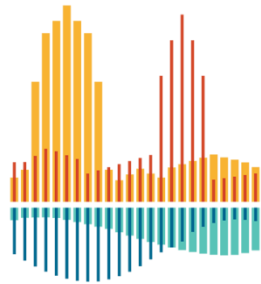


DIVERSITY AND DISEASE: POTENTIAL APPLICATIONS OF *APOL1* IN KIDNEY DISEASE RISK PREDICTION AND KIDNEY TRANSPLANTATION



INSTITUTE FOR
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BIOLOGY

October 13, 2018

Dana C. Crawford, PhD

Associate Professor

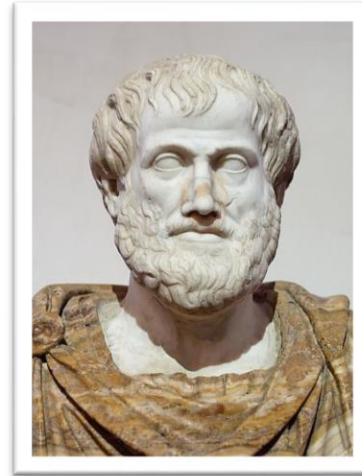
Population and Quantitative Health Sciences

Institute for Computational Biology

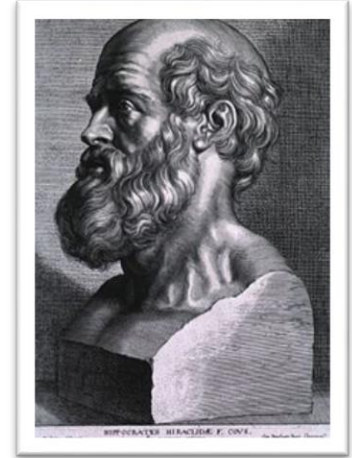
GENETICS AND MEDICINE

A HISTORY

Concepts of heredity

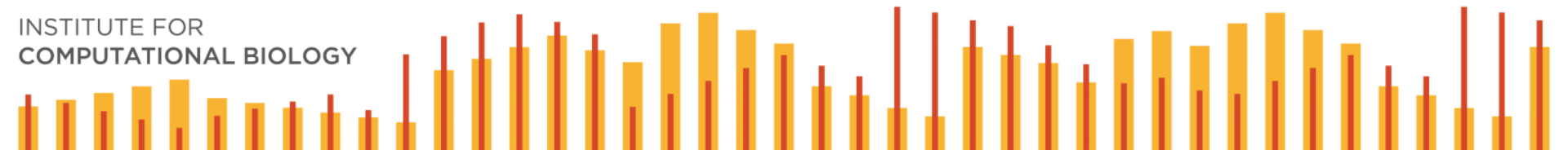


Aristotle



Hippocrates

<https://en.wikipedia.org>



GENETICS AND MEDICINE

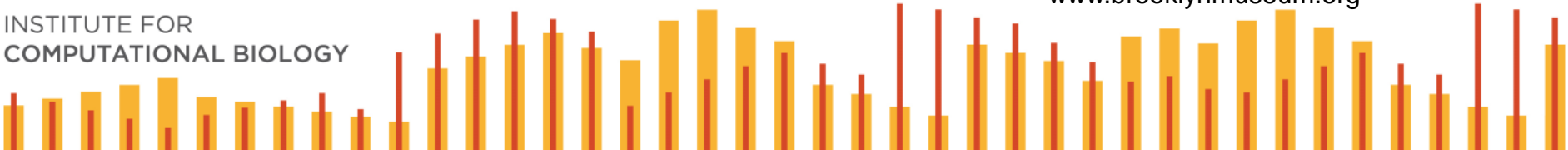
A HISTORY



<https://phys.org/news/2017-08-genome-sequencing-maize-highlands-thousands.html>



She-we-na (Zuni Pueblo)
Kachina Doll (Pakwen [Clown])
www.brooklynmuseum.org



GENETICS, THE BASICS

~20,000 genes!

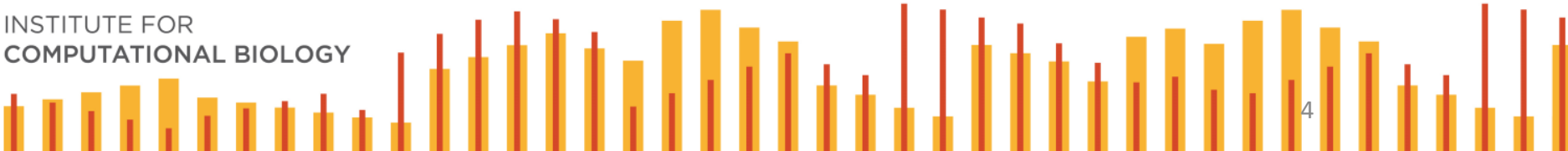
A A T C G T
A A C C G T

Single Nucleotide Polymorphism (SNP)

mitochondri

www.23andme.com

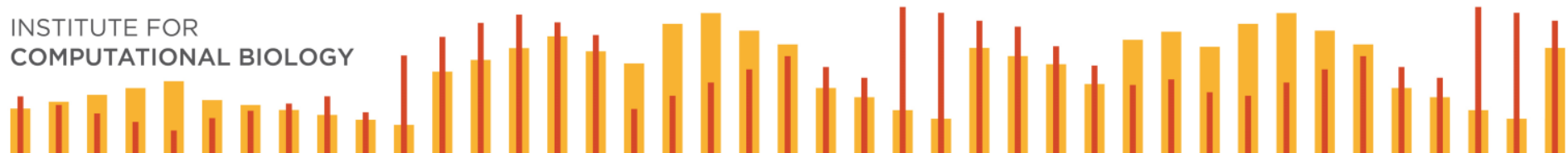
INSTITUTE FOR COMPUTATIONAL BIOLOGY



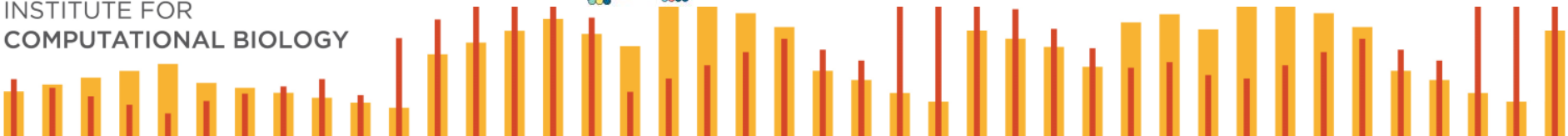
AGE OF GENOMIC DISCOVERY



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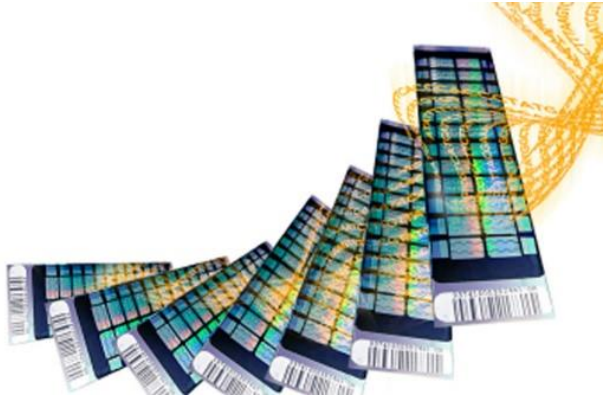


GWAS as of 9/15:
3,567 publications
71,673 associated
SNPs (10^{-5})



GENOTYPING AND SEQUENCING

POPULATIONS AND PATIENTS

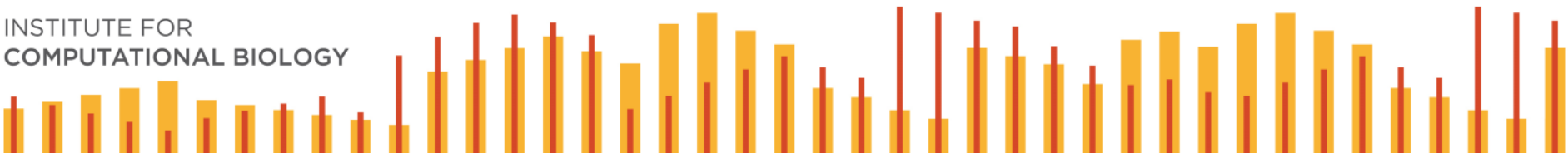


Illumina whole-genome arrays

Limited to *known* variants

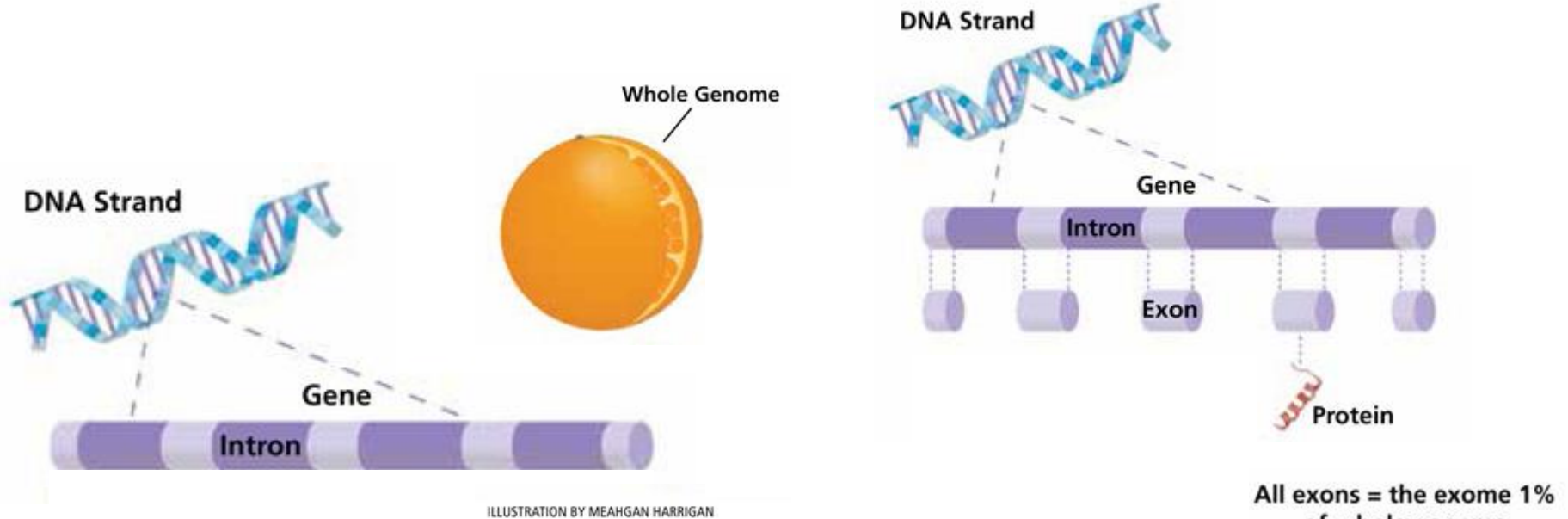
Mostly common variants

European bias*

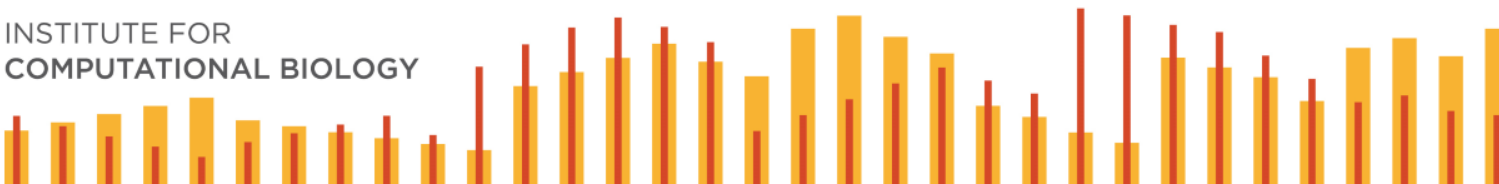


GENOTYPING AND SEQUENCING

POPULATIONS AND PATIENTS



All exons = the exome 1% of whole genome



GENETICS AND PRECISION MEDICINE

Diagnosis

Risk prediction

Treatment



Right Patient

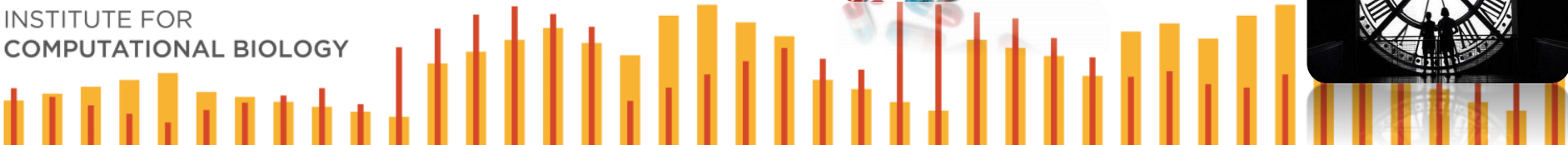


Right Drug

Right Dose



First Time



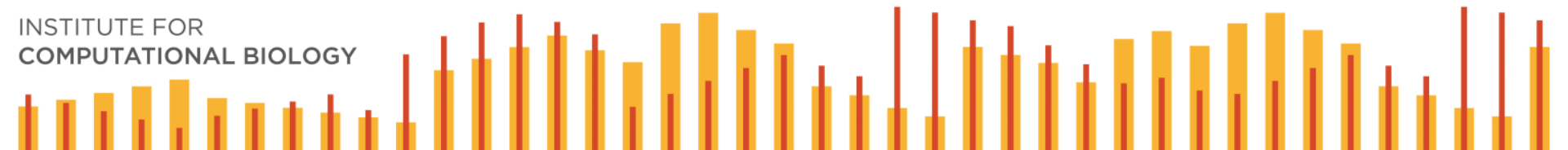
PRECISION MEDICINE

A NEW INITIATIVE



Lancet 385:2448-2449 (2015)

- Launched January 20, 2015
- 2016 budget of \$215M



PRECISION MEDICINE

A NEW INITIATIVE

Aims to ascertain

- At least 1 million US residents
- Representative of the population

Willing to provide

- Biospecimens
- Health data (EHRs)
- Lifestyle/behavior data
- All of the above, longitudinally

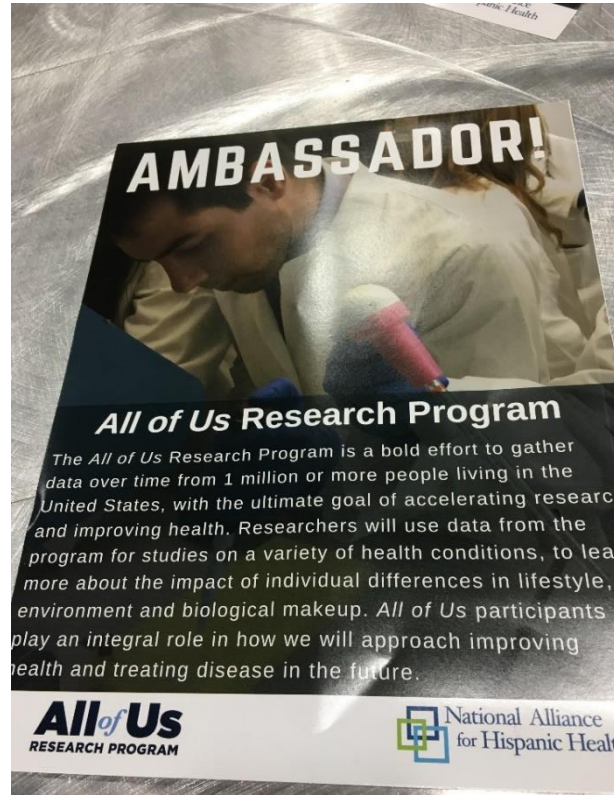
(Photo credit: Dr. Janina Jeff at the 2017 New Balance Bronx 10 Mile)

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PRECISION MEDICINE A NEW INITIATIVE

Emphasis on
participant diversity



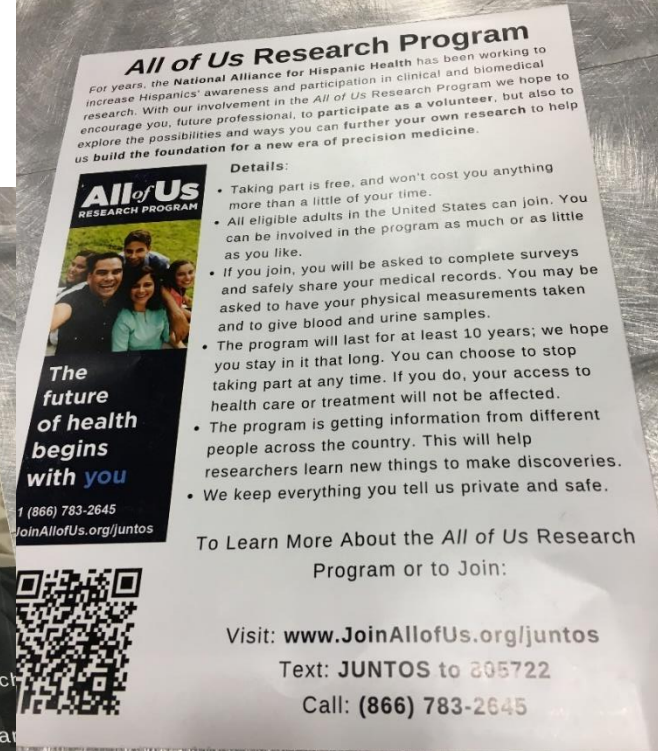
AMBASSADOR!

All of Us Research Program

The *All of Us* Research Program is a bold effort to gather data over time from 1 million or more people living in the United States, with the ultimate goal of accelerating research and improving health. Researchers will use data from the program for studies on a variety of health conditions, to learn more about the impact of individual differences in lifestyle, environment and biological makeup. *All of Us* participants play an integral role in how we will approach improving health and treating disease in the future.

All of Us
RESEARCH PROGRAM

National Alliance
for Hispanic Health



All of Us Research Program

For years, the National Alliance for Hispanic Health has been working to increase Hispanics' awareness and participation in clinical and biomedical research. With our involvement in the *All of Us* Research Program we hope to encourage you, future professional, to participate as a volunteer, but also to explore the possibilities and ways you can further your own research to help us build the foundation for a new era of precision medicine.

Details:

- Taking part is free, and won't cost you anything more than a little of your time.
- All eligible adults in the United States can join. You can be involved in the program as much or as little as you like.
- If you join, you will be asked to complete surveys and safely share your medical records. You may be asked to have your physical measurements taken and to give blood and urine samples.
- The program will last for at least 10 years; we hope you stay in it that long. You can choose to stop taking part at any time. If you do, your access to health care or treatment will not be affected.
- The program is getting information from different people across the country. This will help researchers learn new things to make discoveries.
- We keep everything you tell us private and safe.

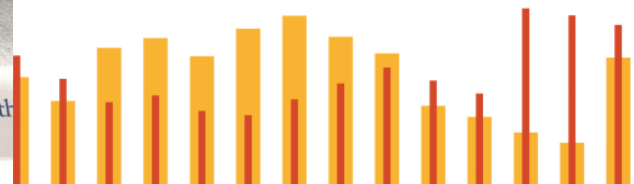

To Learn More About the *All of Us* Research Program or to Join:

Visit: www.JoinAllofUs.org/juntos
Text: **JUNTOS** to 205722
Call: **(866) 783-2645**

All of Us
RESEARCH PROGRAM

The future of health begins with you

1 (866) 783-2645
JoinAllofUs.org/juntos



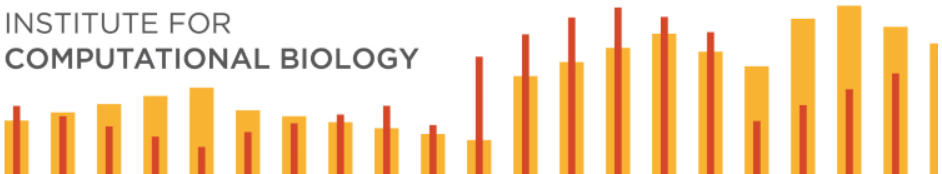
KIDNEY PRECISION MEDICINE PROJECT

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)



- Acute kidney injury (AKI)







- Chronic kidney disease (CKD)



CKD

DIAGNOSIS

- Requires a blood test
- Estimates filtration rate

STAGES OF CHRONIC KIDNEY DISEASE		GFR*	% OF KIDNEY FUNCTION
Stage 1	Kidney damage with normal kidney function	90 or higher	 90-100%
Stage 2	Kidney damage with mild loss of kidney function	89 to 60	 89-60%
Stage 3a	Mild to moderate loss of kidney function	59 to 45	 59-45%
Stage 3b	Moderate to severe loss of kidney function	44 to 30	 44-30%
Stage 4	Severe loss of kidney function	29 to 15	 29-15%
Stage 5	Kidney failure	Less than 15	 Less than 15%



CKD IS COMMON

https://www.cdc.gov/kidneydisease/pdf/kidney_factsheet.pdf



More than **1** in **7**

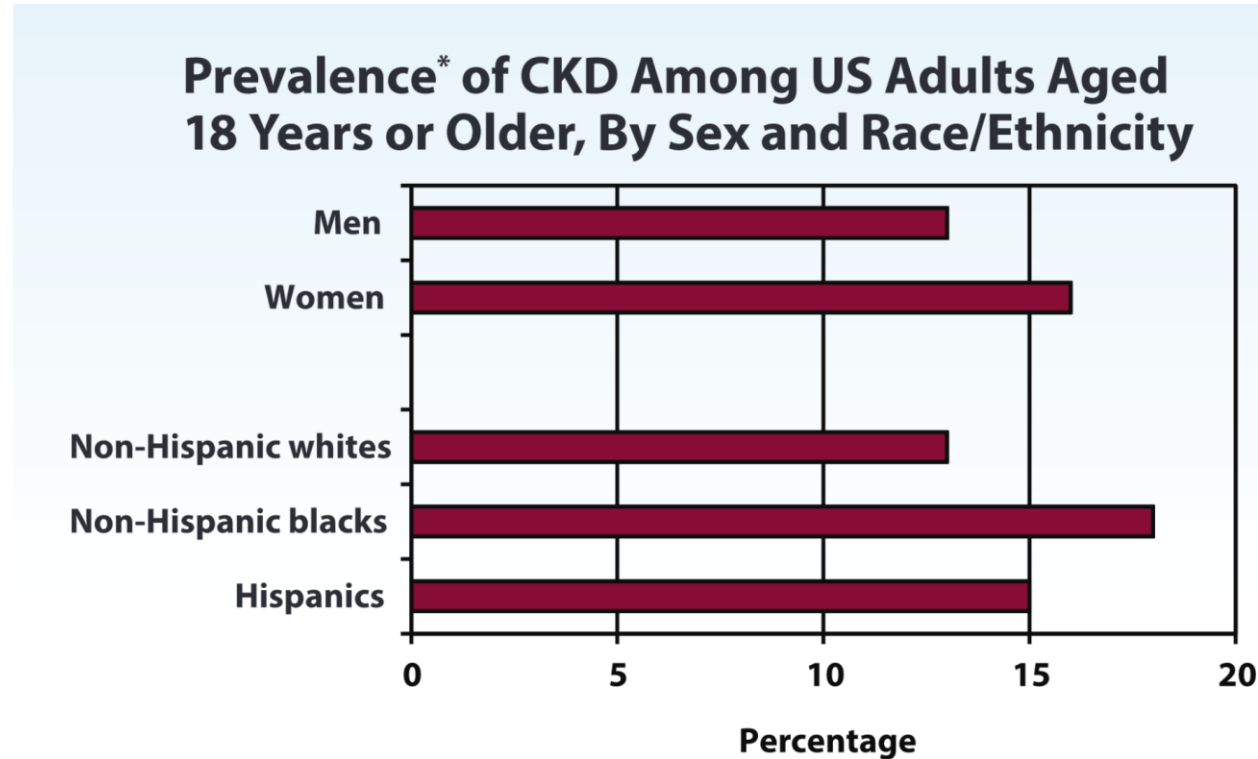
15% of US adults are estimated to have chronic kidney disease—that is about 30 million people.

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CKD IS MOST COMMON AMONG AFRICAN AMERICANS

https://www.cdc.gov/kidneydisease/pdf/kidney_factsheet.pdf



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CKD HAS KNOWN RISK FACTORS



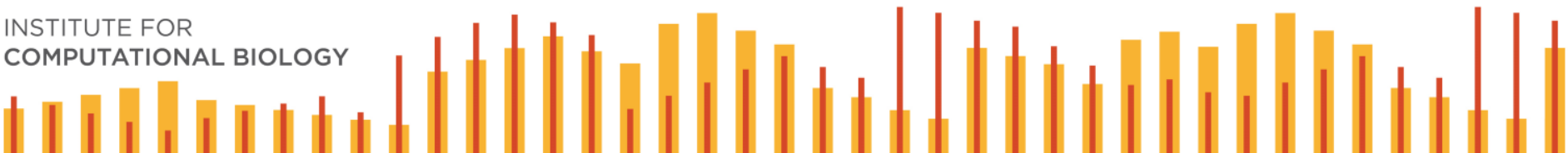
Age

Female

Type 2 diabetes

Hypertension

African-descent



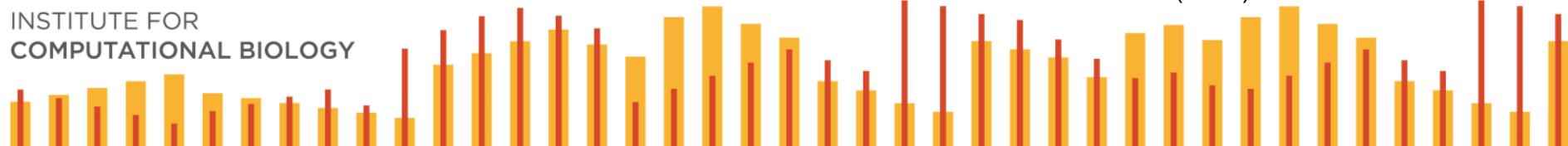
GENETICS AND CKD HEALTH DISPARITY

Common *APOL1* missense variants are associated with end-stage renal disease

rs number	Gene	Type	Chr22 location ^a	Alleles ^b	YRI risk frequency ^c (%)	CEU risk frequency (%)	Mode ^d	OR	<i>p</i> value
rs73885319 ^e	<i>APOL1</i>	exon 5 S342G missense	34,991,852	A/G	46	0	Recessive	6.7	2.71E-06
							Additive	2.22	2.38E-08
							Dominant	2.23	3.11E-06
rs60910145	<i>APOL1</i>	exon 5 I384M missense	34,991,980	T/G	45	0	Recessive	6.74	9.89E-06
							Additive	2.28	3.00E-08
							Dominant	2.32	4.75E-06

*Accounts for up to 70% of observed disparity

Tzur et (2010) *Hum Genet* 128:345-350



APOLIPOPROTEIN L1 (APOL1) RENAL RISK VARIANTS

Limou et al (2014) *Advances in Chronic Kidney Disease* 21:426-433



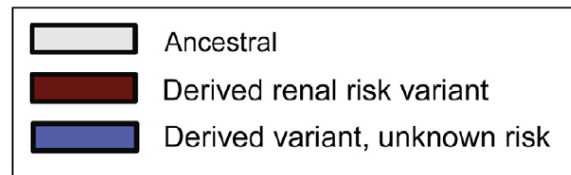
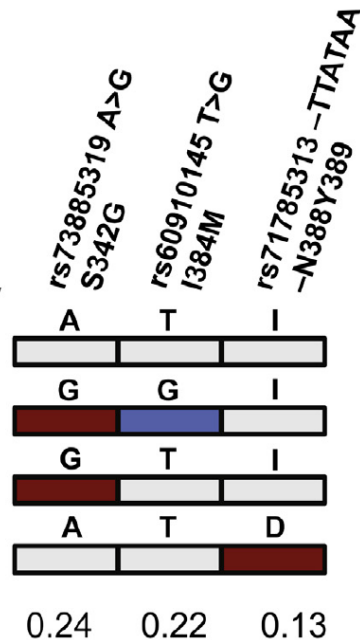
Haplotype: Frequency

G0 0.63

G1^{GM} 0.22

G1^{GI} 0.02

G2 0.13



Risk allele count: Frequency (n = 383)

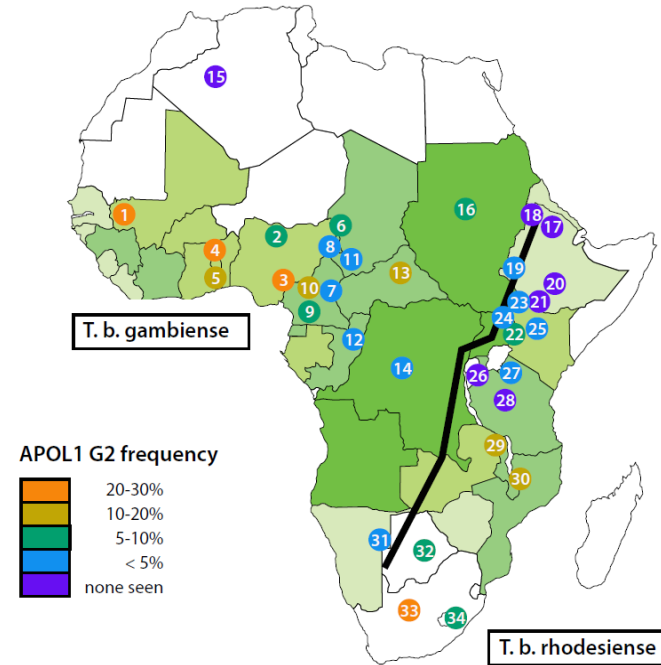
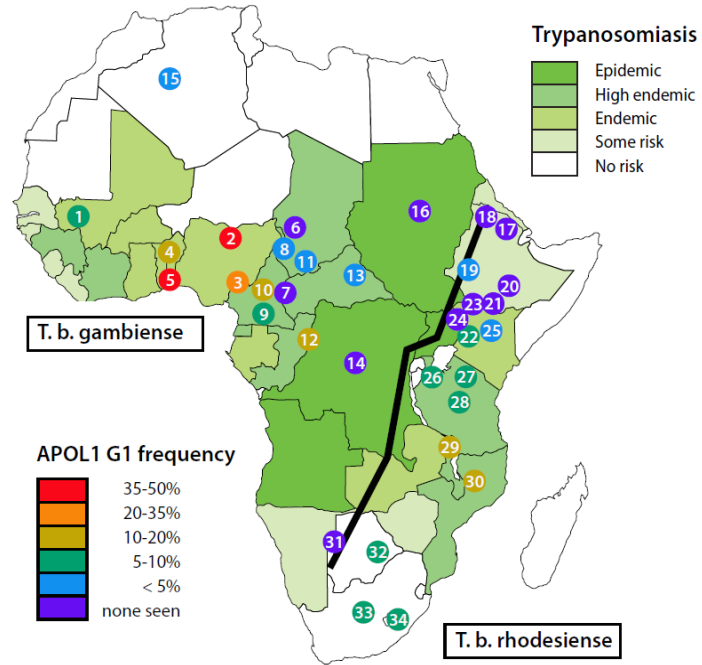
0 RA	40%
1 RA	46%
2 RA	14%

0.24 0.22 0.13

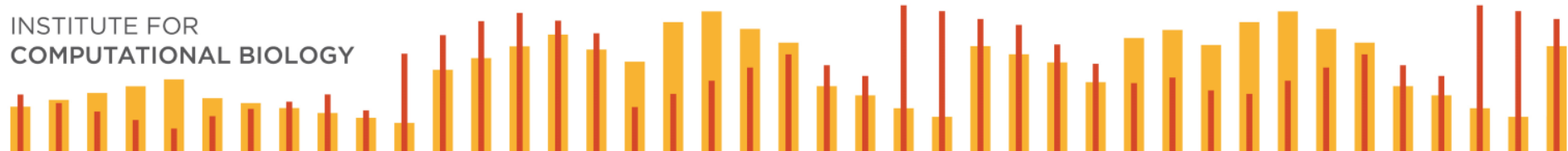
Variant frequency



APOL1 AND NATURAL SELECTION



Limou et al (2014) *Advances in Chronic Kidney Disease* 21:426-433



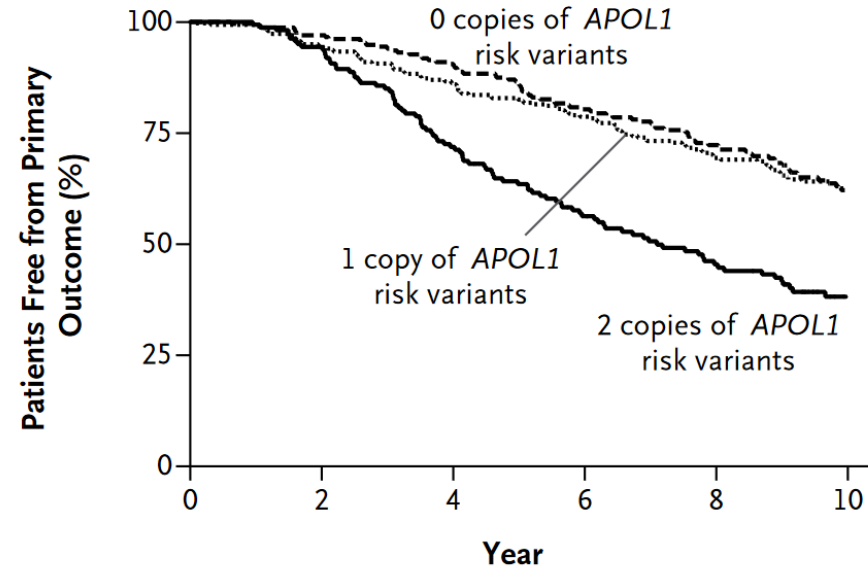
APOL1 AND PRECISION MEDICINE

Genetic testing for risk prediction?

- Lifetime risk of CKD
- Maybe predicts progression of disease

Parsa et al (2013) *NEJM* 369:2183-2196

APOL1 Risk Variants

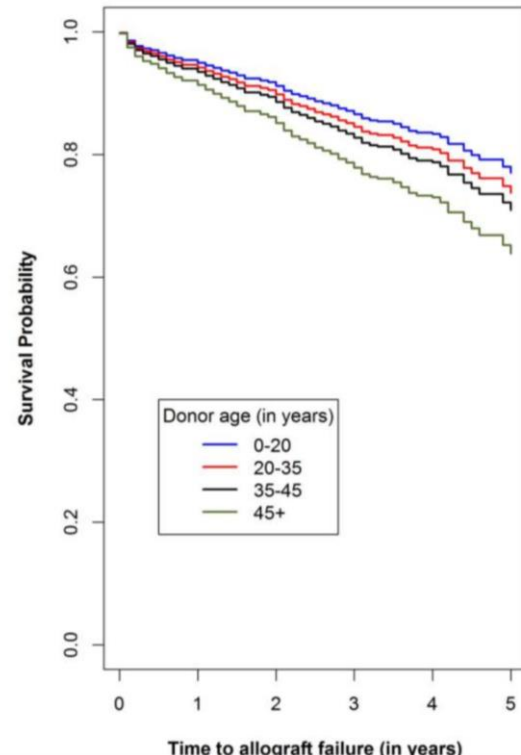
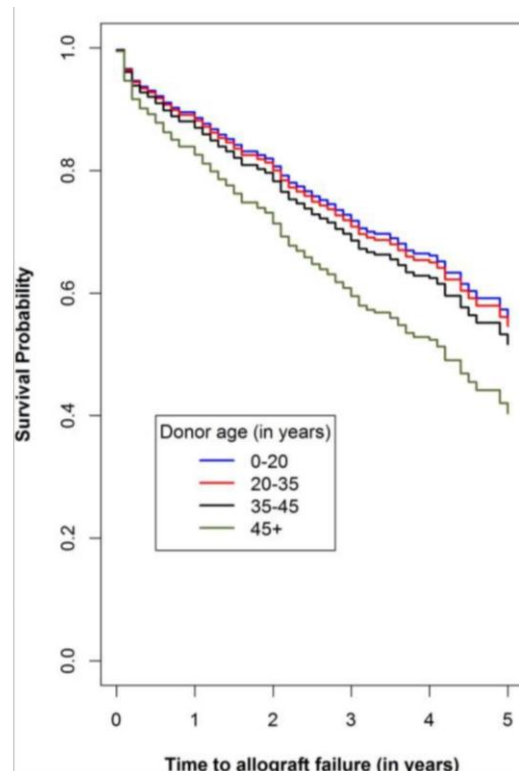


APOL1 AND PRECISION MEDICINE

Genetic testing for kidney transplants?

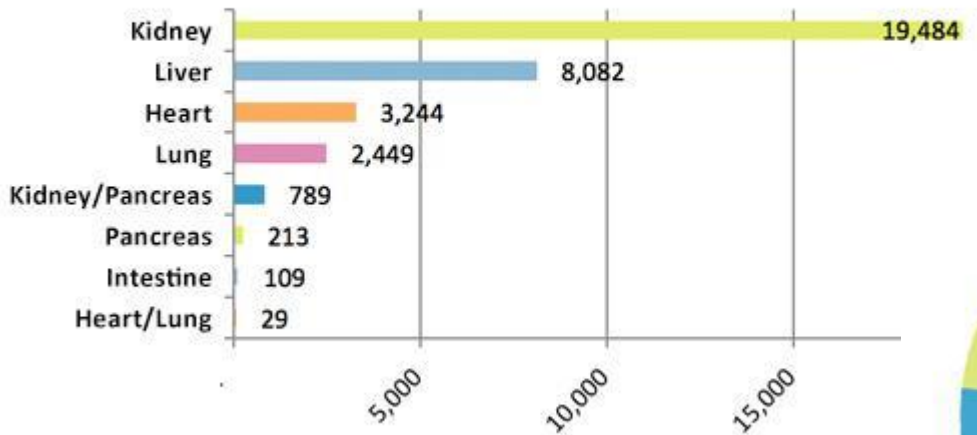
- Carrier donors
- Donated organs

Freedman et al (2016) *Transplantation* 100:194-202



KIDNEY TRANSPLANTS

Transplants Performed in 2017 by Organ



Transplant Recipients by Ethnicity (2017)

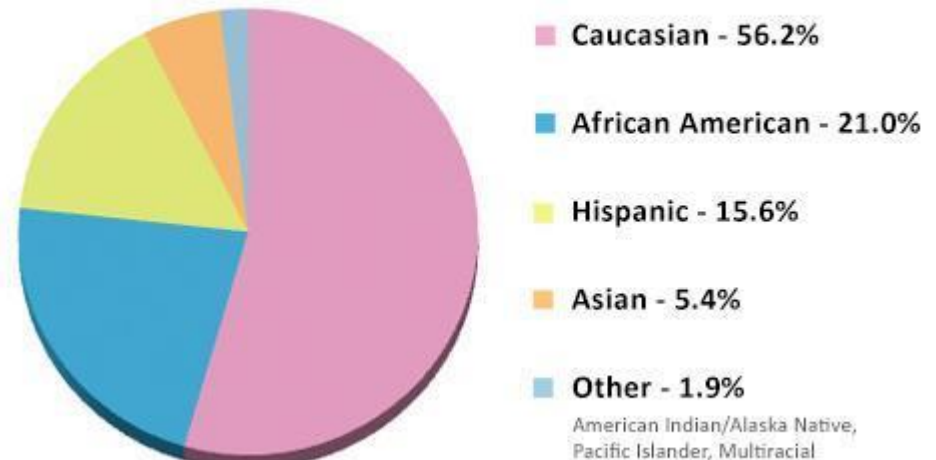


Table 1. Pros and Cons of *APOL1* Genetic Testing

Setting	Pros	Cons
Transplantation	<p>Evidence for decreased cadaveric transplant survival</p> <p>Societal benefit for transplant distribution</p> <p>Right of transplant recipient to know if living donor kidney has <i>APOL1</i> genotypes</p> <p>Living donors have a right to know whether they might be at increased risk of kidney disease, based on their <i>APOL1</i> genotype</p>	<p>No evidence of decreased transplant survival based on recipient genotype</p> <p>Individual right to know or not know the results</p> <p>No evidence that kidneys from living donors with <i>APOL1</i> high risk genotypes have decreased kidney survival</p> <p>No evidence that unilateral nephrectomy increases the risk of development of CKD or ESRD in living kidney donors.</p>
Kidney Disease Prevention	<p>Testing for <i>APOL1</i> to institute preventive measures for development of kidney disease, such as hypertension, obesity, diabetes control</p> <p>Increased risk of non-diabetic kidney ESRD</p>	<p>No evidence to suggest that preventive measures decrease the risk of development of kidney disease among those with low or high risk <i>APOL1</i> genotypes</p> <p>No general population information regarding risk of developing chronic kidney disease with one or more genotypes</p>
Screening	<p>Piece of mind in knowing test results</p>	<p>Increased anxiety, fear, and mistrust of the medical establishment, since evidence of risk is currently unknown</p>

RETURN OF RESEARCH RESULTS, A TREND



???

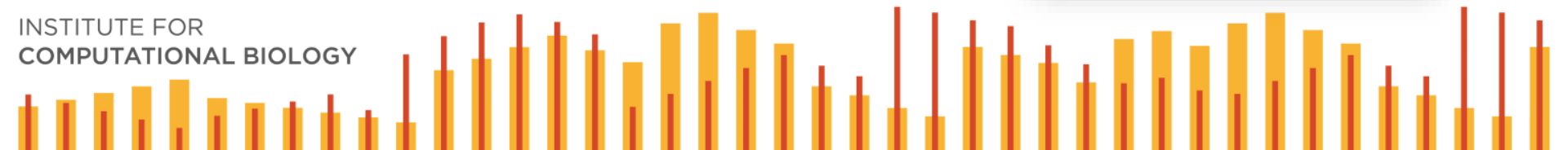
(Photo credit: Dr. Janina Jeff at the 2017 New Balance Bronx 10 Mile)

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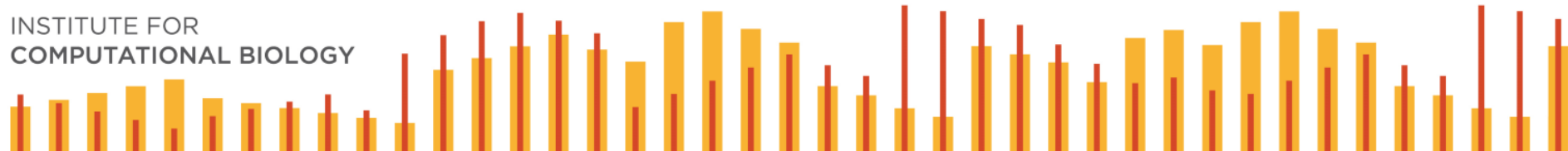
METROHEALTH/ICB PILOT STUDY (MIPs)

- Survey patients about research participation and return of results
- Ascertain participants for biospecimen collection and 'omics



	Demographic Group	Weighted N	% who said the study definitely or probably should be done	Beta	S.E.	p-value	% definitely or probably willing to participate in hypothetical biobank	Beta	S.E.	p-value
<i>Total</i>		2,601	79%				54%			
<i>Gender</i>	Men	1,251	77%	-0.160	0.098	0.10	54%	0.007	0.080	0.93
	Women	1,350	80%	ref			54%	ref		
<i>Race and Ethnic Group</i>	White, non-Hispanic	1,721	79%	ref			53%	ref		
	Black, non-Hispanic	296	77%	-0.032	0.156	0.84	55%	0.100	0.131	0.44
	Hispanic (all races)	385	78%	0.136	0.149	0.36	59%	0.291	0.123	0.02
	Other non-Hispanic	200	81%	0.555	0.541	0.31	56%	0.058	0.167	0.73
<i>Survey language, among Hispanics</i>	Spanish	186	80%	0.159	0.252	0.53	61%	0.383	0.205	0.06
	English	199	80%	ref			56%	ref		
<i>Age</i>	21–29	447	81%	-0.047	0.048	0.32	60%	-0.156	0.039	<0.0001
	30–44	694	80%				58%			
	45–59	735	79%				53%			
	60+	724	77%				47%			

Kaufman et al (2016) *PLoS One* 11(8):e0160461



RETURN OF RESULTS AND PARTICIPATION



9 out of 10 national survey respondents want individual-level data returned

Kaufman et al (2008) *Genet Med* 10(11):831-839

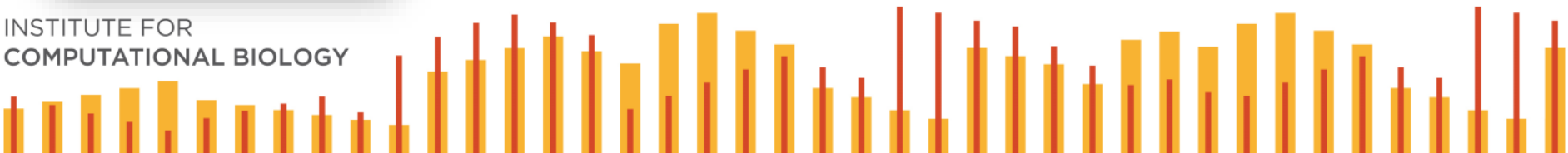
3 out of 4 national survey respondents want genetic results returned

Kaufman et al (2016) *PLoS One* 11(8):e0160461



Two-thirds of respondents would be less likely to participate if return of results were not offered

Kaufman et al (2009) *Genet Med* 11(5):329-337



METROHEALTH/ICB PILOT STUDY (MIPs)

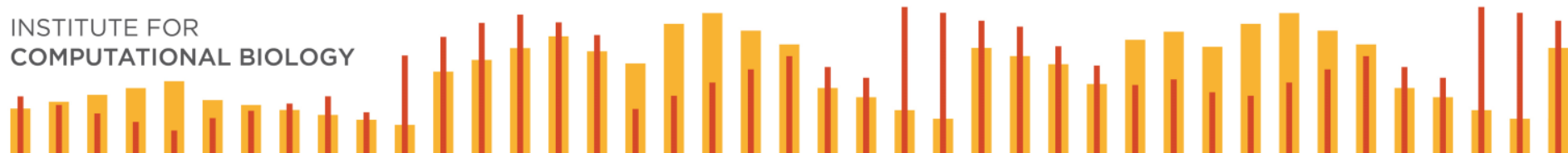
103 patients surveyed at Nephrology Clinic



- 50% African American
- 54% female
- Mean age 61.45 years
(range: 18 – 91 years)

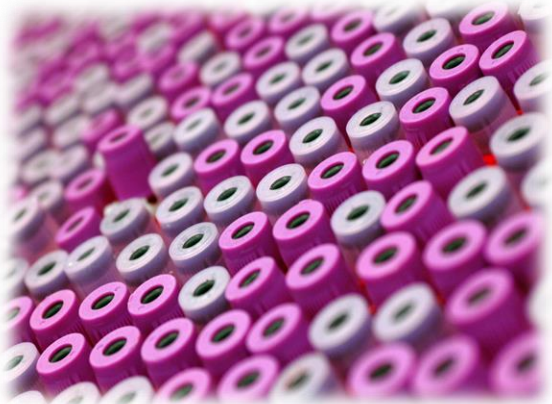


Cooke Bailey et al (2018) *J Pers Med* 8(3)



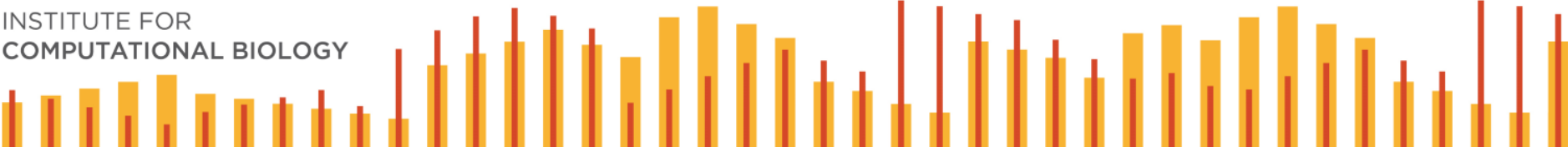
METROHEALTH/ICB PILOT STUDY (MIPs)

Would you be willing to allow your health records and genetic information to be stored in a national biorepository coordinated by the government as a part of their “Precision Medicine Initiative”? If so this information may be available to researchers nationally and internationally with the understanding that your privacy would be protected.



71% YES
69% YES

Cooke Bailey et al (2018) *J Pers Med* 8(3)



METROHEALTH/ICB PILOT STUDY (MIPs)

If you participated in a study that collected your genetic and health information, how important is it to you that you receive results from the study? Circle the number that is closest to how you feel.



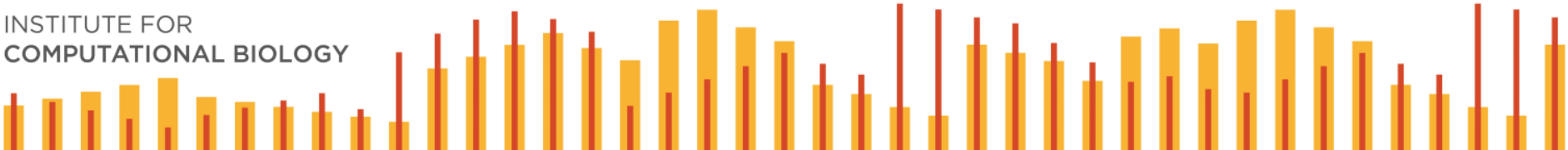
1 - 2 - 3 - 4 - 5
Not at all important Somewhat important Very important

~12%

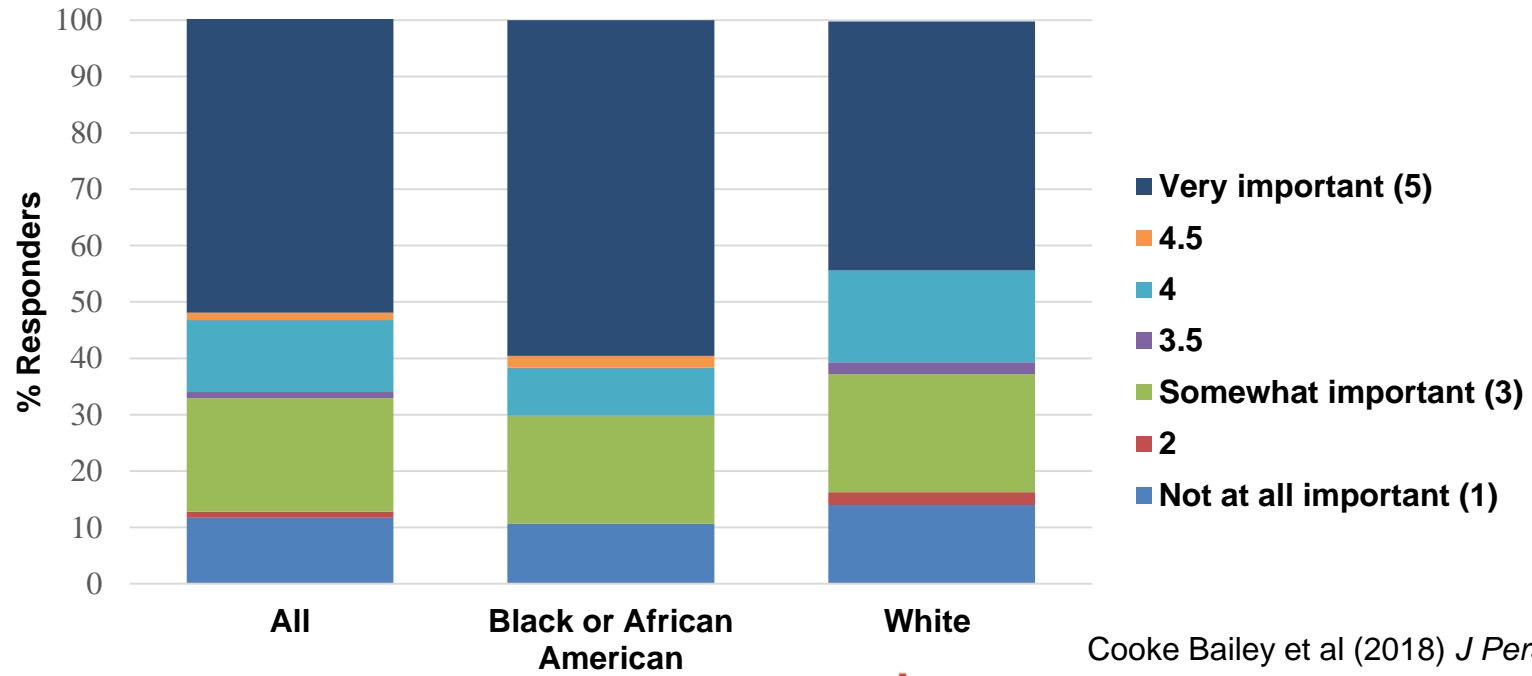
~20%

~62%

Cooke Bailey et al (2018) *J Pers Med* 8(3)

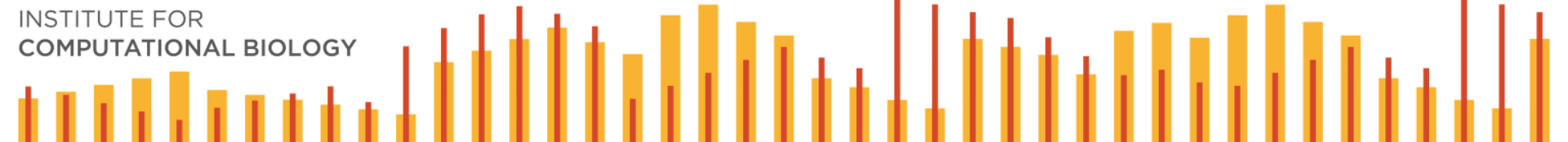


RETURN OF RESEARCH RESULTS IS IMPORTANT FOR EVERYONE



Cooke Bailey et al (2018) *J Pers Med* 8(3)

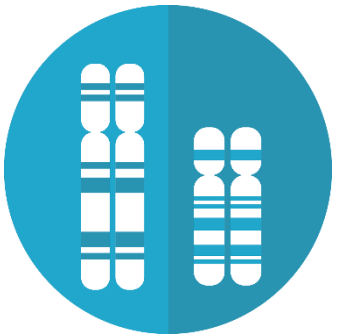
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METROHEALTH/ICB PILOT STUDY (MIPs)

What type of results would you like to receive, please check all that apply

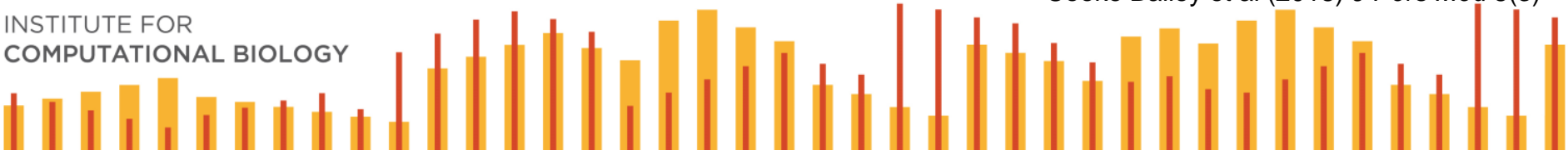
- A – Information about average results – no personal results
- B – Information about yourself your doc may have already told you
- C – Information about your genes that may influence your doc’s approach to care
- D – Information about your genes that has uncertain significance and won’t change treatment
- E – I do not want to receive any results



~77% GENETICS (C)

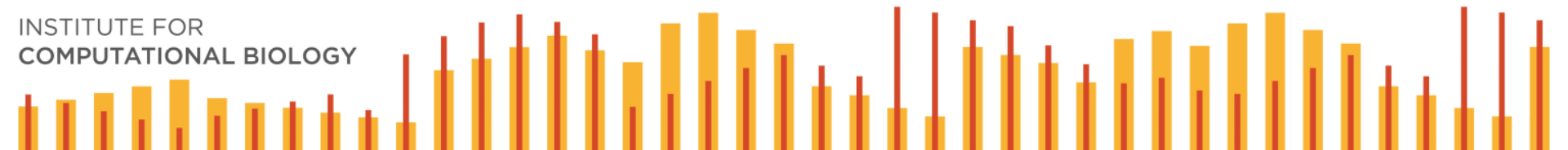
~11% NOTHING

Cooke Bailey et al (2018) *J Pers Med* 8(3)



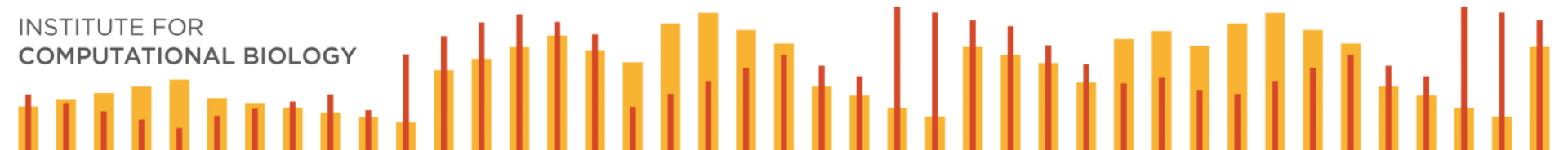
SUMMARY

- *APO1* explains much of CKD observed disparity in prevalence
- *APO1* renal risk variants common among (West) African-descent populations
- Data are still needed to understand the risks and benefits of *APO1* genotyping in precision medicine



**PRECISION
MEDICINE
RESEARCH IS
MULTIDISCIPLINARY**

Biostatistics
Computer Genomics
Medicine Omics
Human Biomedical
Clinical Data Big
Bioethics Science
Bioinformatics
Informatics
Genetics



WHAT DEGREES AND TRAINING DO YOU NEED?



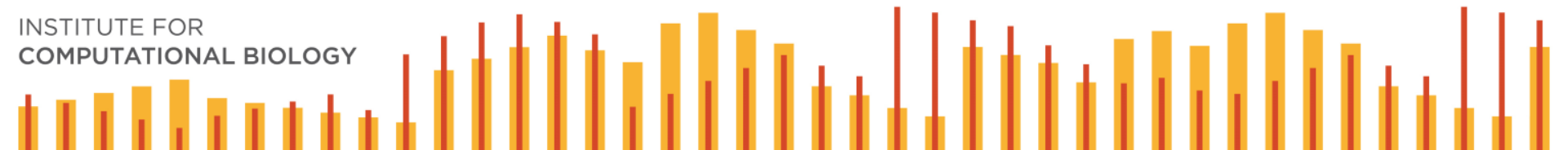
Genetics and Molecular Biology
Emory University
2000



EIS 2000-2002



Genome Sciences
University of Washington
2002-2006



WHAT DEGREES AND TRAINING DO YOU NEED?

PHDS IN HUMAN GENETICS

Logan



Research
Scientist
(Academia)

Janina



Industry
Scientist

Matt



Staff
Scientist
(Industry)

Jennifer



Technical
Writer

Nicole

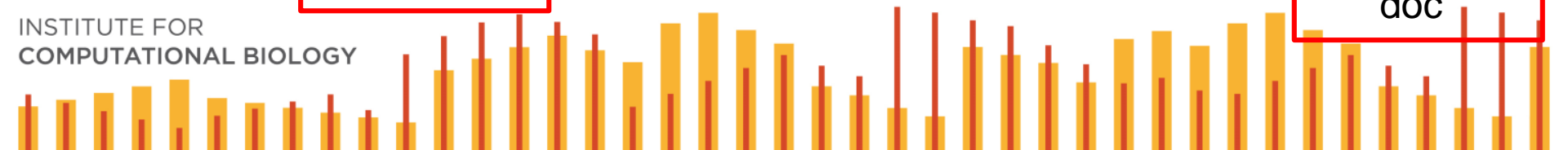


Staff
Scientist
(Industry)

Brittany



NIH Post-
doc



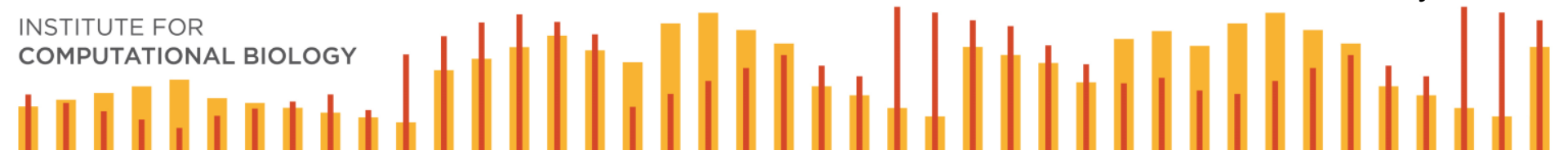
WHAT DEGREES AND TRAINING DO YOU NEED? BIOETHICS AND HUMAN GENETICS



Aaron Goldenberg, PhD
Associate Professor
Case Western Reserve University



Jessica Cooke Bailey, PhD
Assistant Professor
Case Western Reserve University



WHAT DEGREES AND TRAINING DO YOU NEED?

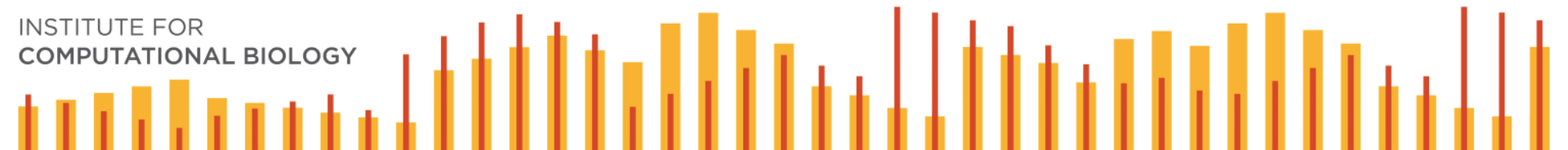
BIOINFORMATICS, COMPUTATIONAL BIOLOGY, COMPUTER SCIENCE



Sarah Pendergrass, PhD, MS
Assistant Professor
Geisinger Health System



Will Bush, PhD, MS
Assistant Professor
Case Western Reserve University



WHAT DEGREES AND TRAINING DO YOU NEED? BIOMEDICAL INFORMATICS AND DOCTORATE OF MEDICINE



David Kaelber, MD
Chief Informatics Officer
MetroHealth System

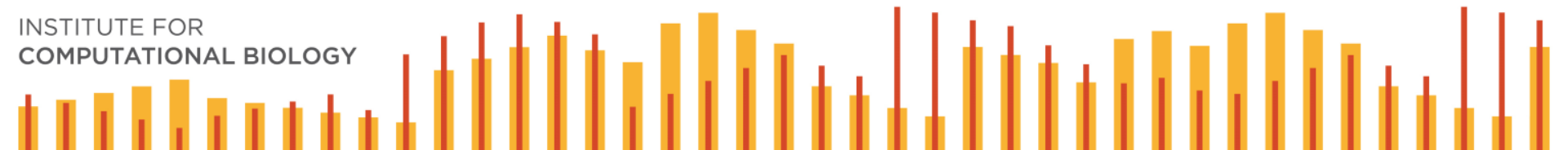


John Sedor, MD



John O'Toole, MD

Nephrologists
Cleveland Clinic



WHAT DEGREES AND TRAINING DO YOU NEED?

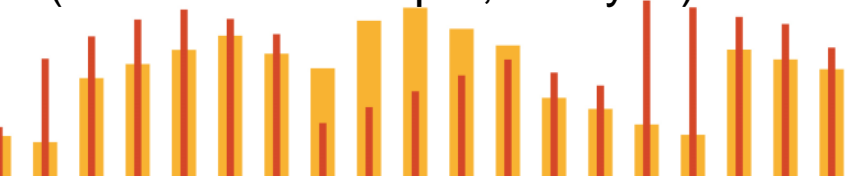
BIOSTATISTICS, DATA MANAGEMENT/ARCHITECTS

Kristin Brown-Gentry, MS
(Health Outcomes Scientist, Magellan Health)

Robert Goodloe, MS
(Consultant Statistician, Eli Lilly)

Bob McClellan, BS
(Senior Application Developer,
Vanderbilt University Medical Center)

Jonathan Boston, BS
(Software Developer, Cicayda)



ACKNOWLEDGEMENTS



John Sedor, MD



John O'Toole, MD



ICB Pilot Study grant
Kidney Foundation of Ohio

NIH KL2TR000440

NIH DK097836

NIH DK108329

NIH DK083912

NIH DK100846

NIH DK114908



Will Bush, PhD, MS

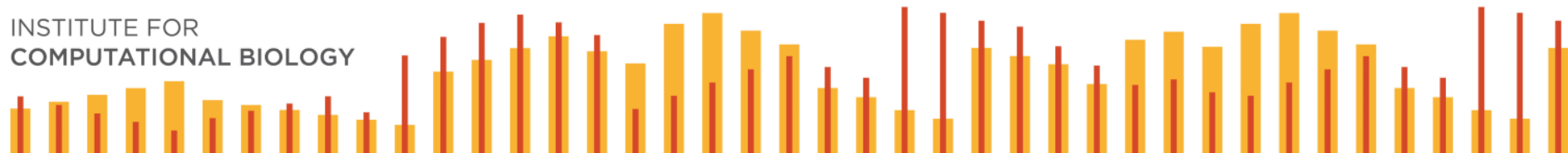


Jessica Cooke
Bailey, PhD



Aaron Goldenberg,
PhD, MA, MPH

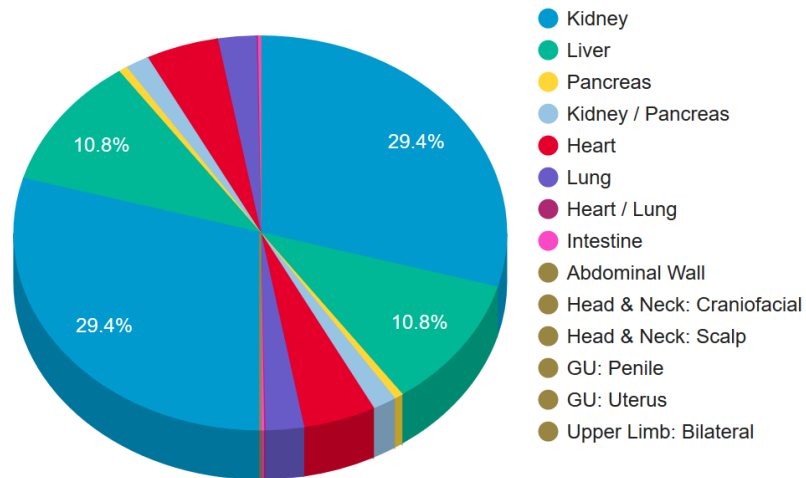
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Transplants By Organ Type January 1, 1988 - September 30, 2018 Based on OPTN data as of October 11, 2018

Unos.org

Organ	Transplants
Kidney	440,926
Liver	162,094
Pancreas	8,713
Kidney / Pancreas	23,546
Heart	71,513
Lung	37,713
Heart / Lung	1,256
Intestine	2,991
Abdominal Wall	1
Head & Neck: Craniofacial	6
Head & Neck: Scalp	1
GU: Penile	2
GU: Uterus	12
Upper Limb: Bilateral	6
Upper Limb: Unilateral	4



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METROHEALTH/ICB PILOT STUDY (MIPs)

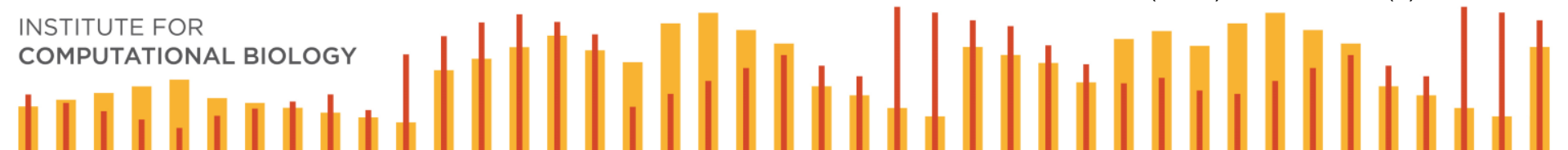
Survey Summary and Comparisons:

- Higher willingness to participate
70% v ~54%*
- Same willingness to send data via phone app
48% v ~43% (to share social media data)*
- Same interest in genetic data
77% (*at least*) v 74%*



Cooke Bailey et al (2018) *J Pers Med* 8(3)

*Kaufman et al (2016) *PLoS One* 11(8):e0160461



METROHEALTH/ICB PILOT STUDY (MIPs)

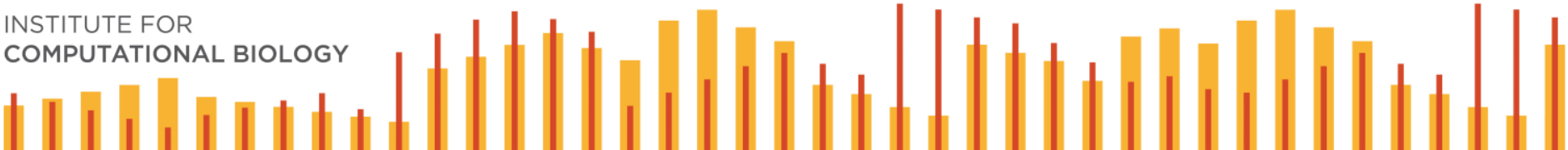
Would you be willing to install a free phone app that would be able to track your physical activity, measures of your health and location with the understanding that your privacy would be protected?



38% YES

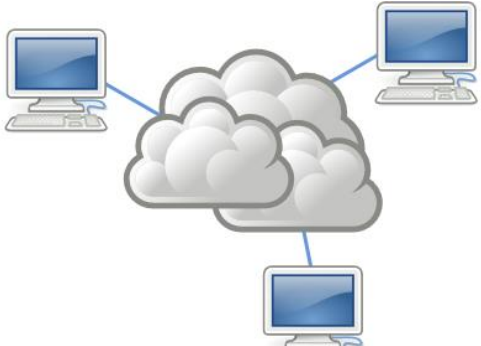
46% YES

Cooke Bailey et al (2018) *J Pers Med* 8(3)



METROHEALTH/ICB PILOT STUDY (MIPs)

Would you be willing to allow the information collected using the phone app (question 3) to be sent to the national coordinating center where it may be shared with researchers nationally and internationally with the understanding that your privacy would be protected?



37% YES
54% YES

Cooke Bailey et al (2018) *J Pers Med* 8(3)

