Computationally efficient and statistically accurate conditional independence testing with spaCRT

International Seminar on Selective Inference
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(Georgia Tech)

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(UPenn)

A model for genetic origins of human diseases

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Normal

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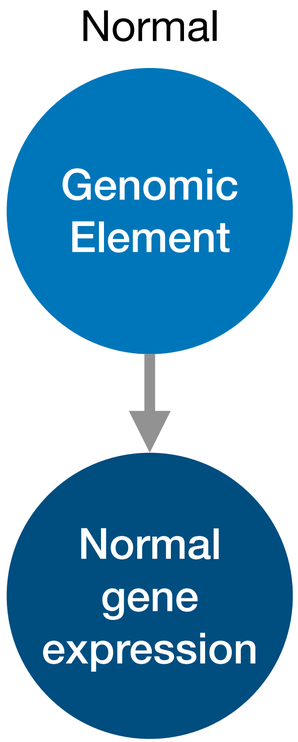

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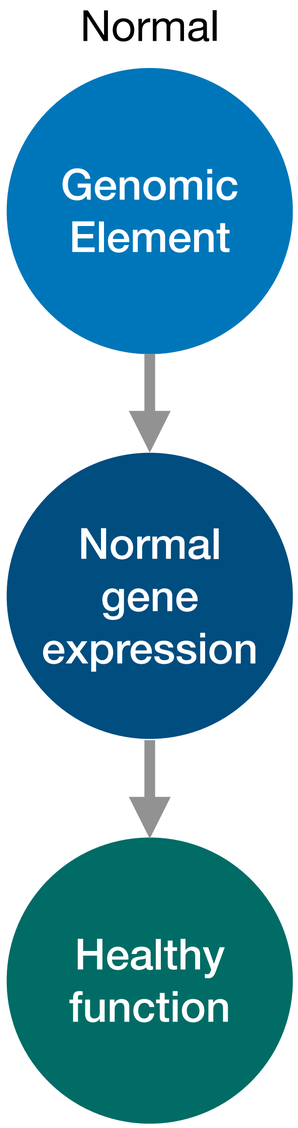

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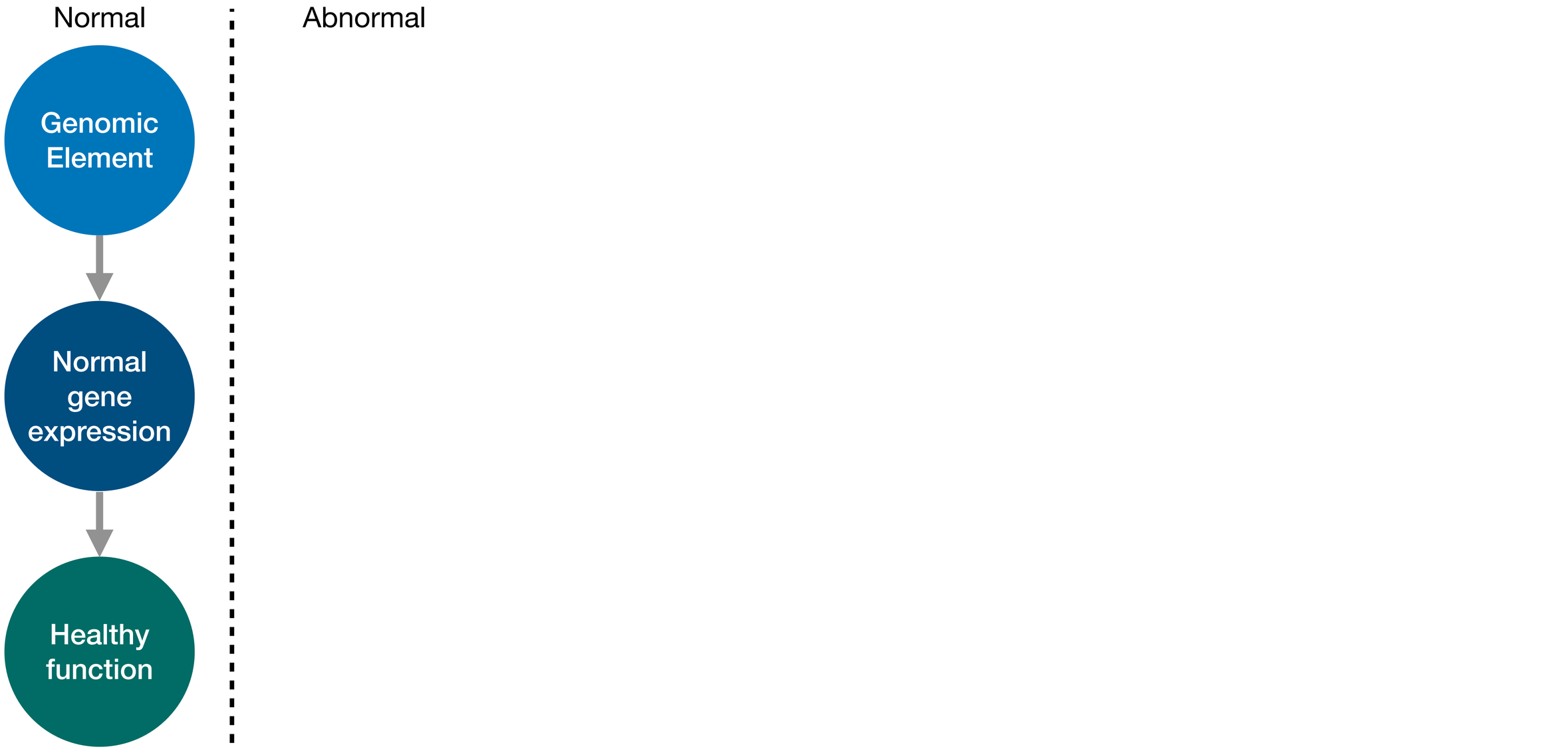

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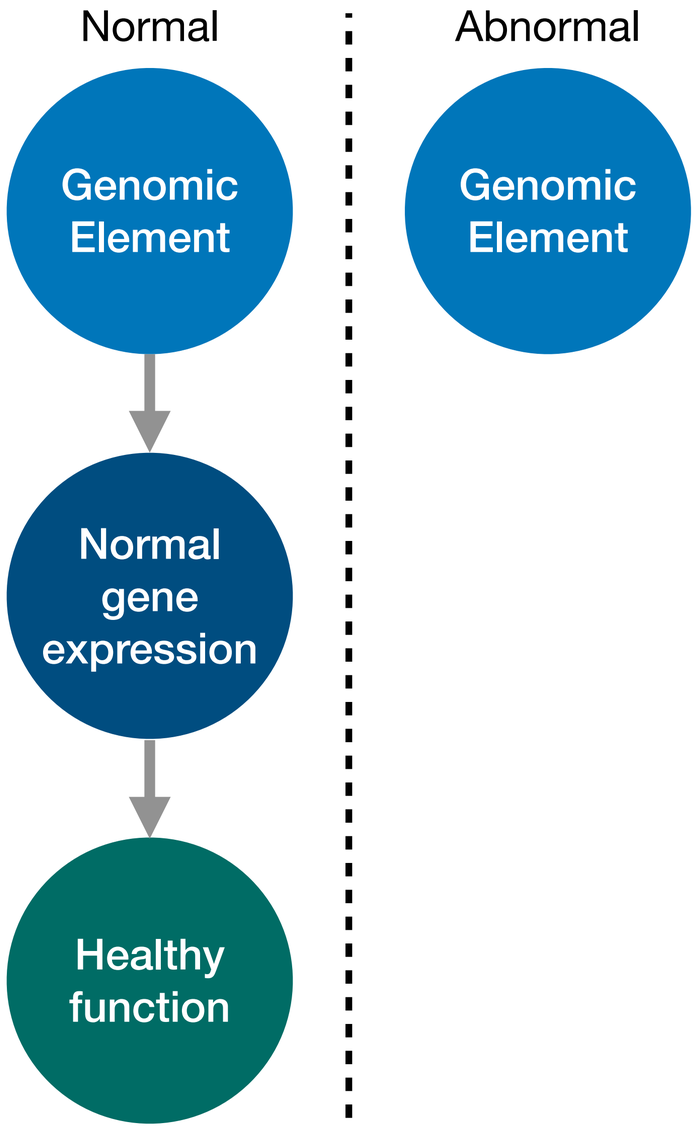

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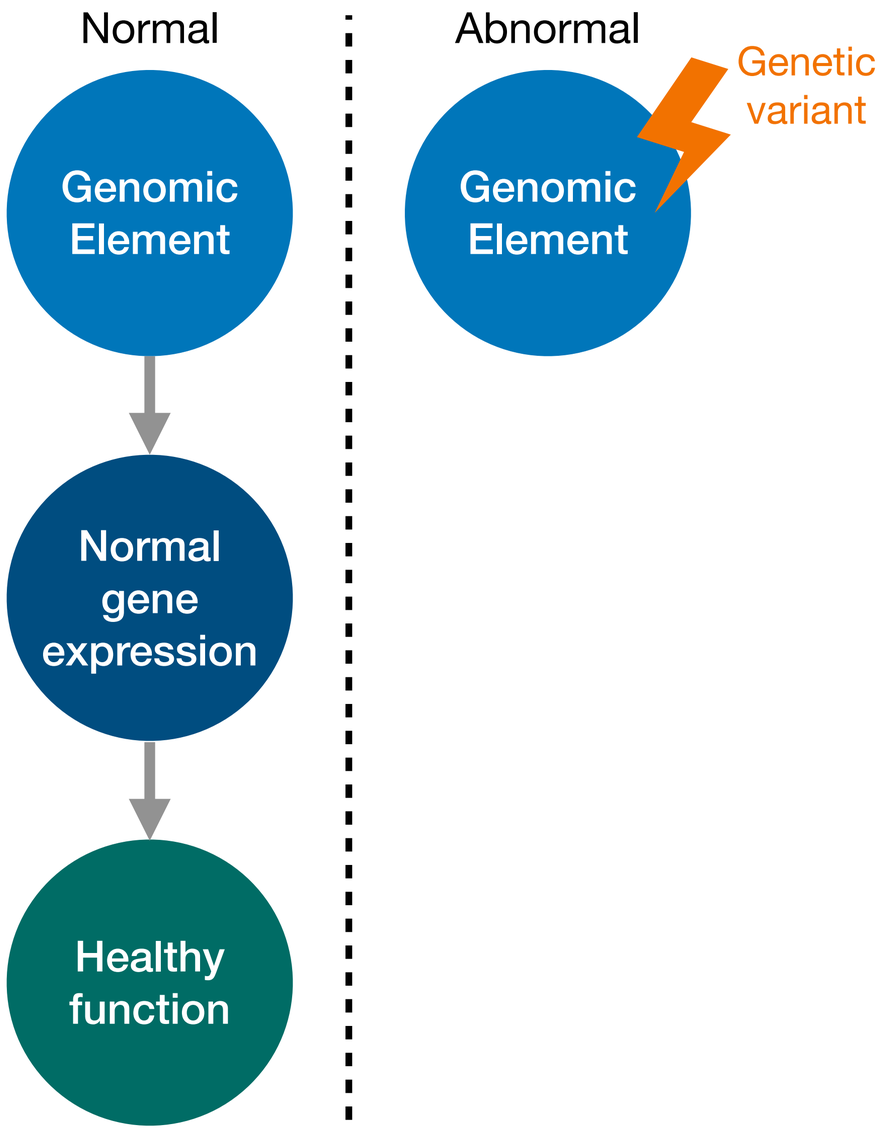

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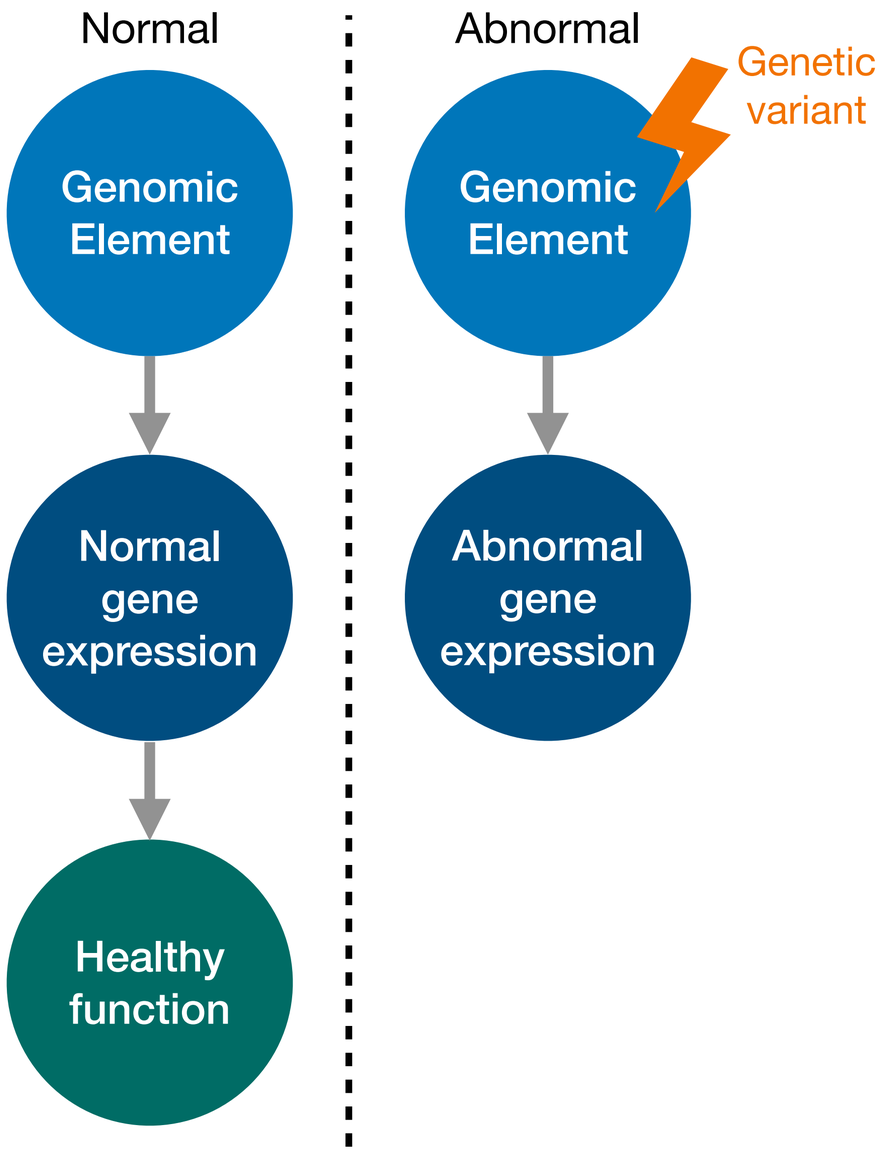

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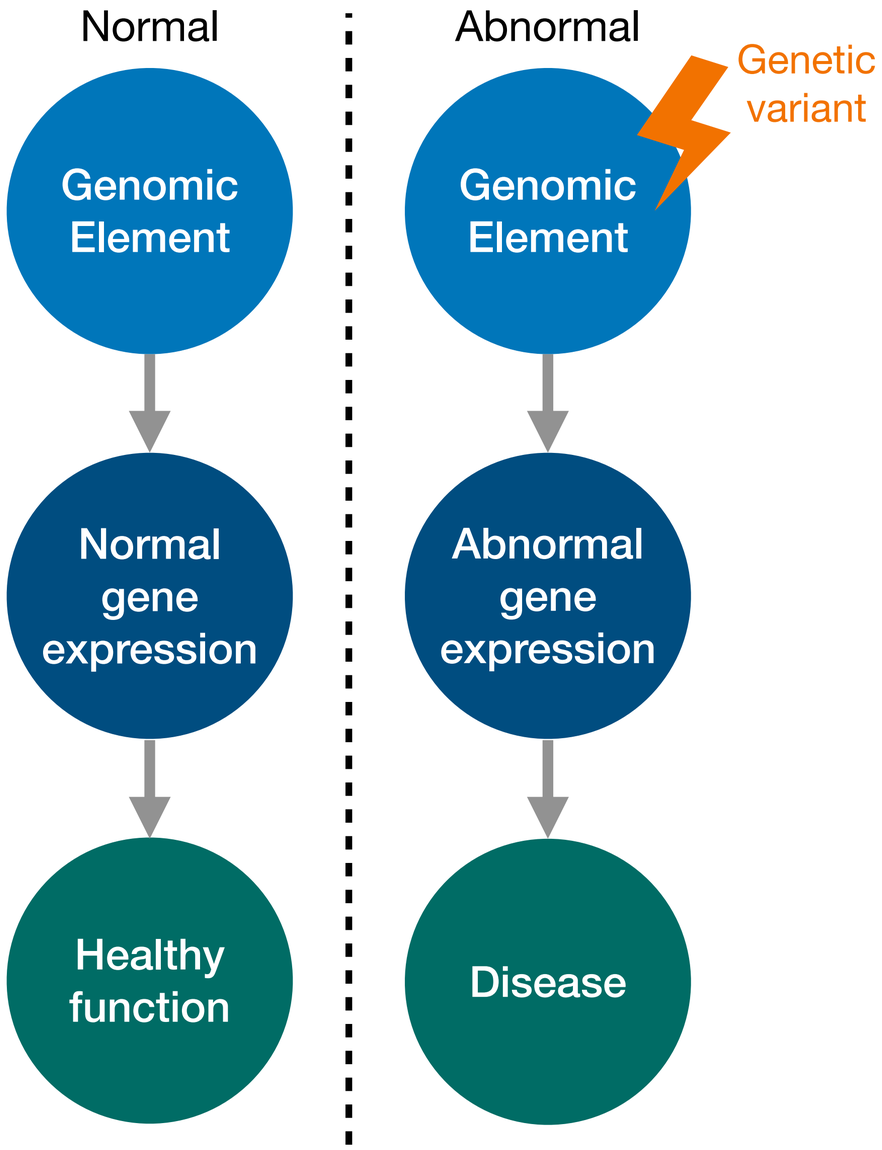

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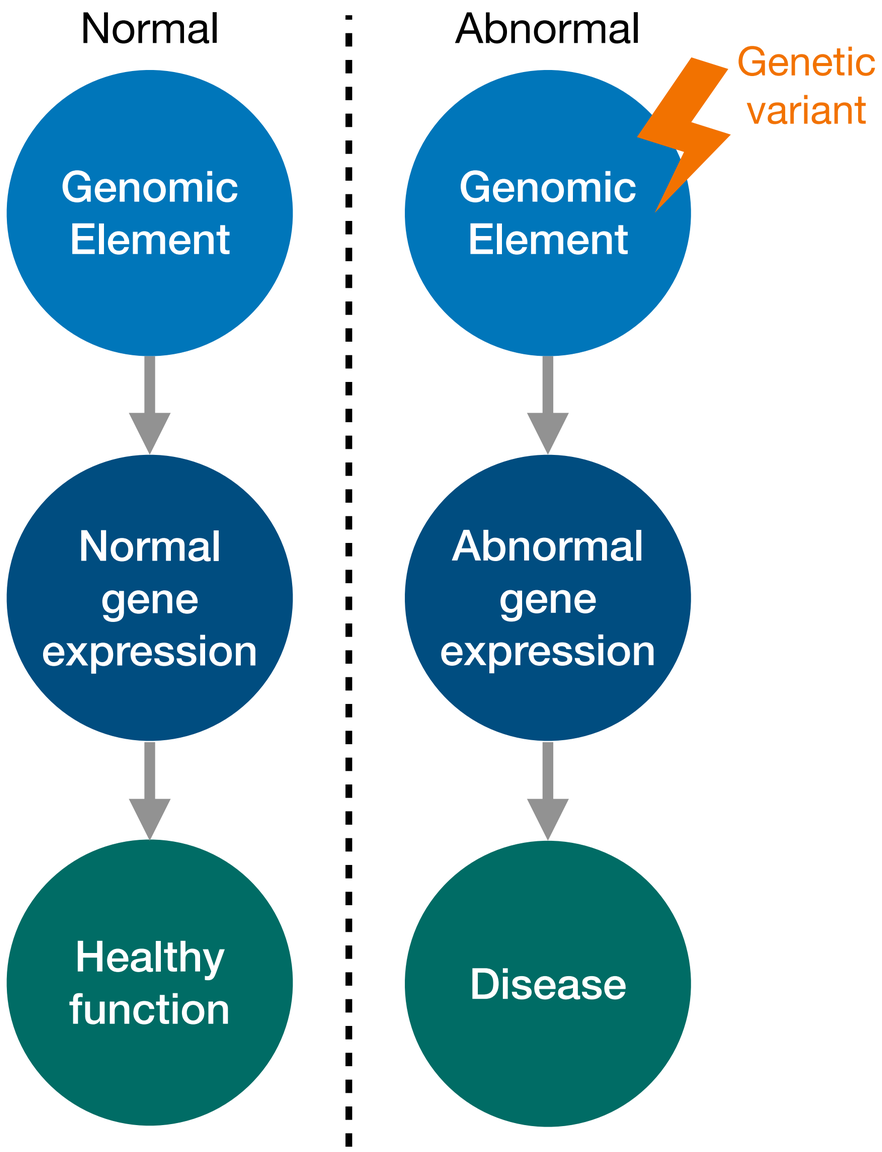
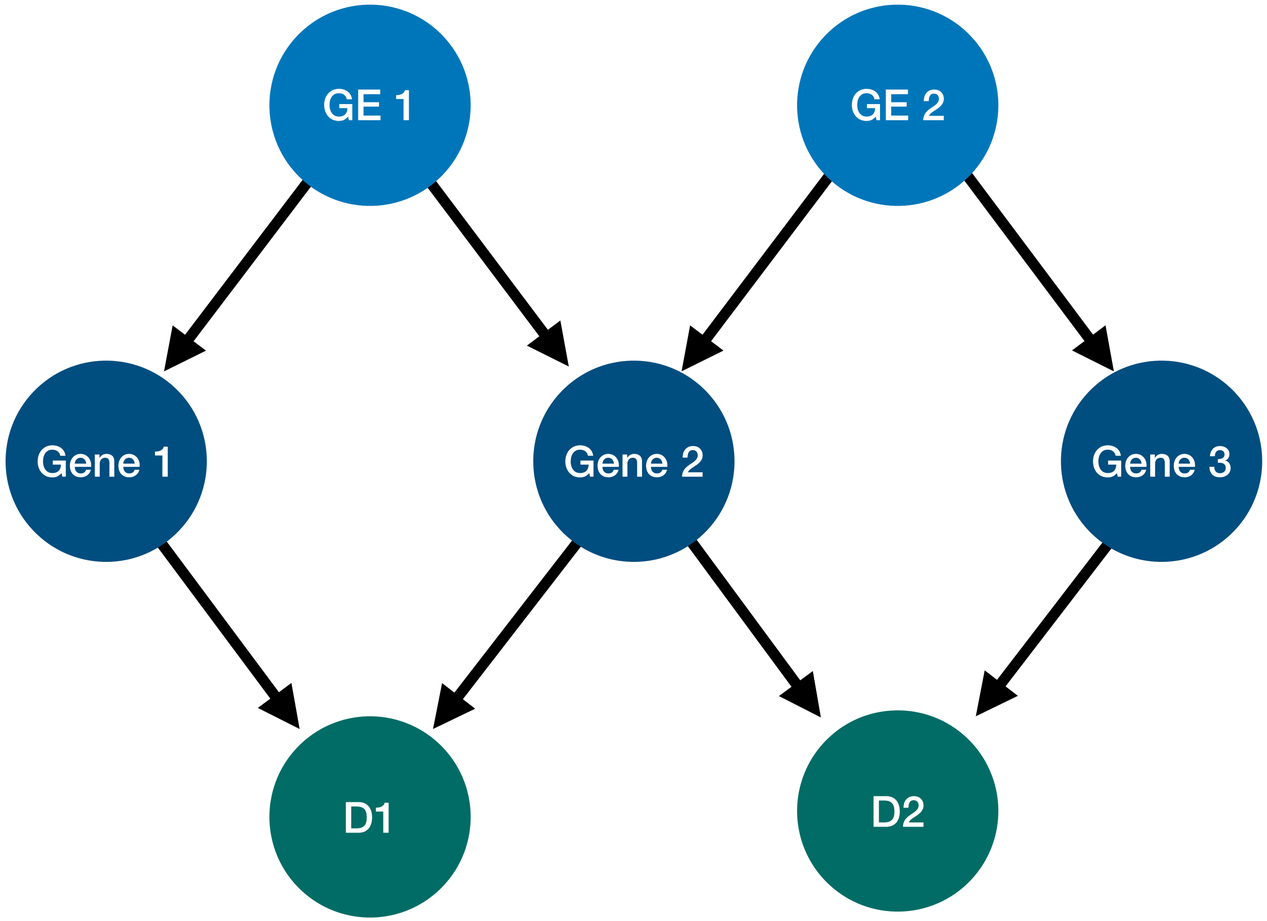
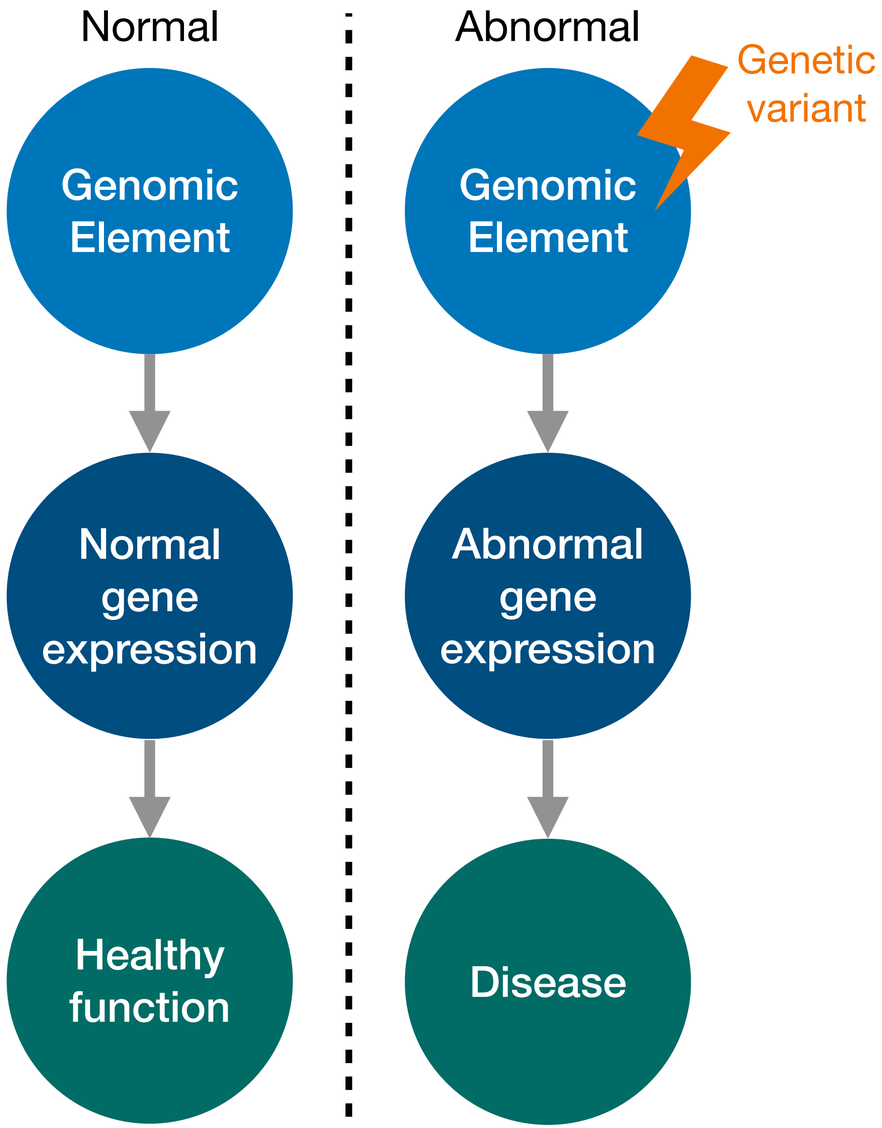
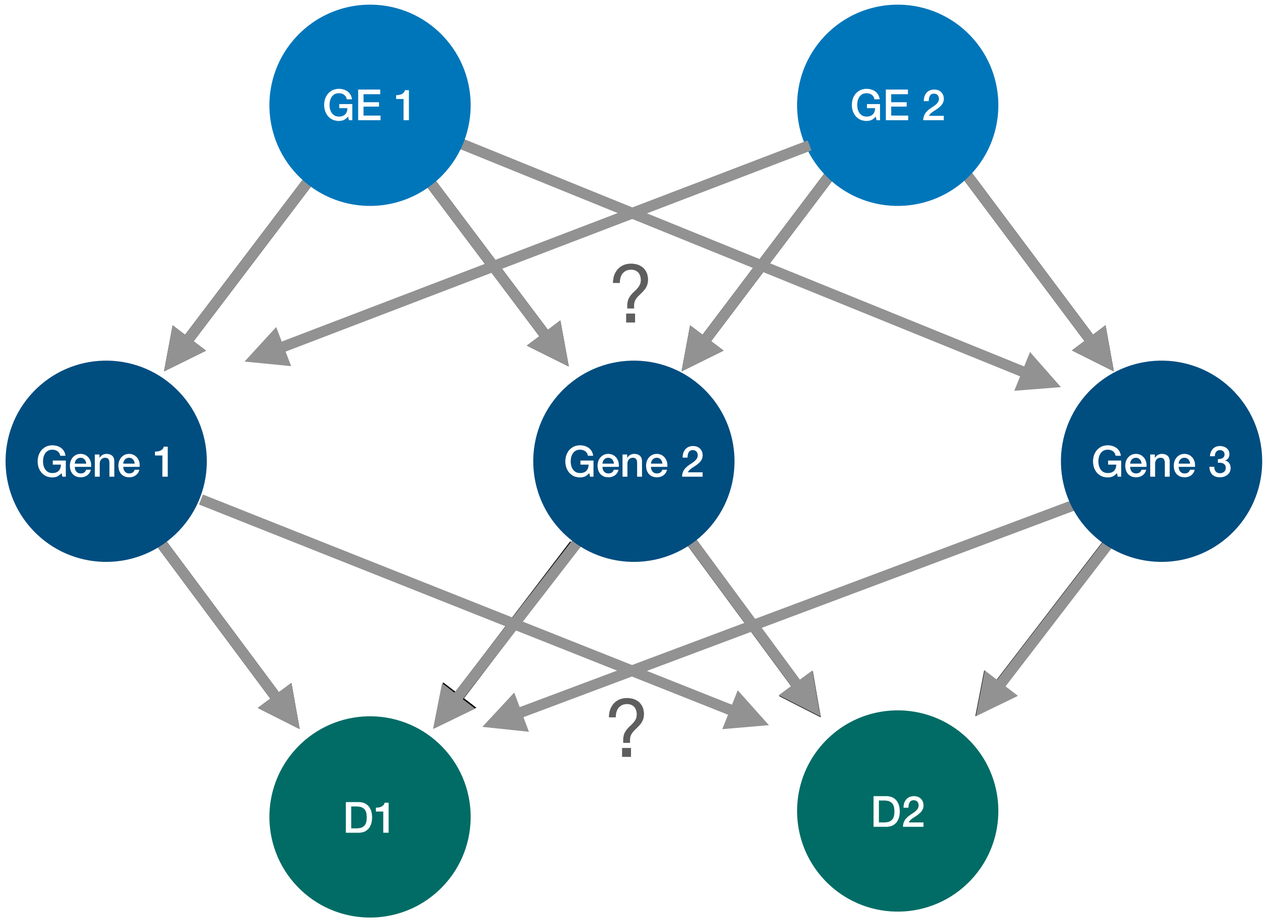




Uncovering genetic origins of human diseases





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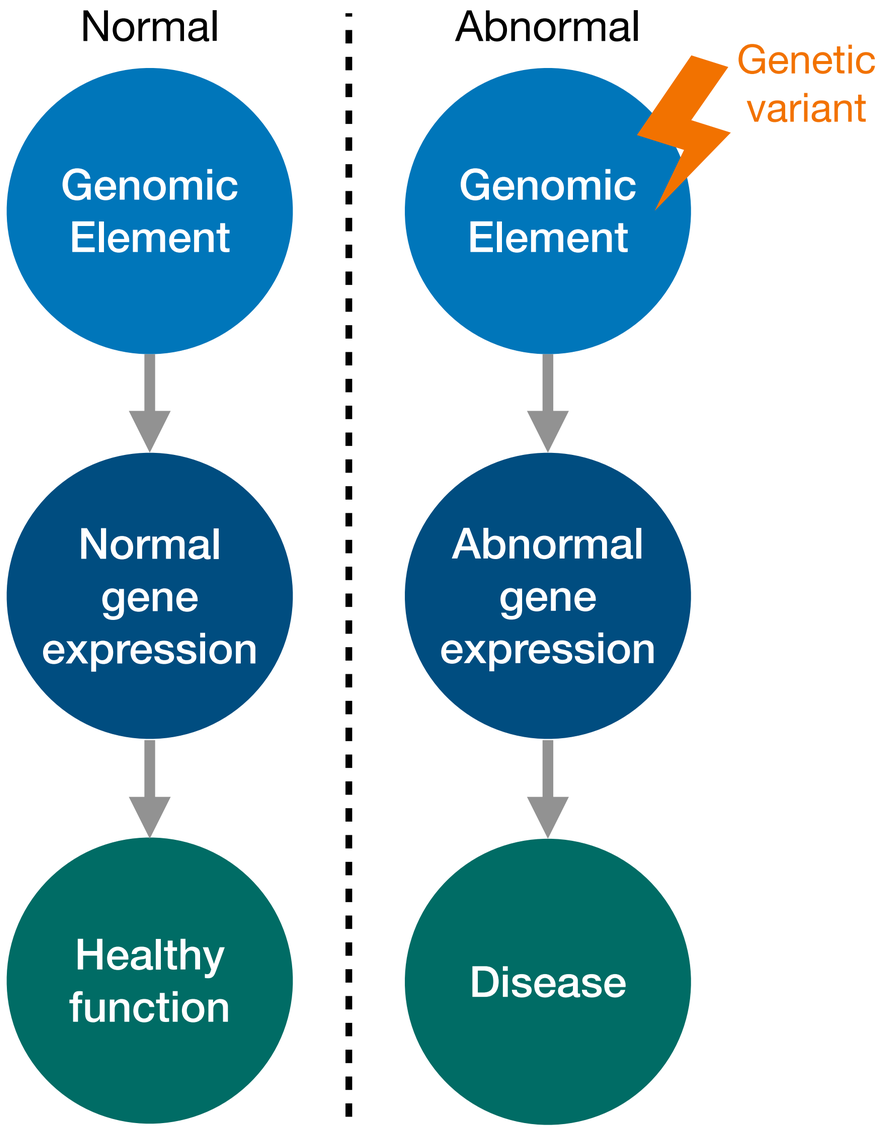

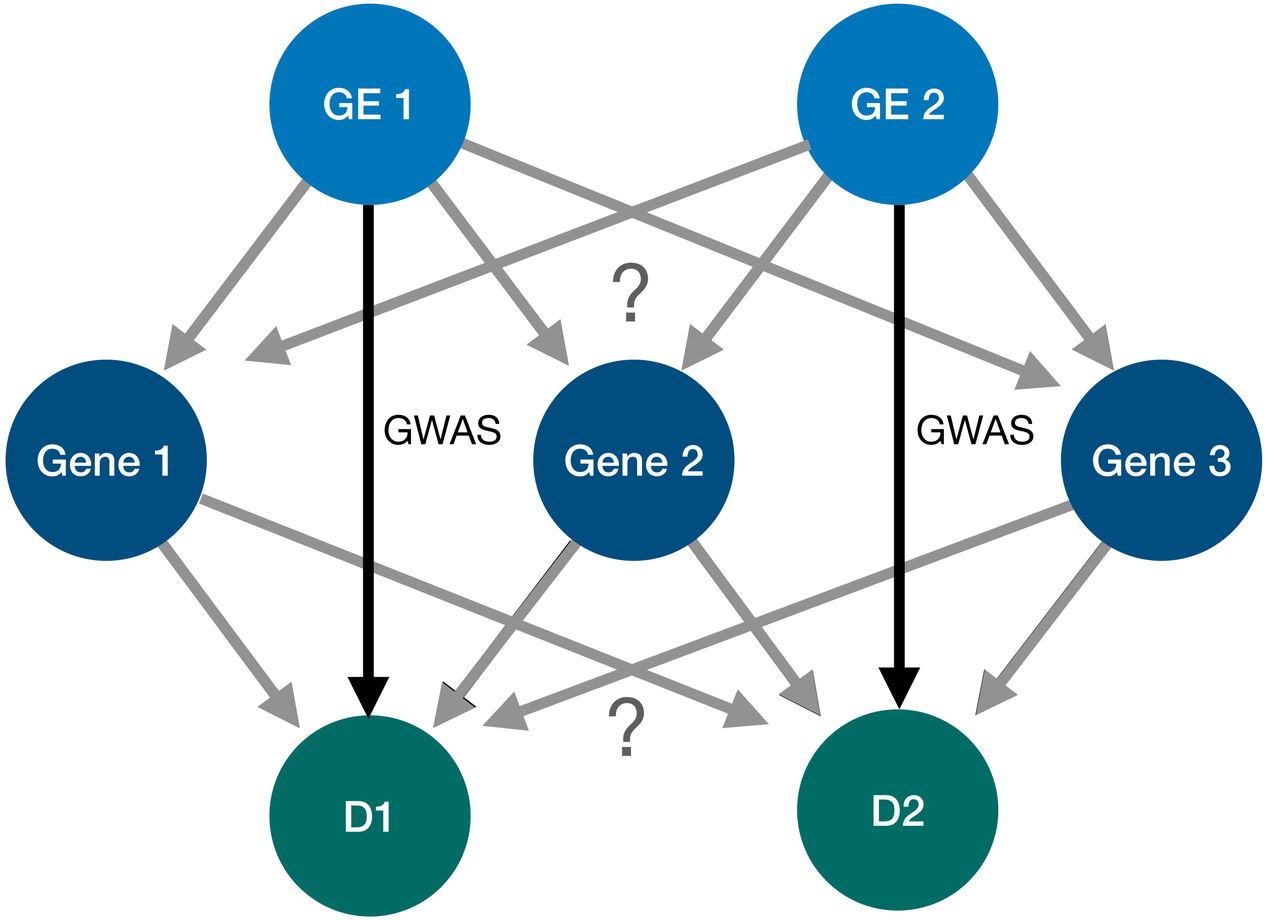

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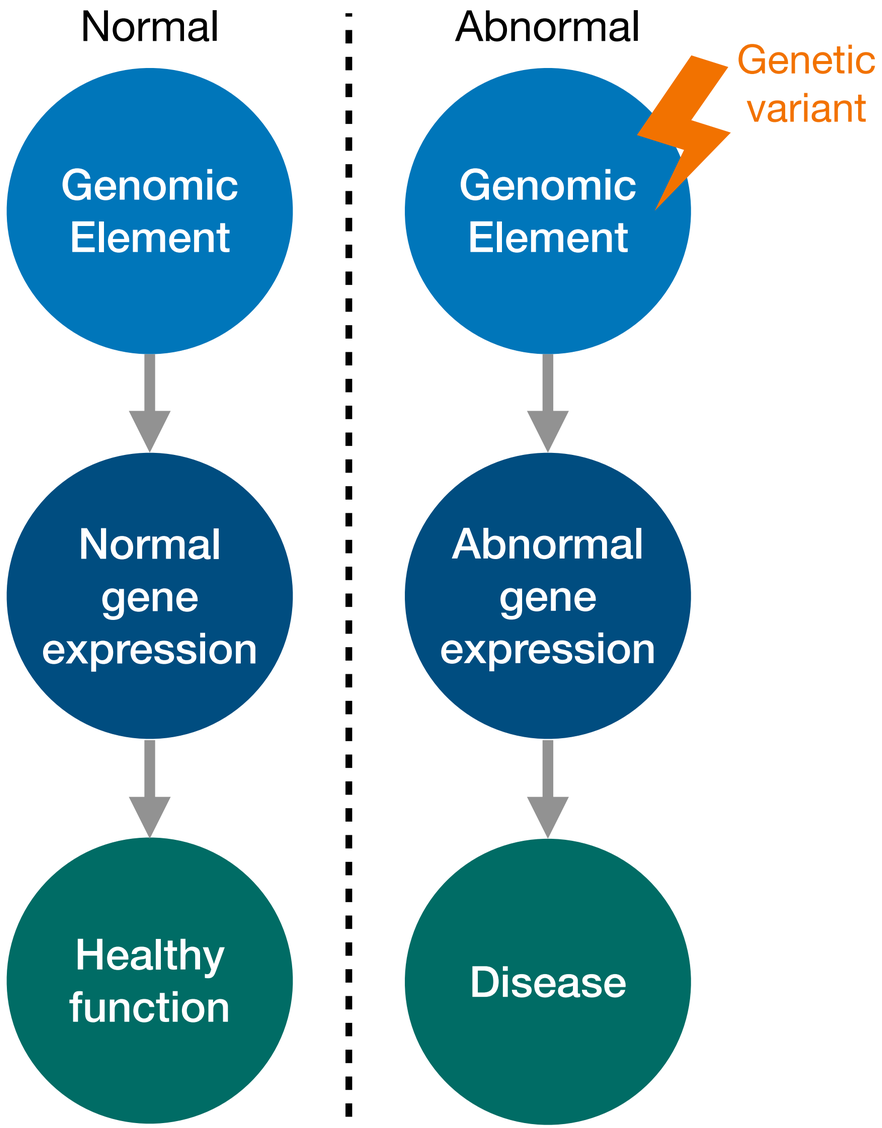
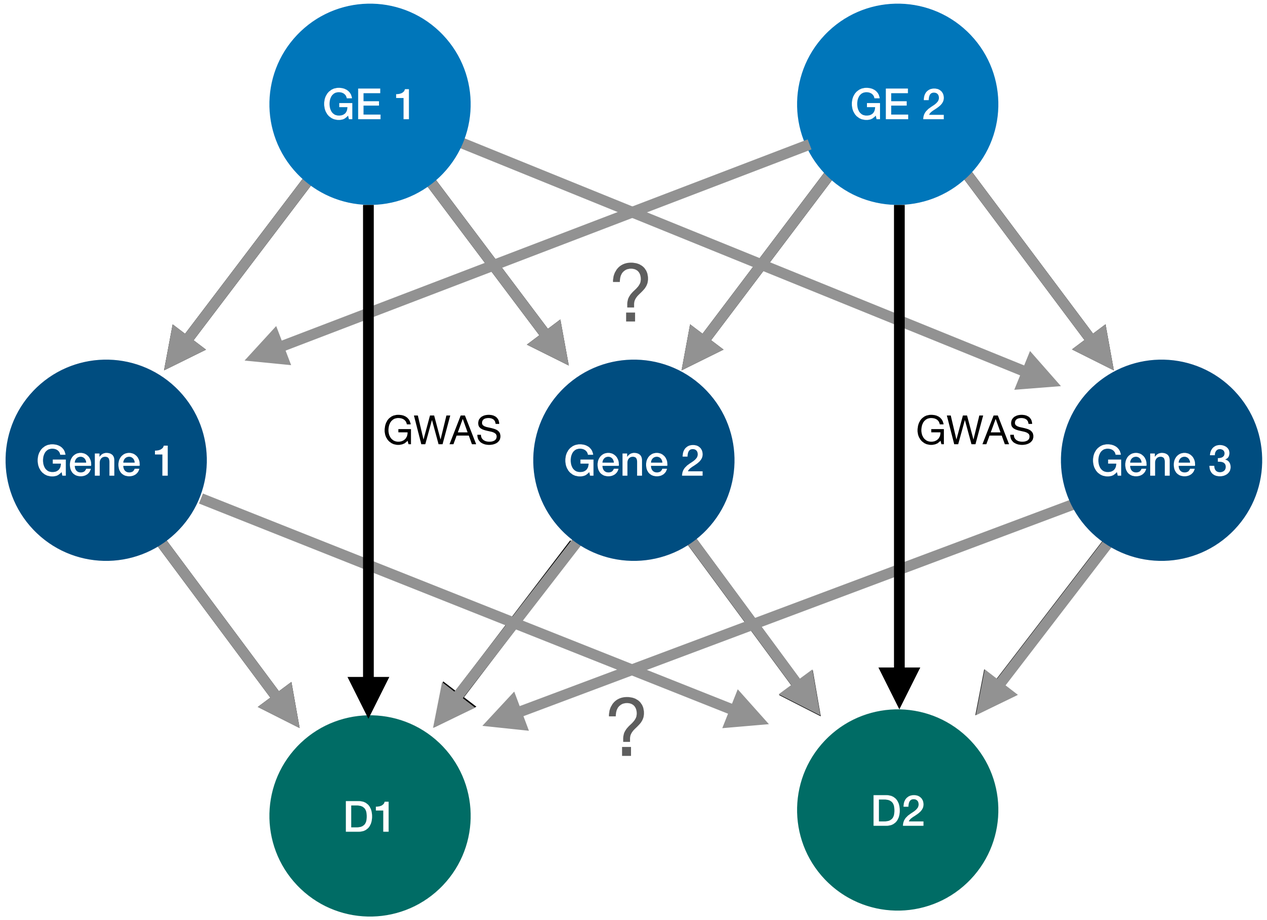
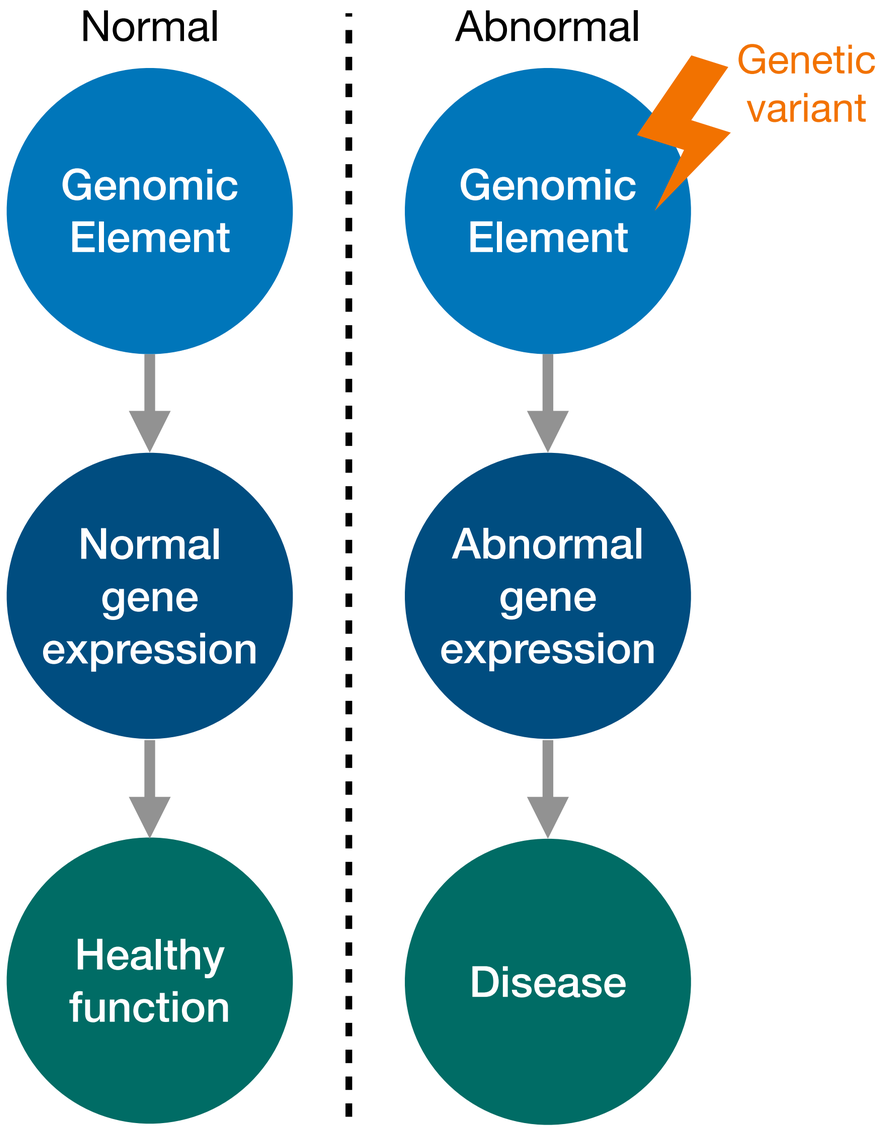
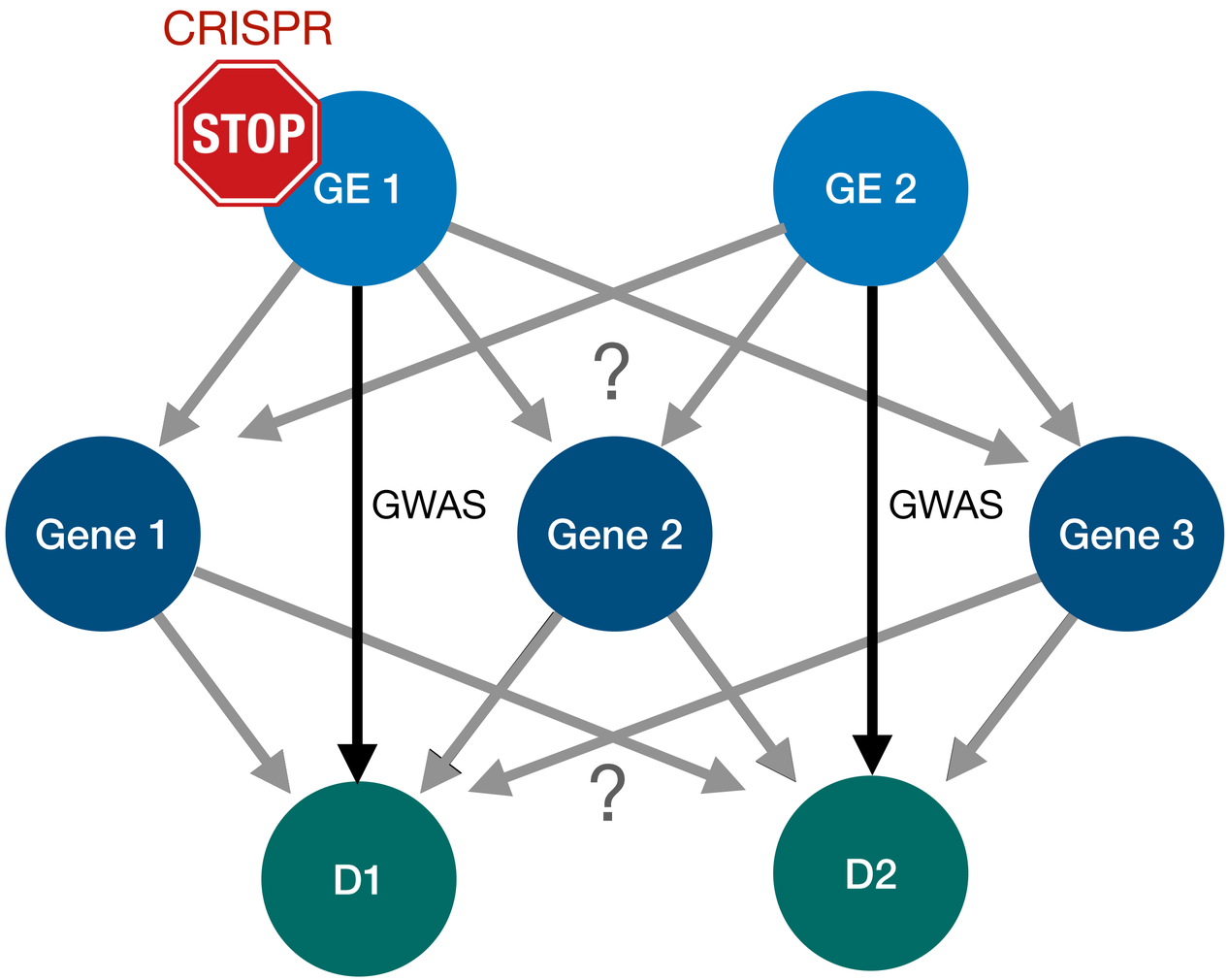




Single-cell CRISPR screens

Uncovering genetic origins of human diseases





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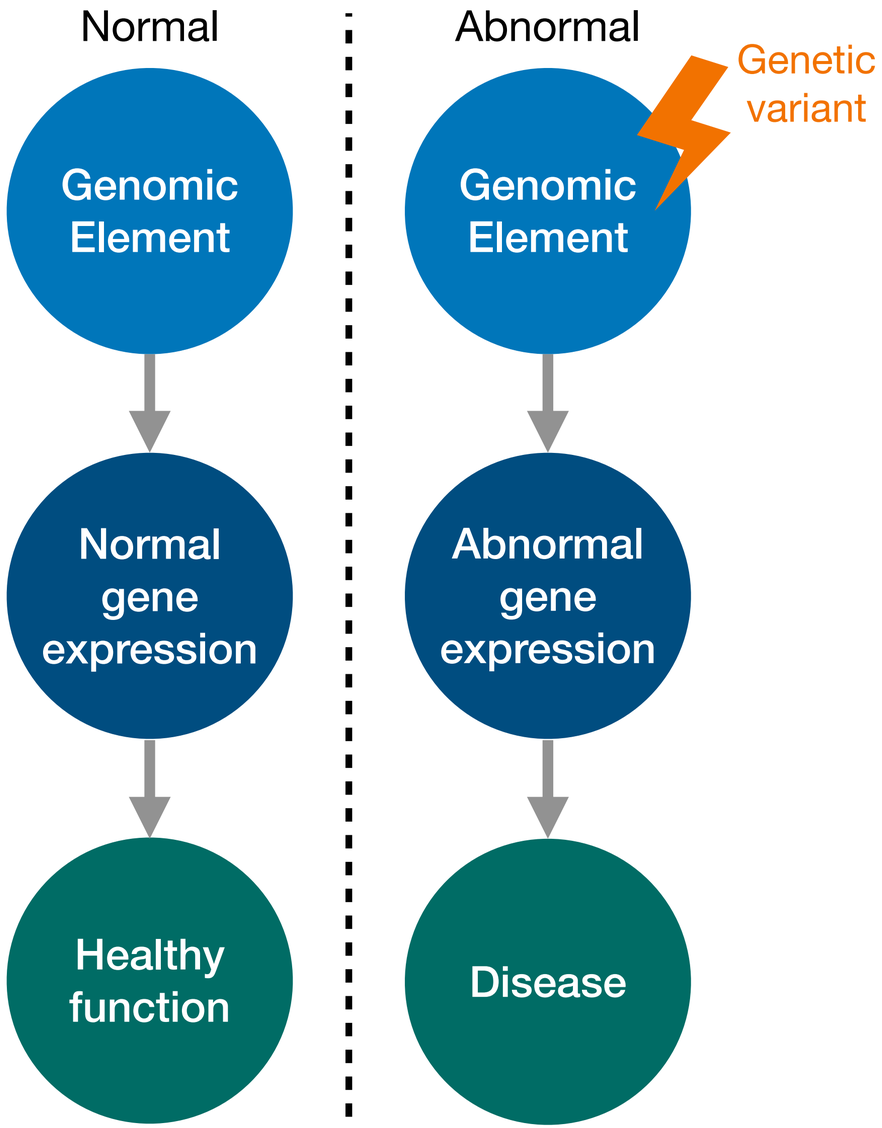

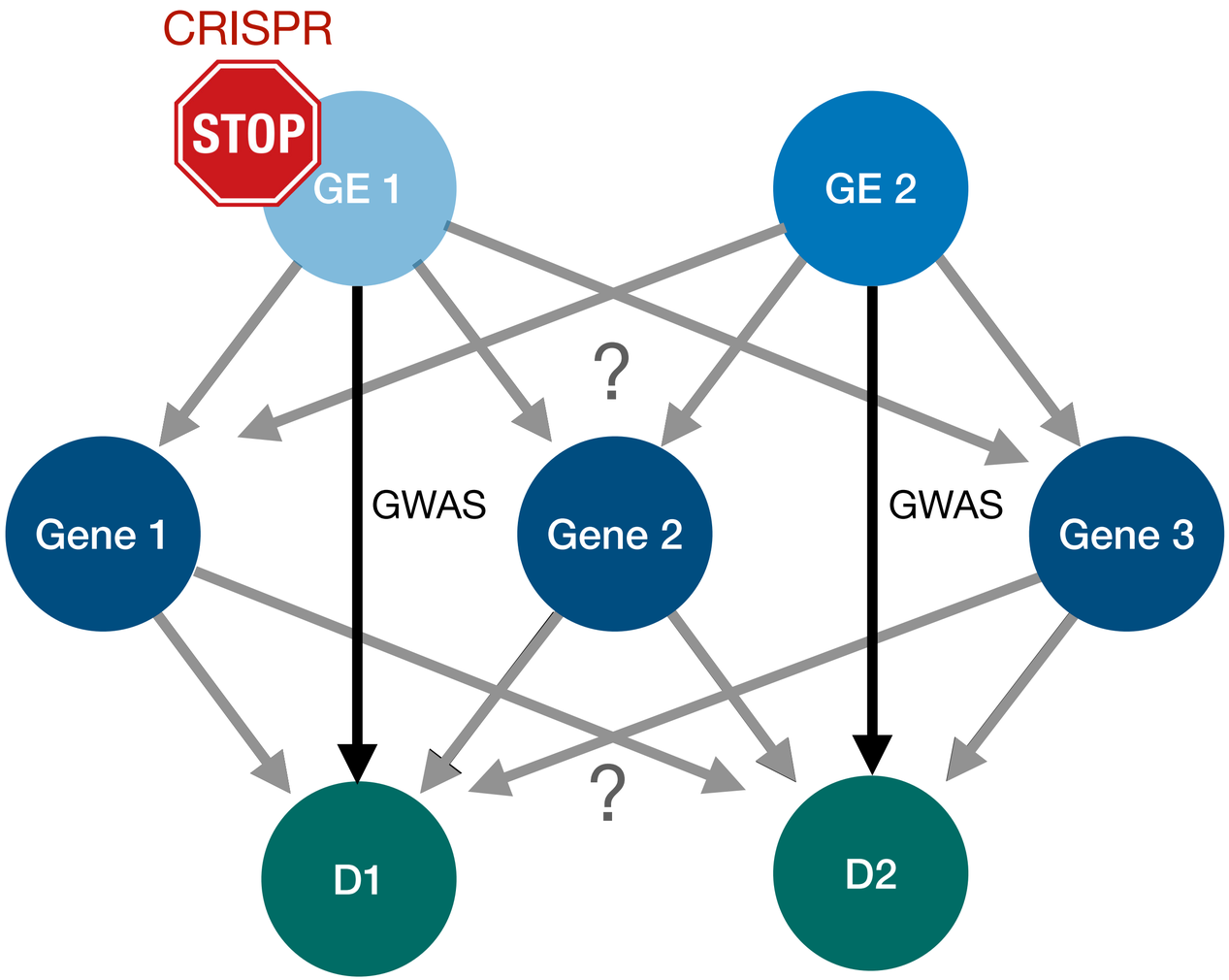

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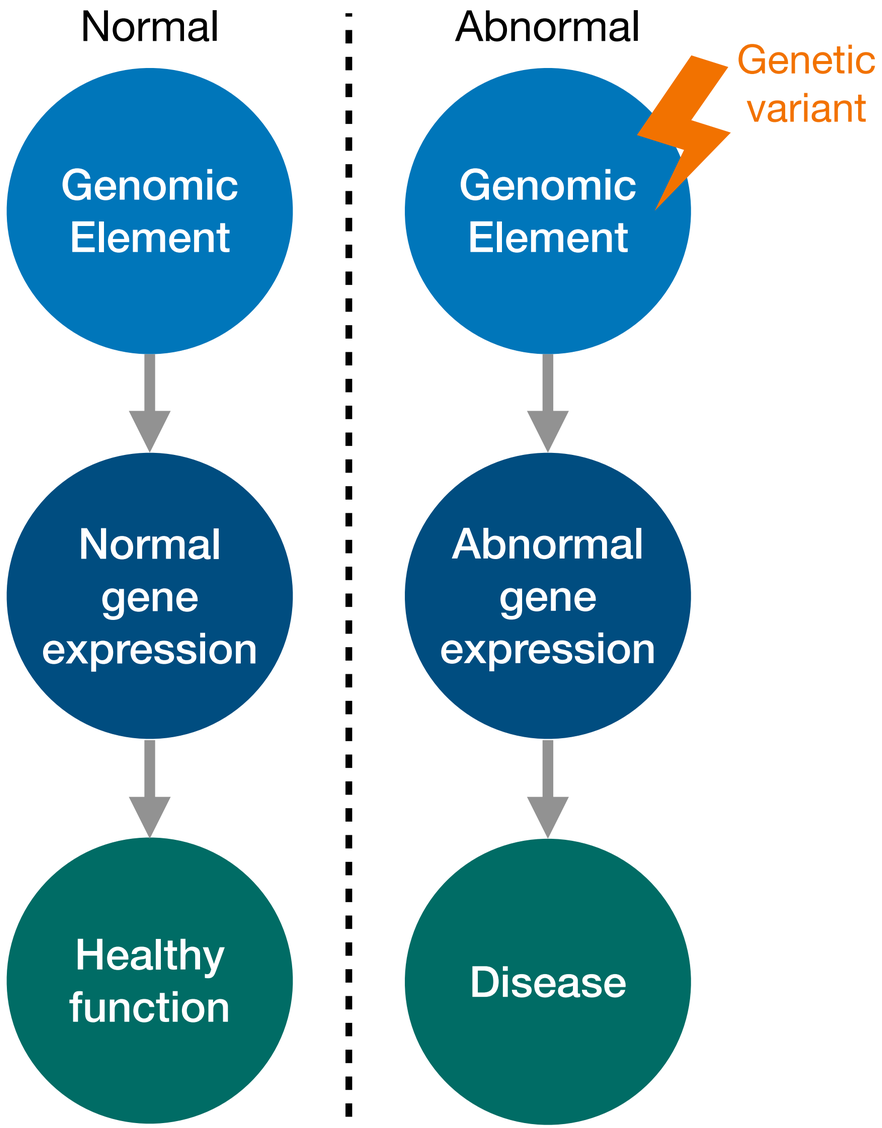

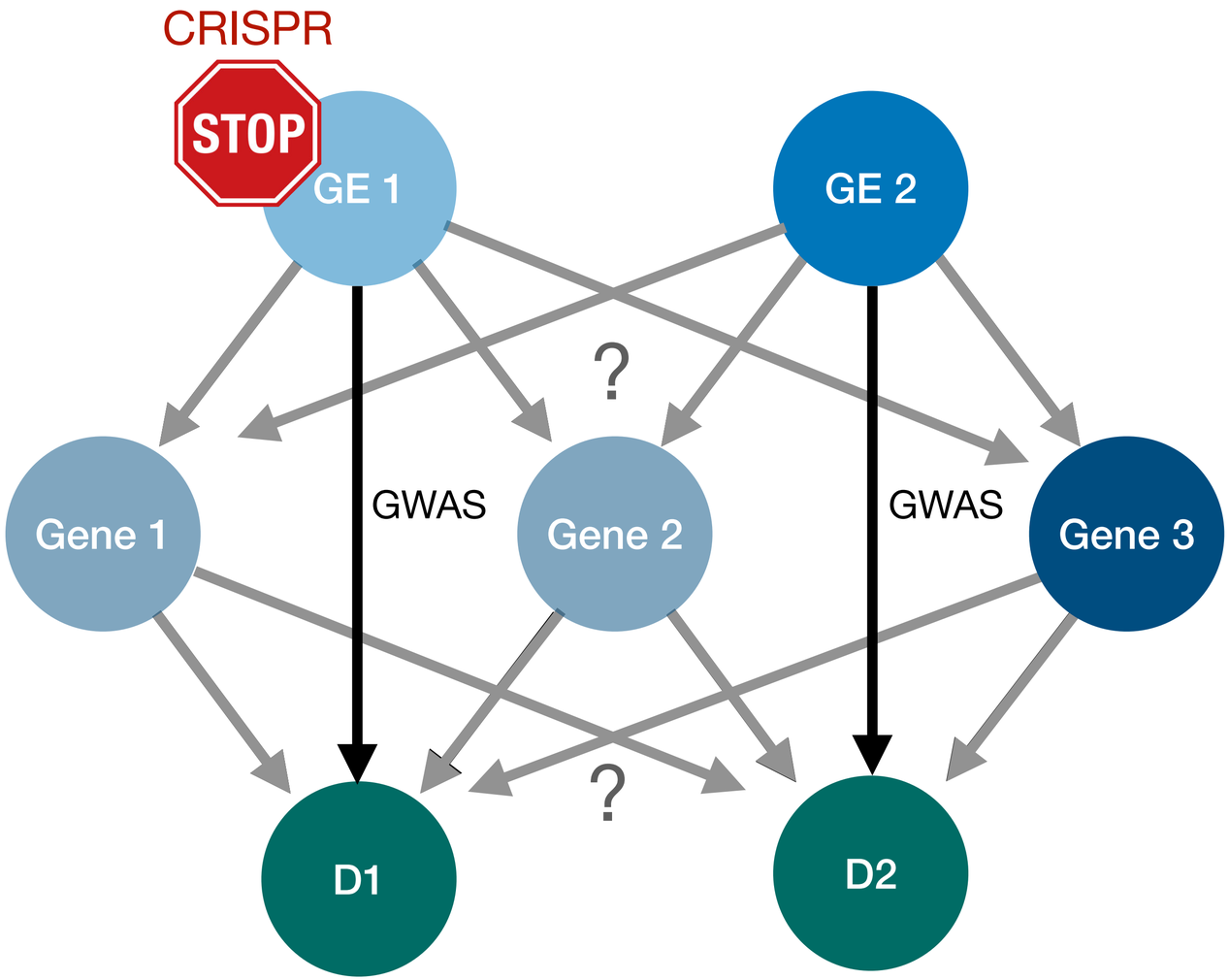

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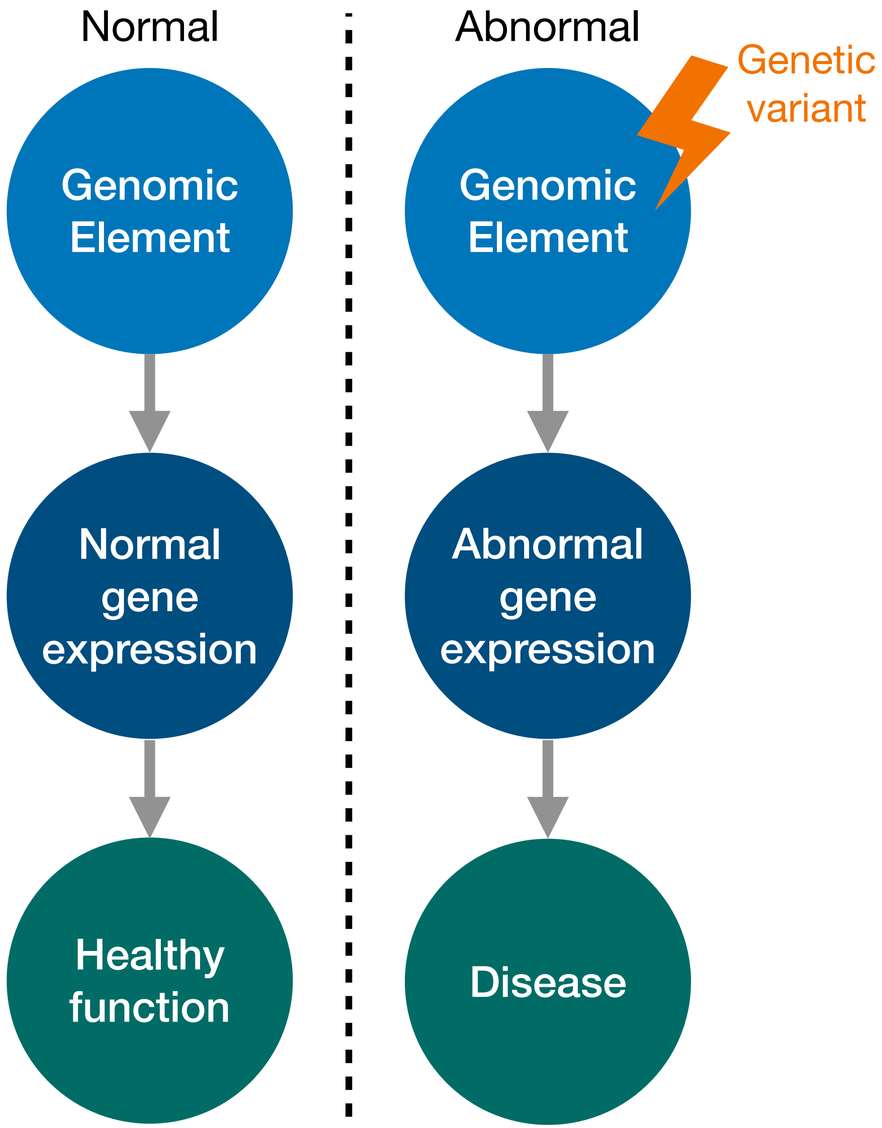

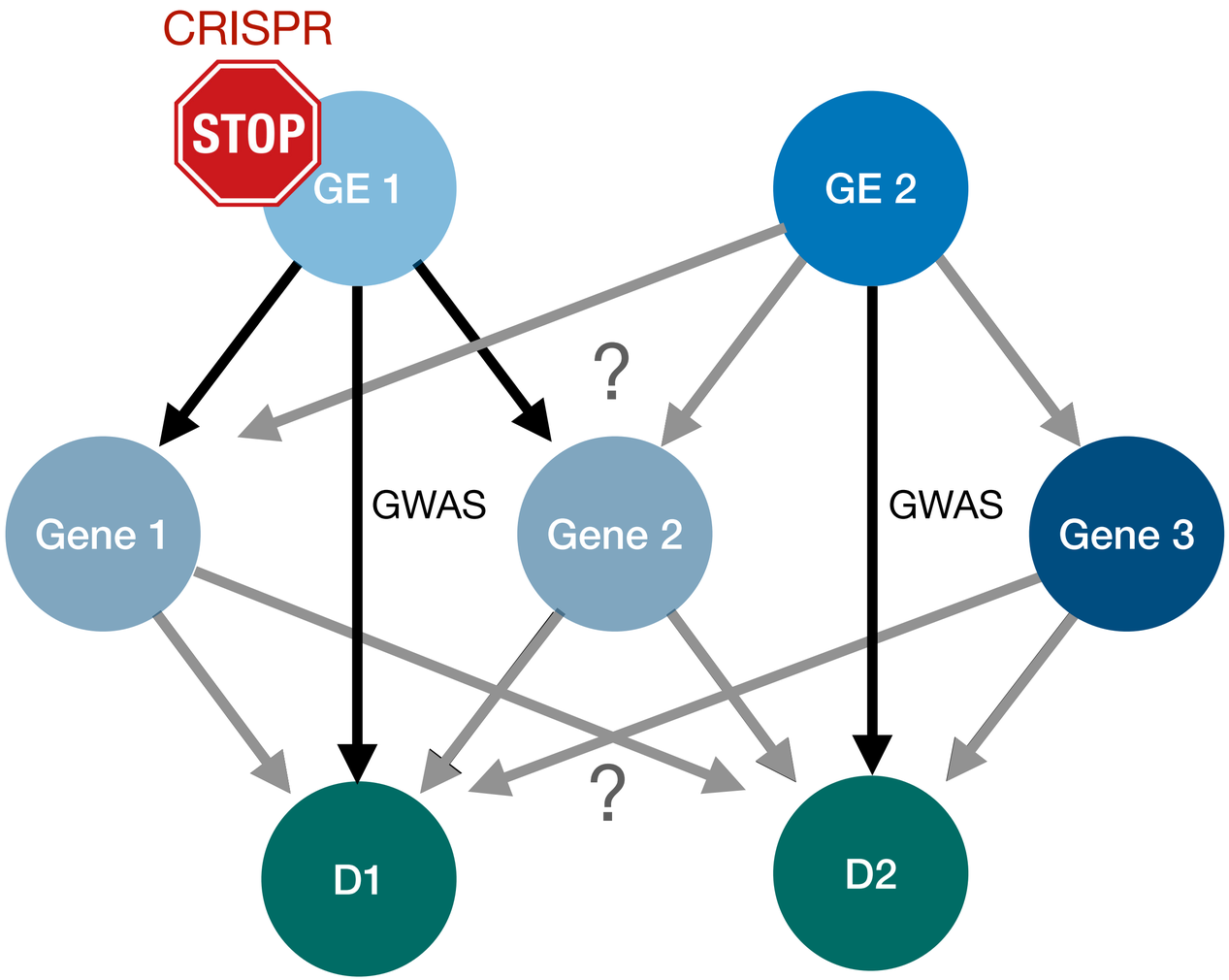

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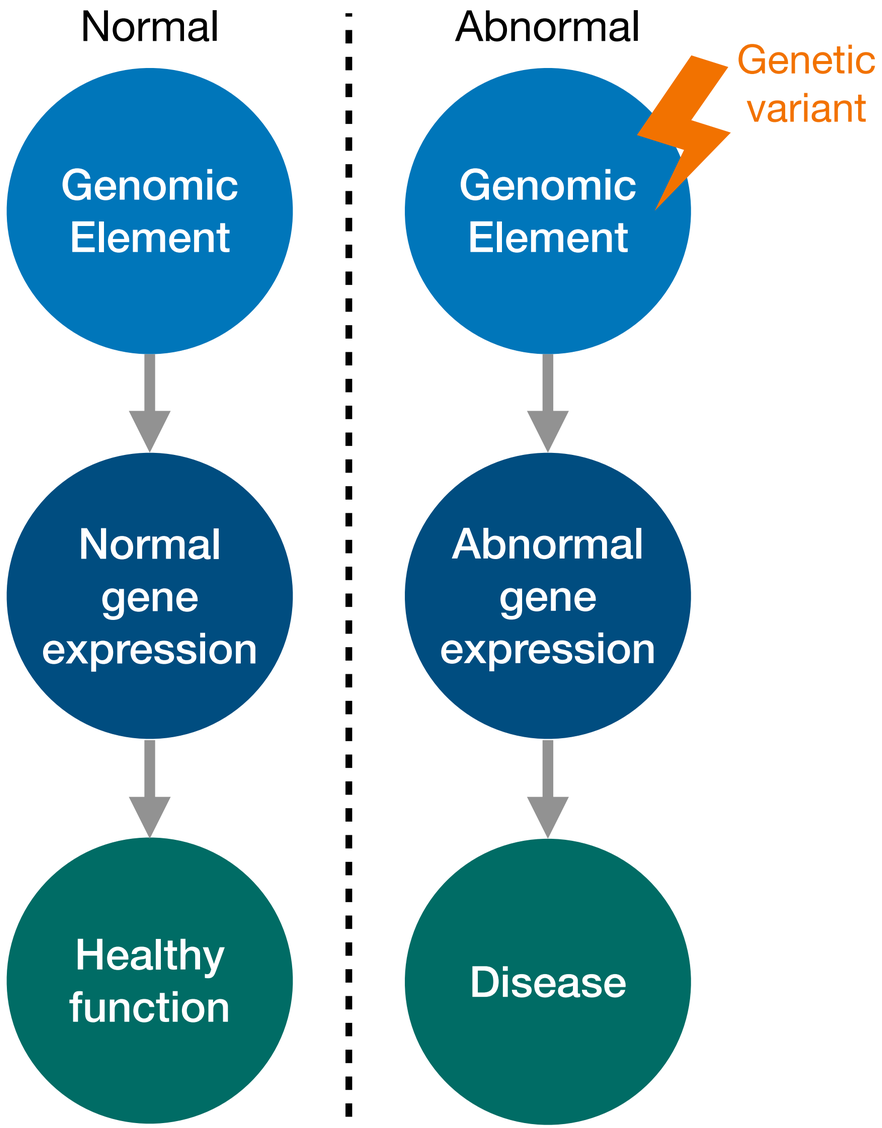

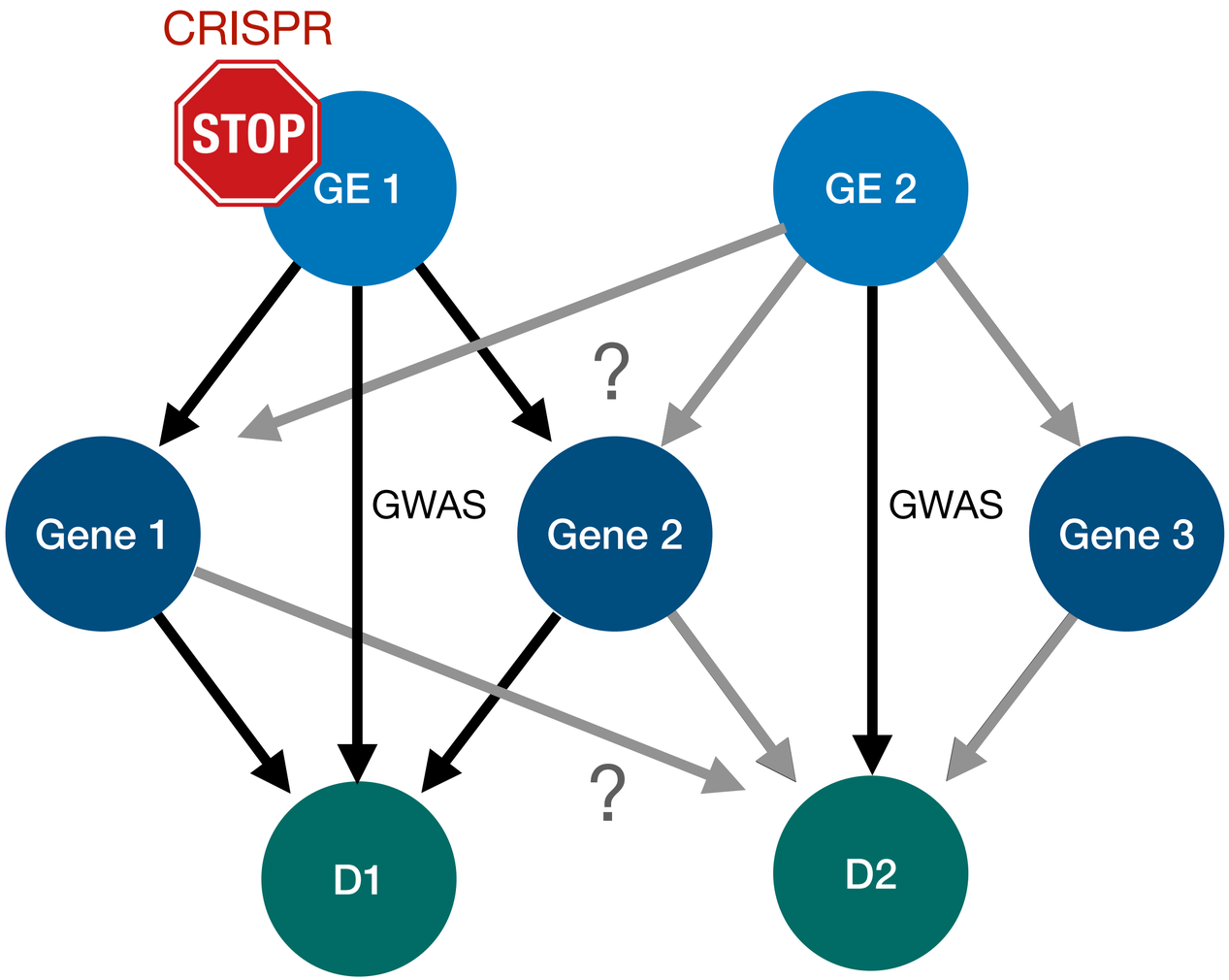

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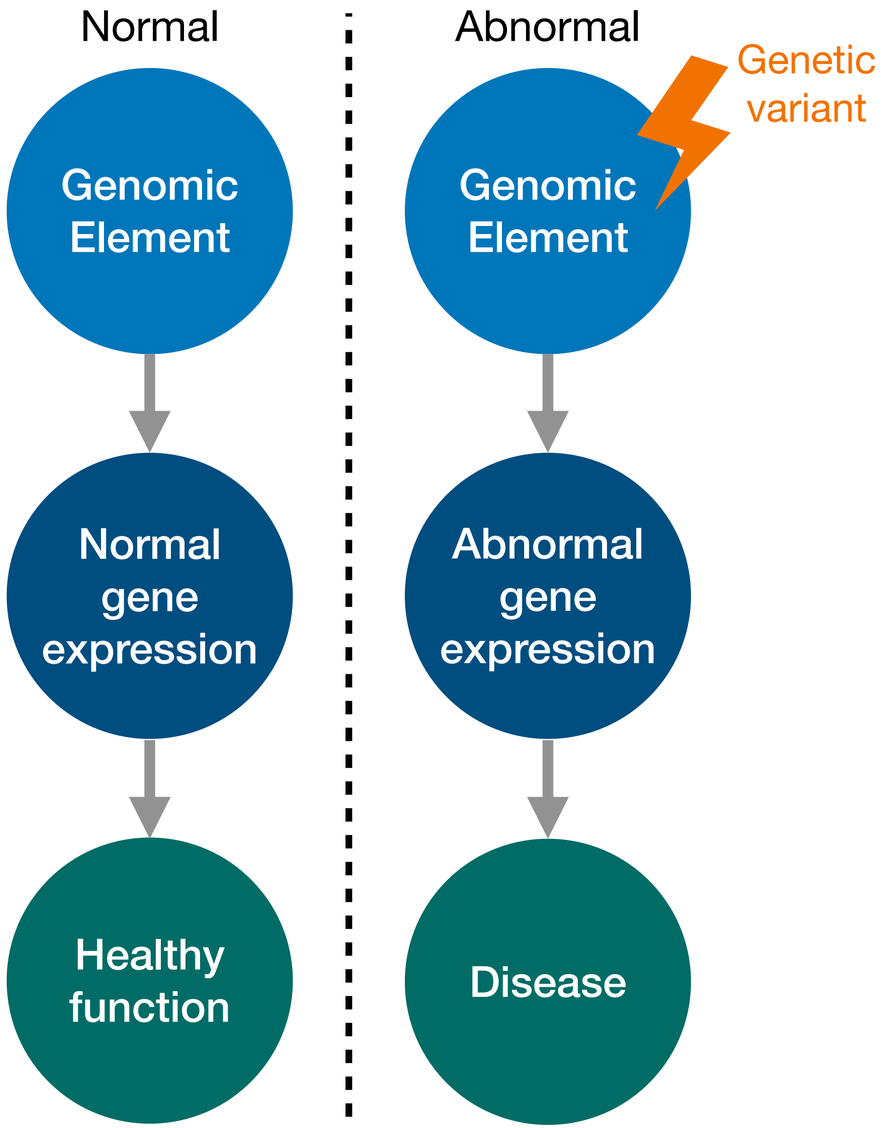

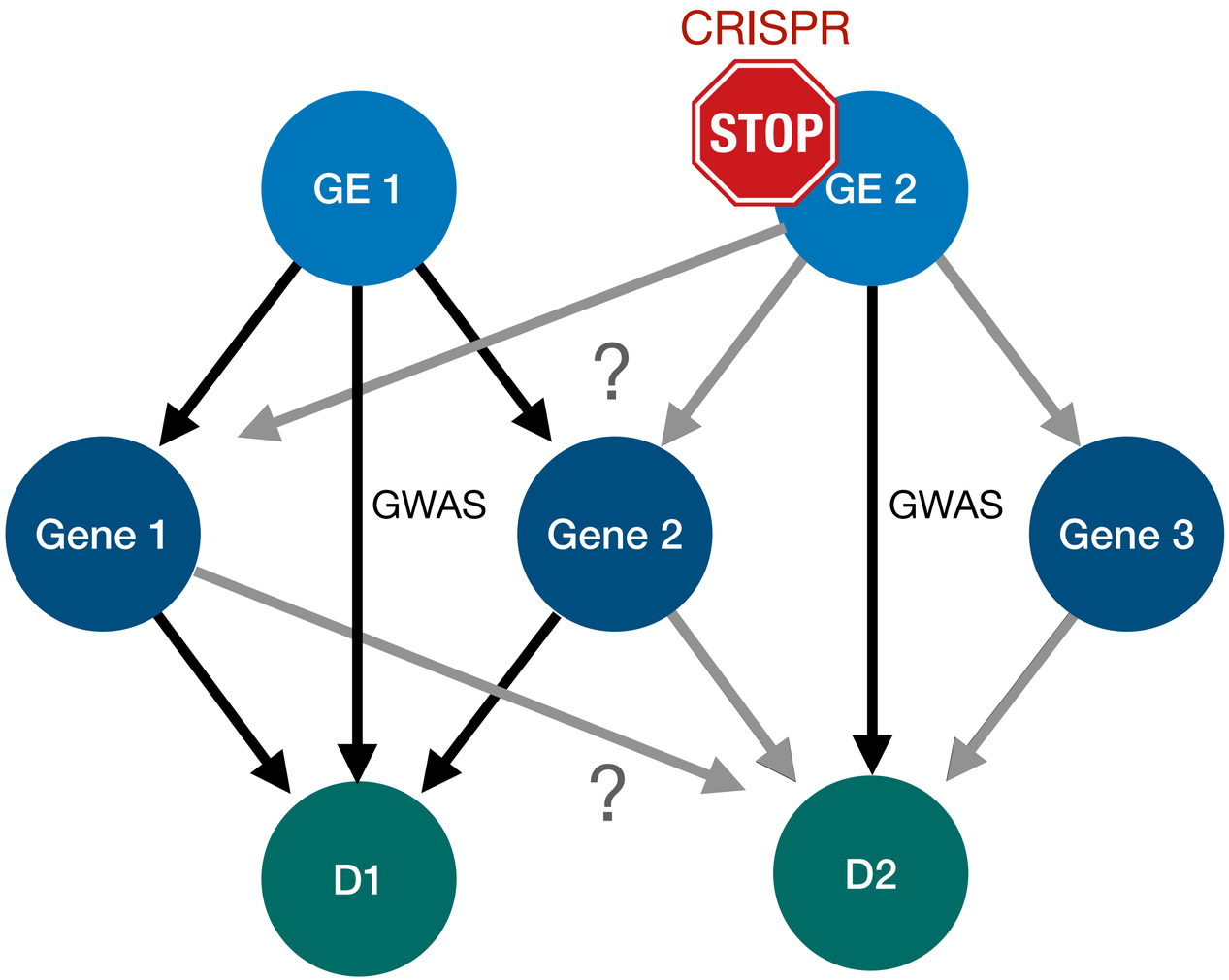

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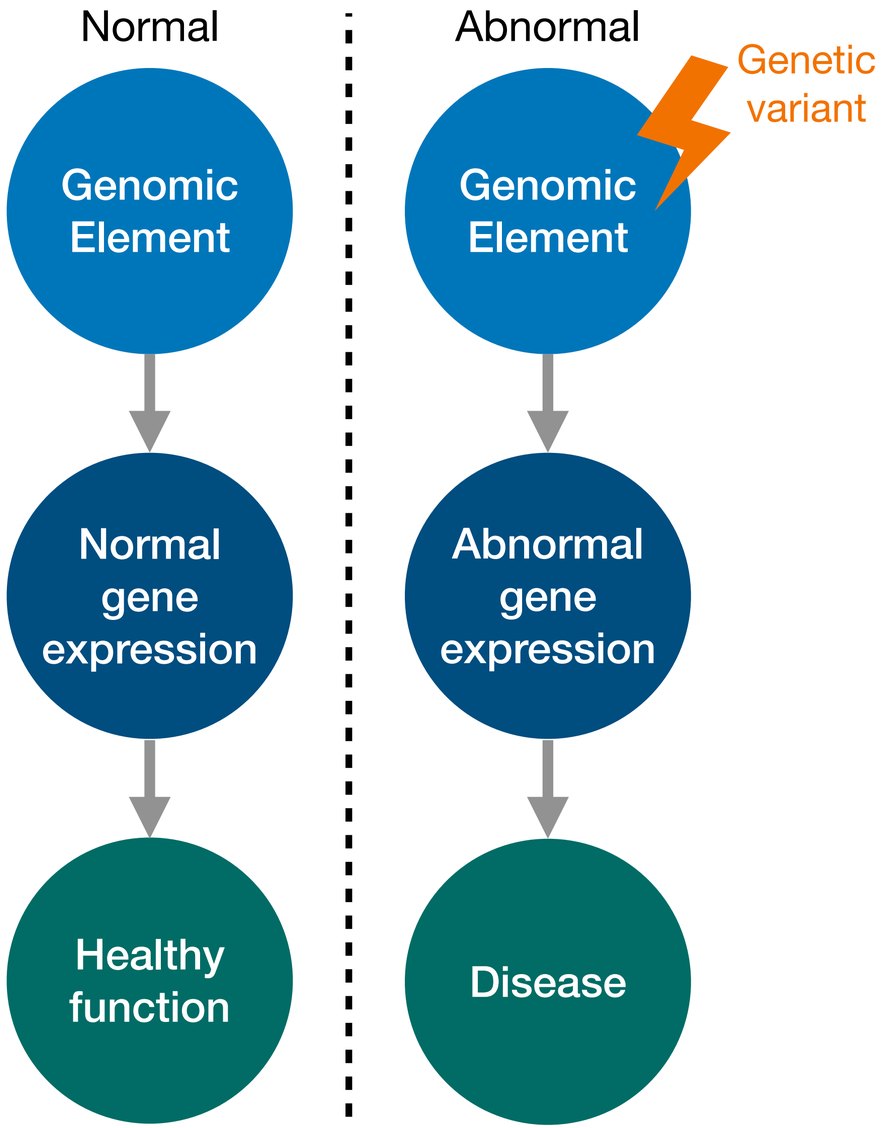

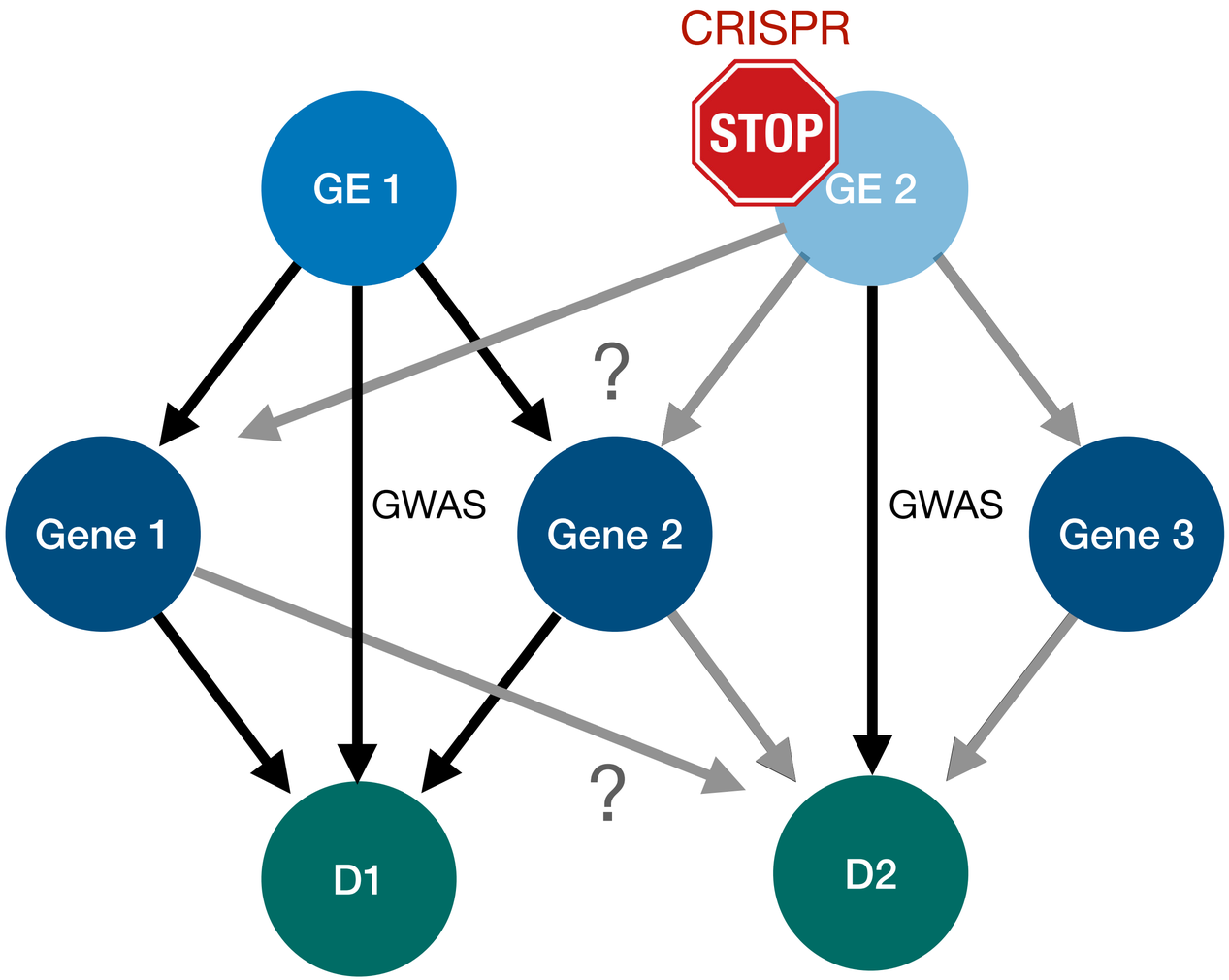

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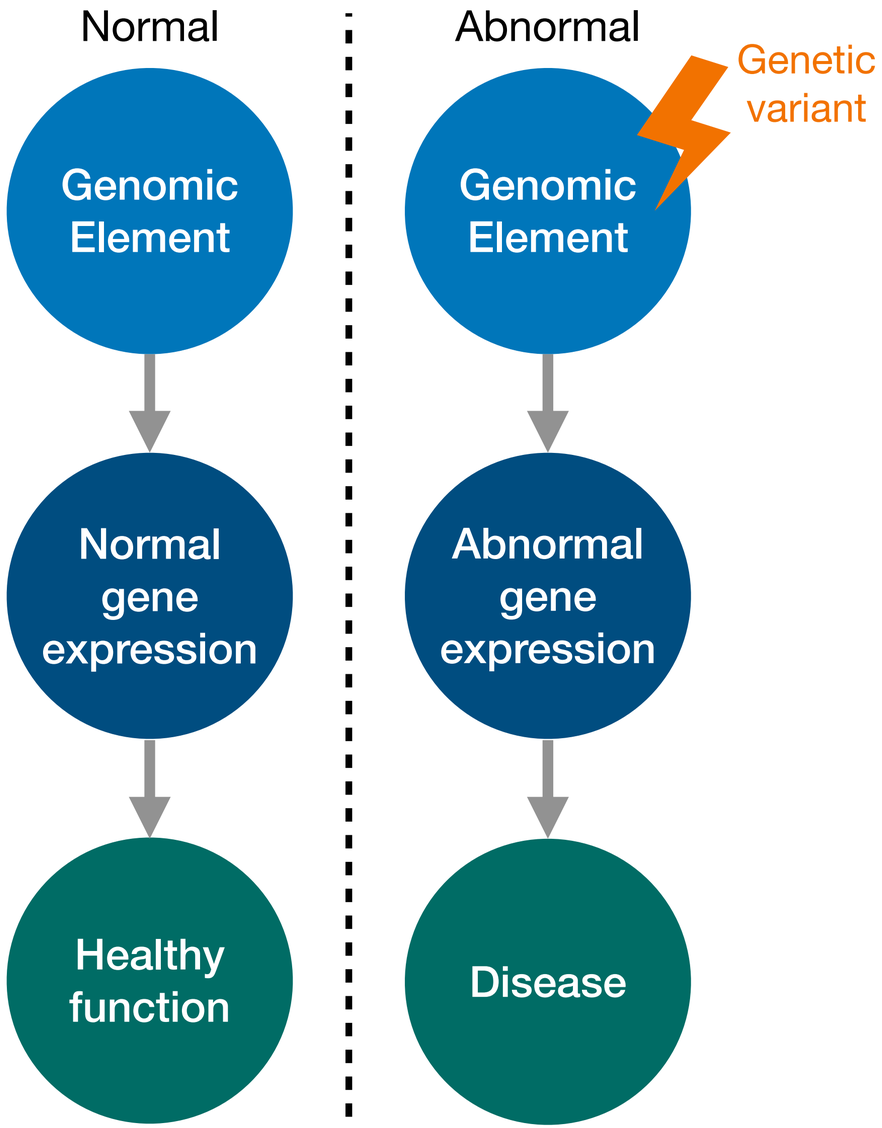

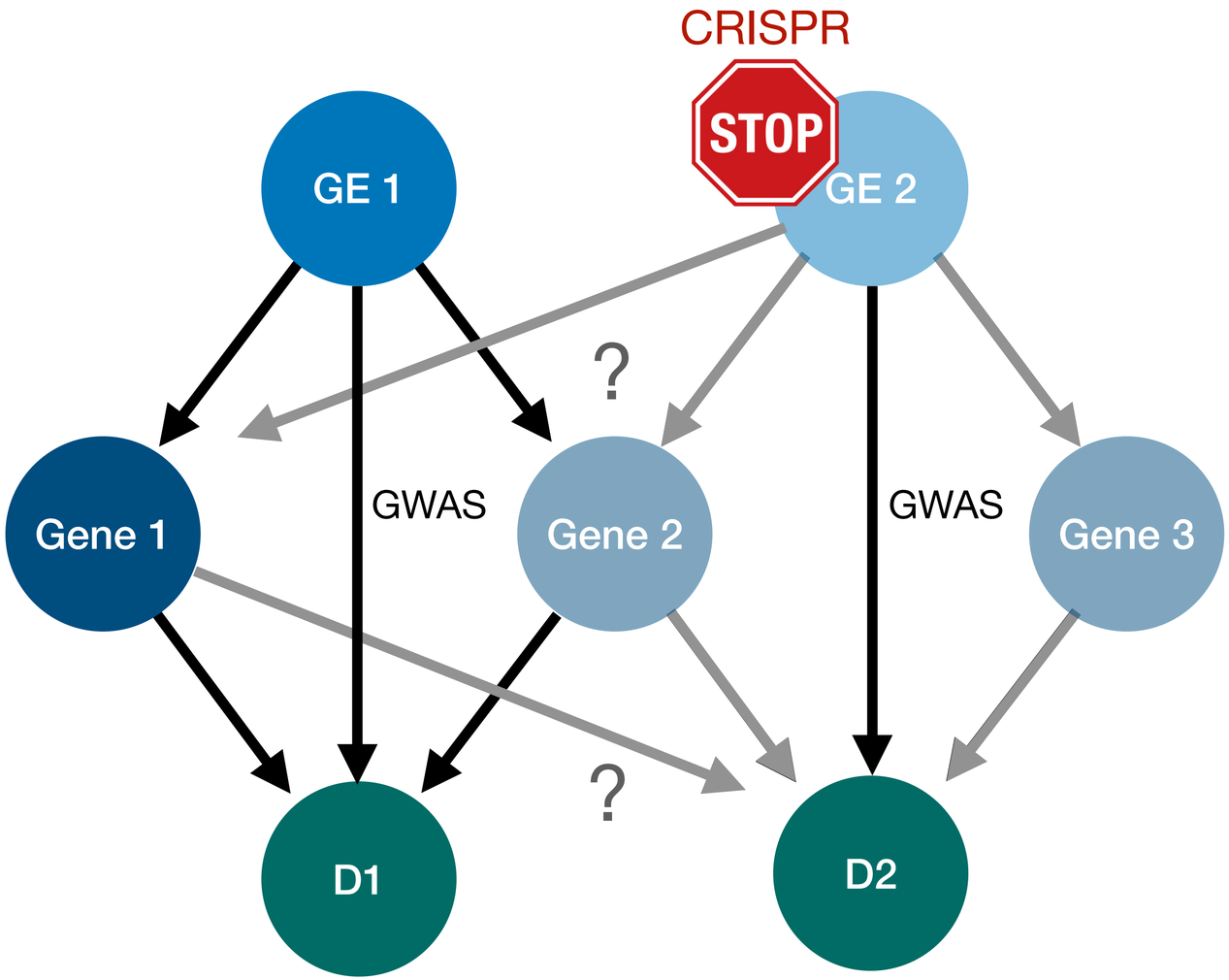

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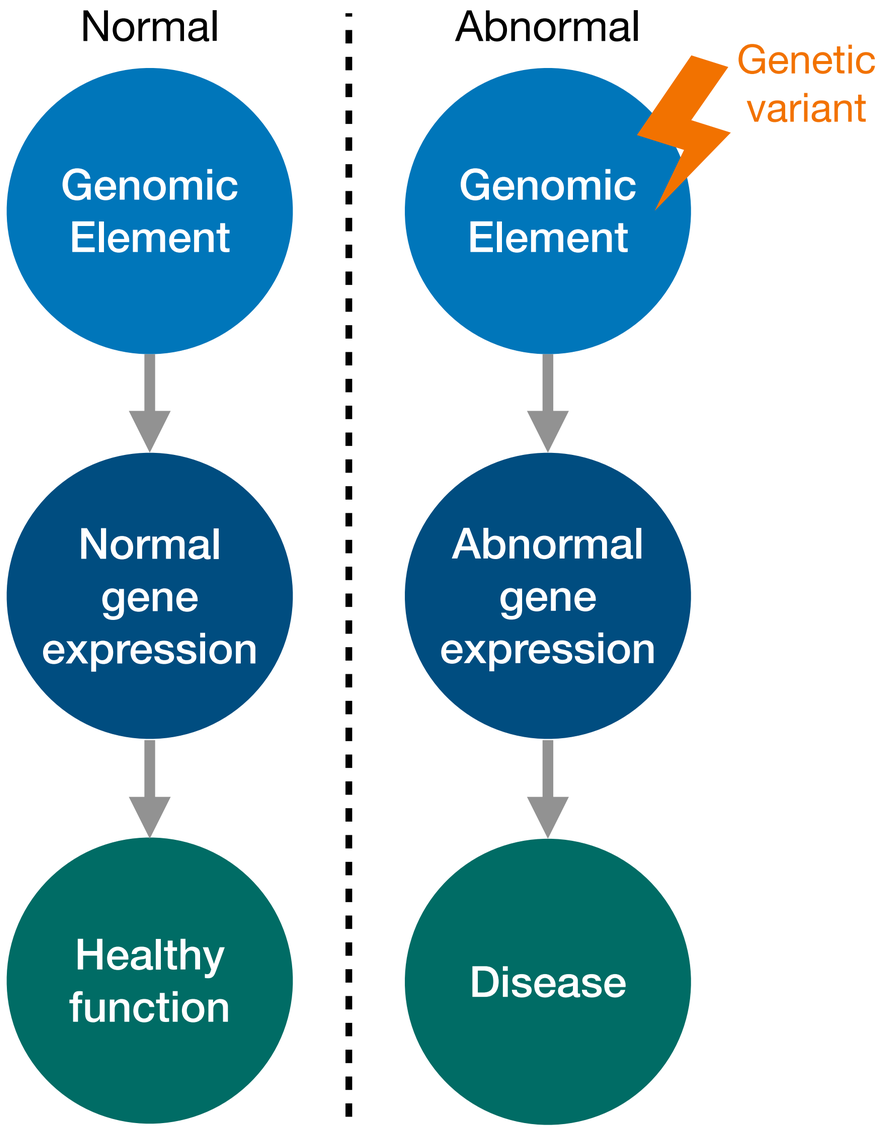

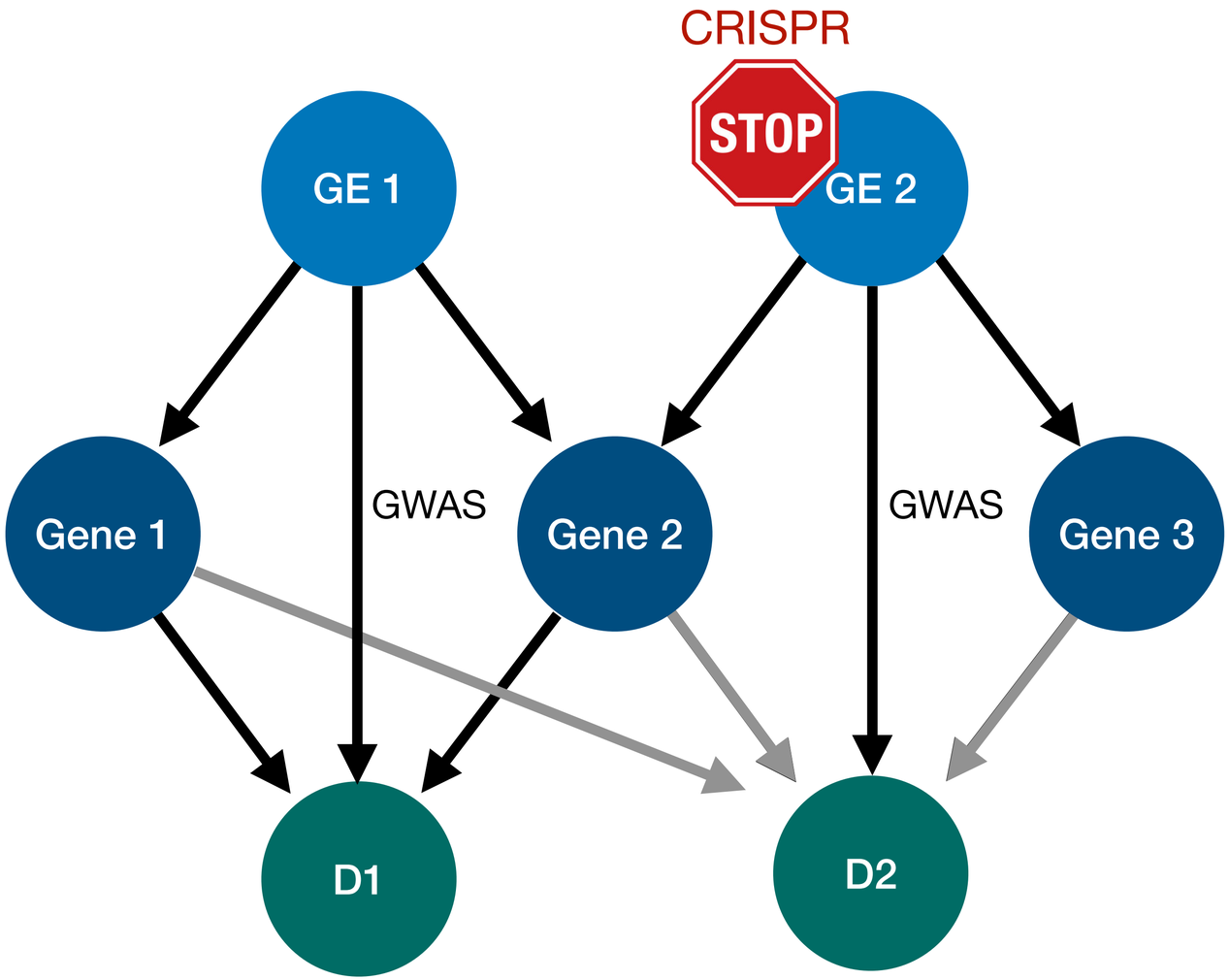

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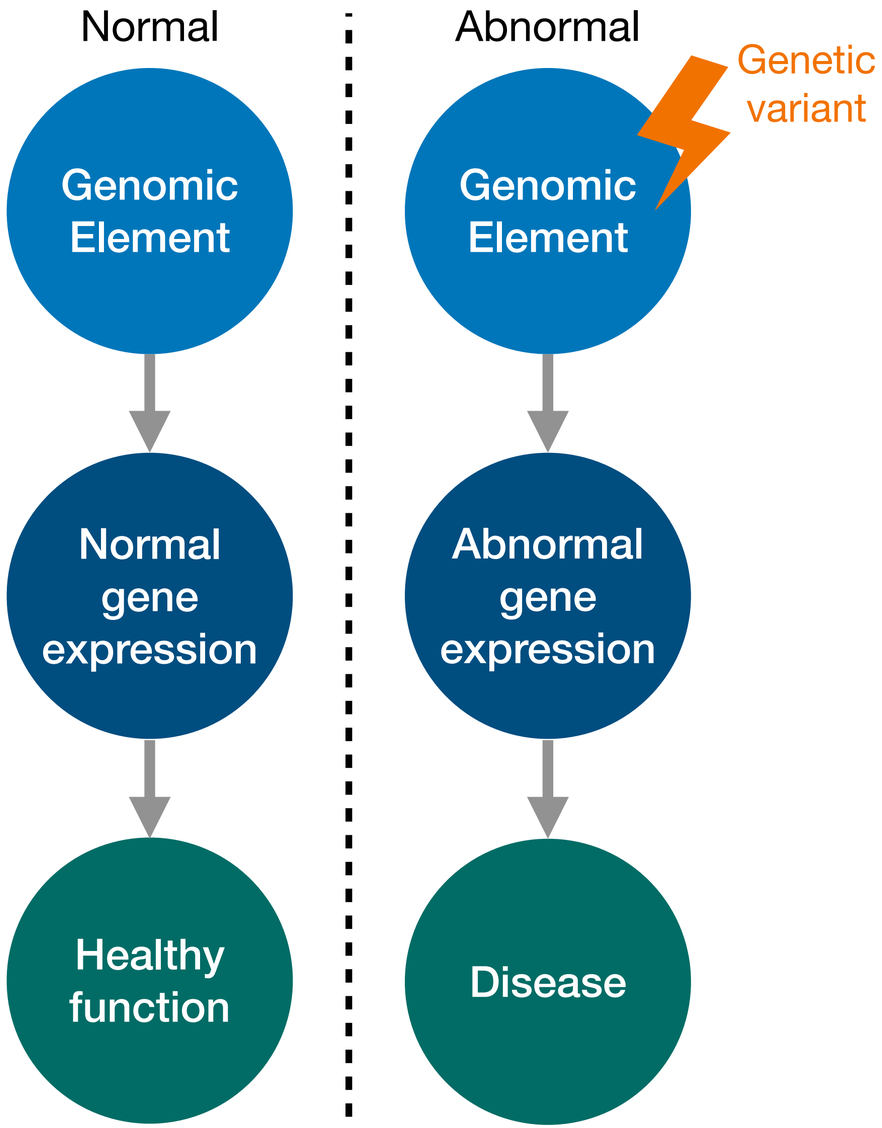

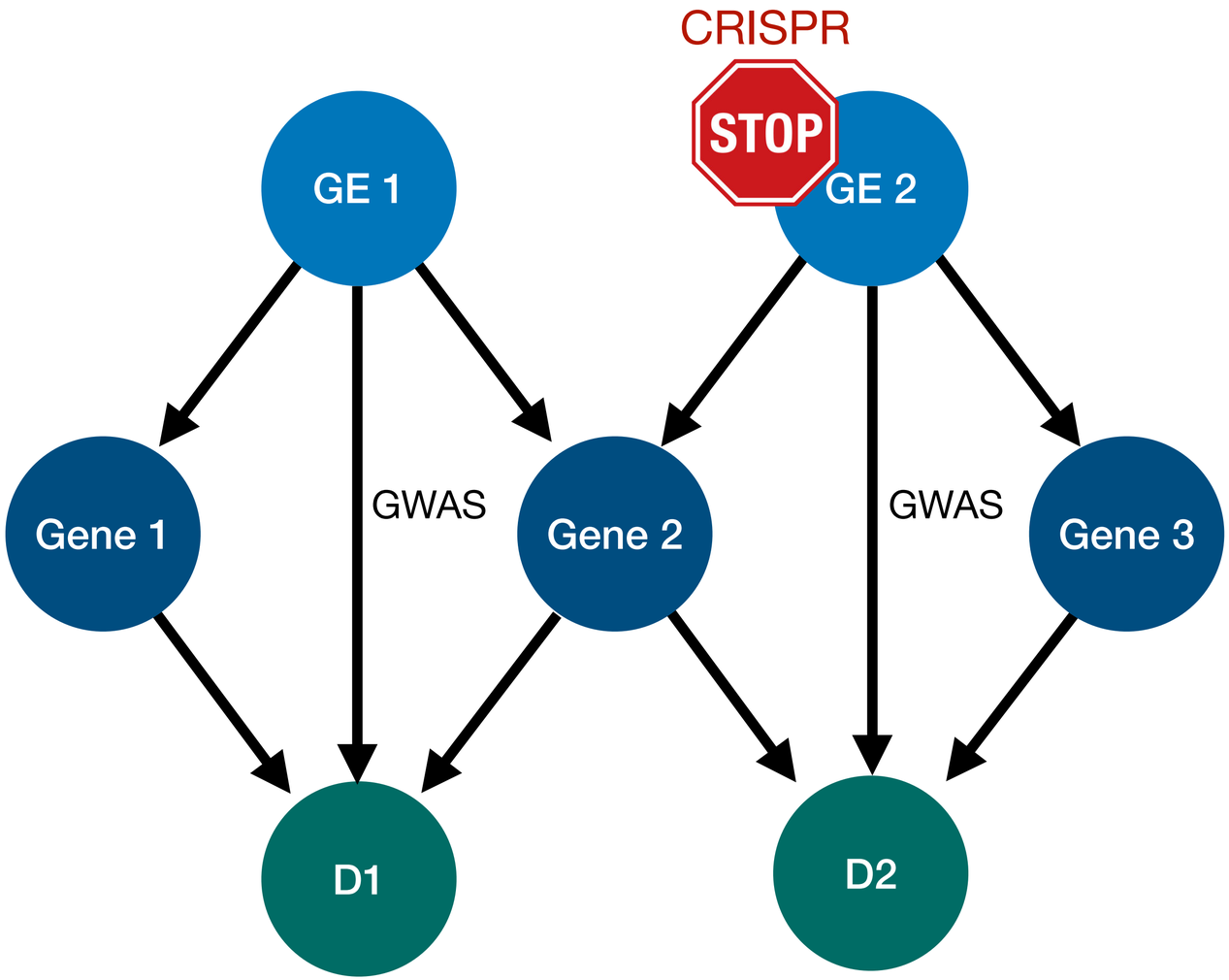

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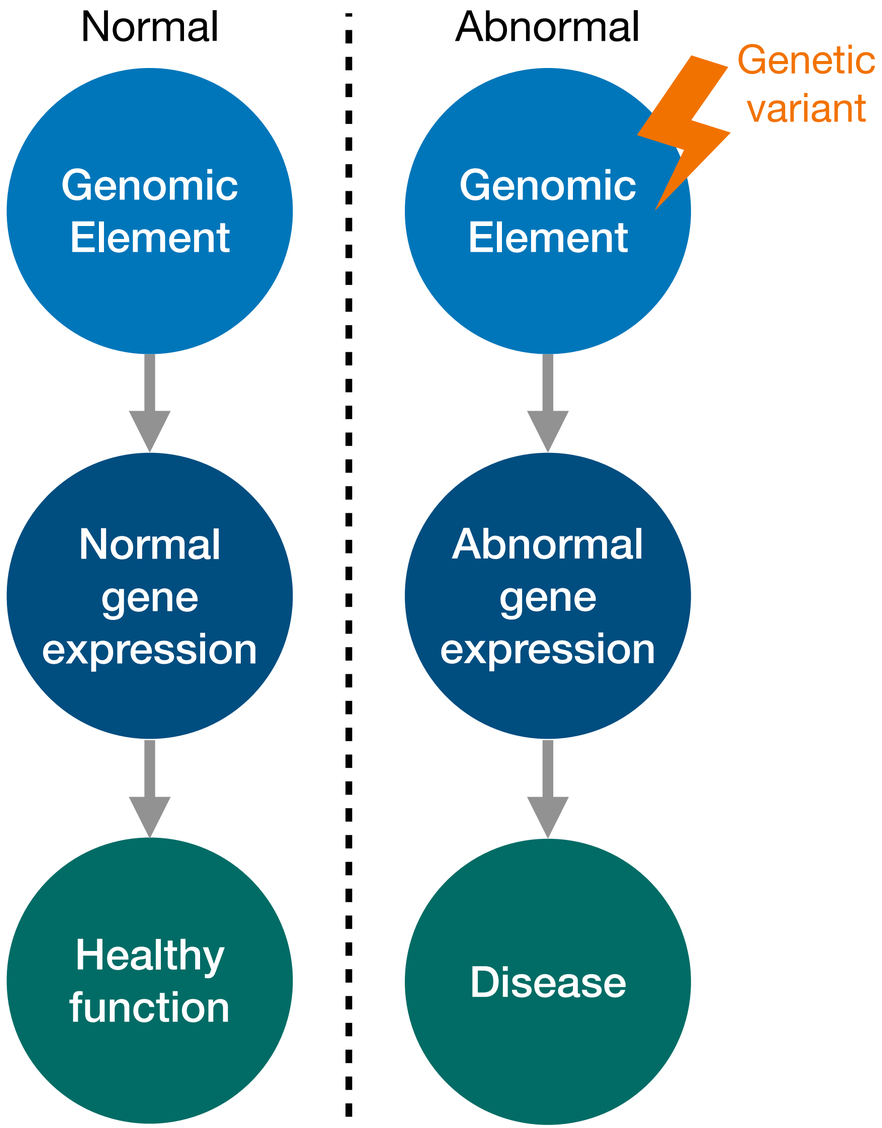

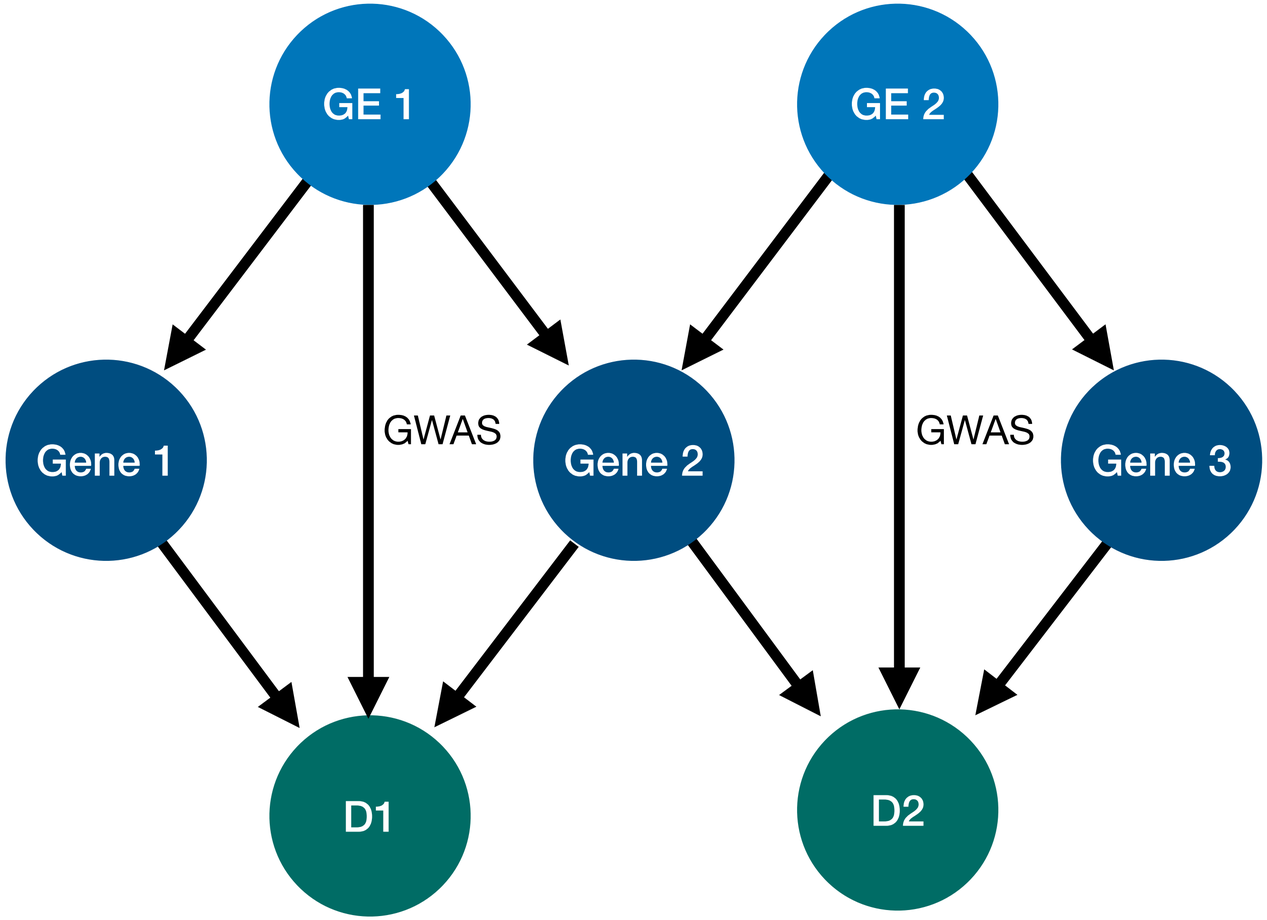

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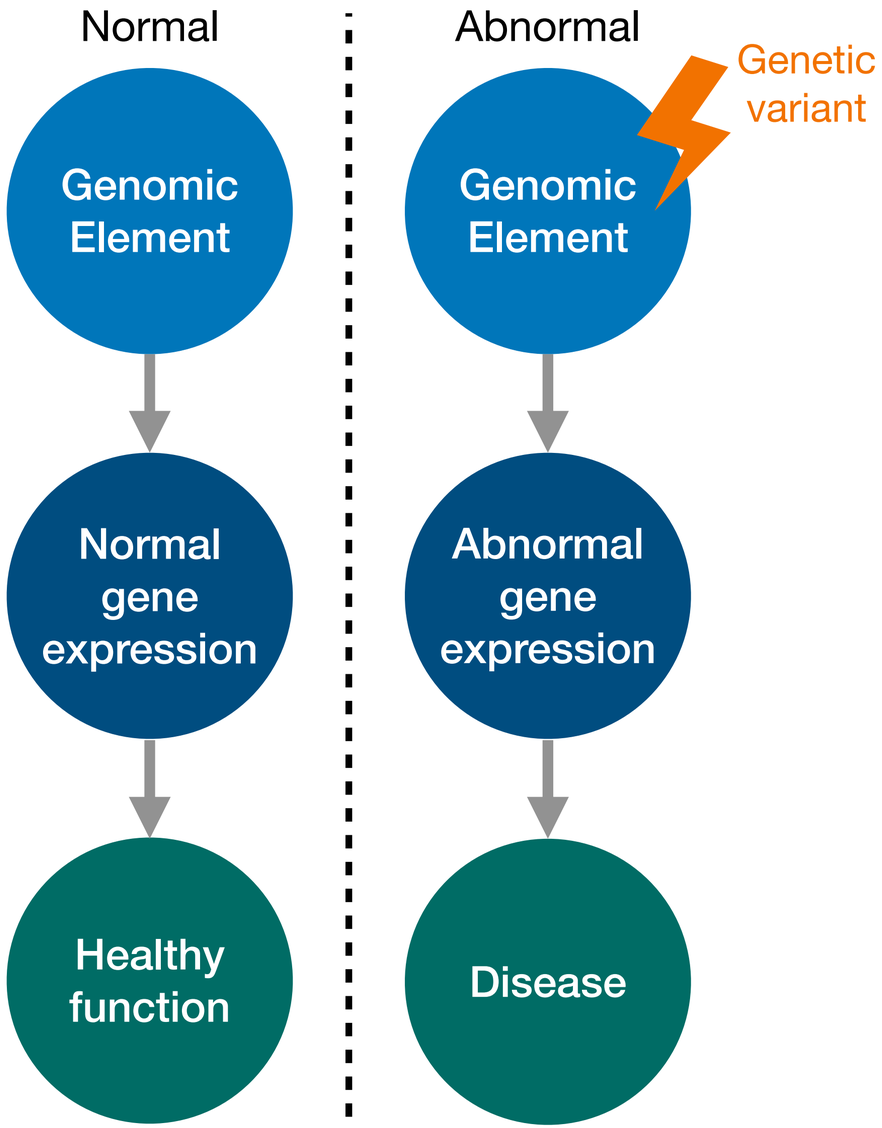

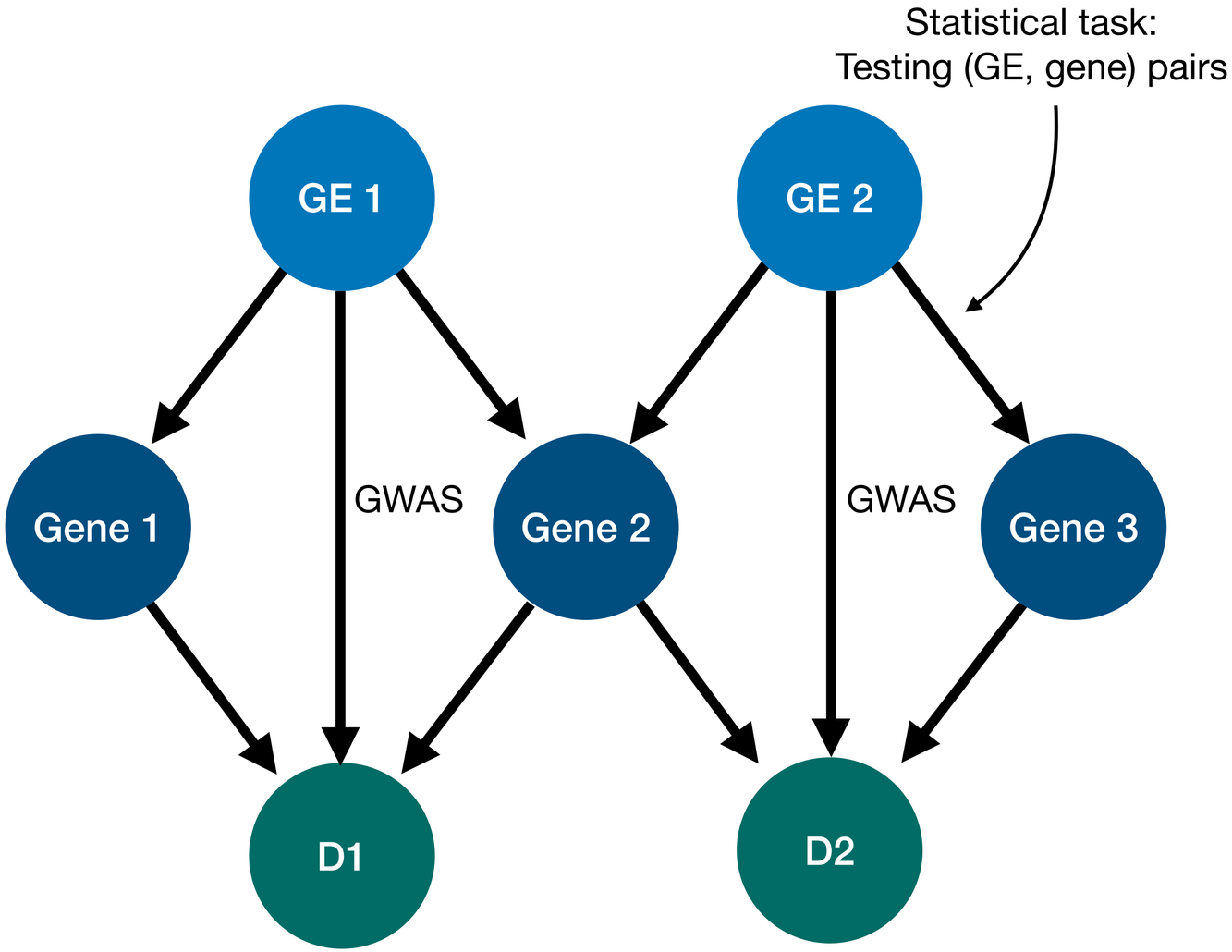

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Perturbation-gene association testing

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Focus on one genomic element and one gene.

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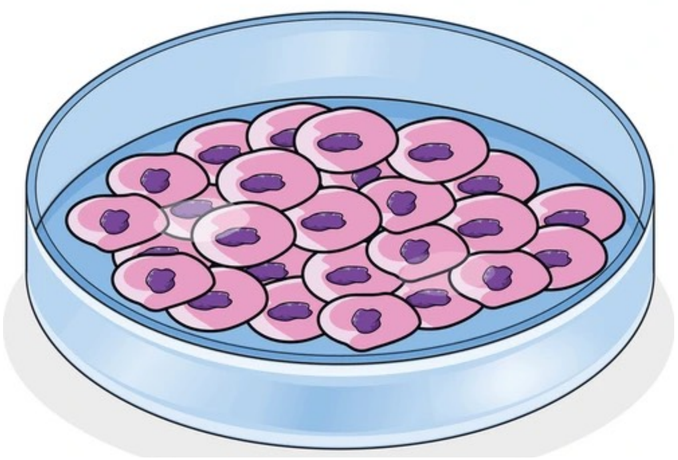

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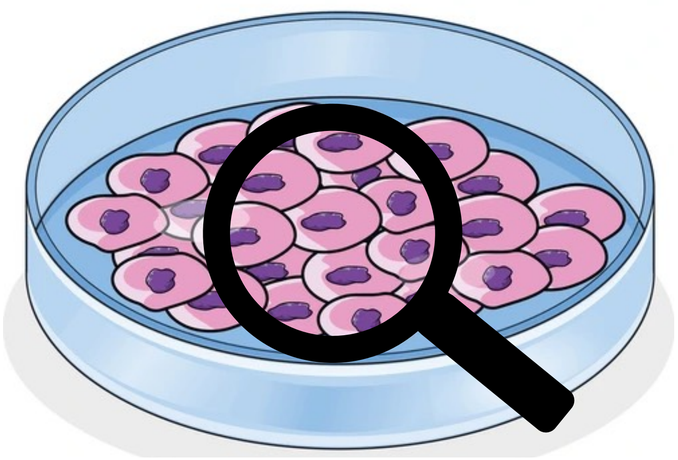

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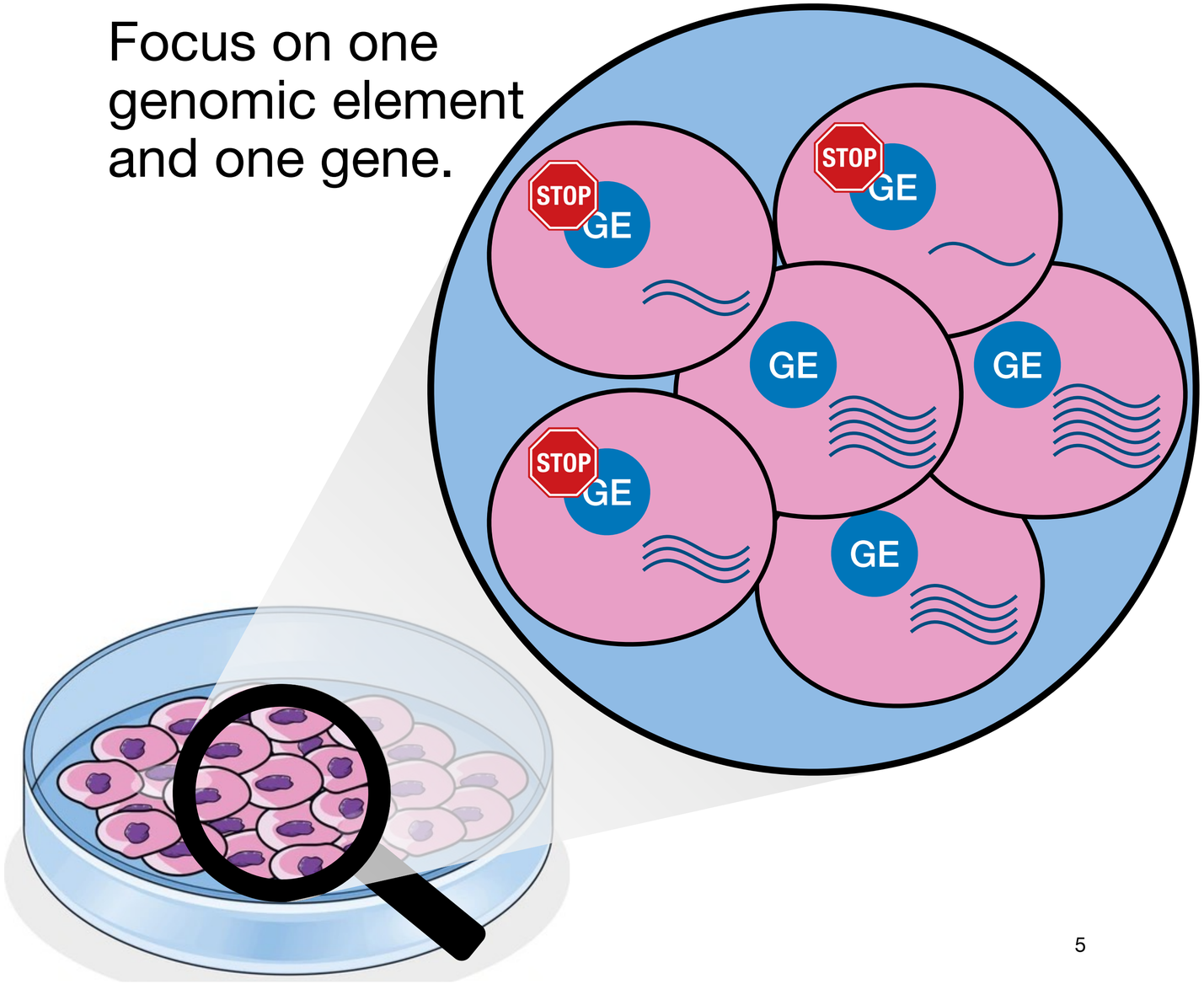

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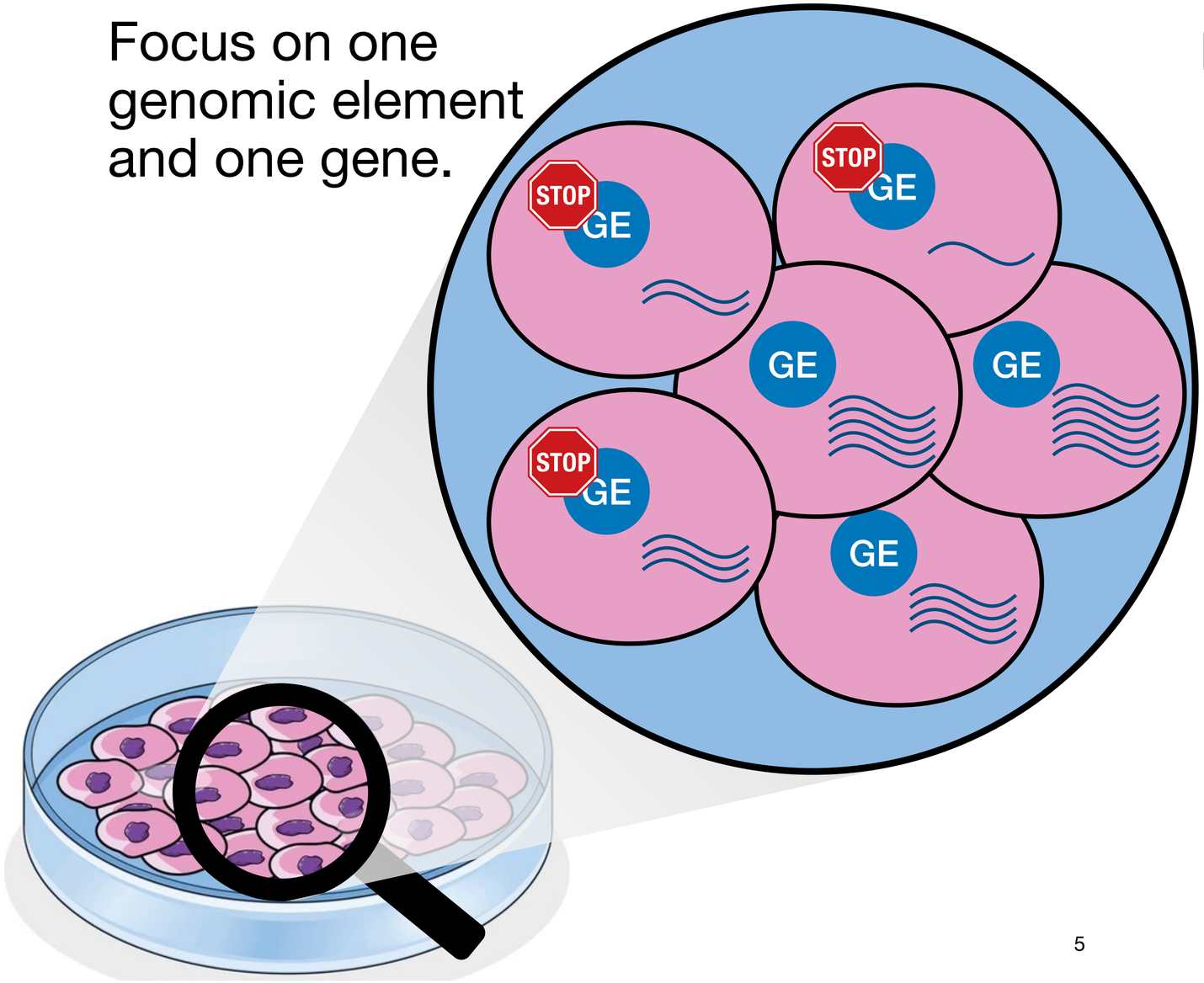

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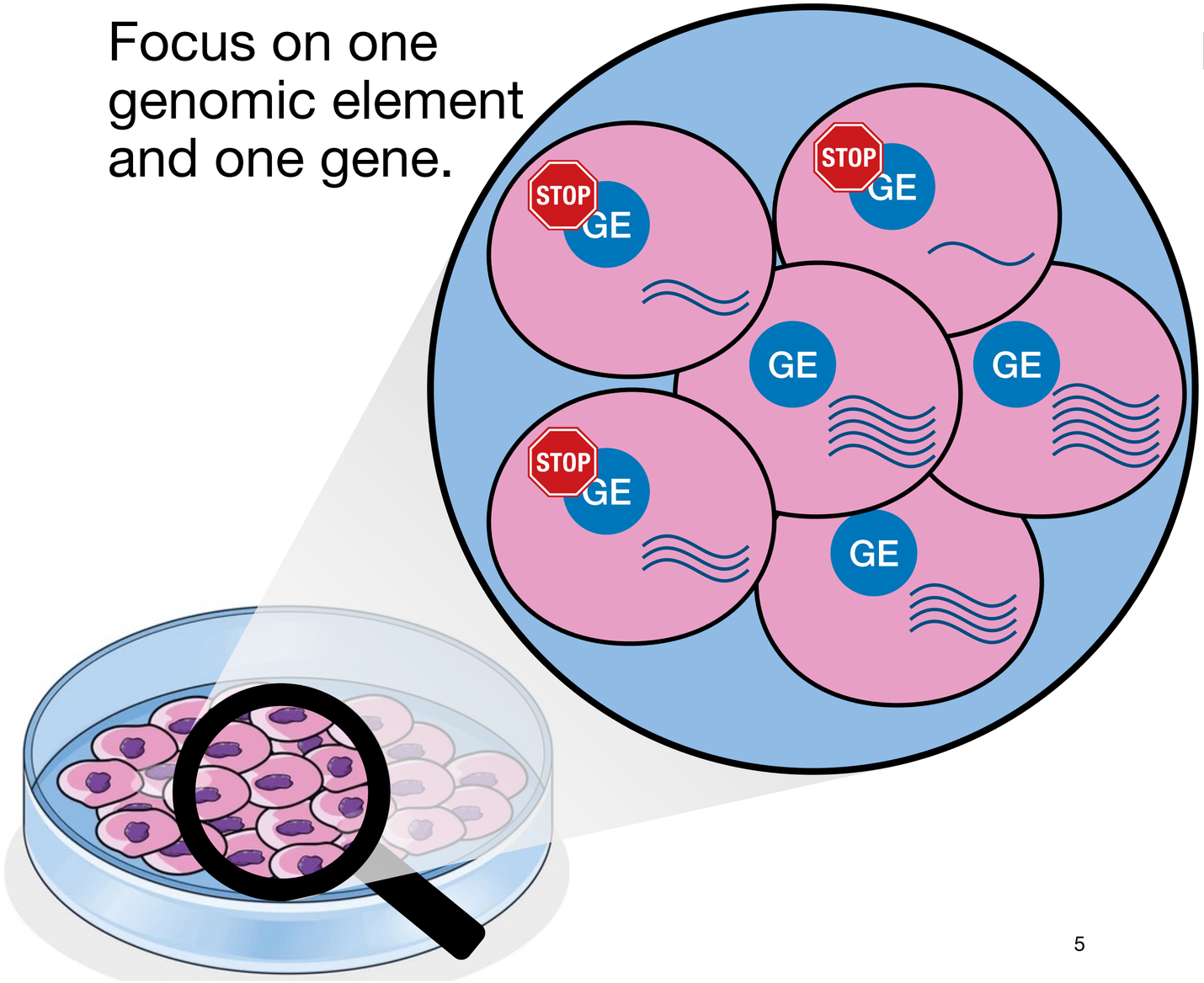

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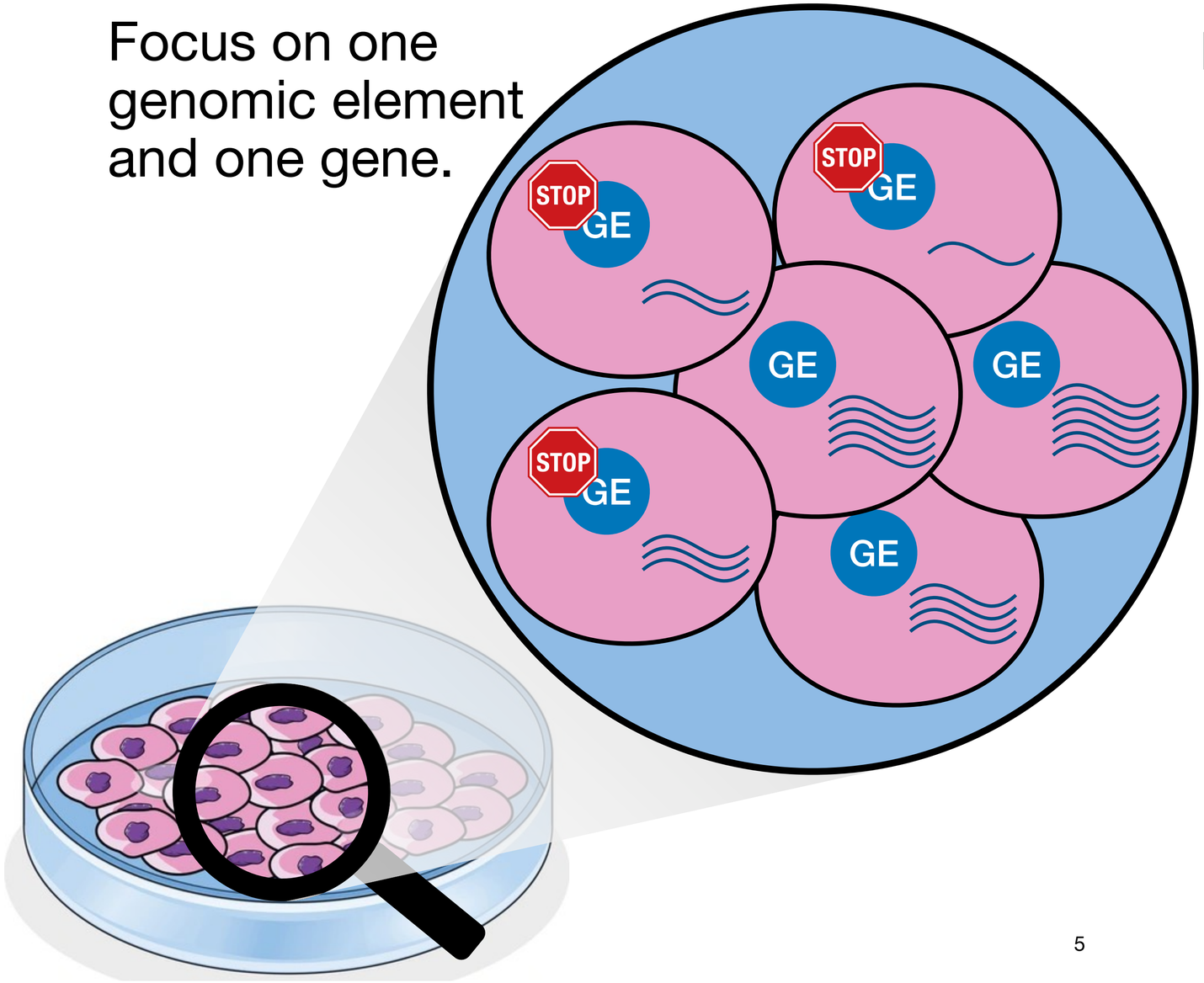

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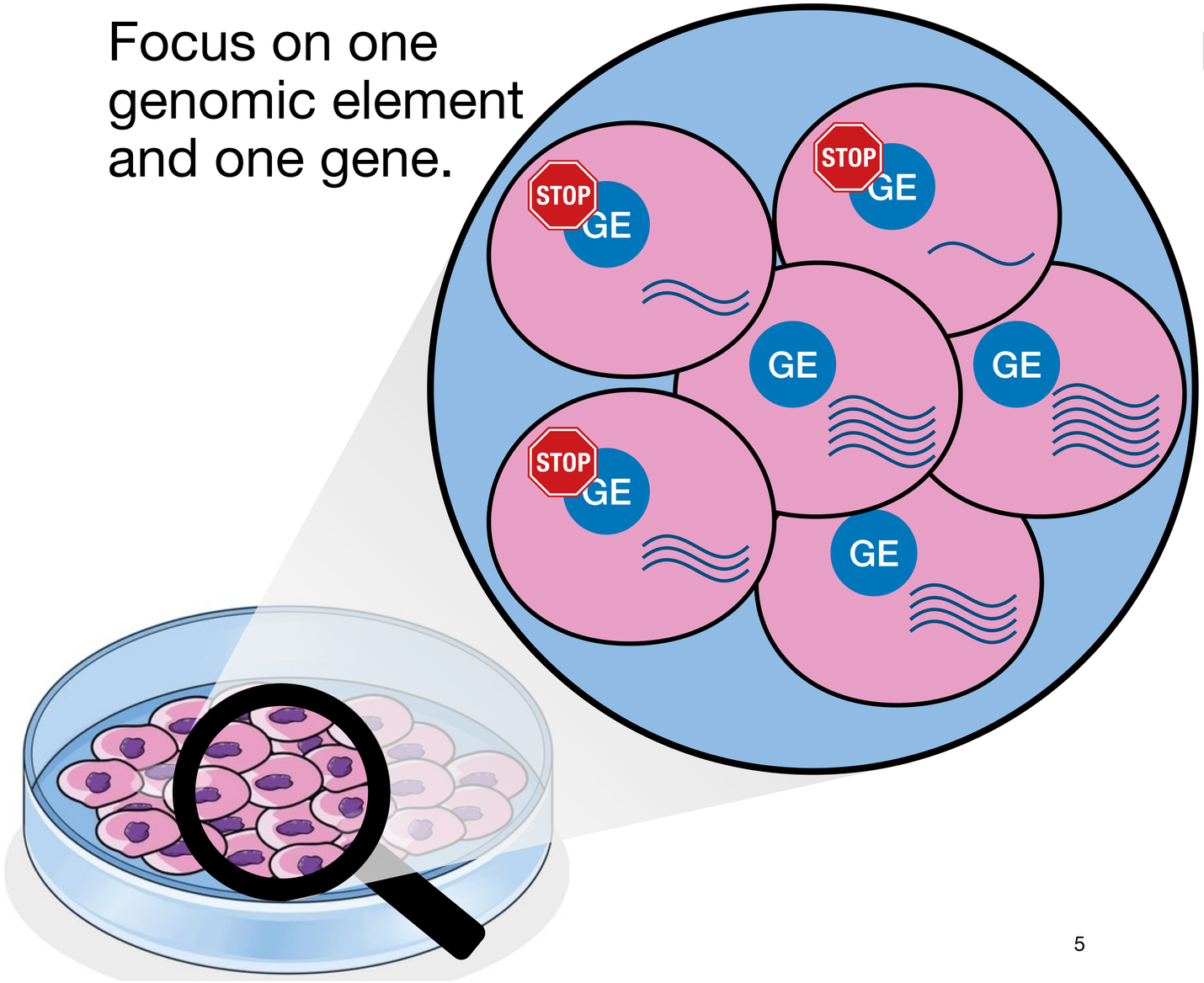

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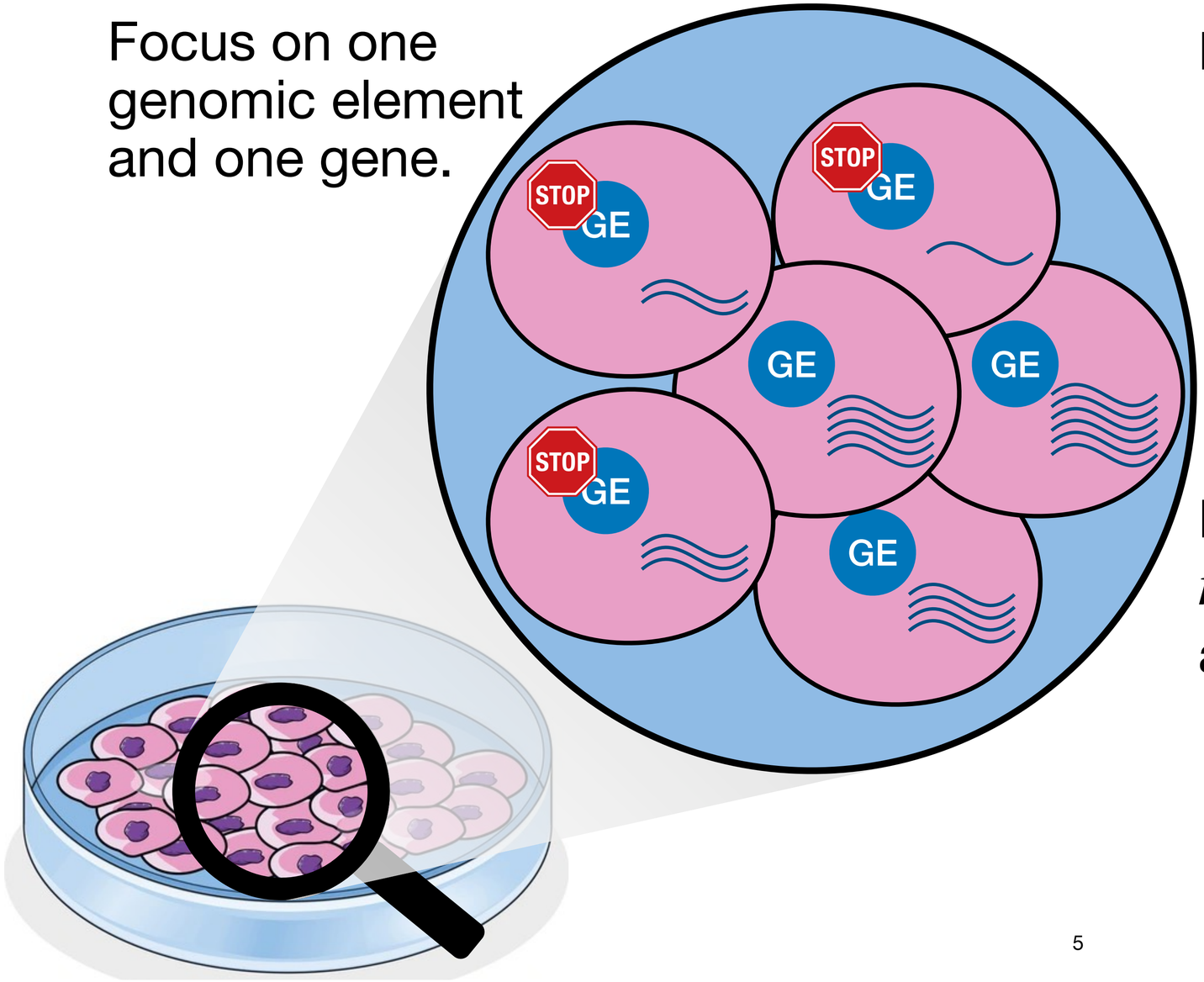

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In Gasperini (2019) data, we have $n \approx 200{,}000$ cells, $\approx 13{,}000$ genes, and $\approx 6{,}000$ genomic elements.

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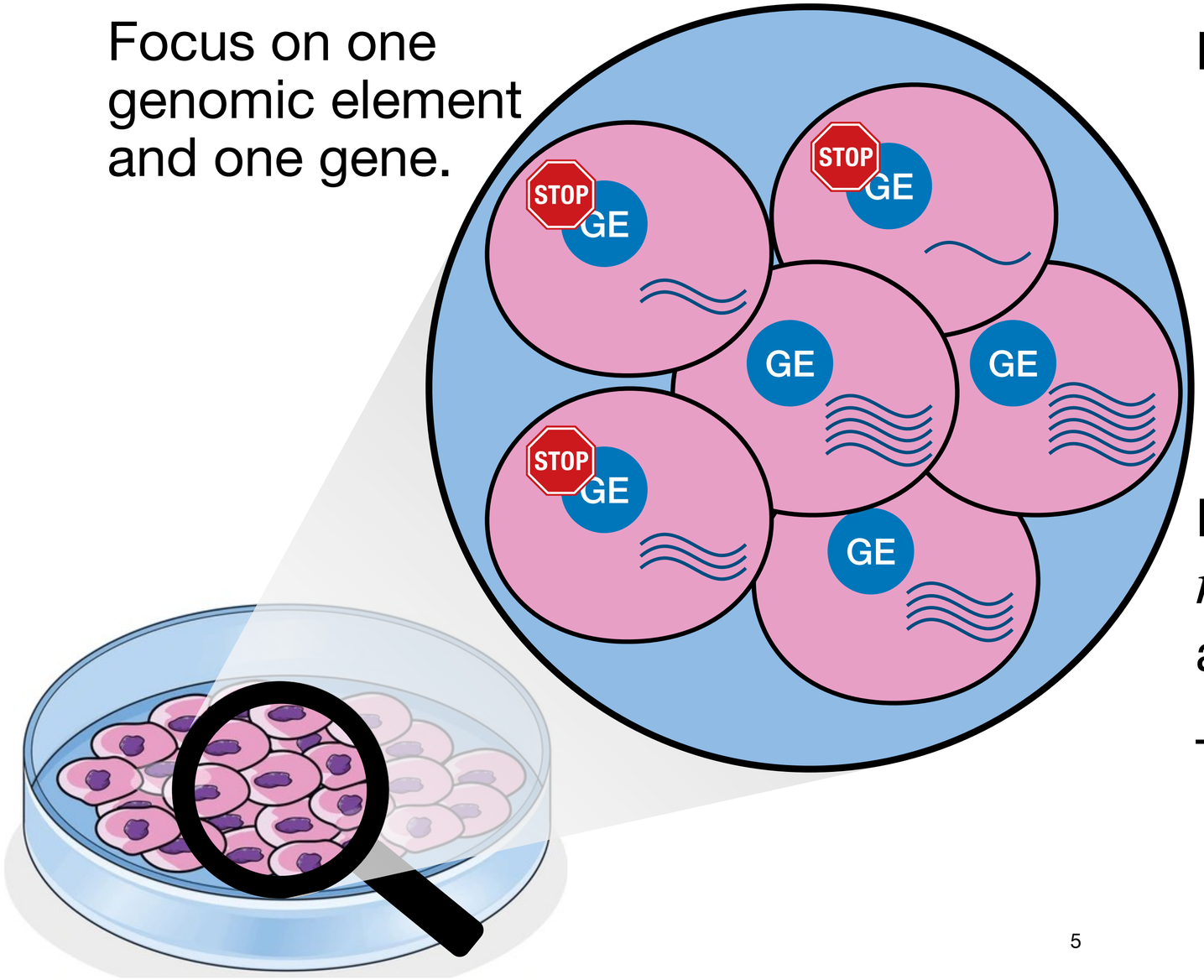

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In Gasperini (2019) data, we have $n \approx 200{,}000$ cells, $\approx 13{,}000$ genes, and $\approx 6{,}000$ genomic elements.

The goal is to test

$$H_0 : X_i \perp\!\!\!\perp Y_i \mid Z_i.$$

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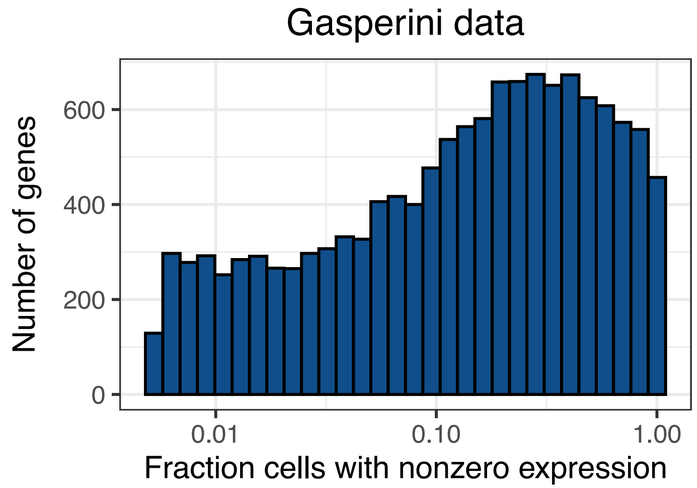

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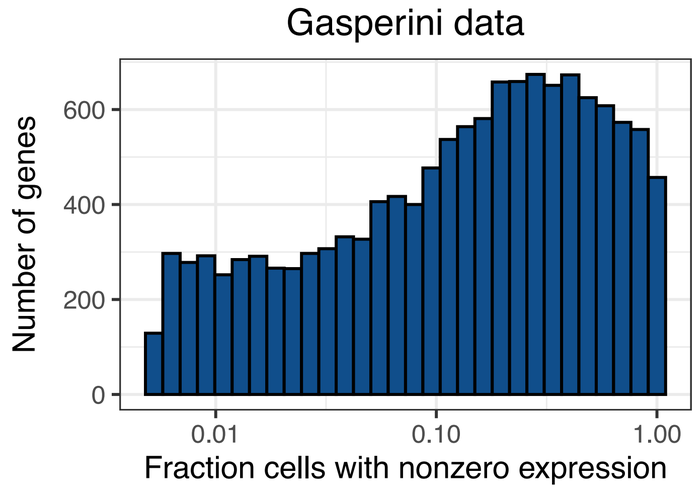

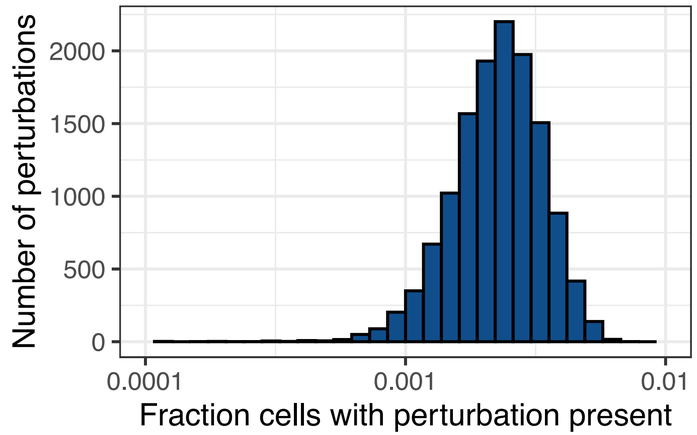

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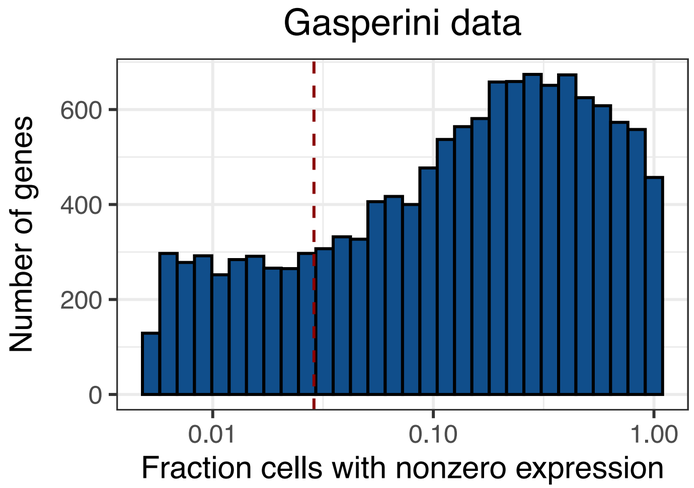

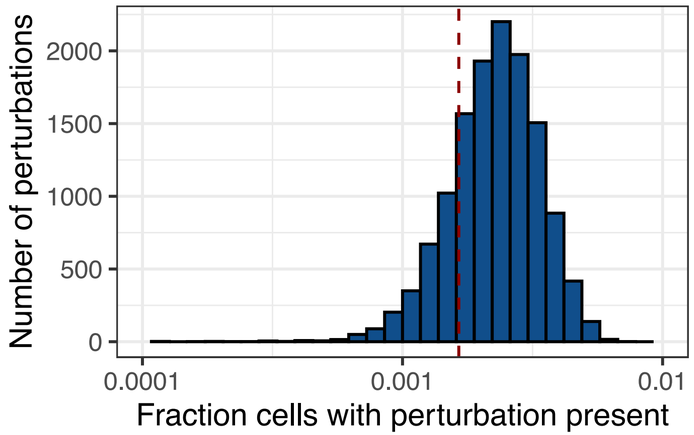

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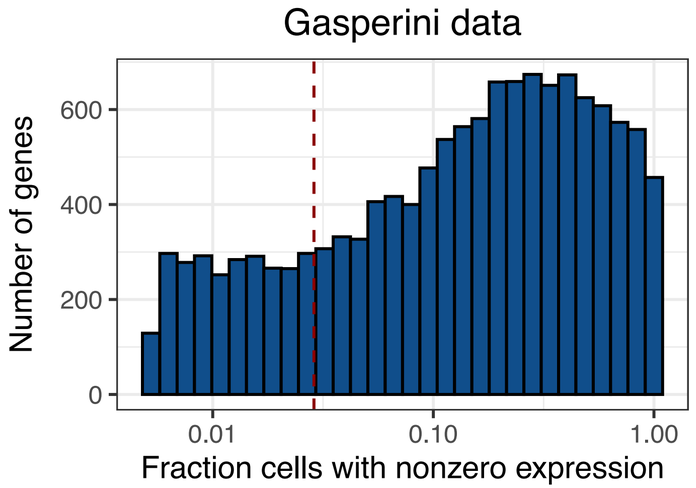

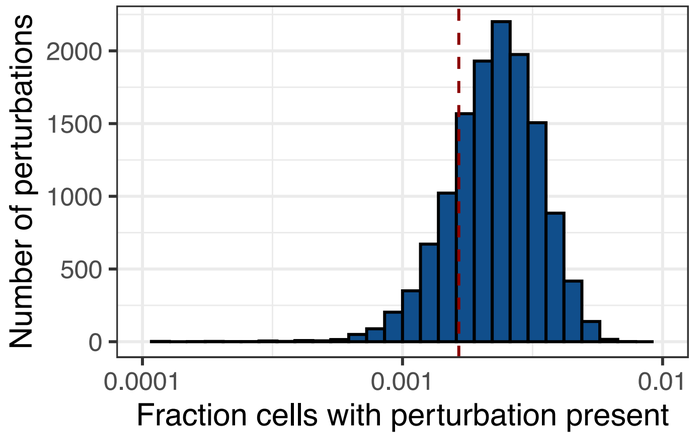

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Cell perturbed	**0**	**1**	**2**	**3**	**4**	**8**
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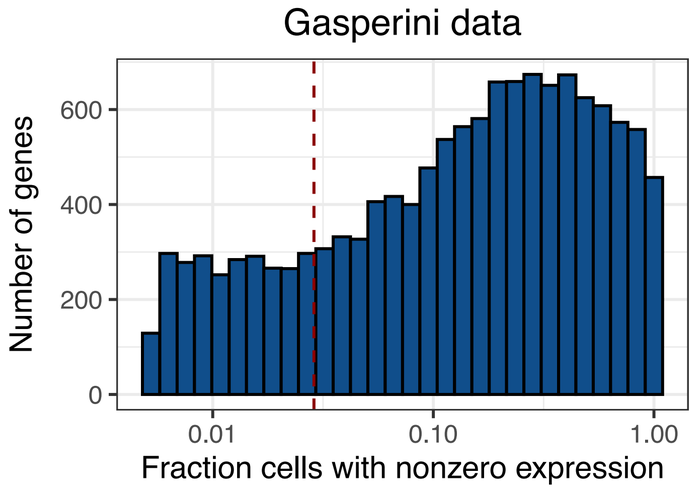

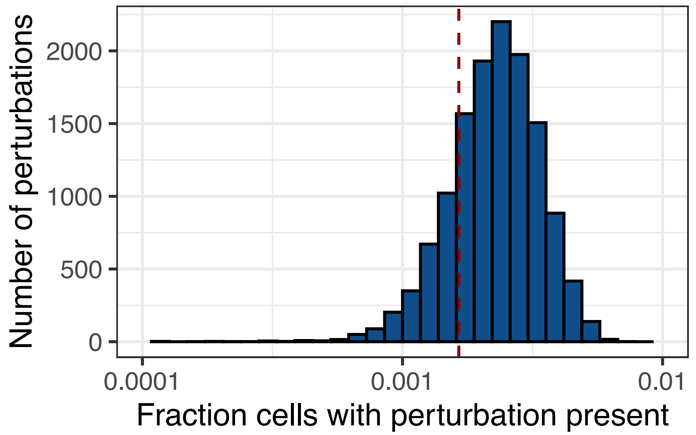

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Consequence: Cannot rely on the CLT, especially in the tails.

Model for the biological data

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Working model:

$$\begin{cases} X_i \mid Z_i \overset{\text{ind}}{\sim} \text{Ber}(\pi_i); & \text{logit}(\pi_i) = Z_i^T \delta \\ Y_i \mid X_i, Z_i \overset{\text{ind}}{\sim} \text{NegBin}(\mu_i, \theta); & \log \mu_i = X_i \beta + Z_i^T \gamma \end{cases}.$$

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[1]Gasperini et al. (2019)

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[3]Liu et al. (2022), Barry et al. (2021)

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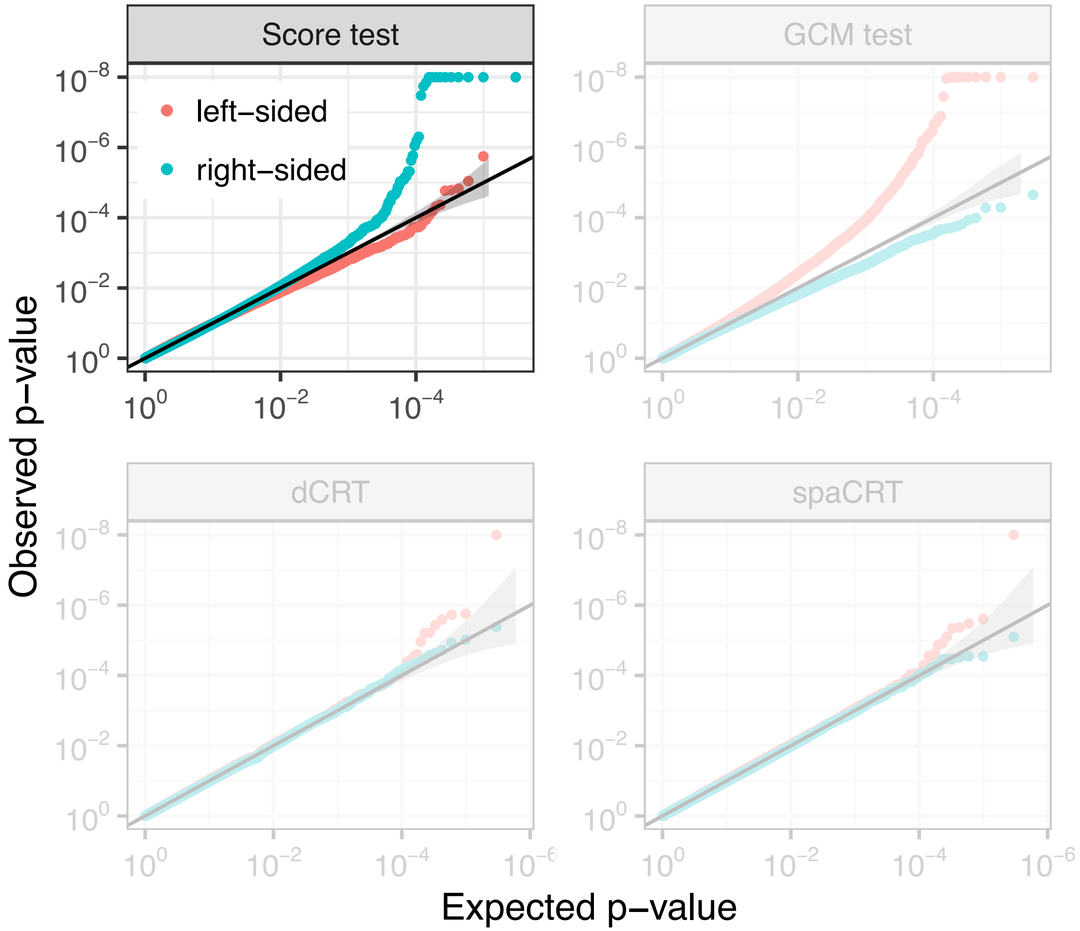

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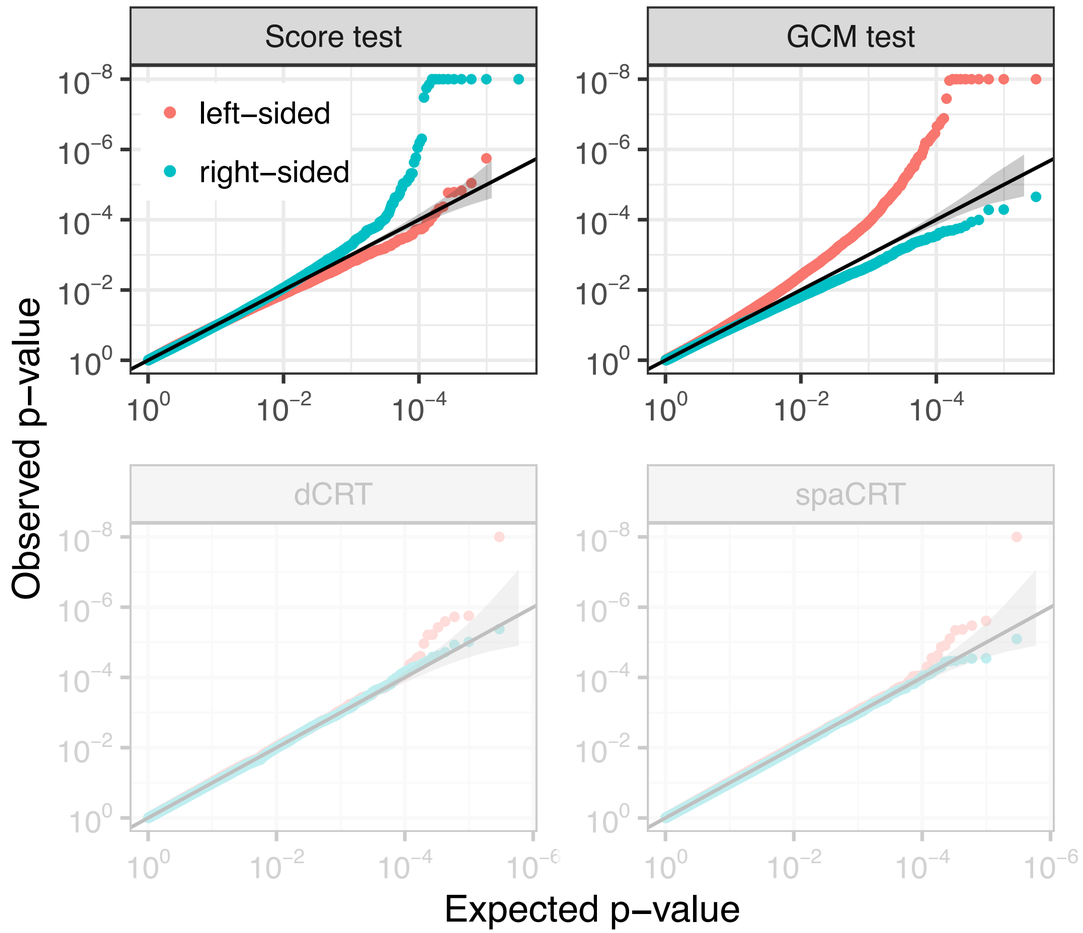

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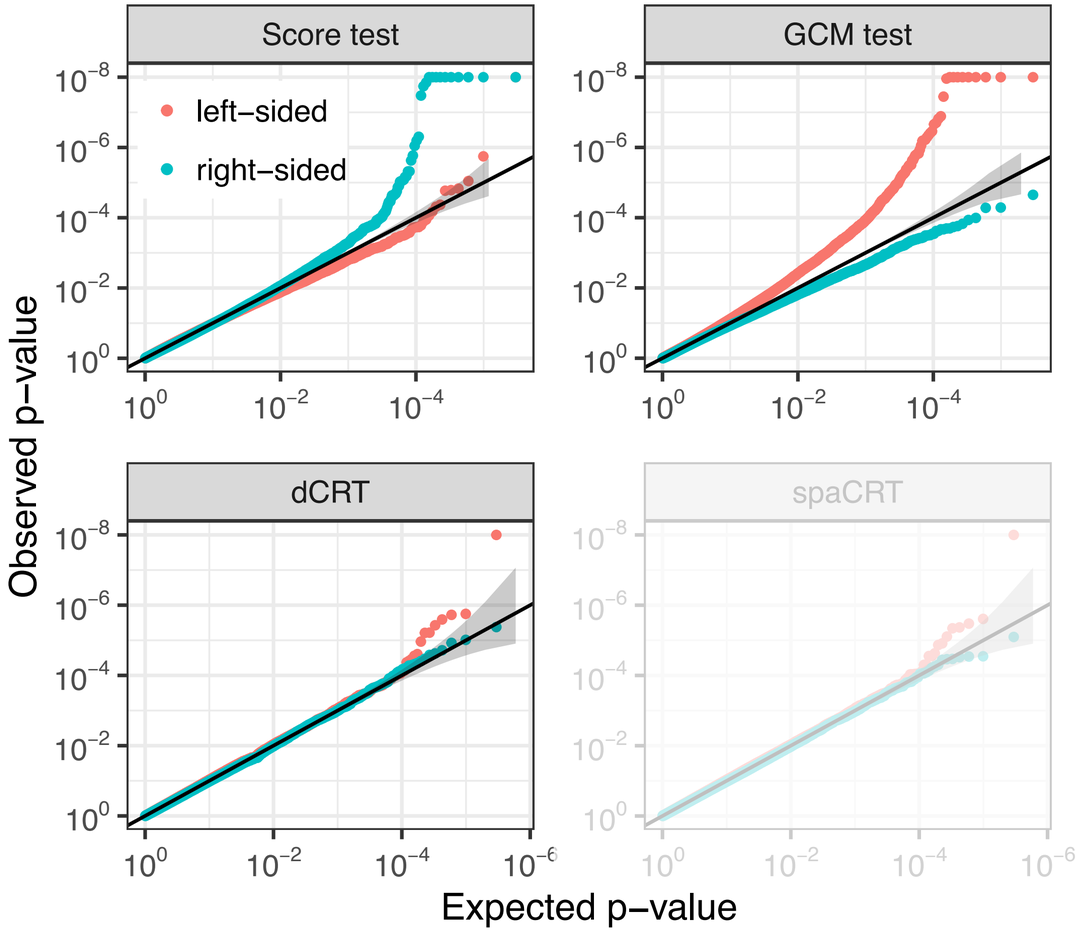

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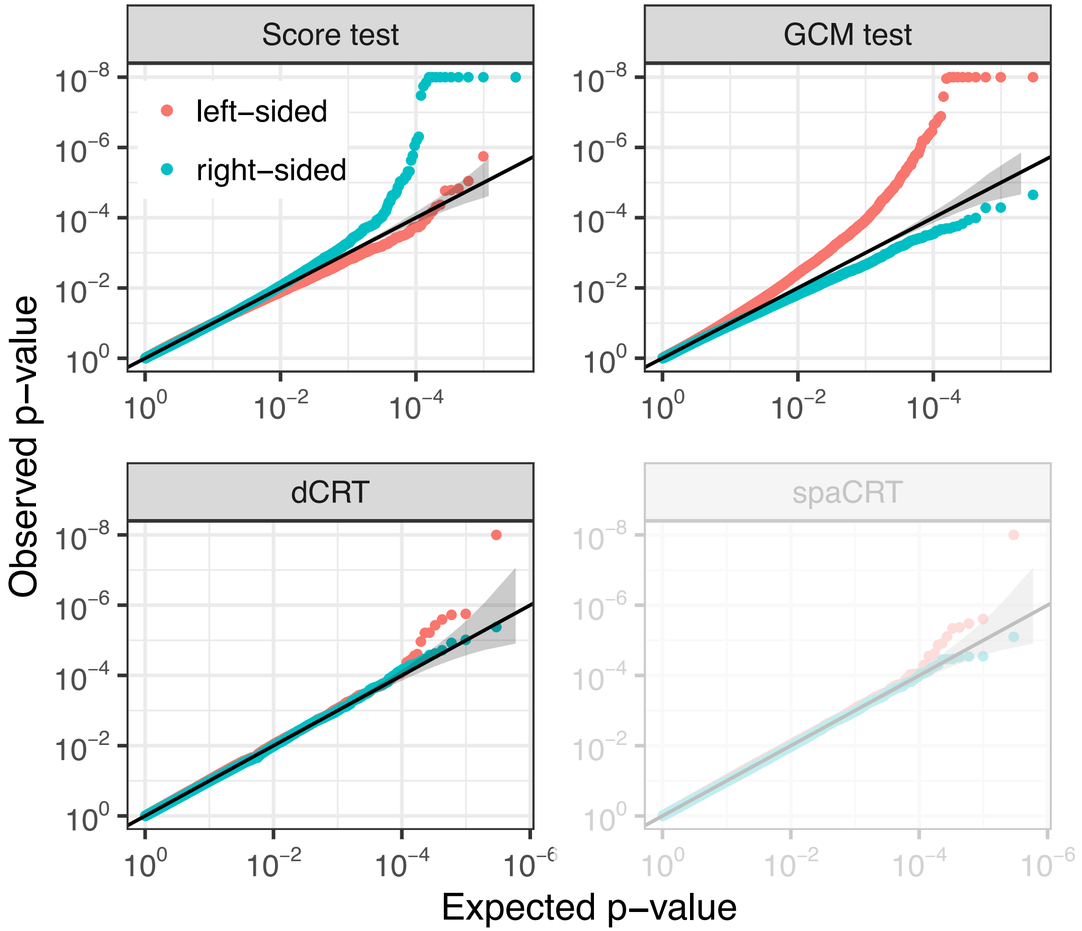

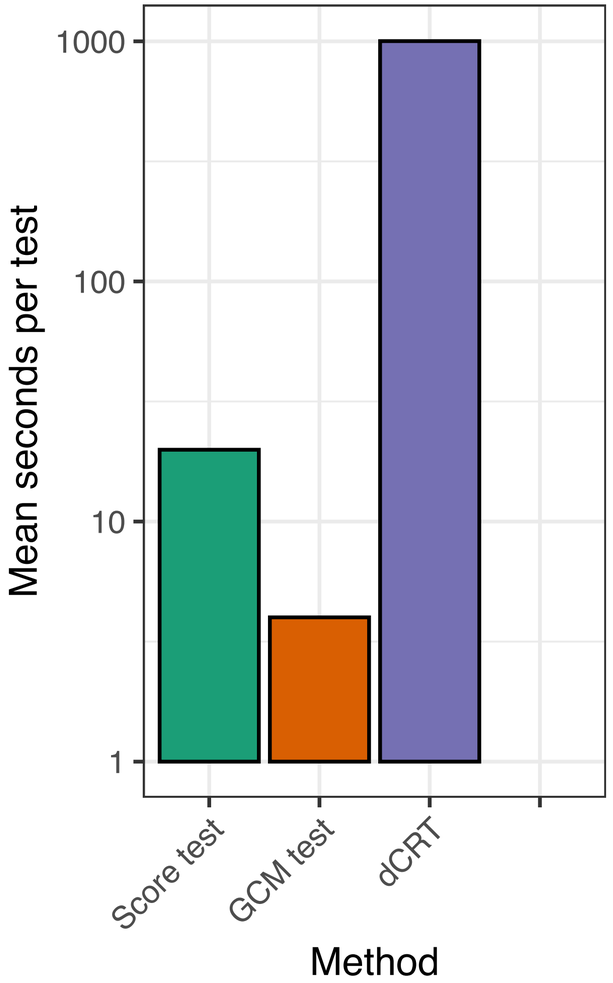

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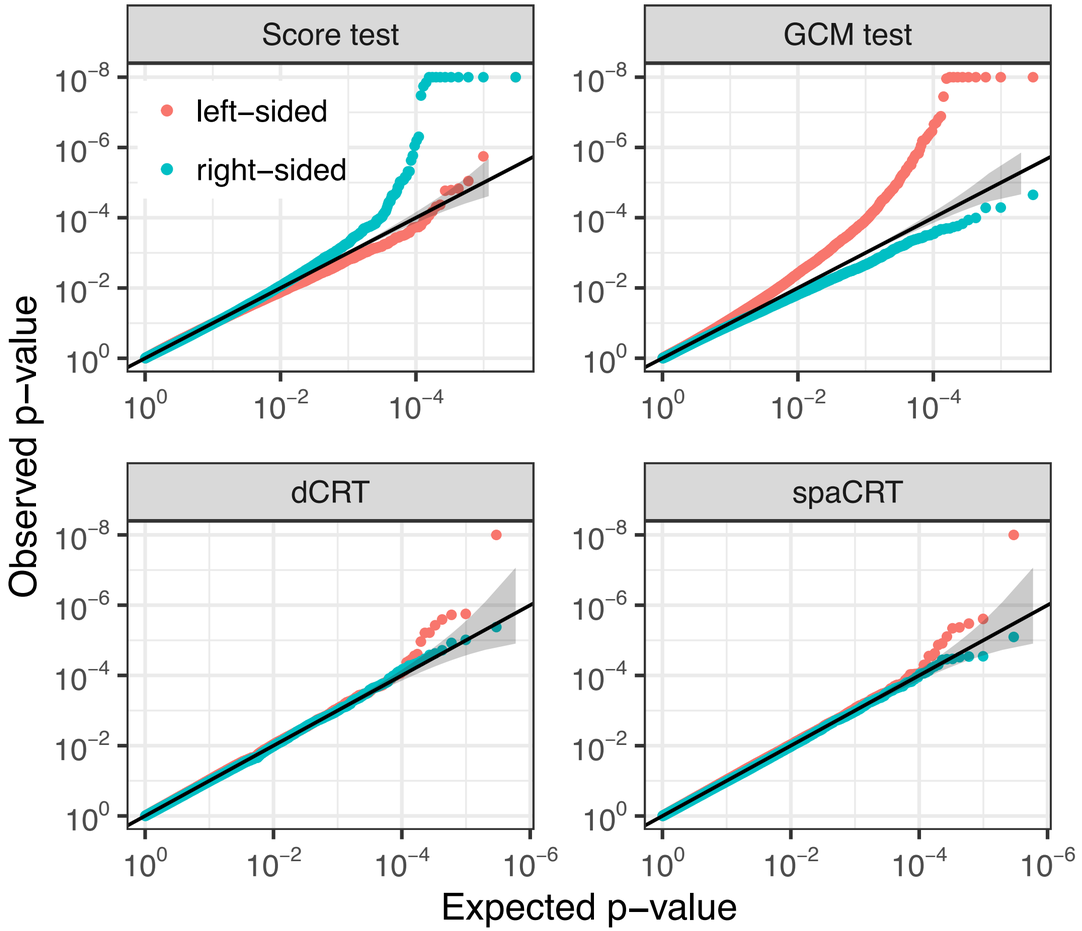

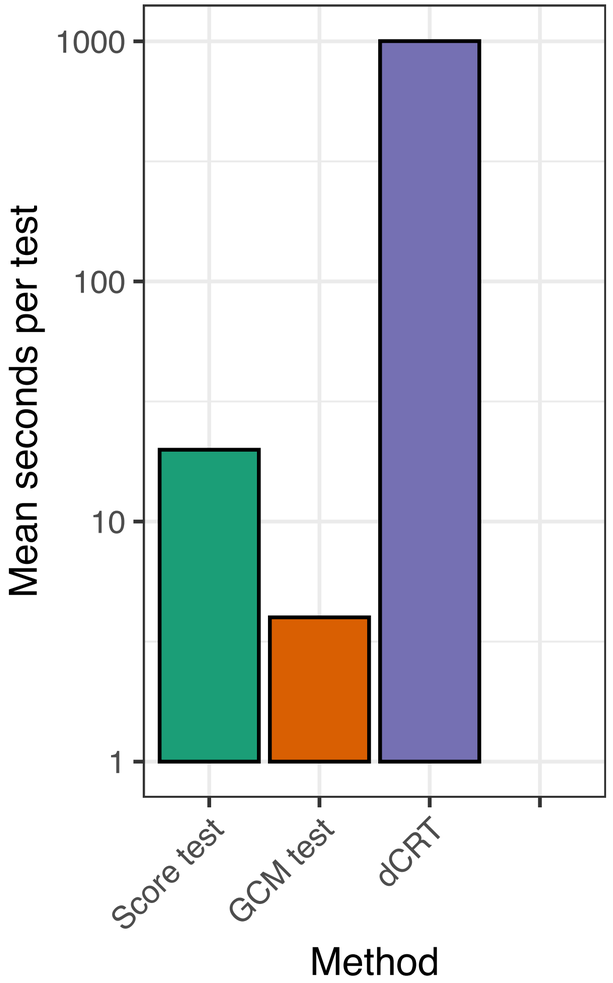

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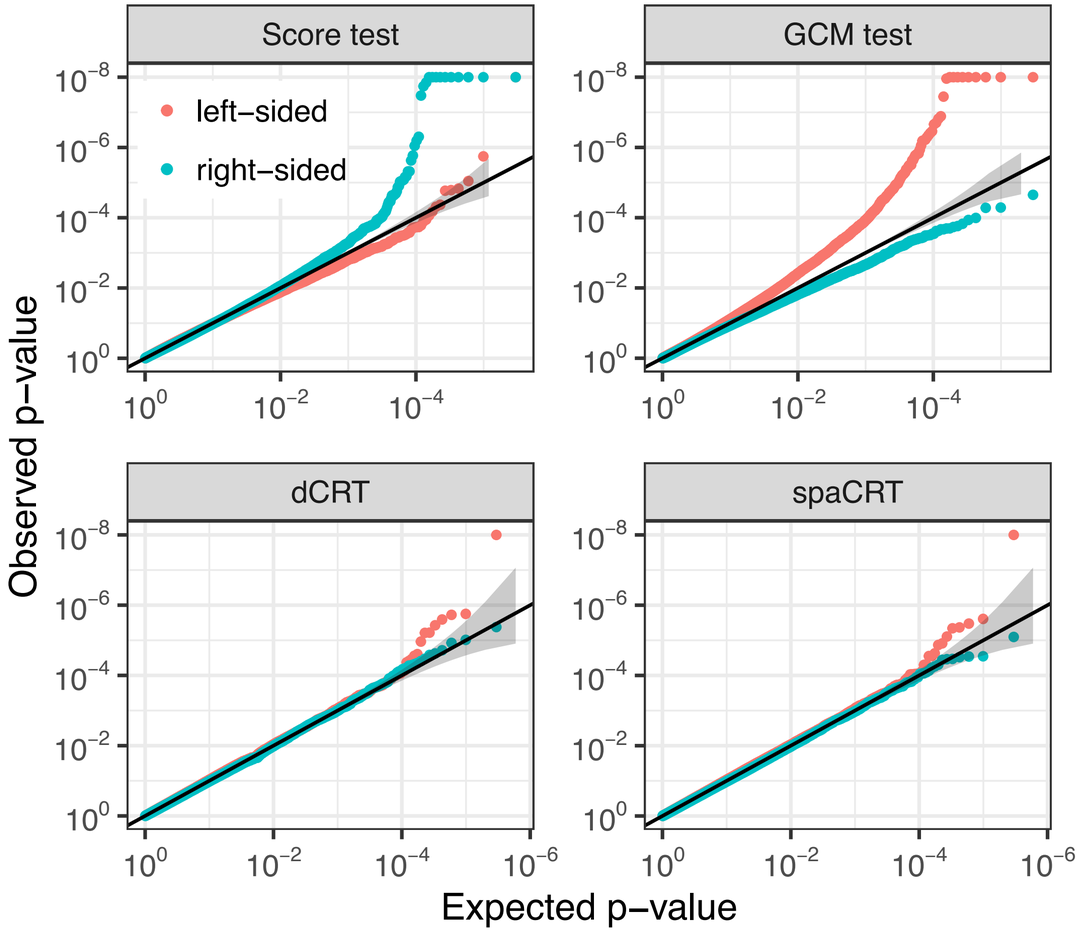

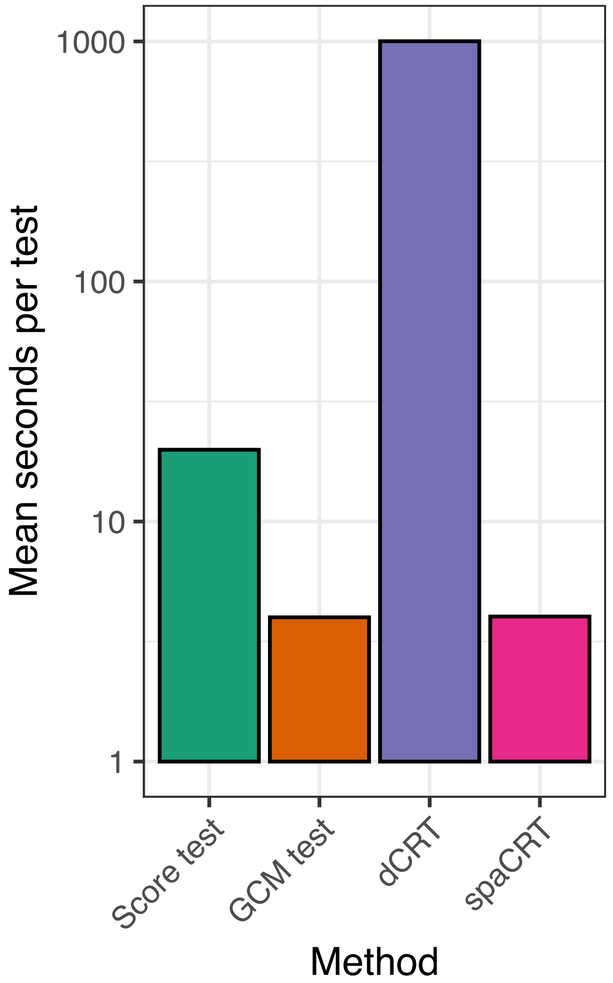

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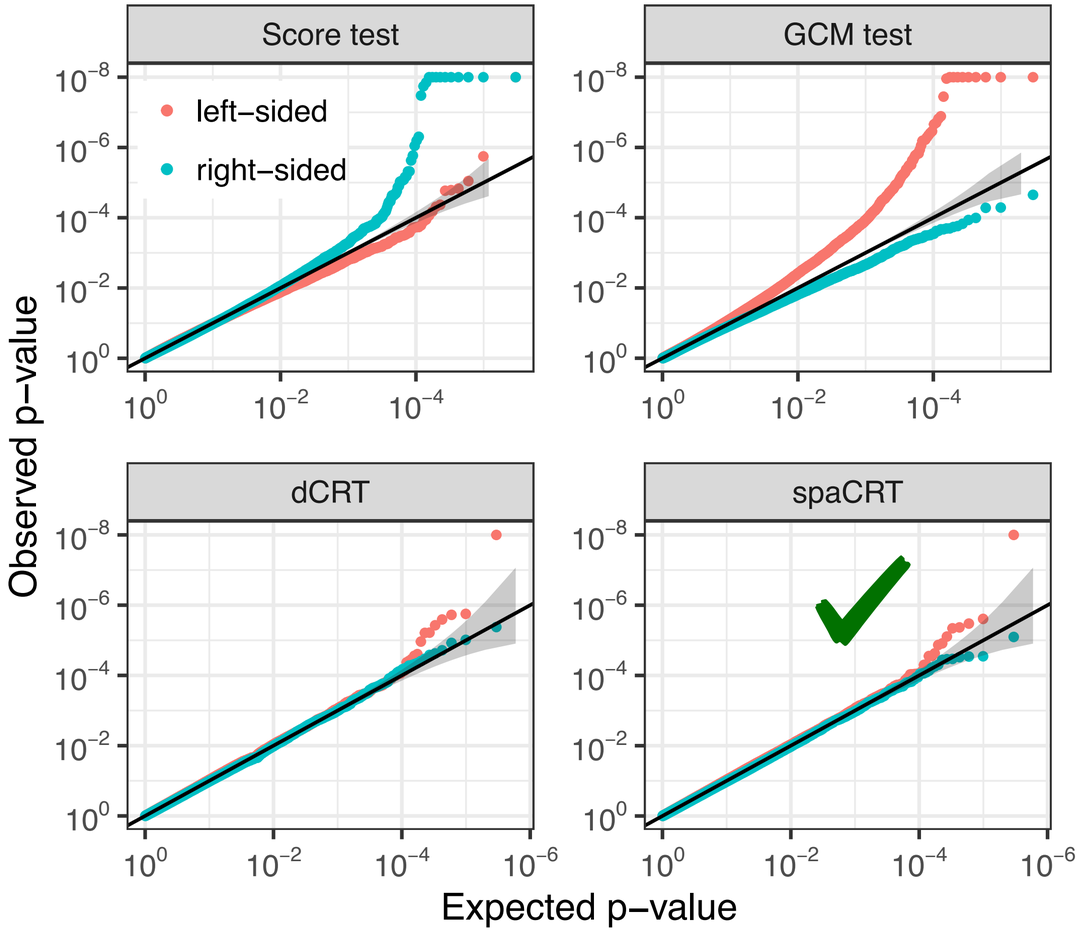

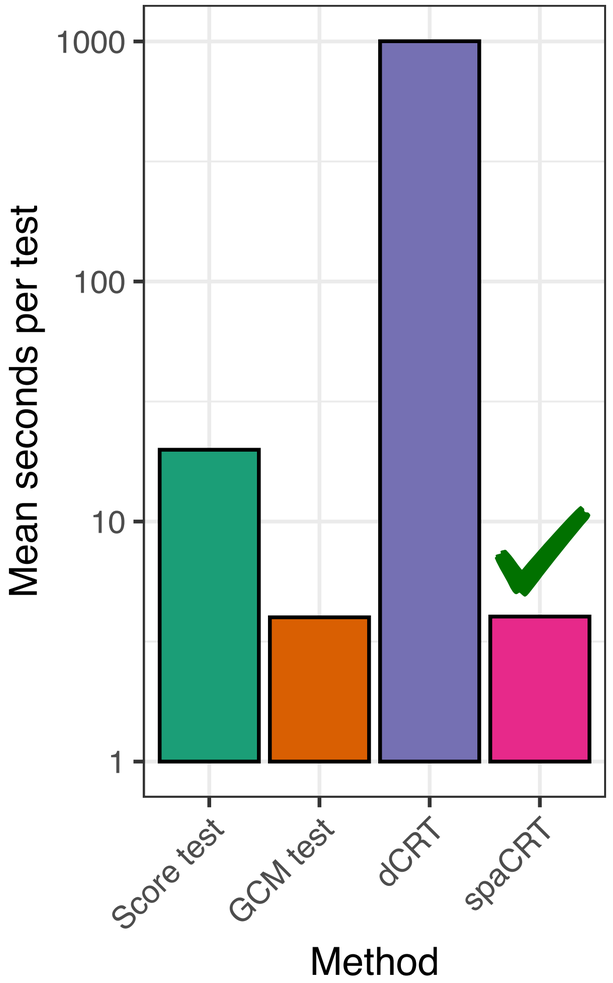

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4. Output dCRT p-value $p_n^{\text{dCRT}} = \frac{1}{B+1}\left(1 + \sum_{b=1}^{B} 1(\tilde{T}_n^{(b)} \geq T_n)\right)$.

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No hope for resampling-based method if advanced parallelization and heuristic approximation is not available!

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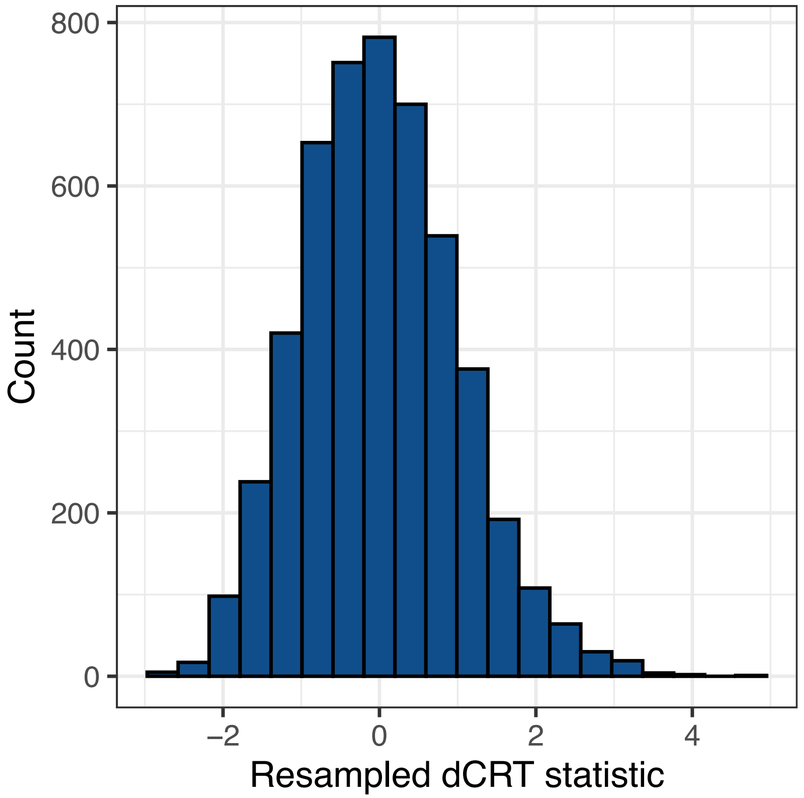

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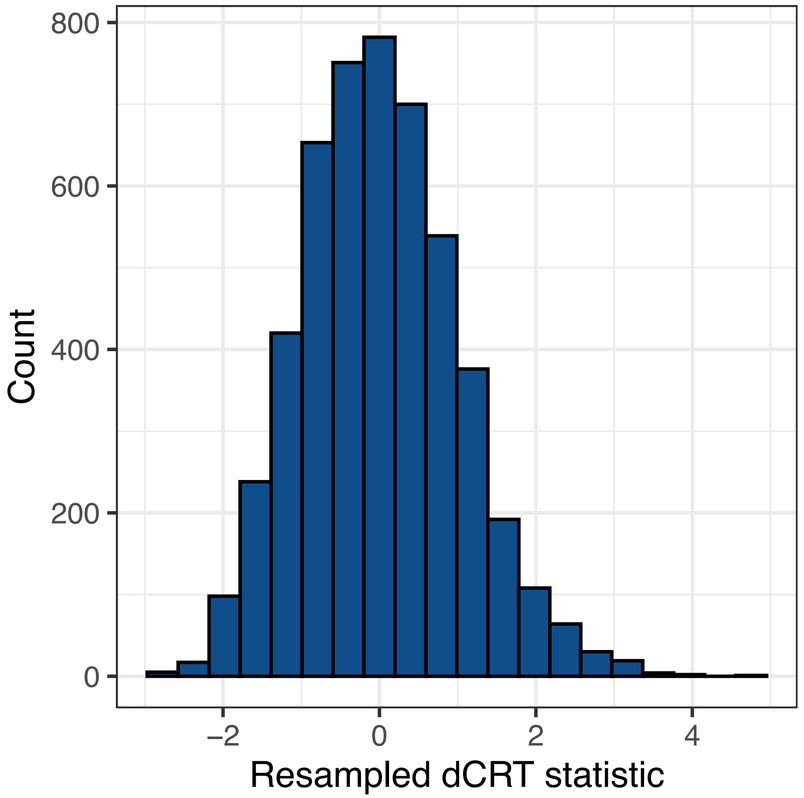

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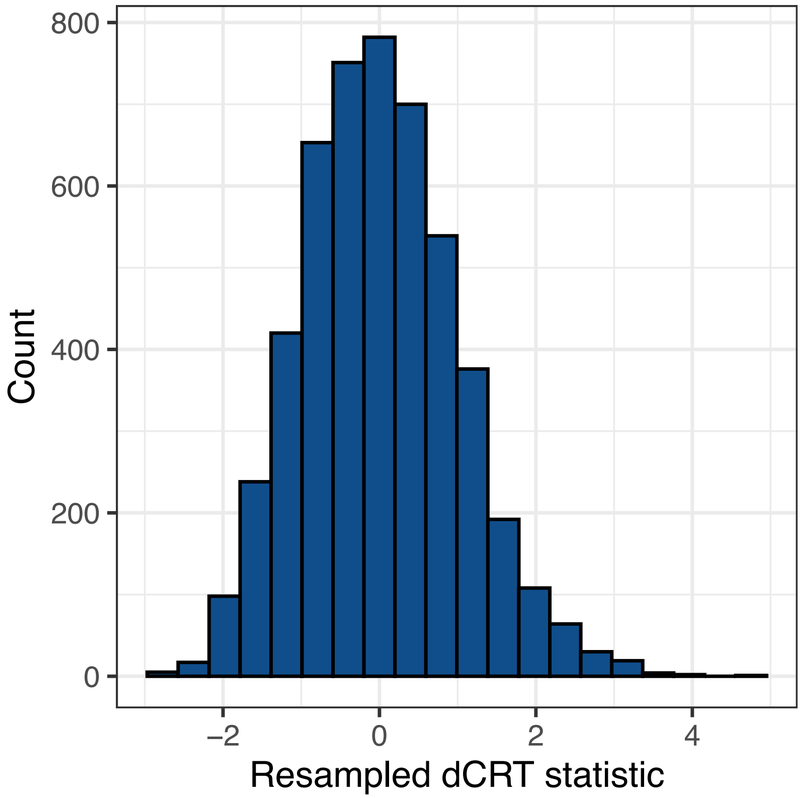

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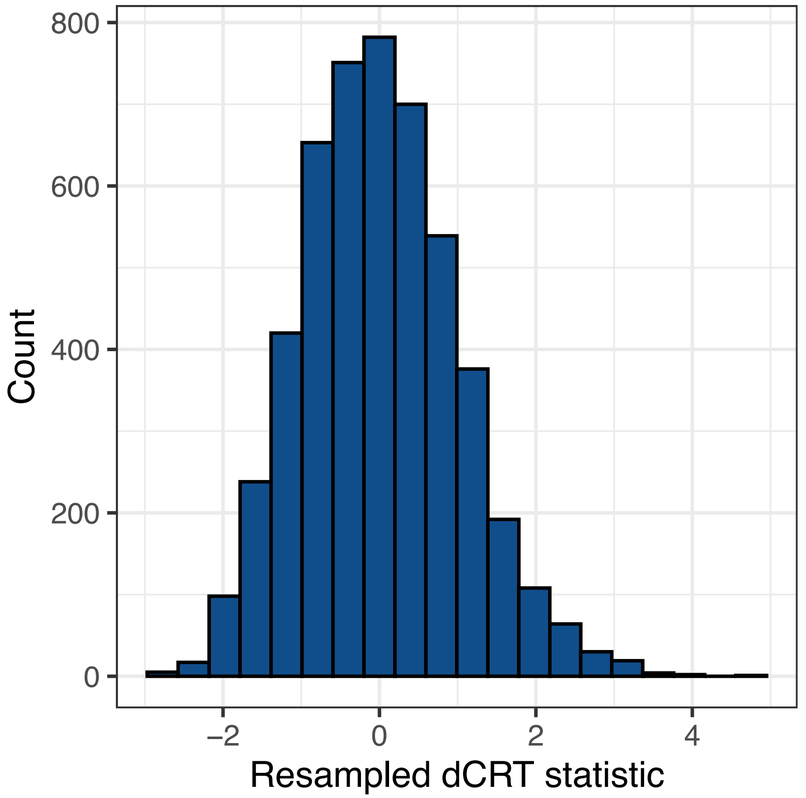

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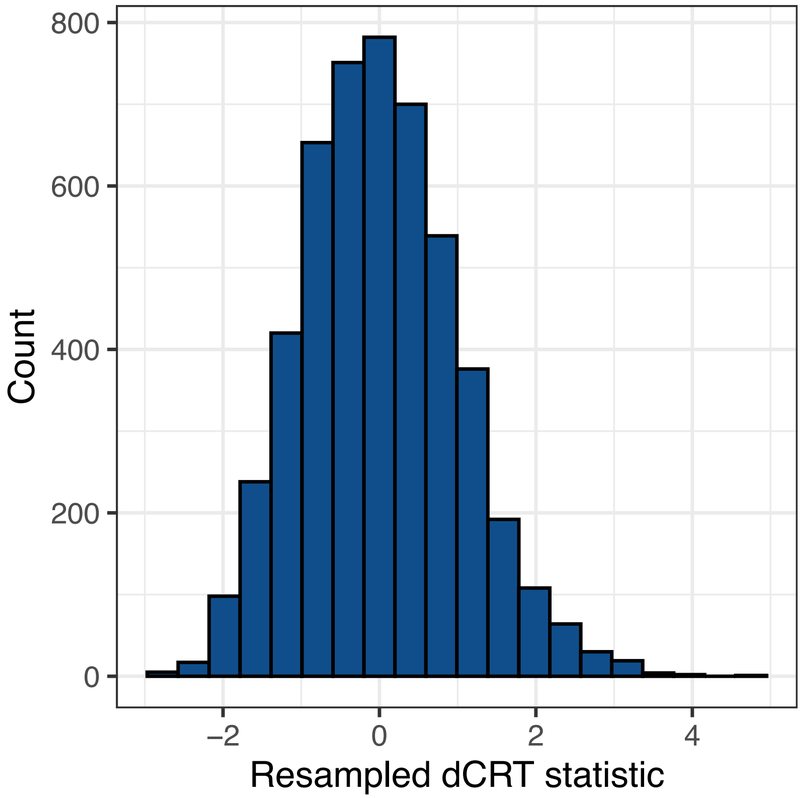

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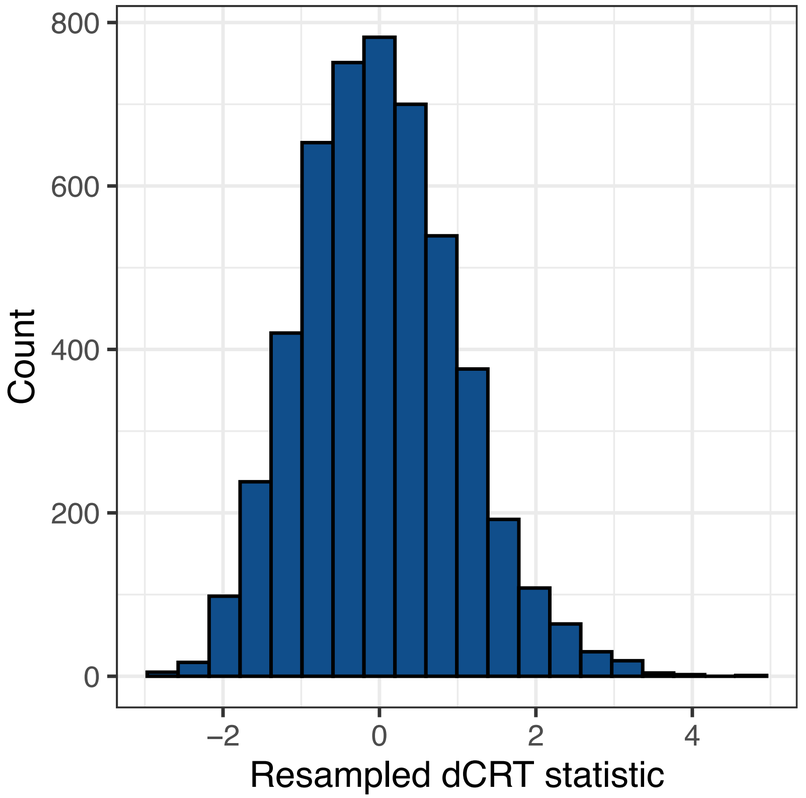

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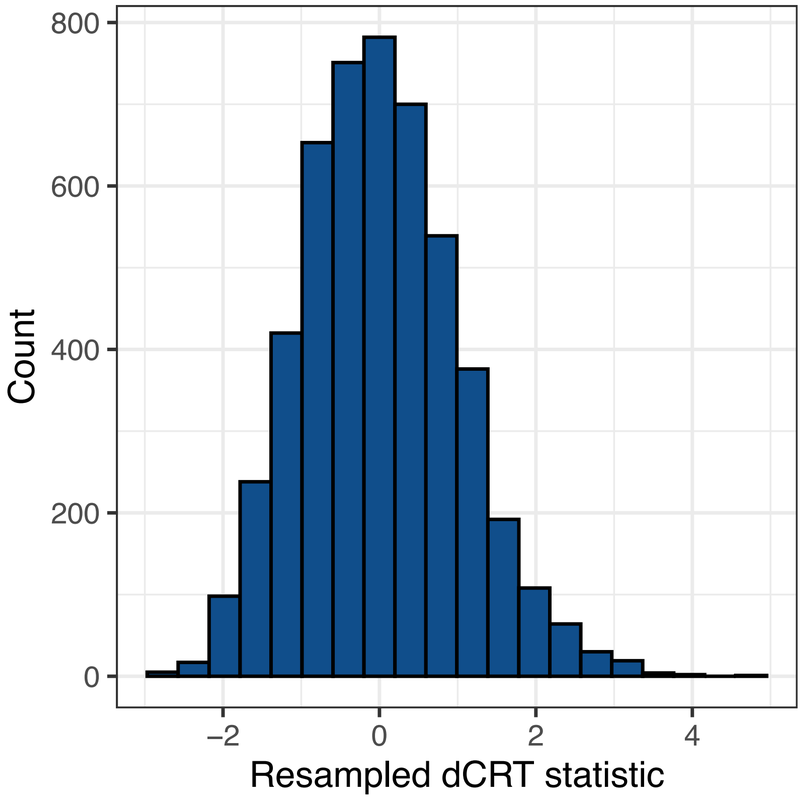

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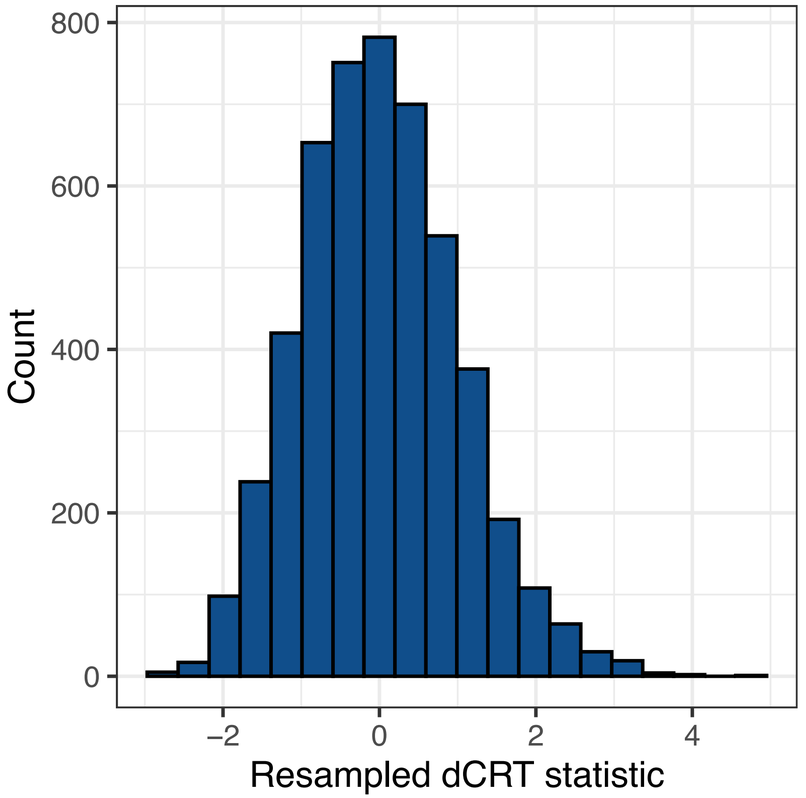

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$$W_{in} = (\tilde{X}_i - \hat{\pi}(Z_i))(Y_i - \hat{\mu}(Z_i)); \quad w_n = T_n; \quad \mathcal{F}_n = \sigma(X, Y, Z).$$

dCRT p-value as conditional tail probability

We wish to approximate the tail probability

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Therefore, we wish to approximate

$$\mathbb{P}\left[\frac{1}{n}\sum_{i=1}^{n} W_{in} \geq w_n \mid \mathscr{F}_n\right],$$

where W_{in} are independent and mean-zero conditionally on $\mathscr{F}_n$ and $w_n \in \mathscr{F}_n$.

Saddlepoint approximations

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In unconditional case, Lugannani-Rice formula[1] gives approximation $\hat{p}_n^{\mathsf{LR}}$ of

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as long as

1. $\mathbb{E}[\exp(sW_{in})] < \infty$ for all $s \in (-\epsilon, \epsilon)$ and all i, n;
2. W_{in} have sufficiently smooth distributions.

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Challenges for SPA application to resampling

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1. Conditioning. We are interested in the conditional probability

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Existing applications of SPA to resampling distributions have ignored these.

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4. Return $p_n^{\text{spaCRT}} = 1 - \Phi(r_n) + \phi(r_n)\left(\frac{1}{\lambda_n} - \frac{1}{r_n}\right)$.

spaCRT is a good approximation to dCRT

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Suppose $\hat{\pi}$ and $\hat{\mu}$ consistent for $\pi(Z_i) = \mathbb{P}[X_i = 1 \mid Z_i]$ and $\mu(Z_i) = \mathbb{E}[Y_i \mid Z_i]$, and $\sup_n \mathbb{E}[Y_{in}^4] < \infty$. Then,

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If dCRT controls Type-I error, then under the above assumptions, so does spaCRT.

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Numerical simulation results

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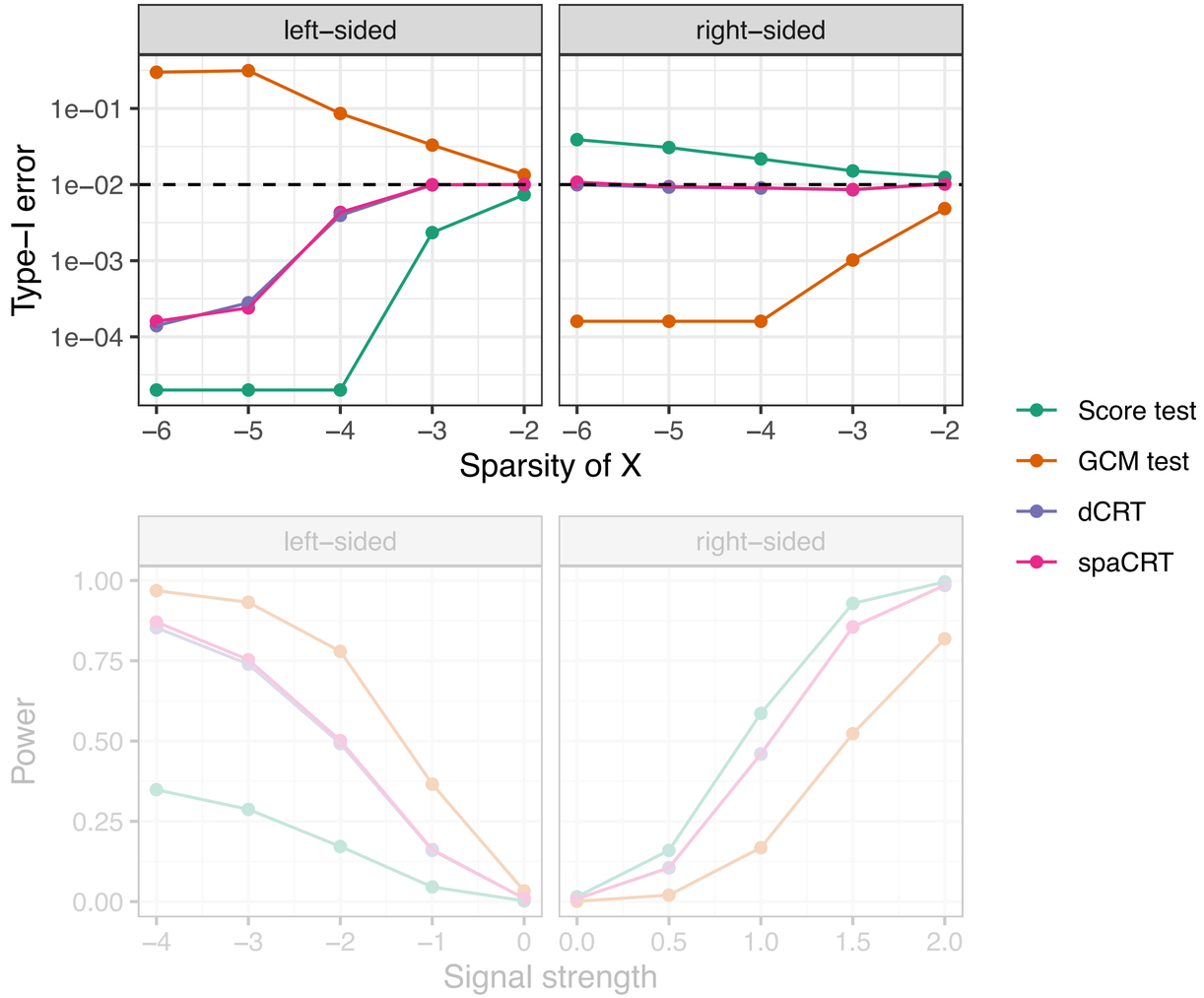

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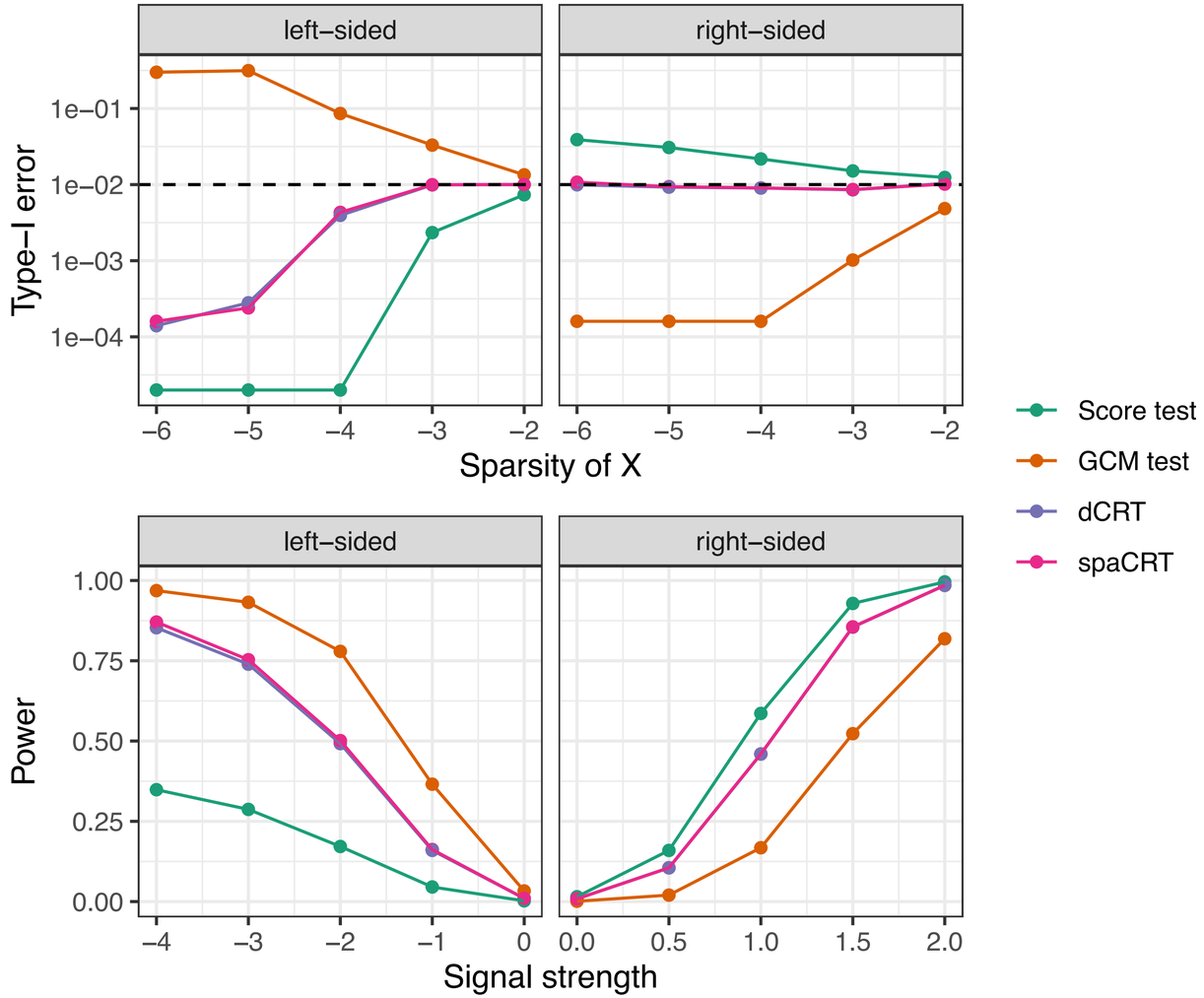

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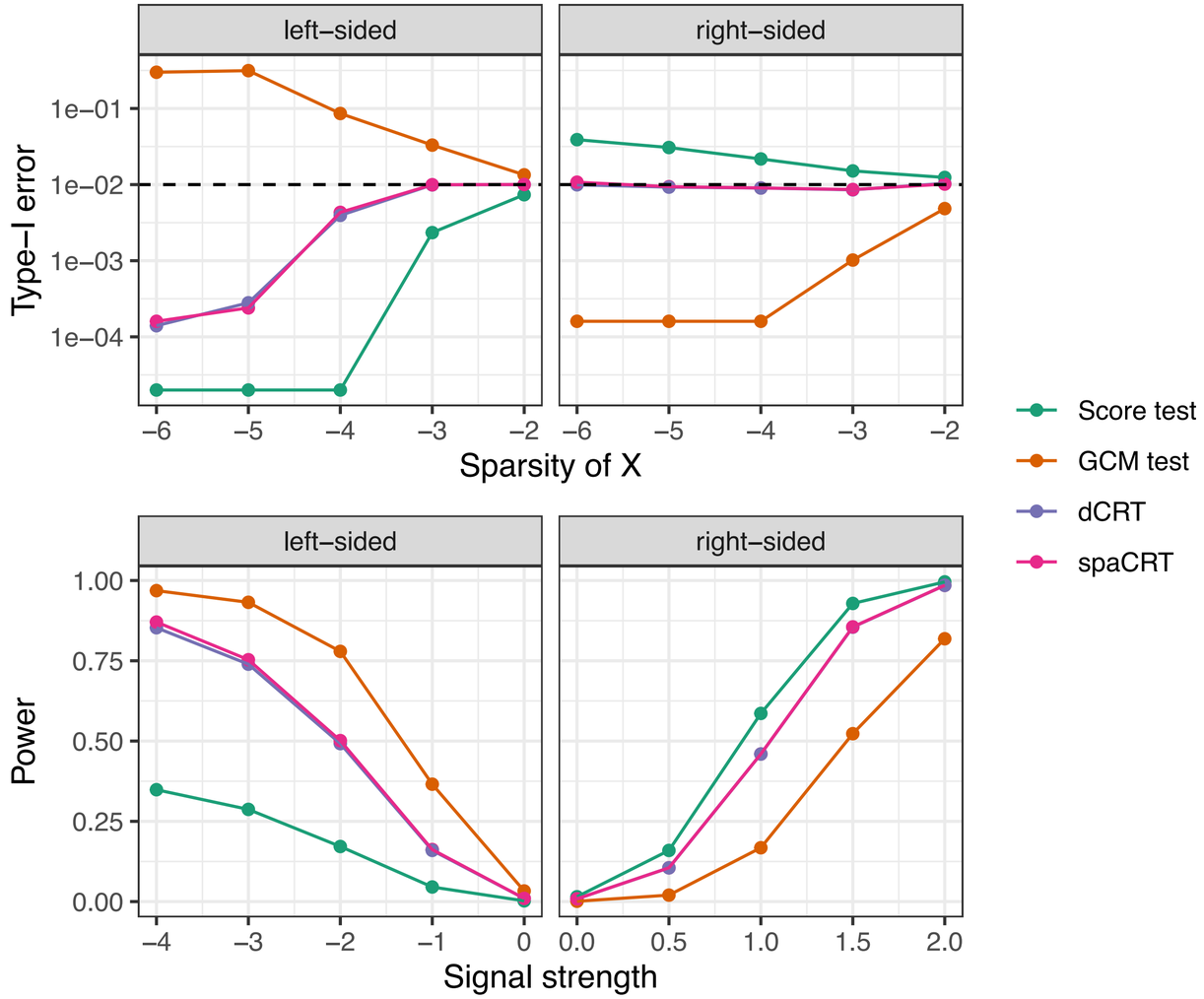

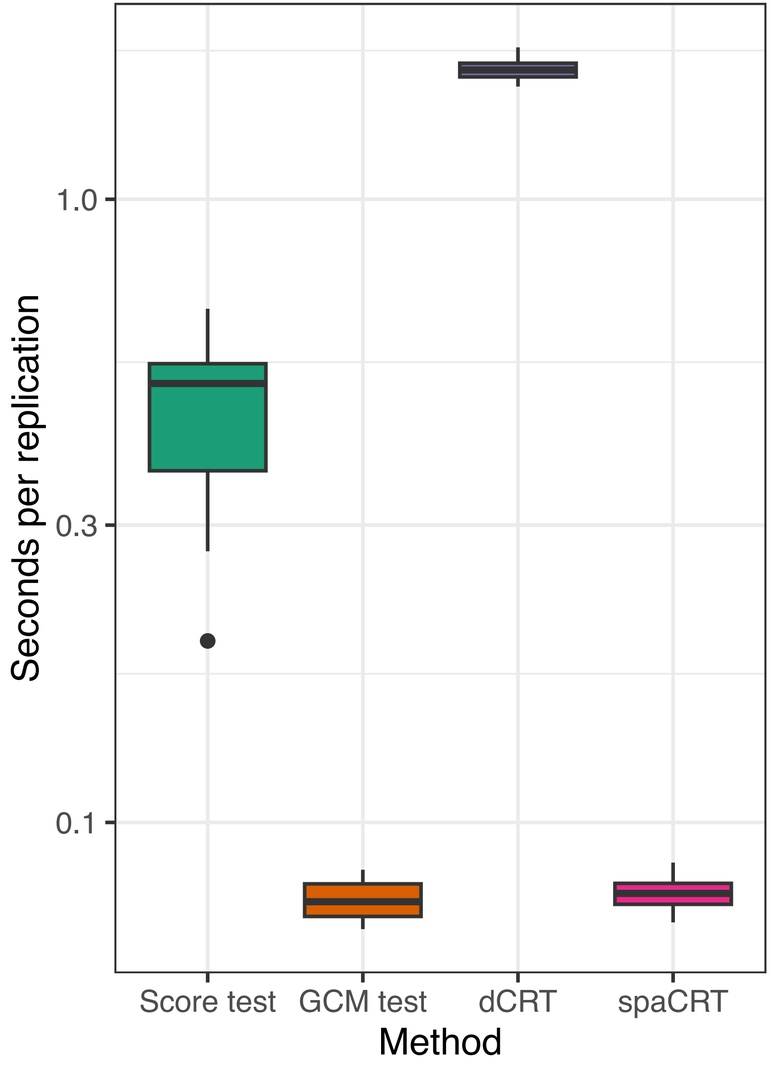

Results on Gasperini data analysis

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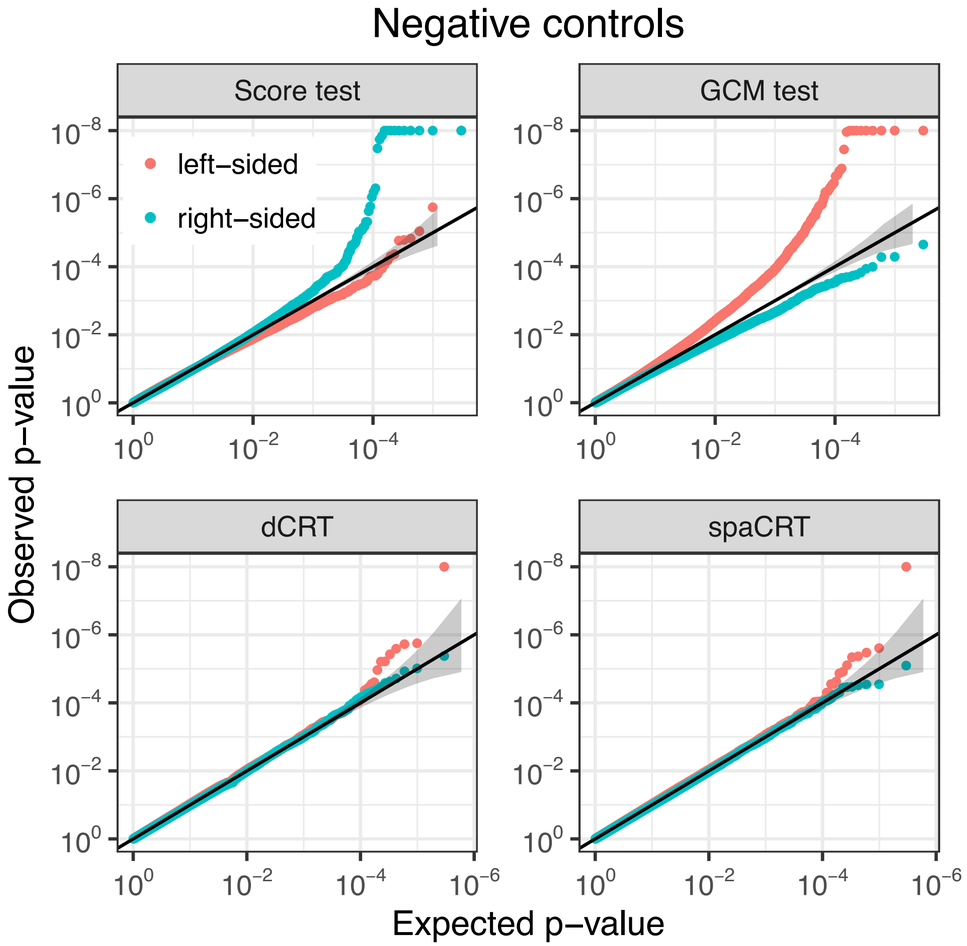

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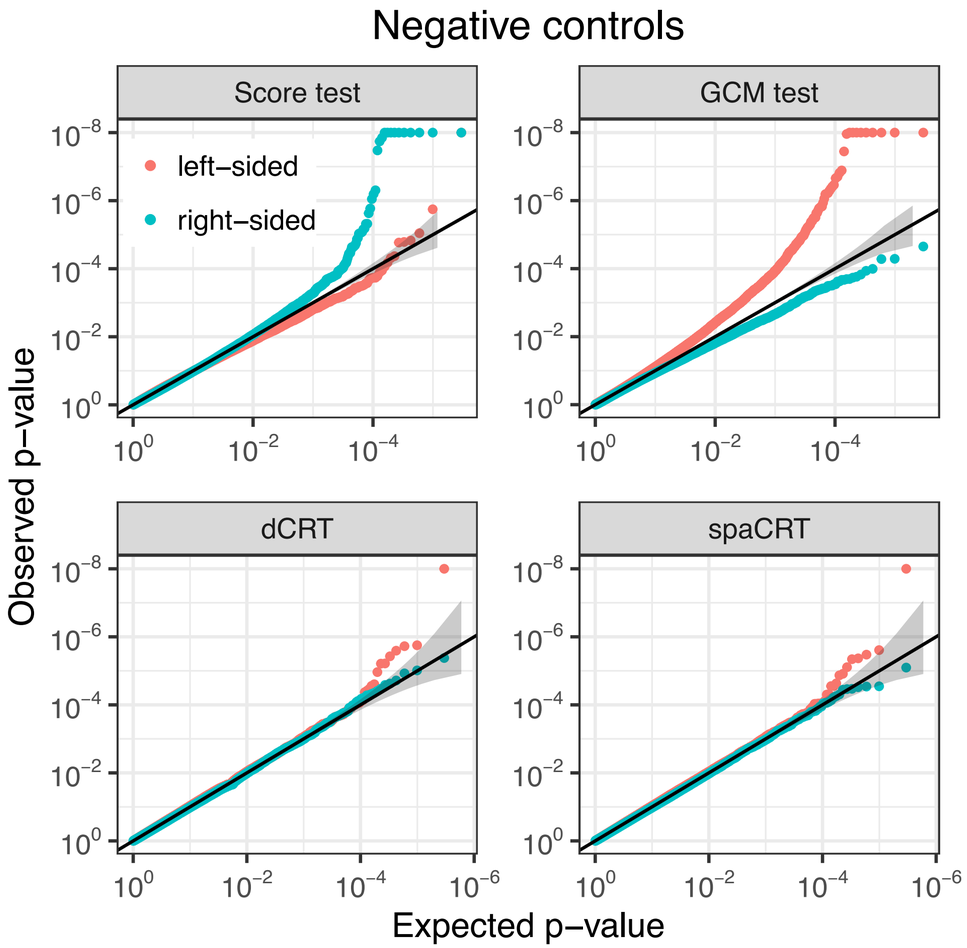

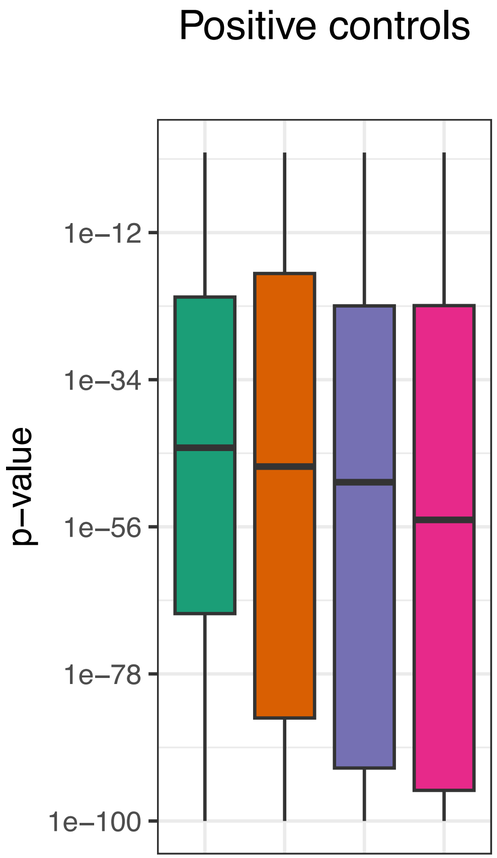

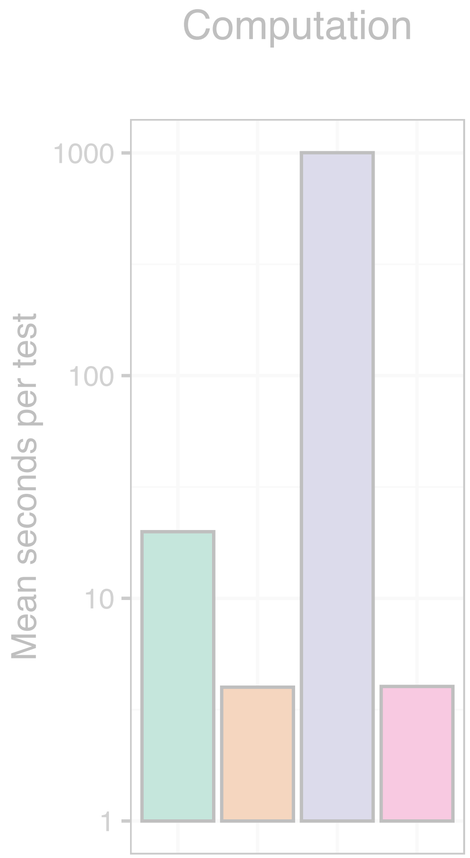

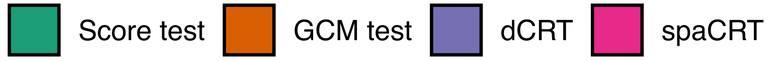

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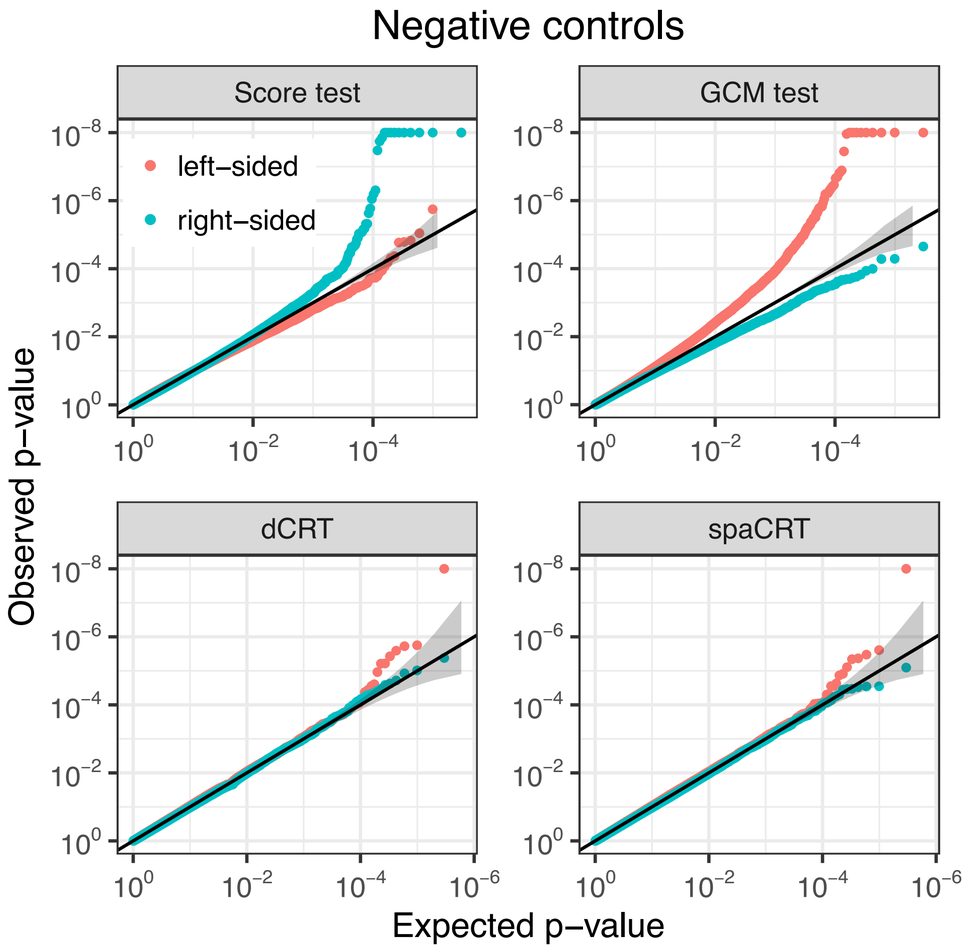

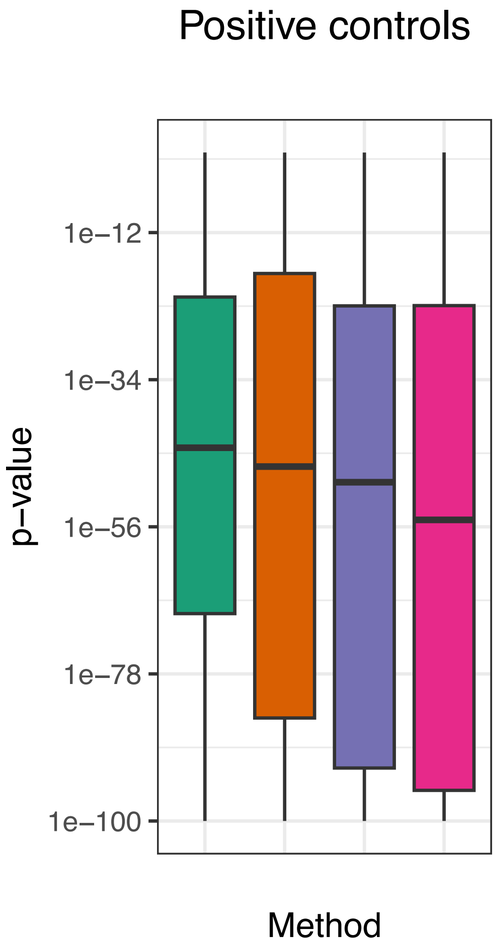

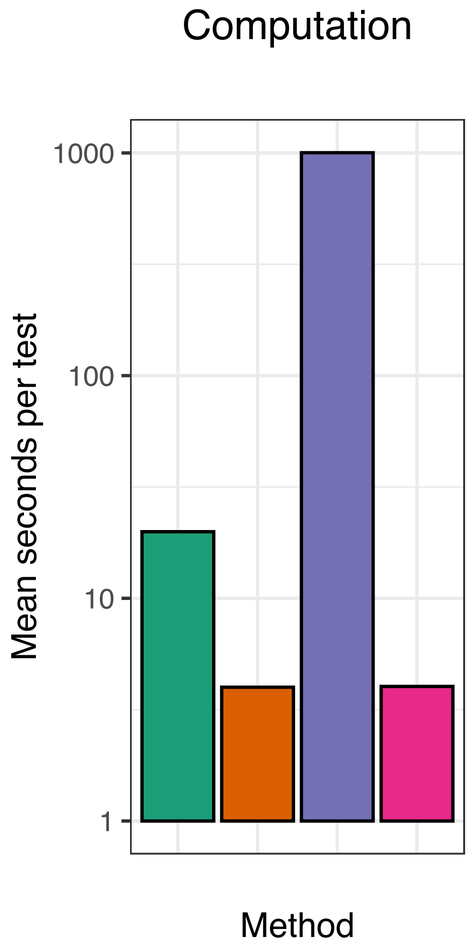

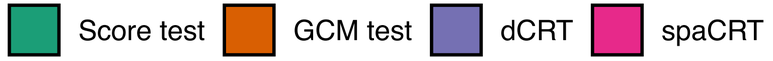

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- Current results do not cover normalized test statistics or large-deviation regime.

References

1. The saddlepoint approximation for averages of conditionally independent random variables. arXiv, 2024.
2. Computationally efficient and statistically accurate conditional independence testing with spaCRT. arXiv, 2024.