



**wellcome
connecting
science**

Introduction to the course

MAVE: Approaches, Analysis, and Interpretation

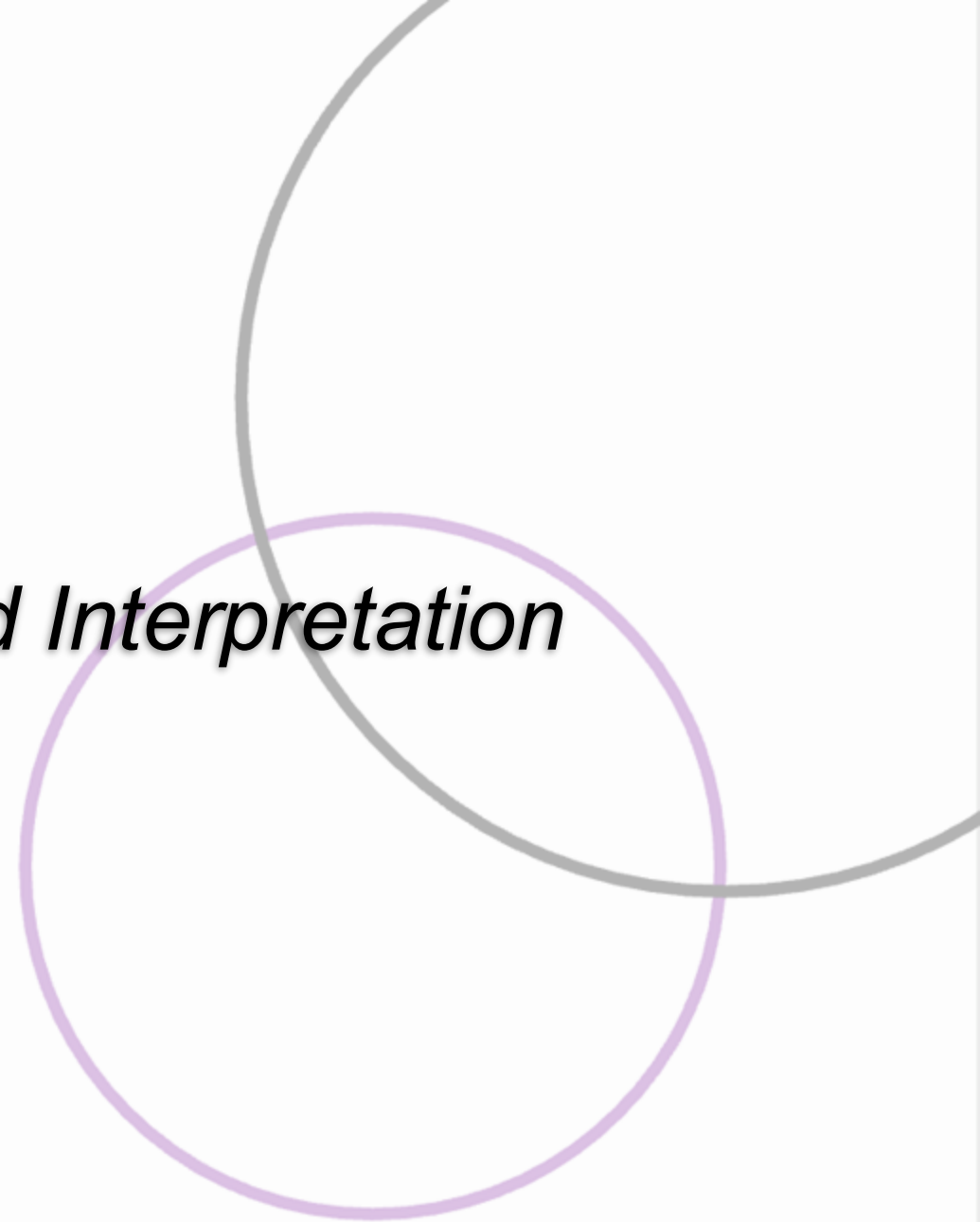
Dr David Adams

Senior Group Leader

Dr Daniel A. Jaramillo-Calle

Clinical PhD Fellow

Nov 2025

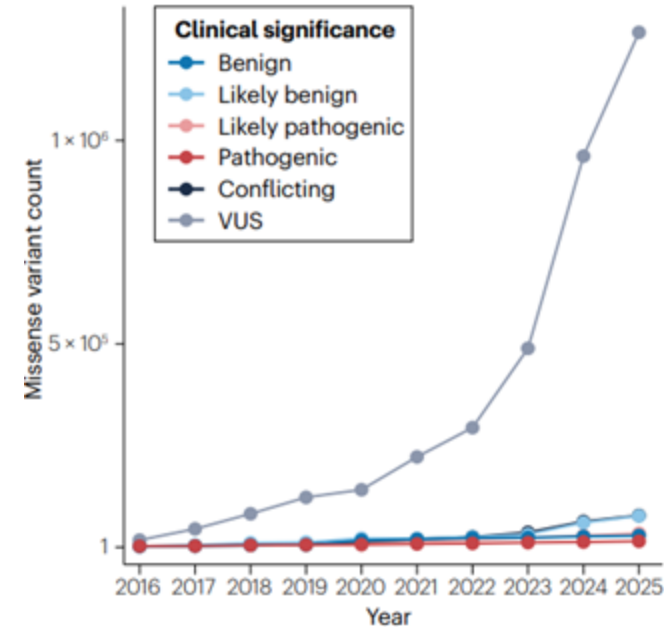
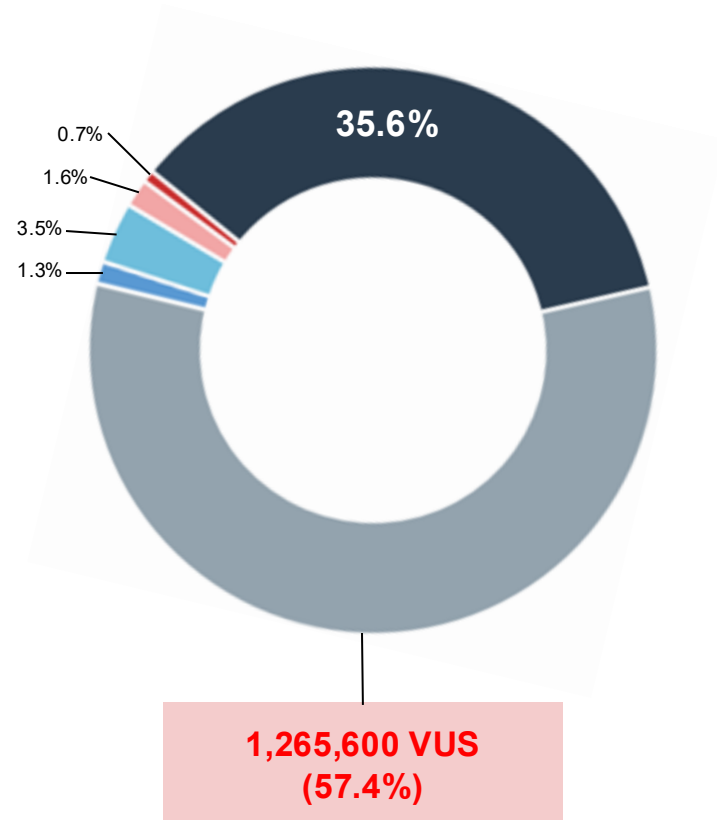




**wellcome
connecting
science**

Why a MAVÉ course?

The Challenge: Variants of Uncertain Significance



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

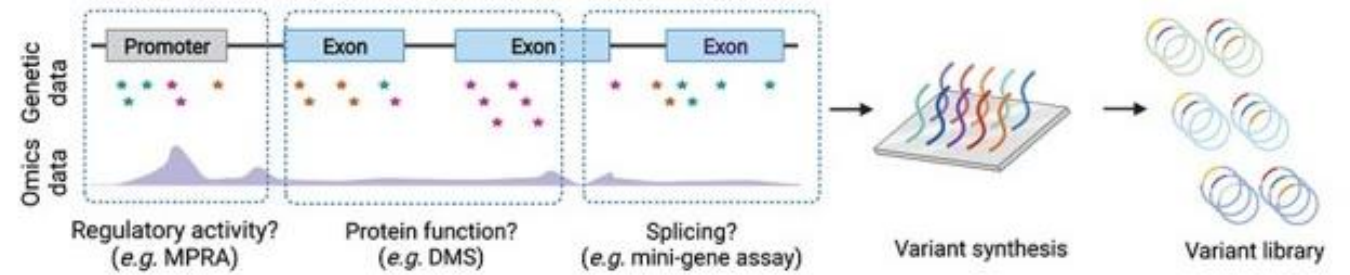
Ambitious goal to **eliminate VUS by 2030** in ~4500 Clinically-relevant genes (AVE Alliance / NHGRI)

1. Functional Data Generation

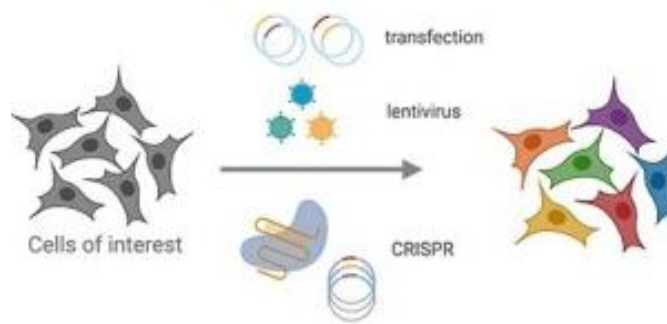
Selection of model system



Generation of a variant library

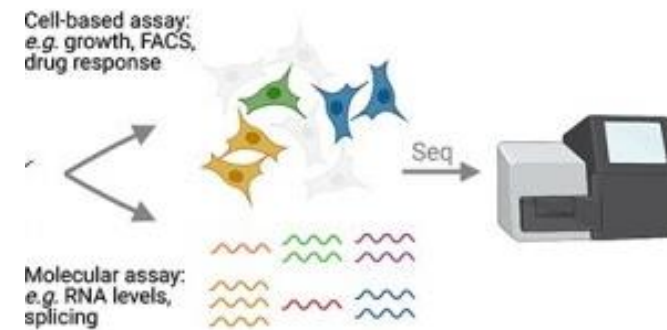


Delivery of the library into a model system

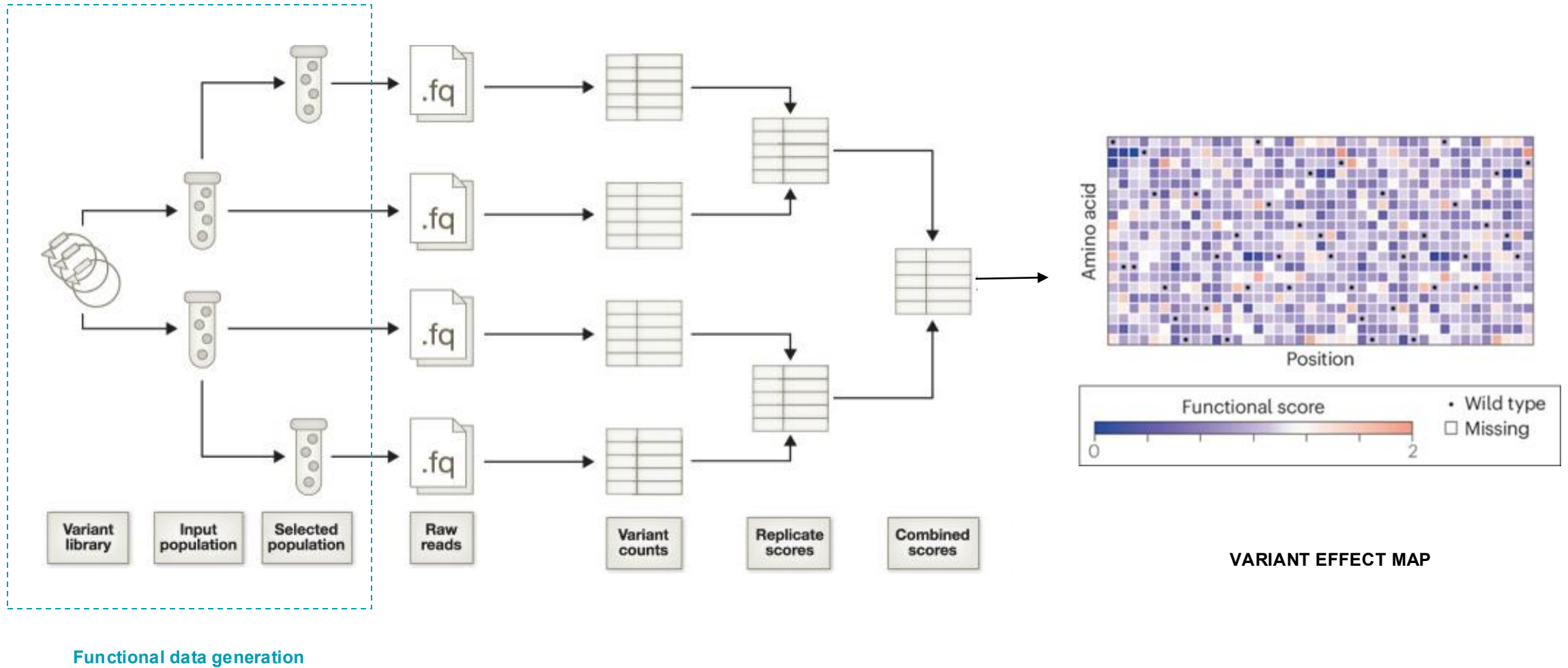


*cDNA-based, Saturation genome editing,
Base editing, Prime editing*

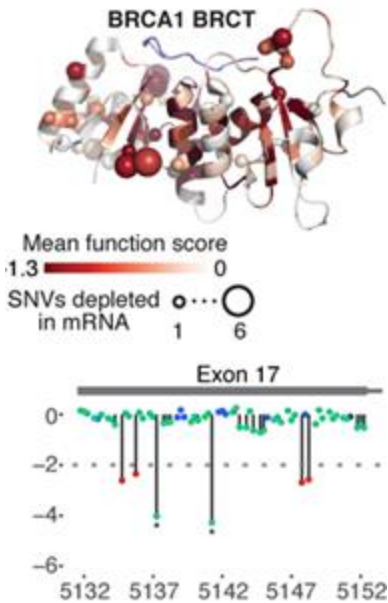
Sequencing pre- and post-selection



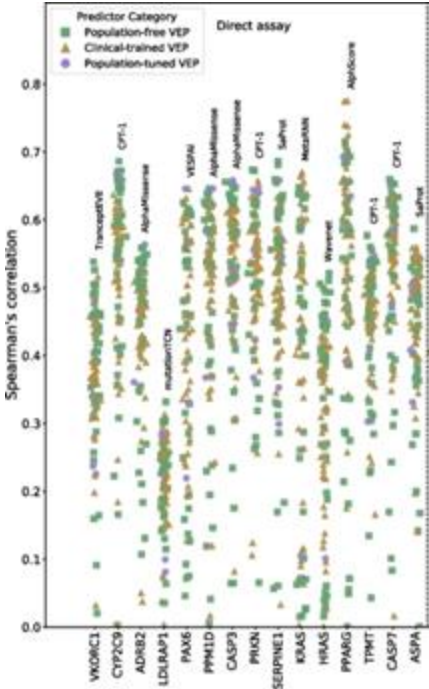
2. Functional Data Analysis



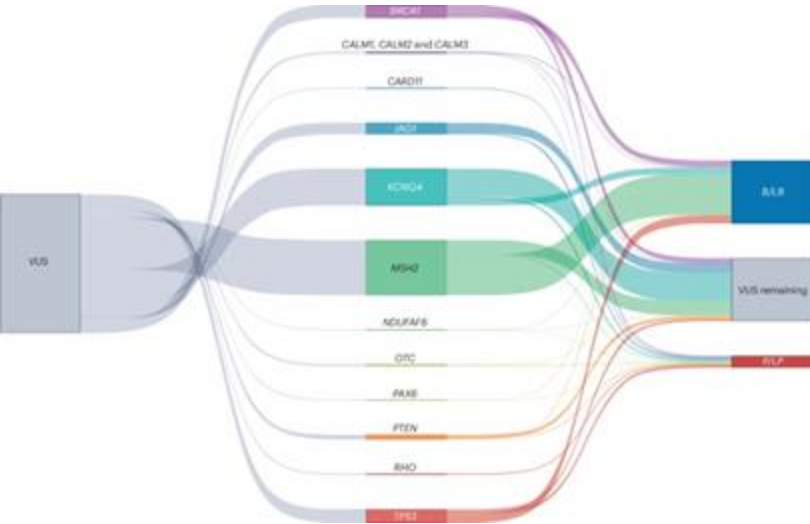
3. Functional Data Applications



Structure-function correlation



Circularity-free benchmarking



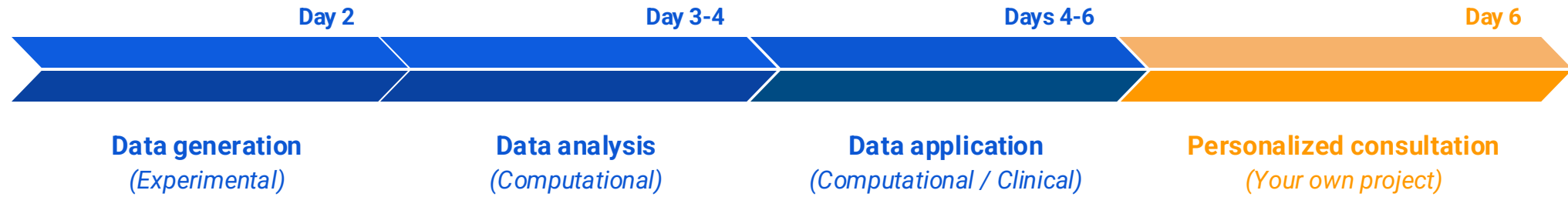
Clinical variant interpretation

And more....
Findlay *et al.*, 2018
Livesey and Marsh, 2025
McEwen *et al.*, 2025



**wellcome
connecting
science**

What makes this course special?



Highly practical to develop real-world skills



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



**wellcome
connecting
science**

**How will this course impact
YOUR OWN Research?**



**wellcome
connecting
science**
wellcome.org.uk

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

questions?

Please contact wellcomeconnectingscience.org
for more information.

