Scientific Poster Session

n-lorem FOUNDATION

Nano-rare Patient Colloquium 2025

Monday, October 20 | 5:15 – 6:15 pm EST

Using ‘Omics’ Data to Inform and Refine ASO Design

This study illustrates how we apply our experience and deep expertise to harness insights from large-scale public genomic and transcriptomic datasets to inform multiple stages of ASO discovery; from feasibility assessment to design and optimization. We will also discuss the critical importance of selecting appropriate datasets to support informed and effective decision-making throughout this process.

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What is “omics” data?

- Data with the **“omics”** suffix generally means that **all** of what is being studied was quantified.
  - Genomics = all genes
  - Transcriptomics = all transcripts/RNAs
  - Proteomics = all proteins
- **High-throughput sequencing** is a method to generate “omics” data.

A data surplus problem

- Sequencing costs have dramatically decreased, consequently the number of “omics” datasets has exploded.
- What can we do with all this data? **Advance ASO discovery**
- Not all data are equal.
- We need to **identify well-annotated, high-quality, and standardized data** to reliably inform key steps in our ASO discovery workflow.

Early stages of ASO discovery

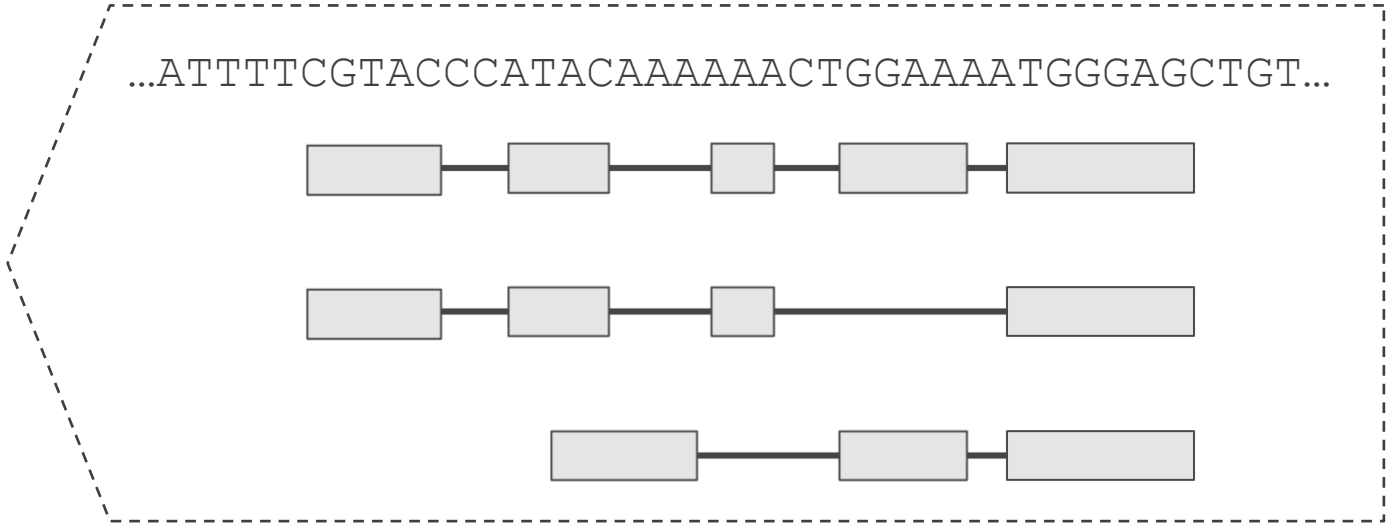
Large-scale public datasets guide the evaluation of feasibility and design strategy

Reference genome assembly

Gene 1

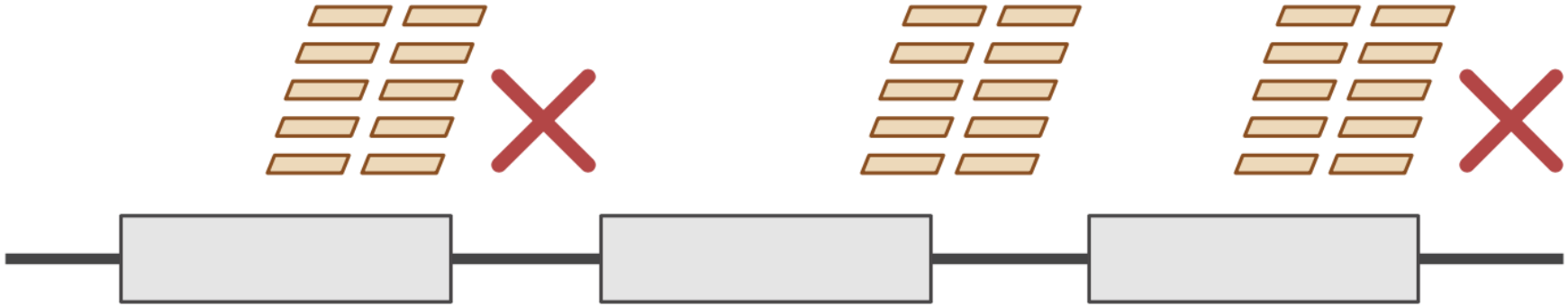
Gene 2

Gene 3



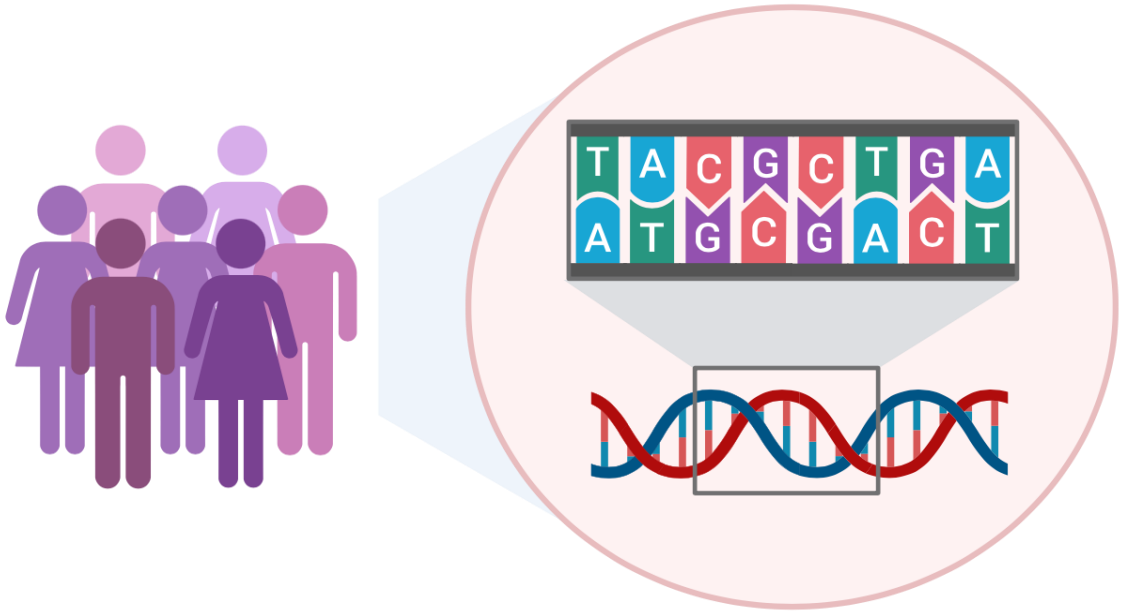
Sources: GENCODE, Ensembl, NCBI

Exclude regions to more efficiently design ASOs



- Problematic sequences (low complexity/repetitive)
- Off-targets (sequences found in another gene)

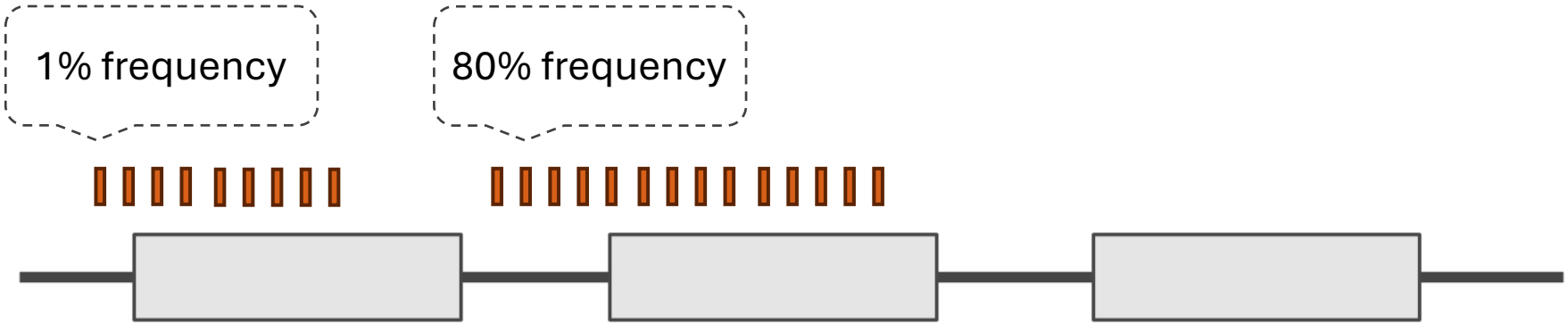
Population-level genomics data



Ref.	TACGCTGA
1	TA**T**GCTGA
2	TA**T**GCTGA
3	TACGCT**C**A
4	TA**T**GCTGA

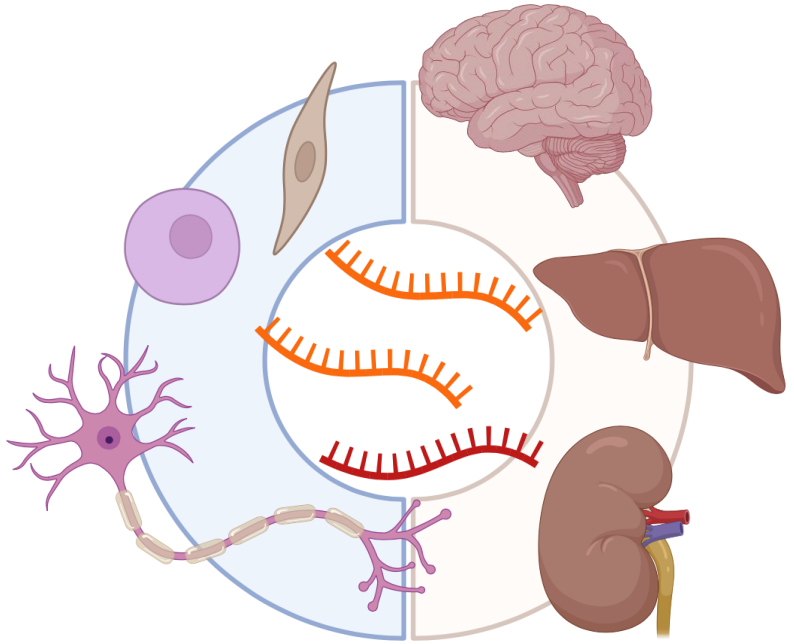
Sources: gnomAD, 1000 Genomes Project

Genetic variants in the population guide our ASO design strategy



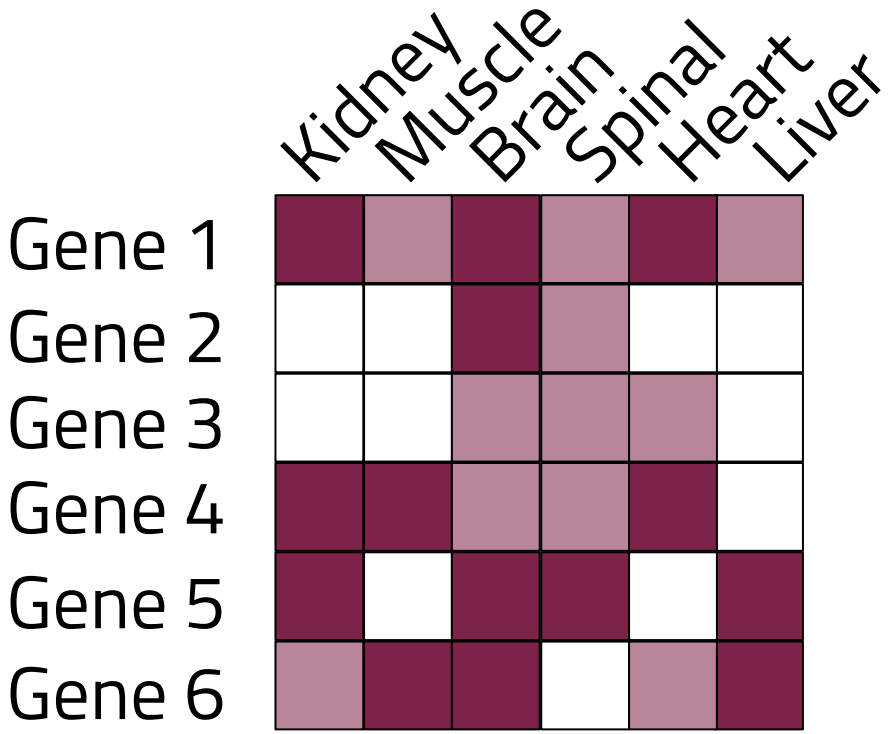
- Distribution (location) within gene
- Allele frequencies (common vs. rare variants, loss-of-function tolerance)

Tissue and cell transcriptomic and proteomic atlases



Sources: GTEx, Human Protein Atlas

Expression profiles inform feasibility and safety assessments

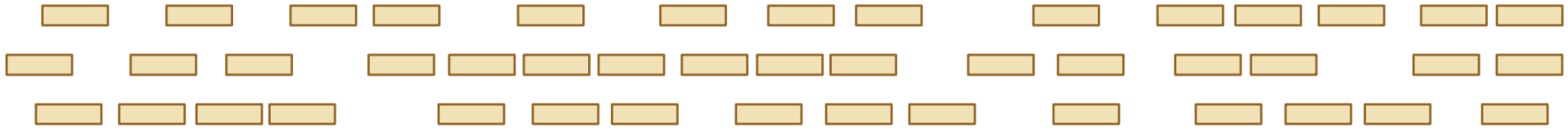


- Cell line(s) for *in vitro* screening
- Off-target RNA expression

Technological advancements in sequencing lead to greater breadth and precision in ASO discovery

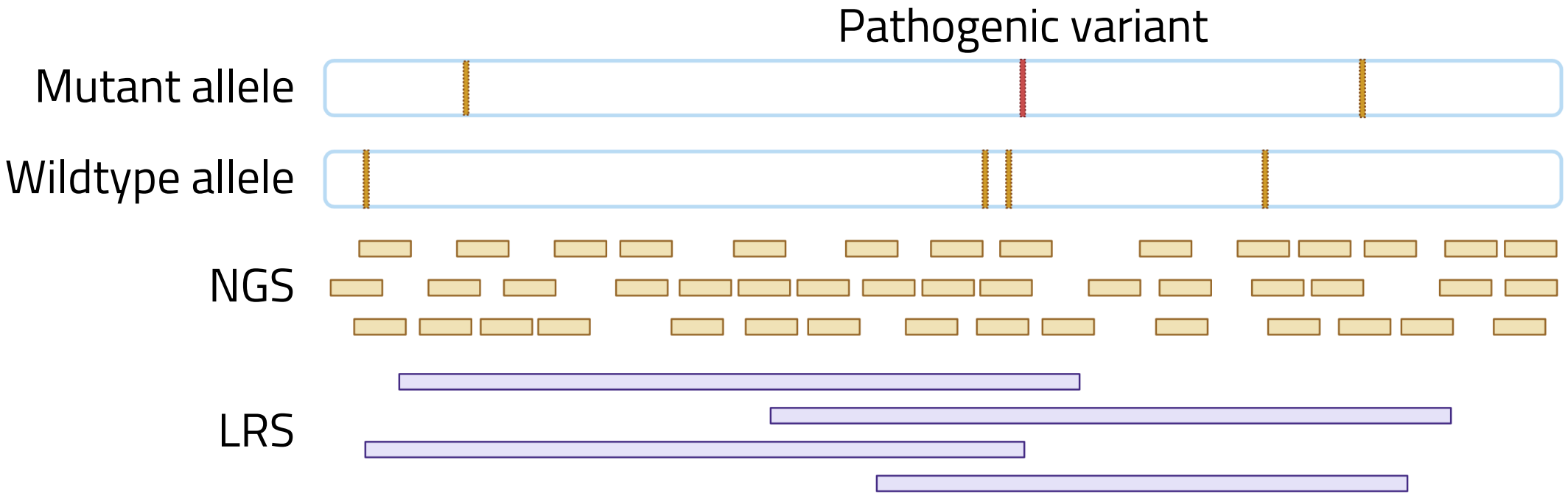
High-throughput sequencing methods

Next-generation (short-read) sequencing



Long-read sequencing

Long-read sequencing for the design of allele-selective ASOs

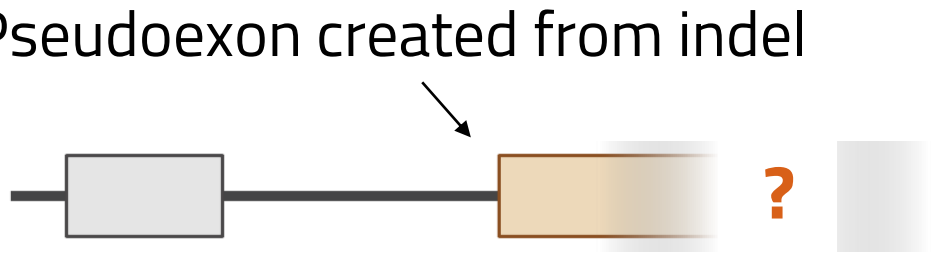


Benefits from long-read sequencing

Gapmer:

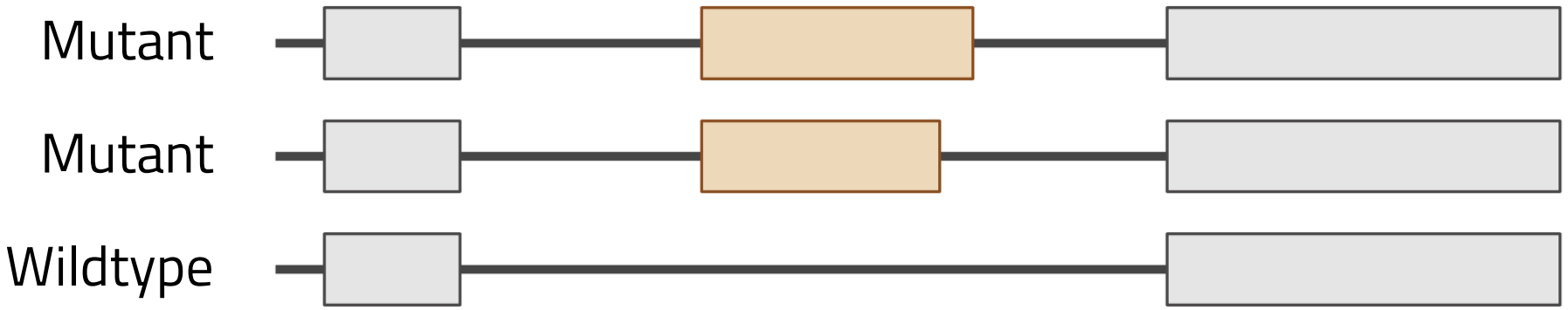
- **Patient's DNA sample alone provides direct evidence** of whether a variant is on the same allele as the pathogenic variant
- **Increases the number of targetable variants**

4 n-Lorem patients with a pathogenic indel in *GBE1*



Akman et al. (2015)

Two mutant *GBE1* isoforms identified by long-read sequencing



Thomas et al. (2025)

Benefits from long-read sequencing

Gapmer:

- **Patient's DNA sample alone provides direct evidence** of whether a variant is on the same allele as the pathogenic variant
- **Increases the number of targetable variants**

Splice-modulating ASO:

- **Complete picture of the mutant transcript** structure(s)
- **Impacts ASO design**, development of **screening assays**, and **safety assessments**

Conclusions

- Careful selection and integration of ”-omic” datasets allows us to
  - Rapidly assess feasibility
  - More efficiently design ASOs with safety in mind
  - Develop ASOs that may benefit more patients
- Application of new technology advances therapeutic development

Acknowledgements

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Thank you

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