Integrating personalized gene expression profiles into predictive disease-associated gene pools

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ARTICLE OPEN

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Jörg Menche[1,2,3], Emre Guney[1,4], Amitabh Sharma[1,4,5], Patrick J. Branigan[6], Matthew J. Loza[6], Frédéric Baribaud[6], Radu Dobrin[6] and Albert-László Barabási[1,2,4,5]

Gene expression data are routinely used to identify genes that *on average* exhibit different expression levels between a case and a control group. Yet, very few of such differentially expressed genes are detectably perturbed in individual patients. Here, we develop

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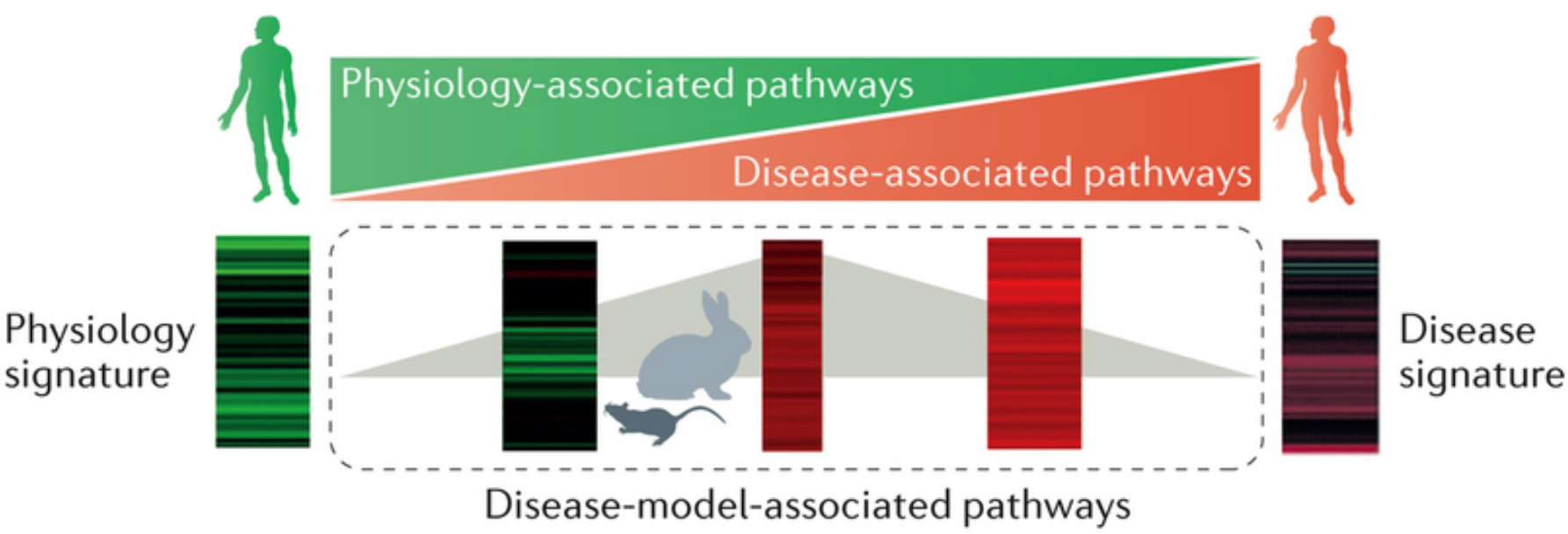
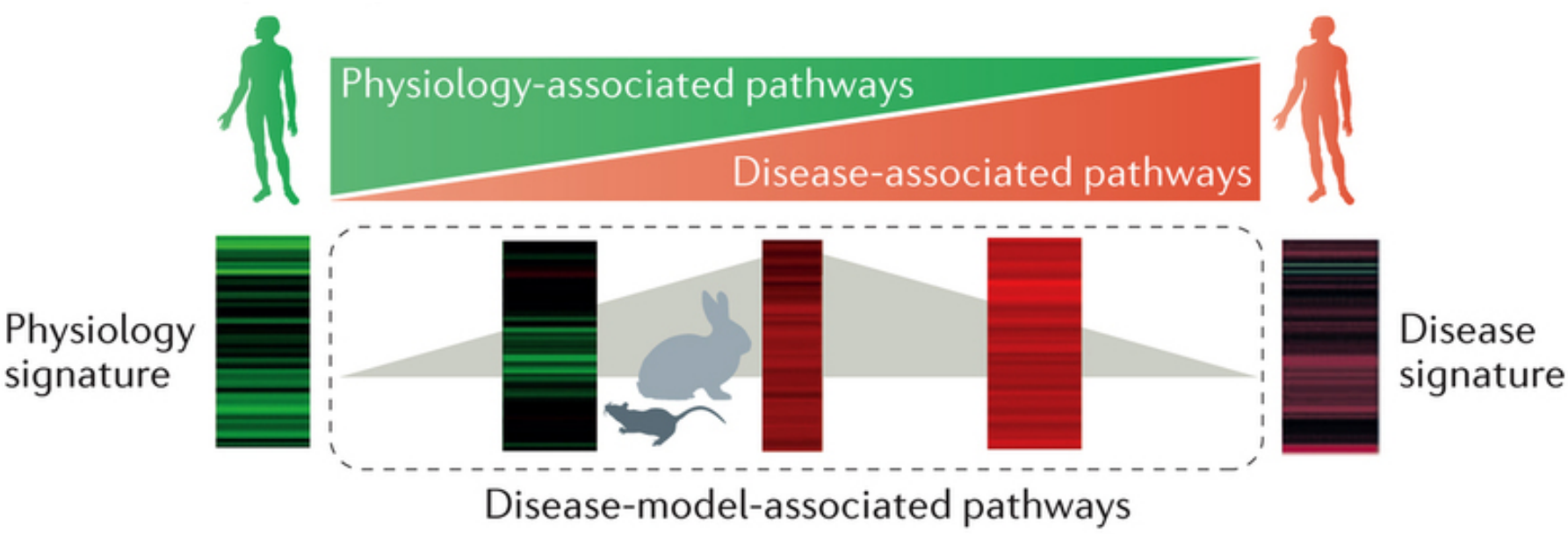


Image from *Moffat et al., 2017, Nat Rev Drug Discov*



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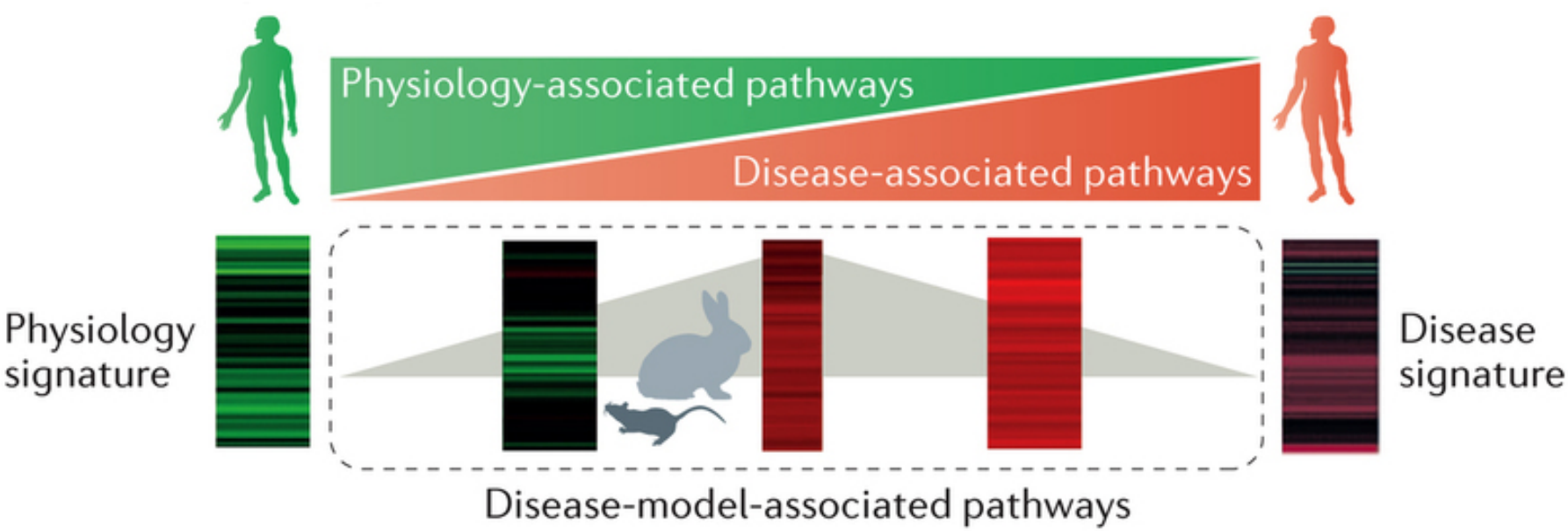

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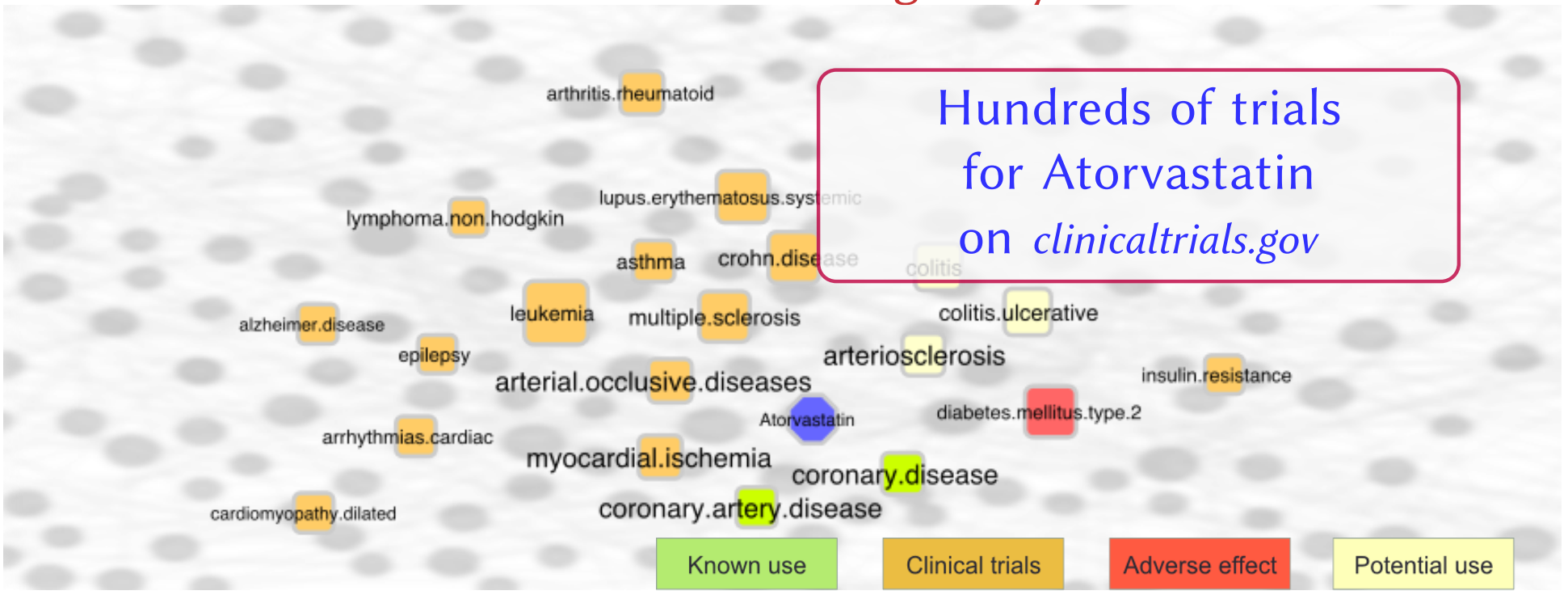
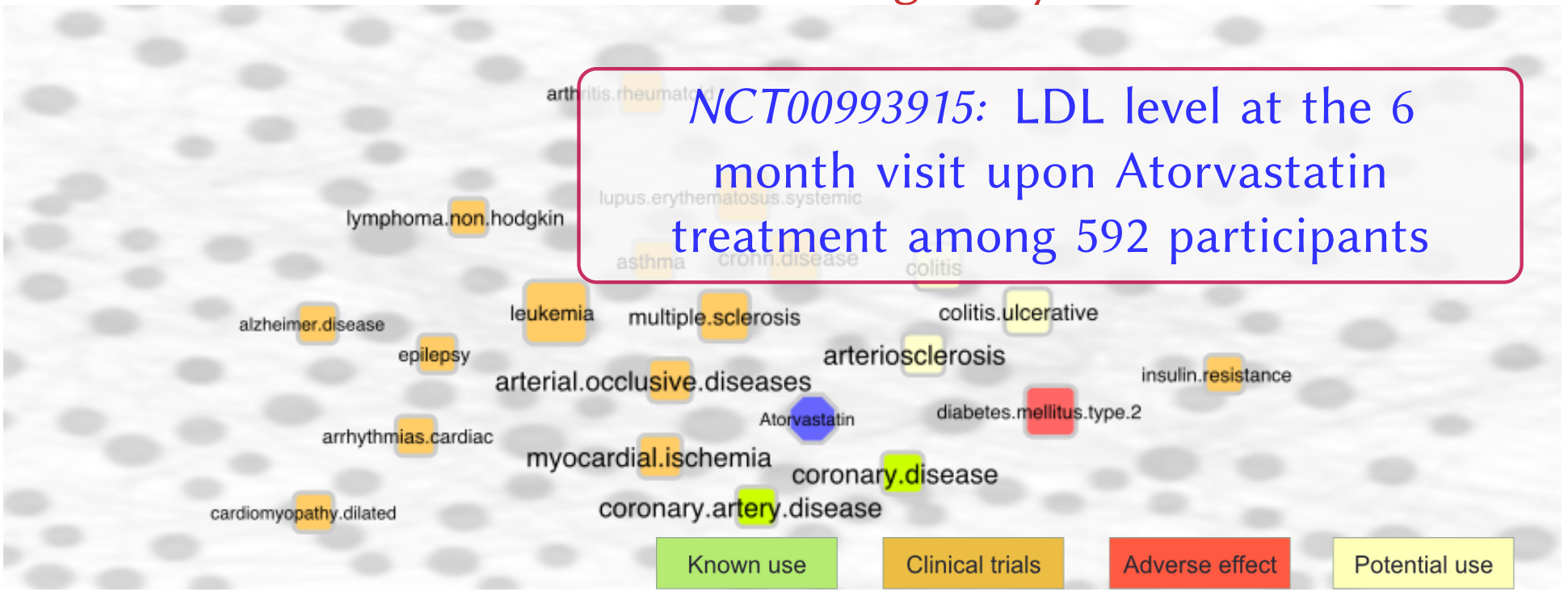
Patient-level heterogeneity



Hundreds of trials for Atorvastatin on *clinicaltrials.gov*

Atorvastatin: one of the most successful cholesterol-lowering drug

Patient-level heterogeneity



Atorvastatin: one of the most successful cholesterol-lowering drug

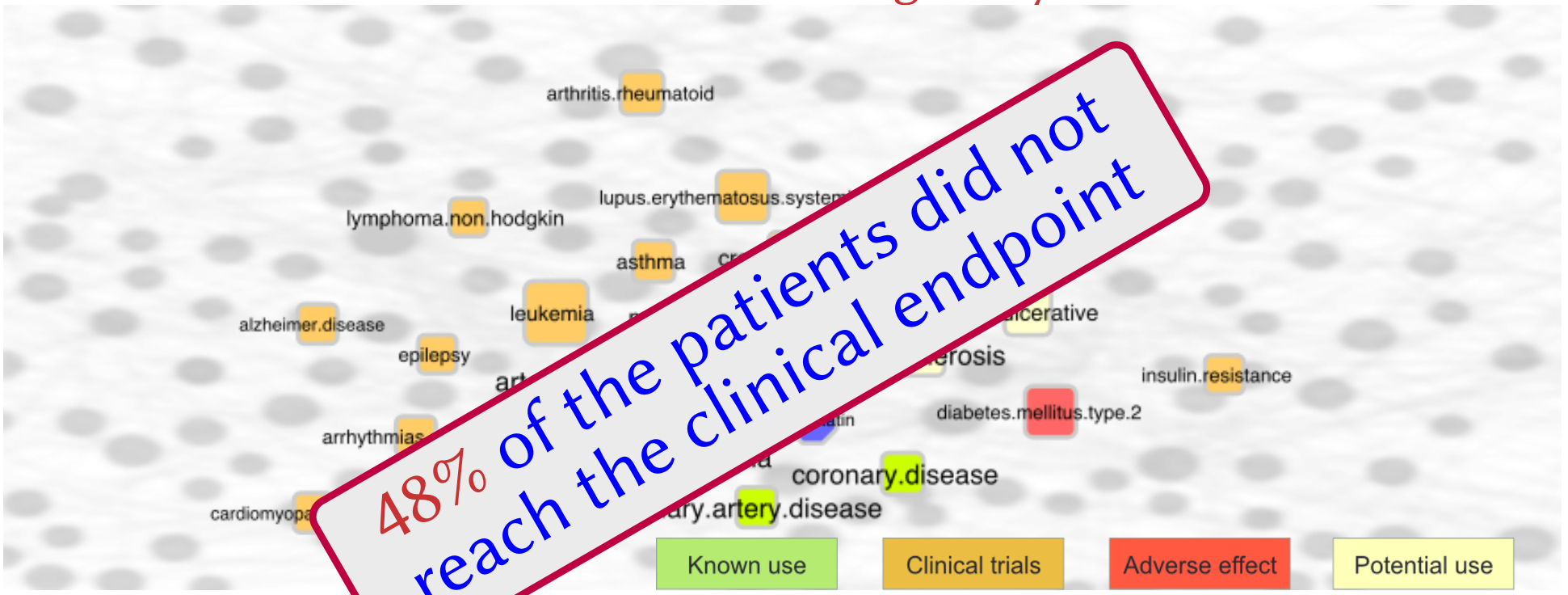
Clinical endpoint: LDL $\leq$ 100 mg/dL after treatment

[*Pre-treatment*] The average LDL level 179 mg/dL

[*Post-treatment*] 52% of the participants had LDL $\leq$ 100 mg/dL

clinicaltrials.gov/ct2/show/results/NCT00993915

Patient-level heterogeneity



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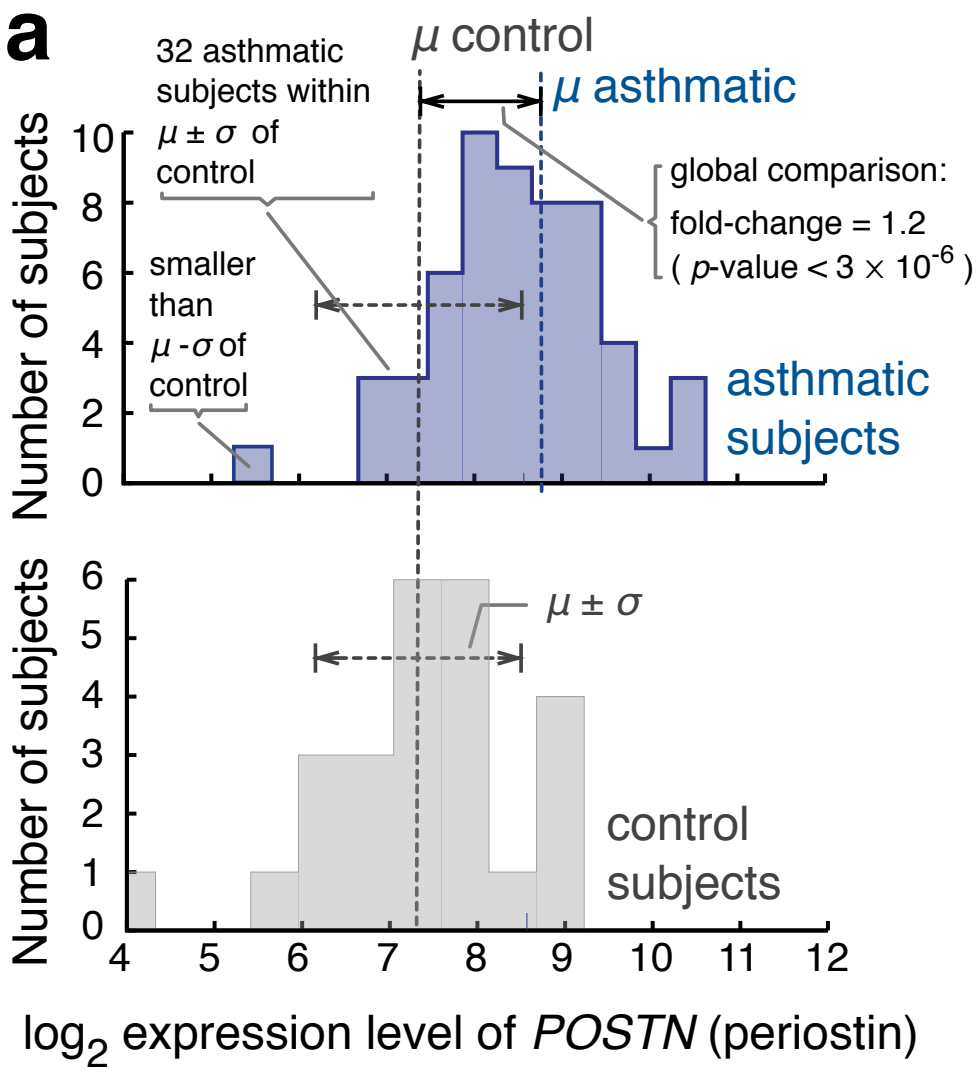
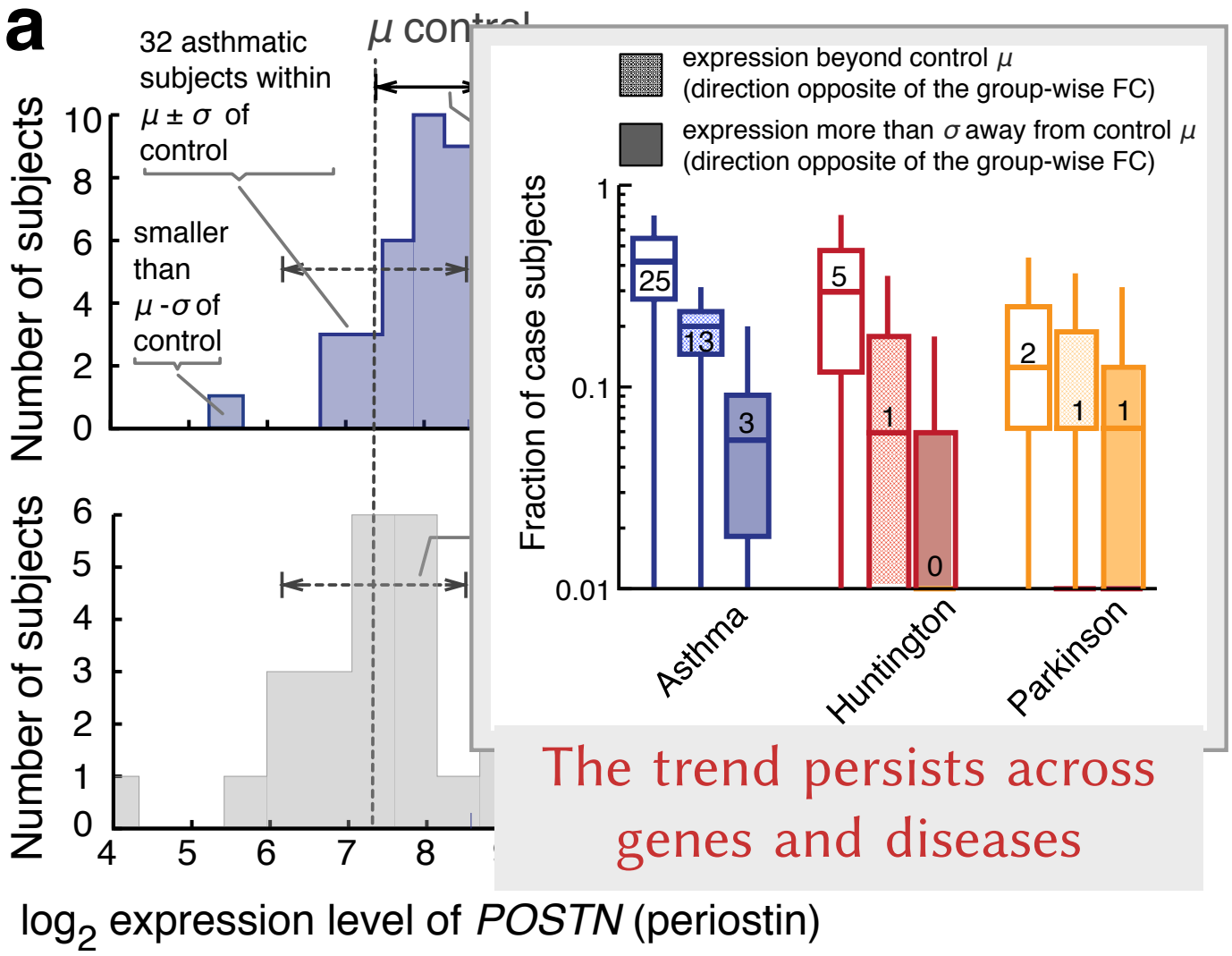
Gene expression of POSTN in asthmatic and control invidividuals



Periostin (*POSTN*) functions in the adhesion and migration of epithelial cells, whose up-regulation is a biomarker for Asthma.

Gene expression of POSTN in asthmatic and control invidividuals



The trend persists across genes and diseases

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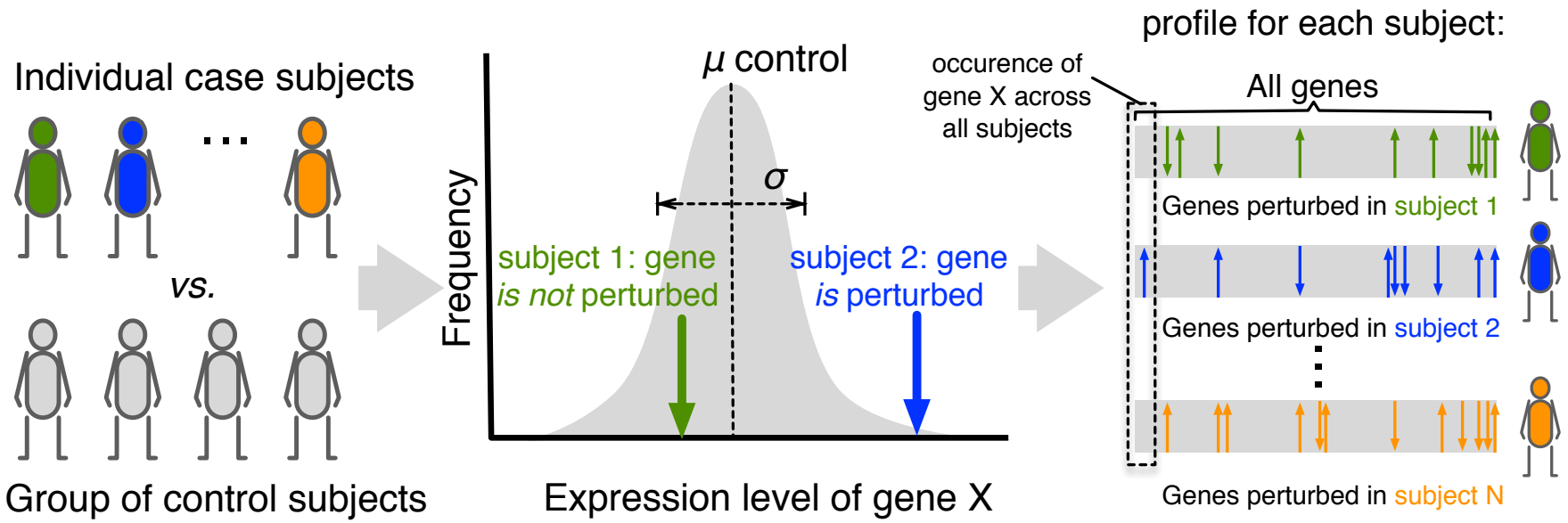
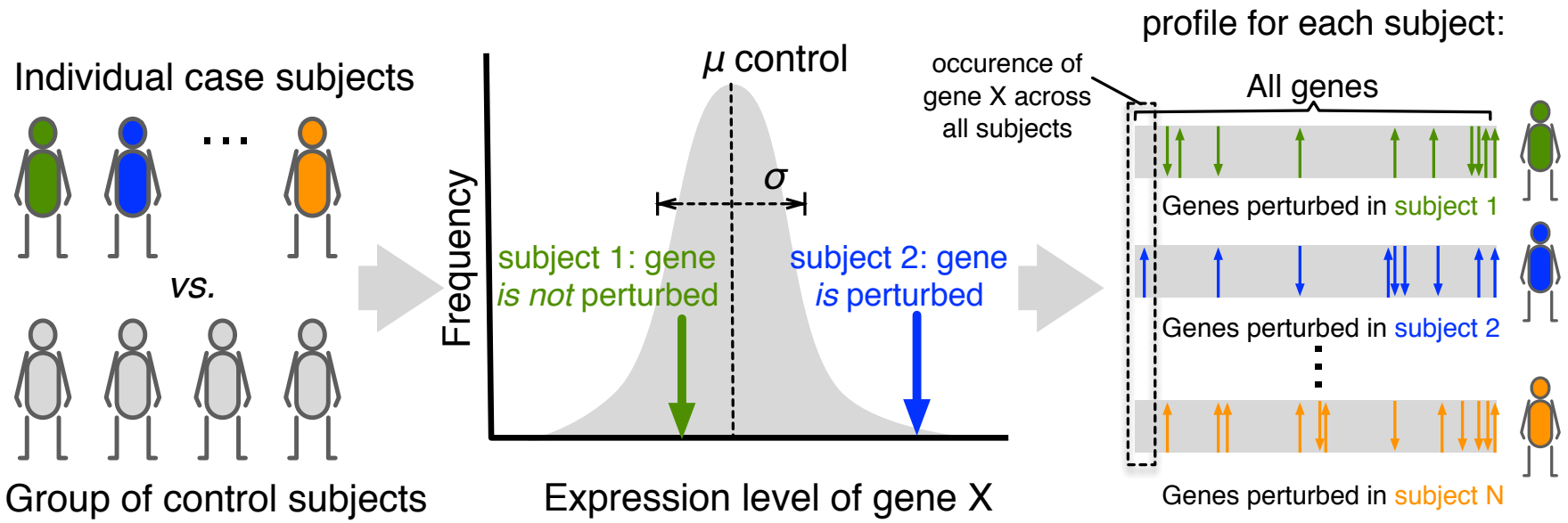
PEEP: PErsonalized Expression Profile



	Samples			
Case	x	x	...	x
Control	c	c	c	c

$$z(gene \text{ in } x) = \frac{expression_x(gene) - \mu_c(gene)}{\sigma_c(gene)}$$

PEEP: PErsonalized Expression Profile



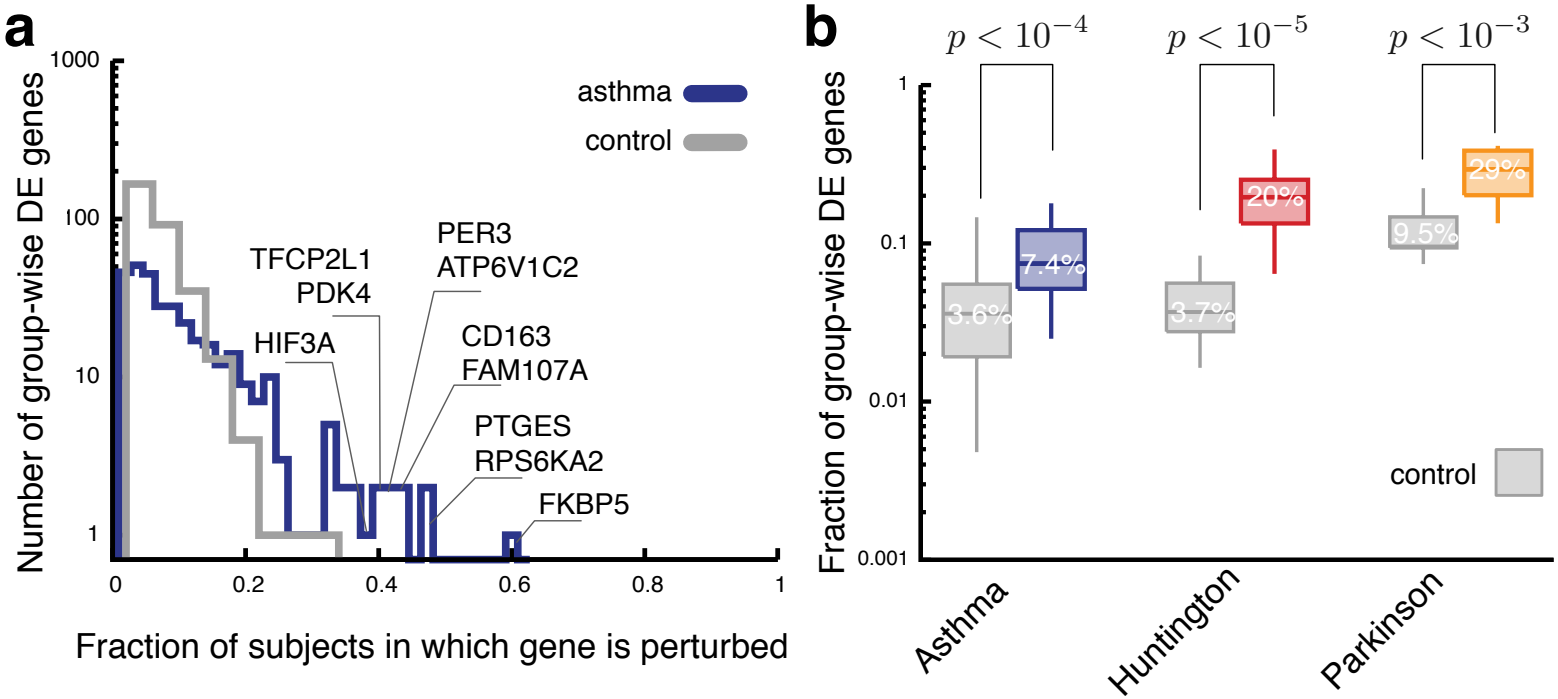
	Samples			
Case	x	x	...	x
Control	c	c	c	c

$$z(gene \text{ in } \mathrm{x}) = \frac{expression_{x}(gene) - \mu_{c}(gene)}{\sigma_{c}(gene)}$$

$$PEEP(x) : \forall gene \; |z(gene \text{ in } \mathrm{x})| > z_{threshold}$$

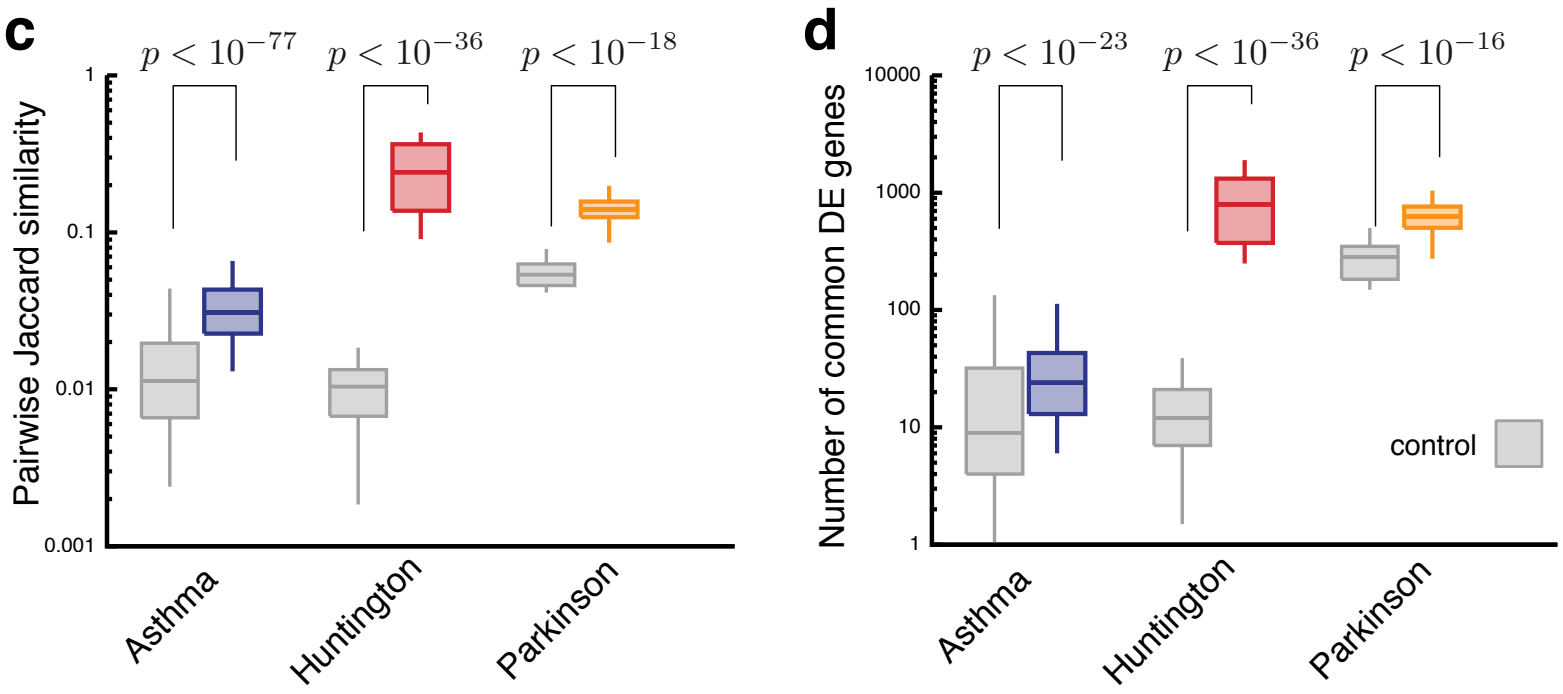
[Genes that are significantly perturbed in each individual]

Quantifying the heterogeneity using PEEPs



Only a small fraction of group-wise DE genes appears in PEEP of each patient

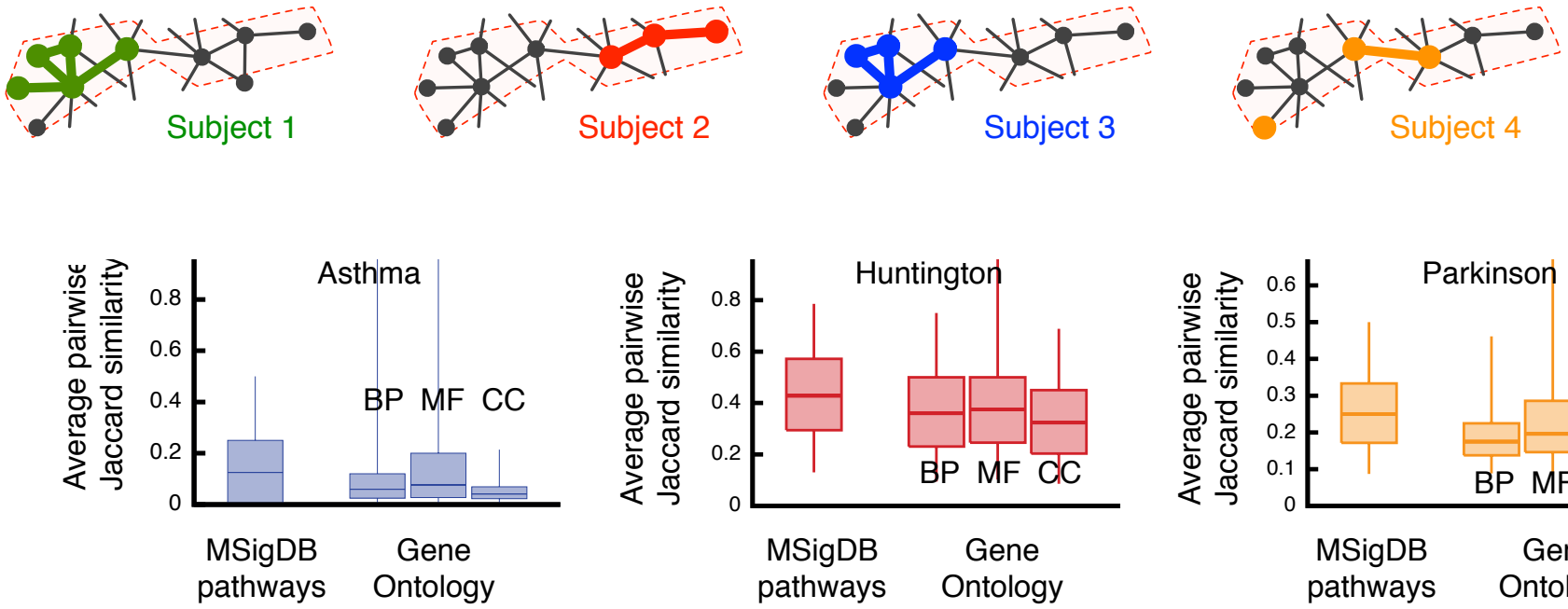
Quantifying the heterogeneity using PEEPs



The overlap between PEEPs of two individuals with the same disease

- is low ($< 30\%$), suggesting high heterogeneity at the transcription level
- is higher than the overlap between the PEEPs of healthy subjects

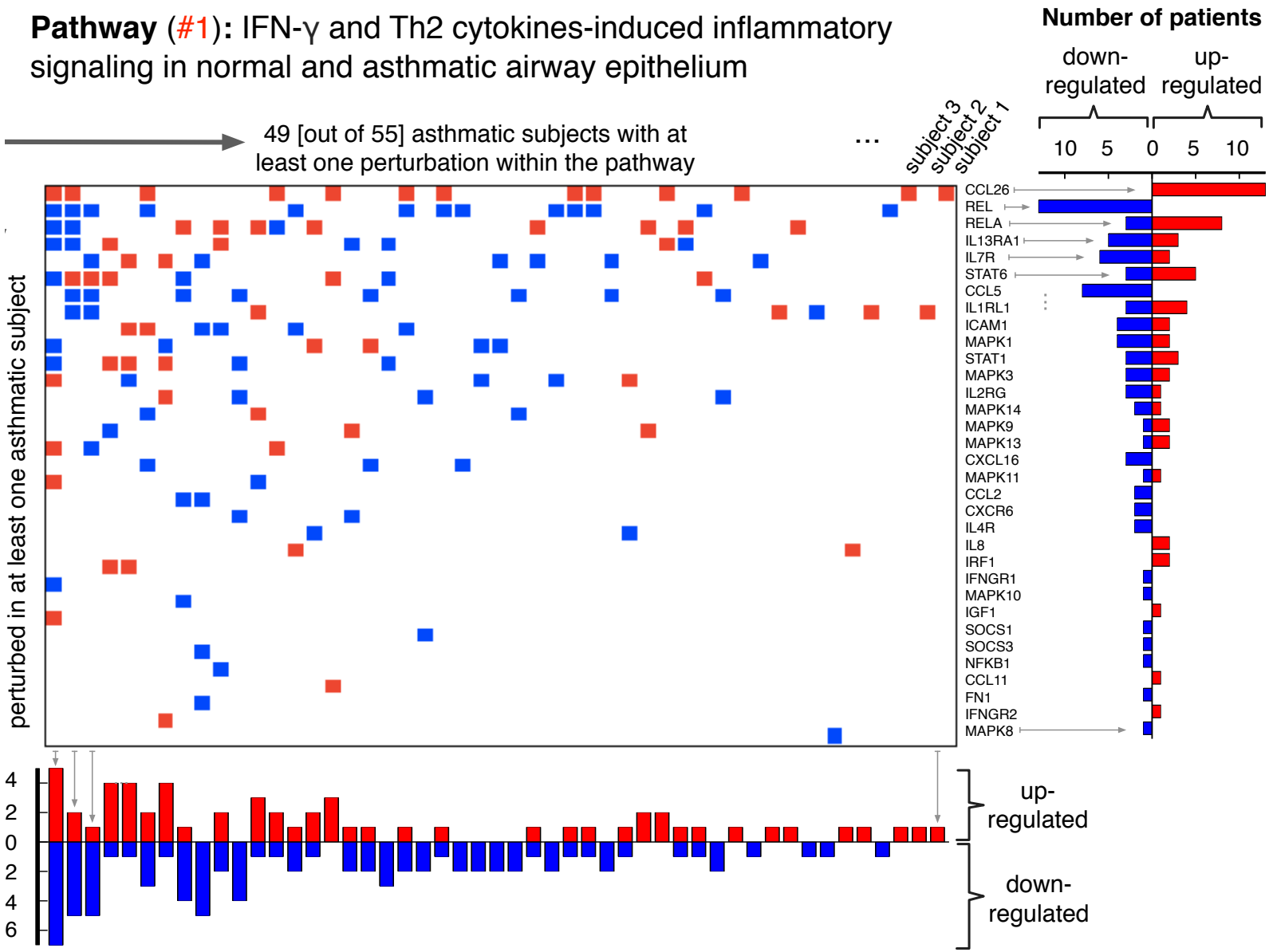
From personalized gene-level signatures to pathway-level signatures



Enrichment of disease-specific pathways in PEEPs (assessed by Fisher's test followed by Bonferroni correction) reveals that

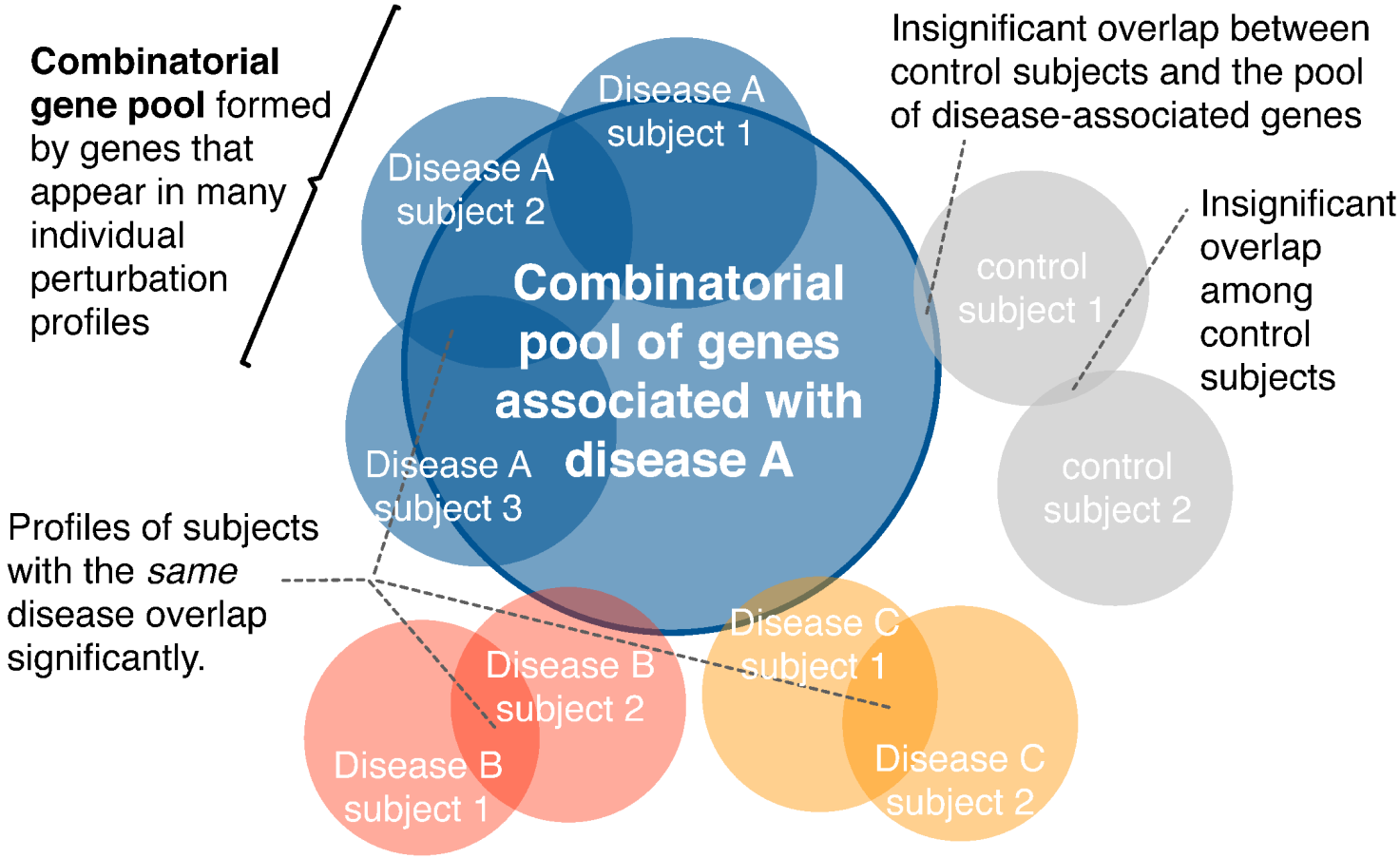
- almost all the individuals show significant perturbations in disease-specific pathways
- the specific perturbations differ greatly across subjects

Personalized pathway-level signatures



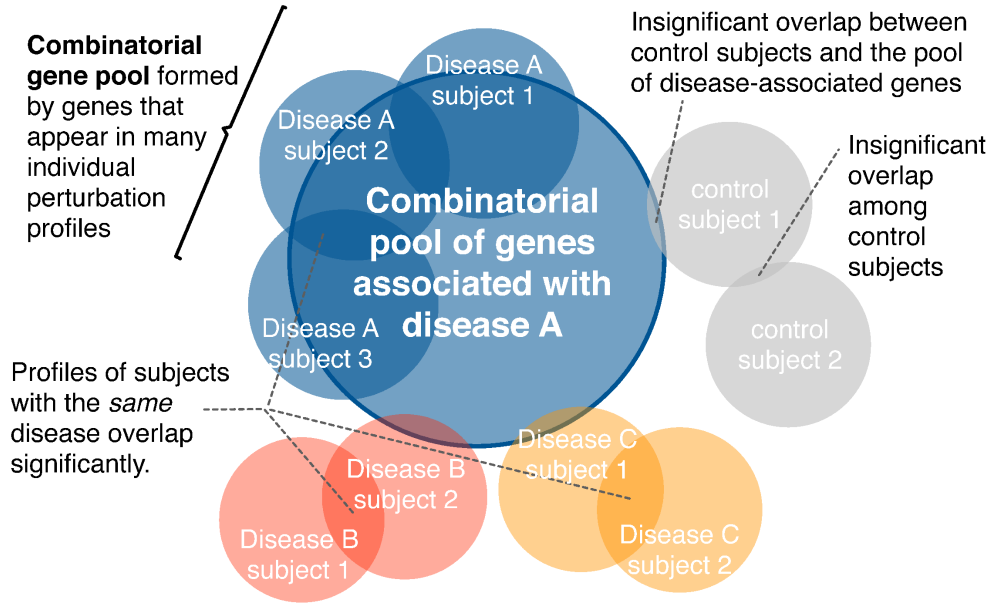
Pathways are perturbed in different ways in different patients

Disease module hypothesis



- Different perturbations within certain molecular pathways lead to the same disease
- Genes that are perturbed in a significant fraction of the case subjects define the disease module

Can PEEPs predict disease status?



Need to make sure that

- PEEPs are not an artifact of technical or biological noise in transcriptomics data
- Disease module captures disease heterogeneity observed across patients

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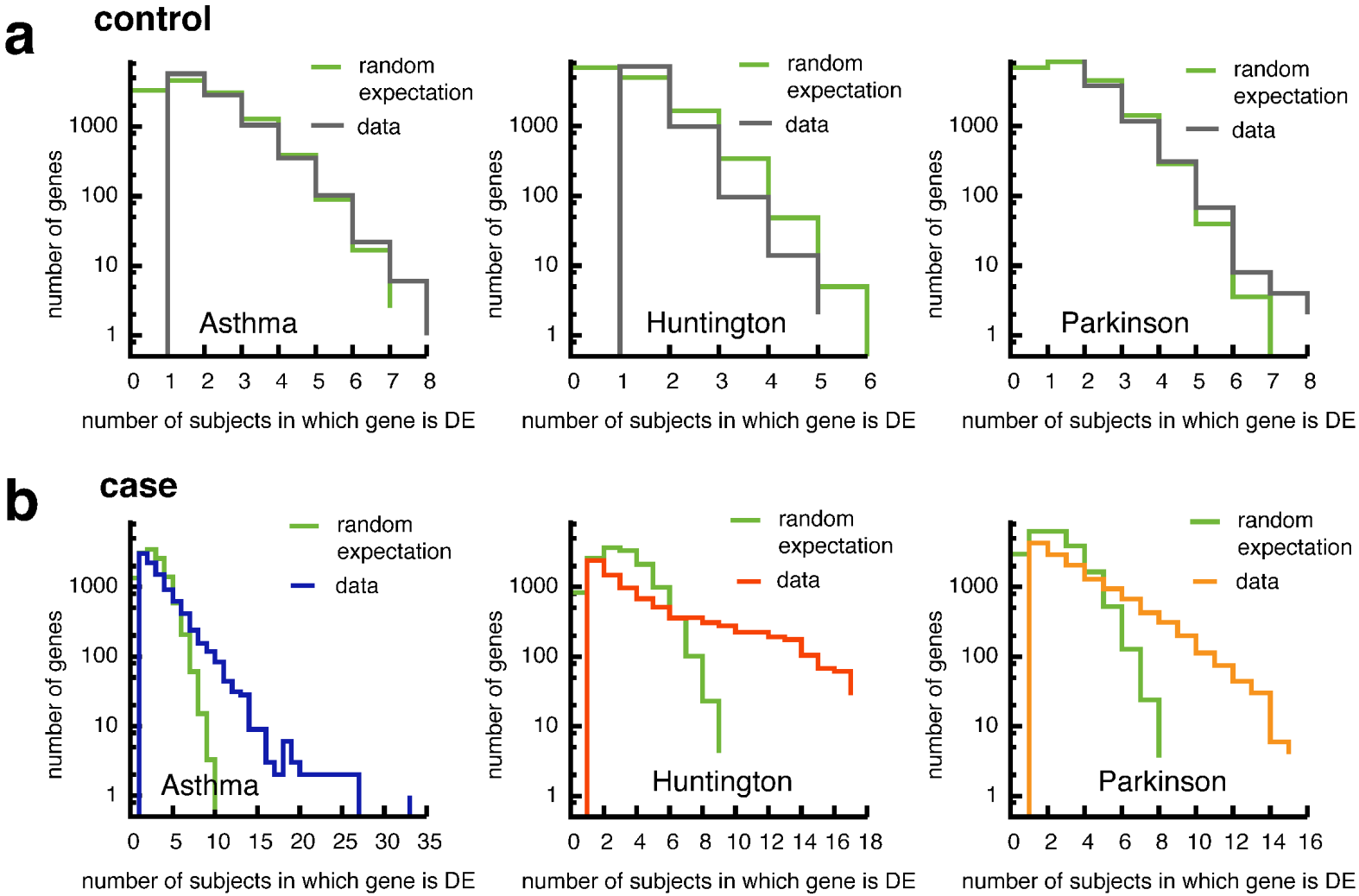
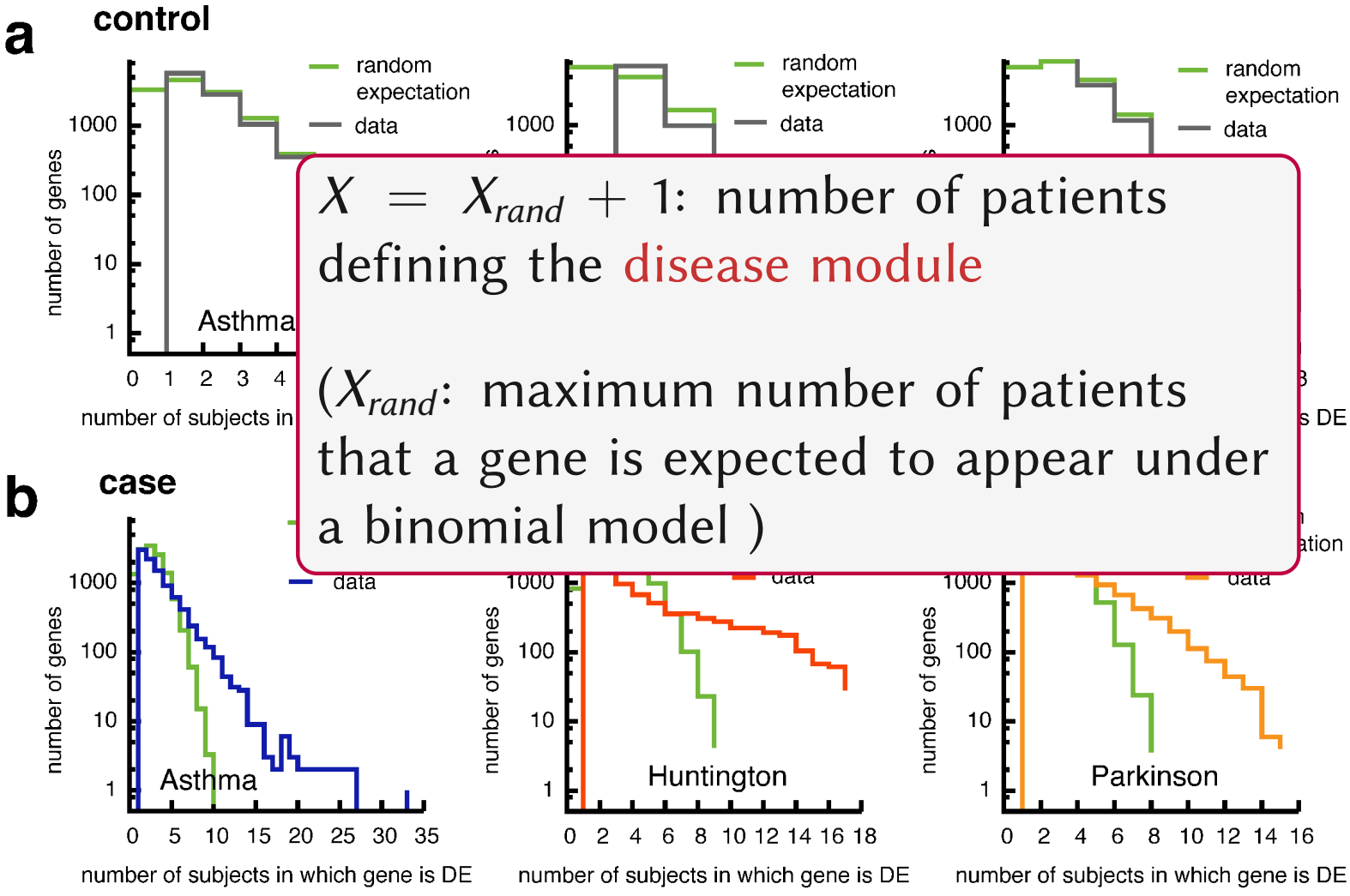


The number of shared genes between case subjects significantly exceeds the random expectation

Can PEEPs predict disease status?

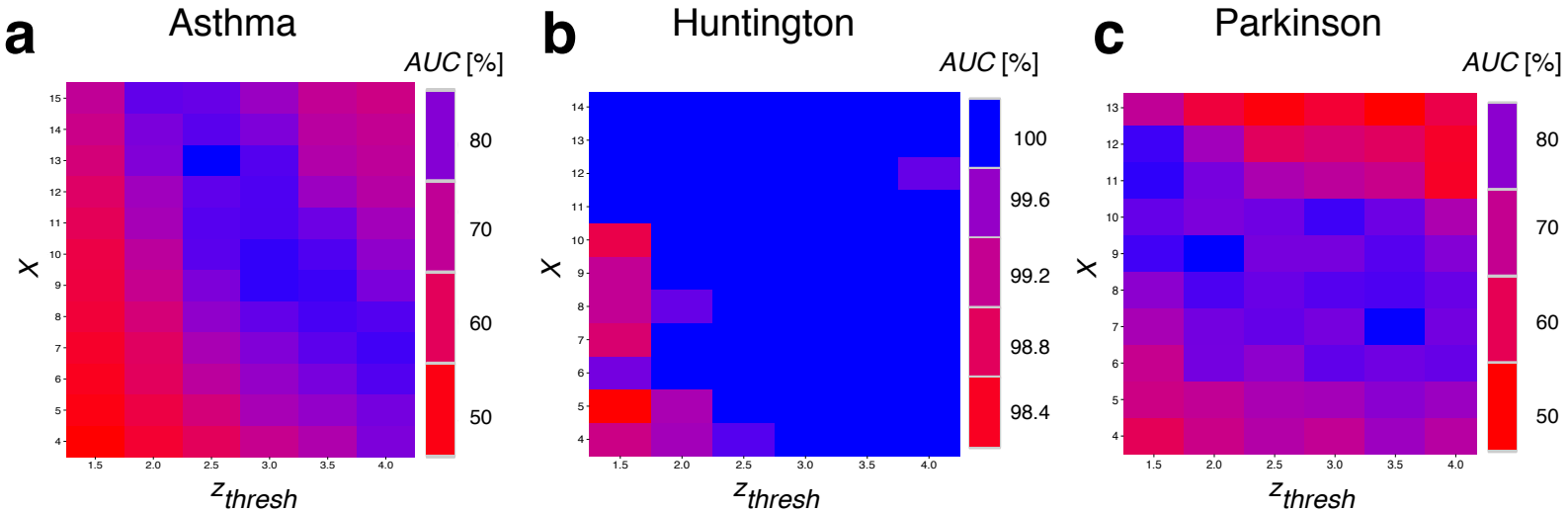


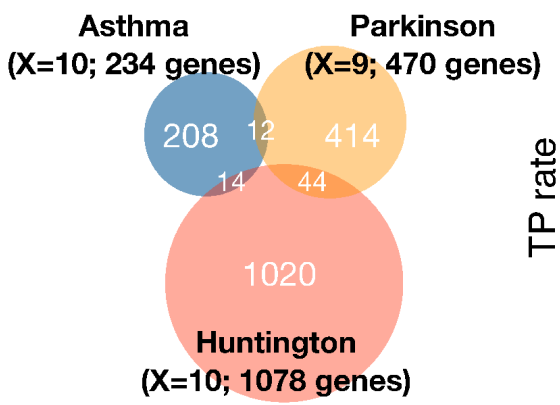
$X = X_{rand} + 1$: number of patients defining the disease module

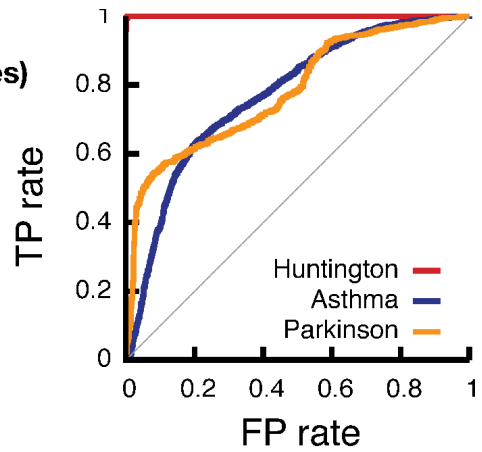
(X_{rand}: maximum number of patients that a gene is expected to appear under a binomial model)

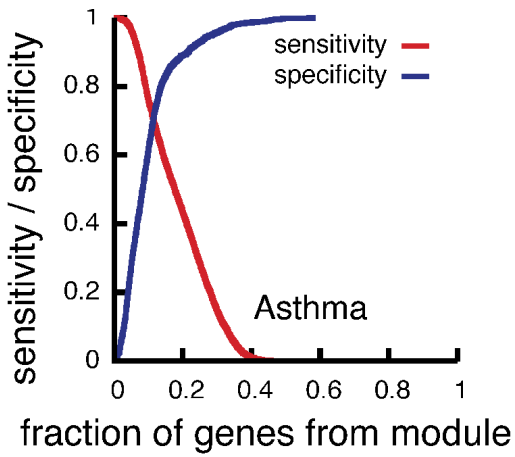
The number of shared genes between case subjects significantly exceeds the random expectation

Predicting diseases from PEEPs









Conclusions

- High heterogeneity across patients at the transcription level
- PErsonalized Expression Profiles (PEEPs)
  - quantify heterogeneity
  - define a pool of perturbed genes across patients
  - predict disease status

R package for generating PEEPs is available at
github.com/emreg00/pepper

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Marc Santolini & Alan Karma

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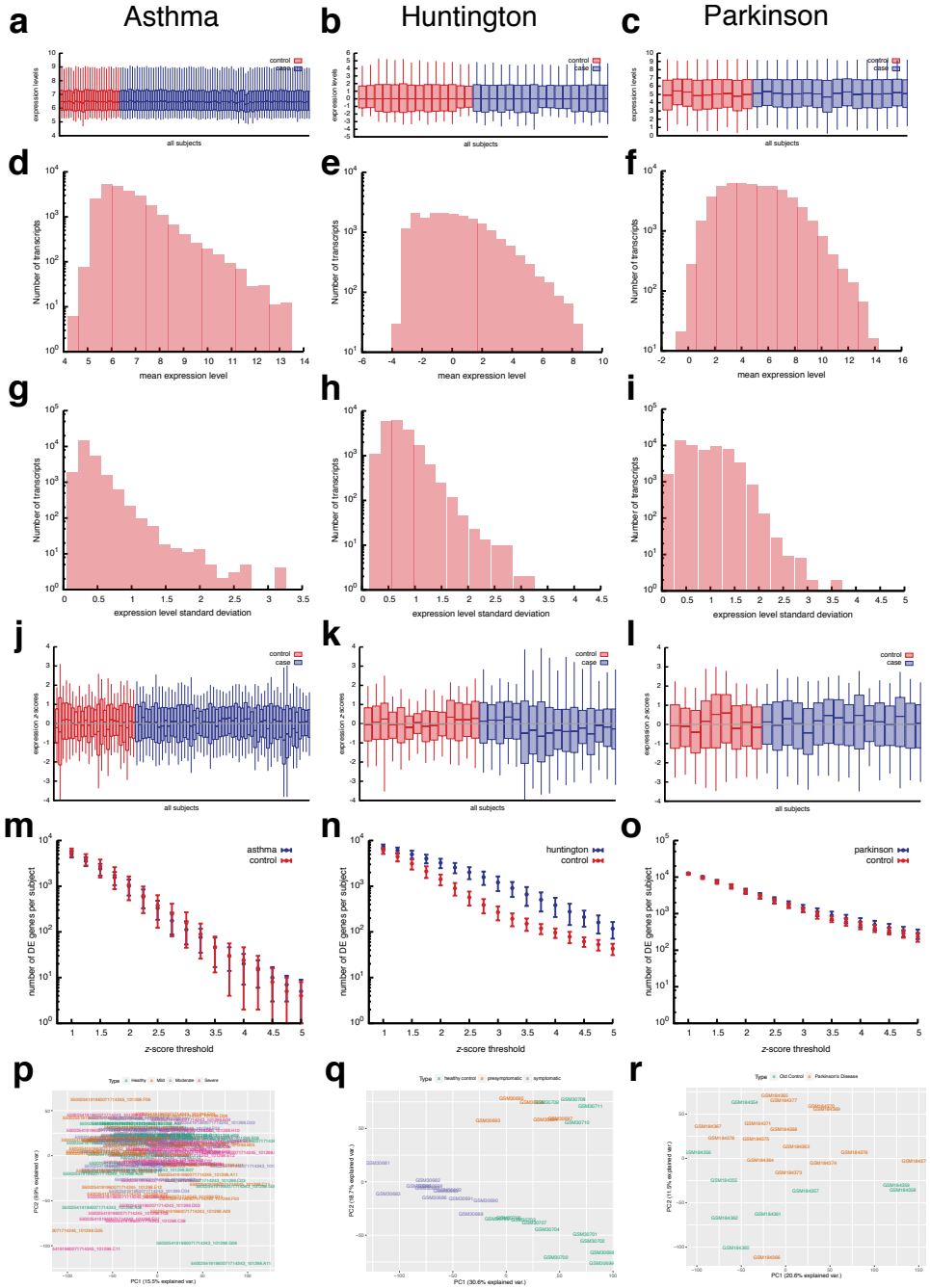
Preprocessing and normalization of transcriptomics data



Defining disease modules

X, the number of patients defining the disease module is given by

$$X = X_{rand} + 1$$

where X_{rand} given by

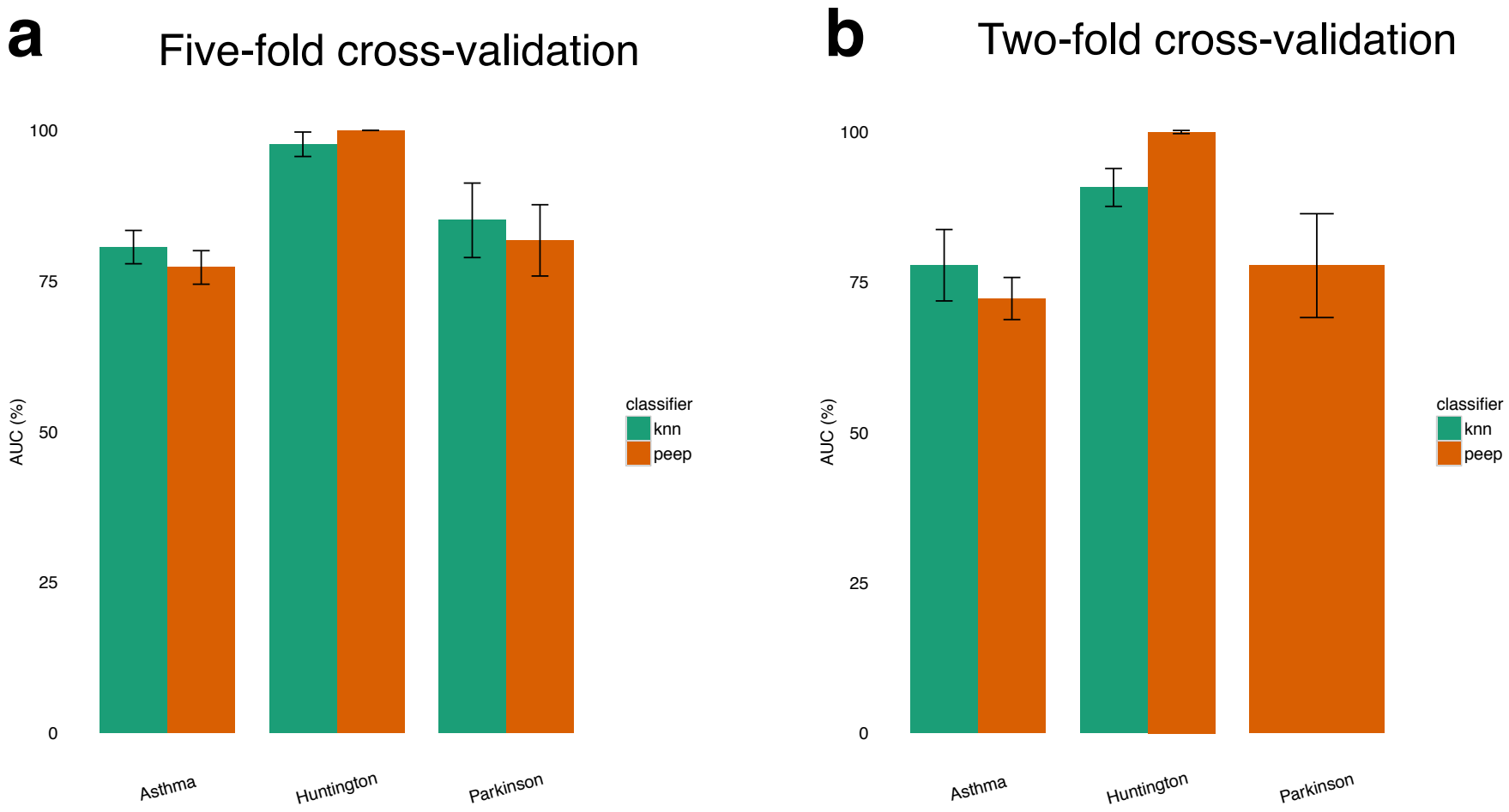
$$argmax_{X_{rand}}\left(\sum_{k=X_{rand}}^{n} G * f(k; n, p) < 1\right)$$

and

$$f(k; n, p) = Pr(x = k) = \binom{n}{k} p^k (1-p)^{n-k}$$

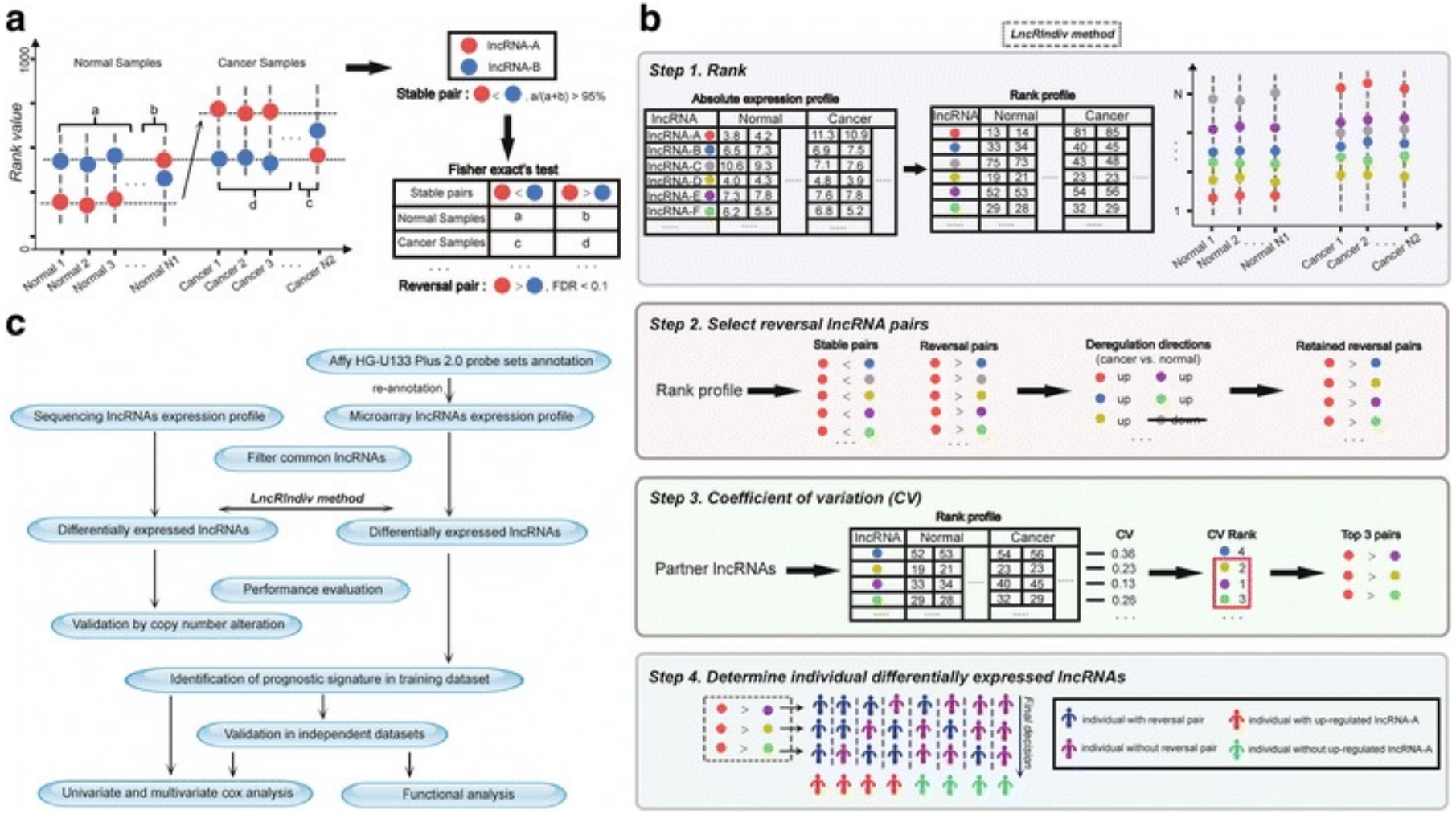
corresponding to the probability for a gene to be perturbed in exactly k out of n subjects given that each subject has g perturbed genes on average (out of all possible G genes in the expression profiling platform) and thus, $p = g/G$

PEEP vs K-nearest-neighbor based predictions



- Results with $K = 15$ (maximizes accuracy among 3, 5, 10, 15, 20)
- AUCs are calculated using a repeated cross validation approach (100 repetitions)

Rank-based approaches for calculating individual perturbation profiles



RankComp *Wang et al., 2015, Bioinformatics*

LncRIndiv *Peng et al., 2017, Mol Cancer*