

**a**

## Missing Tissue Coverage

Example: *GCKR* Locus

Pancreatic Islet ABC  
data unavailable

**Distance fallback fails**

### Solution:

Calibrated fallback  
*ECE = 0.071 (disclosed)*

**b**

## Protein-Coding Variant

Example: *APOC3* R19X

Loss-of-function  
coding variant

**Not enhancer-mediated**

### Scope:

cis-regulatory only  
88-92% coverage

**c**

## Trans-Acting Effects

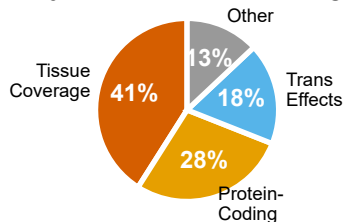
Example: *TF-mediated*

Variant affects TF  
that regulates target  
**Not captured by cis**

### Explicit scope:

cis-eQTL mechanisms  
*in training data*

## Failure Rate Distribution

**d****e**

## Architectural Solutions Summary

- Tissue Coverage Gaps** → **Calibrated Fallback**  
*Distance-based prior with disclosed  $ECE = 0.071$*
- Protein-Coding Variants** → **Explicit Scope Declaration**  
*Framework for cis-regulatory mechanisms (88-92% GWAS)*
- Trans Effects** → **Scope Limitation Acknowledgment**  
*Trans-eQTLs documented; future integration planned*

**KEY RESULT: Despite documented failure modes, overall  $ECE = 0.012$**   
*(Decision-grade threshold: 0.05)*