



MAVE Progress Report, Clinical Implementation of High-Throughput Functional Assays

Daniel Zimmerman, Ashley PL Marsh, Dean Hoffer, John Ranola, Ana Silverstein, Heather Zimmermann, Sean Korpela, Marcy Richardson, Katie Yergert, Rhonda Lassiter, Tina Pesaran

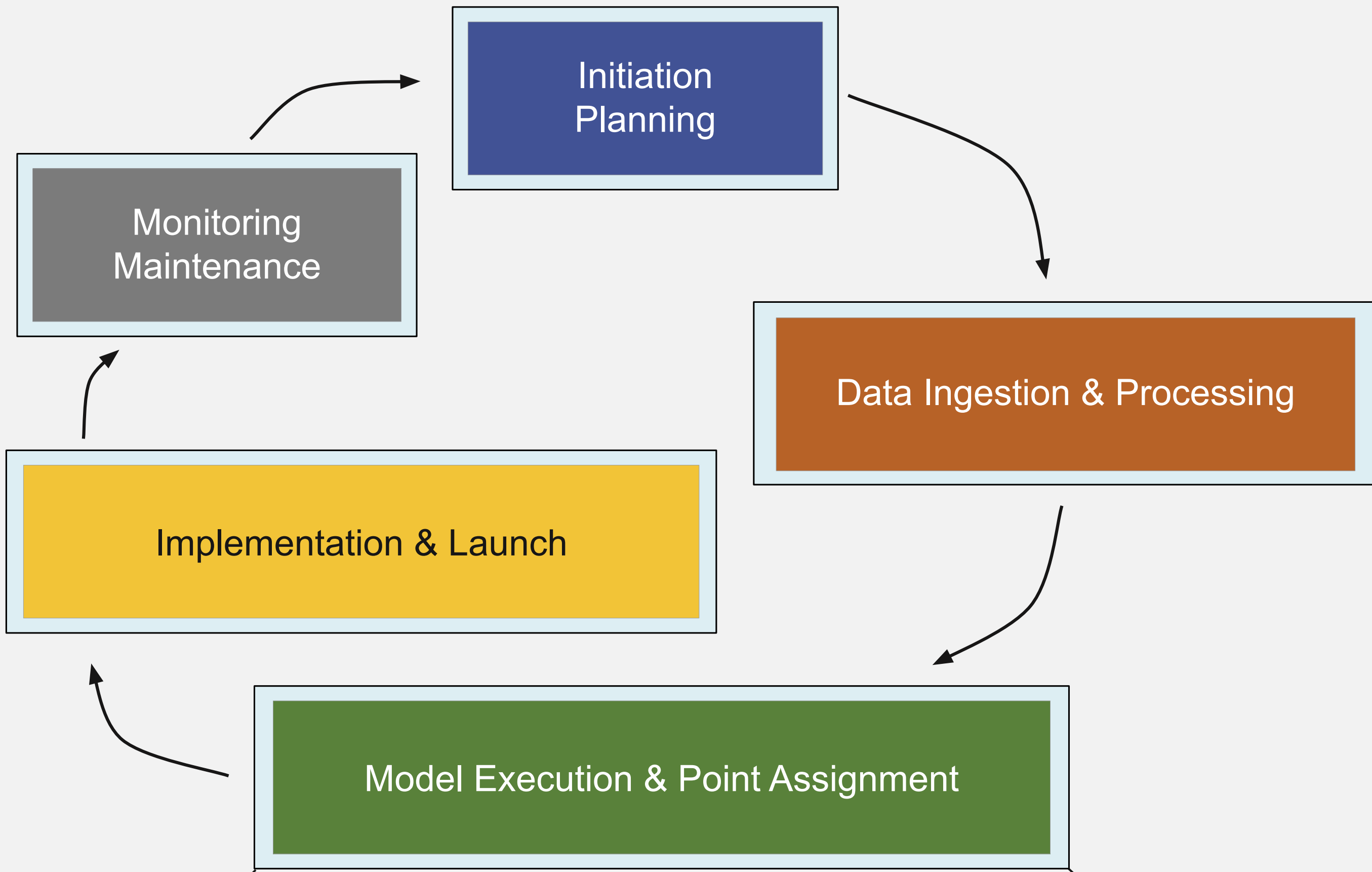


BACKGROUND

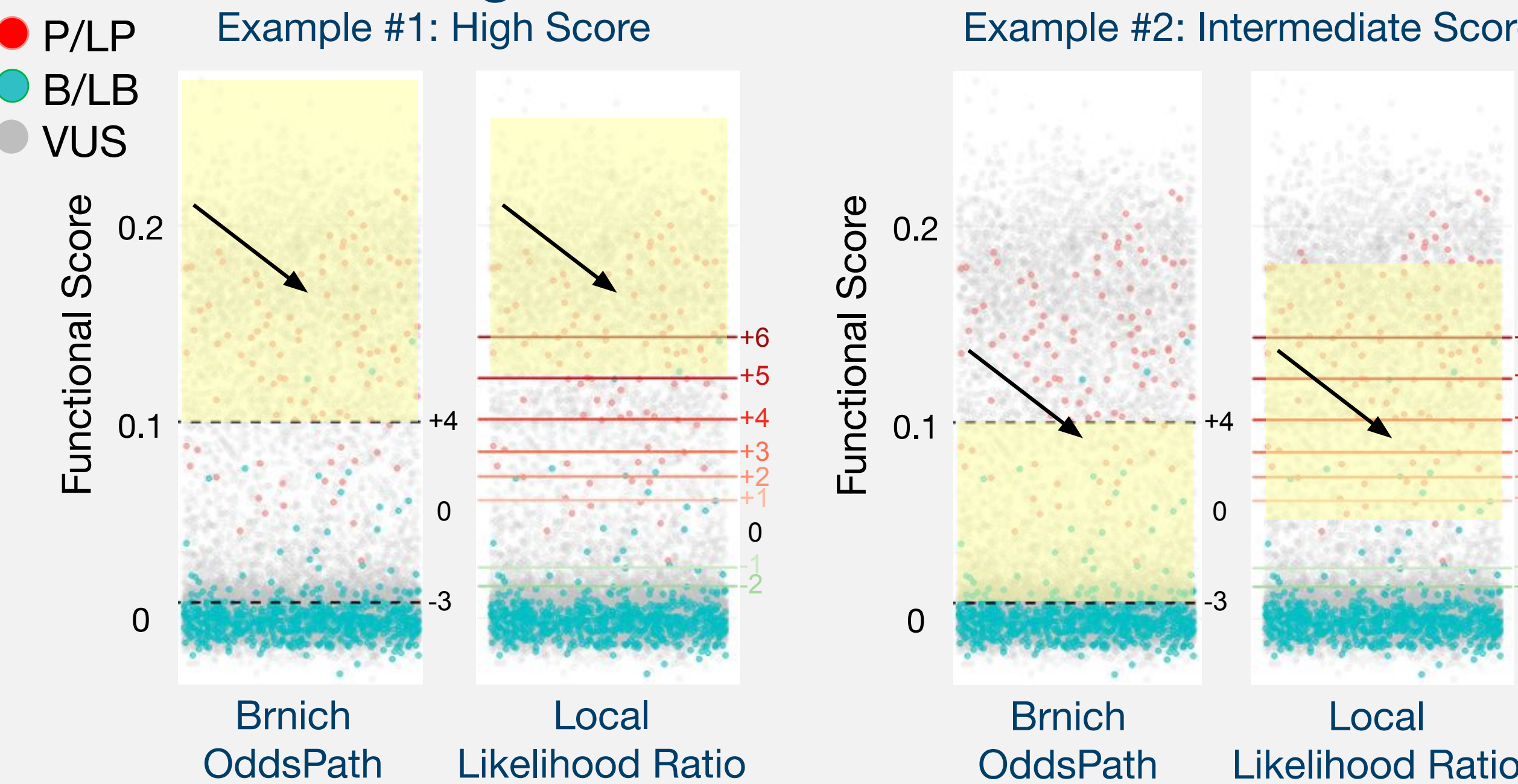
As the research community becomes increasingly proficient at high-throughput experiments, clinical laboratories need to adapt their methodologies to accommodate large-scale variant classification. Analyzing variants on a case-by-case basis will inevitably fall behind the rapid pace of data production, creating an ever-widening gap between the release of new Multiplexed Assays of Variant Effect (MAVE) and implementation into clinical settings. Ambry Genetics is developing automated workflows that identify newly released studies, validate the quality of data, and calibrate results to ACMG/AMP evidence strengths.

Methods

Overview of Processing MAVEs at Ambry Genetics



Addressing Over/Under-Estimation of Evidence



No MAVE MAVE Published MaveRegistry unpublished MAVE pre-print
Gene = gene w/ no or few missense variants classified as P/LP

CancerNext 41 genes				**MLH3**
APC	ATM	**AXIN2**	BAP1	
BARD1	BMPR1A	BRCA1 4	BRCA2 2	
BRIP1	**CDH1**	CDKN2A	**CHEK2** 2	
EPCAM	FH	**FLCN**	**GREM1**	
HOXB13	MBD4	MET	MLH1	
MSH2	**MSH3**	MSH6	MUTYH	
NF1	**NTHL1**	**PALB2** 2	PMS2	
POLD1	POLE	PTEN 2	RAD51C 2	
RAD51D 2	**RPS20**	SMAD4	STK11	
TP53 4	**TSC1**	TSC2	VHL 2	

CancerNext is Ambry's guideline-based test option, which includes genes that are known to have clinical management recommendations for detection, prevention, and/or risk reduction strategies for hereditary cancer predisposition.

MAVE Dashboard - Prioritization & Triage

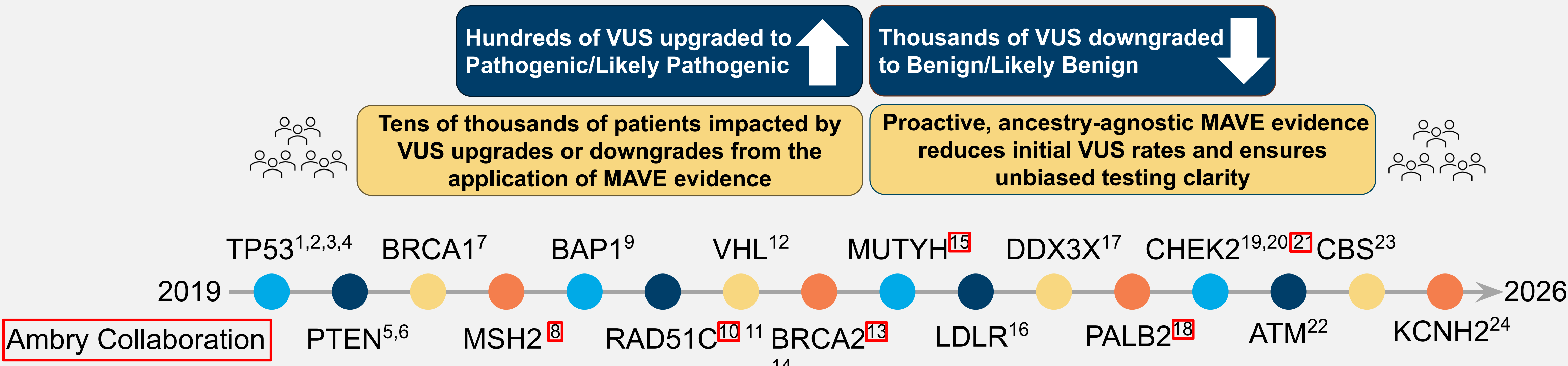
Project Details/Status						
Specialty	Published?	PMID	Author	Priority	Project Status	Review Outcome
Oncology	Unpublished	123456	Example et al	High Priority	Approved - On Hold	Approved
RD	Published	123456	Example et al	High Priority	Approved - On Hold	Approved
Cardio	Published	123456	Example et al	Medium Priority	Submitted and Pending Approval	Pending
Oncology	Published	123456	Example et al	Low Priority	Submitted and Pending Approval	Pending
Oncology	Published	123456	Example et al	Low Priority	Submitted and Pending Approval	Pending
Oncology	Pre-print	123456	Example et al	Low Priority	Submitted and Pending Approval	Pending

Gene/Variant Metrics						
Ambry Author	Prior MAVE	Panel Gene	ACMG Secondary Finding	GDV Status	# Ambry Variants	# Ambry VUS
N	N	Y	Y (1.0)	Moderate	500	320
Y	N	Y	Y (1.0)	Moderate	500	100
N	N	Y	Y (1.0)	Definitive	500	200
N	N	Y	Y (1.0)	Definitive	500	100
N	Y	Y	Y (1.0)	Definitive	500	250
N	N	Y	Y (1.0)	Limited	500	250

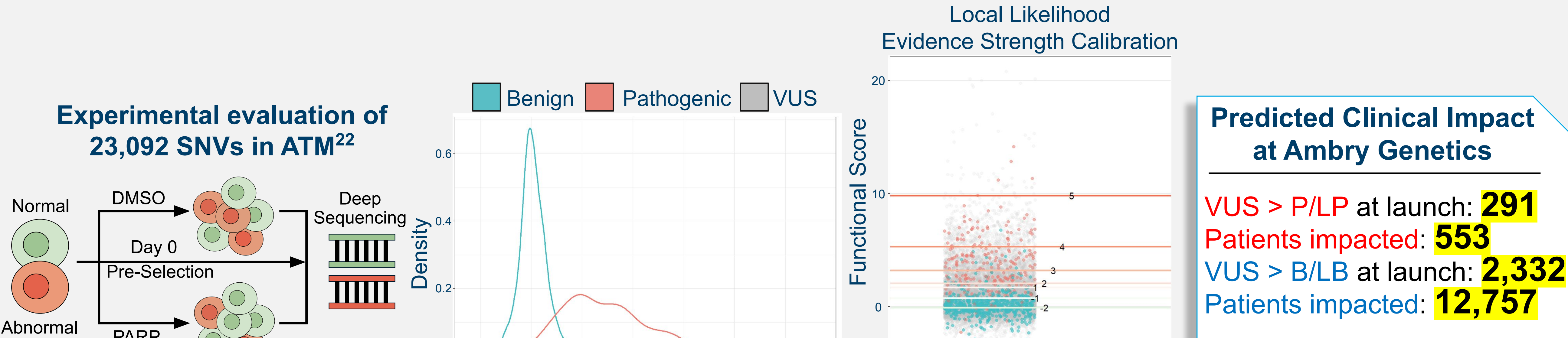
Results

Functional Evidence From MAVEs is a Powerful Tool for Clinical Variant Interpretation

Ambry's variant scientists have been actively translating MAVE data into variant assessment and classification for years, beginning with TP53 in 2019



Real-World Example: Clinical Calibration of the ATM MAVE



TAKE HOME POINTS

- Efficient workflows are needed to handle the increasing number of MAVE datasets
- MAVEs are contributing to clinical management of hereditary cancer risk genes
- Modern calibration methods mitigate over and underestimation of evidence strength
- MAVEs support personalized medicine by proactively stratifying variants
- Collaborations between data generators & consumers facilitates implementation
- A single MAVE can enable reclassification of hundreds to thousands of variants

REFERENCES

TP53 – (1) PMID: 12826609, (2) PMID: 16007150, (3) PMID: 29979965, (4) PMID: 30224644; PTEN – (5) PMID: 29706350, (6) PMID: 29785012; BRCA1 – (7) PMID: 30209399; MSH2 – (8) PMID: 33357406; BAP1 – (9) PMID: 38969833; RAD51C – (10) PMID: 37253112, (11) PMID: 39299233; VHL – (12) PMID: 38969834; BRCA2 – (13) PMID: 39779848, (14) PMID: 39779857; MUTYH – (15) PMID: 40738107; LDLR – (16) PMID: 41166440; DDX3X – (17) PMID: 38057330; PALB2 – (18) PMID: 41554690; CHEK2 – (19) PMID: 39146382, (20) PMID: 39642869, (21) PMID: 37449874; ATM – (22) PMID: 40580951; CBS – (23) PMID: 32000841; KCNH2 – (23) PMID: 39315434