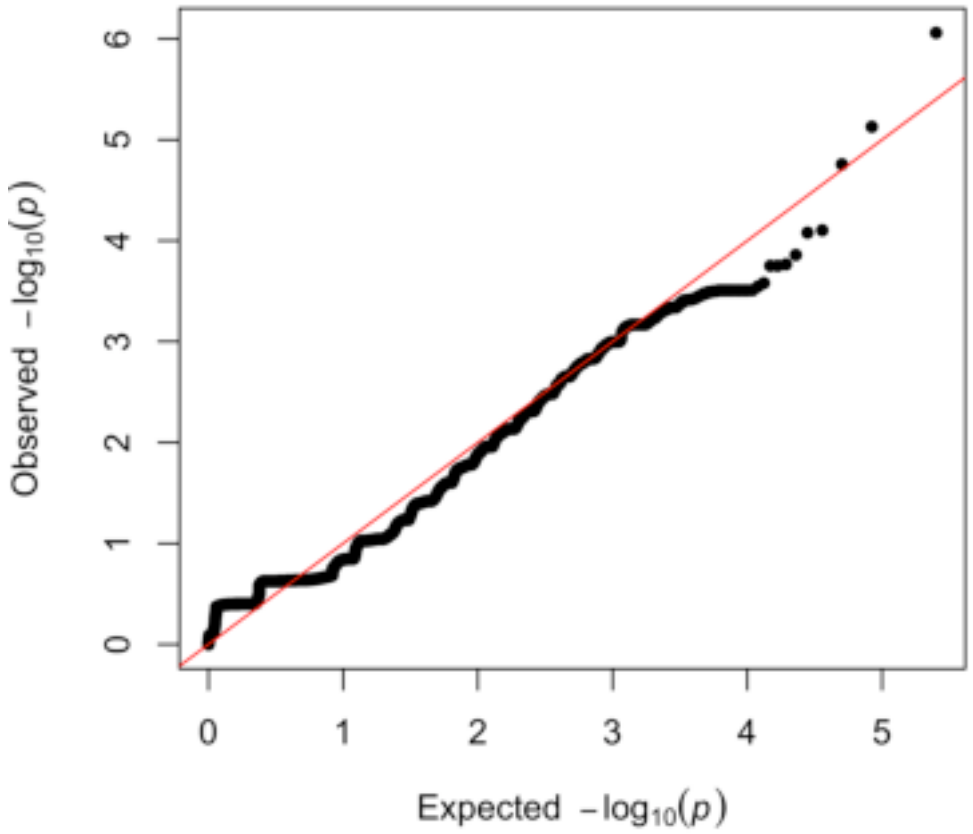

Variance-component
Square of score statistic S_j^2
Weight w_j^2
SKAT test statistic
$Q_{\text{SKAT}} = \sum_{j=1}^{m} w_j^2 S_j^2$
(5)


Fisher combination
SKAT p-value term
Fisher statistic
Burden test p-value term
$\text{Fisher} = -2\log(p_{\text{SKAT}}) - 2\log(p_{\text{burden}})$
(6)


SKAT-O
SKAT test statistic term
Combining parameter ρ
Burden test statistic (Q_b) term
Parameter ρ constraint
$Q_\rho = (1-\rho)Q_{\text{SKAT}} + \rho Q_{\text{burden}} \quad 0 \le \rho \le 1,$
(7)


Kernel
I: The identity matrix of size $N \times N$.
σ_e^2: The error variance component.
V: The marginal variance matrix of the response vector y.
σ_b^2: The variance component for the random effects associated with the
K: The kernel matrix of size $N \times N$, representing the covariance structure of the genetic random effects.
$V = \sigma_e^2 I + \sigma_b^2 K$
(10)
$\hat{\tau} \sim \text{MVN}(0, \sigma_b^2 K)$
(11)
$y_i = \alpha_0 + X_i'\alpha + \hat{f}(G_i) + \epsilon_i$
(12)



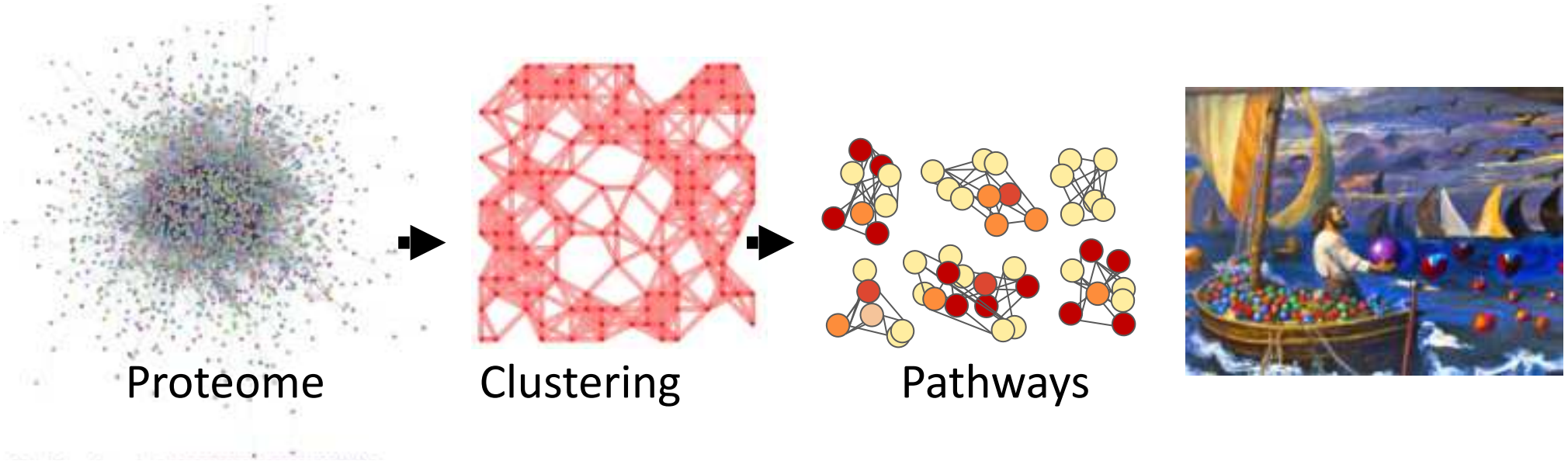


SPSS WES: Lawless, Dylan, et al. "Rare variants in infection response protein pathways associated with sepsis in children" *medRxiv* preprint (2025) doi: https://doi.org/10.1101/2025.06.12.25329504.

$$\chi^2 = \sum_{i=1}^{n} \frac{(O_i - E_i)^2}{E_i}$$

$$h_{(\mu_i)} = \alpha_0 \cdot \alpha'_{X_i} + \beta'_{G_i}$$

ProteoMCLusteR



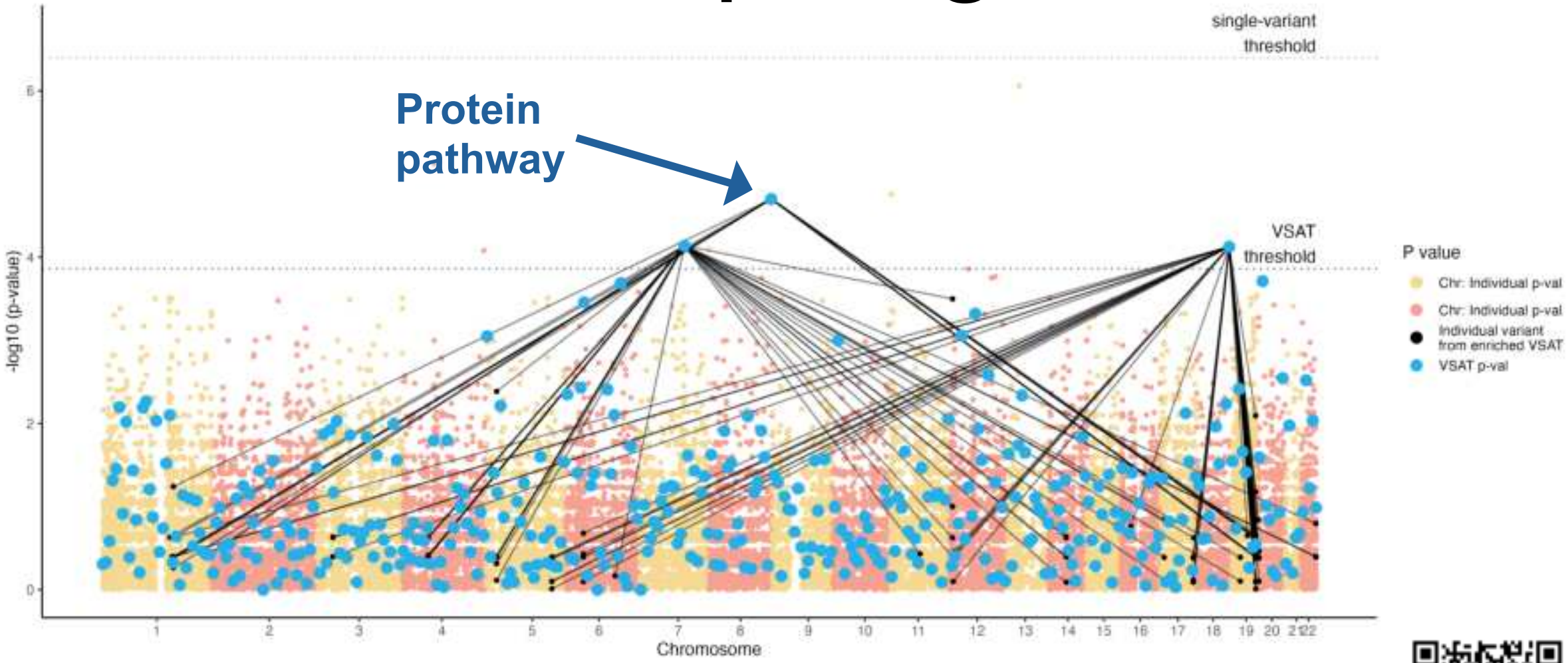
Genome-to-genome analysis reveals associations between human and mycobacterial genetic variation in tuberculosis patients from Tanzania

Zhi Ming Xu, Michaela Zwyer, Daniela Brites, Hellen Hiza, Mohamed Sasamalo, Miriam Reinhard, Anna Doetsch, Sonia Borrell, Olivier Naret, Sina Rüeger, Dylan Lawless, Faima Isihaka, Hosiana Temba, Thomas Maroa, Rastard Naftari, Christian Beisel, Jerry Hella, Klaus Reither, Damien Portevin, Sebastien Gagneux, Jacques Fellay

doi: https://doi.org/10.1101/2023.05.11.23289848

SPSS WES: Lawless, Dylan, et al. “Rare variants in infection response protein pathways associated with sepsis in children” *medRxiv* preprint (2025) doi: https://doi.org/10.1101/2025.06.12.25329504.

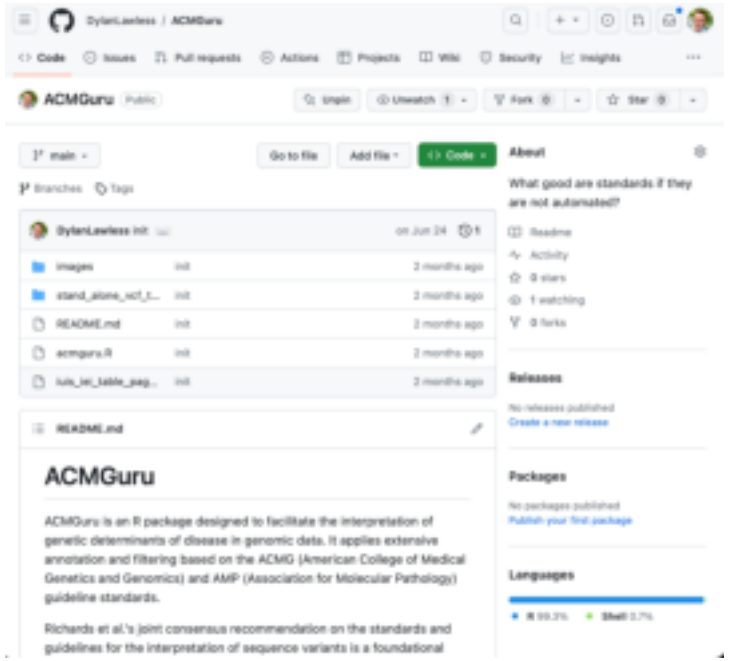
Archipelago



Archipelago: Lawless, Dylan, et al. "Archipelago method for variant set association test statistics" *medRxiv* preprint (2025).
DOI | PDF | Repository

GuRu

- Joint consensus recommendation on the standards and guidelines for the interpretation of sequence variants (Richards 2015).
- Standards and guidelines for the interpretation and reporting of sequence variants in cancer (Li 2017).
- Technical standards for the interpretation and reporting of constitutional copy-number variants (Riggs 2020).
- Effective variant filtering and expected candidate variant yield in studies of rare human disease (Pedersen 2021).
- ...

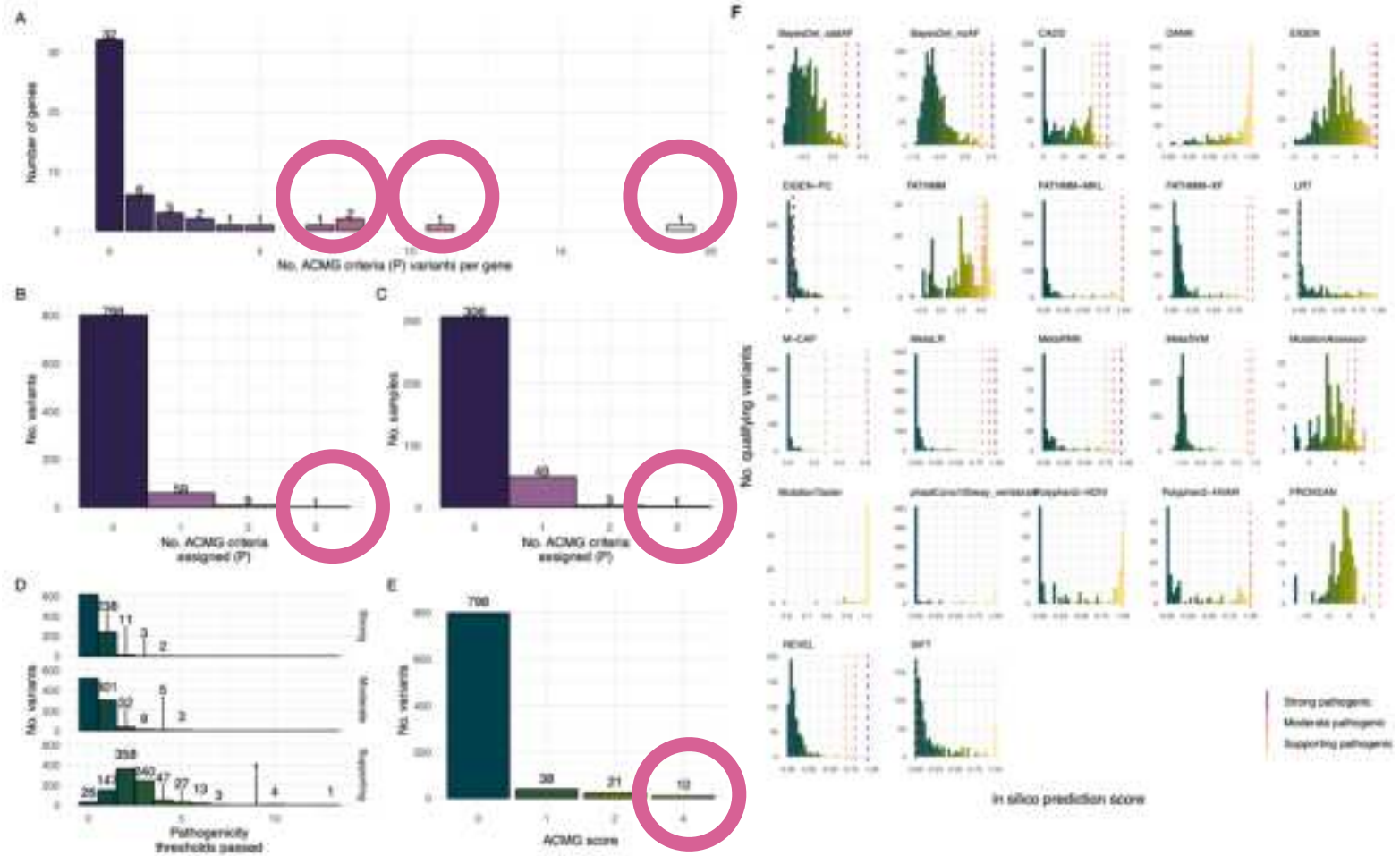


SPSS WES: Lawless, Dylan, et al. “Rare variants in infection response protein pathways associated with sepsis in children” *medRxiv* preprint (2025) doi: https://doi.org/10.1101/2025.06.12.25329504.

Evidence: scoring

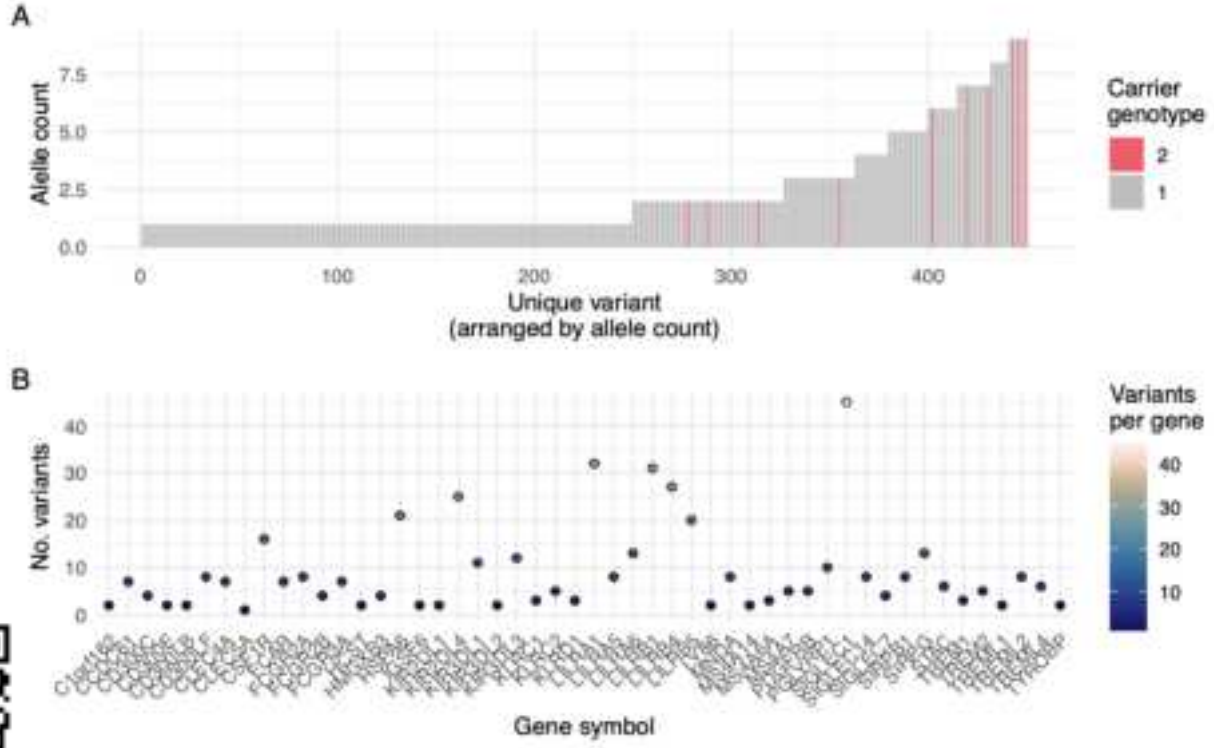
Evident pathogenicity

Predicted pathogenicity



Evidence: technical

Distribution within enriched pathway



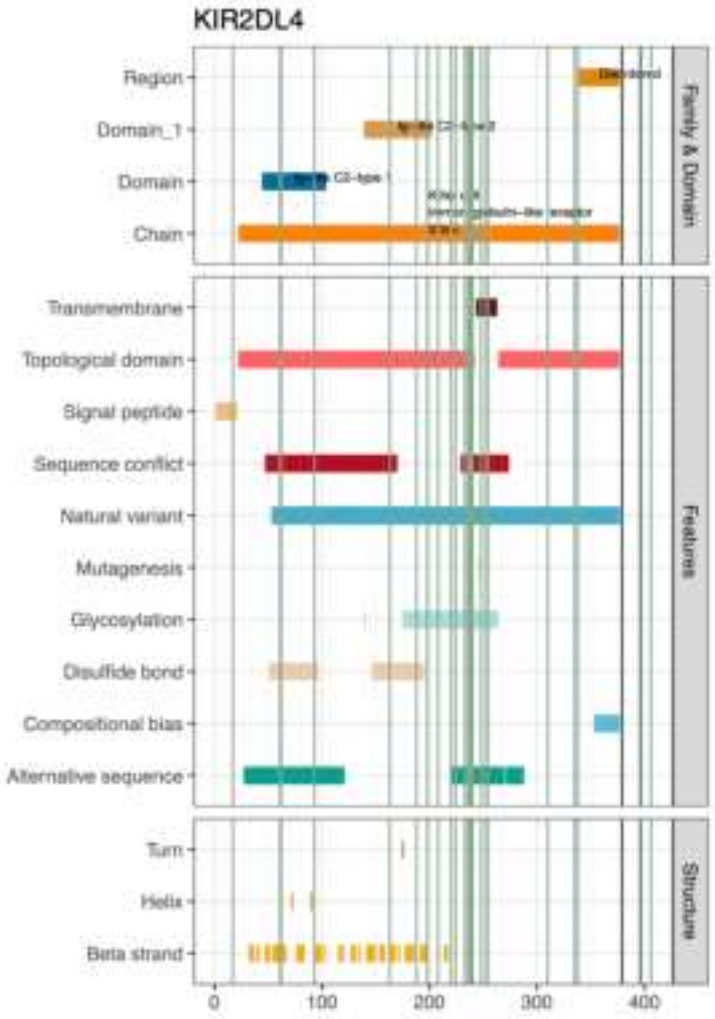
Enriched pathway variants

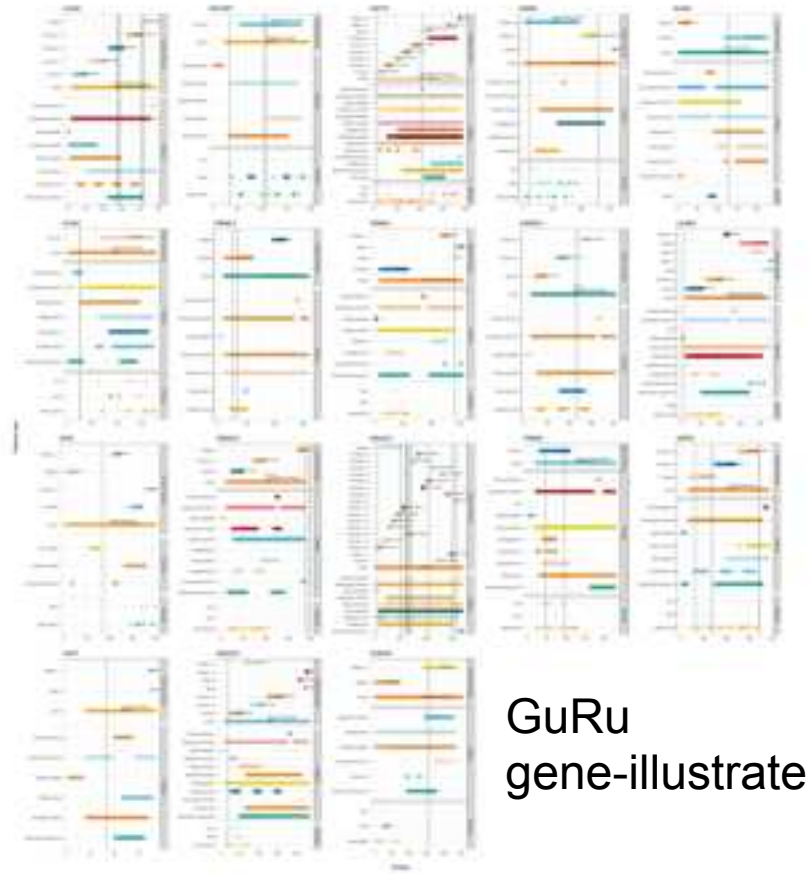
SYMBOL	HGVSp	Consequence	sample.id	genotype
KIR2DL4	ENSP00000379580.3:p.Ala379Val	missense_variant	GE076	1
KIR2DL4	ENSP00000379580.3:p.Asp310LysfsTer5	frameshift_variant	GE076	1
LILRA1	ENSP00000251372.3:p.Glu416Asp	missense_variant	P501	1
LILRA1	ENSP00000251372.3:p.Glu416Gly	missense_variant	P501	1
LILRA1	ENSP00000251372.3:p.Leu277Pro	missense_variant	ZH114	1
LILRA1	ENSP00000251372.3:p.Ser414Pro	missense_variant	P501	1
LILRA1	NA	splice_acceptor_variant	P501	1
LILRA1	NA	splice_acceptor_variant	ZH114	1
SIRPG	ENSP00000305529.3:p.Arg342Cys	missense_variant	LAU176	1
SIRPG	ENSP00000305529.3:p.Pro136GlnfsTer29	frameshift_variant	LAU176	1

Variant effect summaries

Consequence	IMPACT	genotype	unique_variants
frameshift_variant&splice_region_variant	HIGH	1	1
start_lost	HIGH	1	1
stop_gained&splice_region_variant	HIGH	1	1
stop_lost	HIGH	1	1
splice_donor_variant	HIGH	1	3
splice_acceptor_variant	HIGH	1	4
frameshift_variant	HIGH	1	8
stop_gained	HIGH	1	17
inframe_deletion&splice_region_variant	MODERATE	1	1
inframe_deletion	MODERATE	1	2
missense_variant&splice_region_variant	MODERATE	1	9
missense_variant	MODERATE	2	9
missense_variant	MODERATE	1	305

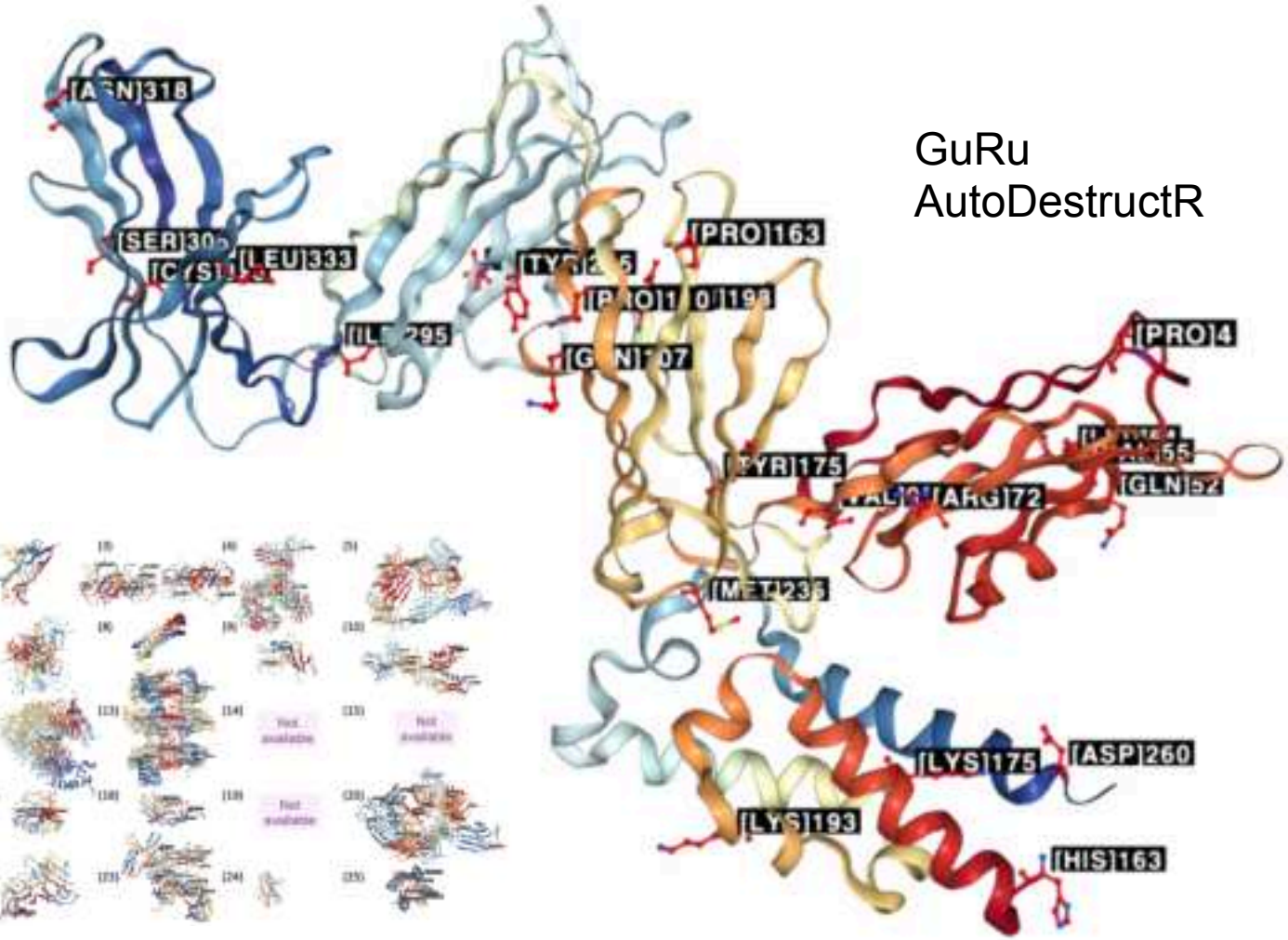
Evidence: protein function





GuRu
gene-illustrate

Evidence: protein structure

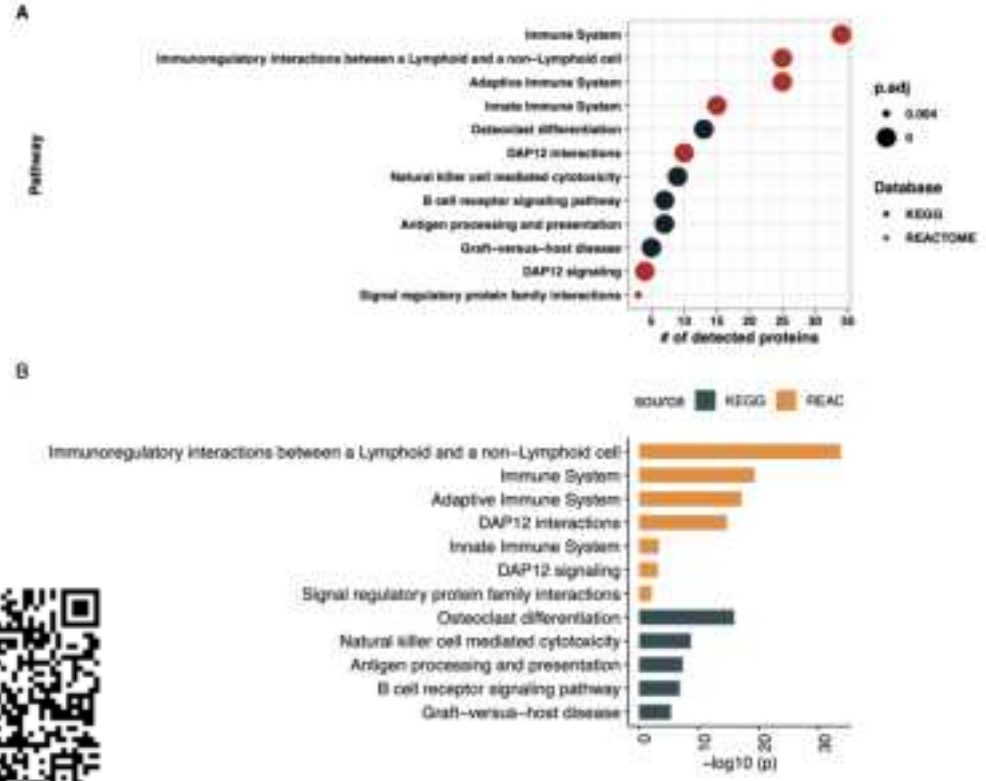


GuRu
AutoDestructR

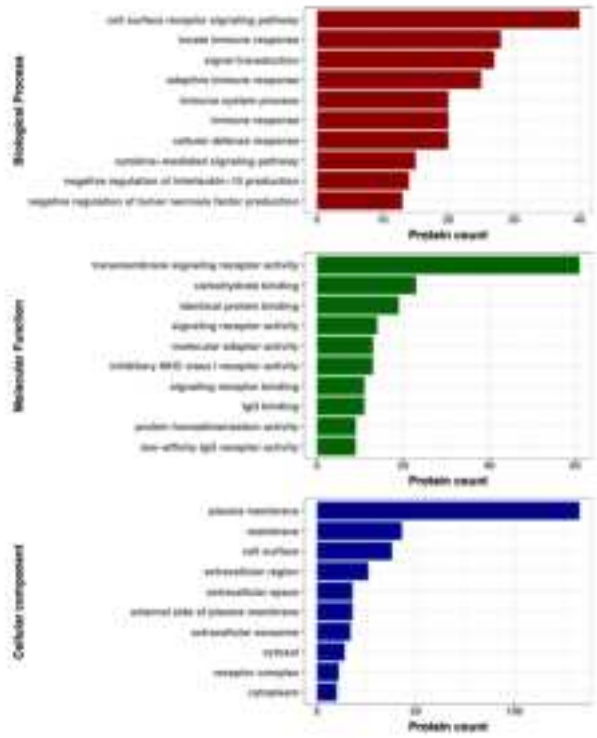
Evidence: pathway

GuRu
uniprotR

Kegg and Reactome pathway interpretation



Gene Ontology (GO) pathway interpretation



Goterm	Count	%
cell surface receptor signaling pathway	40	22.22%
innate immune response	35	19.44%
signal transduction	27	15.00%
adaptive immune response	25	13.89%
cellular defense response	20	11.11%
immune response	20	11.11%
immune system process	20	11.11%
cytokine−mediated signaling pathway	16	8.89%
negative regulation of interleukin−12 production	14	7.78%
negative regulation of tumor necrosis factor production	13	7.22%
Goterm	**Count**	**%**
transmembrane signaling receptor activity	61	33.89%
carbohydrate binding	33	18.33%
identical protein binding	19	10.56%
signaling receptor activity	14	7.78%
inhibitory MHC class I receptor activity	13	7.22%
molecular adaptor activity	13	7.22%
IgG binding	11	6.11%
signaling receptor binding	11	6.11%
low−affinity IgG receptor activity	9	5.00%
protein homodimerization activity	9	5.00%
Goterm	**Count**	**%**
plasma membrane	133	73.89%
membrane	61	33.89%
cell surface	38	21.11%
extracellular region	26	14.44%
external side of plasma membrane	19	10.56%
extracellular space	18	10.00%
extracellular exosome	17	9.44%
cytosol	14	7.78%
receptor complex	11	6.11%
cytoplasm	10	5.56%

Evidence: interpretation

Individual cases

Gene	Pattern	Cases	Pathogen
CFTR	Homozygous	Infant (1mt - 1y)	Klebsiella
APOL1	Homozygous	Term newborn	Streptococcus agalactiae
IKBKG	X-linked	2 preterm newborns	Coagulase-negative staphylococci
IKBKG	X-linked	Child (10y - 16y)	Staphylococcus aureus
ACD	Dominant	Term newborn	Gram-negative urinary tract infection
MEFV	Dominant	8 cases	-
,,,	...	...	...
...	...	...	...

Protein pathways

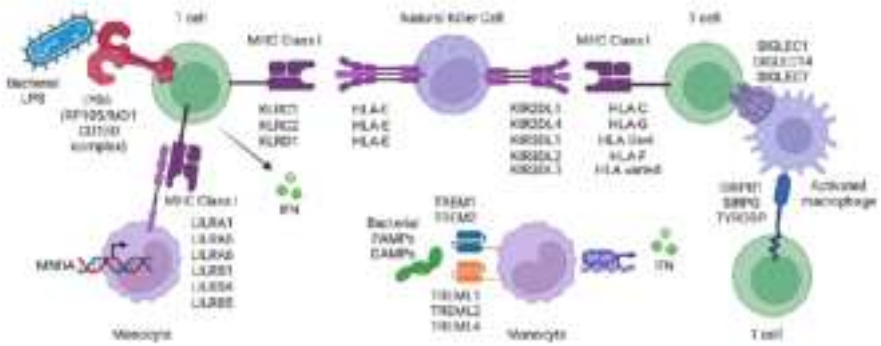
Immunomodulation and overactivation (SIRPG)

MHC class I–mediated signalling (LILR family)

Antigen presentation, Signalling

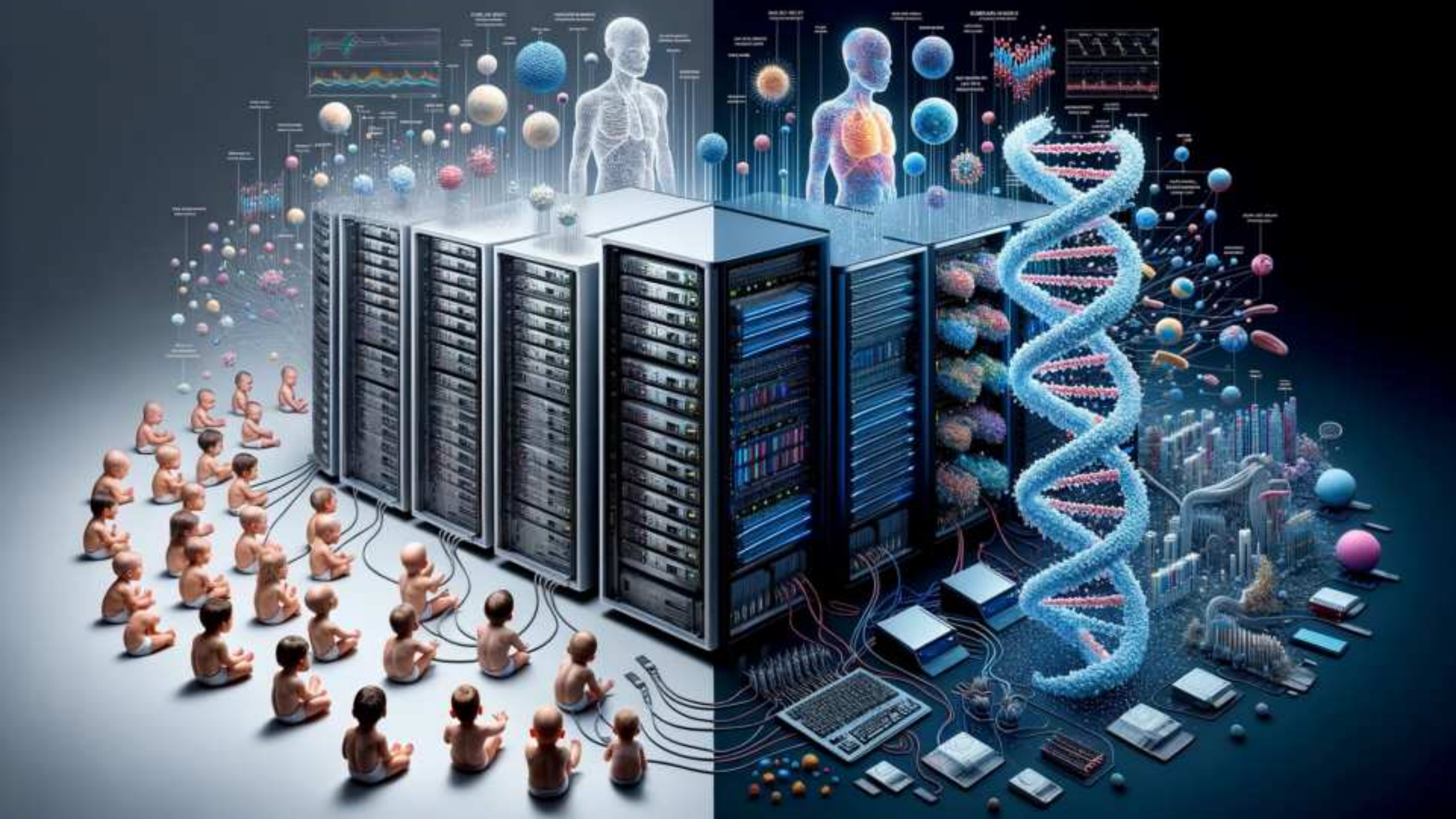
Pathogen recognition (TREML, SIGLEC1)

NK cell regulation (KIR, KLRD1)



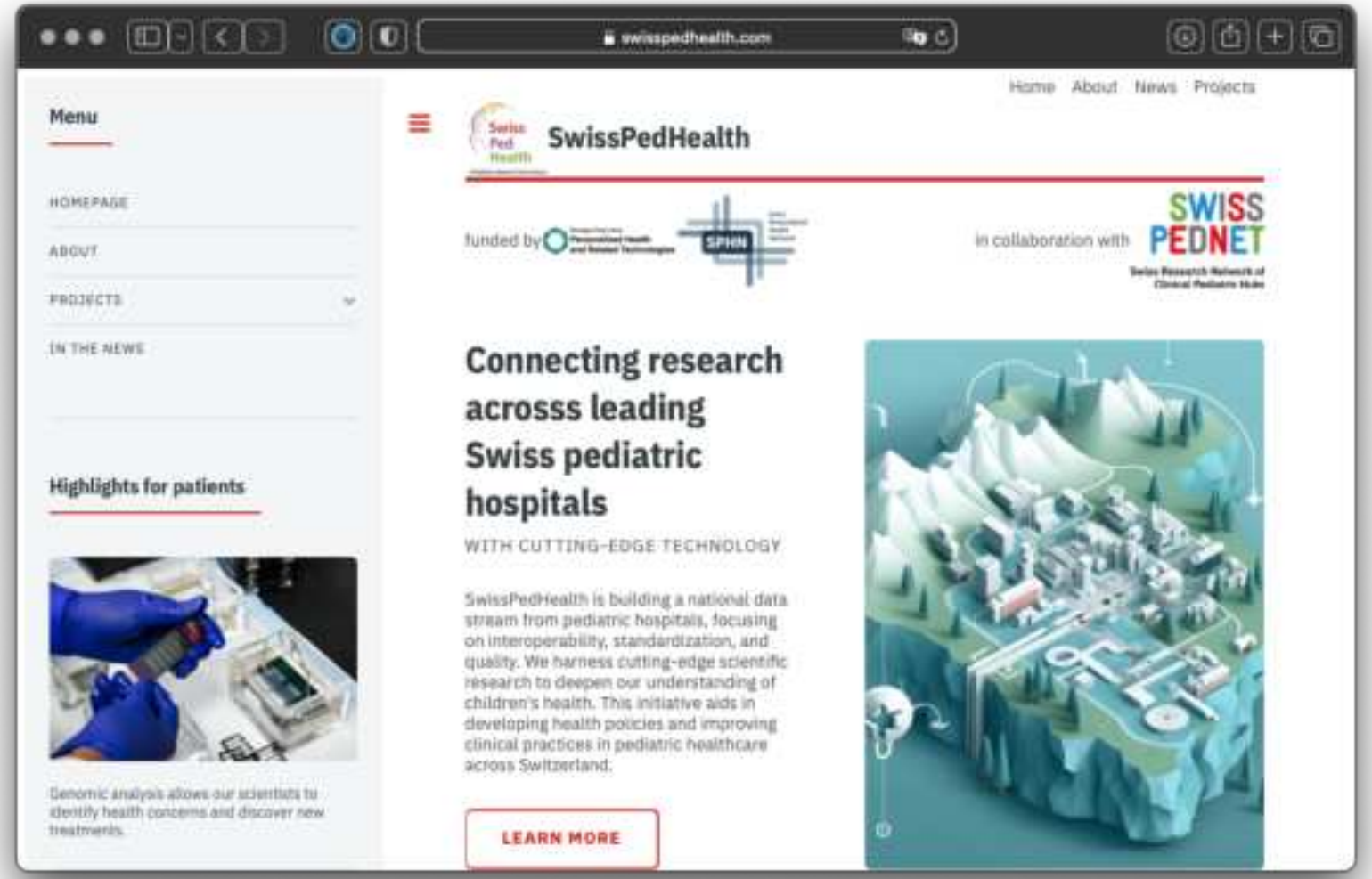
Phase 2.0
Translation


LABOR LEHRE FORSCHUNG
KINDERSPITAL ZÜRICH
UNIVERSITÄTS-KINDERSPITAL ZÜRICH



SwissPedHealth: Mozun R, Belle FN, Agostini A, *et al.* "Paediatric Personalized Research Network Switzerland (SwissPedHealth): a joint paediatric national data stream" *BMJ* (2024) doi: 10.1136/bmjopen-2024-091884.

swisspedhealth.com



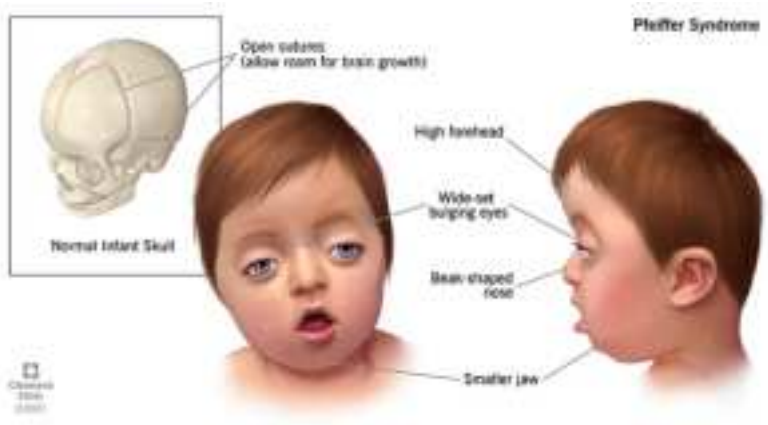
SwissPedHealth: Mozun R, Belle FN, Agostini A, *et al.* "Paediatric Personalized Research Network Switzerland (SwissPedHealth): a joint paediatric national data stream" *BMJ* (2024) doi: 10.1136/bmjopen-2024-091884.

DNA RNA Proteomics Metabolomics

Candidate cause

Variant 1: *FGFR2*
Exomiser Score: 0.998(p=2.0E-6)
Phenotype Score: 1.000
Variant Score: 1.000
Phenotype matches:
Phenotypic similarity 1.000 to Pfeiffer syndrome type 1 associated with FGFR2.

Variant 2: *ENPP1*
Exomiser Score: 0.959(p=6.3E-4)
Phenotype Score: 0.698
Variant Score: 1.000
Phenotype matches:
Phenotypic similarity 0.455 to Autosomal recessive hypophosphatemic rickets associated with ENPP1.

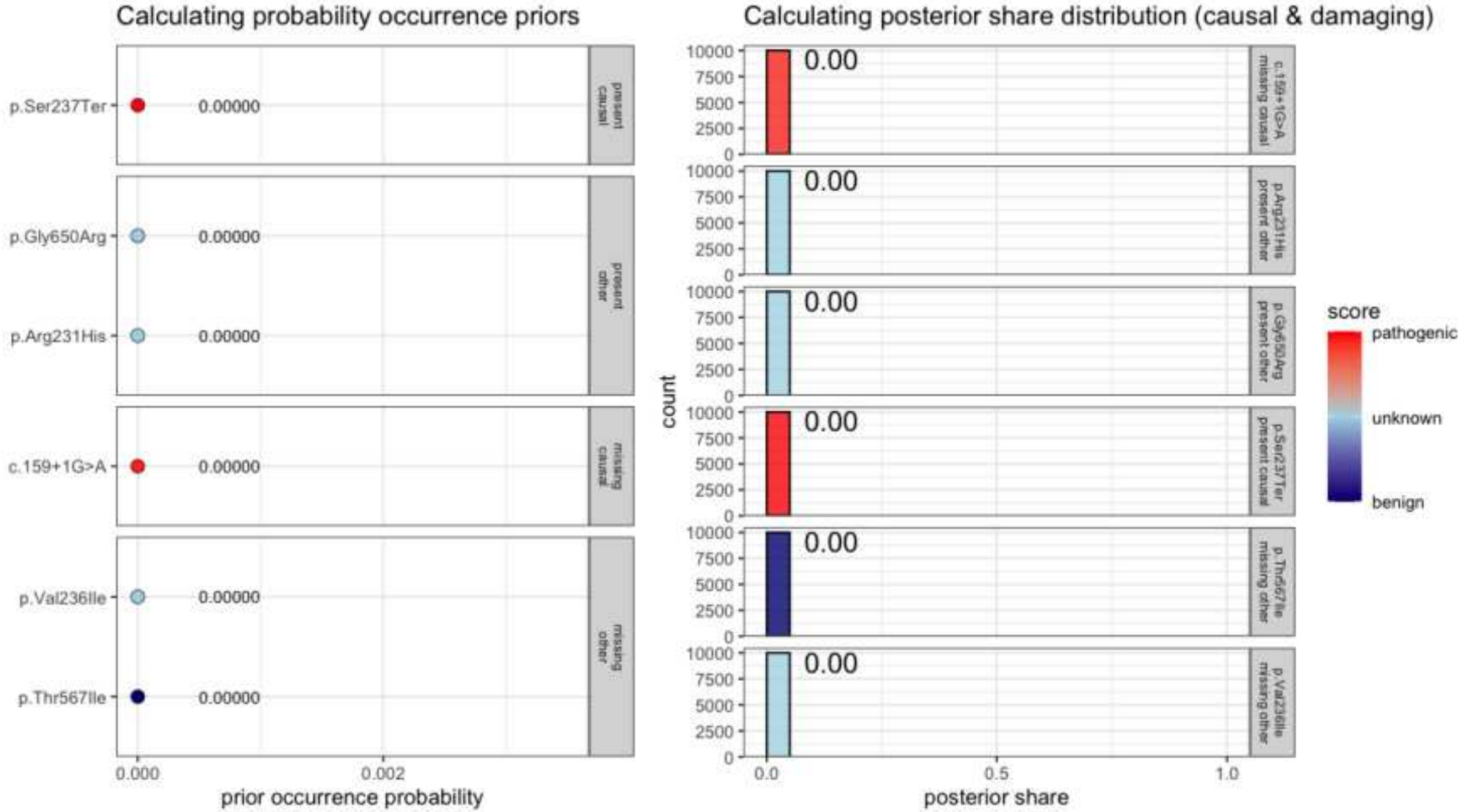


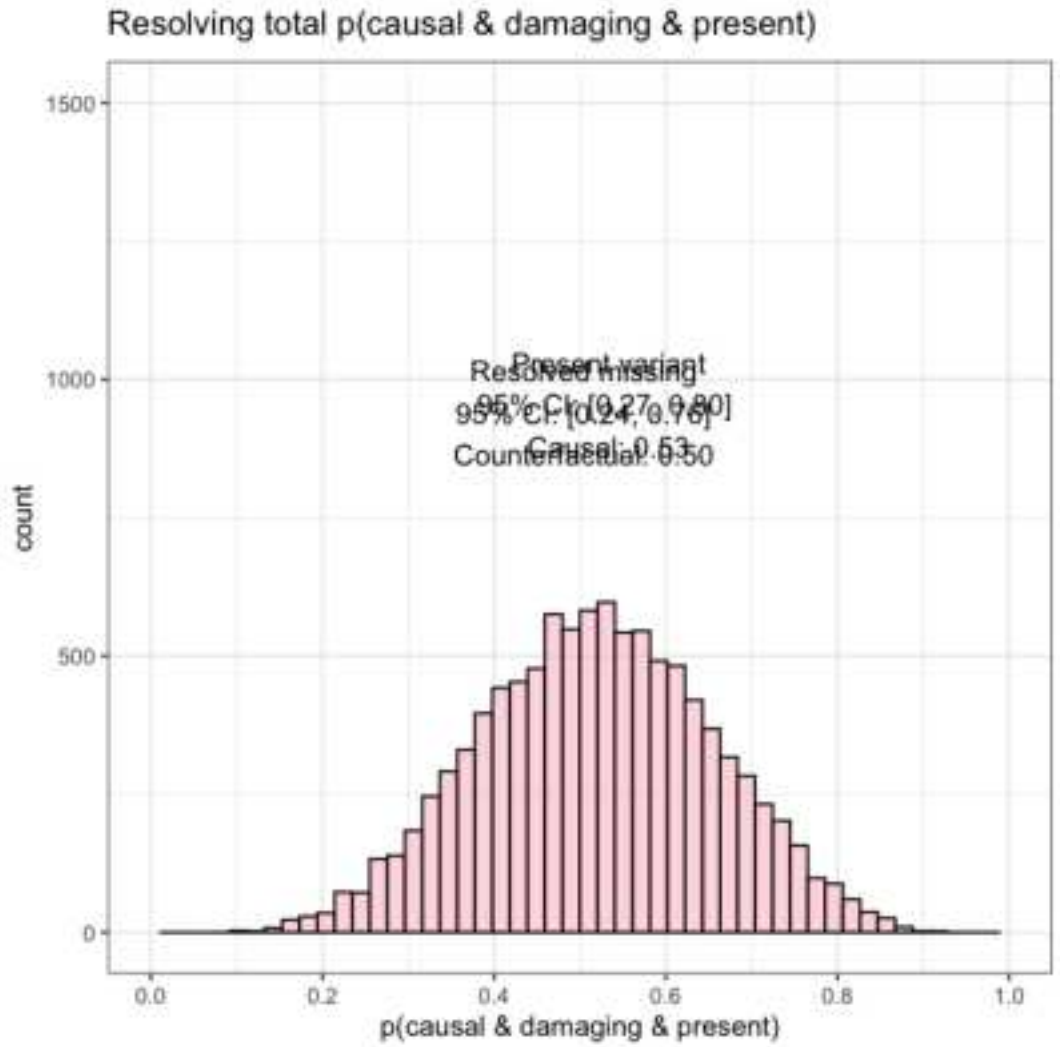
Other:

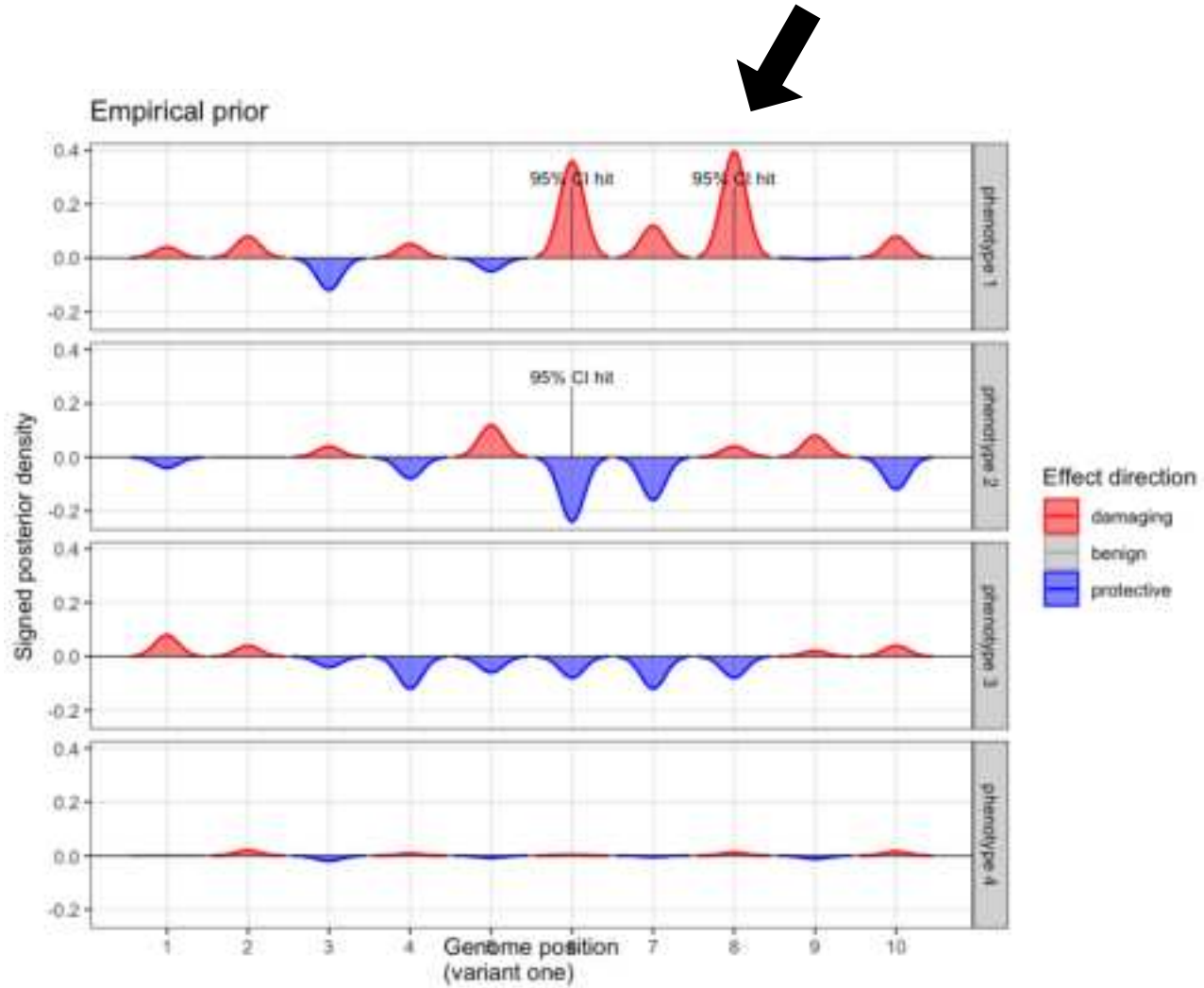
Patient had incomplete coverage:
Chr9:1501451-1601002
Chr12:3202111-3205550
...

Genetic Practice Guidelines ...

Sign here: _____


Calculating probability occurrence priors
p.Ser237Ter
p.Gly650Arg
p.Arg231His
c.159+1G>A
p.Val236Ile
p.Thr567Ile
0.00000
present causal
present other
missing causal
missing other
0.000
0.002
prior occurrence probability
Calculating posterior share distribution (causal & damaging)
count
10000
7500
5000
2500
0
0.00
c.159+1G>A missing causal
p.Arg231His present other
p.Gly650Arg present other
p.Ser237Ter present causal
p.Thr567Ile missing other
p.Val236Ile missing other
0.0
0.5
1.0
posterior share
score
pathogenic
unknown
benign

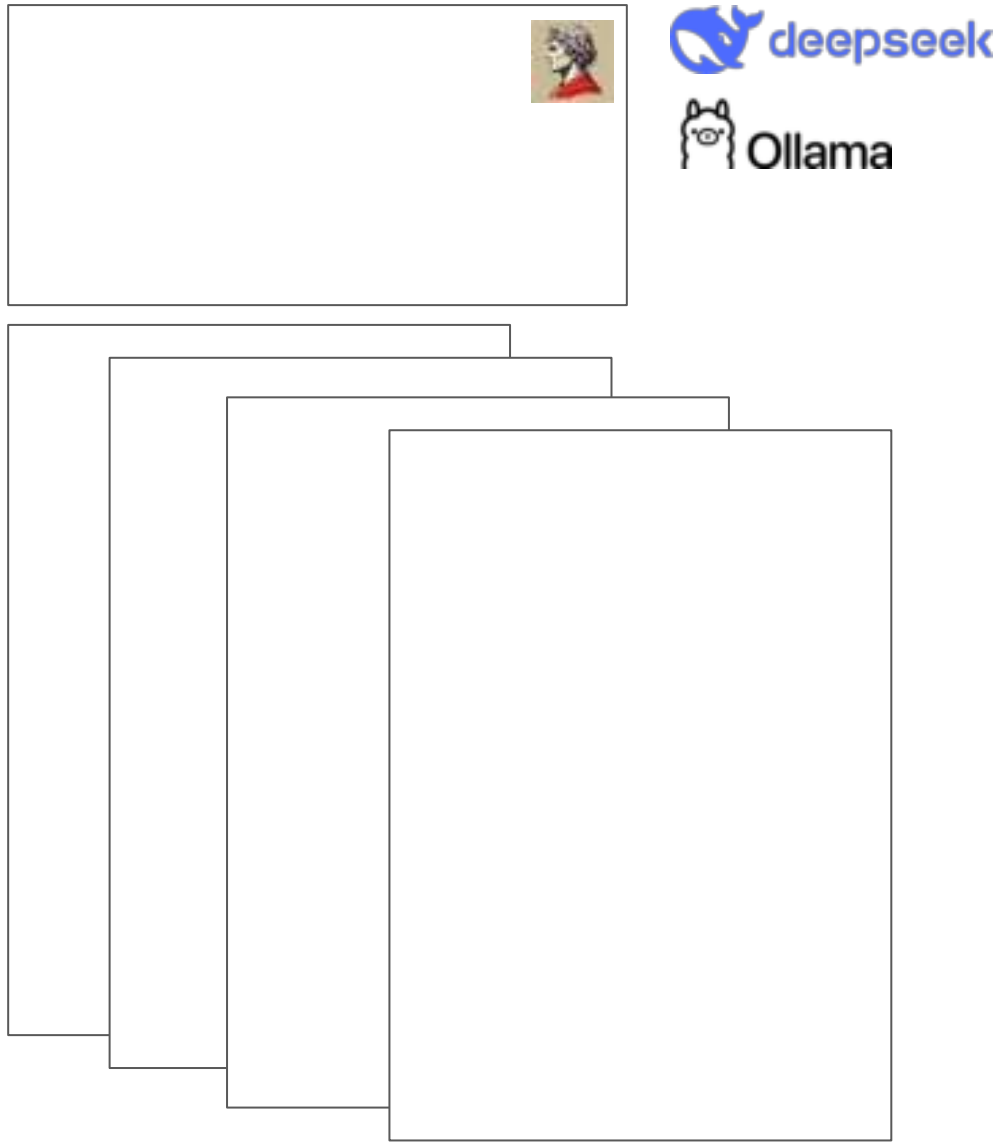




Quant: The quantitative omic epidemiology group, et al. "Quantifying prior probabilities for disease-causing variants reveals the top genetic contributors in inborn errors of immunity" *medRxiv* preprint (2025).
DOI | PDF | Video

Actionable

Parameter	present	missing
Gene	NFKB1	NFKB1
HGVSc	c.710C>G	c.159+1G>A
HGVSp	p.Ser237Ter	.
Inheritance	AD	AD
Patient sex	Male	Male
gnomAD frequency	6.57e-06	6.57e-06
95% CI lower	0.003	NA
p(median)	0.090	NA
95% CI upper	0.551	NA
Posterior p(causal)	0.377	0.364
Interpretation	Reported causal; variant observed	Reported causal; variant not detected — consider follow-up
Summary	Overall probability of correct causal diagnosis due to SNV/INDEL given the currently available evidence: 0.511 (95% CI 0.237–0.774).	



Verifiable evidence interpretation RAG:

“ Multiomic analysis showed that the nonsense variant is technically robust and functionally deleterious. RNA sequencing confirmed that the transcript is preserved without evidence of decay, yet proteomic profiling demonstrated absence of the normal protein product, consistent with truncation and loss of function. Metabolomic readouts supported disruption of ... ”

Phase 3.0
Simplify

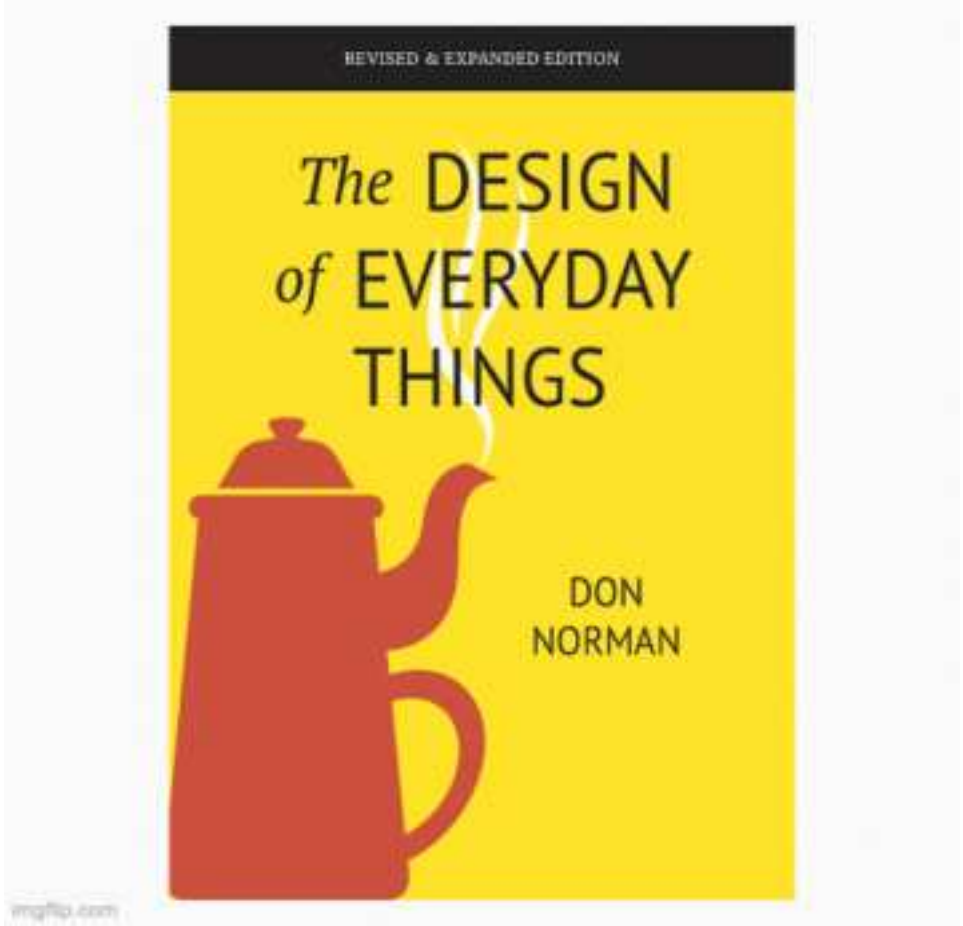

LOOK UP!
JAMES BOND DOES IT EVERYWHERE
IN "THUNDERBALL"!

Chic. Not geek.

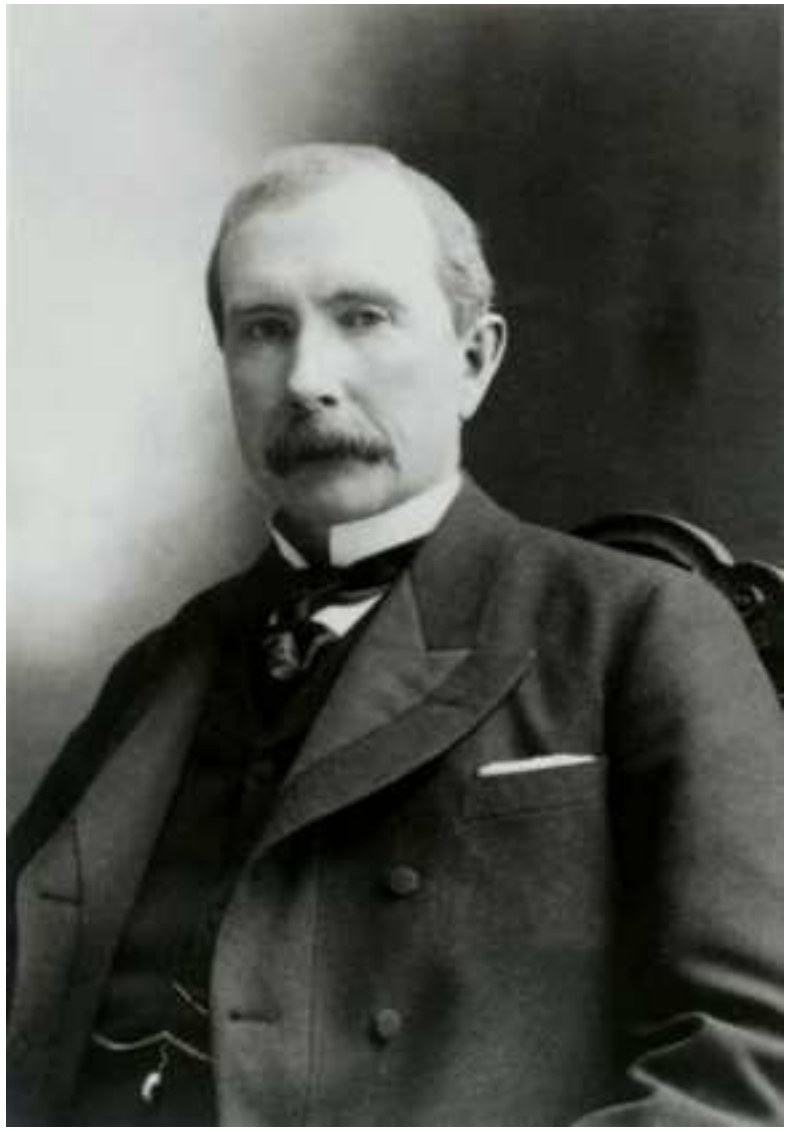
Think different.

826-5432-A

Simplicity is the ultimate sophistication



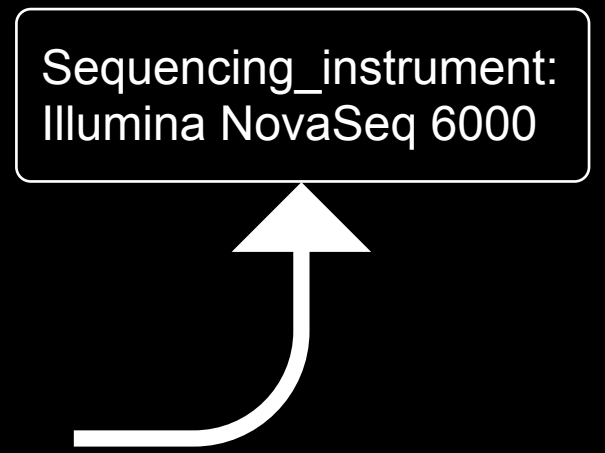
Supply chain



J.D. Rockefeller

SPHN-compliant RDF for clinical integration

Resource Description Framework Turtle metadata stored in parallel to encrypted genomics. Ready if you want to involve hospitals, clinics, or national projects.



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DOI | PDF

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DOI | PDF | Video

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DOI | PDF

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Strategic Focus Area Personalized Health and Related Technologies

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The Hyve

SMC

CHUV

SIB Swiss Institute of Bioinformatics

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Date and time : Wednesday 10 September,
from 11:00 to 12:30, in Room Montreal.
Talk duration: 15 min (incl. 3 min for Q&A)
Session chairs: Katja Bärenfaller and David Gfeller.