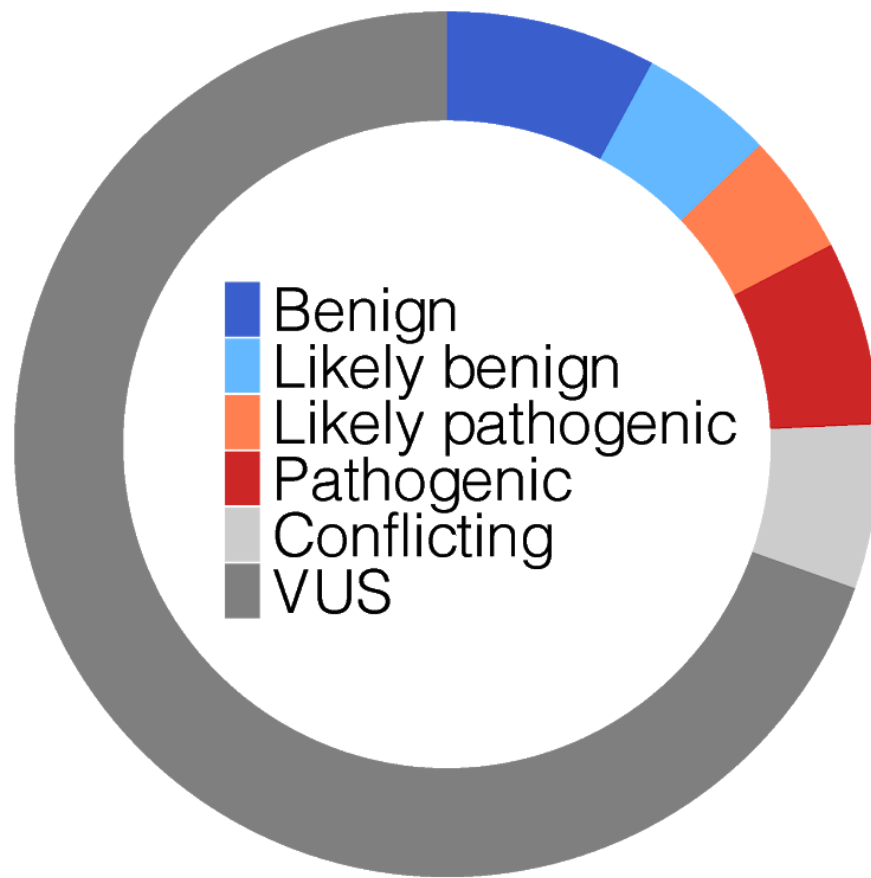


Understanding the functional effects of coding variation at scale

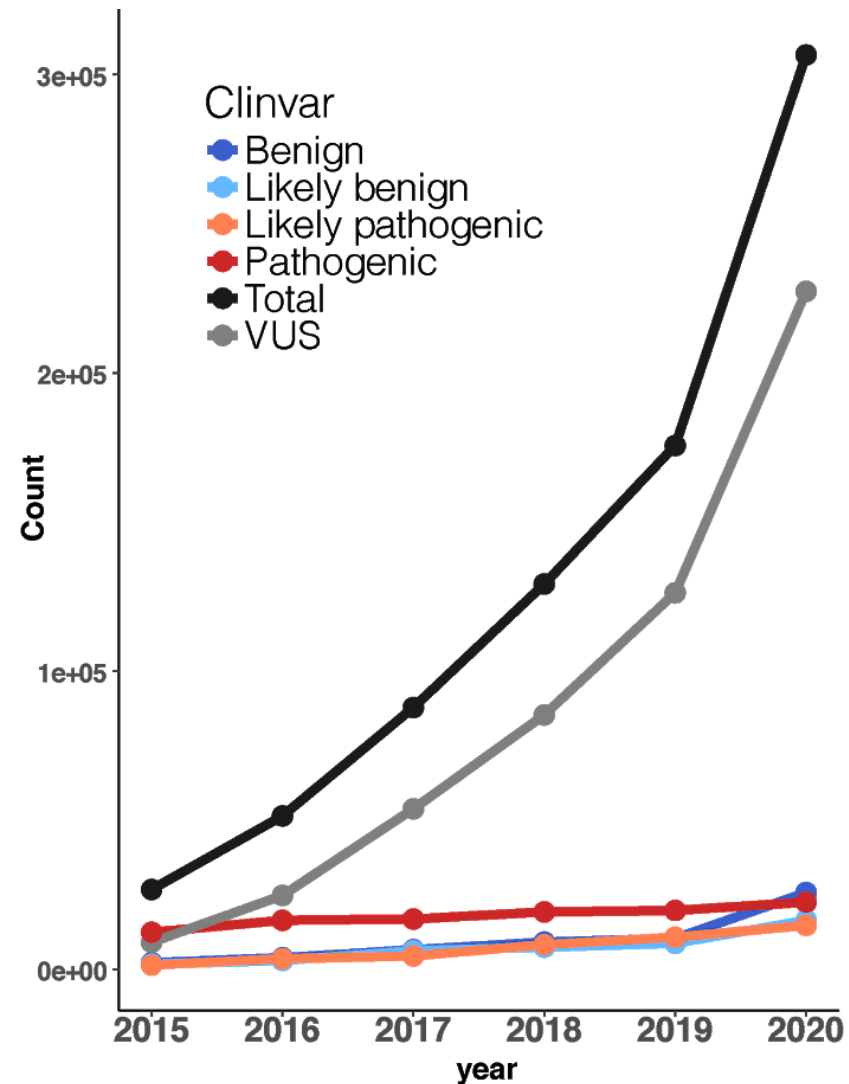
Lea Starita PhD
@lea_starita



Most missense variants are Variants of Uncertain Significance (VUS)

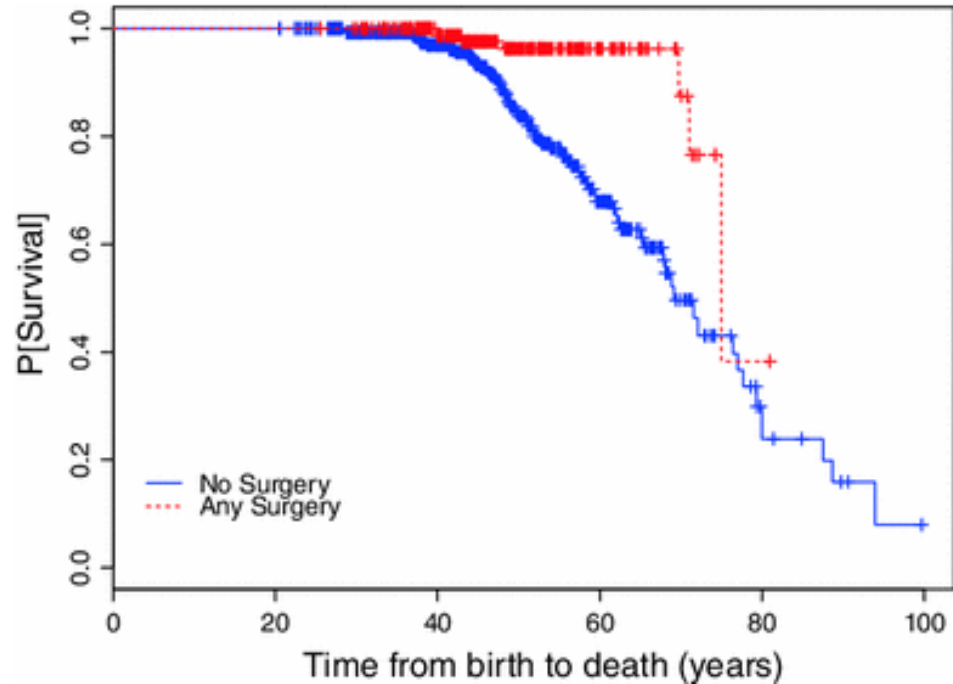


S. Fayer

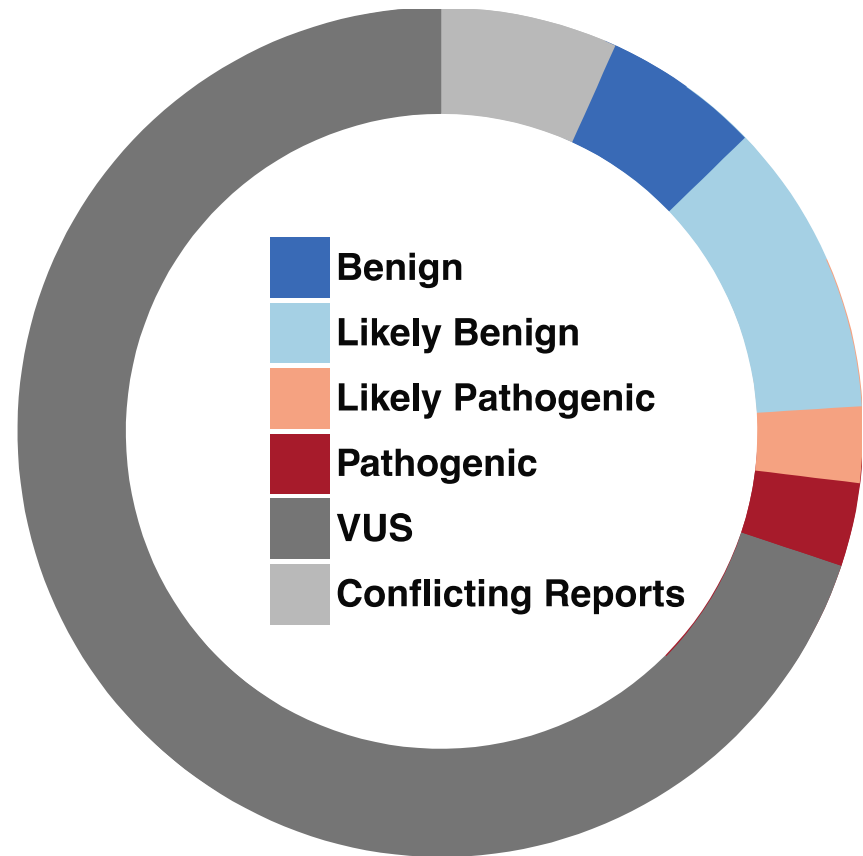


Variants in *BRCA1* are “actionable”

All missense variants
in *BRCA1*

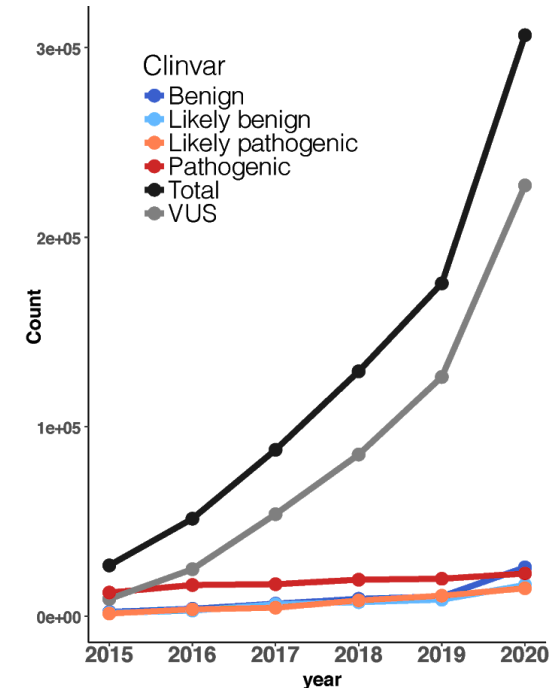
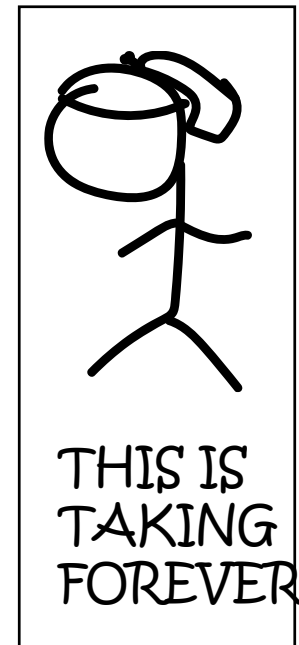
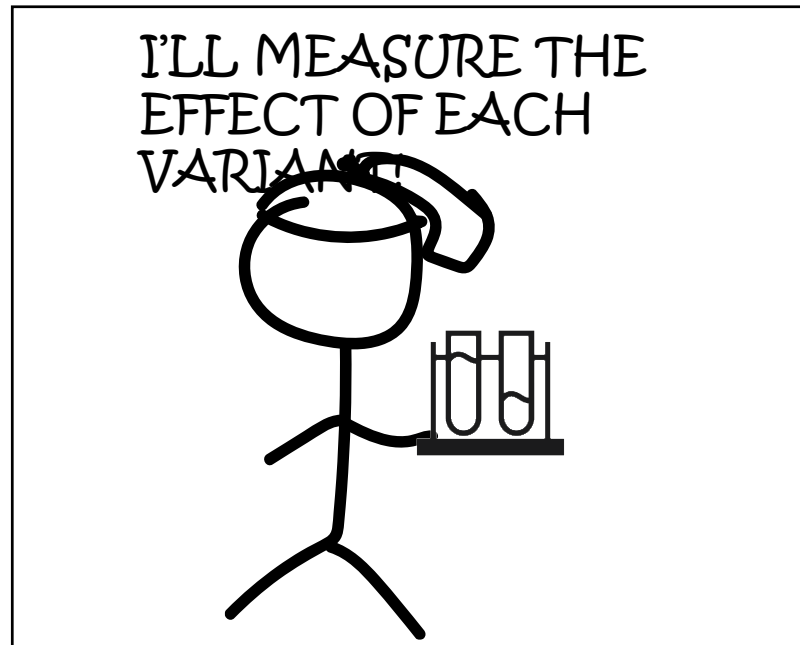


Ingham et al. 2013, *Epidemiology*

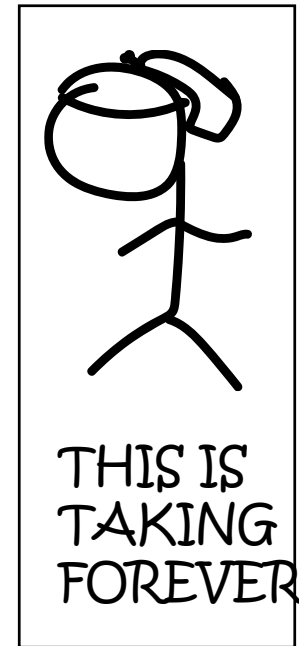
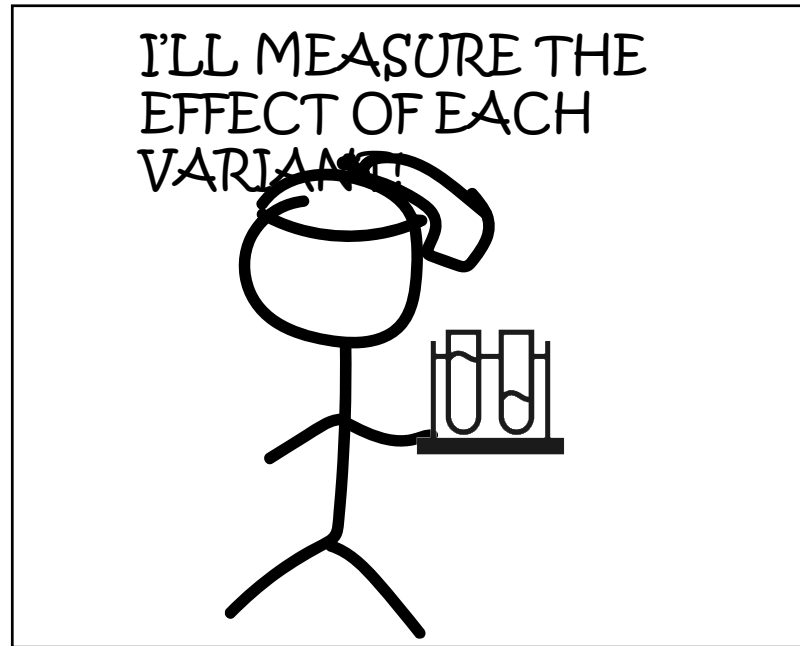


N = 2,084

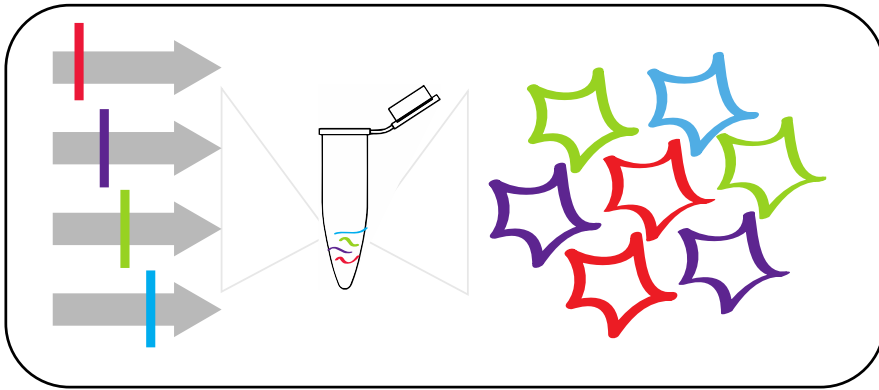
How are we going to solve the VUS problem?



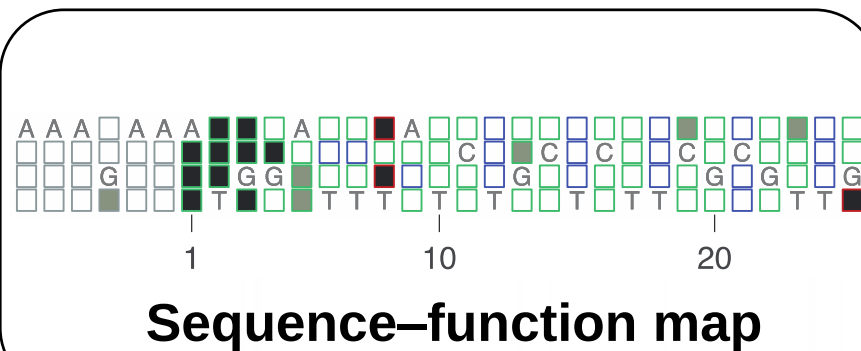
How are we going to solve the VUS problem?



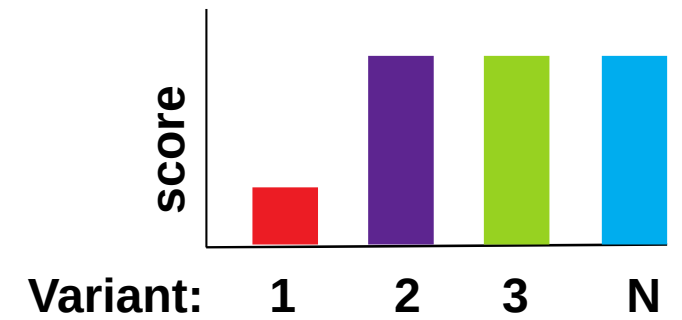
Multiplexed functional assays test thousands of variants **simultaneously**



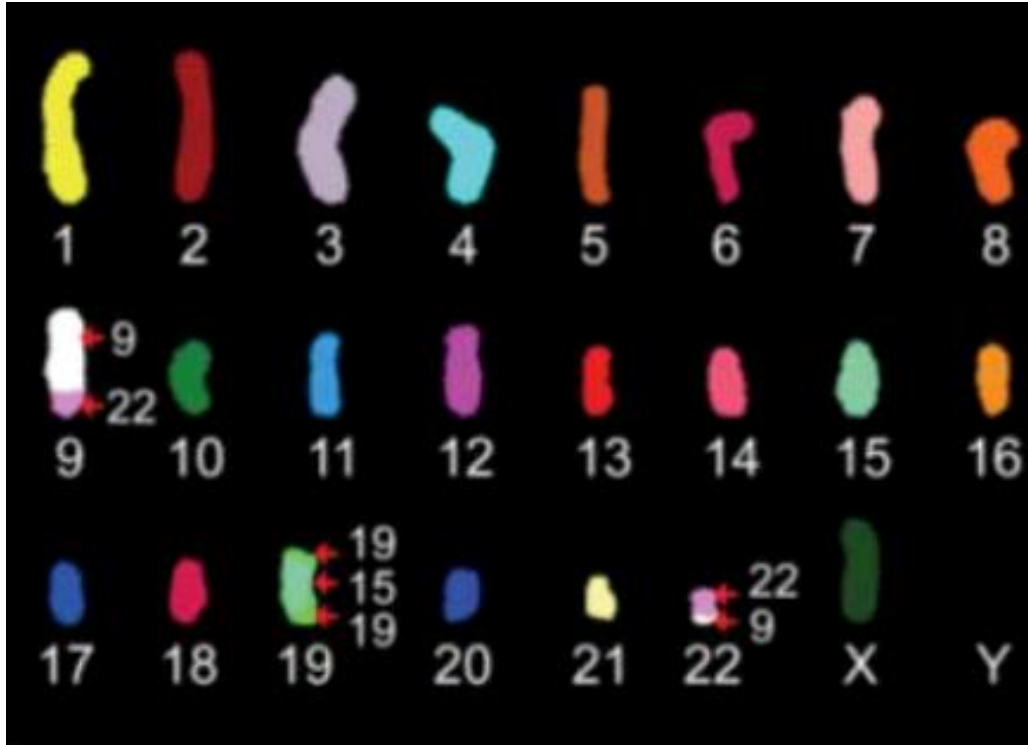
**Functional
Assay**



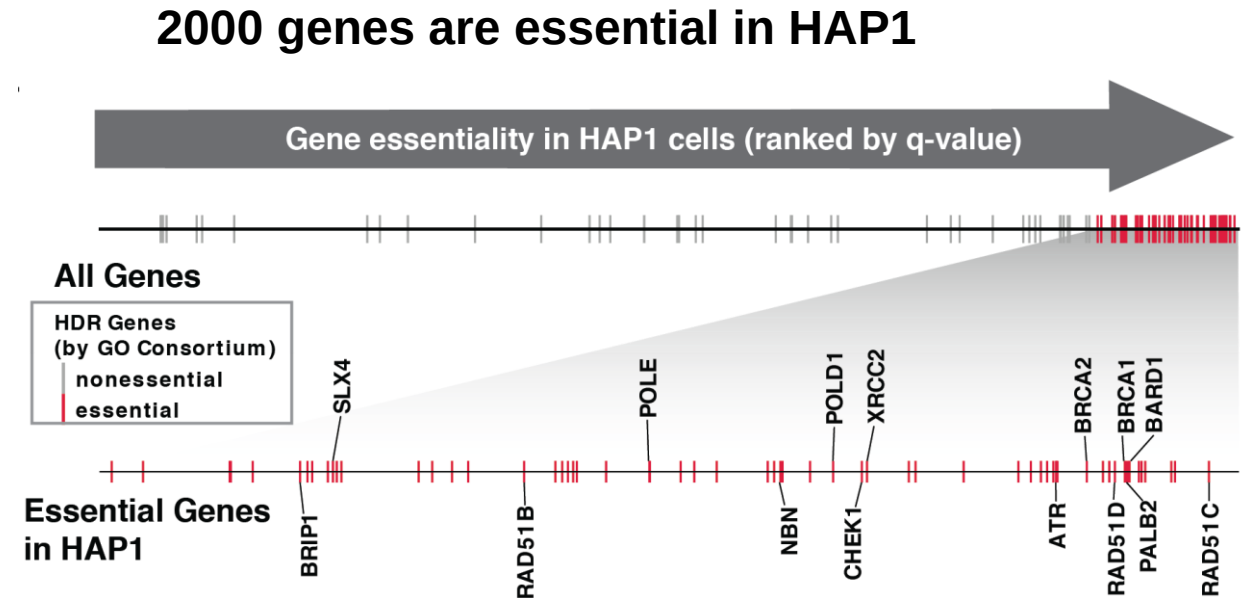
**Calculate scores
for variants
After / Before**



Exploiting essential genes in haploid cells

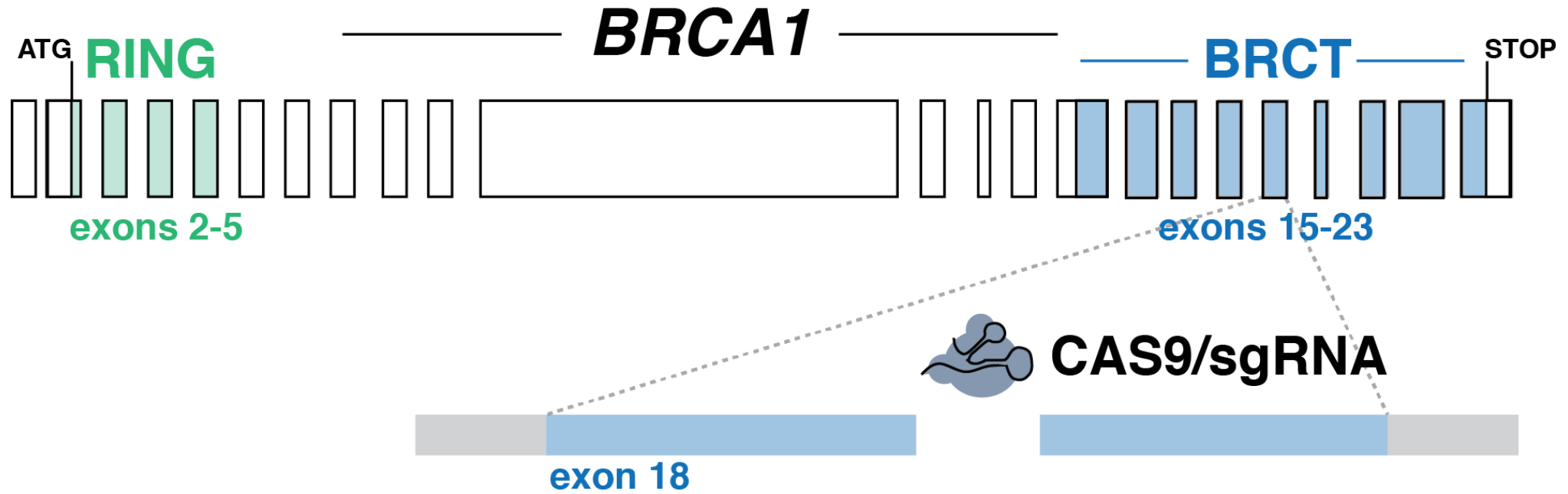


HAP1 karyotype

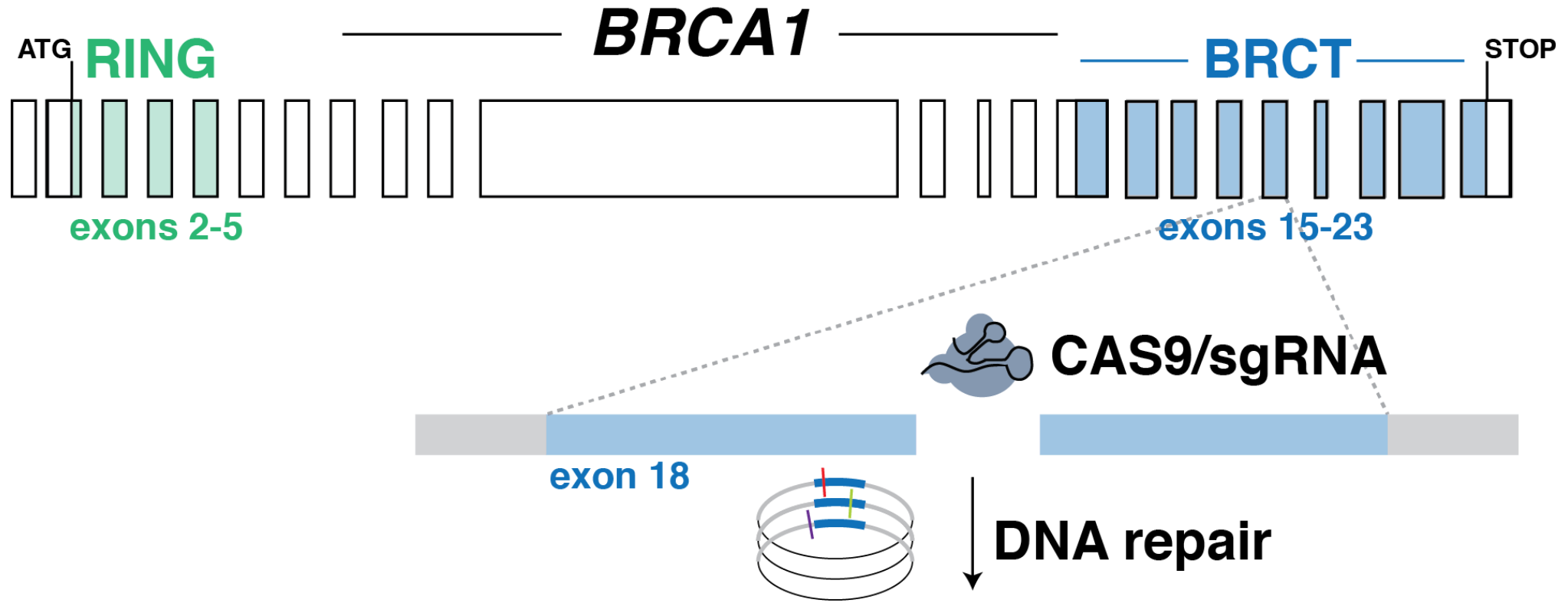


Blomen et al. Science 2015

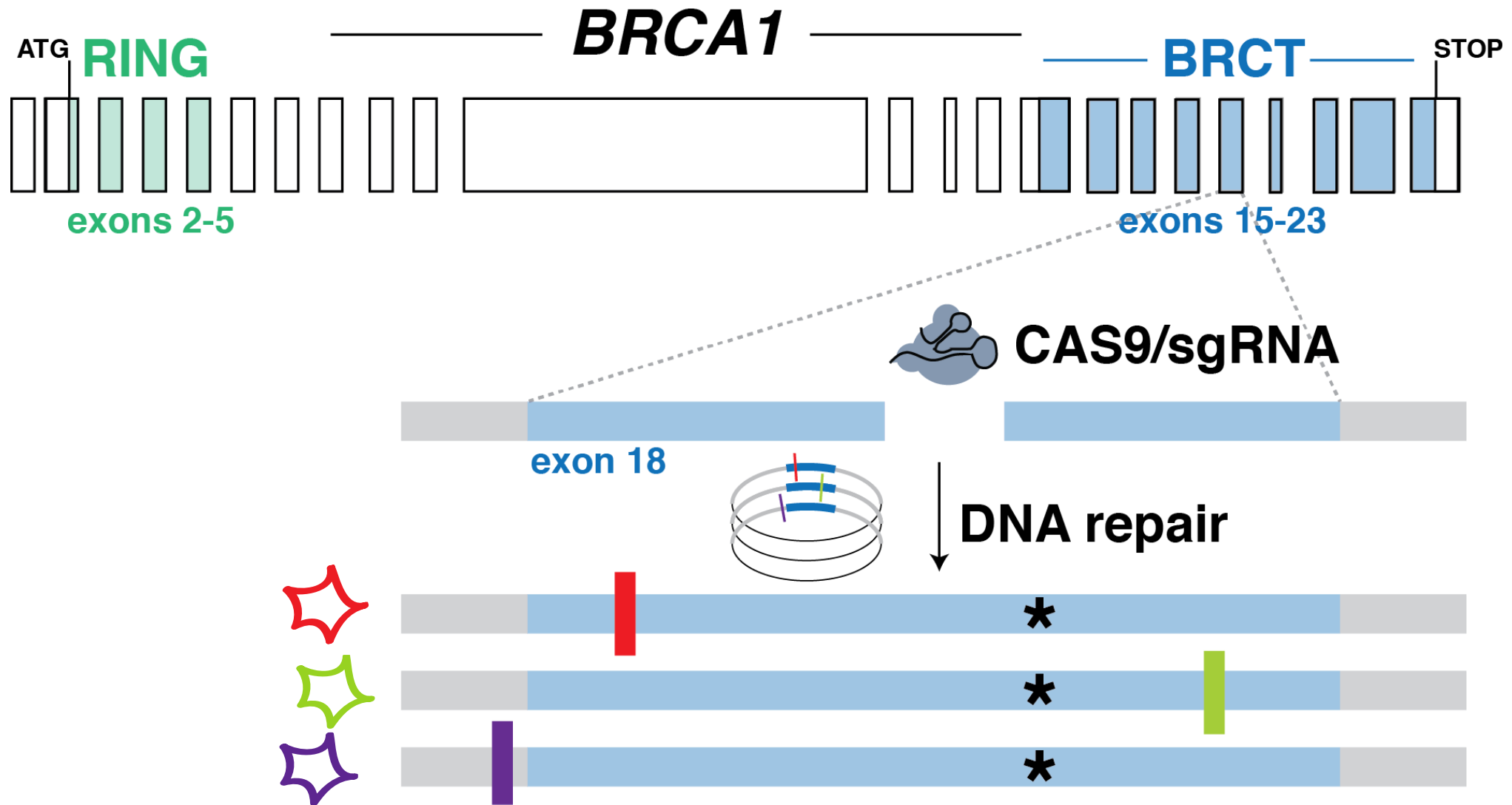
Saturation genome editing of *BRCA1*



Saturation genome editing of *BRCA1*



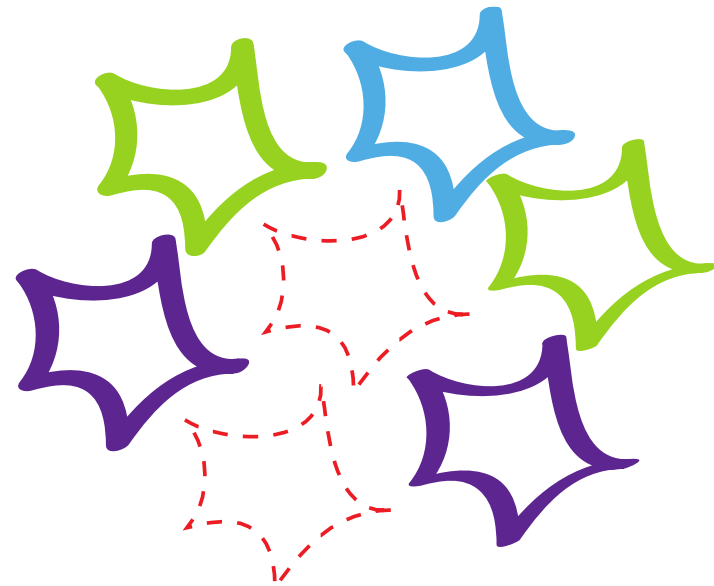
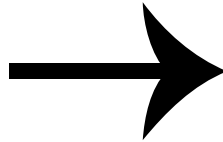
Saturation genome editing of *BRCA1*



SGE of *BRCA1* queries survival



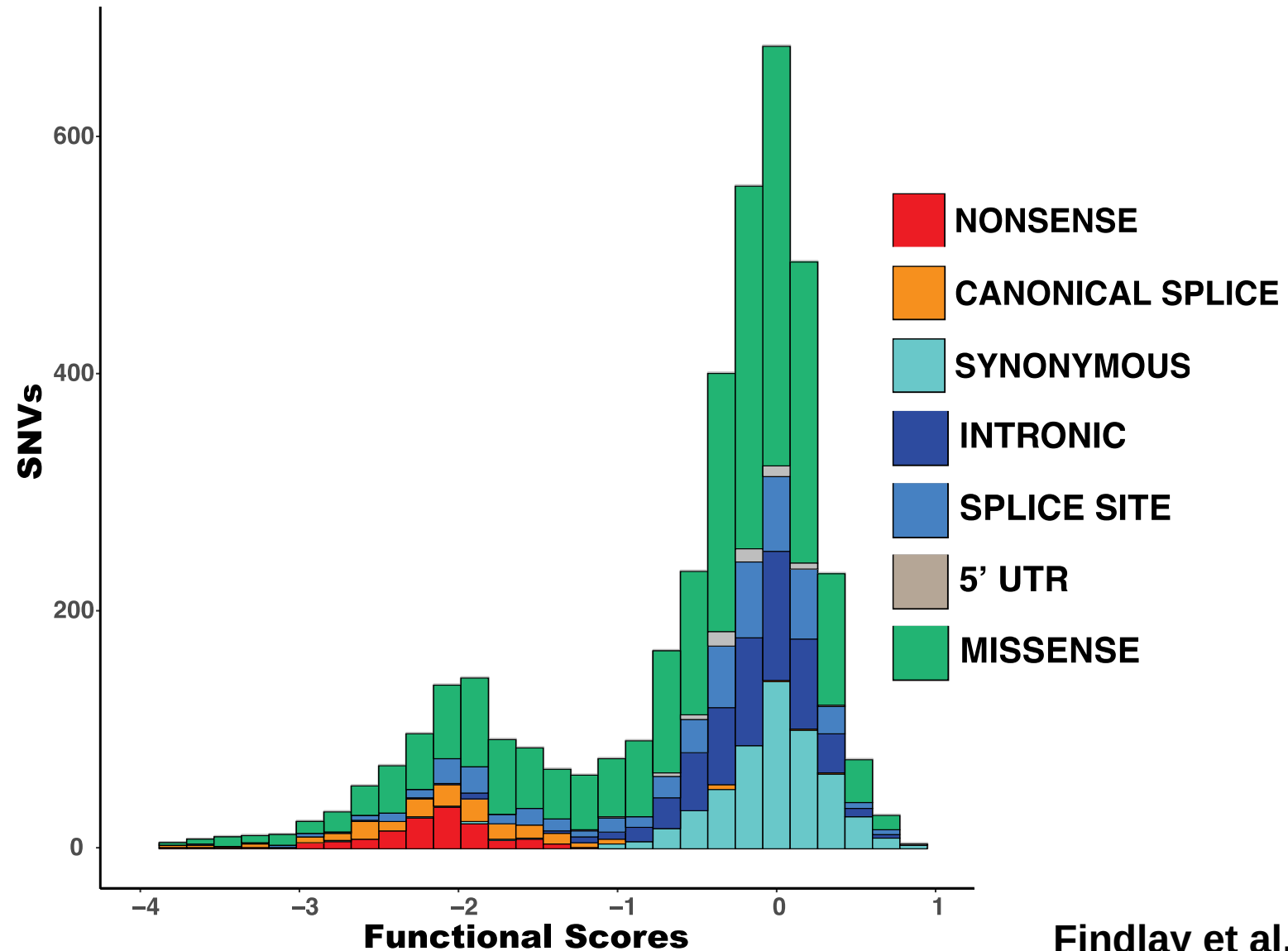
Edited Cells
Day 5



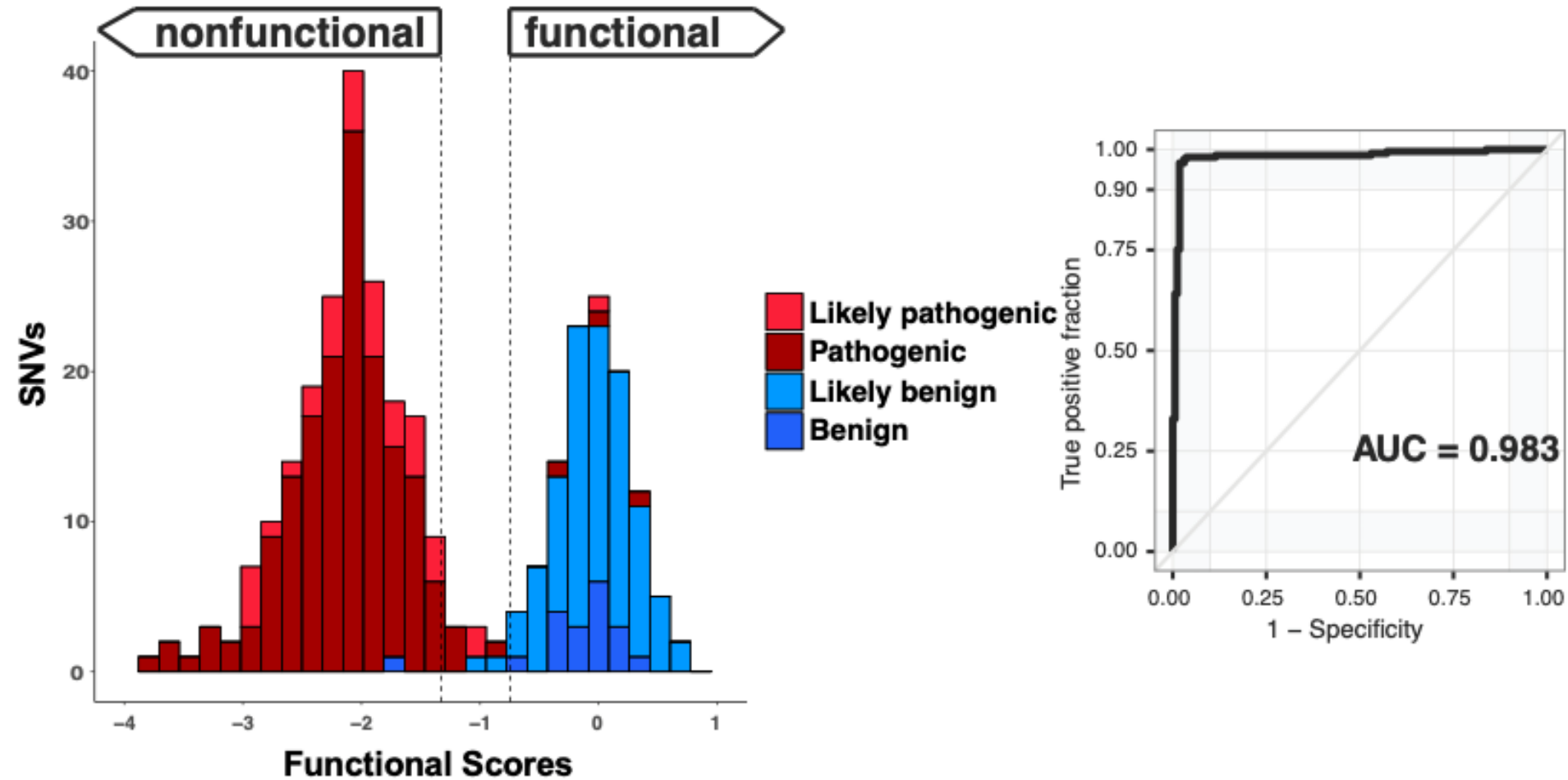
Edited Cells
Day 11



Functional scores for ~4000 variants of *BRCA1*

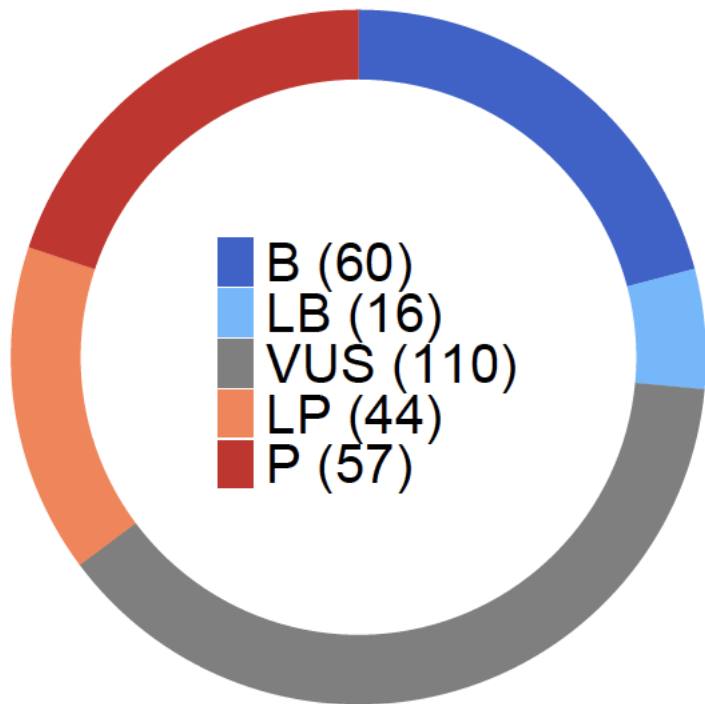


SGE accurately predicts clinical outcome

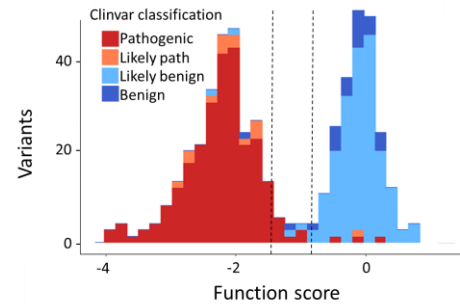


Multiplexed functional data informs clinical variant interpretation for *BRCA1*

BRCA1 classifications



287 *BRCA1* variants from Ambry Genetics

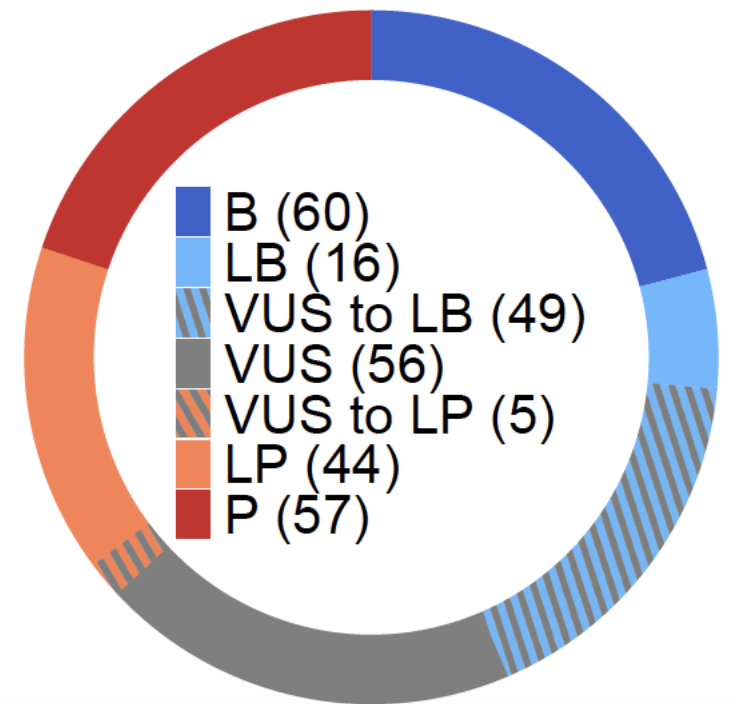


Strong evidence for pathogenic

Strong evidence for benign

ACMG interpretation framework

BRCA1 classifications with MAVE data



50% fewer VUS

Fayer and Ambry Genetics, coming soon

Ready to tackle challenges ahead!

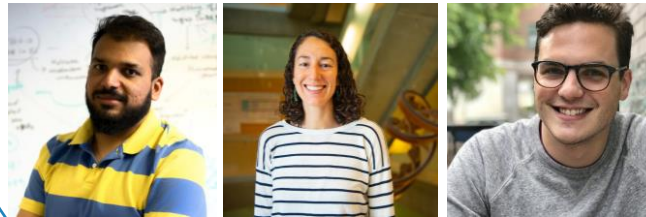
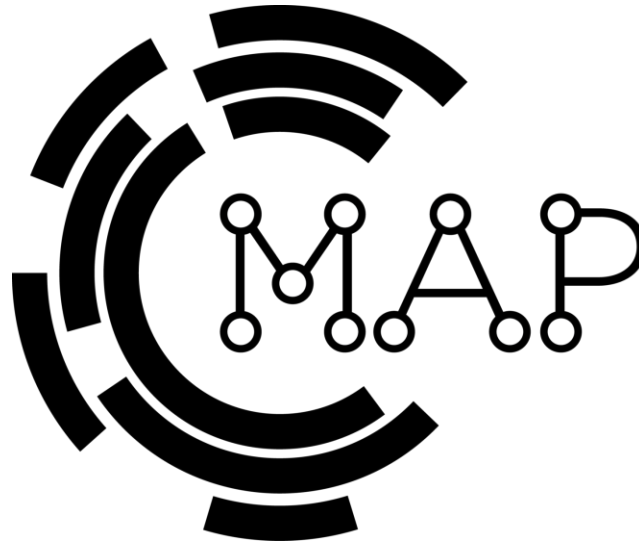
Scale



progress bar



New Technology



Gather



200 members globally

varianteffect.org

Join Us!



BBI Advanced Technology Lab

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Roshella Gomes
Saskia Iliscin
Mai Le
Aishwarya Gogate
Hannah Pliner
Brent Ewing
Lilu Martin

Flu BATs

Peter Han
Shari Cho
Melissa Truong
Sadie van den Bogaerde
Brian Pfau
Jordan Ospahl
Evan McDermot
Sarah Heidl

Luis Gamboa
Eloise Santa Cruz
Lauren Huynh
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Ruben Crew
Leslie Rodriguez
Sabrina Best
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Jeremy Stone

Mutant BATs

Ian Hill
Andrej Patoski
Nahum Smith
Kara de Leon

Starita lab

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Mark Reider
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Casey Hudlow

Noun project

Funding

