Improving Diagnoses with the Awesome Power of Yeast Genetics

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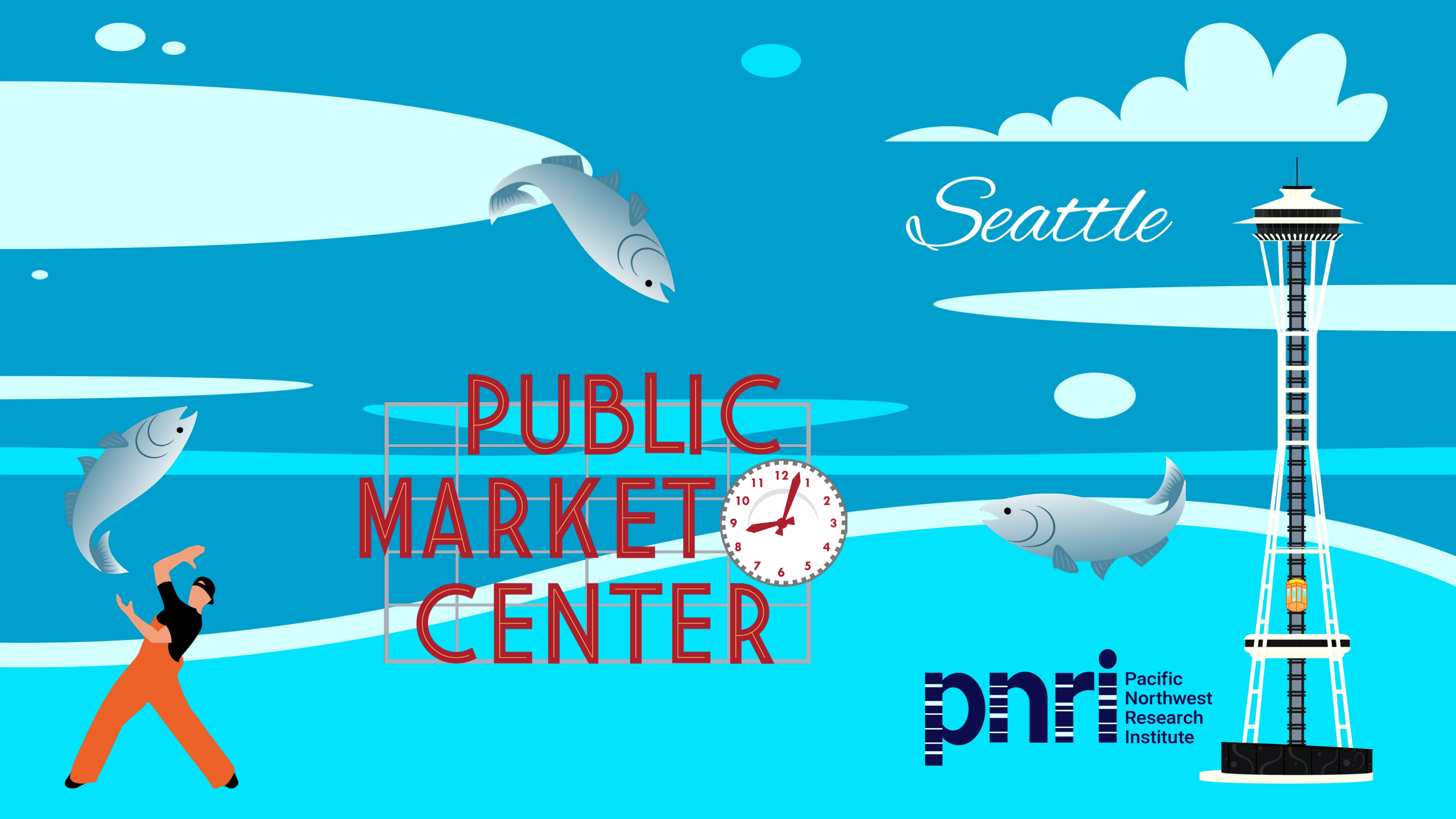
https://pnri.org/dudley-lab/

pnri Pacific Northwest Research Institute

My lab receives sponsored research funding from Moderna, a company that is developing therapeutics for OTC deficiency. Moderna did not fund any of the research that will be presented in this seminar.

I am a Scientific Advisor with a financial interest in FenoLogica Biosciences.

Who are we and how did we start doing urea cycle disorder research?


Seattle
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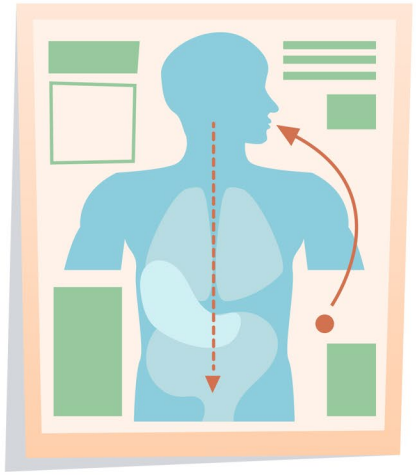
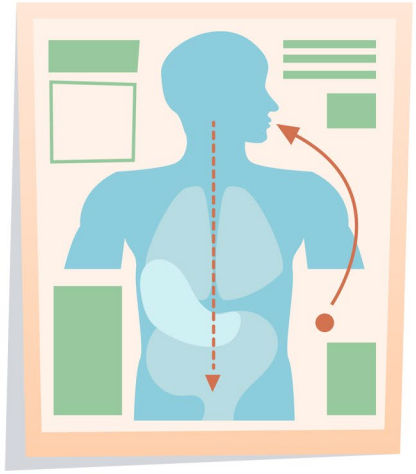
What kind of research do we do?

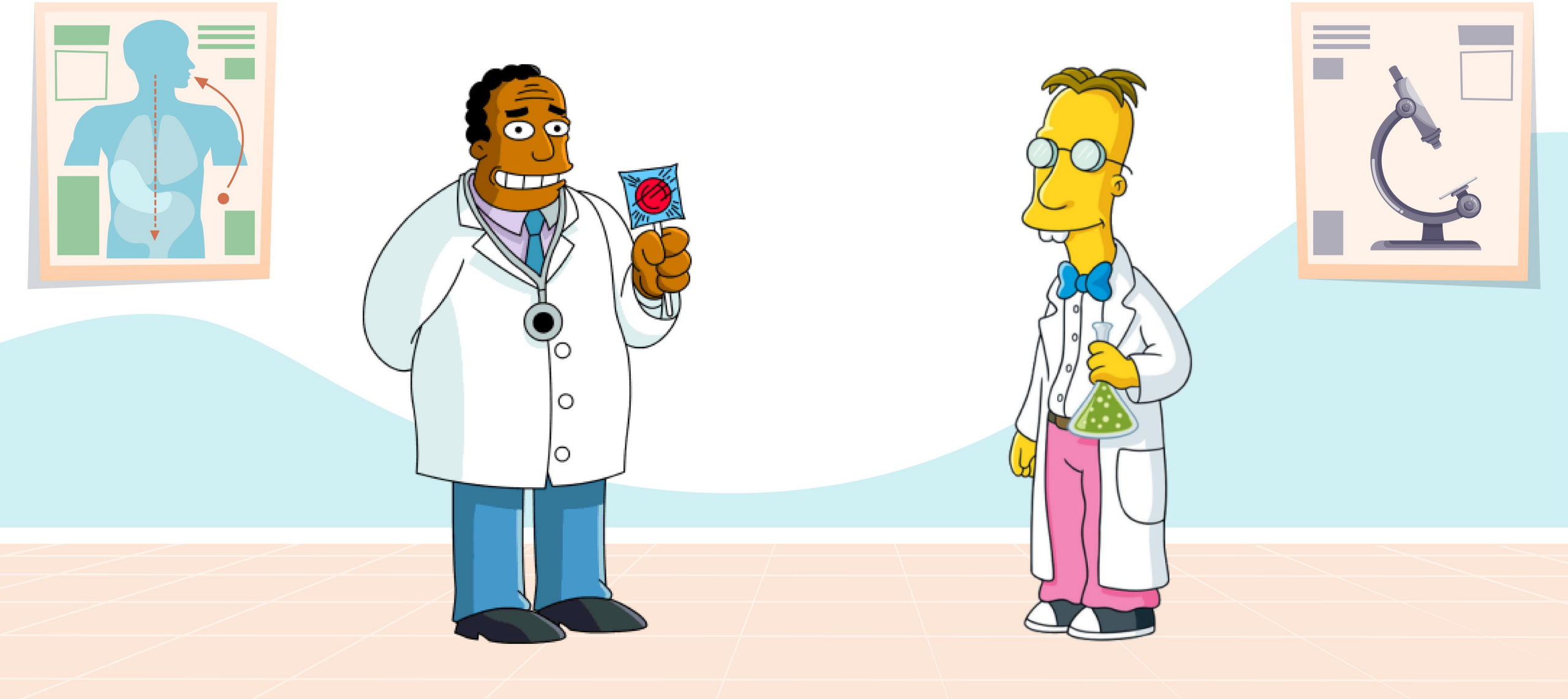


Doctors, patients, and families who participate in clinical research



Thank you!

Yeah, we're that kind of scientist



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Aimée Dudley, Ph.D.

Russell Lo

Michelle Tang, Ph.D.

Gareth Cromie, Ph.D.

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Gareth Cromie, Ph.D.

Children's National Hospital

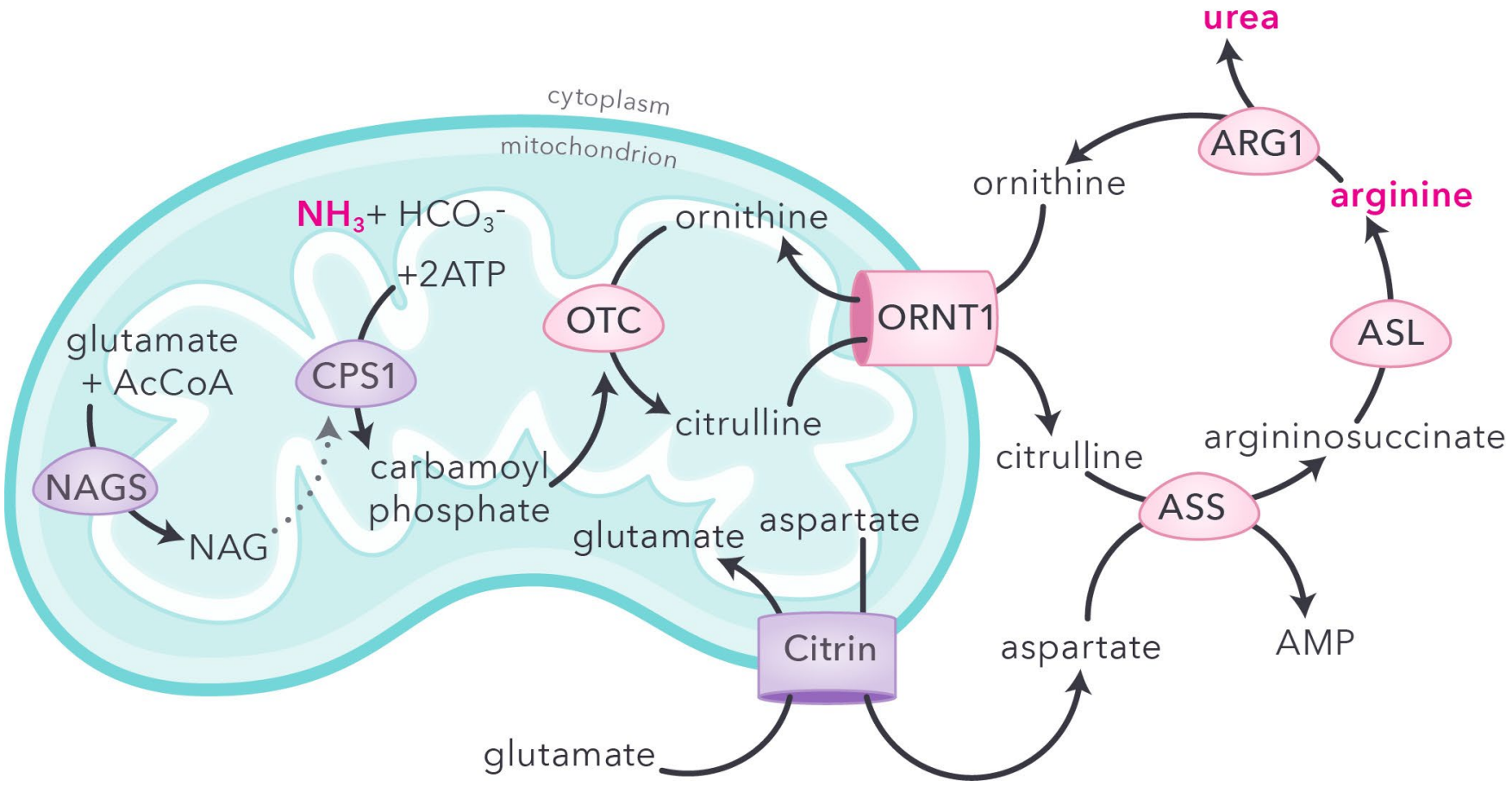
Andrea Gropman, M.D.

Nicholas Ah Mew, M.D.

Ljubica Caldovic, Ph.D.

Hiroki Morizono, Ph.D.

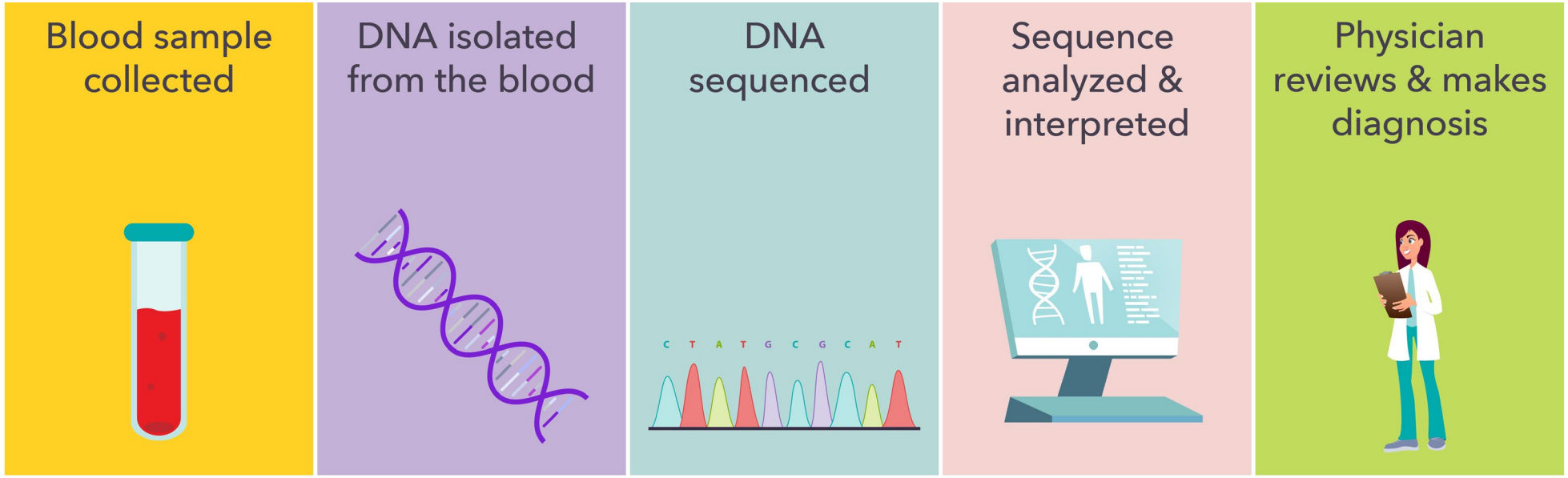
OTC is the example… more (in pink) coming soon!



How can genetics give faster and more informative diagnoses?

Let’s first talk a little about genetics…

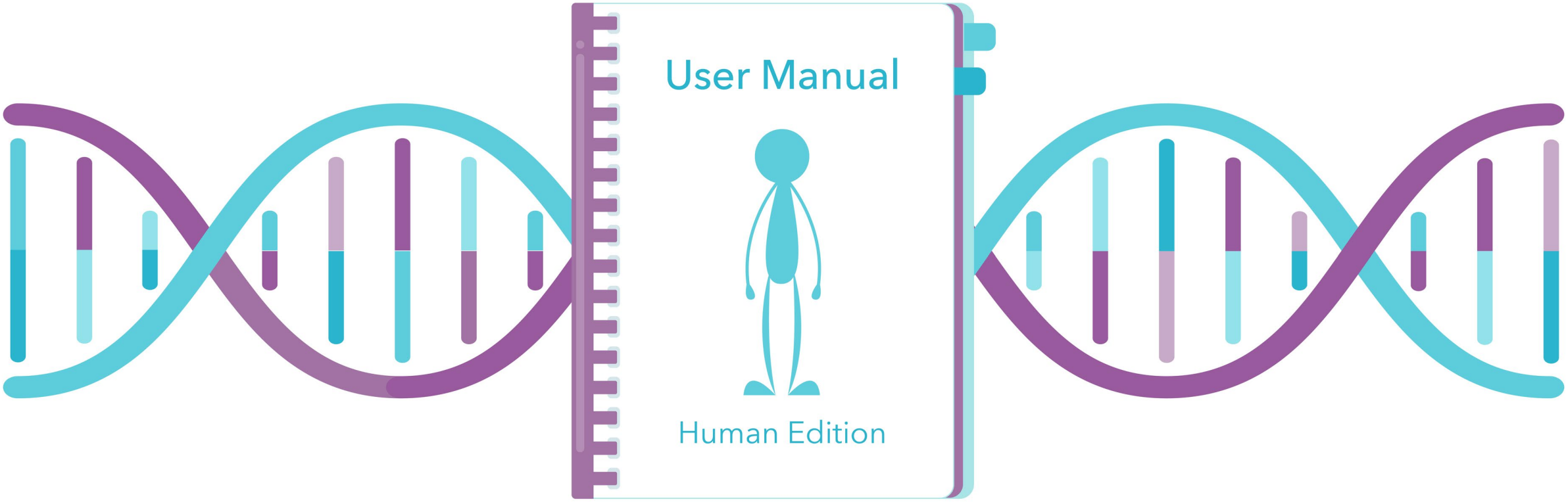
Genetic diseases can be diagnosed by DNA sequencing



New DNA sequencing technologies can:

- shorten diagnostic odysseys
- rapidly diagnose sick newborns
- expand newborn screening
- provide a non-invasive prenatal test (from maternal blood)

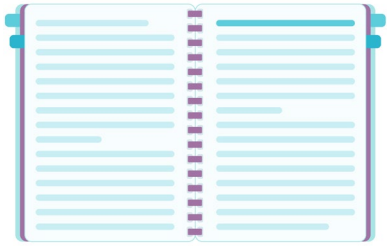
A few things to know about your DNA



Each of our genomes is like a really long book of ~6 billion (GATC) letters.
Think of it as an instruction manual for how to build and operate a human.

The sequence of a gene is like a sentence in a book

wildtype



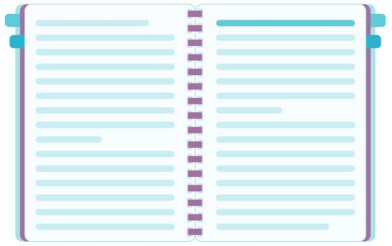
A cat sat on my pillow.

ATG CAT GGT CCC CAC GTT TAA

Let’s pretend that this sequence is the gene that makes the working version of OTC.

Benign sequence changes do not cause disease

wildtype



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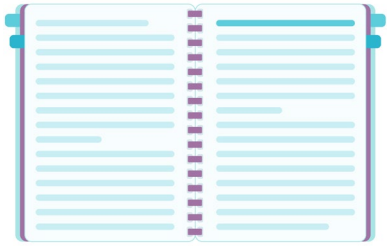
benign

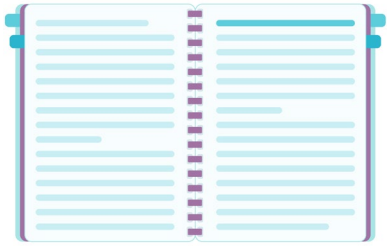


The cat sat on my pillow.

TTG CAT GGT CCC CAC GTT TAA

Pathogenic sequence changes have the potential to cause disease

wildtype



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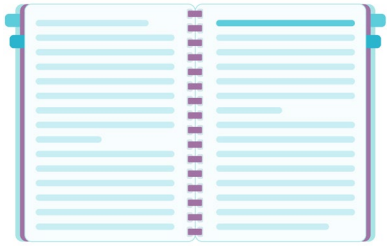
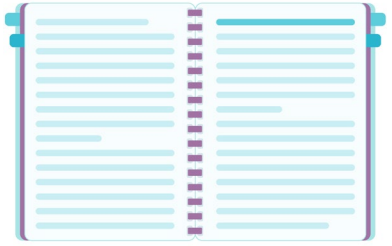
benign



The cat sat on my pillow.

TTG CAT GGT CCC CAC GTT TAA

pathogenic

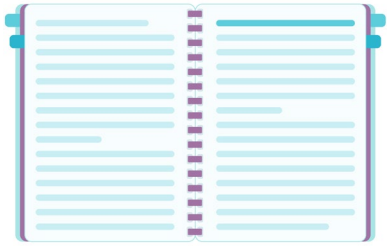


A rat sat on my pillow.

ATG CCT GGT CCC CAC GTT TAA

Most sequence changes are Variants of Uncertain Significance (VUS)

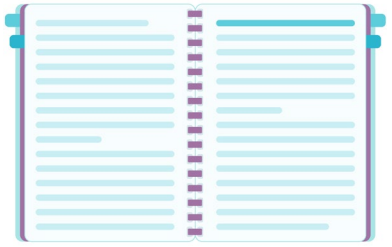
wildtype



A cat sat on my pillow.

ATG CAT GGT CCC CAC GTT TAA

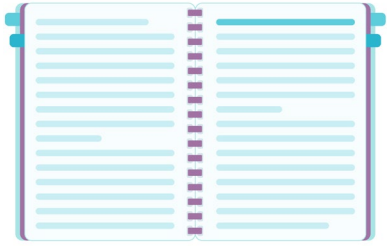
VUS



?

ATG CAT GGT CC**C** CAC GTT TAA

VUS



?

ATG CAT **G**GT CCC CAC GTT TAA

VUS cannot be used to diagnose or treat people

Good news! You don’t need to remember any of those terms.

What's important:

- some DNA changes are harmless
- some can cause disease
- but for most we just don't know

The scale of this problem is enormous!

60 million of the type of variants
that my lab studies could arise
in the human population.

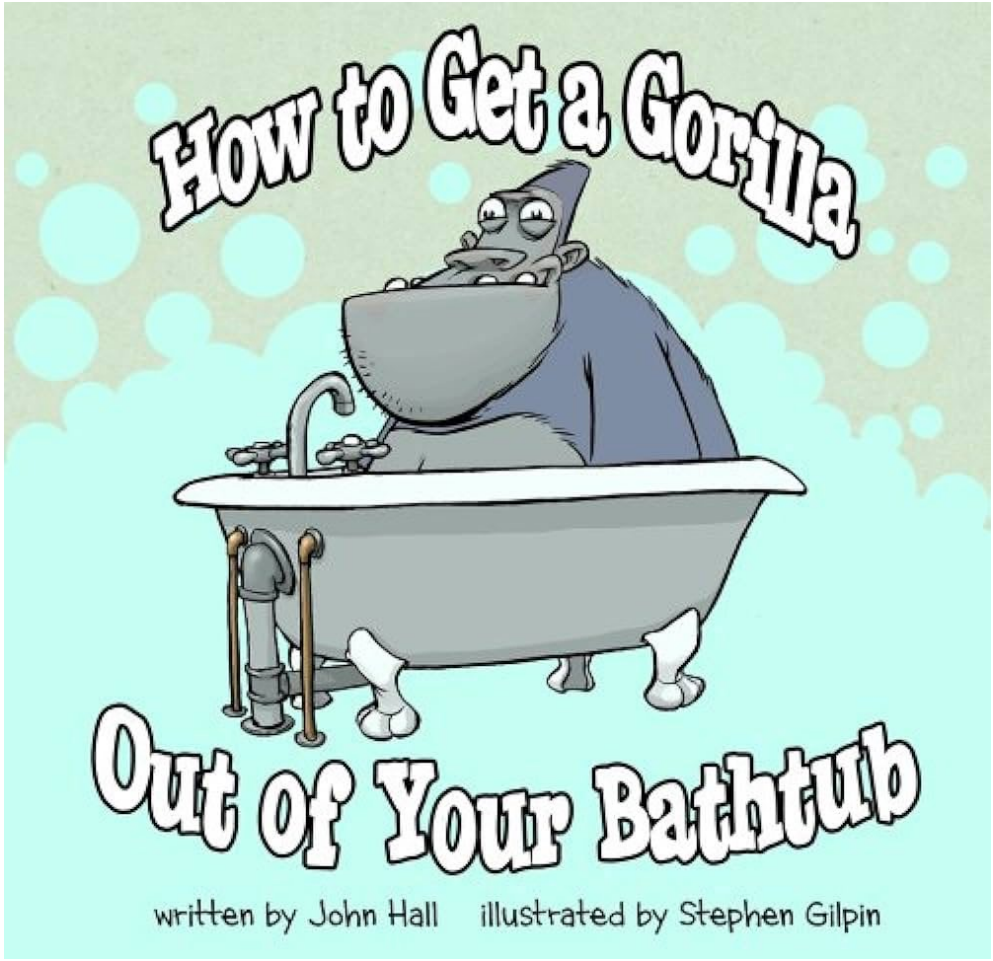
59.9 million are currently VUS.

“My, my but you do have a problem- a BIG problem!”

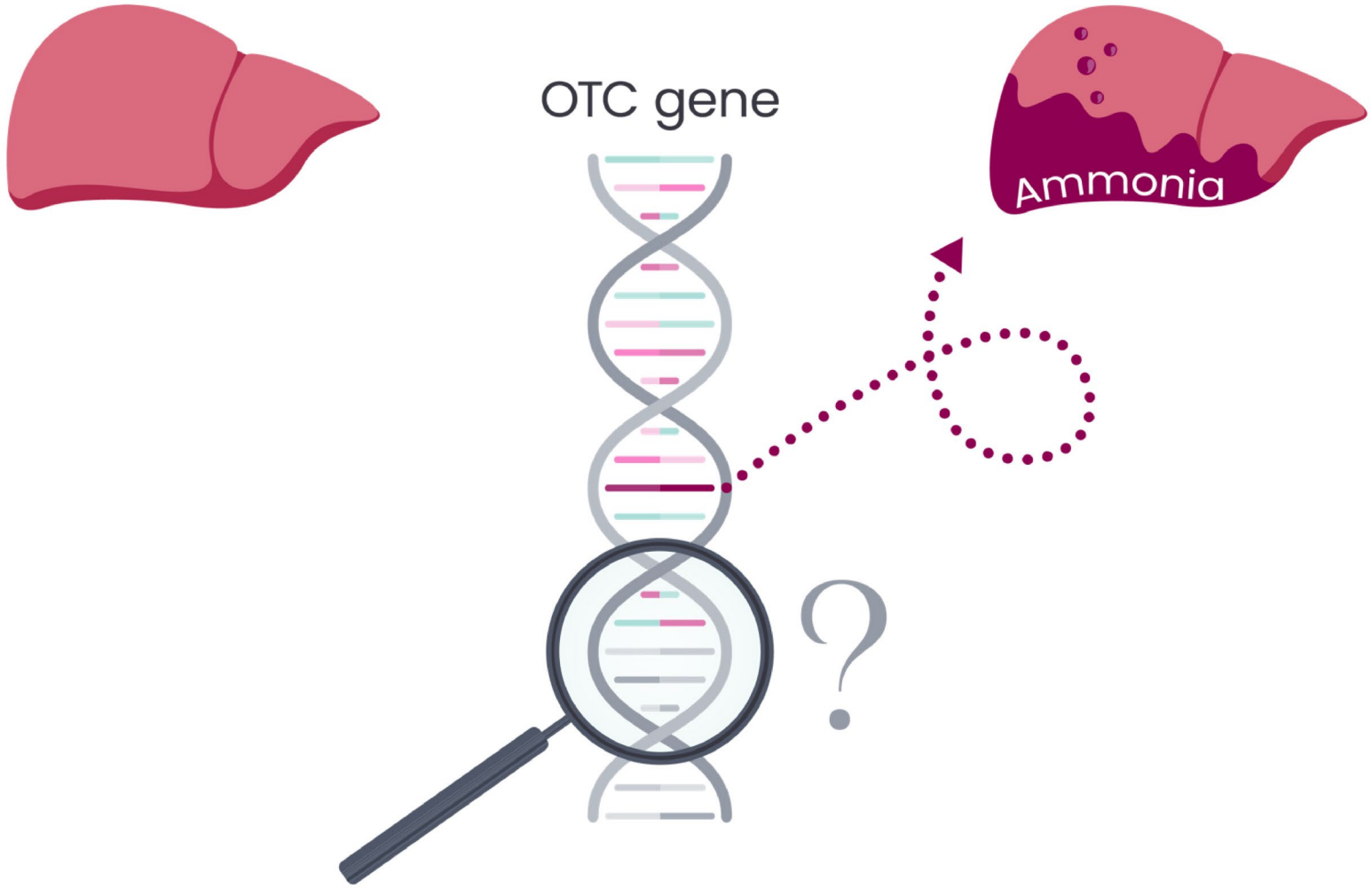
- John Hall, *How to Get a Gorilla Out of Your Bathtub*

60 million of the type of variants that my lab studies could arise in the human population.

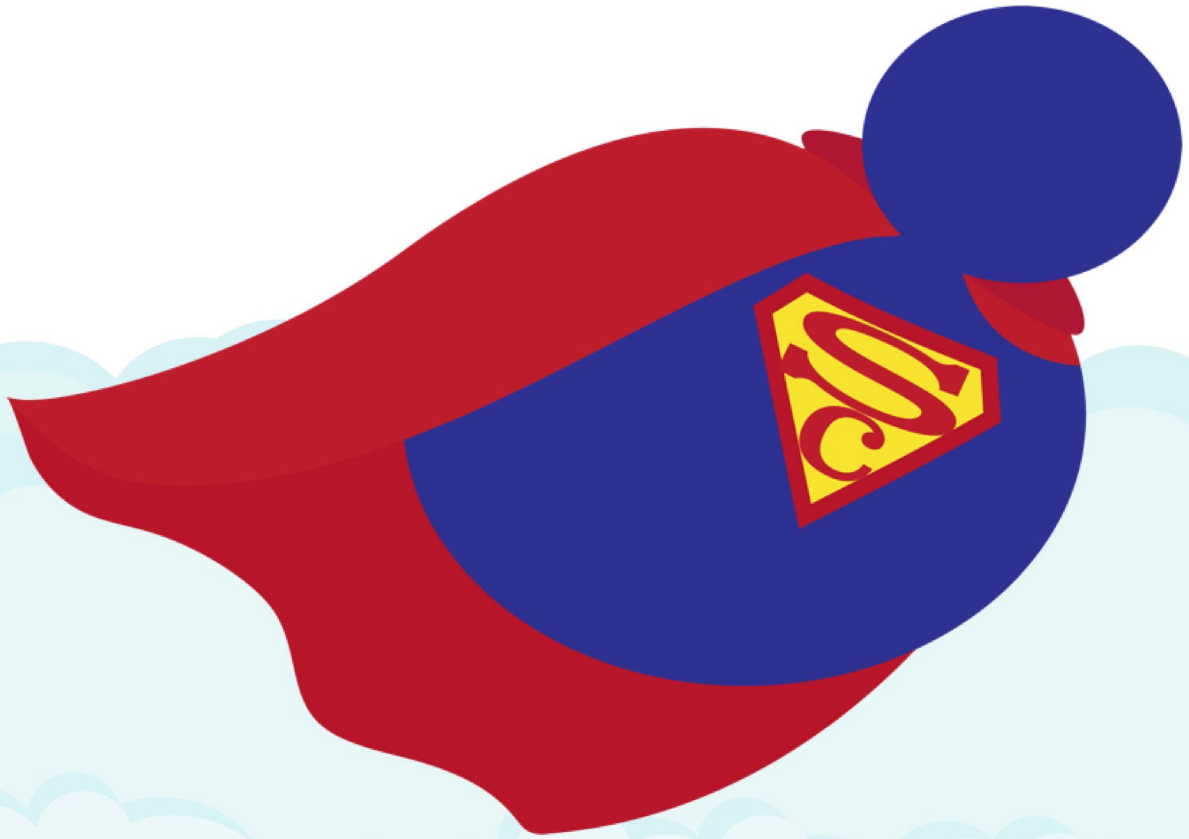
59.9 million are currently VUS.



Which of the 2,000 OTC variants are likely to cause disease?



We can test them all, but not in humans

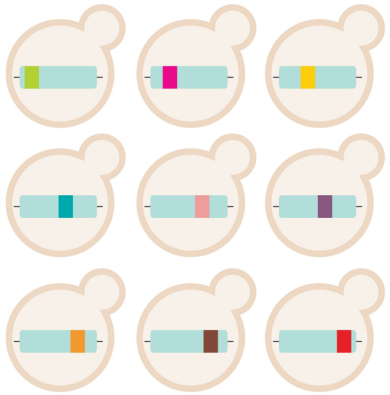


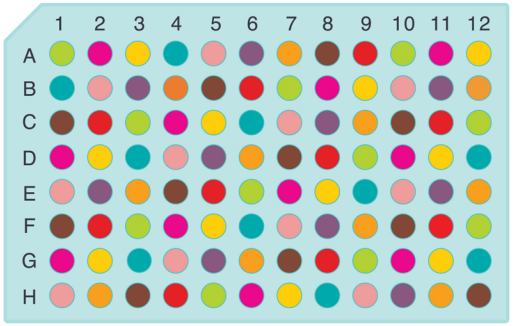
The Awesome Power of Yeast Genetics

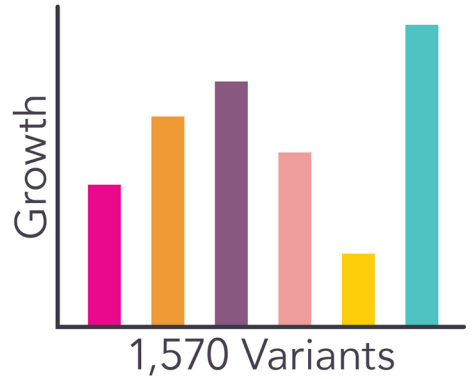
Yeast is a powerful model organism

- We can do experiments faster, cheaper, and more easily than in other systems
- Many biological processes that are important in human cells function the same way in yeast cells, including the urea cycle!

How did Russell test 1,570 variants in OTC?







Synthetic OTC variant library

Construct variant strains

Measure growth of yeast variant strains

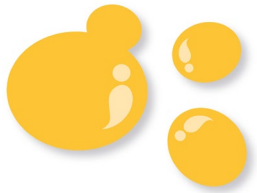
Analyze growth data

Comparing activity in yeast to disease presentation in people

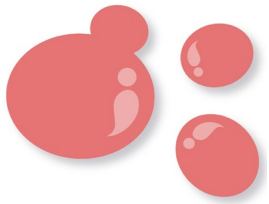
Yeast activity

> 90%
(high)

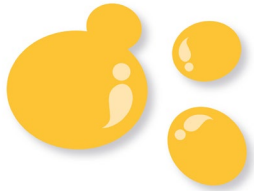
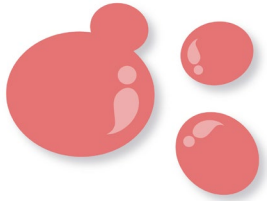
5%-90%
(medium)



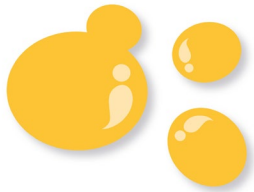
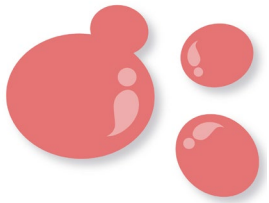
< 5%
(low)



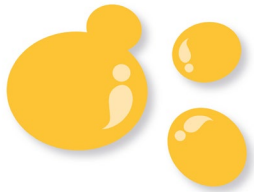
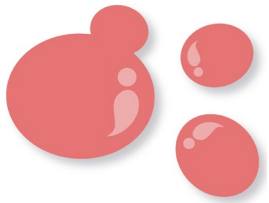
Most early onset male patients have very low activity variants

Yeast activity	Neonatal male presentation
> 90% (high) 	1%
5%-90% (medium) 	29%
< 5% (low) 	70%

Most late onset males have low to medium activity variants

Yeast activity	Neonatal male presentation	Late male presentation
> 90% (high) 	1%	2%
5%-90% (medium) 	29%	75%
< 5% (low) 	70%	23%

Most symptomatic females have very low activity variants

Yeast activity	Neonatal male presentation	Late male presentation	Female presentation
> 90% (high) 	1%	2%	0%
5%-90% (medium) 	29%	75%	23%
< 5% (low) 	70%	23%	77%

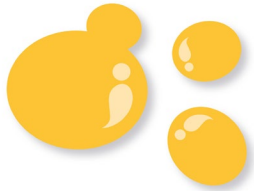
What does this say about a person's genetic risk?

Yeast activity

> 90% (high)

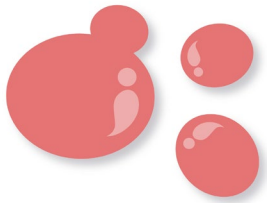
Do not expect disease in males or females

5%-90% (medium)



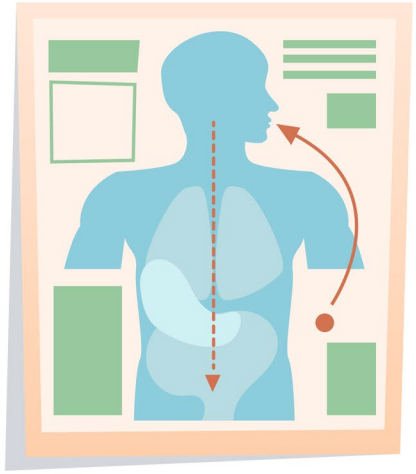
Consistent with late onset disease in males. Female presentation is possible, but less likely

< 5% (low)



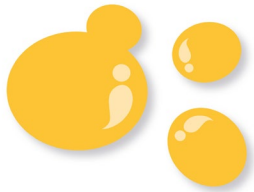
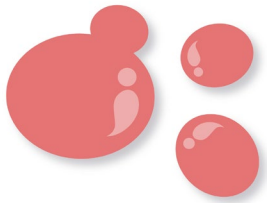
Consistent with neonatal onset disease in males and female presentation

A very important point:



Functional information about genetic variants is only one piece of information that doctors, patients, and families can use to make decisions.

1,356 of the variants in Russell's study do not have patient data

Yeast activity			
> 90% (high)		Do not expect disease in males or females	270 (18%) variants
5%-90% (medium)		Consistent with late onset disease in males. Female presentation is possible, but less likely	864 (55%) variants
< 5% (low)		Consistent with neonatal onset disease in males and female presentation	430 (27%) variants

What does this mean?

The variants that are most difficult for geneticists are the ones no one has seen before.

There are a lot of them, and a huge number have the potential to cause the most severe form of the disease.

National Urea Cycle Disorders Foundation

Thank you!

Patients and families that participate in clinical research

PNRI
Gareth A. Cromie, Ph.D.
Russell S. Lo
Michelle Tang, Ph.D.
Martin S. Timour
Julee A. Ashmead
Kevin Tang
Katherine Owens, Ph.D.

Children's National Hospital
Hiroki Morizono, Ph.D.
Ljubica Caldovic, Ph.D.
Nicholas Ah Mew, M.D.
Andrea Gropman, M.D.

University of Washington
J. Nathan Kutz, Ph.D.

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