From Population and Personalized Genomics to Personalized/Precision Medicine

Manolis Dermitzakis

University of Geneva
Dept Genetic Medicine and Development
University of Geneva Medical School
and
Swiss Institute of Bioinformatics

emmanouil.dermitzakis@unige.ch

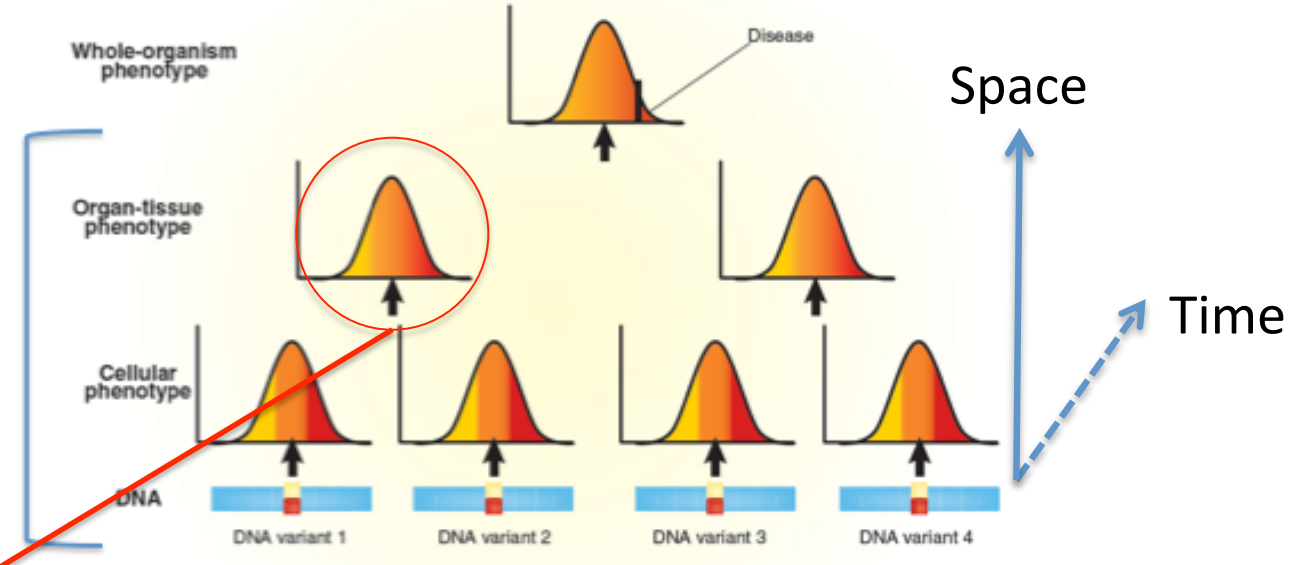
Our “engine”

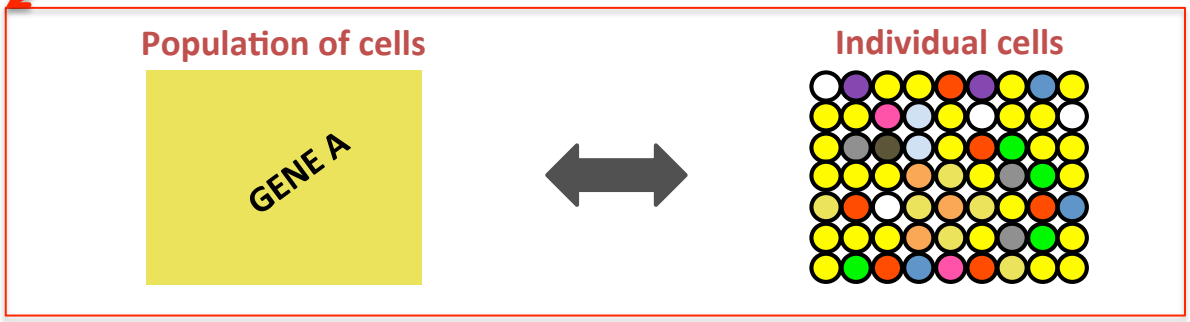
Revolution in Medicine

- Advances in technology
- Deep learning of human biology

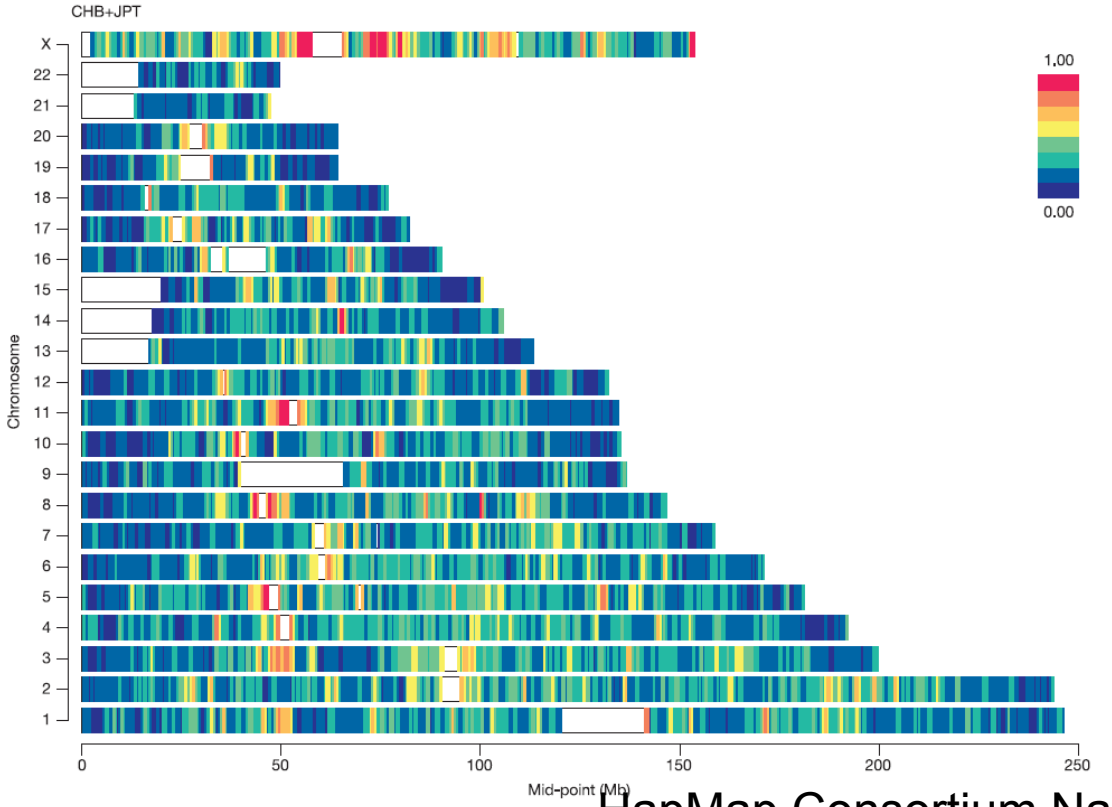
Complex traits/disease

ENVIRONMENT
- Behavior
- Infections
- External factors
- etc





HapMap: cataloguing "common" genetic variation



HapMap Consortium Nature 2005

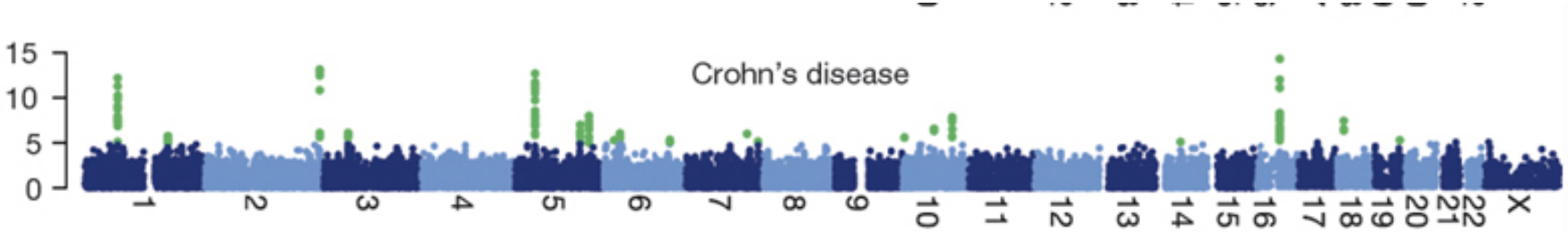
1000 genomes: cataloguing “all” genetic variation

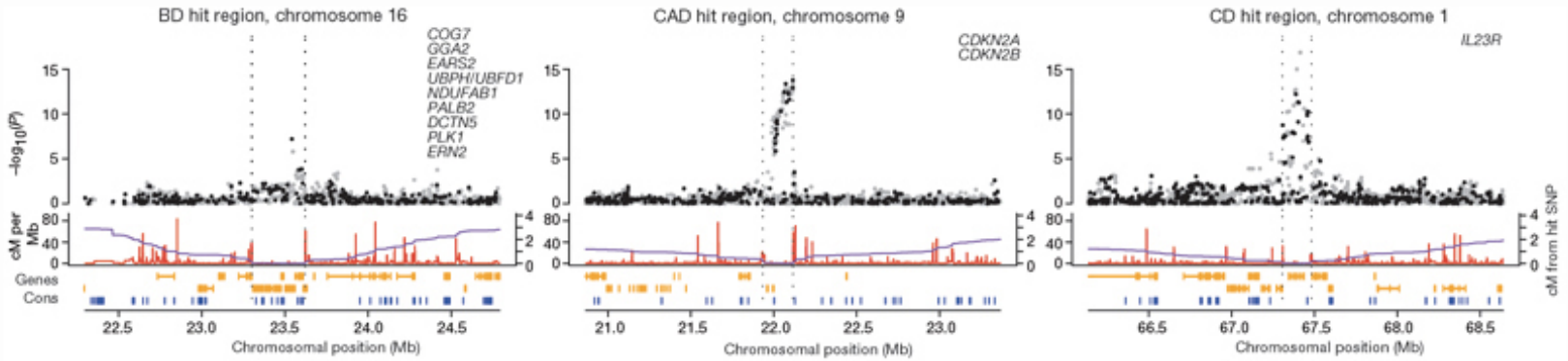
IGSR and the 1000 Genomes Project

Populations: - African; - American; - East Asian; - European; - South Asian;

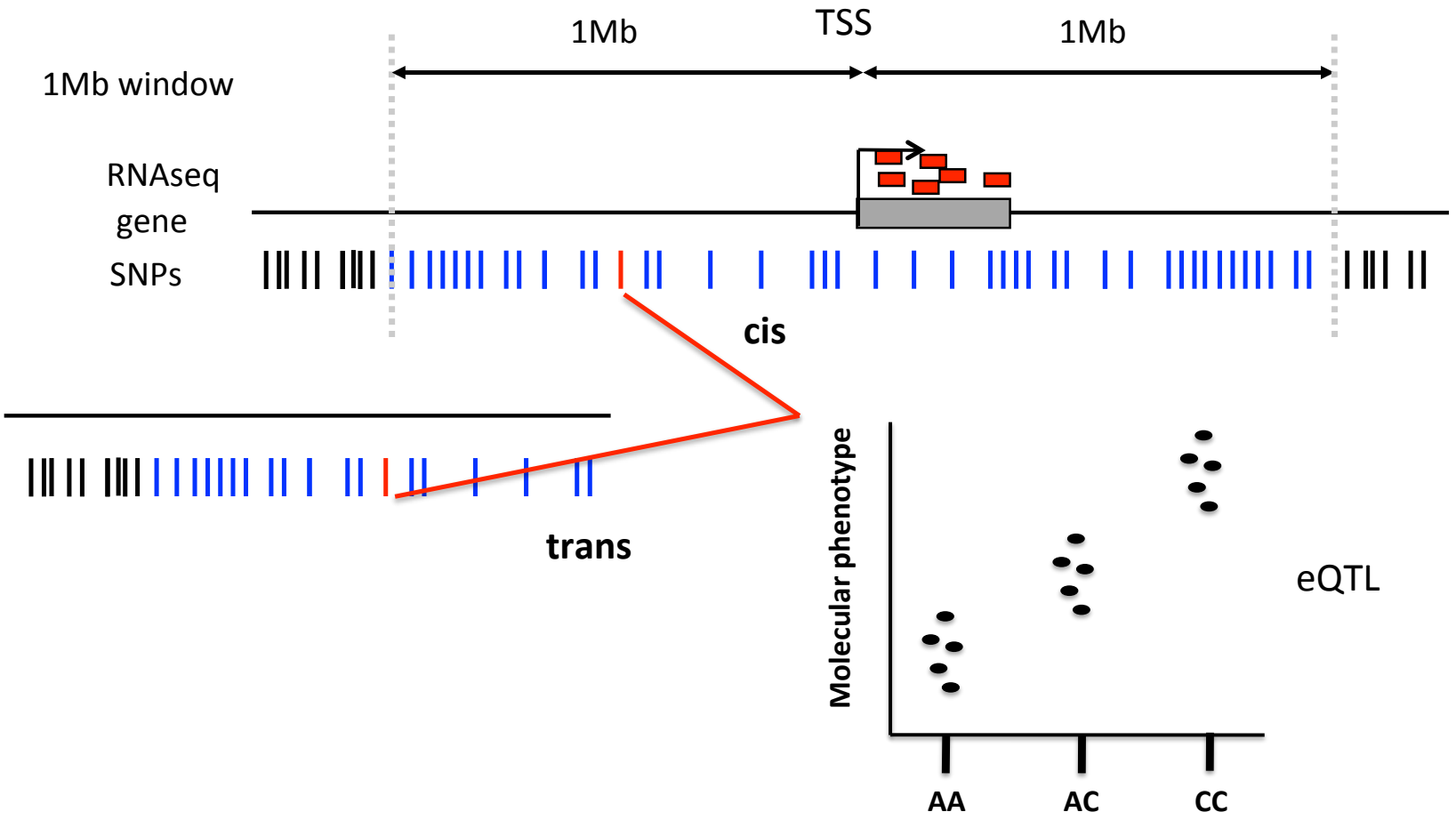
The International Genome Sample Resource (IGSR) was established to ensure the ongoing usability of data generated by the 1000 Genomes Project and to extend the data set. More information is available about the IGSR.

Genome-Wide association studies (GWAS)



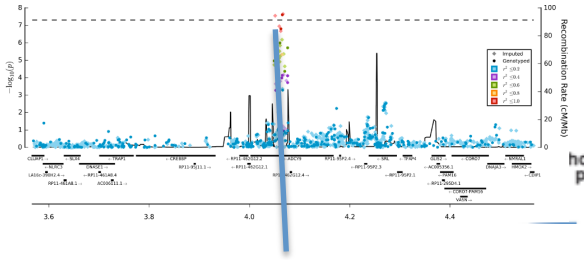


Gene expression as a key molecular phenotype – expression QTL (eQTL) analysis

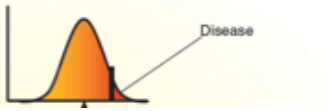


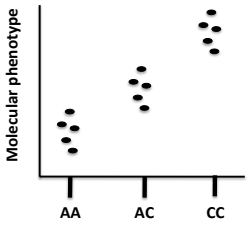
Functional variation to organismal phenotype

GENETIC ASSOCIATION IS A CAUSAL LINK



hole-organism phenotype

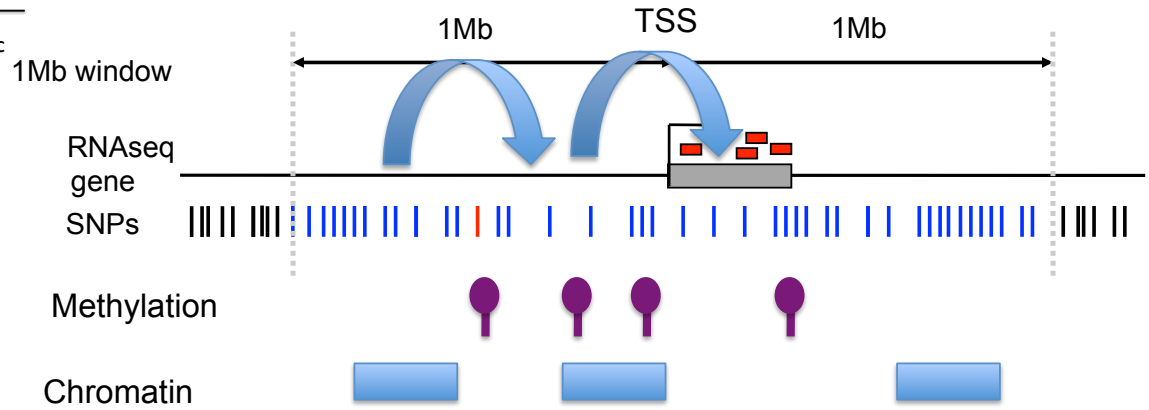




eQTL

Interpretation of GWAS using molecular QTLs

eQTLs

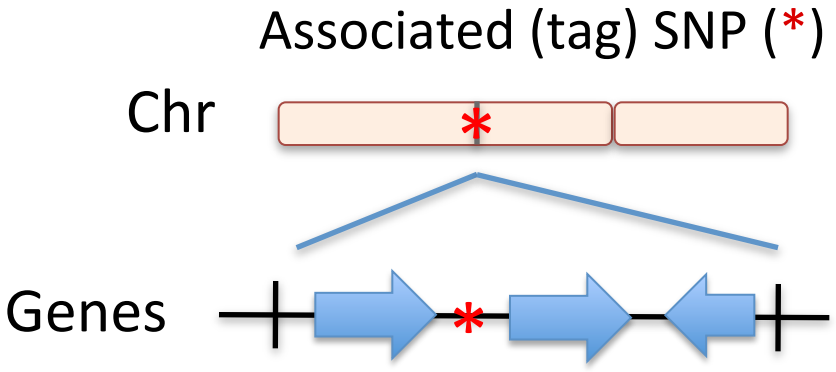


Mechanistic insights to Genetic variation

Background Rationale

Genome-wide association studies (**GWAS**) have identified **hundreds of common DNA variants** associated with multiple **complex diseases and traits**.

~90% of GWAS SNPs lie in noncoding regions (e.g. intergenic, introns).



Causal mechanism?
Causal gene/s?

Many studies show trait-associated SNPs enriched for eQTLs

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Trait-Associated SNPs Are More Likely to Be eQTLs: Annotation to Enhance Discovery from GWAS

LCL eQTLs

Dan L. Nicolae[1,2,3], Eric Gamazon[1], Wei Zhang[1], Shiwei Duan[1¤], M. Eileen Dolan[1,2], Nancy J. Cox[1,2*]

1 Department of Medicine, University of Chicago, Chicago, Illinois, United States of America, 2 Department of Human Genetics, University of Chicago, Chicago, Illinois, United States of America, 3 Depar

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LCL eQTLs

Candidate Causal Regulatory Effects by Integration of Expression QTLs with Complex Trait Genetic Associations

Alexandra C. Nica[1,2], Stephen B. Montgomery[1,2], Antigone S. Dimas[1,2], Barbara E. Stranger[1,3], Claude Beazley[1], Inês Barroso[1], Emmanouil T. Dermitzakis[1,2*]

1 Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge, United Kingdom, 2 Department of Genetic Medicine and Development, University of Geneva Medical School, Geneva, Switzerland, 3 Harvard Medical School/Brigham and Women's Hospital, Boston, Massachusetts, United States of America

Coanalysis of GWAS with eQTLs reveals disease-tissue associations

Hyunseok Peter Kang, M.D.[1], Alex A. Morgan, Ph.D.[1], Rong Chen, Ph.D.[1], Eric E. Schadt, Ph.D.[2], Atul J. Butte, M.D, Ph.D.[1]
[1] Division of Systems Medicine, Department of Pediatrics, Stanford University School of Medicine, Stanford, CA

[2] Department of Genetics and Genome Sciences, Mount Sinai School of Medicine, New York, NY

Peripheral blood monocyte, liver and adipose eQTLs

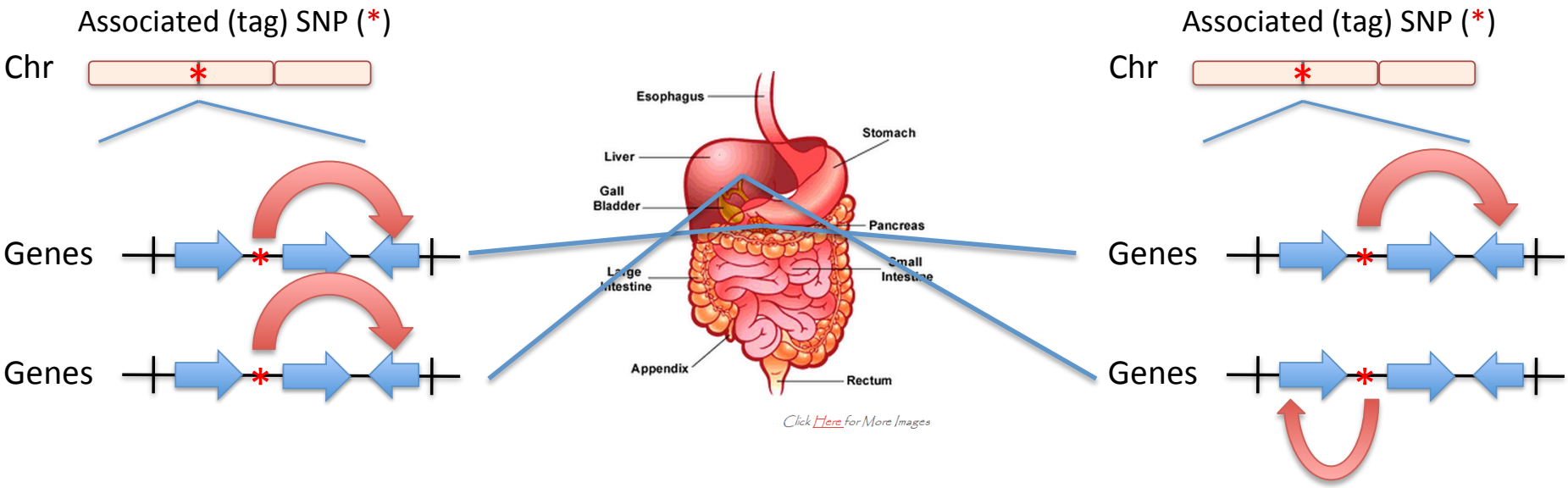
Challenges in using eQTLs to interpret disease associations

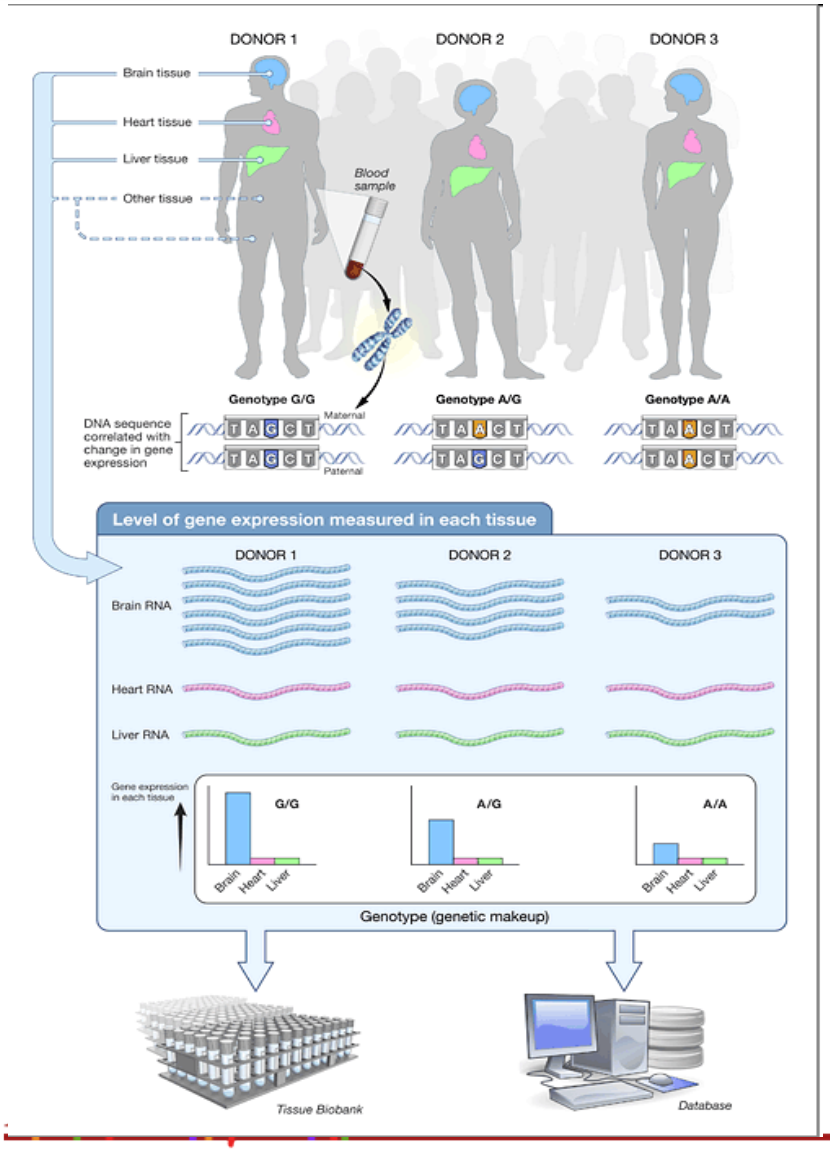
- Measuring eQTLs in disease-relevant tissues or cell types

- Most human tissue types are hard to obtain

- Large sample sizes are required for statistical power

Causal tissue inference





GTEx GOALS:

- Atlas (database) of gene expression, regulation, and eQTLs from a wide range of non-diseased human tissues
- Biobank of tissues, DNA, RNA

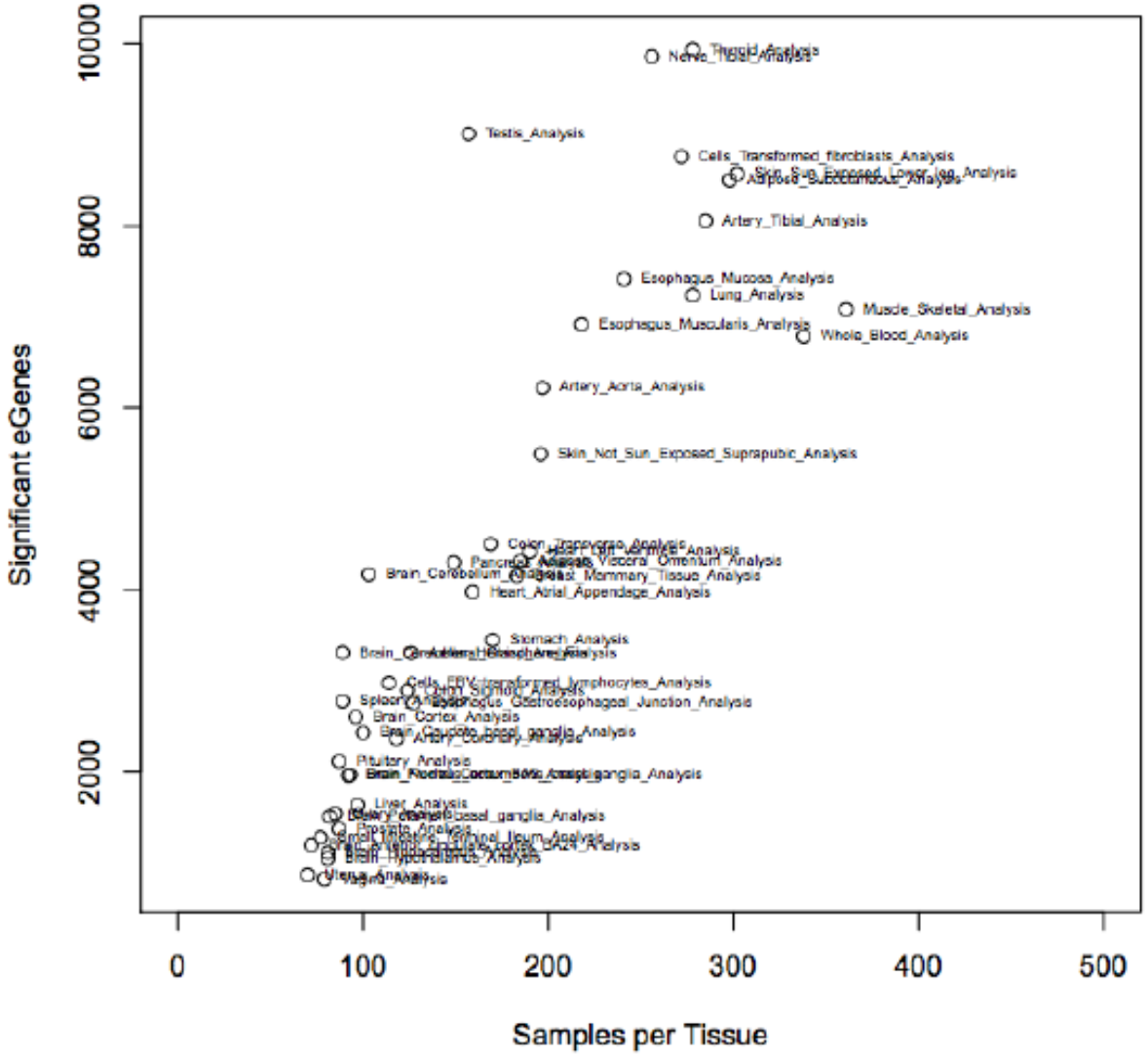
ULTIMATE STUDY SIZE (by 1/2016):

- 900 Postmortem Donors
- Whole exome sequencing
- Whole genome sequencing
- RNA-Seq of ~30 tissues/donor (>20,000 tissues)

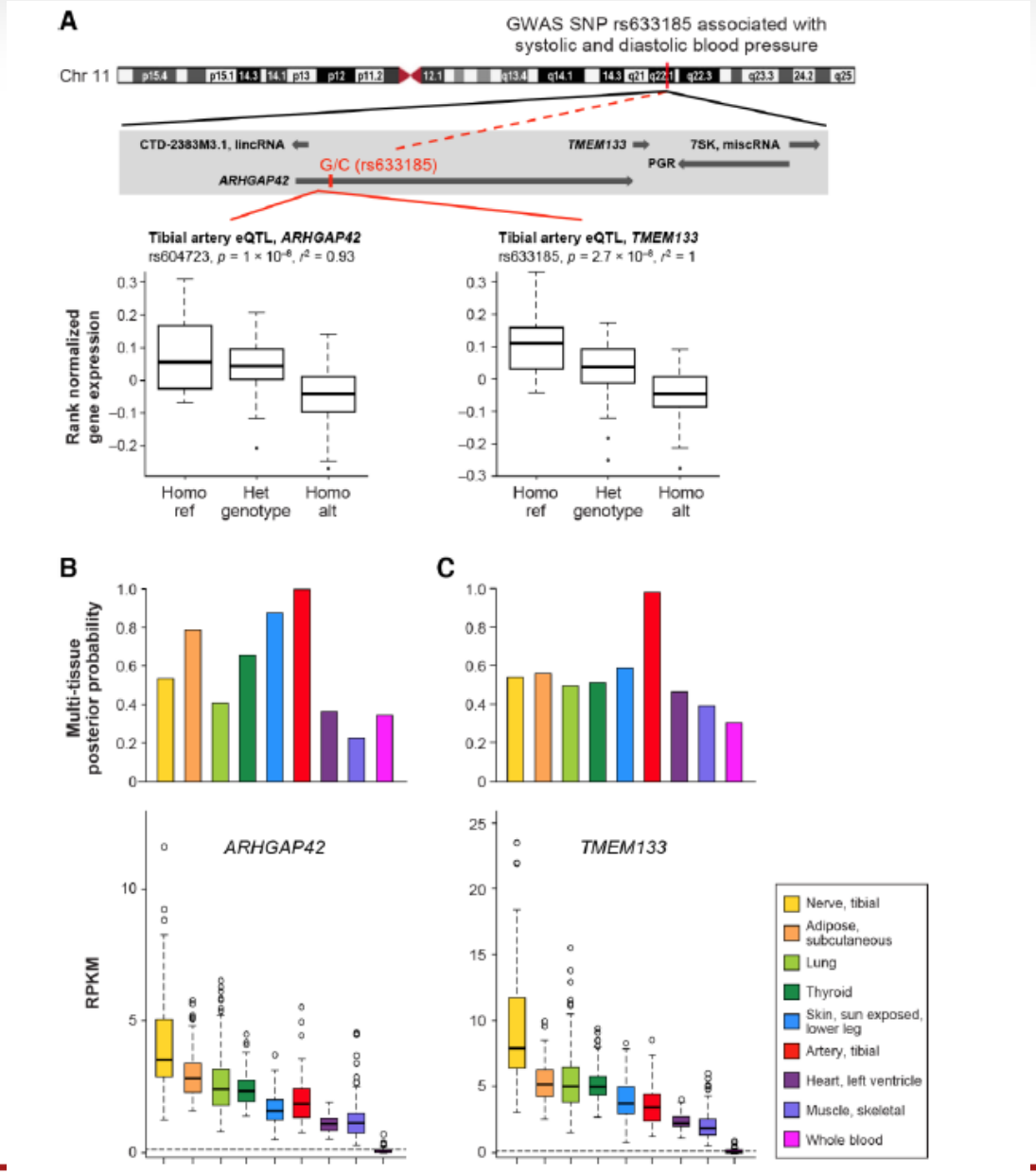
PILOT PHASE (in 2010):

- 175 Postmortem Donors
- 1641 RNA-Seq of ~28 tissues/donor

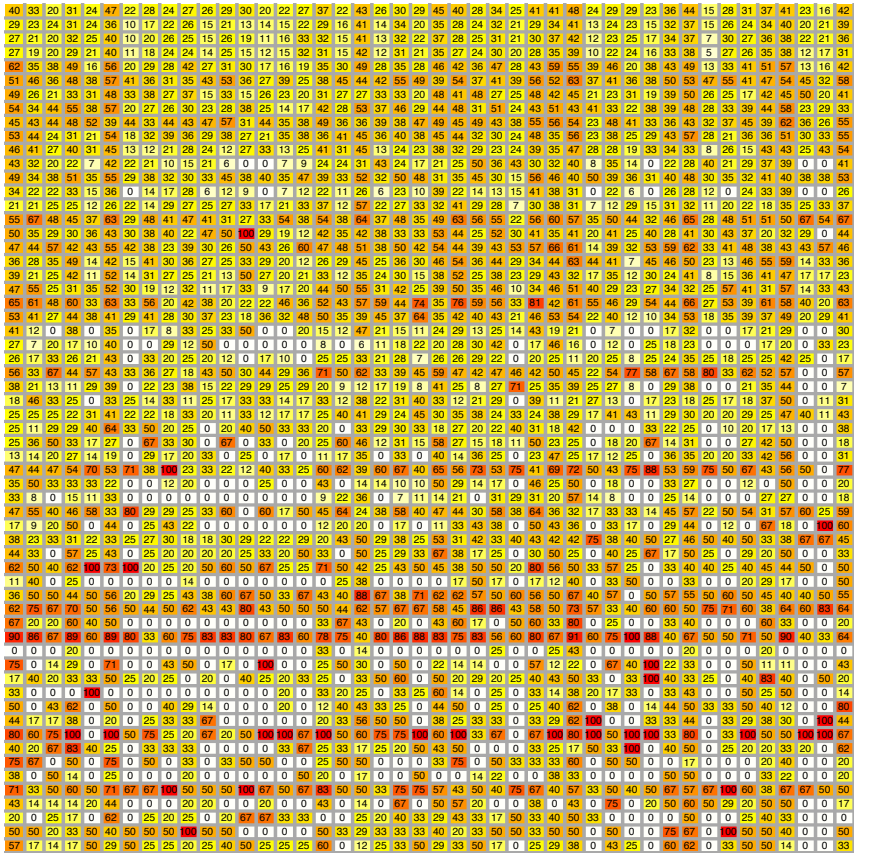
GTEx eQTL discovery



Link eQTLs to GWAS



Tissue activity of GWAS in multiple tissues



body height
body mass index
body weight
lean body mass
schizophrenia
rheumatoid arthritis
crohn's disease
bipolar disorder
multiple sclerosis
anthropometry
coronary heart disease
type ii diabetes mellitus
inflammatory bowel disease
breast carcinoma
alzheimer's disease
ulcerative colitis
prostate carcinoma
systemic lupus erythematosus
attention deficit hyperactivity disorder
unipolar depression
asthma
type i diabetes mellitus
parkinson's disease
colorectal cancer
migraine disorder
coronary artery calcification
psoriasis
chronic kidney disease
venous thromboembolism
chronic obstructive pulmonary disease
celiac disease
metabolic syndrome
alcohol dependence
chronic lymphocytic leukemia
hypertension
stroke
biliary liver cirrhosis
obesity
lung carcinoma
mental or behavioural disorder
allergy
sporadic amyotrophic lateral sclerosis
longevity
graves disease
large artery stroke
narcolepsy
sudden cardiac arrest
intelligence
pancreatic carcinoma
bladder carcinoma
testicular carcinoma
mucocutaneous lymph node syndrome
eosinophilic esophagitis
Behcet's disease
hypospadias
conduct disorder
lupus nephritis
acute lymphoblastic leukemia
immune system disease
squamous cell carcinoma
ovarian carcinoma

Adipose_Subcutaneous
Adipose_Visceral_Omentum
Adrenal_Gland
Artery_Aorta
Artery_Coronary
Artery_Tibial
Brain_Anterior_cingulate_cortex_BA24
Brain_Caudate_basal_ganglia
Brain_Cerebellar_Hemisphere
Brain_Cerebellum
Brain_Cortex
Brain_Frontal_Cortex_BA9
Brain_Hippocampus
Brain_Hypothalamus
Brain_Nucleus_accumbens_basal_ganglia
Brain_Putamen_basal_ganglia
Breast_Mammary_Tissue
Cells_EBV-transformed_lymphocytes
Cells_Transformed_fibroblasts
Colon_Sigmoid
Colon_Transverse
Esophagus_Gastroesophageal_Junction
Esophagus_Mucosa
Esophagus_Muscularis
Heart_Atrial_Appendage
Heart_Left_Ventricle
Liver
Lung
Muscle_Skeletal
Nerve_Tibial
Ovary
Pancreas
Pituitary
Prostate
Skin_Not_Sun_Exposed_Suprapubic
Skin_Sun_Exposed_Lower_leg
Small_Intestine_Terminal_Ileum
Spleen
Stomach
Testis
Thyroid
Uterus
Vagina
Whole_Blood

FunPopGen

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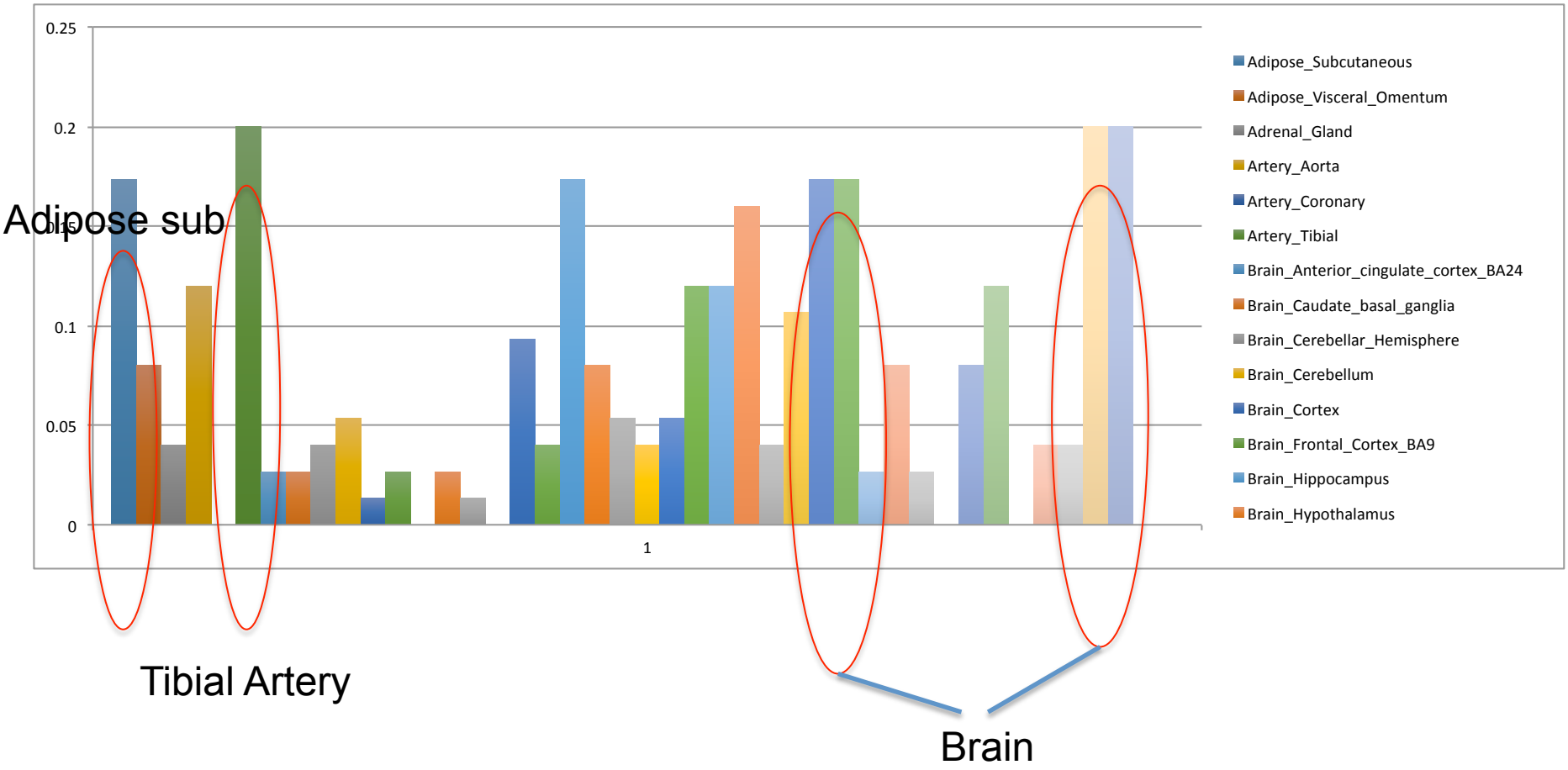
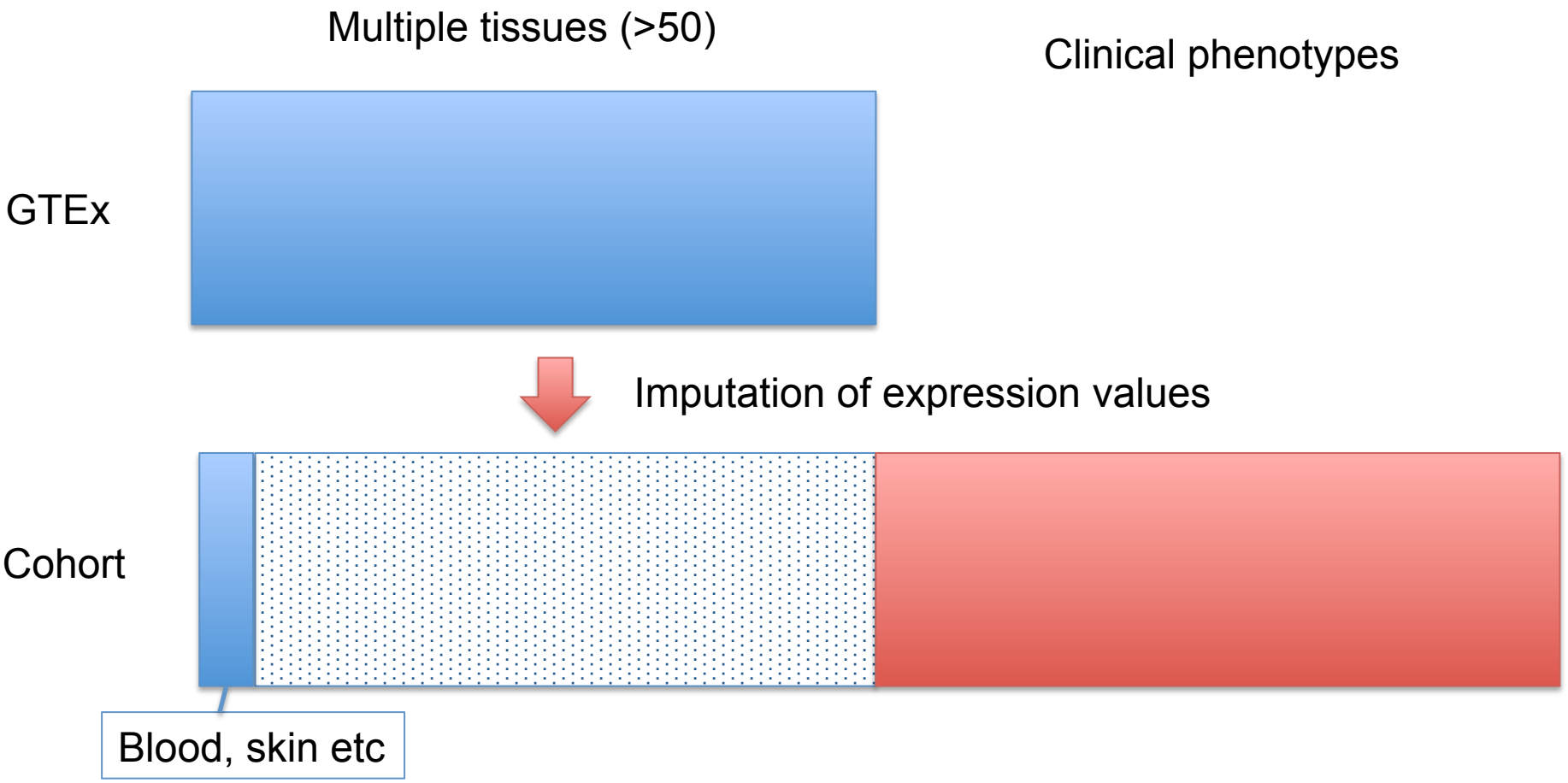
Type II Diabetes tissue activity



Use of GTEx as reference



So what's next?

- Learning human biology
- Implementing in Medicine

From Population and Personal Omics to Personal Biology

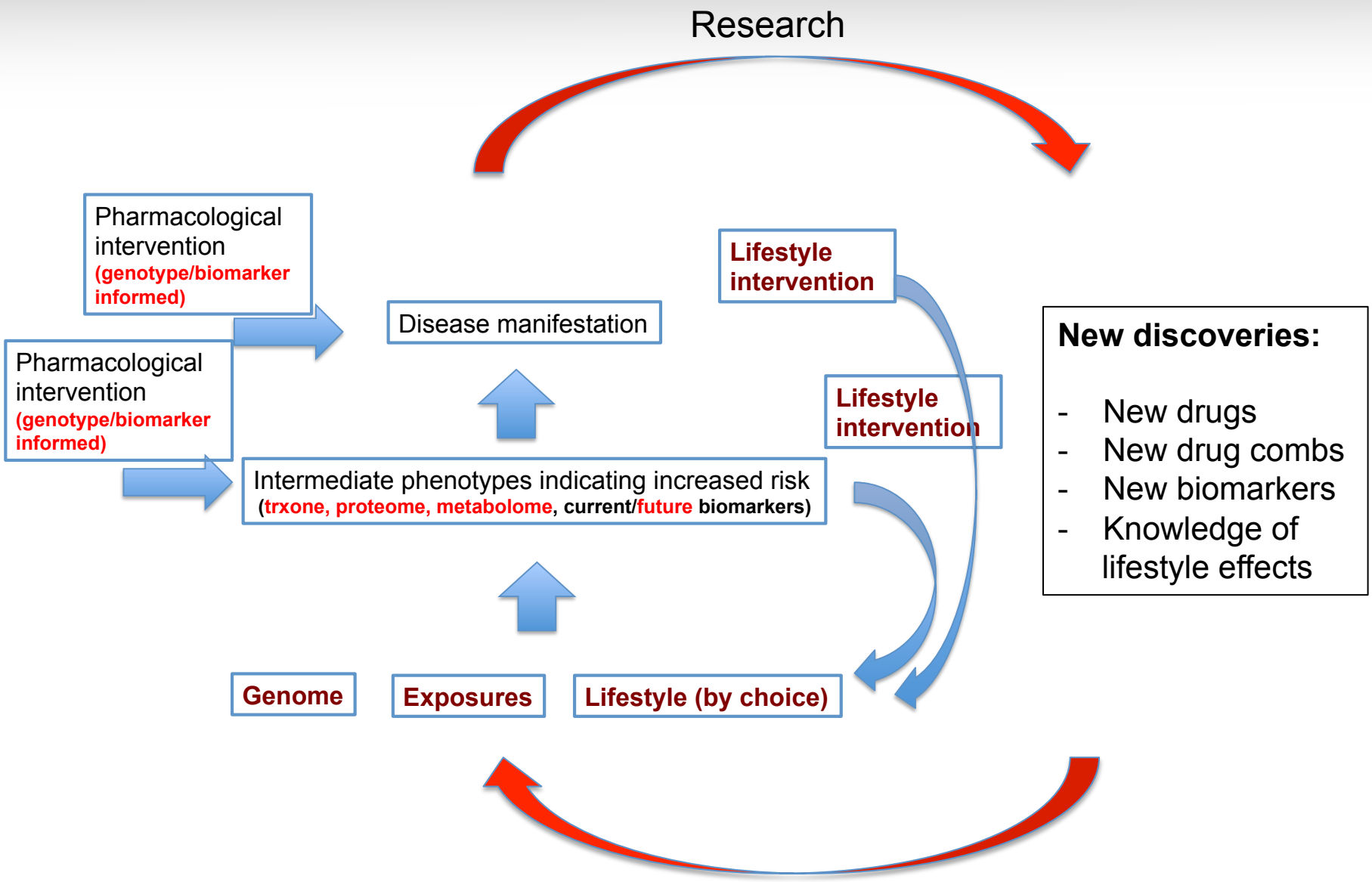
Key components missing:

- Interpretation of the non-coding genome
- Rare and private variants
- Rare and private environments
- Context dependence

Molecular phenotype context:

- Tissue
- Time
- Disease
- Sex
- Genotype
- Environment

Learning Human Biology – Implementing in Medicine

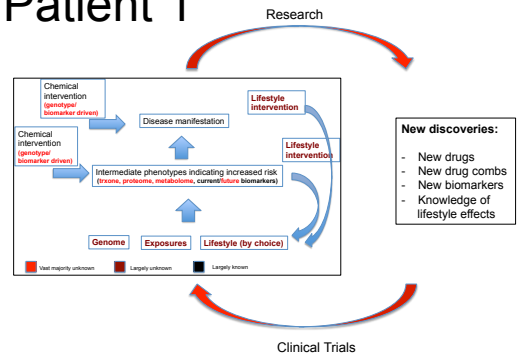


New discoveries:

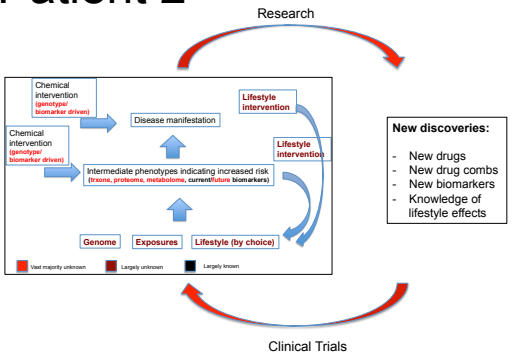
- New drugs
- New drug combs
- New biomarkers
- Knowledge of lifestyle effects

Each patient a research project

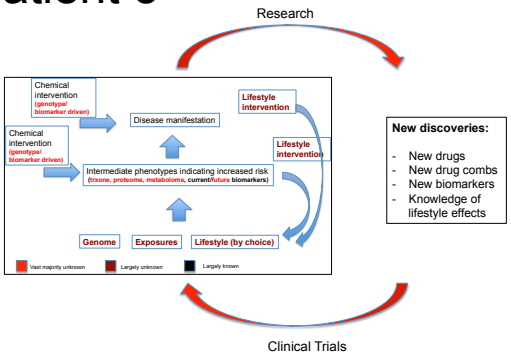
Patient 1



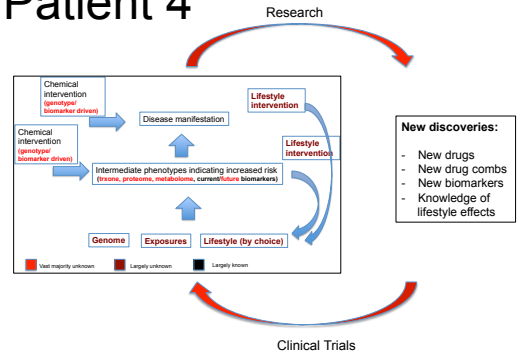
Patient 2



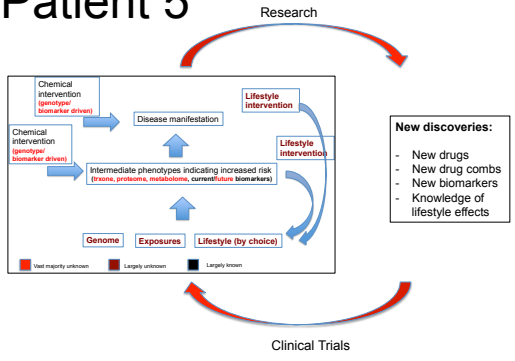
Patient 3



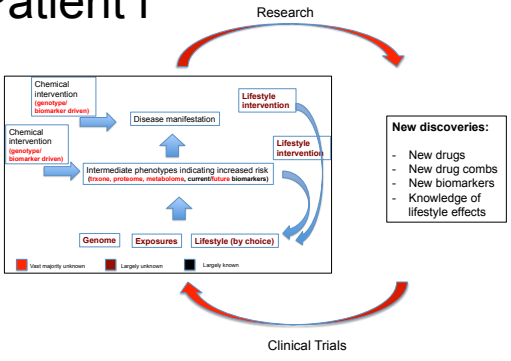
Patient 4



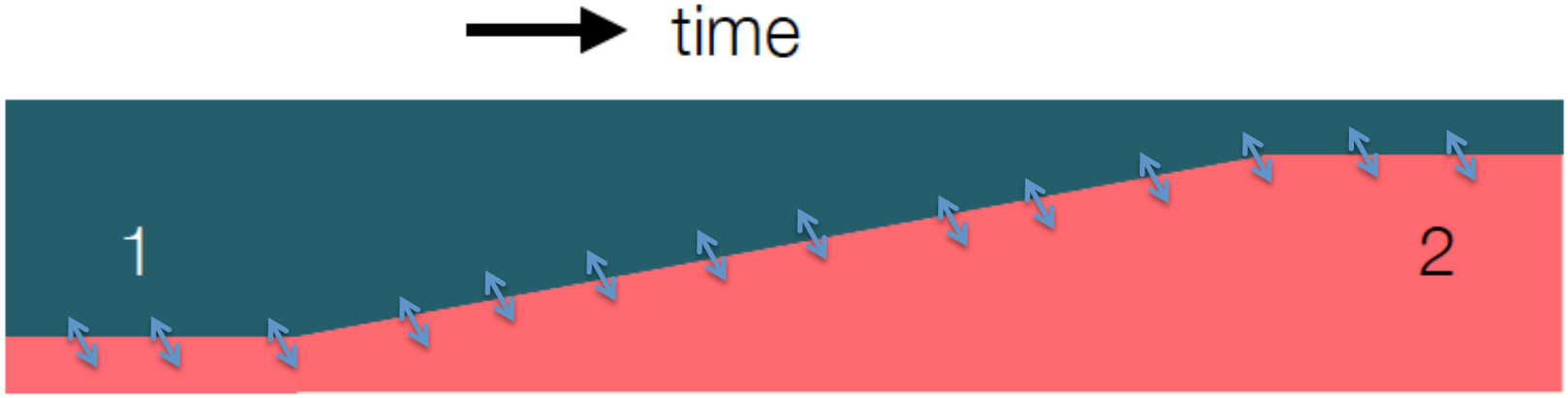
Patient 5



Patient i

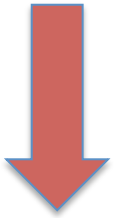


Relative investment of resources over time



1. Discovery
2. Direct medical application

Revolution in medicine



Deep understanding of the variability of the human body

GTEx Acknowledgments

The GTEx Consortium

Analysis Working Group:

LDACC: Kristin G. Ardlie[1], Gad Getz[1,2], David S. Deluca[1], Taylor R. Young[1], Ellen T. Gelfand[1], Ayellet V. Segrè[1], Timothy J. Sullivan[1], Casandra A. Trowbridge[1], Daniel G. MacArthur[1,3], Julian B. Maller[1,3], Taru Tukiainen[1,3], Monkol Lek[1,3], Manolis Kellis[1,4], Lucas D. Ward[1,4], Pouya Kheradpour[1,4], Joel Hirschhorn[1,5], Yan Meng[1], Cameron D. Palmer[1,5].

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caHUB Biospecimen Source Sites:

NDRI - Amanda Brown[36], Bernadette Mestichelli[36], Denee Tidwell[36], Edmund Lo[36], John T. Lonsdale[36], Jeffrey A. Thomas[36], Mike Salvatore[36], Saboor Shad[36].

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caHUB Comprehensive Biospecimen Resource:

Van Andel – Scott Jewel[43], Daniel C. Rohrer[43], Dana R. Valley[43].

caHUB Pathology Resource Center:

NCI - Philip Branton[44,46].

Leidos Biomedical Research Inc. - Leslie H. Sobin[45].

caHUB Comprehensive Data Resource:

Leidos Biomedical Research Inc. - Charles Shive[45], David Tabor[45], Liqun Qi[45], Pushpa Hariharan[45], Shenpei Wu[45].

caHUB Operations Management:

Leidos Biomedical Research Inc. - Anna M. Smith[45], Stephen A. Buia[45], Anita H. Undale[45], Karna L. Robinson[45], Nancy Roche[45], Kimberly M. Valentino[45], Angela Britton[45], Robin Burges[45], Debra Bradbury[45], Kenneth W. Hambright[45], John Seleski[45], Greg E. Korzeniewski[45].

Sapient Government Services - Kenyon Erickson[47].

Brain Bank Operations:

University of Miami – Deborah C. Mash[48], Margaret Basile[48], Yvonne Marcus[48], Jorge Tejada[48], Mehran Taherian[48], Chunrong Lu[48], Barnaby E. Robles[48].

Program Management:

NCI – Latarsha J. Carithers[46,49], Helen M. Moore[46,49], Ping Guan[44,46], Carolyn Compton[46,49], Sherilyn J. Sawyer[44,46], Joanne Peter Demchok[44,46], Jimmie B. Vaught[44,46], Chana A. Rabiner[44,46], Nicole C. Lockhart[44,46].

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Writing Committee: Kristin G. Ardlie[1], Gad Getz[1,2], Fred A. Wright[8], Manolis Kellis[1,4], Simona Volpi[46,50], Emmanouil T. Dermitzakis[10,11,12].

Acknowledgments

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SIB Swiss Institute of Bioinformatics
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