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# **Introduction to the course**

*MAVE: Approaches, Analysis, and Interpretation*

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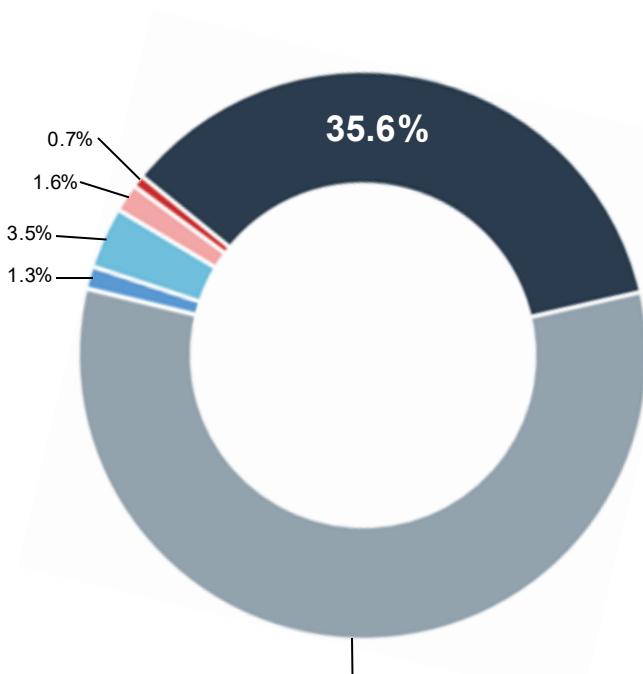
Nov 2025



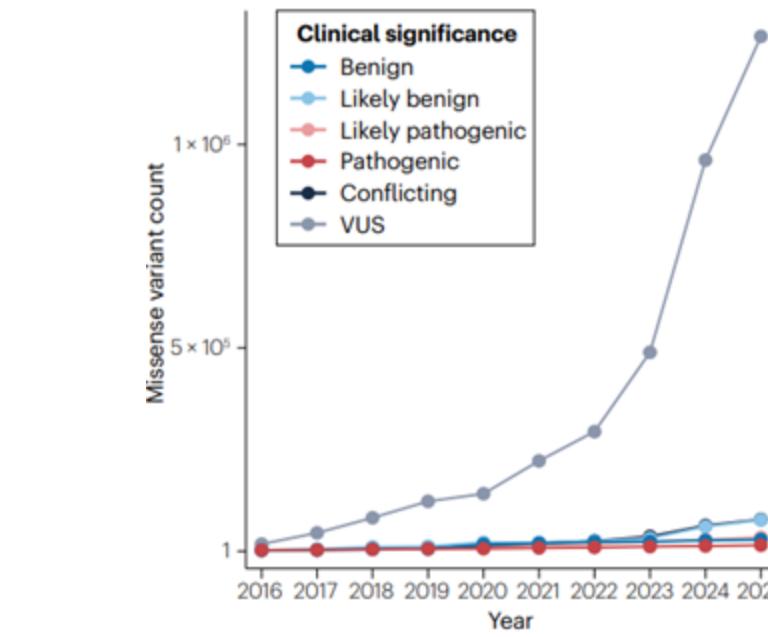
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# Why a MAVE course?

# The Challenge: Variants of Uncertain Significance



1,265,600 VUS  
(57.4%)



Gap between variant discovery and classification widening  
> 10X increase in the last decade

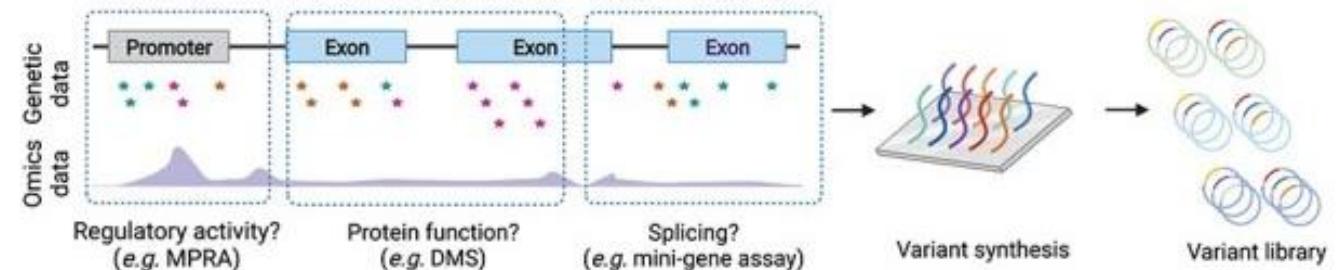
Ambitious goal to **eliminate VUS** by 2030 in ~4500 Clinically-relevant genes (AVE Alliance / NHGRI)

# 1. Functional Data Generation

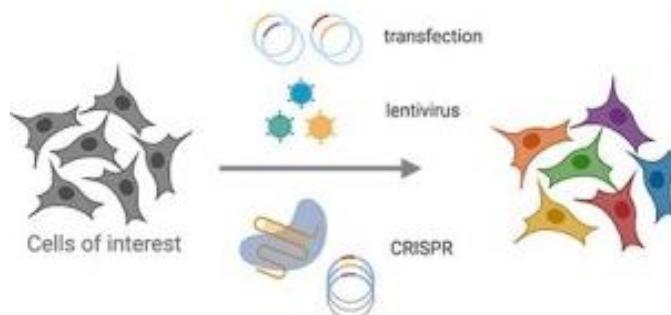
## Selection of model system



## Generation of a variant library

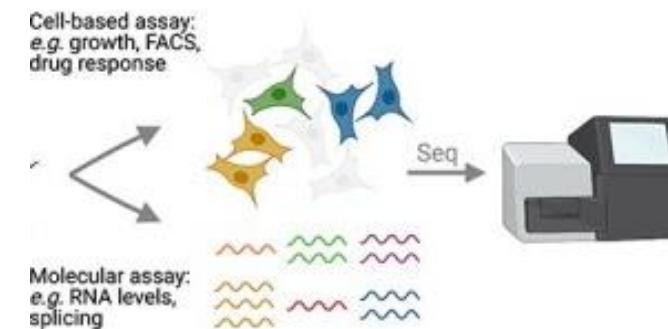


## Delivery of the library into a model system

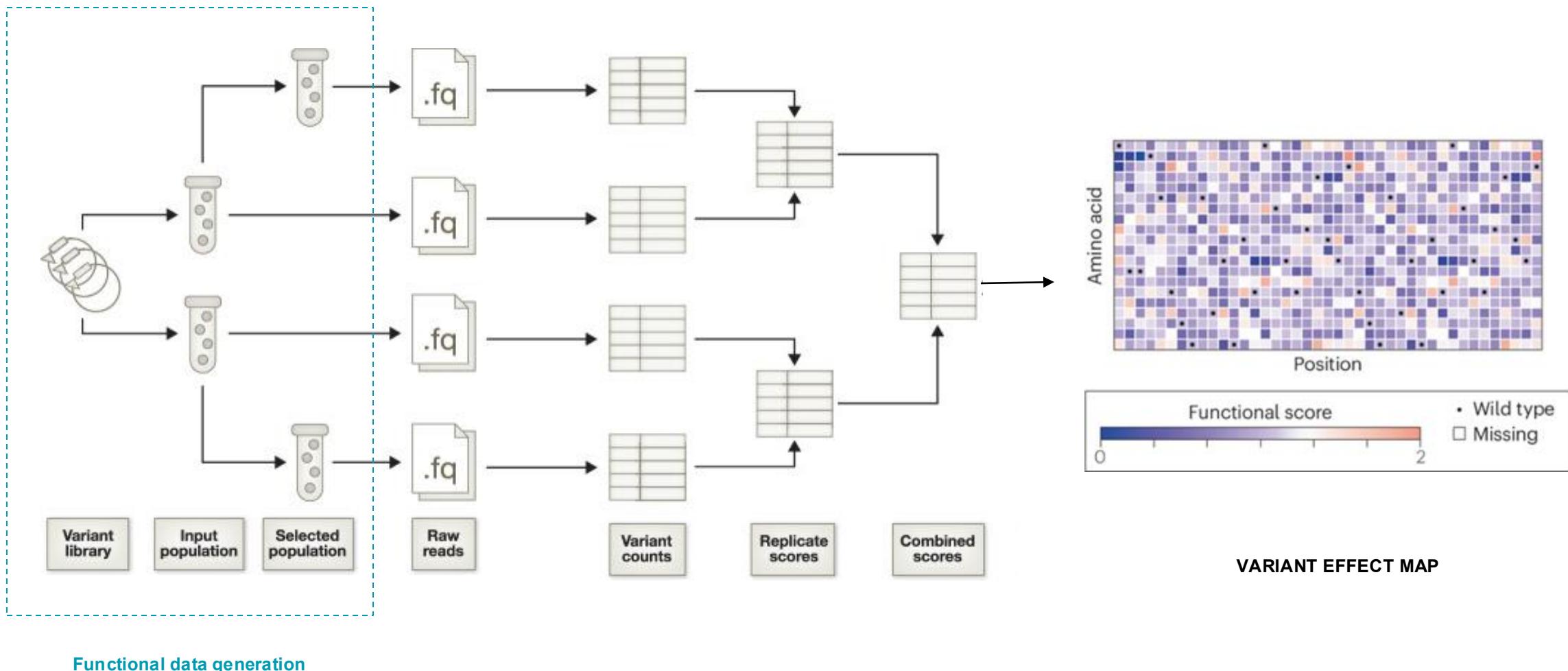


*cDNA-based, Saturation genome editing,  
Base editing, Prime editing*

## Sequencing pre- and post-selection

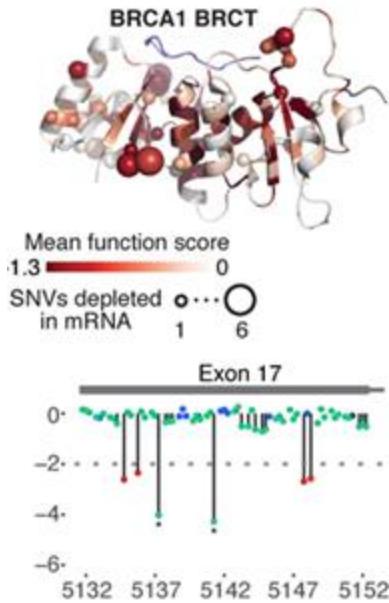


## 2. Functional Data Analysis

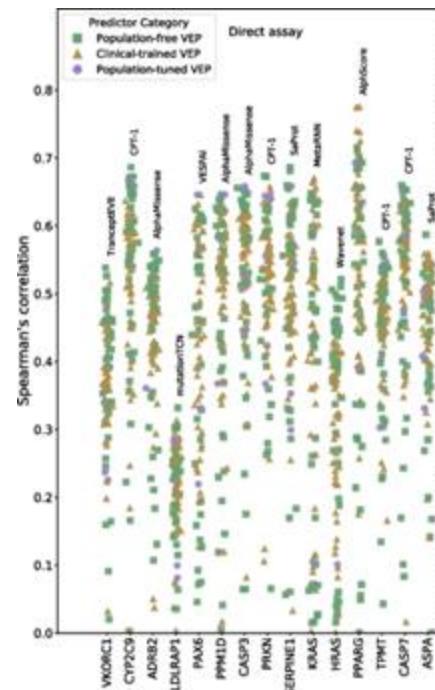


Functional data generation

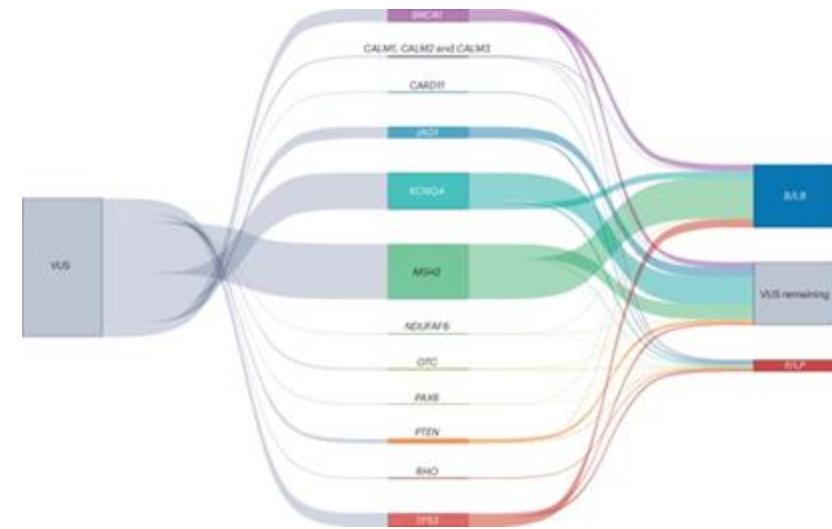
### 3. Functional Data Applications



Structure-function correlation



Circularity-free benchmarking



Clinical variant interpretation

And more....

Findlay *et al.*, 2018

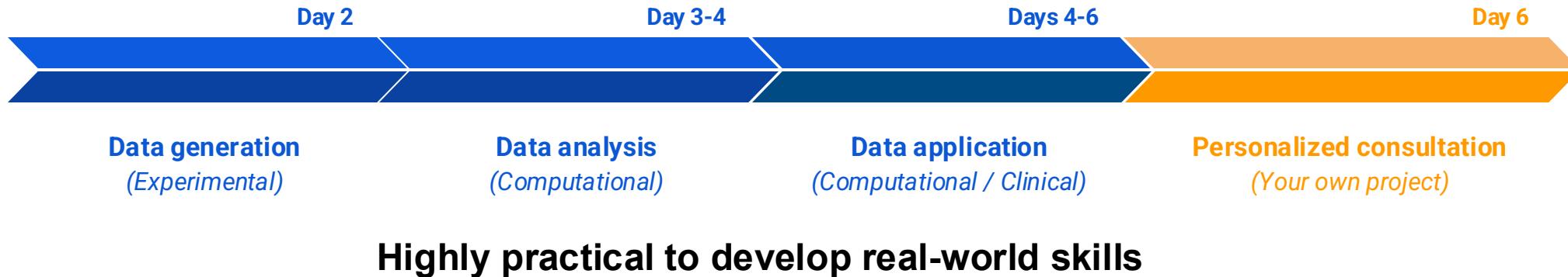
Livesey and Marsh, 2025

McEwen *et al.*, 2025



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# **What makes this course special?**



## World-class instructors

Pioneers and developers of MAVE:

- Technologies
- Analytical tools
- International standards
- Clinical guidelines



- Dedicated SGE pipeline (+4 years)
- 4 Published gene maps
- 20-30 targetons / month (~12-24 average size genes / year)
- Analytical tools development: VaLiAnT, QUANTS and MAVEQC
- AVE alliance leadership
- Generative and Synthetic Genomics

# Day 2 | Data Generation



## Morning Session: Why MAVEs?

- **Instructors:** Elizabeth Radford, Alan Rubin
- Disease mechanisms, penetrance, functional assays
- Clinical and molecular scenarios
- Introduction to MaveDB

## Morning Session: SGE Experimental Design

- **Instructors:** Greg Findlay, Sofia Obelenski, Rebeca Olvera-León
- Saturation genome editing methodology
- Design considerations for different applications
- Case studies from published SGE experiments

## Afternoon Session: Base Editing & Endogenous MAVEs

- **Instructor:** Matthew Coelho
- Base and prime editor technologies
- Advantages vs HDR-based approaches

## Afternoon Session: Sanger MAVE Pipeline

- **Instructor:** Adam Hunter
- Operational SGE platform walkthrough
- From experimental design to data generation

# Day 3-4 | Data Analysis

## Tuesday: MAVE Data Analysis I-III

- **Instructors:** Victoria Offord, Alan Rubin
- FASTQ → read counts → variant scores
- Hands-on with SGE datasets
- Enrich2/CountESS for cDNA datasets
- Building analysis skills progressively



## Wednesday Morning: Dataset QC

- **Instructor:** Irene Gallego Romero
- Quality control for count-based genomics data
- Diagnosing wet-lab problems from data
- Technical replicate assessment



## Wednesday: Data Integration I-III

- **Instructors:** Sarah Hunt, Jorge Batista da Roche, Alan Rubin
- Ensembl VEP annotation
- MaveDB data sharing

# Day 4-5 | Data Application

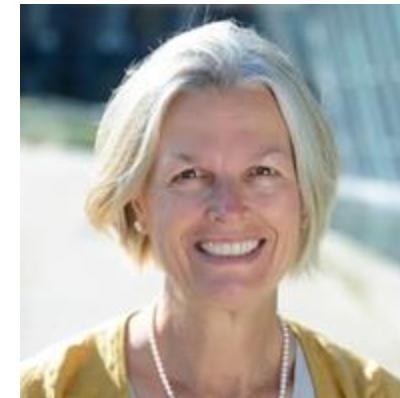


## Wednesday: Data Integration I-III

- **Instructor:** Joe Marsh
- Protein structure-function visualization

## Thursday: Variant Effect Predictors I-II

- Types of predictors, training, benchmarking
- Comparing experimental vs computational approaches



## Thursday Afternoon: Clinical Validation/Calibration of MAVES

- **Instructors:** Sophie Allen, Charlie Rowlands, Miranda Durkie
- ACMG/ACGS guidelines overview
- PS3/BS3 functional evidence weighting
- Constructing variant truthsets
- Future methods: GMMs, kernel density estimates
- Combining multiple MAVES

## Friday Morning: Variant Classification Using MAVE Data

- **Instructors:** Helen Firth, Julia Foreman, Miranda Durkie
- **DECIPHER** platform for variant interpretation
- Combining functional + other evidence types
- Interactive case studies with polls
- Disease mechanism and phenotype context

# How will this course impact YOUR OWN Research?

# Day 6 | Personalized Consultation

Friday Late Morning/Afternoon

**Present YOUR PROJECT and tell us how we can help you (5 minutes)**

## What to Present:

- Your problem statement/research question
- Key learnings from this week
- How you'll incorporate MAVEs into your work
- Knowledge gaps or challenges you still face
- Next steps for your project

## Pro tips:

- 1) Be specific
- 2) Link to the different modules
- 3) The presentation is your mean to get feedback
- 4) Use the daily evening prep time to organize your presentation

## How to maximize your benefit

**Throughout the week, reflect after every module:**

- How does this module apply to my project?
- Which concepts are unclear?
- What challenges does this session help me solve?
- What questions do I need answered?

**By Thursday evening, you should have:**

- Your presentation drafted
- Your top consultation question identified
- A clear sense of your next steps after the course
- Ideas on what we could have done better to help you more



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# questions?

Please contact [wellcomeconnectingscience.org](http://wellcomeconnectingscience.org)  
for more information.

