Accelerating Medicines Partnership

Common Metabolic Diseases

Inaugural Meeting

May 27, 2021

Content

AMP CMD
Inaugural Meeting
Thursday, May 27, 2021
10:00 a.m. – 1:00 p.m. EDT

Join Zoom Meeting
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- +1 669 900 6833 US (San Jose)
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Accelerating Medicines Partnership—Common Metabolic Diseases

Inaugural Meeting | May 27, 2021 | 10:00 AM-1:00 PM EDT

SESSION I: INTRODUCTIONS AND PROJECT OVERVIEW

10:00 AM	**Welcome Remarks and Introduction to AMP CMD** **Griffin Rodgers,** Director, NIDDK **David Wholley,** SVP of Research Partnerships, FNIH
10:15 AM	**Meeting Overview** **Phil Smith,** NIDDK, Co-chair AMP T2D, AMP CMD Plan Development
10:20 AM	**AMP CMD Organizational Overview and Project Governance** **Tania Kamphaus,** FNIH
10:25 AM	**Introducing Private Partners** **Amgen, Eli Lilly, Novo Nordisk, Pfizer**
10:40 AM	**AMP CMD Research Plan** **Melissa Thomas,** Eli Lilly, Co-chair AMP T2D, AMP CMD Plan Development
10:50 AM	**Introduction to NIDDK Foundational Grants and Projects** **Norann Zaghloul,** NIDDK

SESSION II: FOUNDATIONAL AWARDS AND ONGOING RESEARCH

11:00 AM	**Evolution of AMP Knowledge Portal and Plans for AMP CMD** **Nöel Burtt and Jason Flannick,** Broad Institute
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12:00 PM	***Break***

SESSION III: PARTNERSHIP VISION AND DELIVERABLES

12:10– 12:40 PM	**Eli Lilly**	**Novo Nordisk**	**Pfizer**	**Amgen**
12:40 - 12:50 PM	**A Shared Vision** **Phil Smith,** NIDDK			
12:55 PM	**Next Steps and Adjournment** **Tania Kamphaus,** FNIH			

David Wholley, FNIH Griffin Rodgers, NIDDK

FNIH

Welcome and Introduction to AMP Common Metabolic Diseases

Phil Smith, NIDDK

FNIH

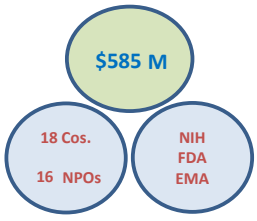
Meeting Overview

Tania Kamphaus, FNIH

FNIH

AMP CMD Organizational Overview and Project Governance

AMP Organizational Structure



Extended Executive Committee (EEC)

Participants listed on backup slide

Executive Committee (EC)

Co-chairs
- Francis Collins, NIH
- Mikael Dolsten, Pfizer

Members
- Griffin Rodgers, NIDDK
- Joshua Gordon, NIMH
- Richard Hodes, NIA
- Walter Koroshetz, NINDS
- Sharon Terry, Genetic Alliance
- John Reed, Sanofi
- Paul Stoffels, Janssen

Executive and Steering Committee Support
- David Wholley, FNIH
- Joseph Menetski, FNIH
- Tania Kamphaus, FNIH
- Eline Appelmans, FNIH
- Noam Keren, FNIH
- Steve Hoffmann, FNIH

Alzheimer's Steering Committee 1.0

Co-chairs
- David Collier, Lilly
- Laurie Ryan, NIA

EC Liaison
- Richard Hodes, NIA

OD Liaison
- Ellen Gadbois, Ellen Wann NIH/OD

Members
- Billy Dunn, FDA
- Maria Carrillo, Rebecca Edelmayer, Alzheimer's Association®
- Mark Mintun, Avid RP and Eli Lilly
- Matt Townsend, AbbVie
- Sanjay Kumar, GlaxoSmithKline plc (GlaxoSmithKline plc (GSK))
- Suzana Petanceska, NIA
- TBD, Biogen Idec
- Walter Koroshetz, Deb Babcock, NINDS

Alzheimer's Steering Committee 2.0

Co-chairs
- Suzana Petanceska, NIA
- *Private partner*

EC Liaison
- Richard Hodes, NIA

OD Liaison
- Ellen Gadbois, Ellen Wann NIH/OD

Members
- Billy Dunn, FDA
- Eliezer Masliah, Laurie Ryan, NIA
- Janna Hutz, Rosa Canet-Aviles, Eisai Inc.
- Maria Quinton, Arthur Simen, Takeda Pharmaceutical Company Limited Pharmaceutical Company Limited
- Rebecca Edelmayer, Percy Griffin, Alzheimer's Association®
- Sanjay Kumar, Gopi Ganji, GlaxoSmithKline plc (GSK)
- Sharon Bergquist, Niranjan Bose, Gates Ventures
- Walter Koroshetz, Deb Babcock, NINDS

Common Metabolic Diseases Steering Committee

Co-chairs
- Industry TBD
- Norann Zaghloul, NIDDK

EC Liaison
- Griffin Rodgers, NIDDK

OD Liaison
- Ellen Gadbois, Ellen Wann NIH/OD

Members
- Eric Fauman, Melissa Miller, Pfizer
- Melissa Thomas, Corey James, Eli Lilly
- Beena Alkokar, Norann Zaghloul, Afshin Parsa, NIDDK
- Karin Conde-Knape, Rasmus Rabøl, Oona Dierickx, Novo Nordisk
- Saptarsi Haldar, Narimon Honarpour, Erin Whalen, Amgen

RA, SLE Steering Committee

Co-chairs
- Marty Hodge, Pfizer
- Bob Carter, NIAMS

EC Liaison
- Lindsey Criswel, NIAMS

OD Liaison
- Ellen Gadbois, Ellen Wann NIH/OD

Members
- Dan Rotrosen, Ellen Goldmuntz, NIAID
- Francisco Ramirez-Valle, BMS
- Frank Nestle, Virginia Savova, Sanofi
- Fred Baribaud, Matt Loza, Janssen
- Marc Levesque, AbbVie
- Rab Prinjha, GlaxoSmithKline plc (GSK)
- Rohit Panchakshari, Takeda Pharmaceutical Company Limited
- Scott Jelinsky, Pfizer
- Stephen Alves, Nancy Kim, Merck
- Steven Taylor, Arthritis Foundation
- Susana Serrate-Sztein, NIAMS
- Teo Staeva, Mary Collins, LRA

Parkinson's Disease Steering Committee

Co-chairs
- Deb Babcock, NINDS
- Pablo Sardi, Sanofi

EC Liaison
- Walter Koroshetz, NINDS

OD Liaison
- Ellen Gadbois, Ellen Wann NIH/OD

Members
- David Glazer, William Marks, Verily
- Ekemini Riley, ASAP
- Gerald Podskalny, Billy Dunn, FDA
- Guhan Nagappan, GlaxoSmithKline plc (GSK)
- Richard Hargreaves, Leslie Shinobu, Celgene/BMS
- Robert Bell, Pfizer
- Suzana Petanceska, NIA
- Todd Sherer , MJFF
- Patrick Bellgowan, NINDS

Schizophrenia Steering Committee

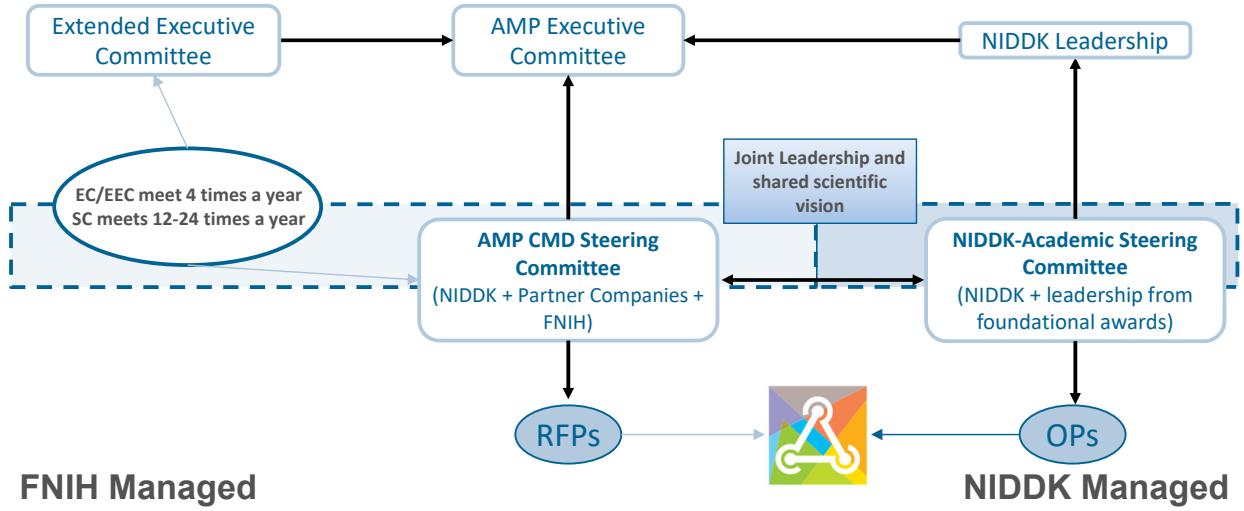
Co-chairs
- Linda Brady, NIMH
- Carlos Larrauri, NAMI

EC Liaison
- Joshua Gordon, NIMH

OD Liaison
- Ellen Gadbois, Ellen Wann NIH/OD

Members
- Adam Savitz, Gahan Pandina, Janssen
- Ken Duckworth, Teri Brister, NAMI
- Lynsey Bilsland, Wellcome
- Maria Tome, EMA
- Michael Davis, Bernard Fischer, FDA
- Michael Sand, Boehringer Ingelheim
- Mona Hicks, Brandon Staglin, One Mind
- Sharin Roth, Andy Forbes, Otsuka
- Tristan Gorrindo, APA Foundation

AMP CMD Program Management



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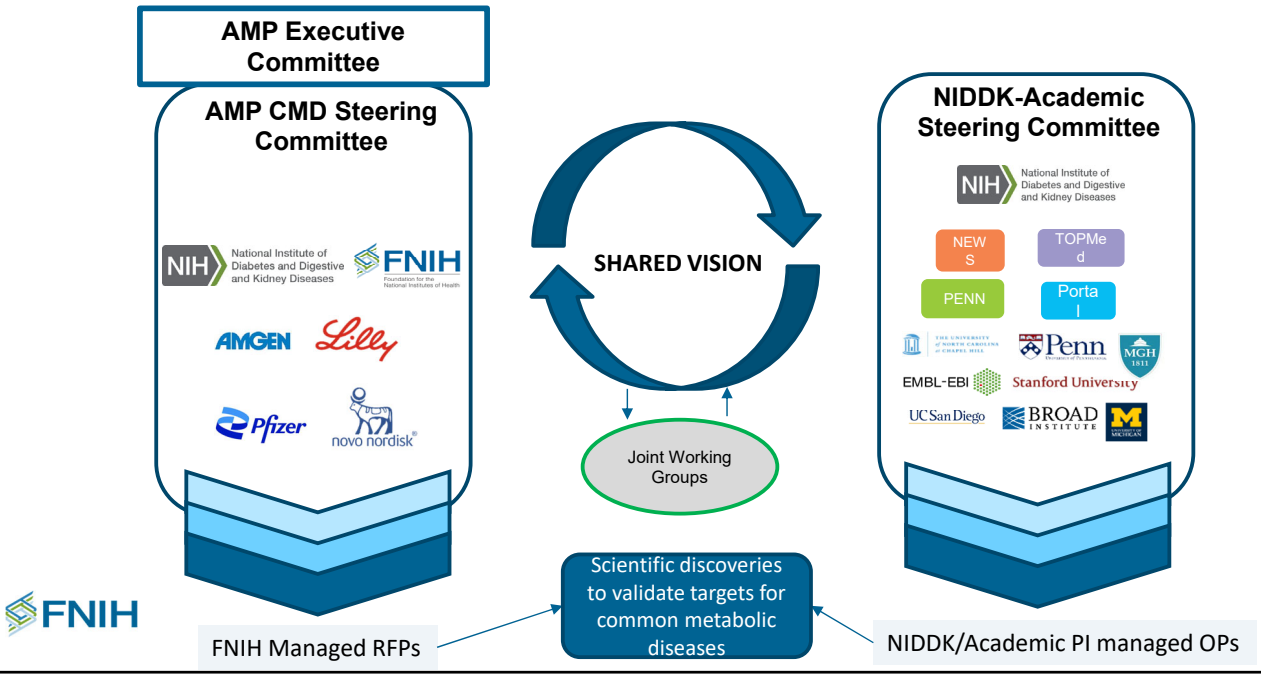
AMP CMD Consortium – Shared Vision, Independent Funding Streams



FNIH

AMGEN®

Saptarsi M. Haldar

Narimon Honarpour

Erin Whalen

FNIH

Lilly

Melissa Thomas

James Corey

FNIH

Rasmus Rabøl

Karin Conde-Knape

Oona Dierickx

novo nordisk®

FNIH

Pfizer

Eric Fauman **Melissa Miller**

FNIH

Accelerating Medicines Partnership Common Metabolic Diseases Research Plan

Melissa Thomas, MD, PhD

FNIH
Foundation for the National Institutes of Health

From Target Validation Consortium to Accelerating Medicines Partnerships

Unprecedented AMP public-private partnerships to improve therapeutic target identification and validation

- **2011:** Heads of NIH and Pharma R&D meet and agree: gaps in understanding human disease drivers fuel high drug attrition rates
- **2012:** Workshop and consulting drive consensus: **a key cause of drug failures is insufficient target validation**; broad support for private-public research collaboration to address gaps
- **2013:** Target validation consortium public-private technical groups form: collaboration designs and prioritizes plans for AMP projects
- **2014: AMP-T2D launches and far exceeds original vision**

World class "exemplar" knowledge portal combines growing, large scale genotype, phenotype, epigenetic, and genomic data

Evolving advanced analytic tools enable rapid, public access to accelerate translation of complex data to human target prioritization

- **2019-2021**: Productivity of AMP-T2D research expands scale of data and phenotypes, and generates new analytic tools and approaches to **set stage for accelerating common metabolic disease research**

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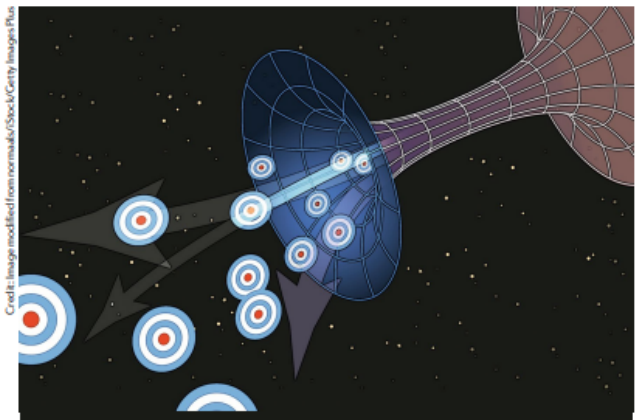


Nature Reviews Drug Discovery - February 27, 2019
https://www.nature.com/articles/d41573-019-00033-8

High Level Objectives and Approaches Guide Framing of AMP Programs: *Breakthrough Understanding of Key Diseases*

Problem

- We do not have systematic understanding of the pathways involved in complex diseases, and hence a clear idea of the right targets for intervention
- The few examples that exist of systematic investigation give us a tantalizing glimpse of the advances such efforts can provide
- No single group is positioned to do this efficiently: the scale is beyond that achievable even by large academic labs/ R01 grants, and the benefits too diffuse for any one pharma company to pursue. Necessary skills span these groups

Solution

- Systematic characterization of heterogeneous, poorly understood diseases in human populations, combining clinical and molecular information to facilitate rational selection of targets, identification of patients, subpopulations for trials and customized treatment decisions
- Working collaboratively across government, academia and industry through harmonized efforts that harness collective capabilities and scale

FNIH

Project Framing Considerations

Is this a high-priority research topic to pursue?

Impactful/ fundable

Strong potential to accelerate development of effective therapies

High ROI for industry funders - ie, resultant therapies likely to be:

- "Discoverable" in the near/ mid-term (eg, expected increase in # of POC starts within 5-10 years)
- Reimbursed by payers once brought to market

Feasible

High likelihood to achieve impact

- Acceptable level of scientific risk
- Existing foundation to build from (eg, academic experts, industry interest/ investment, publications, etc)

Is the topic "fit for purpose" for a private-public partnership focused on targets?

Requires a consortium effort

Addresses gaps in available target validation approaches

- Lack of robust, replicable data
- Inability to translate animal /cell data to successful human trials

Could not be successfully pursued by any one constituent

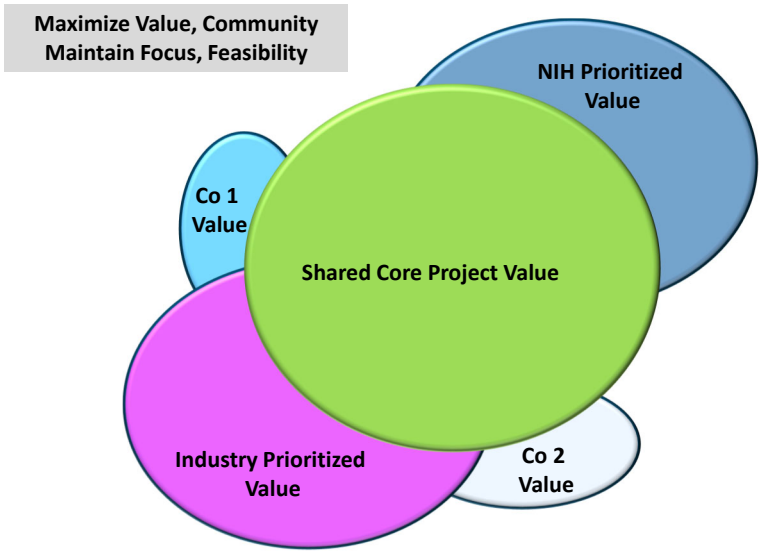
- Limitations in individual expertise, tools or resources
- Insufficient scale

Distinct from ongoing initiatives

Not currently being pursued – either at all, or at sufficient scale

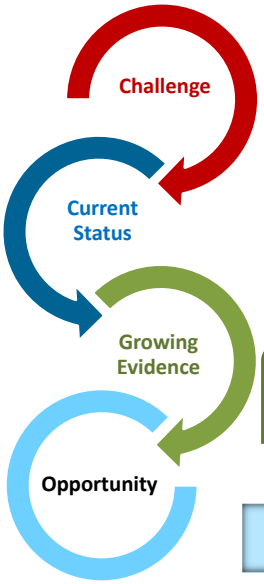
FNIH

In Private-Public Partnerships, Not All Project Activities are Prioritized by Every Partner, yet Project Yields Value for All



FNIH

Common Metabolic Diseases are Major Global Public Health Challenges



Common metabolic diseases collectively represent a major challenge for public health

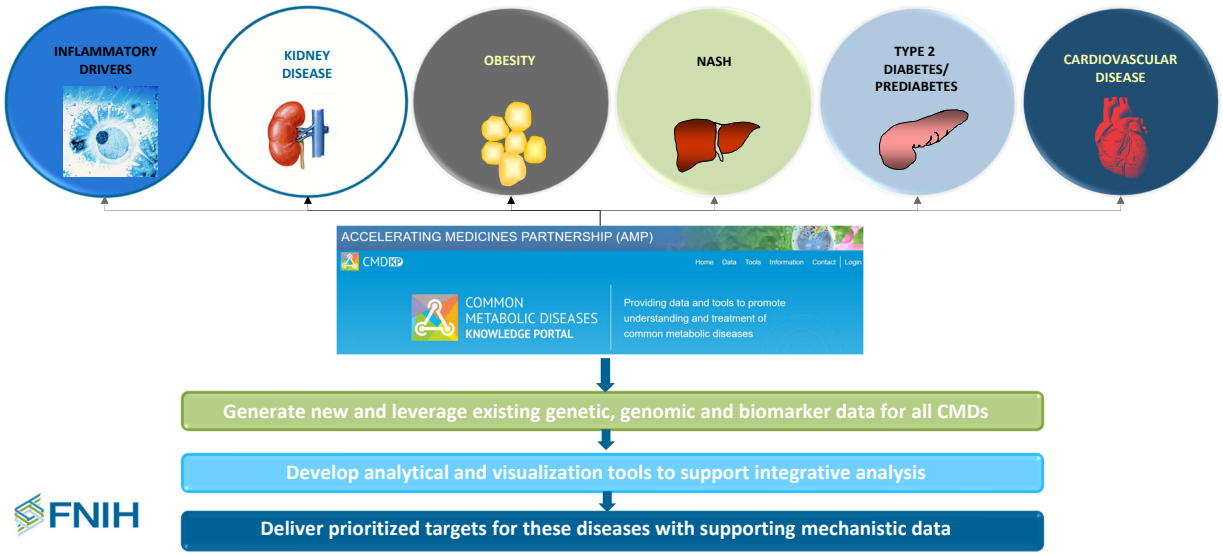
Therapeutic interventions have primarily targeted single diseases

Common pathogenic drivers likely exist across multiple common metabolic diseases

- Increased risk of developing additional common metabolic diseases if one occurs
- Individuals often experience several metabolic diseases throughout a lifetime
- Recent therapeutics for T2D also reduce risk of CVD, KD suggesting common disease drivers may be tractable

The opportunity to modify multiple metabolic disease outcomes by addressing common pathophysiologic disease drivers is compelling

AMP Common Metabolic Diseases Program will Evolve the Knowledge Portal and Prioritize Targets for Common Metabolic Diseases



Generate new and leverage existing genetic, genomic and biomarker data for all CMDs

Develop analytical and visualization tools to support integrative analysis

Deliver prioritized targets for these diseases with supporting mechanistic data

FNIH

AMP Metabolic Diseases: Program Overview

Part A: Knowledge Portal Expansion Module

CLINICAL DATA EXPANSION	HUMAN GENOMIC DATA EXPANSION	ENHANCED DATA HARMONIZATION AND INTEGRATION	NEW ADVANCED ANALYTIC TOOLS
• Phenotypes • Traits • Endotypes • Clusters • Biomarkers	• Genetic data • Genomic, epigenetic data • Tissue and single cell data • Perturbation data • Genome wide screens	• Genetic with genomic • Multi trait analyses • Endotypes and clusters • Biobank data scaling	• Target prioritization • Functional annotation (noncoding variants) • Cluster analyses • Pathways/networks

Part B: Disease-Focused Modules

NASH	KIDNEY DISEASE	CARDIOVASCULAR	OBESITY	DIABETES PRE-DIABETES	INFLAMMATORY DRIVERS
Prioritize, acquire, harmonize, and integrate existing high value genetic and genomic data in portal					
Enhance mechanistic understanding of disease					
Generate new disease-related data to address prioritized gaps for target identification					
Prioritize new therapeutic targets and elucidate their mechanism of action					

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How will the AMP CMD Research Partnership Accelerate CMD Disease Deconstruction and Therapeutic Development?

INNOVATION

- **Assemble global innovators**, emerging and established thought leaders within all-star academic investigator research teams
- **Discover new analytic approaches** and methods to deconvolute disease drivers
- **Incorporate technology advances** in deep molecular phenotyping to generate and integrate disparate data types

ENGAGEMENT

- **Bring industry and academic scientists together** with industry and academic perspectives to frame new research trajectories
- **Identify gaps in disease understanding**, proposing research options, and framing solutions to accelerate progress
- **Pursue therapeutic target prioritization** by triangulating data scale and dimensionality with speed of discovery

COMMUNITY

- **Attract diverse disease-focused communities** to share data and drive discovery across former silos
- **Collaborate across consortia** to combine and harmonize deep phenotypes, longitudinal outcomes data, genetic, and biomarker data at scale
- **Partner with biobanks and investigators to generate data** from human biosamples linked to clinical traits and outcomes

Thank you to all of the academic and industry scientists who demonstrated these values enabling AMP-T2D successes.

We look forward to our work together as we develop the AMP-CMD research community together!

FNIH

Accelerating Medicines Partnership Common Metabolic Diseases

National Institute of Diabetes and Digestive and Kidney Diseases

Norann Zaghloul, PhD

NIDDK

AMP CMD Launch Meeting

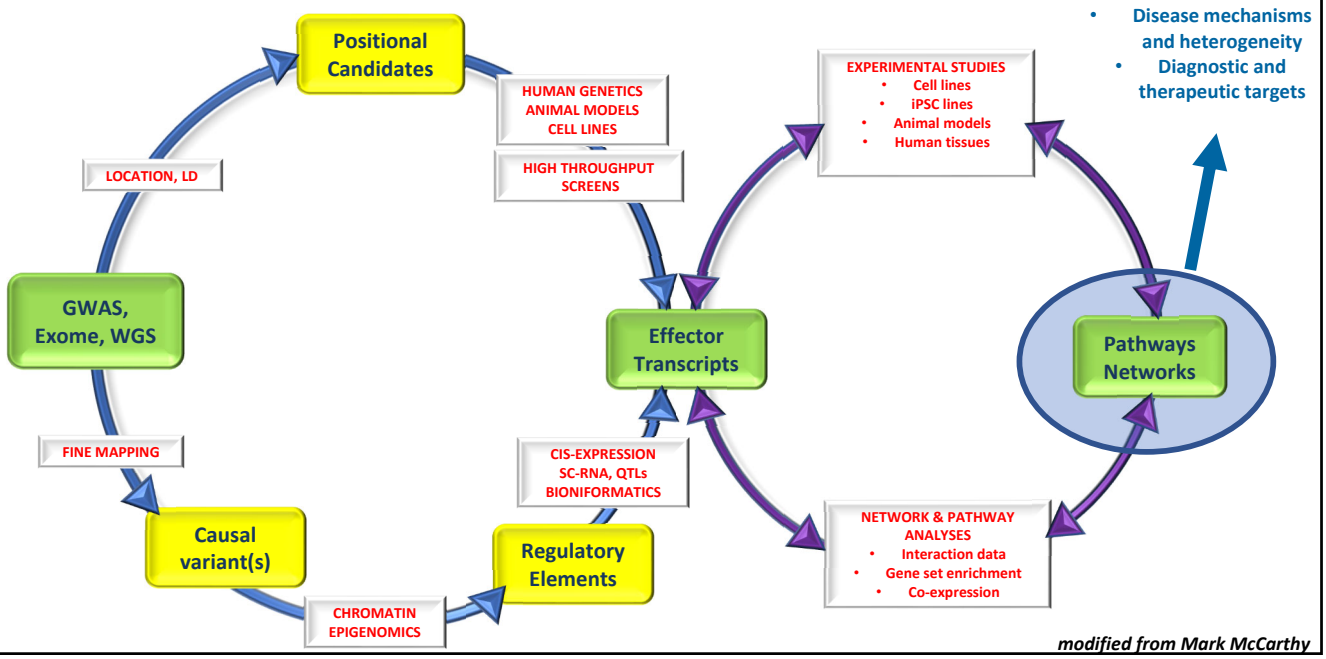
May 27, 2021

Building on the success of AMP T2D

- AMP T2D built an unprecedented resource for public access to T2D genomic data
- International catalog of large T2D/metabolic genomic datasets
- Data from over 1.5M individuals
- An expanding suite of powerful analytic tools that are free and easily accessible

- *Setting the stage for the next challenges*
  - Expanding this success
    - Complications
    - Related metabolic diseases
  - Making sense of it all

Translating variants to knowledge



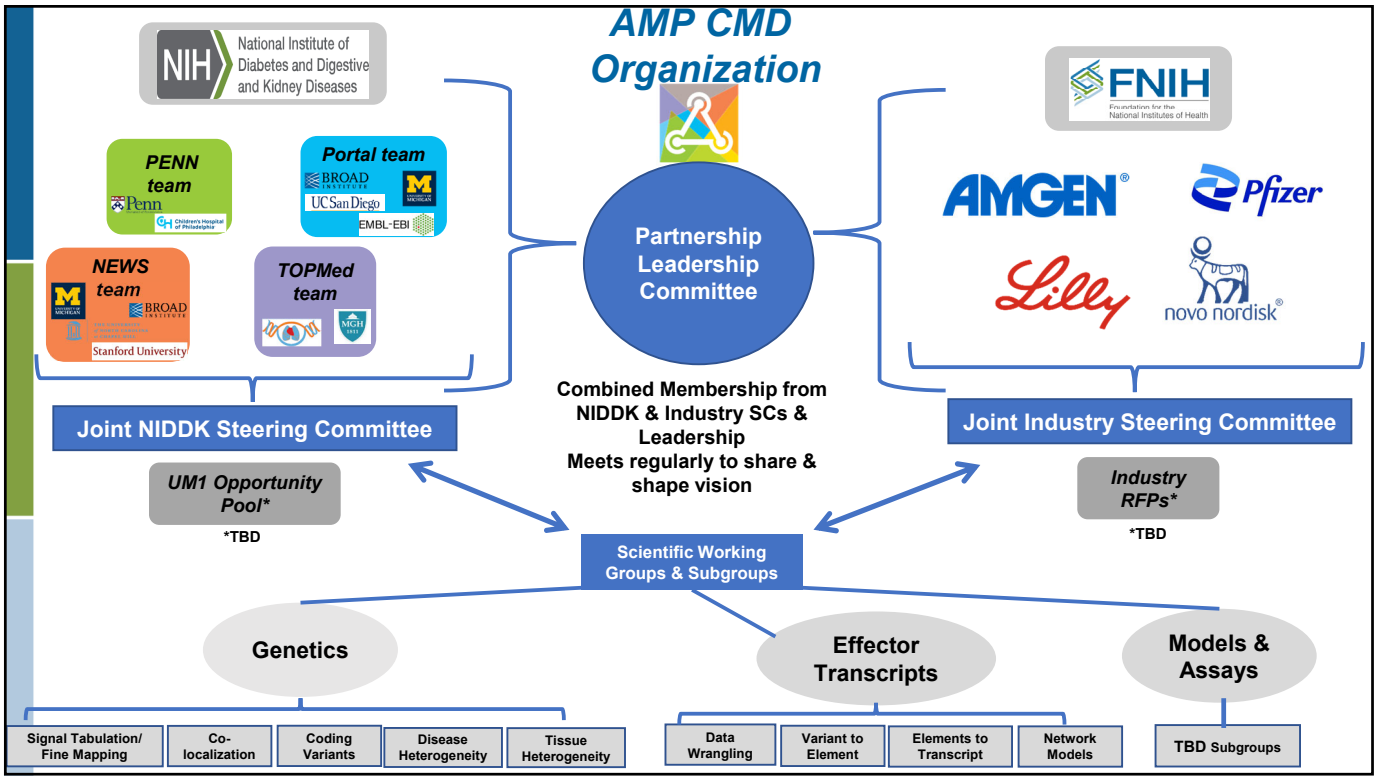
modified from Mark McCarthy

NIDDK Foundational Support for AMP CMD

- NIDDK issued two calls in late 2019 for projects to form a new consortium that will leverage the successes of AMP T2D
- Four foundational projects were selected for NIDDK funding through Cooperative Agreements, launched in August 2020
- The funded projects include continued support for the Knowledge Portal as well as three Functional Genomics Projects that will use large scale -omics and targeted experimental approaches to identify effector transcripts and elucidate their functional impact in a range of metabolic tissue and cell types

NIDDK Foundational AMP CMD Awards

Portal Team	NEWS Team	Penn Team	TOPMed Team
Jason Flannick Noel Burtt Michael Boehnke	Karen Mohlke Jose Florez Anna Gloyn Stephen Parker	Patrick Seale Struan Grant Klaus Kaestner Daniel Rader Benjamin Voight Wenli Yang	James Meigs
Continue to develop and expand the AMP-CMD Knowledge Portal (CMDKP). This KP is a public resource of genomic datasets and analysis tools relevant to metabolic diseases including T2D, its complications, and related traits.	Identify the causal variants, the regulatory gene networks affected by the change in DNA sequence, and the mechanisms by which such variation leads to disease.	Functionally interrogate genomic variants and their target genes in human stem cell-derived models and mice.	Use whole genome sequence data from TOPMed to identify novel common and rare variants associated with T2D and quantitative traits and to use other omics data towards identification of target genes and pathways in relevant metabolic cell types



AMP CMD Scientific Working Groups

- **Genetics**

  "Aggregate and integrate human genetics association data sets to identify and characterize and disseminate signals related to T2D and related traits to support the activities of other working groups

  · Identify genetic datasets, synthesize distinct association signals for T2D, QTs, complications
  · Identify and prioritize credible set variants at these signals
  · Identify coding variants that suggest/implicate effector genes via Exomes or other data (with Effector Transcripts WG)
  · Use datasets from multiple individuals to identify QTL; colocalize with GWAS (with Effector Transcripts WG)
  · Consider impact of tissue and cell-type heterogeneity in QTL data (with Models and Assays WG)
  · Characterize individual disease heterogeneity"

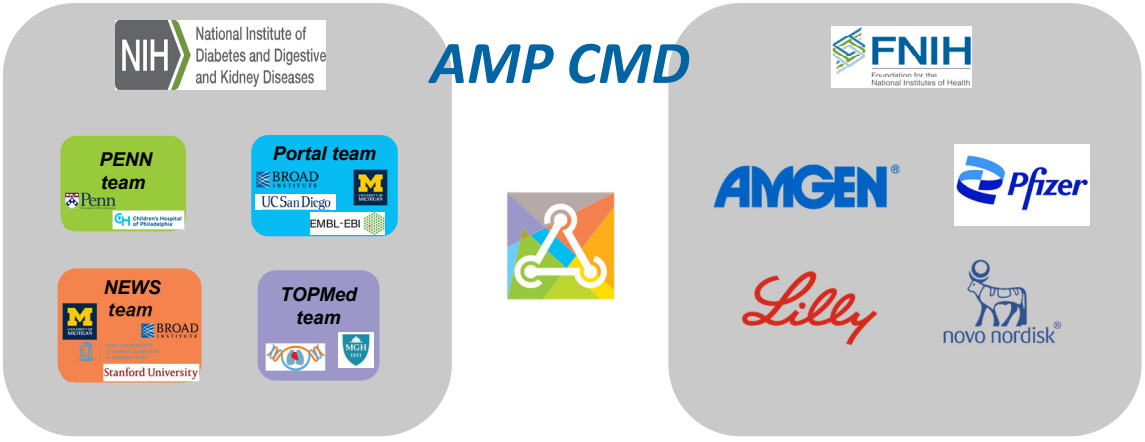
- **Effector Transcripts**

  "Apply and compare strategies to prioritize effector transcripts at GWAS signals for T2D and related traits. We will identify the relevant contexts for effector transcripts, including key regulatory elements, cell types, and cell states. Finally, we will integrate effector transcripts, along with their associated contexts, into network models to implicate nodes/hubs, with particular attention to those sensitive to eventual targeted perturbation."

- **Models and Assays**

  "Bring together researchers across the career life-span (student to PI) working in three main areas: *1. animal models, 2. cell model development 3. assay development,* to achieve the following objectives:

  · Share expertise in animal and cell model development
  · Share tools (as possible) across the UM1 consortium
  · Consensus building on assay and cell model validation
  · Design and create new common tools for work across the UM1
  · Provide a platform to discuss and interpret data from cellular assays
  · Reach consensus on data interpretation to support effective gene prioritization
  · Advise on how cellular data can be formatted for deposition into the portal"

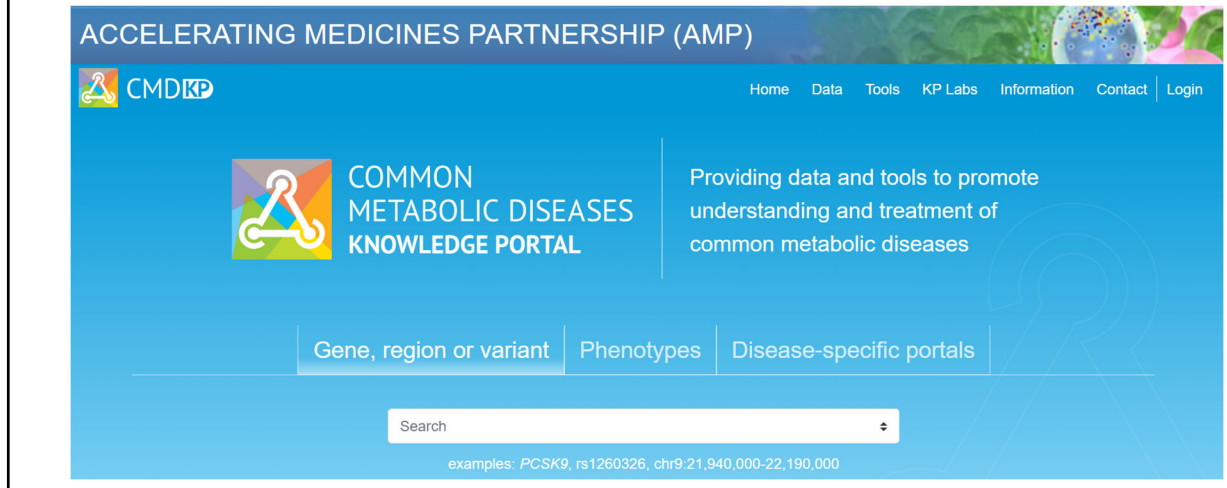


Evolution of AMP Knowledge Portal & plans for AMP CMD

Noël Burtt
Jason Flannick

May 27, 2021

AMP Accelerating Medicines Partnership
Common Metabolic Disease



cmdkp.org

An open-access resource that presents integrated & analyzed genetic & genomic data to spark insights into complex metabolic diseases & traits

How it started:

Target Validation Consortium: Type 2 Diabetes Technical Group
Detailed Research Plan

Contents

Vision

How its going:

ACCELERATING MEDICINES PARTNERSHIP (AMP)

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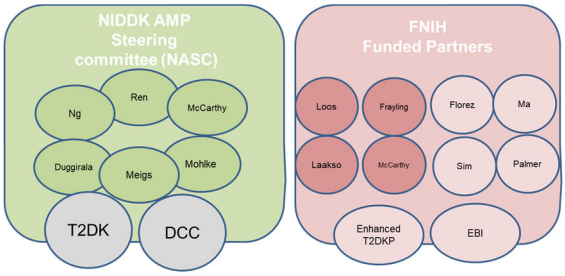
12:40 - 12:50PM	**NIDDK Divisions: Diabetes, Kidney, Digestive Diseases**	
12:55PM	**Next Steps and Adjournment**	**Tania Kamphaus**, FNIH

Program

How it started:



18 Awardees

How its going:

26 Awardees
140+ investigators & full time staff

How it started:

2 Portal staff members

How its going:

Team

Alumni

Ben Alexander
Mary Carmichael
Todd Green
Tad Jordan
Ali Kluge
Michael Sanders
David Siedzik
Marcin von Grotthuss
Kaan Yuksel

Matrixed team with alumni

How it started:

T2D-GENES

oT2D

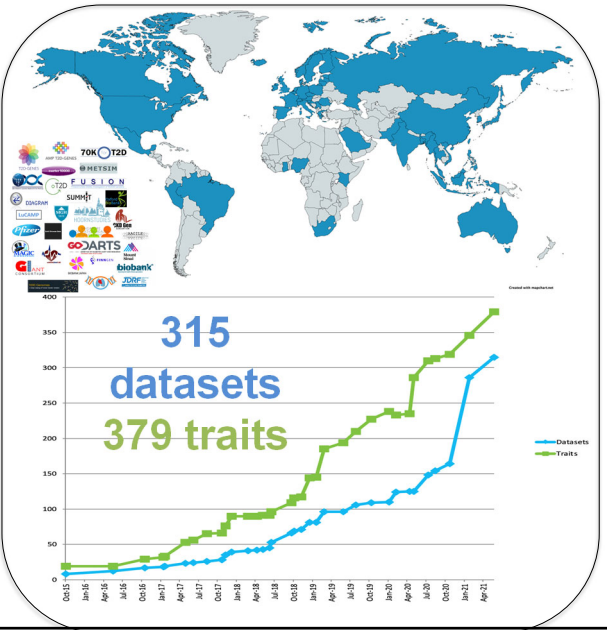
Slim Initiative in Genomic Medicine for the Americas

MAGIC

DIAGRAM

9 Datasets
25 traits

How its going:



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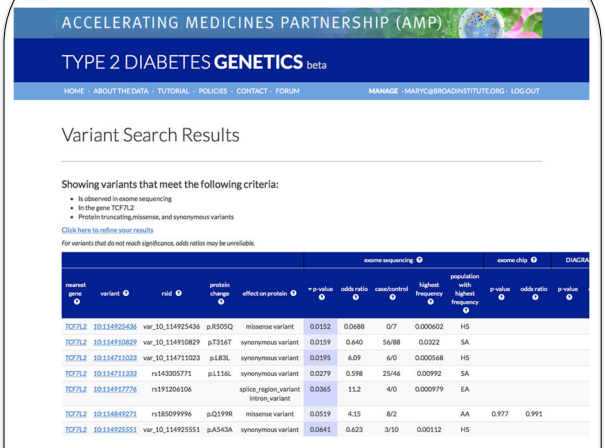
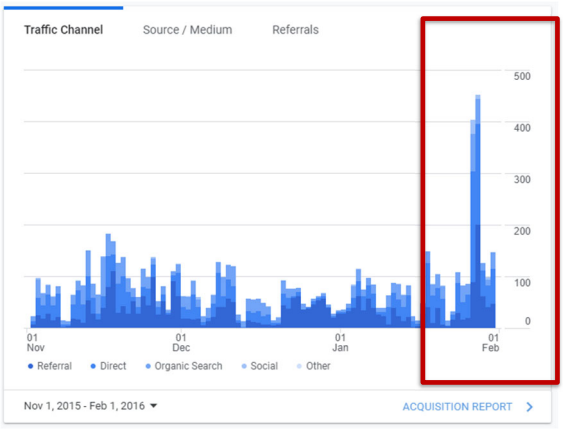


Tables with lists of results

Intuitive, Integrated Visualizations

How it started:

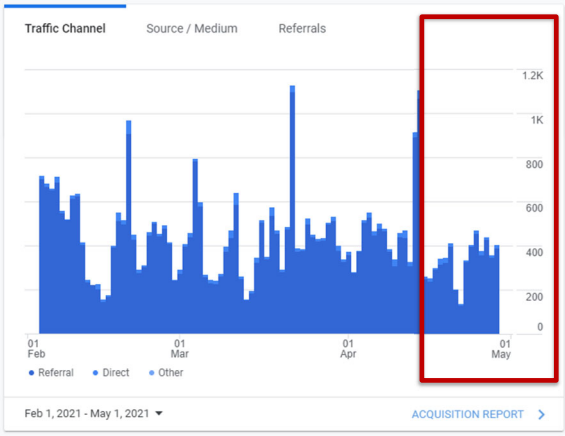
First 3 months



Local community usage

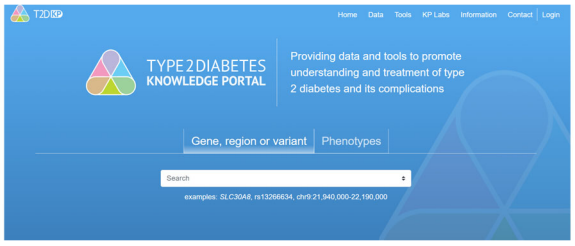
How its going:

Last 3 months



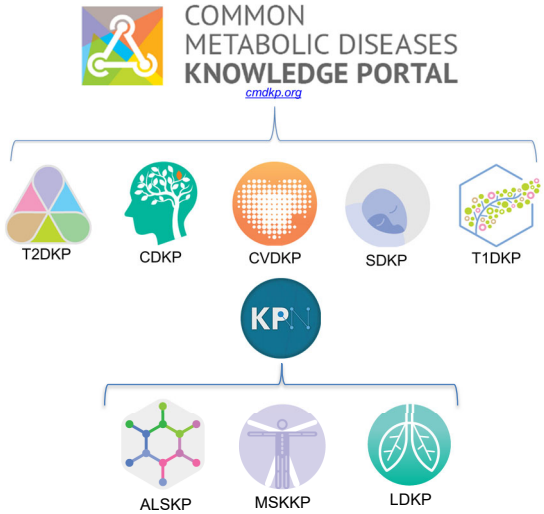
International Resource

How it started:



1 Portal

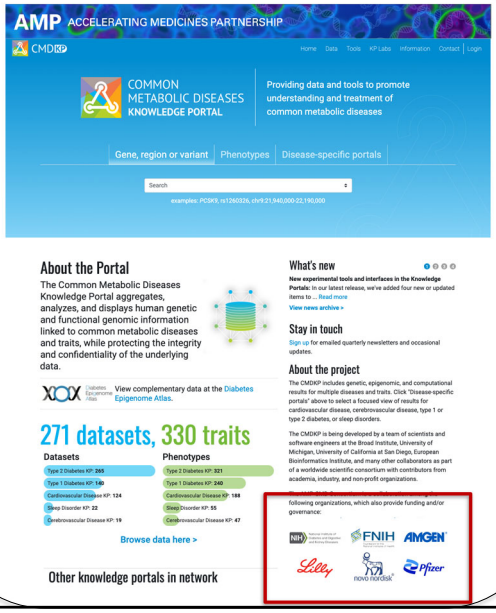
How its going:



8 Portals

How it started:

How its going:



How it started:

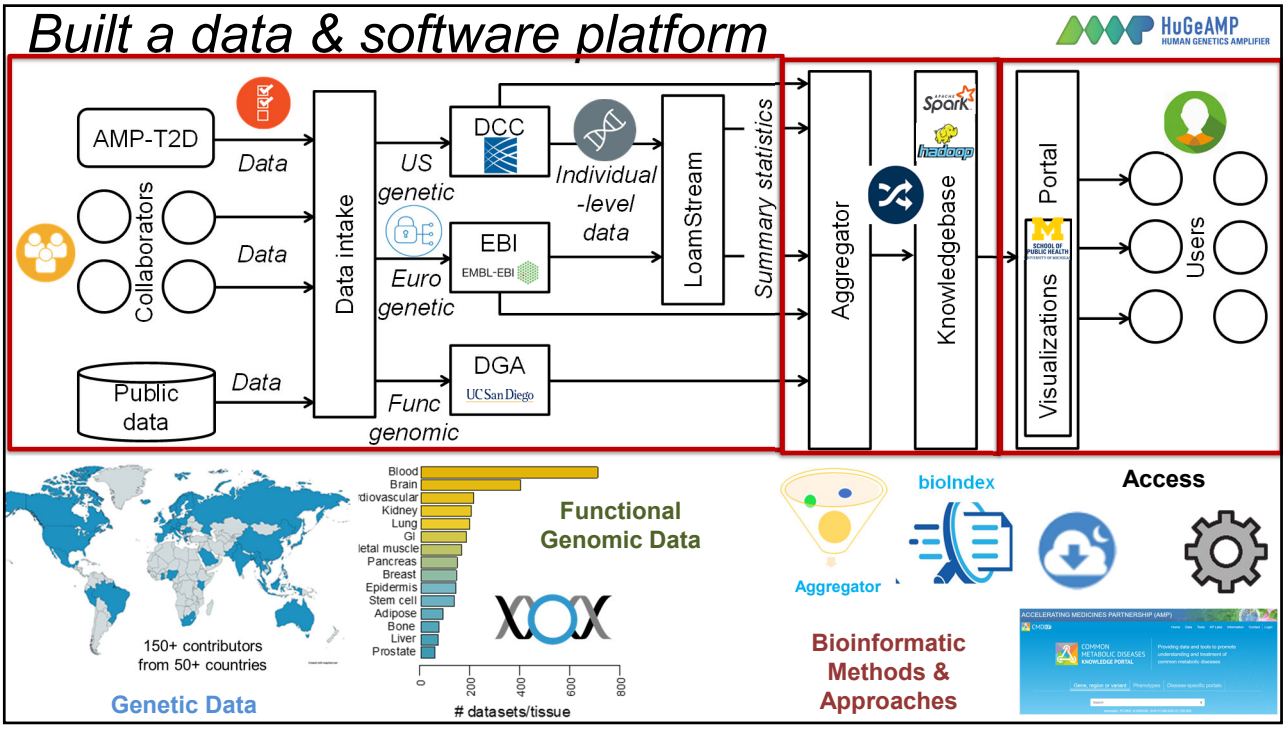
How its going:

We will miss you, Phil!

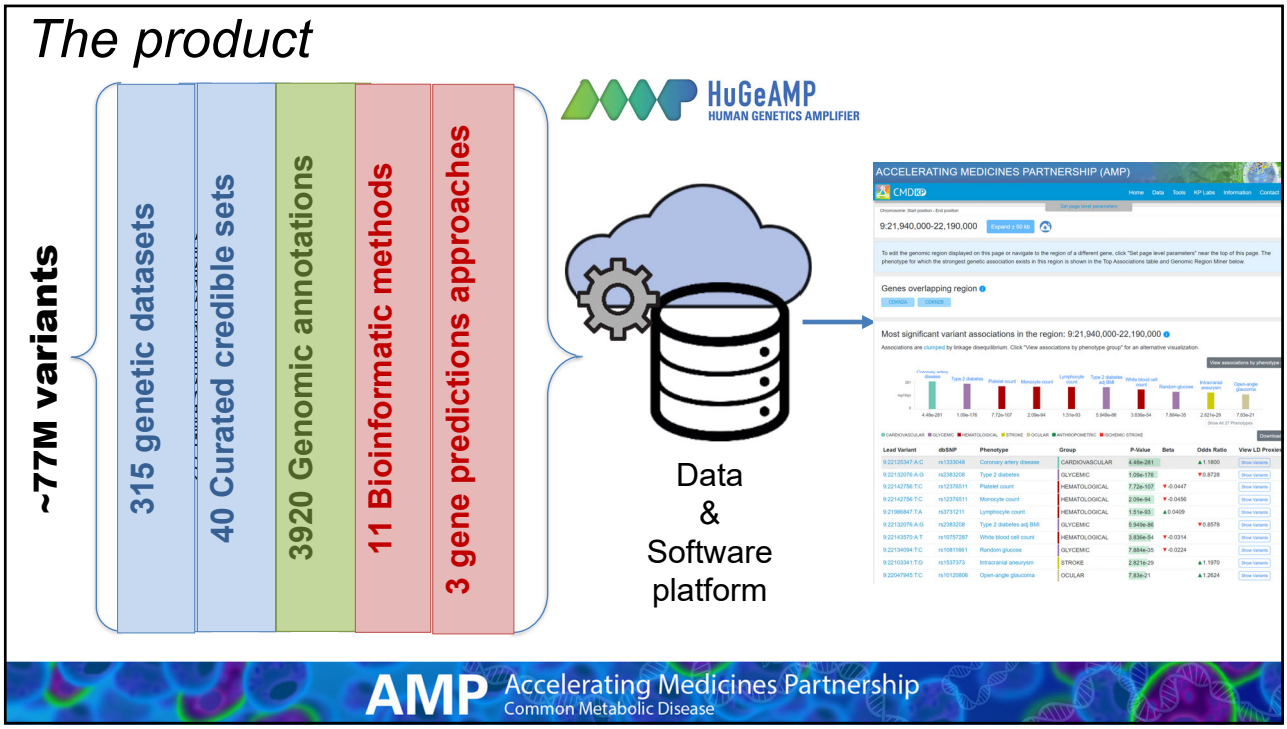
How did we do this?

AMP Accelerating Medicines Partnership
Common Metabolic Disease

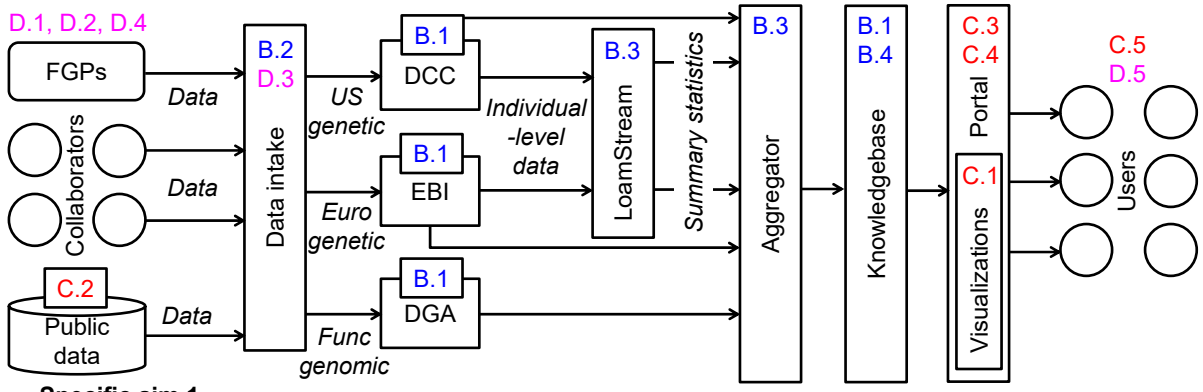
Built a data & software platform



The product



Our award



Specific aim 1

B.1. Represent additional data types
B.2. Identify and integrate new data
B.3. Develop new pipelines to analyze these data
B.4. Enable public access to these data

Specific aim 2

C.1. Develop new tools to visualize these data
C.2. Augment tools to integrate other public data
C.3. Maintain curated lists of T2D mechanisms
C.4. Allow users to customize data and tools shown
C.5. Update portal in response to stakeholders

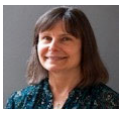
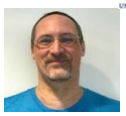
Specific aim 3

D.1. Provide operational support to AMP-T2D
D.2. Foster collaborations with external partners
D.3. Track and timely release data
D.4. Administer opportunity pool funds
D.5. Conduct outreach and training

Team

Broad/DCC
Kenneth Bruskiewicz
Lizz Caulkins
Maria Costanzo
Marc Duby
Clint Gilbert
Quy Hoang
DK Jang
Ryan Koesterer
Jeffrey Massung
Oliver Ruebenacker
Preeti Singh

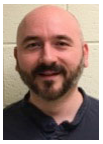







UM
Ryan Welch
Andy Boughton
Alan Kwong
Laura Scott




UCSD/DGA
Parul Kudtarkar
Ying Sun
Sharvari Narendra



Leadership
Jason Flannick
Noël Burtt
Mike Boehnke
Kyle Gaulton
Thomas Keane
Jose Florez






HuGeAMP
HUMAN GENETICS AMPLIFIER

Primary focus: maintain the CMDKP

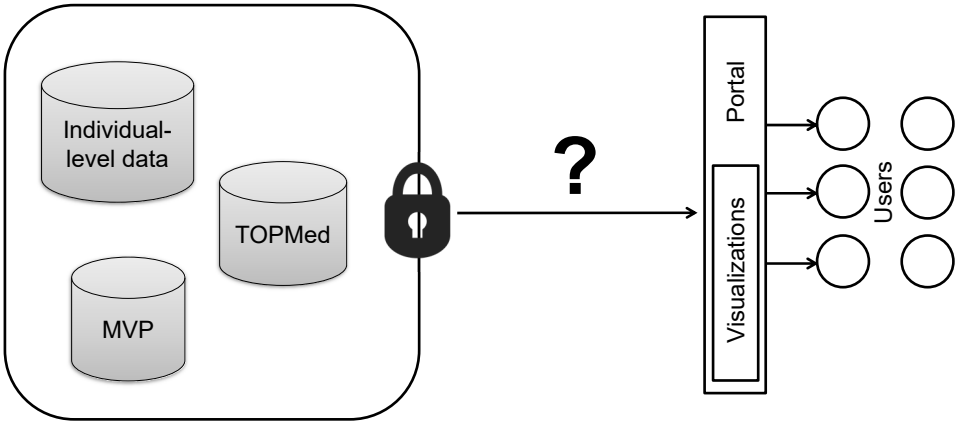
- Identify new datasets inside and out of the consortium
- Transfer these to the DCC, QC/analyze them as needed, and represent them on the portal
- Maintain and extend web-based tools for accessing and visualizing these data
- Provide operational support for the consortium
- Manage consortium-wide data tracking

But, in addition:

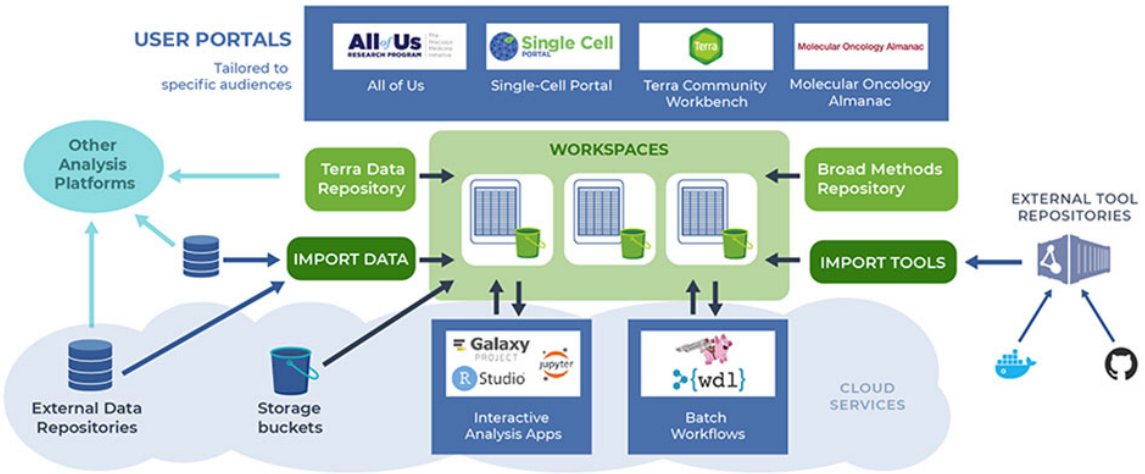
Research and develop new ways to improve the accessibility of data to help translate genetic associations to biological insights

Aim 1: one area of focus

- Making protected data more accessible



The rise of data commons



- High barrier of entry to those who want simple summaries of the data

An example

HuGeAMP HUMAN GENETICS AMPLIFIER

Genetic Association Interactive Tool

Start by entering a gene name, then select one or more masks to filter the available variants. Click "Search Variants" to see the list of available variants. Individual variants may be removed from the list by un-checking them. Next, select a dataset, one or more phenotypes, and one or more methods. Click "Run analysis" to see gene-level association scores for each phenotype and method.

Association statistics for selected variants

Criteria — SLC30A8 5/5

Variants — TopMed | Fasting glucose | Type 2 diabetes | Collapsing Burden

Results

Fasting glucose

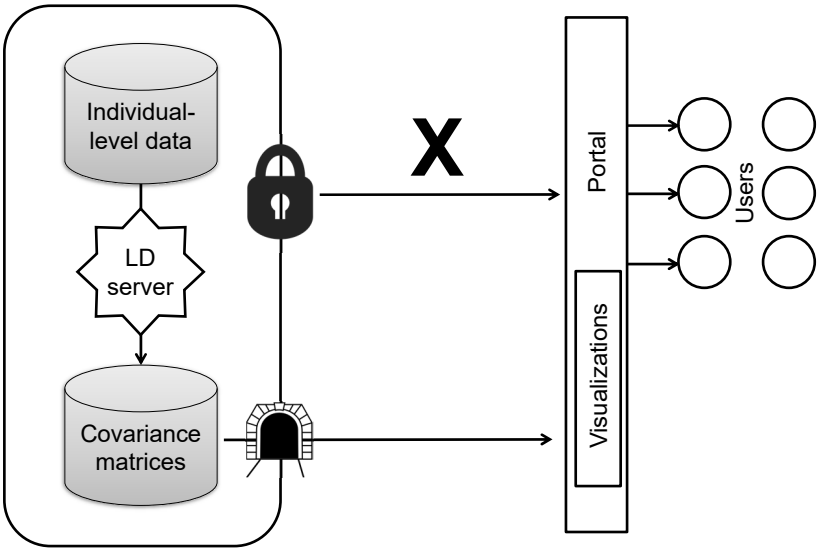
Test	Variants	Z-Score	P-Value	Beta	Standard Error	Sample Size
Collapsing Burden Show Plot	19	-3.5921937	0.0003279	▼ -0.1107	0.0308079	26,807

Type 2 diabetes

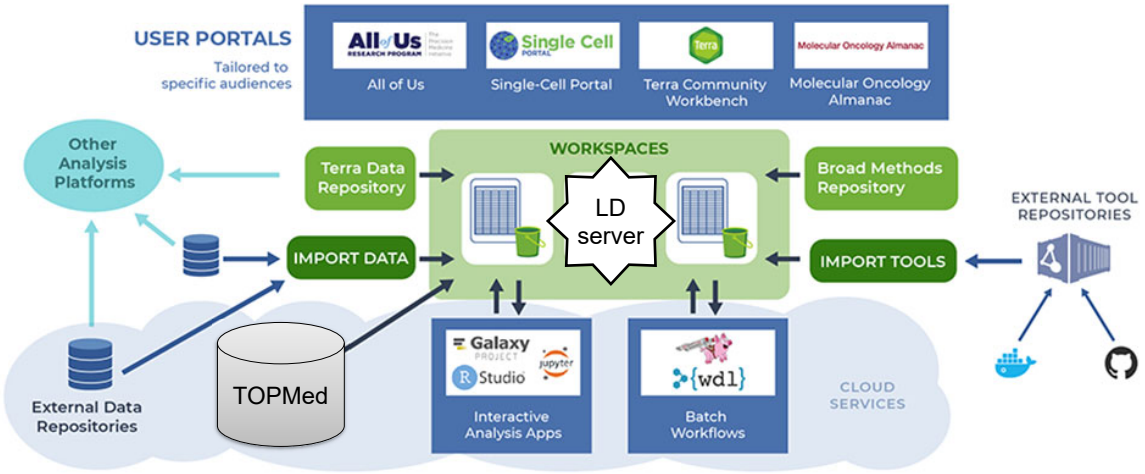
Test	Variants	Z-Score	P-Value	Odds Ratio	Standard Error	Sample Size
Collapsing Burden Show Plot	24	-2.9837776	0.0028471	▼ 0.7030	0.1180989	44,083

Implementation of GAIT

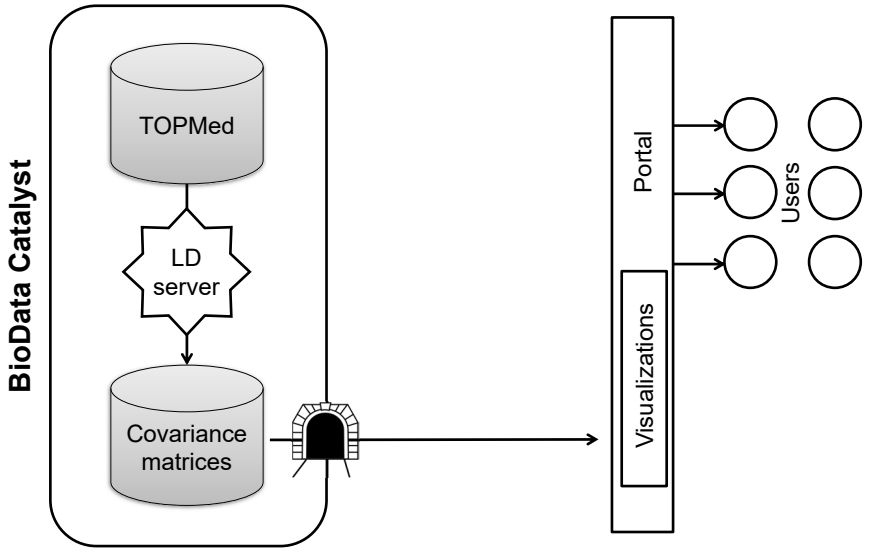
HuGeAMP HUMAN GENETICS AMPLIFIER



Next extension: TOPMed + BioData catalyst

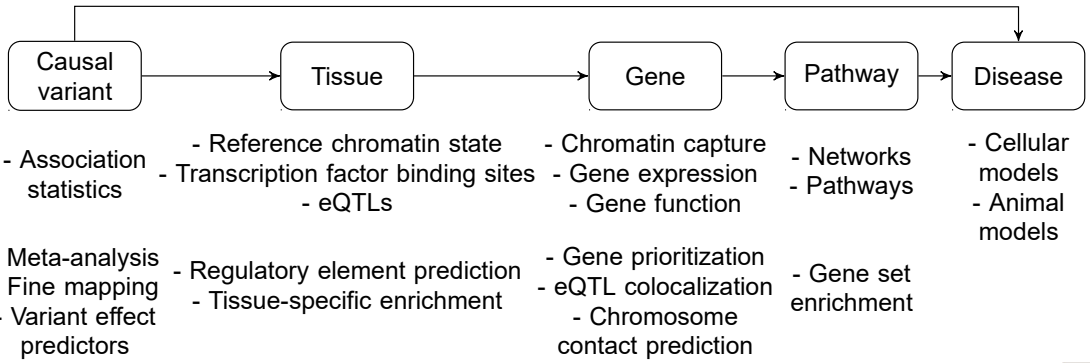


Next extension: TOPMed + BioData catalyst

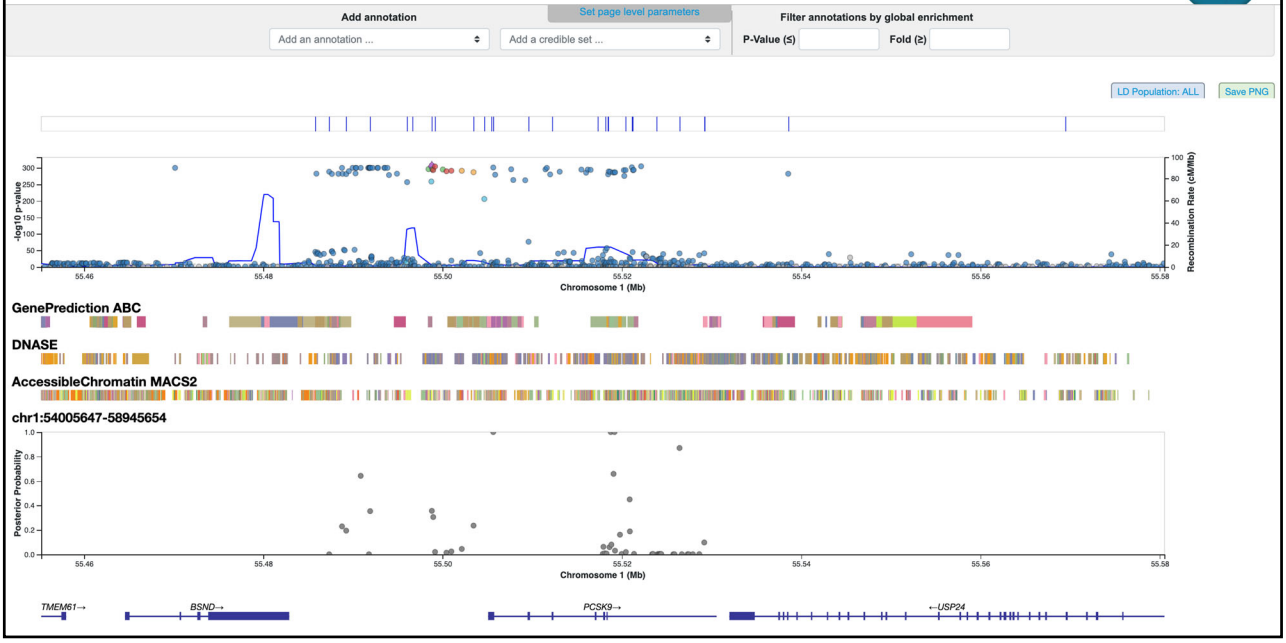


Aim 2: one area of focus

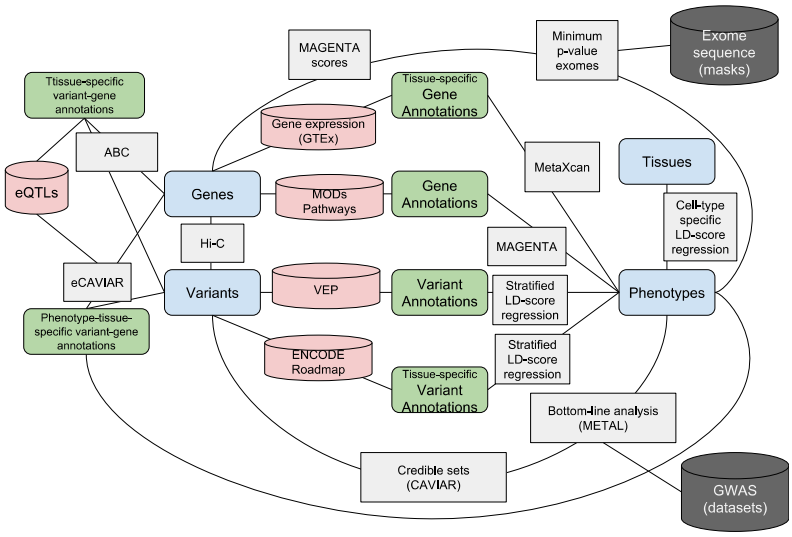
- Representing functional genomic data



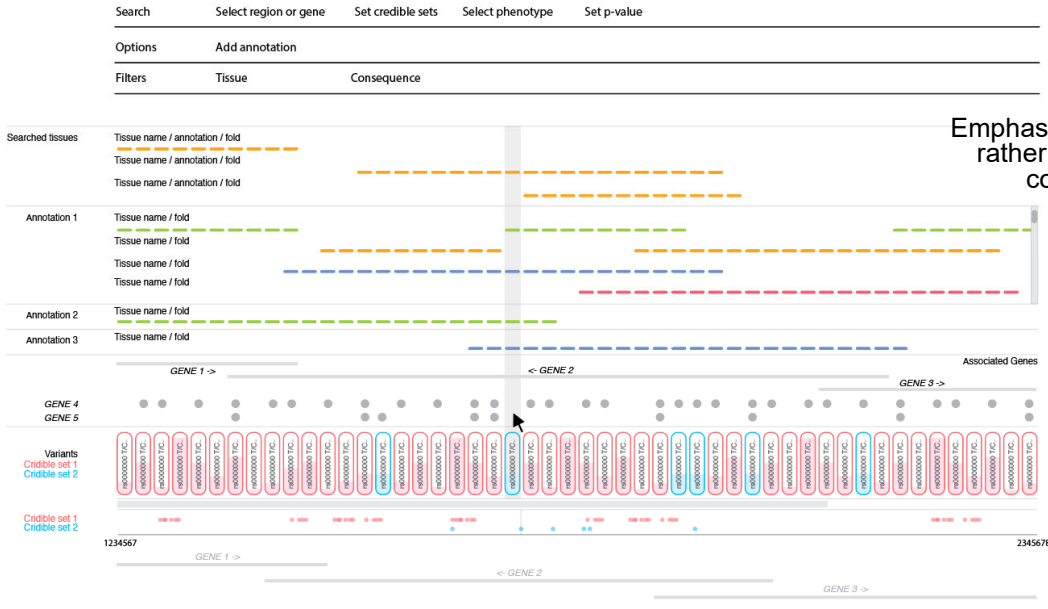
Standard browser view



Another model: relationships



Alternative visualizations



Emphasize relationships rather than genomic coordinates

Leverage integrated data

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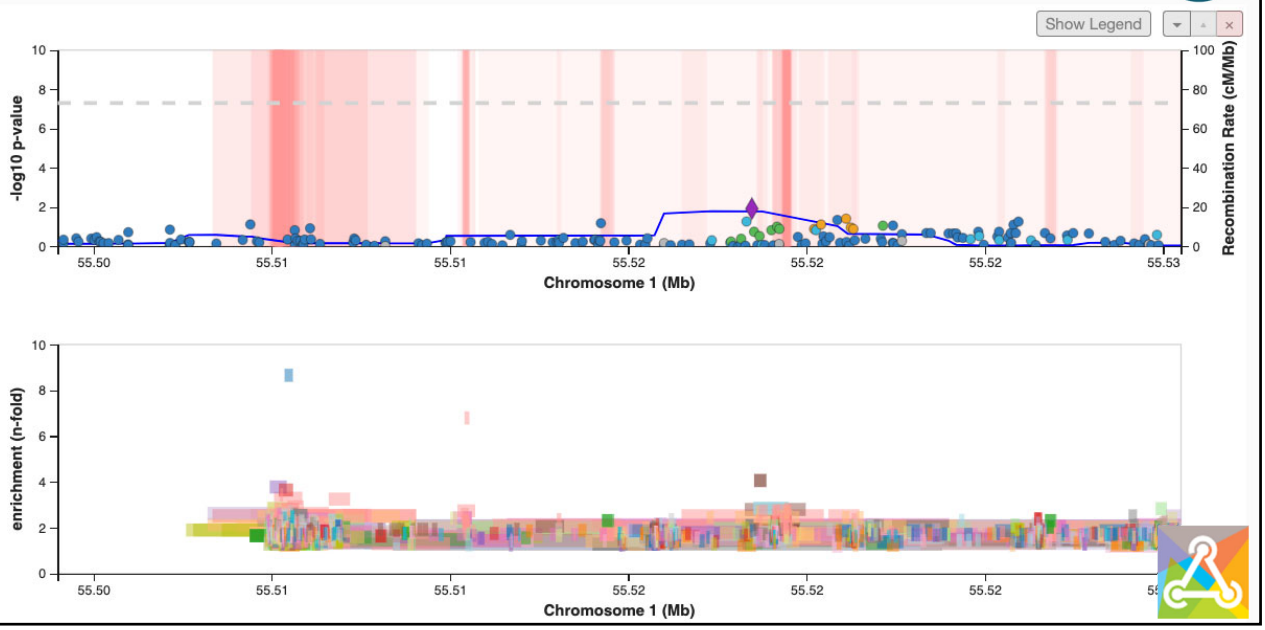
HUMAN GENETICS AMPLIFIER

KPN



Evolution of analytical tools and plans for AMP CMD

Michael Boehnke for the Michigan team

AMP CMD Inaugural Meeting, May 27, 2021

FNIH
Foundation for the National Institutes of Health

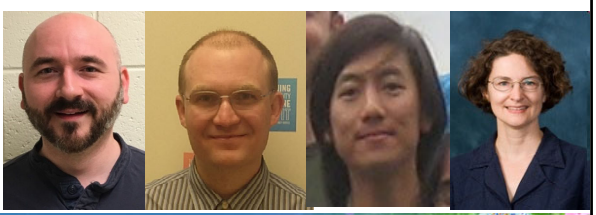
Acknowledgements

Michigan: **Ryan Welch, Andy Boughton, Alan Kwong, Laura Scott,** Daniel Taliun, Peter VandeHaar, Chris Clark, Matthew Flickinger, Sebanti Sengupta, Seunggeun Lee, Hyun Min Kang, Gonçalo Abecasis

Broad DCC: Noël Burtt, Jason Flannick, Jose Florez, Jeffrey Massung, Kenneth Bruskiewicz , DK Jang, Marc Duby, Maria Costanzo, Lizz Caulkins, Clint Gilbert, Quy Hoang, Ryan Koesterer, Oliver Ruebenacker, Preeti Singh

UCSD: Kyle Gaulton, Parul Kudtarkar

Funding: FNIH, NIH. Thanks!



Michigan team role in the portal project

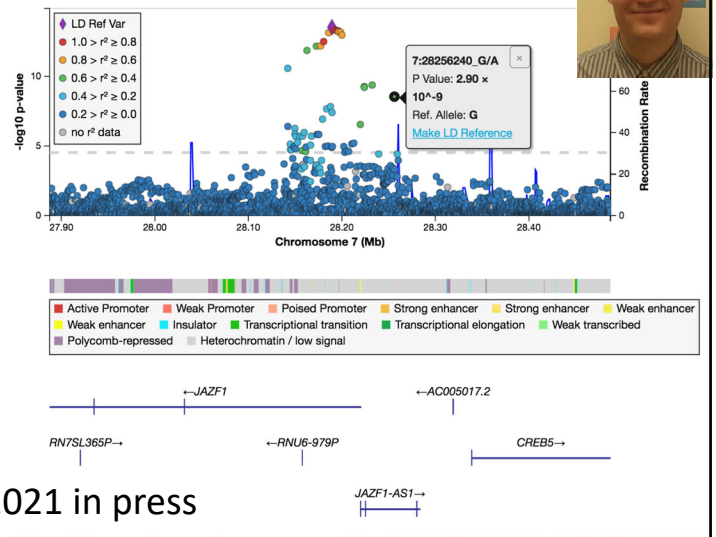
- Goal: accelerate investigation and discovery for common metabolic disease genetics
- Build tools for data analysis and visualization to facilitate data exploration
- Integrate tools onto the portal while also making them broadly available as standalone tools
- Examples: LocusZoom, PheWeb, bottom-line analysis, FIVEx, …

LocusZoom: explore GWAS results

Visualization tool for regional plotting of association results

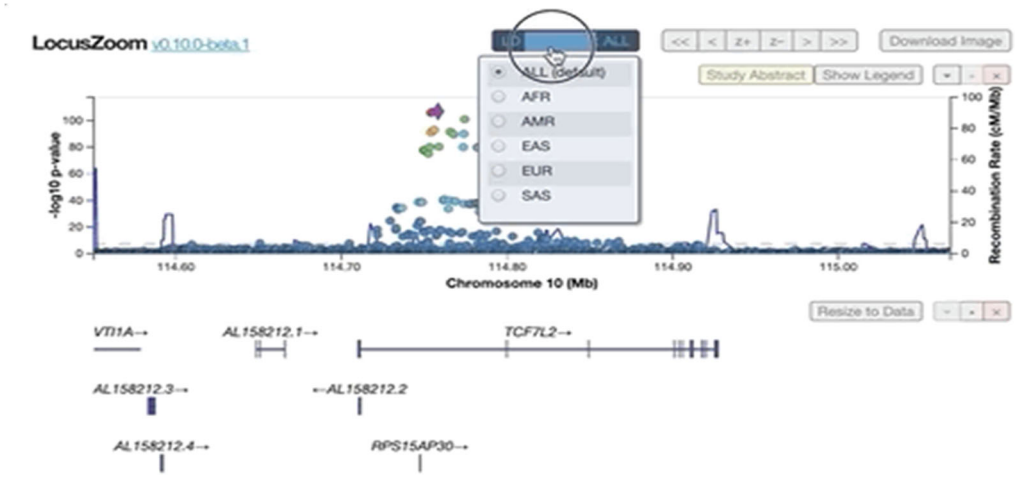
Originally a command-line tool in R and Python (Pruim, Welch et al. 2010)

Now interactive web version deployed on portal, PheWeb, and my.locuszoom.org



Boughton et al. *Bioinformatics* 2021 in press

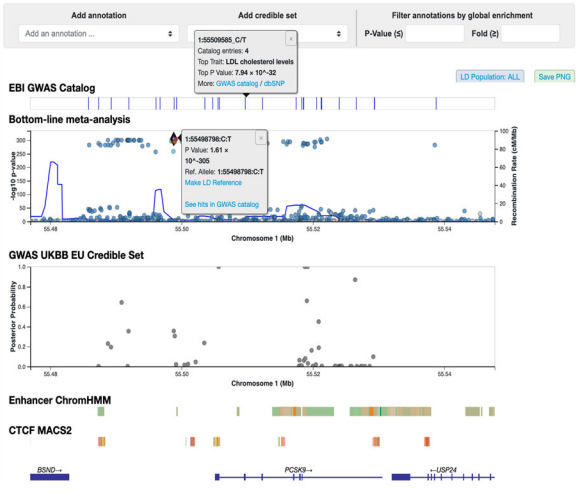
Population-specific linkage disequilibrium (LD)



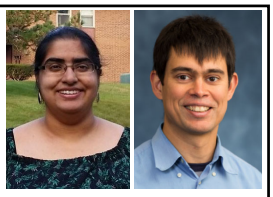
Powered by Michigan LDServer

Joint display of regional plots and annotation tracks

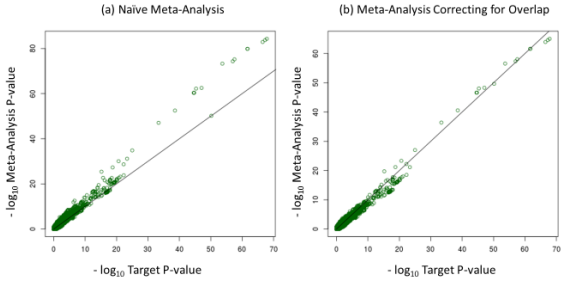
- Specify a regional association plot
- Choose from wide range of annotations to build customized display within the browser
- Customized information shown in dropdown menus and the chosen panels are stacked
- Filter results based on p-value or fold change for enrichment analysis



Bottom-line analysis

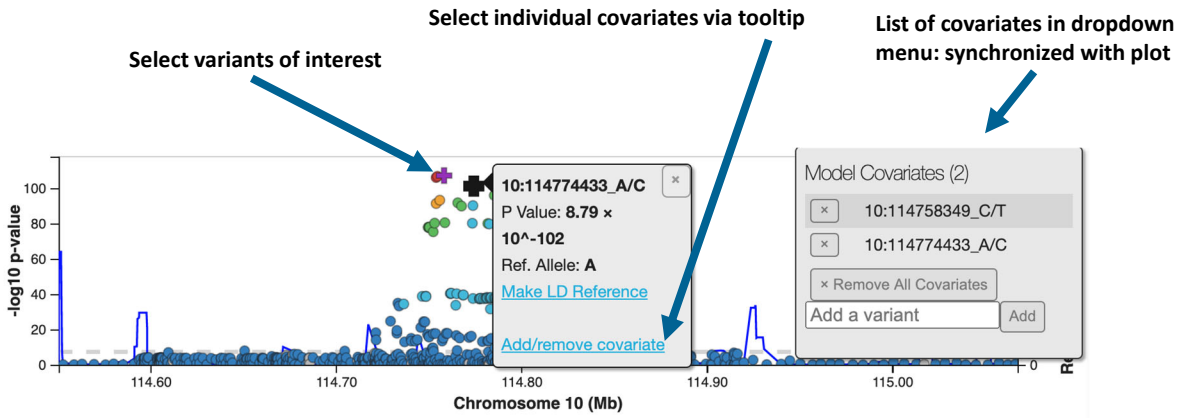


- Portal includes results for many (overlapping) datasets
- Naive meta-analysis ignores overlap, misstates evidence
- We (Sengupta et al. 2021) developed method to estimate the overlap and adjust for it
- Use pair-wise correlation estimates between Z-scores to estimate overlap and adjust meta-analysis weights
- Incorporated into METAL, portal
- Example: HDL cholesterol



Planned near-term additions to LocusZoom and the portal

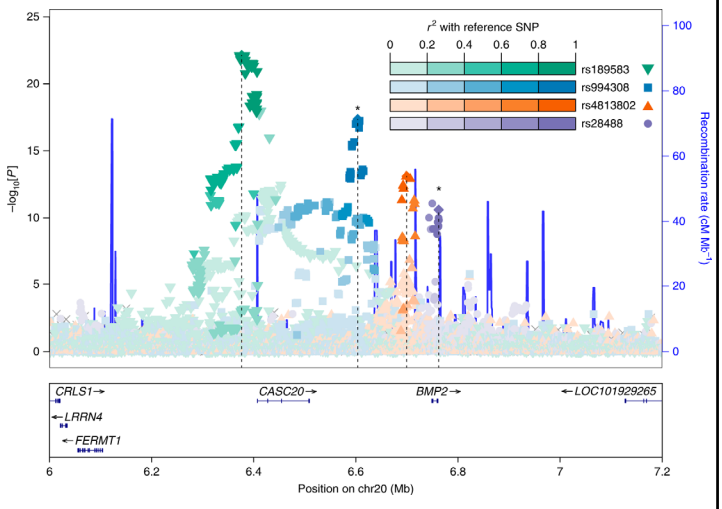
Conditional analysis: proposed user interface



Results will be shown by re-drawing same points with new p-values. Toggle view (before/after conditioning).

Display LD for multiple signals on same plot

- Conditional analysis often identifies multiple independent signals
- Useful to differentiate multiple signals on one plot
- This example uses color for that purpose
- Huyghe et al. *Nat Genet* 2019



Aggregation tests: WGS data on the portal

- On-the-fly rare variant aggregation tests are available for exomes on the portal
- WGS data: (a) individual-level or (b) summary statistics and covariance matrices
- Individual-level data: GoT2D, METSIM (soon)
- Summary statistics: TOPMed
- Updating LocusZoom and portal (covariance ingest pipeline, storage) to handle WGS data
- Continue to intake relevant non-coding annotations

Under development: eQTL browser

FIVEx: Visualization for Genotypes, Expressions, and Tissues

Search for a variant, region, or gene: chr19:488506, rs10424907, or SHC2

Search for: **Variant by position:** chr1:109274968 • chr2:21044589 • **rsID:** rs12740374 • rs934197
Region: chr1:108774968-109774968 • chr2:20501429-21544073 • **Gene:** *SORT1* • *APOB*
First time? **View the tutorial here** to see what FIVEx can do

https://eqtl.pheweb.org/

- A new tool to explore and compare eQTLs
- Two different views of gene expression associations
  - Region view: effects of multiple variants on a single gene in a single tissue
  - Variant view: effect of a single variant on multiple genes across multiple tissues
- Real-time visualization to suit researcher needs

Kwong, Boughton, Wang, VandeHaar, Boehnke, Abecasis, Kang, *Bioinformatics*, in revision

eQTLs: region view

Explore variants' effects on gene expression in different tissues
- Compare genes/tissues in stacked plots
- Show LD information across panels

Multiple eQTL metrics
- P-value
- Effect size
- Posterior inclusion probability

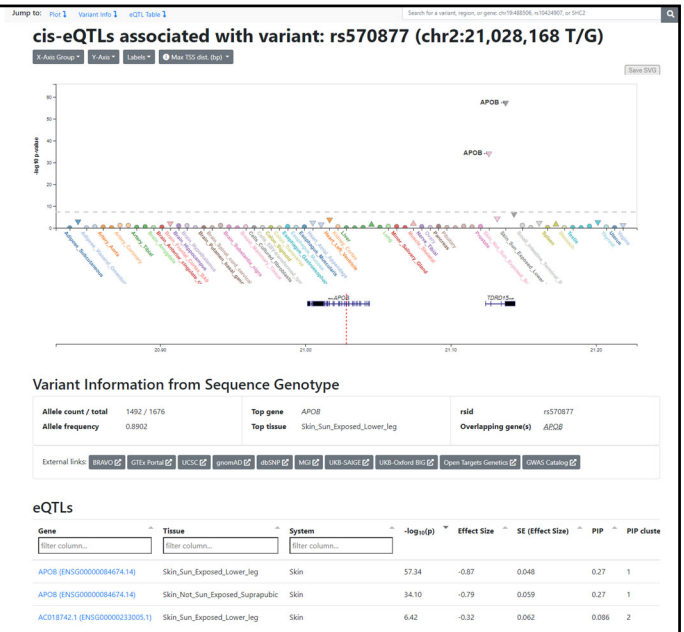
Interactive interface
- Clicking on any point shows eQTL info
- Navigate to single variant view

eQTLs: variant view

Explore a variant's association with gene expression across tissues

Interactively change grouping and coloring to aid comparison

See strength of signals, direction of effect



Summary

- Continuing goal: bring together data and tools to accelerate investigation and discovery for genetics of common metabolic diseases and related traits
- Create reusable visualization and analysis tools applicable to a wide array of problems on the portal and more generally

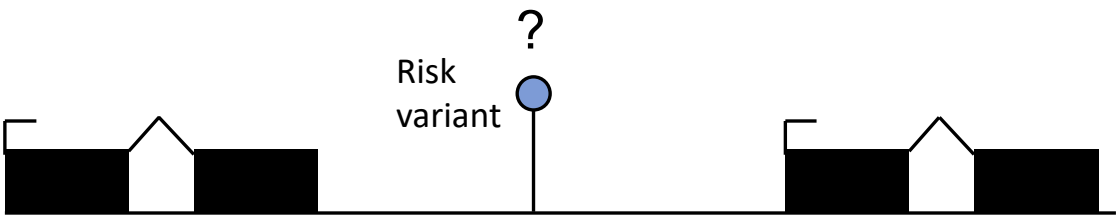
Diabetes Epigenome Atlas: annotating non-coding risk variants for complex disease

Kyle Gaulton
Assistant Professor, UCSD
May 27, 2020

Most common disease risk variants are non-coding

Determining the function of non-coding risk variants is critical to understanding the cell types, genes, and pathways involved in common disease

However - requires effective annotation of the genome and epigenome



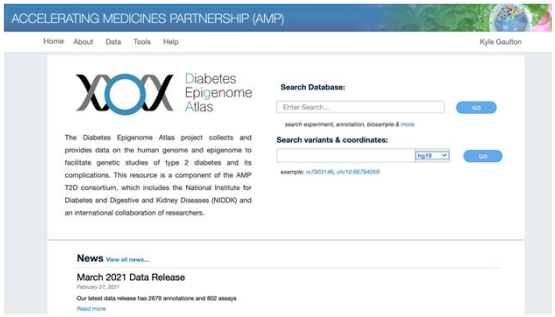
Epigenome data repository and web server

Diabetes Epigenome Atlas

https://www.diabetesepigenome.org

Database of epigenomic and other functional genomics data from human tissues and cells relevant to diabetes, complications and other common diseases

Based on open-source software developed by ENCODE



Primary goals:
Collect, process and deposit relevant experimental and annotation data and meta-data

Create forum for AMP CMD and other consortia to share experimental and annotation data

Enable comprehensive annotation of non-coding variants

Provide data to the CMDKP to annotate disease-associated non-coding variants

Intake and representation of data in DGA

Sources

- ENCODE, GTEx and other resources
- GEO/EGA for published studies
- AMP-CMD consortium
- Other consortia (e.g. HPAP)

Data types

- Experiments
  - e.g. ATAC-seq, RNA-seq, HI-C, snRNA-seq, Perturb-seq
- ⬇
- Annotations (derived from experiments)
  - e.g. chromatin state, cCREs, gene expression, ABC predictions

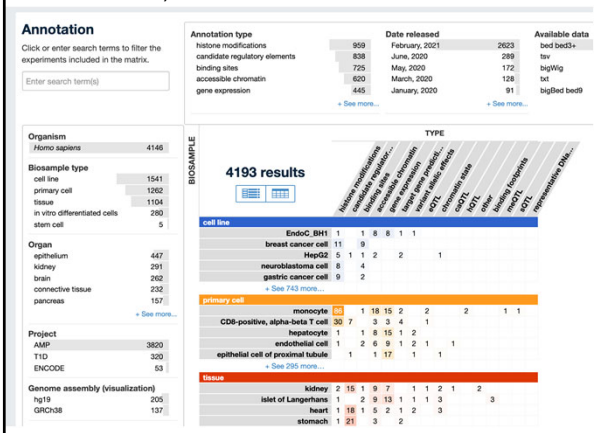
Availability

- **DGA**
  - Web interface, API
- ⬇ Custom API
- **CMD KP**

Data currently in DGA

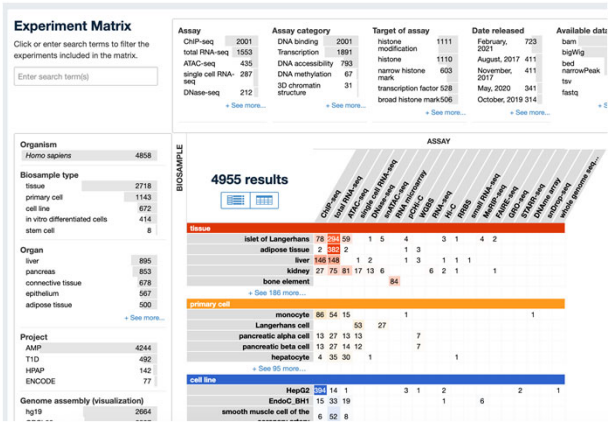
Total experiments and annotations (released and pending) as of 05/19:

Annotations: 4,193



https://www.diabetesepigenome.org/matrix/?type=Experiment

Experiments: 4,955

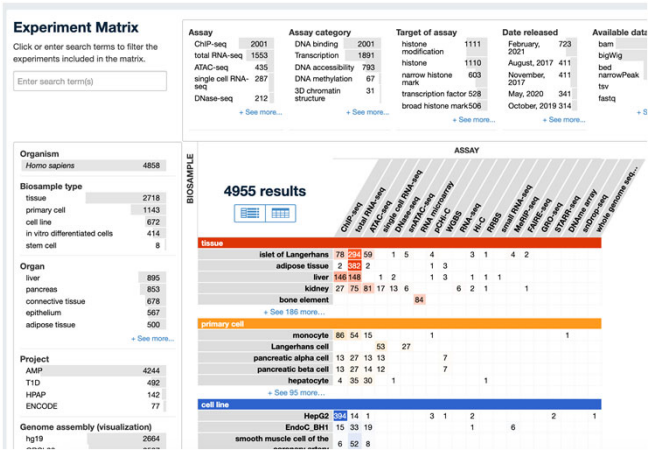


https://www.diabetesepigenome.org/matrix/?type=Annotation

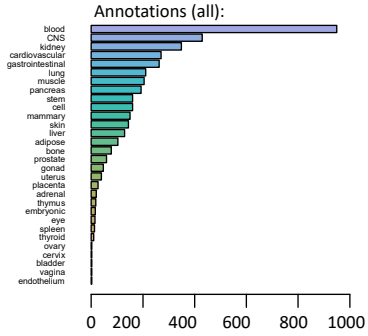
Data currently in DGA

Annotations broken down by tissue category

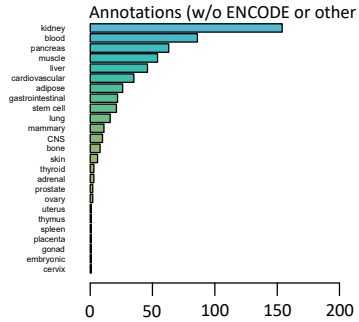
https://www.diabetesepigenome.org/matrix/?type=Annotation



Annotations (all):

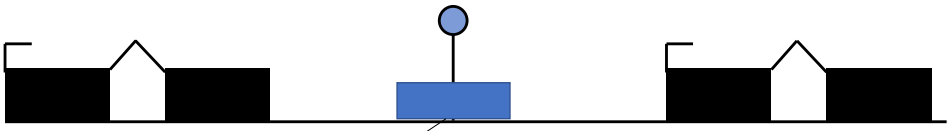


Annotations (w/o ENCODE or other resources):



Types of data in DGA

Cis-regulatory elements



Chromatin state (ChIP-seq)
Histone modification sites (ChIP-seq)
TF binding sites (ChIP-seq)
Accessible chromatin (ATAC/DHS-seq)

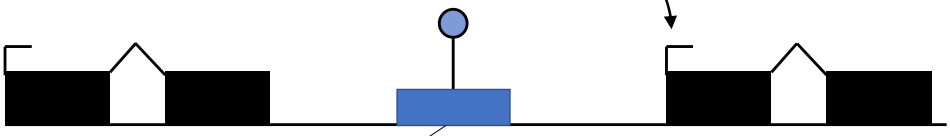
Cis-regulatory elements (cREs)

Types of data in DGA

Cis-regulatory elements
Gene target predictions

Genes linked to cCREs

Chromatin interactions (Hi-C/pcCHi-C)
Co-accessibility (ATAC-seq)
ABC predictions (ATAC-seq/Hi-C/ChIP-seq)

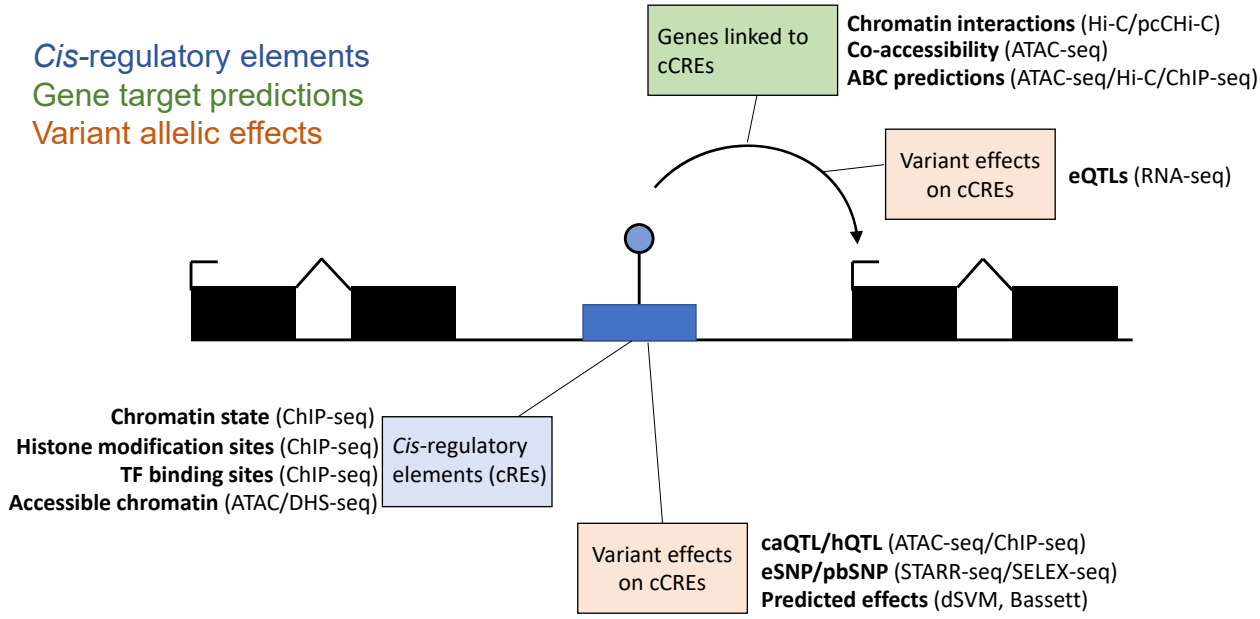


Chromatin state (ChIP-seq)
Histone modification sites (ChIP-seq)
TF binding sites (ChIP-seq)
Accessible chromatin (ATAC/DHS-seq)

Cis-regulatory elements (cREs)

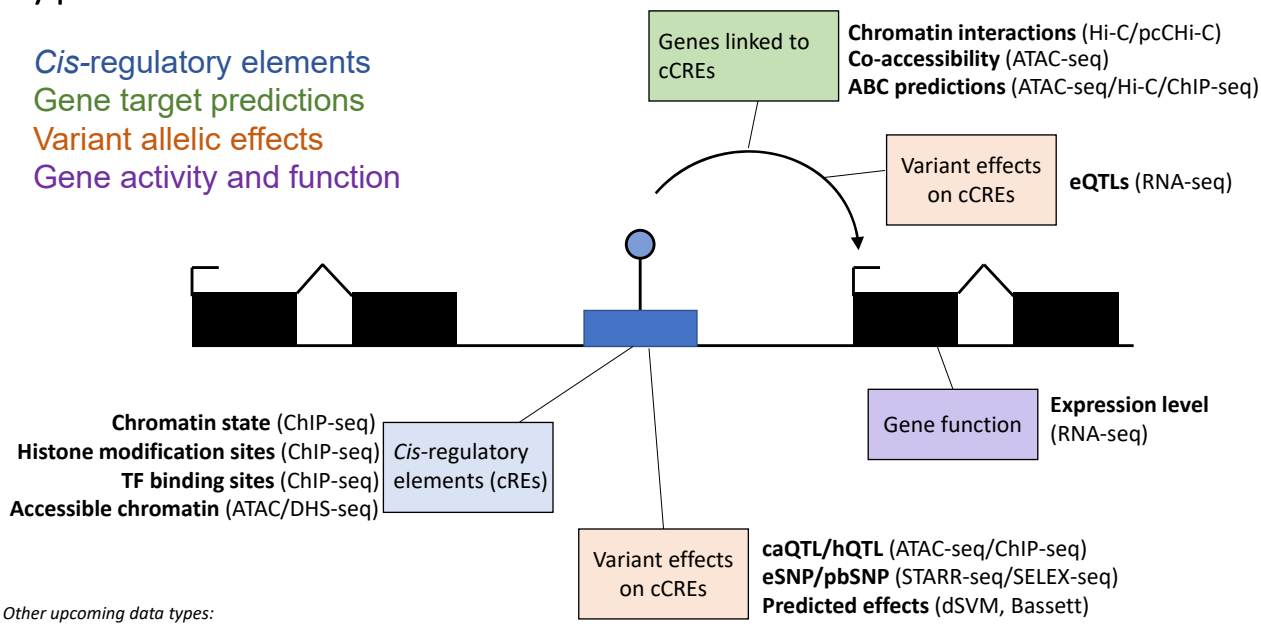
Types of data in DGA

Cis-regulatory elements
Gene target predictions
Variant allelic effects



Types of data in DGA

Cis-regulatory elements
Gene target predictions
Variant allelic effects
Gene activity and function

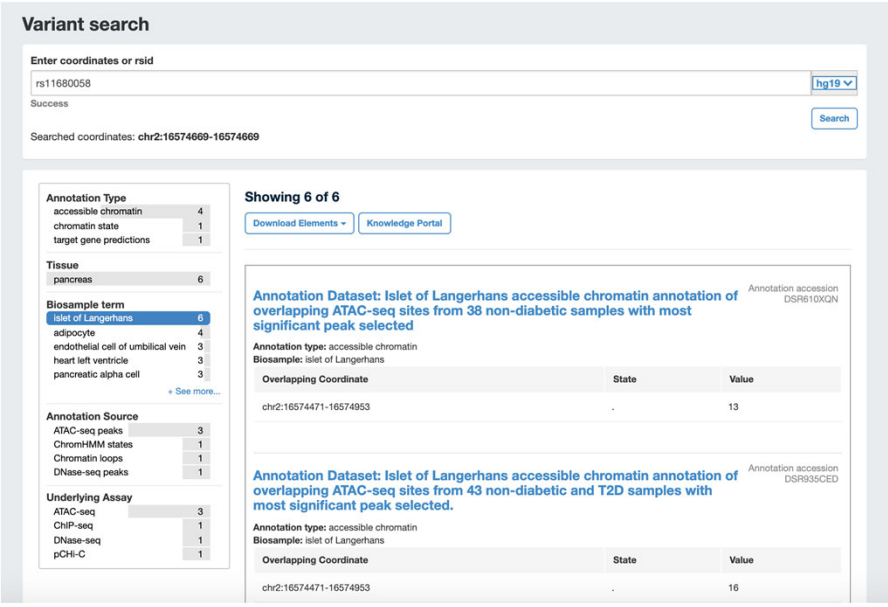


Other upcoming data types:
CRISPRi screens, Gene manipulation (e.g. KO), spatial imaging

Annotating variants in DGA directly

rs11680058
T2D DIAMANTE PPA=0.98

Pancreatic islets:
Accessible chromatin
Active Enhancer
Chromatin loop to *MYCN*

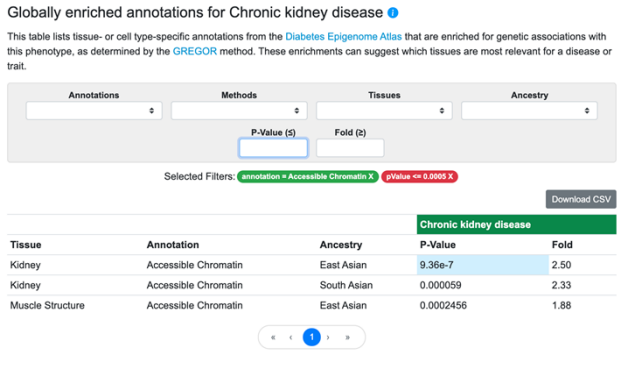


DGA annotation data in CMD KP

Cis-regulatory elements

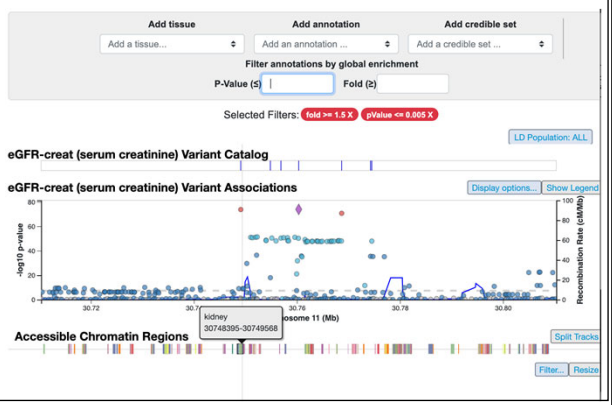
Globally enriched annotations

Which cis-regulatory elements are enriched for trait or disease association?



Genomic region viewer

Which variants at a specific locus overlap cis-regulatory elements?

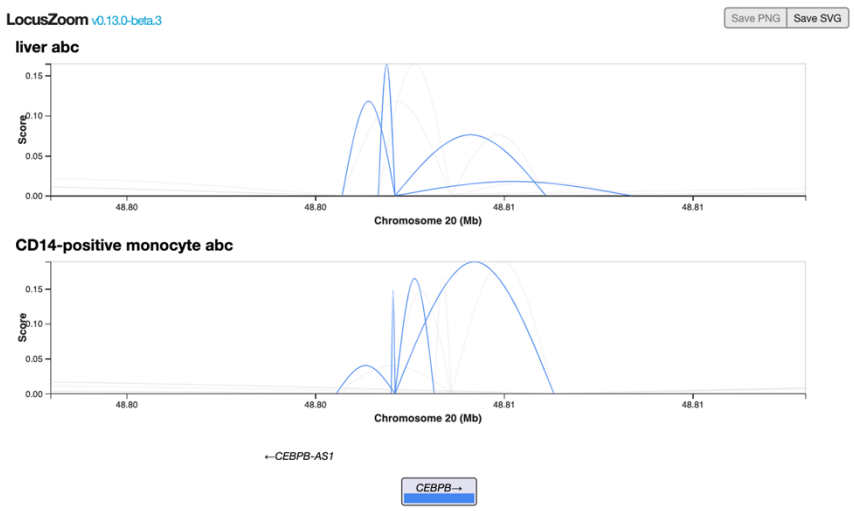


DGA annotation data in CMD KP

Gene target predictions

Genomic region viewer (*in progress*)

Which genes are affected by cis regulatory elements?



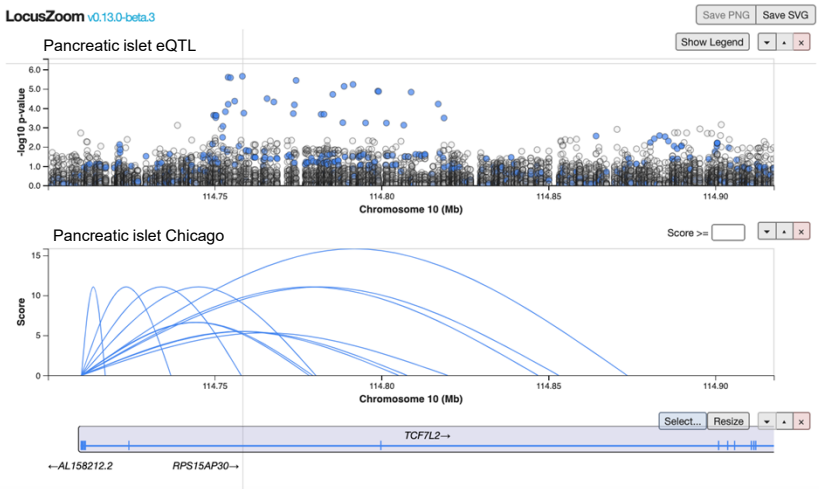
Andy Boughton
Mike Boehnke
Parul Kudtarkar

DGA annotation data in CMD KP

Gene target predictions

Genomic region viewer (*in progress*)

Which genes are affected by cis regulatory elements?



Andy Boughton
Mike Boehnke
Parul Kudtarkar

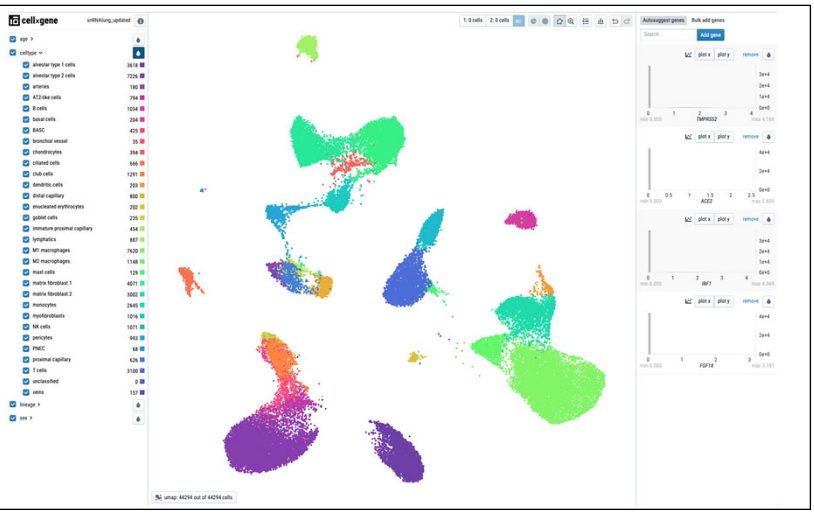
DGA annotation data in CMD KP

Other developments in progress

Single cell browser

Creating comprehensive catalog of single cell embeddings from AMP and other relevant studies:
e.g. pancreas, pancreatic islets, peripheral blood, heart, skeletal muscle, kidney + many other tissues

What cell types/states are genes expressed in? What cell types/states are relevant cis regulatory elements active in?



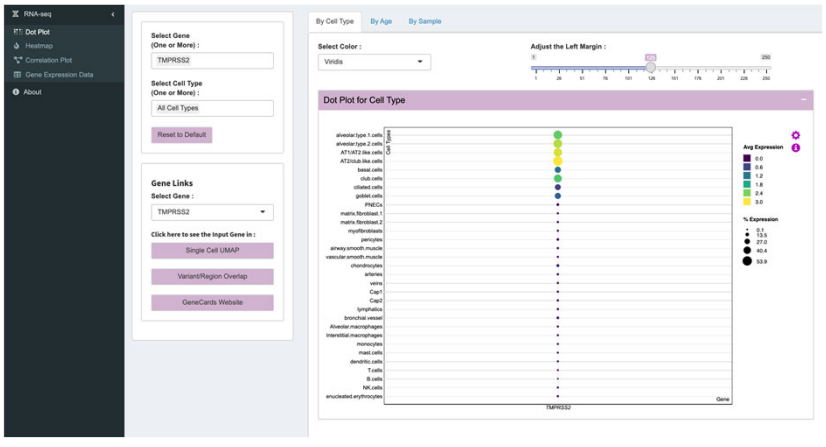
Parul Kudtarkar

DGA annotation data in CMD KP

Other developments in progress

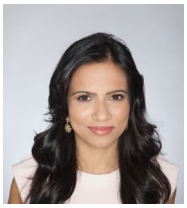
Gene expression browser

What cell types/states are genes expressed in? How does expression change across relevant phenotypes, e.g. sex, age, disease status, drug status etc.

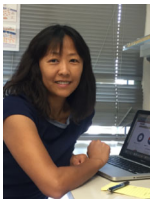


Parul Kudtarkar
Sharvari Nardendra

Acknowledgements



Parul Kudtarkar
Developer



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Sharvari Narendra

Knowledge portal
Jason Flannick, Ben Alexander, Noel Burtt, Jeffrey Massung, Lizz Caulkins, Maria Constanzo, Ali Kluge

AMP-T2D functional group
Mark McCarthy, Karen Mohlke, Steve Parker, Rob Sladek, James Meigs, Alisa Manning, Beena Akolkar and many others

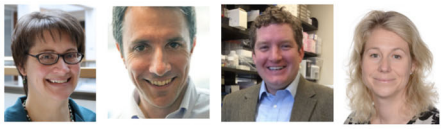
UCSD
Bing Ren, Kelly Frazer, Maike Sander

UMich
Mike Boehnke, Andy Boughton

National Institute of Diabetes and Digestive and Kidney Diseases

COMMON METABOLIC DISEASES KNOWLEDGE PORTAL

The NEWS Team: Bridging the gap between T2D GWAS and therapeutic targets



From T2D GWAS to therapeutic targets

Variant ⇒ Element ⇒ Tissue ⇒ Potential effector transcript

Transcript ⇒ Function ⇒ Mechanism ⇒ Therapeutic hypotheses

Data integration ⇒ Network analysis ⇒ Target prioritization

From Variant → Element → Tissue → Potential Effector Transcript

Genetics Working Group

Genetic Variants from GWAS and Sequencing Studies

Type 2 diabetes, related traits, complications
Individual populations and trans-ancestry analyses
Dissect signals, fine-map variants

Genome-Wide Omics

Colocalize with QTLs for chromatin accessibility: caQTL
gene expression: eQTL
splicing/isoform level: sQTL
metabolites: mQTL
proteins: pQTL

Perturb Variants

STARR-seq massively parallel reporter assays
General and cell-specific promoters

Perturb Elements

CRISPRi of regulatory elements
Assay effects on gene expression

Perturb Cells

Assay effects on transcriptome and epigenome across development and stimulation conditions

Working Group Effector Transcripts

Prioritize Tissues of Action & Link Regulatory Elements to Genes

Systematic predictions of regulatory element connections to genes
Tissue of action based on expression and epigenomic annotation
PheWas – agnostic to transcript based on physiology

Models and Assays Working Group

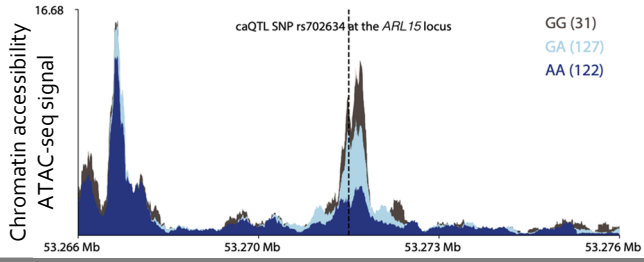
From Variant → Element → Tissue → Potential Effector Transcript

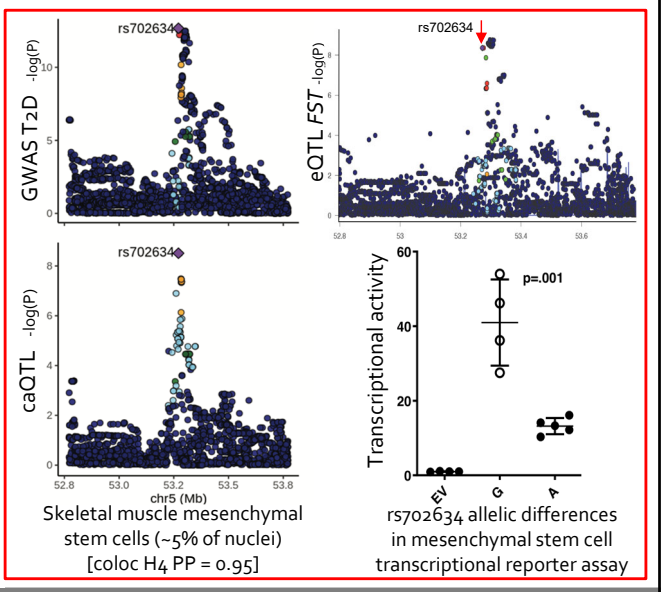
GWAS colocalization with molecular QTLs

QTL data available or in process

QTL & tissue	n
eQTL-islet	420
eQTL-islet	~1500
eQTL-liver	1183
eQTL-adipose	~2400
eQTL-muscle	977
eQTL-sn-muscle	343
eQTL-blood	31684
sQTL-islet	~1500
sQTL-liver	208
sQTL-adipose	434
sQTL-muscle	706
pQTL-blood	6861

QTL & tissue	n
caQTL-islet	228
caQTL-liver	149
caQTL-adipocyte	50
caQTL-sn-muscle	343
methylQTL-islet	125
methylQTL-adipose	276
methylQTL-muscle	265
miQTL-adipose	263
miQTL-muscle	290
metaboQTL-adipose	276
metaboQTL-muscle	293
metaboQTL-blood	184





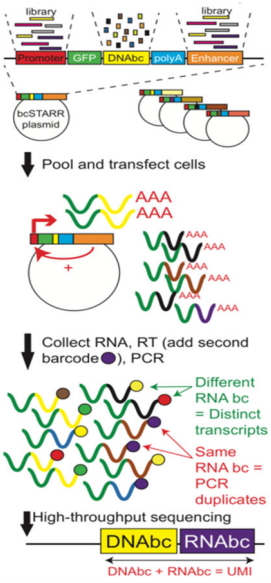
Skeletal muscle mesenchymal stem cells (~5% of nuclei)
[coloc H_4 PP = 0.95]

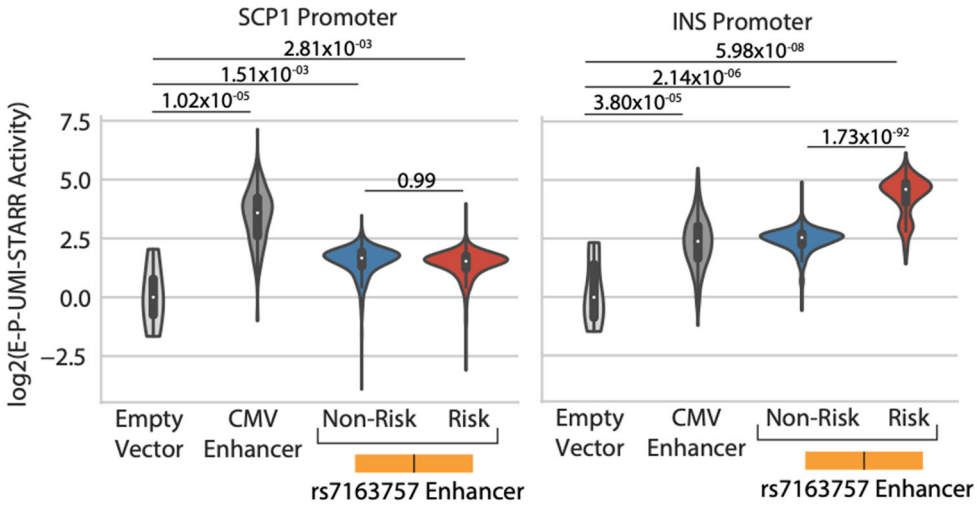
rs702634 allelic differences in mesenchymal stem cell transcriptional reporter assay

Arushi Varshney, Steve Parker, Swarooparani Vadlamudi

From Variant → Element → Tissue → Potential Effector Transcript

Perturb variants: STARR-seq





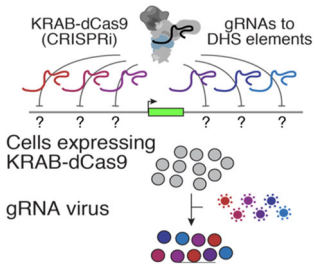
Enhancer variant only affects transcription with a cell-type-specific promoter

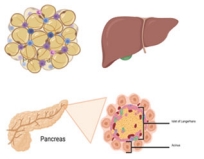
Q H Z V#W hdp

Steve Parker, Jacob Kitzman

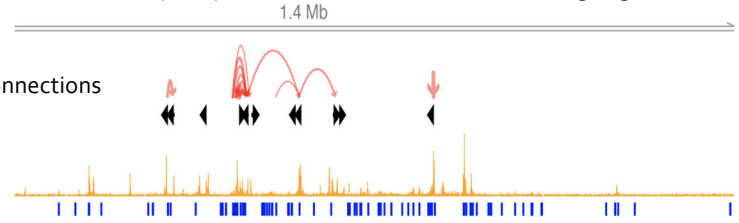
From Variant → Element → Tissue → Potential Effector Transcript

Perturb elements: CRISPRi



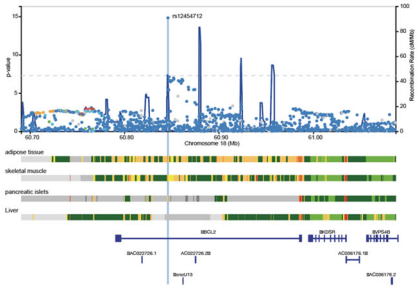


CRISPRi sensitively maps the effects of enhancers on target genes



Example: *BCL2* locus
Associated with increased risk for T2D, insulin resistance, WHRadjBMI, & decreased subcut. adipose tissue mass

Predicted effector *BCL2* affects subcutaneous adipocyte storage capacity via mitochondrial impairment.



Q H Z V#W hdp

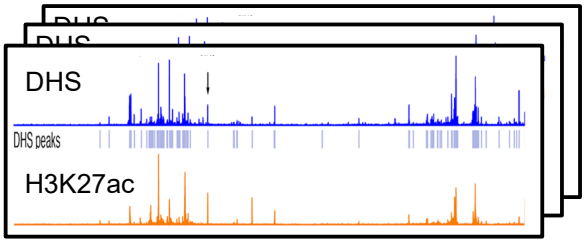
Fulco CP*, Nasser J* *et al.* Nat Genet (2019); Strobel*, Laber* et al manuscript in preparation

From Variant → Element → Tissue → Potential Effector Transcript

Integrative analysis

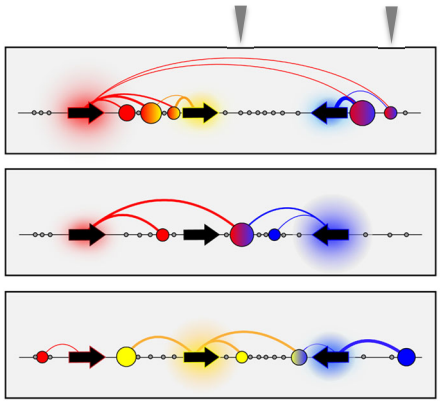
Activity-by-contact (ABC)

Epigenome maps in 131 cell types



ABC

Fine-mapped T2D variants



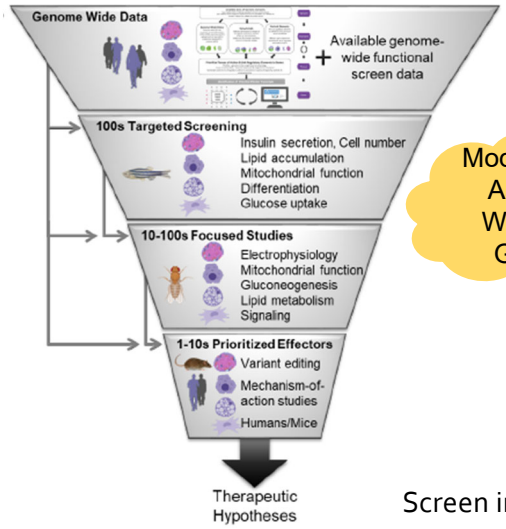
Enhancer-promoter maps

Q H Z V#W hdp

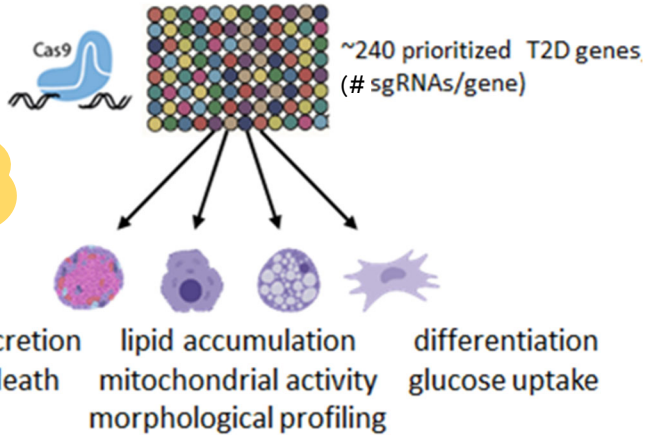
Fulco CP*, Nasser J* *et al.* Nat Genet (2019)

From Potential Effector Transcript→ Function→ Mechanism→ Therapeutic Hypotheses

Systematic evaluation of transcripts



Models and Assays Working Group



insulin secretion
beta cell death
ER stress

lipid accumulation
mitochondrial activity
morphological profiling

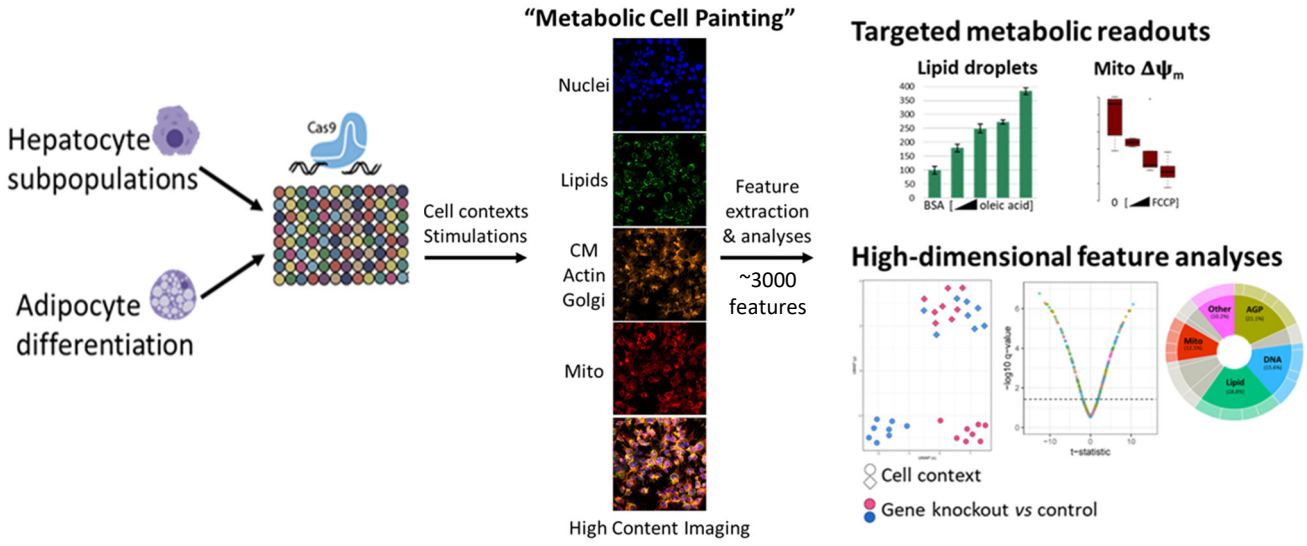
differentiation
glucose uptake

Screen in doxycycline-inducible dCas9-KRAB-expressing human cell lines

Q H Z V#W hdp

From Potential Effector Transcript→ Function→ Mechanism→ Therapeutic Hypotheses

Targeted arrayed screens



Q H Z V#W hdp

Suzanne Jacobs, Melina Claussnitzer

From Potential Effector Transcript→ Function→ Mechanism→ Therapeutic Hypotheses

Selected genes – detailed mechanistic studies

Expertise in focused mechanistic studies across metabolic tissues

Type 2 Diabetes Variants Disrupt Function of SLC16A11 through Two Distinct Mechanisms

Victor Rusu, Eitan Hoch, Josep M. Mercader, Danielle E. Tenen, Melissa Gymrek, Christina R. Hartigan, Michael DeRan, Marcin von Grotthuss, Pierre Fontanillas, Alexandra Spooner, Gaelen Guzman, Amy A. Deik, Kerry A. Pierce, Courtney Dennis, Clary B. Clish, Steven A. Carr, Bridget K. Wagner, Monica Schenone, Maggie C.Y. Ng, Brian H. Chen, MEDIA Consortium, SIGMA T2D Consortium, Federico Centeno-Cruz, Carlos Zerrweck, Lorena Orozco, David M. Altshuler, Stuart L. Schreiber, Jose C. Florez, Suzanne B.R. Jacobs, and Eric S. Lander

Type 2 diabetes risk alleles in *PAM* impact insulin release from human pancreatic β-cells

Soren K. Thomsen, Anne Raimondo, Benoit Hastoy, Shahana Sengupta, Xiao-Qing Dai, Austin Bautista, Jenny Censin, Anthony J. Payne, Mahesh M. Umapathysivam, Aliya F. Spigelman, Amy Barrett, Christopher J. Groves, Nicola L. Beer, Jocelyn E. Manning Fox, Mark I. McCarthy, Anne Clark, Anubha Mahajan, Patrik Rorsman, Patrick E. MacDonald and Anna L. Gloyn

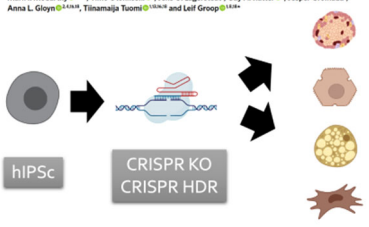
A regulatory variant at *3q21.1* confers an increased pleiotropic risk for hyperglycemia and altered bone mineral density

Nasa Sinnott-Armstrong, Isabel S. Sousa, Samantha Laber, Elizabeth Rendina-Ruedy, Simon E. Nitter Dankel, Teresa Ferreira, Gunnar Mellgren, David Karasik, Manuel Rivas, Jonathan Pritchard, Anyonya R. Guntur, Roger D. Cox, Cecilia M. Lindgren, Hans Hauner, Richard Sallari, Clifford J. Rosen, Yi-Hsiang Hsu, Eric S. Lander, Douglas P. Kiel, and Melina Claussnitzer

Sharing of IPS cell resources across groups with domain expertise

Loss of ZnT8 function protects against diabetes by enhanced insulin secretion

Om Prakash Dwivedi, Mikko Lehtovirta, Benoit Hastoy, Vikash Chandra, Nicole A. J. Krentz, Sandra Kleiner, Deepak Jain, Ann-Marie Richard, Fernando Abaitua, Nicola L. Beer, Antje Grotz, Rashmi B. Prasad, Ola Hansson, Emma Ahlqvist, Ulrika Krus, Isabella Artner, Anu Suoranta, Daniel Gomez, Aris Baras, Benoite Champon, Anthony J. Payne, Daniela Morali, Soren K. Thomsen, Philipp Kramer, Ioannis Spiliotis, Reshma Ramracheya, Pauline Chabosseau, Andria Theodoulou, Rebecca Cheung, Martijn van de Bunt, Jason Flannick, Maddalena Trombetta, Enzo Bonora, Claes B. Wolheim, Leena Sarelin, Riccardo C. Bonadonna, Patrik Rorsman, Benjamin Davies, Julia Brosnan, Mark I. McCarthy, Timo Otonkoski, Jens O. Lagerstedt, Guy A. Rutter, Jesper Gromada, Anna L. Gloyn and Leif Groop



Confirming CRISPRi results using CRISPR editing of SNPs in enhancers in isogenic lines

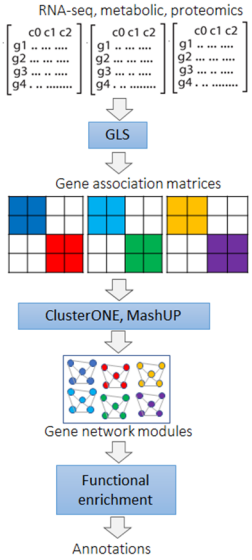
Drosophila models

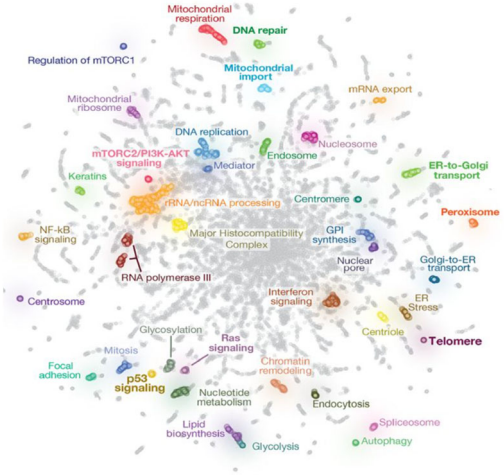
Recruit by genotype

Q H Z V#W hdp

Data Integration → Network Analysis → Target Prioritization

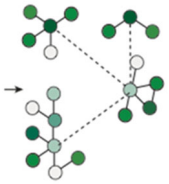
Map multi-omic gene networks and modules



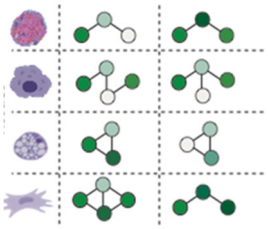


Network visualization

Network hubs & modules containing effector transcripts

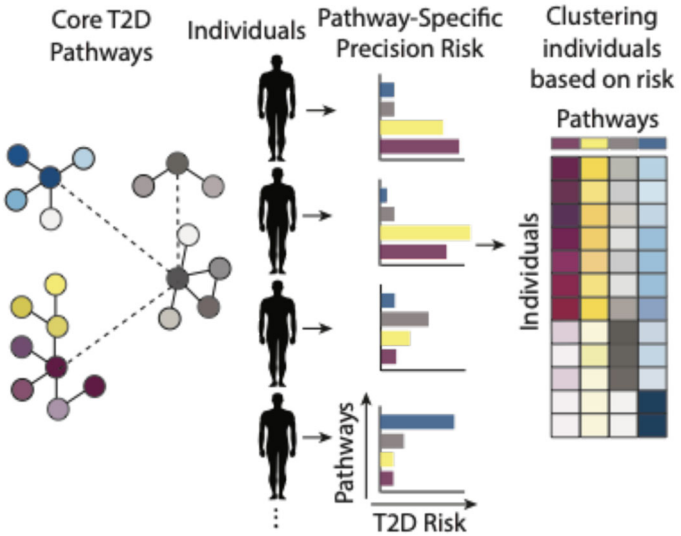


Differential network module activity across cell types & conditions



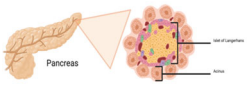
Data Integration → Network Analysis → Target Prioritization

Individual disease heterogeneity



Summary





Variant ⇒ Element ⇒ Tissue ⇒ Potential effector transcript

- e/caQTL Colocalization
- STARR-seq
- CRISPRi screens
- Activity By Contact

Transcript ⇒ Function ⇒ Mechanism ⇒ Therapeutic hypotheses

- Targeted screens
- Mechanistic studies
- *Drosophila* models
- Allelic series

Data integration ⇒ Network analysis ⇒ Target prioritization

- Gene networks and modules
- Network visualization
- Cell-specific regulators
- Individual disease heterogeneity

The NEWS Team

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Arushi Varshney
Christa Ventresca
Amedeo Vetere
Bridget Wagner
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Yingying Ye
Grace Yu
Cynthia Zajac
Weichen Zhao

Q H Z V#W hdp

Functional Interrogation of T2D-associated genes in human stem cell-derived models and mice

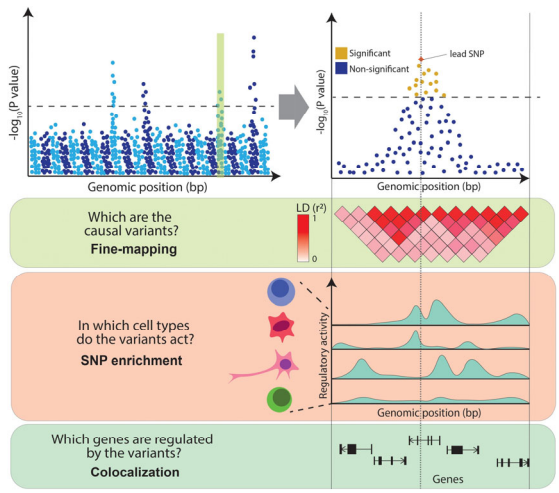
FNIH AMP CMD Inaugural Meeting • May 27, 2021

Penn Medicine

Children's Hospital of Philadelphia

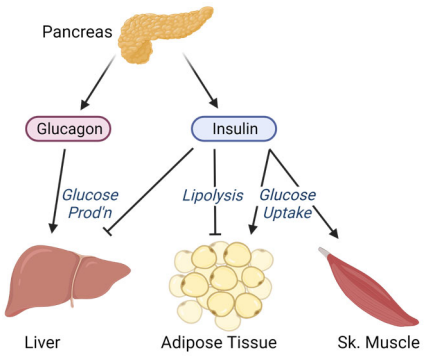
Project Workflow

Computational Genetics
Variant-to-Gene Mapping



Adapted from Cano-Gamez & Trynka, Front. Genet. 2020

Physiological Assessment of Effector Transcripts
Mechanistic/Pathway Analyses



Primary cell & iPSC-models
Disease Modeling
Mechanistic Studies

Mouse models of obesity & diabetes
- Integrated Physiology

Penn Medicine Children's Hospital of Philadelphia

Ben Voight

Co-Leader, Genetics Working Group

Computational Genetics

Computation studies using human genomics data

Causal inference Studies via Mendelian Randomization

Multivariate association studies (mvGWAS)

Statistical Genetics + Genetic Epi: Post-GWAS analysis

Population Genomics Studies

Focal Traits (Beyond T2D)

CVD and PAD

Non-alcoholic Fatty Liver Disease

Causal traits related to CVD, PAD, T2D, and NAFLD

Active involvement with the Million Veteran Program

15 to 20 years of EHR data, >450,000 participants: Genotyped + Imputed Data

Importantly: Diverse Ancestries, ~1M by 2022; + exome sequencing, + genome sequencing

Causal inference studies for cardiometabolic, glycemic traits, NAFLD

The search for insulin-resistance and non-beta-cell biology T2D associated loci

*Methods development + analysis with **multi-ancestry** data: causal inference, polygenic risk scores, and mvGWAS*

QTL discovery and analysis efforts using data generated by the Human Pancreatic Analysis Program (HPAP)

Penn Medicine | Children's Hospital of Philadelphia

Struan Grant

Functional Genomics

Co-Director, Center for Spatial & Functional Genomics

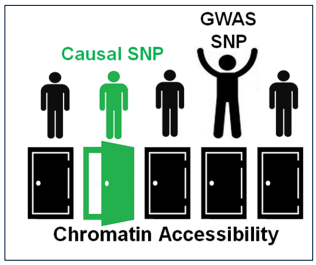
Co-Leader Effector Transcripts Working Group

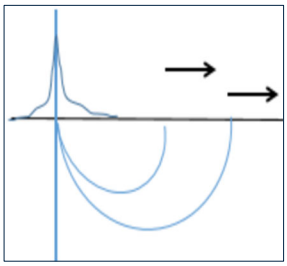
Andrew Wells

Chromatin Regulation Immune Signaling

Co-Director, Center for Spatial & Functional Genomics

'Variant-to-Gene Mapping – At Scale'





Identify proxy SNPs in LD with sentinels

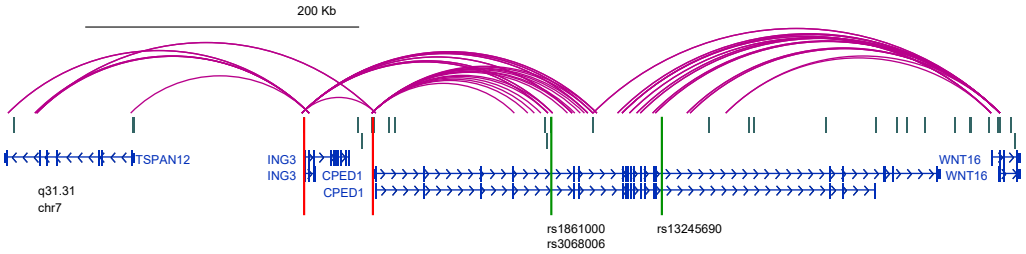
Identify open SNPs with ATAC-seq

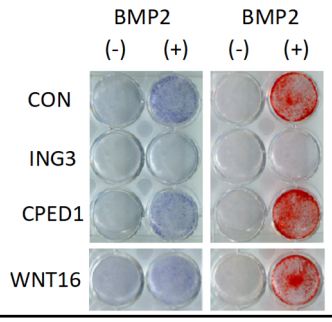
High-resolution Capture C: Contacts with putative effector gene promoters

Cousminer, Wagley, Pippin et al. Genome Biology 2021

Penn Medicine | Children's Hospital of Philadelphia | Center for Spatial & Functional Genomics

e.g. Identification of *ING3* at '*CPED1*' locus for Bone Mineral Density





Knockdown of *ING3* expression

- Impairs osteoblast differentiation
- But not *WNT16* or *CPED1*

Chesi,..,Wells, Grant *et al. Nature Commun.* 2019

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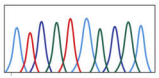
Paul Gadue

Human stem cell models, β-cell biology

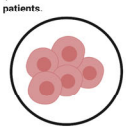
Assoc. Director, CHOP ES cell Core

Human Pluripotent Stem Cell Discovery Platform for the Study of Genetic Contributions to Diabetes



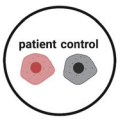
1 Identify Mutations/Variants
From either sequencing of diabetic patients or large scale genomics studies, define mutations or variants associated with diabetes.

2 Patient-derived iPS cell lines
Generate induced pluripotent stem (iPS) cell lines from diabetic patients.



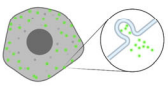
3 Correct/Introduction of mutations
Generate corrected patient iPS cell lines through genome editing. Alternatively, introduce mutation into WT iPS or ES cell line.

4 Differentiaion beta cells
Using genetically matched isogenic stem cell lines harboring various genomic lesions, differentiate into pancreatic beta cells.

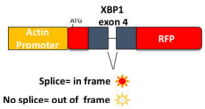


5 Assay impacts on beta cell development and function
Assay gene expression, functionality such as insulin secretion and metabolic activity.

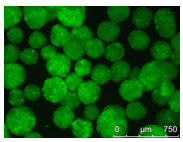
Insulin reporter
Fluorescent protein NeonGreen is targeted to the endogenous INS locus, creating a fusion protein that traffics with endogenous insulin. Allows quantification of insulin content and localization.



ER stress reporter
Various cell stressors, such as ER stress, induce splicing of XBP1 into XBP1s. This splice changes the frame of the protein. Including a portion of XBP1 with the splice site allows the generation of a spliced in frame RFP only upon cell stress.



5A Use of reporter stem cell lines to study beta cell biology (2 examples shown above).



INS-GFP+ beta-like cells

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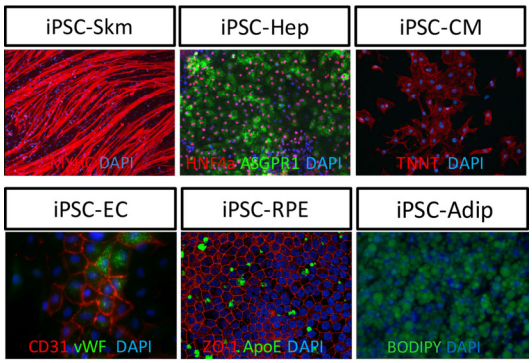
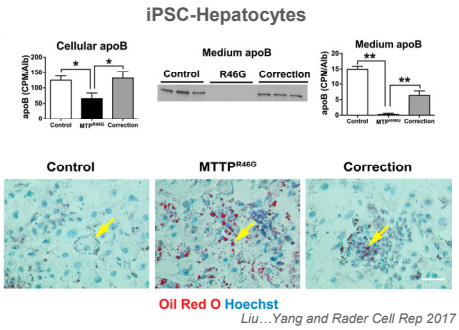
Wenli Yang
iPSC models
Director,
Penn iPSC Core
Co-Leader,
Models & Assays
Working Group

iPSC-derived cell and disease models

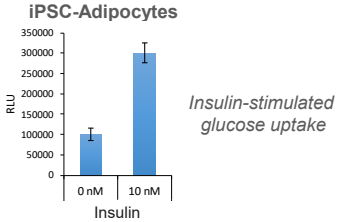




Liu…Yang and Rader Cell Rep 2017

Stem cell resources for this project

- Human induced pluripotent stem cell (hiPSC) lines from 132 healthy donors
- All donor and hiPSC DNA are fully genotyped
- 90+ lines differentiated into hepatocytes and RNA sequenced
- All lines are available at WiCell repository
- These lines provide a rich source of common variants for investigation



Insulin-stimulated glucose uptake

Penn Medicine Children's Hospital of Philadelphia

Mouse Modeling

- Developed over 50 T2D-relevant genetic and disease models
- Derivation of a new targeted point mutation or loxP allele in less than 2 months
- Outstanding capability for metabolic phenotyping via DRC-supported cores
  - Mouse metabolic phenotyping (Joe Baur)
  - Islet Biology Core (Doris Stoffers)
  - Metabolomics Core (Josh Rabinowitz/Princeton)
  - Penn Human Metabolic Tissue Bank (Ray Soccio)

Jax.org

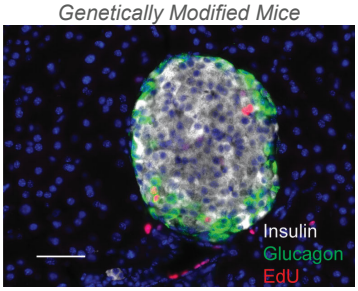
Penn Medicine Children's Hospital of Philadelphia

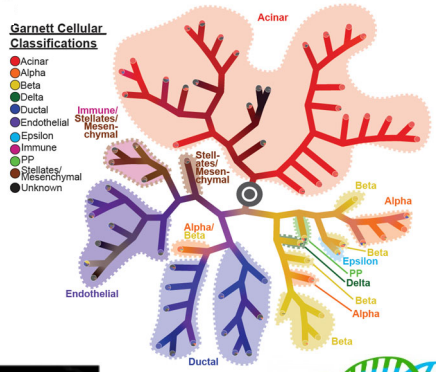
Pancreatic Islet Biology

Klaus Kaestner

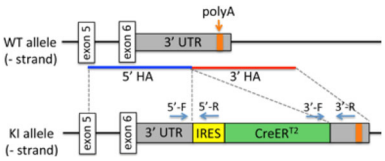
Diabetes mechanisms, Pancreas & liver biology
Mouse Modeling
Investigator, Human Pancreas Analysis Program

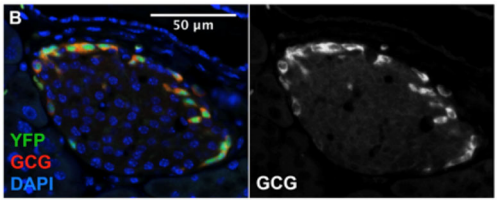
Assessment of Islet Function in Genetically Modified Mice





High efficiency, high specificity alpha cell CreER line





HPAP
human pancreas analysis program

Penn Medicine
Children's Hospital of Philadelphia

Liver Biology and Disease

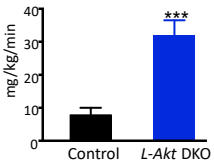
Paul Titchenell
Insulin Signaling
Integrated Metabolic Physiology

Dan Rader
Lipid Metabolism
Functional Genomics

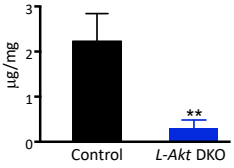
Klaus Kaestner
Liver development & physiology

Hepatic Metabolism

Lipogenesis

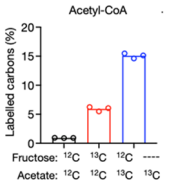


Glucose Output



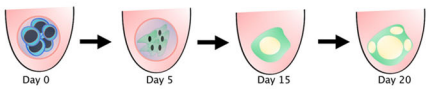
In vivo metabolism
(Titchenell et al Cell Met 2016)

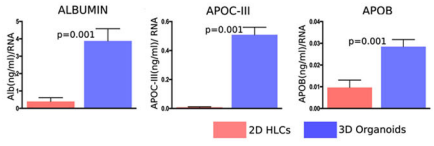
Primary hepatocytes



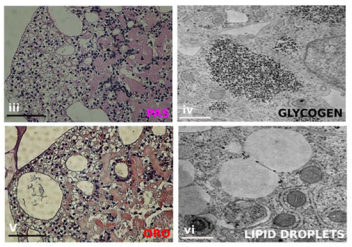
Flux studies analysis
(Zhao et al Nature 2020)

3D hPSC-differentiation





Abbey *et al., Hepatol Commun*, 2020



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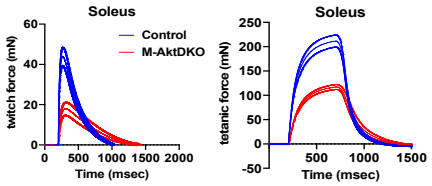
Children's Hospital of Philadelphia

Paul Titchenell
Integrated metabolic analyses

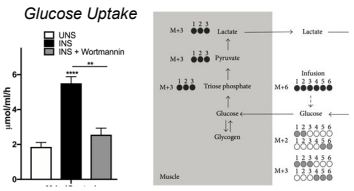
Wenli Yang
Cellular models

Skeletal Muscle Biology

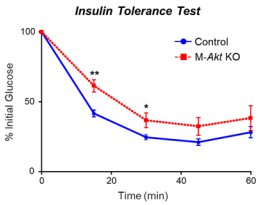
Muscle Metabolism and Function



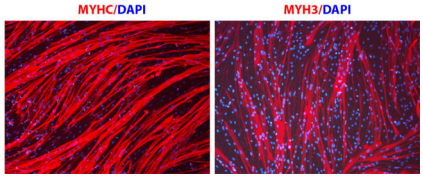
Ex vivo physiology (Jaiswal *et al Mol Met* 2019)



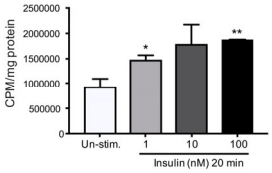
In vivo glucose uptake & flux analysis



Insulin resistance in Akt-KO mice



hPSC-derived muscle cells for functional analyses

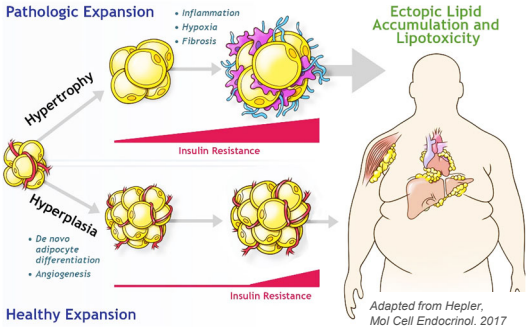


Insulin-stimulated glucose uptake Human primary muscle cells

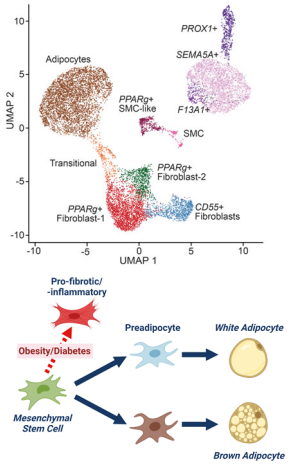
Penn Medicine Children's Hospital of Philadelphia

Patrick Seale
Adipocyte biology, Obesity pathogenesis

Adipose tissue and obesity pathogenesis

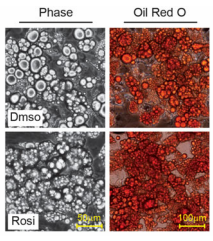


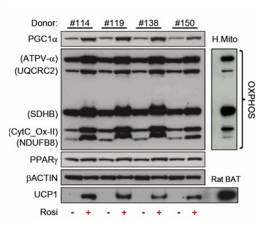
Adapted from Hepler, Mol Cell Endocrinol. 2017



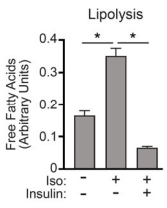
Wang et al, PNAS, 2014; Merrick, Sakers et al. Science 2019; Angueira, Sakers et al., Nat Metab, 2021;

hASC-adipocytes





Bartesaghi et al, Mol Cell Endocrinol. 2015



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Summary & Current Focus

- Refine list of T2D-related transcripts and site(s) of action
- Additional development and validation of iPSC models
- Establishment and validation of robust cellular assays for insulin-action
- Emphasis on development of novel mouse models, integrated physiology studies

Thanks!

Investigators

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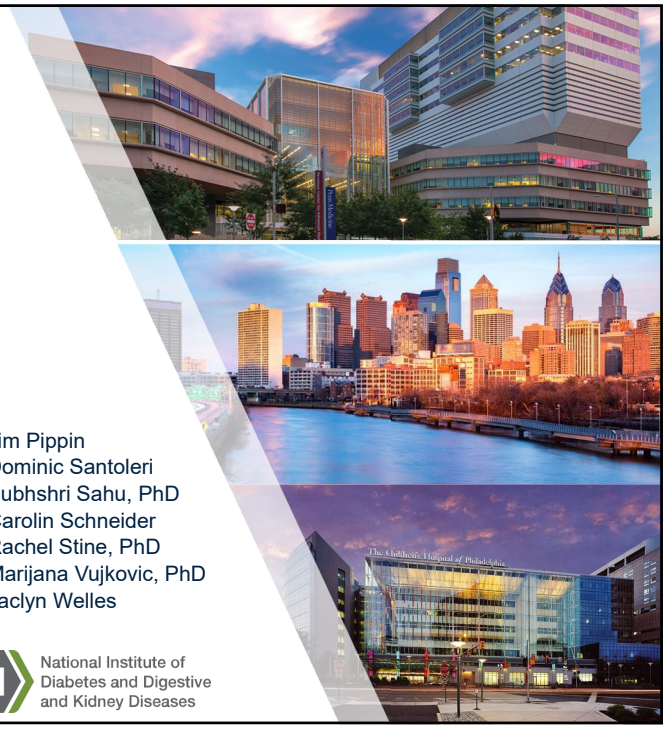
NIH National Institute of Diabetes and Digestive and Kidney Diseases



Accelerating Medicines Partnership
Common Metabolic Diseases Inaugural Meeting
May 27, 2021

TOPMed 'Omics of Type 2 Diabetes and Quantitative Traits

James B Meigs MD MPH
Division of General Internal Medicine
Massachusetts General Hospital
Harvard Medical School

MASSACHUSETTS GENERAL HOSPITAL | Harvard Medical School | BROAD INSTITUTE | FRAMINGHAM HEART STUDY | NHLBI TOPMed

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Denver VA

2 UM1DK078616-13 *TOPMed Omics of Type 2 Diabetes and Quantitative Traits*

Project Period Start Date 04/01/2008 – End Date 12/31/2025

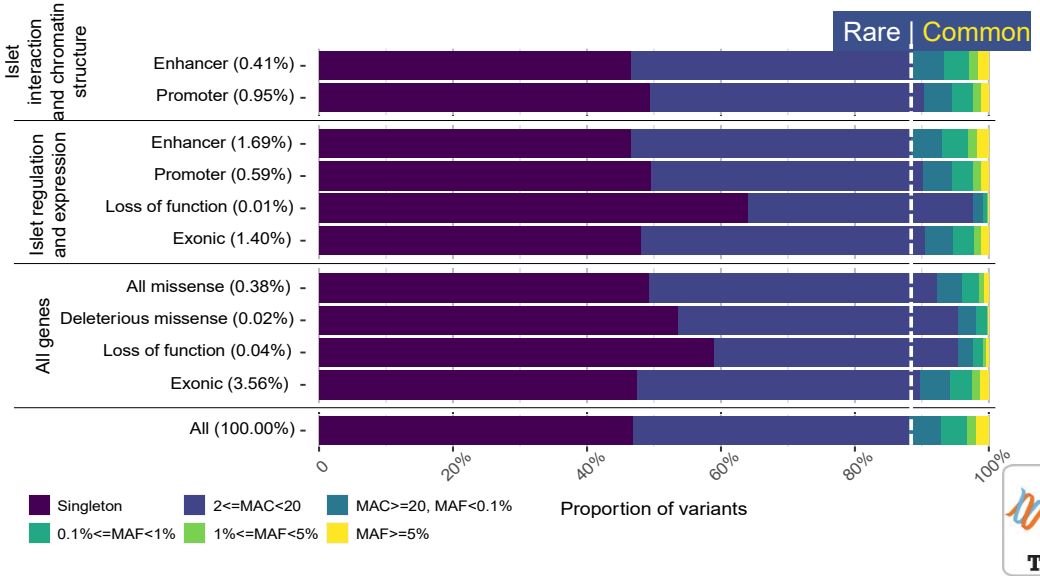
- Aim 1: Test WGS-wide for known and new T2D and QT- associated loci in five ancestry groups
  - Common and rare variant tests will find validated variants associated with T2D, FG, FI and HbA1c
  - MR, PRS and allelic series tests will reveal T2D physiology and disease etiology
- Aim 2: Test omic measures individually and in multilevel network models of T2D pathobiology
  - Methylomic, transcriptomic, proteomic and metabolomic signatures are associated with T2D and QTs
  - Multidimensional omic and genomic network models will reveal new pathobiology of T2D
- Aim 3: Integrate TOPMed WGS, omics with AMP T2D DGA, T2DKP for variant-to-function analyses
  - Tissue-specific DGA epigenomic data will inform variant-to-function knowledge for T2D associations
  - Genomic and phenomic cardiometabolic data in the T2DKP will inform variant-to-function and health impact for T2D associations
- Aim 4: Participate in AMP T2D CMD Consortium activities

AMP T2D “OP6” - TOPMed Freeze 5b Whole Genome Sequence

Outcome	Sample	Manuscript Status	Reference
Type 2 Diabetes	9,639 T2D cases and 34,994 T2D controls from 16 studies and 5 ancestries	Submitted and in preprint	Wessel, J. et al. Rare Non-coding Variation Identified by Large Scale Whole Genome Sequencing Reveals Unexplained Heritability of Type 2 Diabetes. Medrxiv 2020. https://dx.doi.org/10.1101/2020.11.13.20221812
Fasting Glucose & Insulin	26,920 non-diabetic individuals from 15 cohorts and 5 ancestries	Submitted and in preprint	DiCorpo, D. et al. Whole Genome Sequence Association Analysis of Fasting Glucose and Fasting Insulin Levels in Diverse Cohorts from the NHLBI TOPMed Program. Medrxiv 2020. https://dx.doi.org/10.1101/2020.12.31.20234310
HbA1c	10,338 non-diabetic individuals from 5 studies and 4 ancestries	Published AJHG	Sarnowski C. et al. Impact of Rare and Common Genetic Variants on Diabetes Diagnosis by Hemoglobin A1c in Multi-Ancestry Cohorts: The Trans-Omics for Precision Medicine Program. Am J Hum Genet 2019. https://dx.doi.org/10.1016/j.ajhg.2019.08.010

TOPMed WGS Variant Frequency Spectrum by Islet Functional Annotation

T2D Prevalent Case-Control Freeze 5b Analysis, 373.3M variants, average sequence depth 38x



TOPMed Freeze 9 Diabetes

- T2D: Fasting Glucose ≥ 7 mmol/L or HbA1c ≥ 6.5%
- Prediabetes : Fasting Glucose ≥ 5.6 mmol/L or HbA1c ≥ 5.7%

Self Reported Race/Ethnicity	
African	24%
Asian	7%
European	46%
Hispanic	21%
Samoan	2%

Cohort	Controls	Prediabetes	Type 2 Diabetes	Total
Amish	933	0	29	**962**
ARIC	3,114	3,406	1,836	**8,356**
BioMe	2,461	3,389	4,747	**10,597**
CCAF	324	0	15	**339**
CFS	477	226	223	**926**
CHS	2,651	0	866	**3,517**
DHS	20	0	342	**362**
FHS	1,641	1,692	695	**4,028**
GeneSTAR	1,155	318	210	**1,683**
GENOA	415	208	306	**929**
GenSalt	1,133	470	153	**1,756**
GOLDN	656	87	58	**801**
HCHS_SOL	1,947	3,013	2,274	**7,234**
HVH	608	0	61	**669**
HyperGEN	1,382	27	350	**1,759**
JHS	709	1,300	980	**2,989**
MESA	2,687	1,467	1,149	**5,303**
MGH_AF	910	0	56	**966**
Partners	97	0	20	**117**
SAFS	733	226	315	**1,274**
Samoan	801	186	198	**1,185**
THRV	815	521	529	**1,865**
VAFAR	144	0	27	**171**
VU_AF	921	0	186	**1,107**
WHI	1,944	3,573	3,099	**8,616**
Total	**28,678**	**20,109**	**18,724**	**67,511**

TOPMed Freeze 9 Glycemic Traits

Fasting Glucose (mmol/L)

Self Reported Race / Ethnicity	Count	Mean	(SD)
African	11,657	5.27	(1.58)
Asian	4,799	4.80	(1.74)
European	23,013	5.23	(0.87)
Hispanic American	6,174	5.21	(0.47)
Hispanic	6,146	5.52	(2.60)
Samoan	987	4.94	(0.75)
Other	8	5.61	(0.60)
Total	**52,784**	**5.22**	**(1.42)**

Fasting Insulin (mIU/L), Log Transformed

Self Reported Race / Ethnicity	Count	Mean	(SD)
African	8,819	2.29	(0.70)
Asian	2,802	2.96	(1.95)
European	19,275	2.30	(0.77)
Hispanic American	6,194	4.07	(0.68)
Hispanic	1,998	2.32	(0.83)
Samoan	987	2.42	(0.78)
Other	8	2.68	(0.40)
Total	**40,083**	**2.62**	**(1.09)**

NHLBI TOPMed

TOPMed Omics Resources May 2021

	Studies with prevalent T2D harmonized data	Sample size	Platform	Generated through TOPMed?	Currently available?
Metabolomics*	FHS	3025	LC/MS	TOPMed and other	yes
	MESA	982	LC/MS	TOPMed	yes
	WHI	1400	LC/MS	TOPMed	yes
	Total	**5407**			
Proteomics	FHS	2128	SOMAscan™	TOPMed and other	yes
	MESA	982	SOMAscan 1.3k	TOPMed	yes
	WHI	1400	Olink	TOPMed	yes
	Total	**4510**			
RNA-seq	FHS	3780	TrueSeq	TOPMed	yes
	MESA	794	TrueSeq	TOPMed	yes
	WHI	1400	TrueSeq	TOPMed	yes
	Total	**5974**			
Methylation	FHS	5265	EPIC	Other/TopMed	yes
	MESA	907	EPIC	TOPMed	yes
	WHI	1400	EPIC	TOPMed	yes
	Total	**7572**			

*Metabolites include C8 (Fatty acids and bile acids), C18 (TAGs, DAGs, Ceramides), HILIC pos (amino acids, acylcarnitines)
†Expecting an additional 2730 metabolomic samples and 2900 RNA-seq samples from MESA in 2021

NHLBI TOPMed

TOPMed Omics of Cardiovascular Disease in Diabetes

1 R01HL151855-01 - Project Period: 07/01/2020 – 06/30/2024

Aim 1: Test WGS-wide for known and new CVD-T2D associated loci

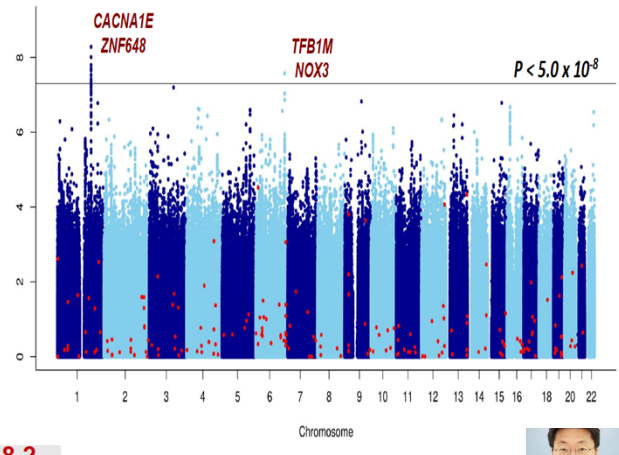
Aim 2: Test individual omic measures for associations with CVD in T2D

Aim 3: Integrate omics in a multilevel network model of CVD in T2D

GWAS of Incident Cardiovascular Disease in Type 2 Diabetes Confirms Known CHD Loci and Identifies Two Novel Loci

Sample Size and CVD Event Rate

Ancestry	Cohort	Total N	Event N	Event Rate
European/ European American	ARIC	2,184	543	24.9
	BIOME	851	160	18.8
	CHS	379	225	59.4
	FHS	762	283	37.1
	MESA	392	64	16.3
	MGB	1,161	389	33.5
	PMBB	603	244	40.5
	PROSPER	452	39	8.6
	UKBB	15,643	1,499	9.6
	REGARDS	303	195	64.4
	ROTTERDAM	611	98	16.0
	SANFORD	2,062	174	8.4
	WGHS	2,043	105	5.1
	WHI	4,542	998	22.0
	Subtotal	**31,988 (66.5%)**	**4,918 (57.3%)**	**15.5**
African American	ARIC	1141	310	27.2
	BIOME	1764	467	26.5
	CHS	130	76	58.5
	MESA	508	85	16.7
	PMBB	1,242	388	31.2
	REGARDS	2,483	733	29.5
	WHI	3,208	693	21.6
	Subtotal	**10,476 (21.8%)**	**2,752 (31.4%)**	**26.3**
Hispanic/Latinx	BIOME	2681	668	24.9
	MESA	482	89	18.5
	WHI	1229	177	14.4
	Subtotal	**3,163 (6.6%)**	**757 (8.6%)**	**23.9**
East Asian	KOGES	2,317	185	8.0
	MESA	194	42	21.6
	WHI	178	33	18.5
	Subtotal	**2,511 (5.1%)**	**227 (2.7%)**	**9.0**
Total		**48,138**	**8,752**	**18.2**



Soo Heon Kwak

UM1 DK078616 – TOPMed - Next Steps

- Association analyses
  - Complete incident T2D harmonization; begin MI and stroke in T2D harmonization
  - Invent regulatory functional units based on functional data from four tissues to frame or mask RV burden tests
  - Produce all association summary data sets for easy CMDK Portal posting
- How to become a TOPMed investigator
  - Join TOPmed work group: ask James or Alisa
  - Get your hands on TOPMed data
    - Get on “the list” of 8 approved cohort sites for TOPMed analysis
    - Get data yourself from dbGaP (not recommended)
    - We do analysis for you
- dbGaP – upload curated phenotype files for others to download
  - Aspirational, has NCBI and NHLBI support, and underway with our leadership


Partner's Vision
FNIH
Lilly

AMP-CMD:

A shared vision

Novo Nordisk at a glance

Novo Nordisk is a leading global healthcare company, founded in 1923 and headquartered in Denmark.

Our purpose is to drive change to defeat diabetes and other serious chronic diseases such as obesity and rare blood and endocrine disorders.

We do so by pioneering scientific breakthroughs, expanding access to our medicines and working to prevent and ultimately cure disease.

Products marketed in **169** countries

Total net sales **126.9** billion DKK

Supplier of nearly **50%** of the world's insulin

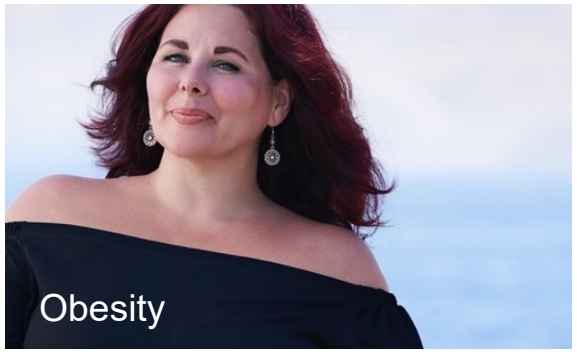
32.8 million people use our diabetes care products

Affiliates in **80** countries

R&D centres in China, Denmark, India, UK and US

Strategic production sites in Denmark, Brazil, China, France and US

About **45,300** employees



Among the world's **10** largest pharma companies measured by market value [1]

Chronic diseases are an urgent global health challenge

Our heritage enables us to defeat diabetes and other serious chronic diseases

Novo Nordisk's

PURPOSE

Otávio Domingos da Costa
Otávio has type 2 diabetes and obesity
Brazil

Our corporate strategy

Diabetes care

Strengthen leadership by offering innovative medicines and driving patient outcomes

Obesity care

Strengthen treatment options through market development and by offering innovative medicines and driving patient outcomes

Novo Nordisk Way

Driving change to defeat diabetes and other serious chronic diseases

Sustainable business

Biopharm

Secure a leading position by leveraging full portfolio and expanding into adjacent areas

Other serious chronic diseases

Establish presence by building competitive pipeline and scientific leadership

Our core technology platforms

Proteins & peptides

Injection devices

Oral delivery

RNAi

Stem cells

Gene editing

Innovation and therapeutic focus

Pipeline overview

● ○ ○ ○ Phase 1 ● ● ○ ○ Phase 2 ● ● ● ○ Phase 3 ● ● ● ● Submission and/or approval

Diabetes care

Project	Indication	Description	Phase
Semaglutide 2.0 mg NN9535	Type 2 diabetes	A long-acting GLP-1 analogue for once-weekly treatment.	● ● ● ●
Oral semaglutide HD NN9924	Type 2 diabetes	A long-acting oral GLP-1 analogue, 25 and 50 mg, intended for once -daily oral treatment.	● ● ● ○
Icodec NN1436	Type 1 and 2 diabetes	A long-acting basal insulin analogue intended for once -weekly treatment.	● ● ● ○
Insulin 965 NN1965	Type 1 and 2 diabetes	A novel basal insulin analogue intended for once -daily treatment.	● ○ ○ ○
Icosema NN1535	Type 2 diabetes	A combination of GLP -1 analogue semaglutide and insulin icodec intended for once -weekly treatment.	● ○ ○ ○
FDC Sema – OW GIP NN9389	Type 2 diabetes	A combination of semaglutide and novel GIP intended for once -weekly treatment.	● ○ ○ ○
Glucose-sensitive insulin NN1845	Type 1 and 2 diabetes	A glucose-sensitive insulin analogue intended for once -daily treatment.	● ○ ○ ○
Ideal Pump Insulin NN1471	Type 1 diabetes	A novel insulin analogue ideal for use in a closed loop pump device as delivery.	● ○ ○ ○
DNA Immunotherapy NN9041	Type 1 Diabetes	A novel plasmid encoding pre - and pro-insulin intended for preservation of beta cell function.	● ○ ○ ○

Obesity care

Semaglutide 2.4 mg NN9536	Obesity	A long-acting GLP-1 analogue intended for once-weekly treatment.	● ● ● ●
AM833 NN9838	Obesity	A novel long -acting amylin analogue intended for once -weekly treatment.	● ● ○ ○
AM833 + semaglutide NN9838	Obesity	A combination of amylin analogue and GLP -1 analogue semaglutide intended for once -weekly treatment.	● ○ ○ ○
LA-GDF15 NN9215	Obesity	A long-acting GDF15 analogue intended for appetite regulation leading to weight loss.	● ○ ○ ○
PYY1875 NN9775	Obesity	A novel analogue of the appetite -regulating hormone, PYY, intended for once -weekly treatment.	● ○ ○ ○

Biopharm

Project	Indication	Description	Phase
Sogroya ® NN8640	Adult GHD [1]	A long-acting HGH [1] derivative intended for once-weekly subcutaneous administration in adults.	● ● ● ●
Somapacitan NN8640	GHD	A long-acting HGH [2] analogue intended for once-weekly subcutaneous administration in children.	● ● ● ○
Concizumab NN7415	Haemophilia A and B w/wo inhibitors	A monoclonal antibody against tissue factor pathway inhibitor intended for subcutaneous prophylaxis treatment.	● ● ● ○
MacrilenTM EX2020	GHD	An oral diagnostic agent used for the diagnosis of GHD in adolescents and children.	● ● ○ ○
Mim8 NN7769	Haemophilia A with or without inhibitors	A next generation FVIII mimetic bispecific antibody for subcutaneous prophylaxis of haemophilia A regardless of inhibitor status.	● ● ○ ○
Eclipse NN7533	Sickle cell disease	An oral combination treatment of sickle cell disease and beta thalassaemia. Project is developed in collaboration with EpiDestiny.	● ○ ○ ○

Other serious chronic diseases

Semaglutide NN9931	NASH [3]	A long-acting GLP-1 analogue for once -weekly treatment of NASH.	● ● ○ ○
Ziltivekimab NN6018	CVD [4]	A novel once-monthly monoclonal antibody intended for inhibition of IL -6 activity.	● ● ○ ○
PCSK9i peptide NN6434	CVD [4]	A long-acting PCSK9 inhibitor for subcutaneous treatment.	● ○ ○ ○
Anti-ApoC3 NN5058	CVD [4]	A novel monoclonal antibody intended for inhibition of ApoCIII activity. Project is developed in collaboration with STATEN.	● ○ ○ ○

1. GHD = Growth hormone deficiency 2. HGH = Human growth hormone 3. NASH = Non -alcoholic steatohepatitis 4. CVD = Cardiovascular disease

Source: Adapted from Novo Nordisk Annual Report 2020

AMP-CMD & Novo Nordisk:

because in union there is strength

PREVENTION

1. Reduce overweight and obesity in children
2. Strengthen prevention by focusing on health inequality in cities
3. Bend the global obesity curve

ACCESS AND AFFORDABILITY

4. Offer affordable insulin to vulnerable patients in every country
5. Expand patient access through supply chain improvements and heat stable insulins
6. Strengthen capacity to treat diabetes

INNOVATION

7. Keep people at high risk from developing diabetes
8. Explore transformative treatments for people living with diabetes
9. Strive for curative therapies starting with type 1 diabetes

defeat diabetes

Chronic diseases are an urgent global health challenge

Prevention

AMP-CMD & Novo Nordisk

This partnership will provide a comprehensive, integrated approach for understanding **disease triggers & path to prevention** as AMP-CMD's therapy areas also address co-morbidities for many people living with diabetes and obesity and support our existing internal core capabilities.

Additional elements

- A common **core strategy** : **common metabolic diseases**
- Novo Nordisk's first significant Public-Private Partnership participation in **US**
- Synergies with Public-Private Partnerships in **Europe** such as IMI SOPHIA
- A **long-term partnership** to look forward to

Nadia Sadi
Nadia lives with NASH
Denmark

CVD

70% of people with diabetes die from atherosclerotic CVD [1]

40% of people hospitalised for heart failure have diabetes [2]

NASH

80% of people with NASH have obesity [3]

40% of people with NASH have diabetes [3]

CKD

40% of people with diabetes have diabetic nephropathy [5]

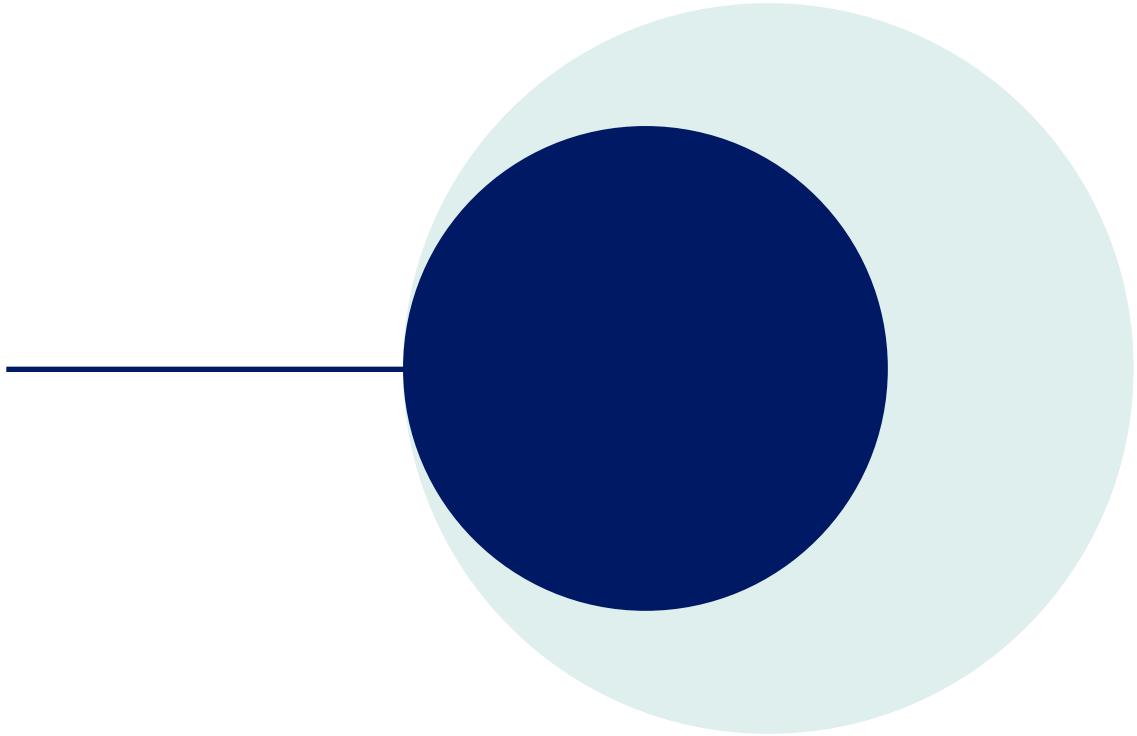
50% of people with diabetic nephropathy have obesity [6]

1. Laakso M. Cardiovascular disease in type 2 diabetes from population to man to mechanisms: the Kelly West Award Lecture 2008. Diabetes Care. 2010;33(2):442-449. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2809299/ Accessed: Feb 2020. 2. Thomas MC. Type 2 Diabetes and Heart Failure: Challenges and Solutions. Curr Cardiol Rev. 2016;12(3):244-255. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5011193/ Accessed: Feb 2020. 3. Diehl AM, Day C. Cause, Pathogenesis and Treatment of Nonalcoholic Steatohepatitis. N Eng J Med. Available at: https://www.nejm.org/doi/full/10.1056/NEJMra1503519 Accessed: Feb 2020. 4. Alzheimer's Disease International. World Alzheimer Report 2015 The Global Impact of Dementia. Available at: https://www.alz.co.uk/research/WorldAlzheimerReport2015.pdf. Accessed July 2020 and Alzheimer's Society. Dementia UK Update. Available at: https://www.alzheimers.org.uk/sites/default/files/migrate/downloads/dementia_uk_update.pdf. Accessed July 2020; and Petersen RC. Continuum (Minneap Minn) 2016;22:404-418; and United Nations. Population Division World Population Prospects 2019. Available at: https://population.un.org/wpp/. [Custom data acquired via website]; 5. Busse A et al. Br J Psychiatry 2006;189:399-404 5. Gheith O, Farouk N, Nampoory N, Halim MA, Al-Otaibi T. Diabetic kidney disease: world wide difference of prevalence and risk factors. J Nephropharmacol. 2015 Oct 16;5(1):49-56. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5297507/ Accessed: Feb 2020. 6. Marie-Bilkan C. Obesity and diabetic kidney disease. Med Clin North Am. 2013 Jan;97(1):59-74. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3539140/ Accessed: Feb 2020.

Non-communicable diseases (NCDs) are the leading cause of death and disability globally[1]

74%

of global deaths
in 2019 were due to NCDs [1]



1. World Health Organization. Global health estimates 2019: estimated deaths by age, sex, and cause. https://www.who.int/data/gho/data/themes/mortality -and-global-health-estimates. Published 2020. Accessed January 2021.

Partner's Aspirations for AMP CMD

Eric Fauman, Senior Scientific Director,
Internal Medicine Research Unit,
Pfizer Worldwide Research Development and Medical

FNIH

Pfizer

Pfizer's purpose: Breakthroughs that change patients' lives

For Internal Medicine this means we're looking for novel therapies to address unmet medical need in common metabolic disorders or diseases which have a metabolic dysfunction component.

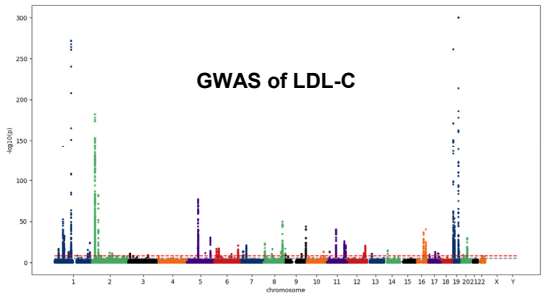
Currently the Internal Medicine Research unit focuses on disease including NAFLD and NASH, cachexia, diabetes and diabetic complications, obesity, and abnormalities in cardiac metabolism.

FNIH

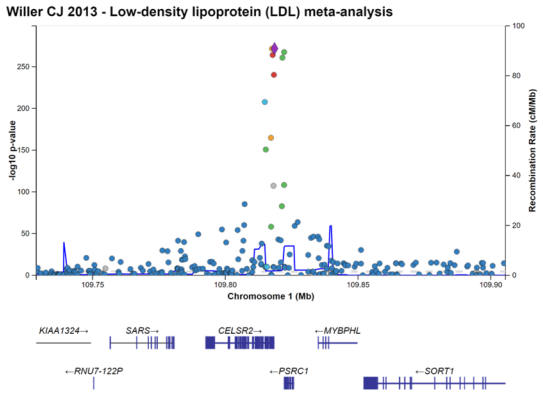
Pfizer's aspiration for AMP CMD: Super-powered human genetics

Evolve from: **rs646776 has a p-value of $5x10^{-241}$ for LDL-cholesterol**

To this: **80% decrease in sortilin activity in human livers results in a doubling of circulating LDL-C levels**



https://hugeamp.org/phenotype.html?phenotype=LDL



FNIH

Pfizer's aspiration for AMP CMD: Super-powered human genetics

Evolve from: **rs646776 has a p-value of $5x10^{-241}$ for LDL-cholesterol**

To this: **80% decrease in sortilin activity in human livers results in a doubling of circulating LDL-C levels**

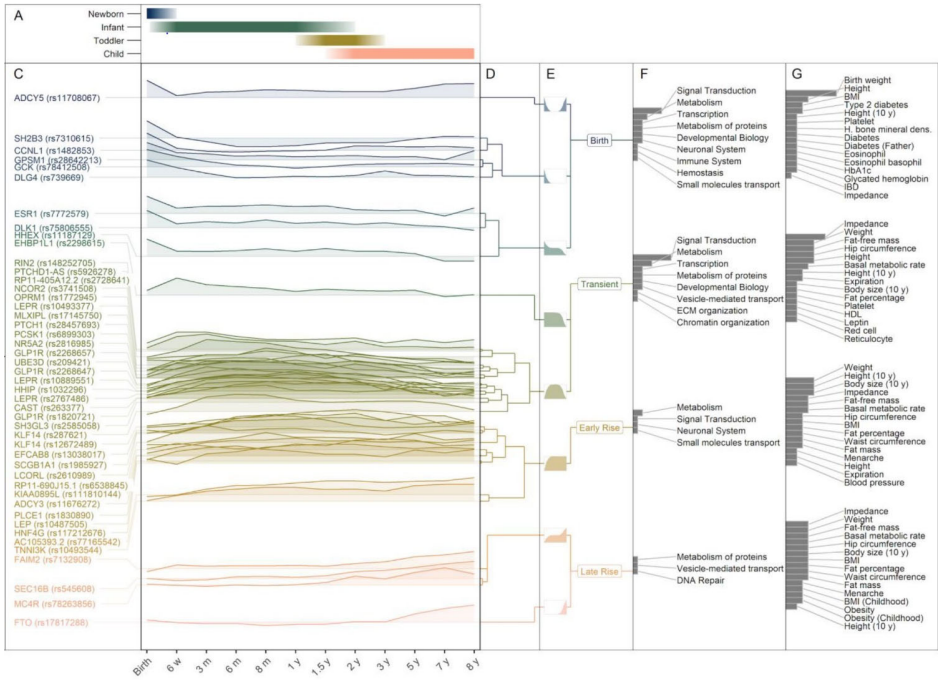
- What **gene** is implicated by a particular genetic association?
  What is the certainty or **confidence** in that conclusion?
- What **tissue** and **cell type** is responsible for the genetic association?
- What is the **maximum possible effect** of inhibiting or activating the implicated gene?
- What **pathway** or **mechanism** is implicated by a specific variant/gene or an entire GWAS?
- What **other phenotypes** are likely to accompany a therapeutically-meaningful alteration in target activity?

FNIH

Musunuru et al, Nature. 2010 466(7307):714–719

Future directions:

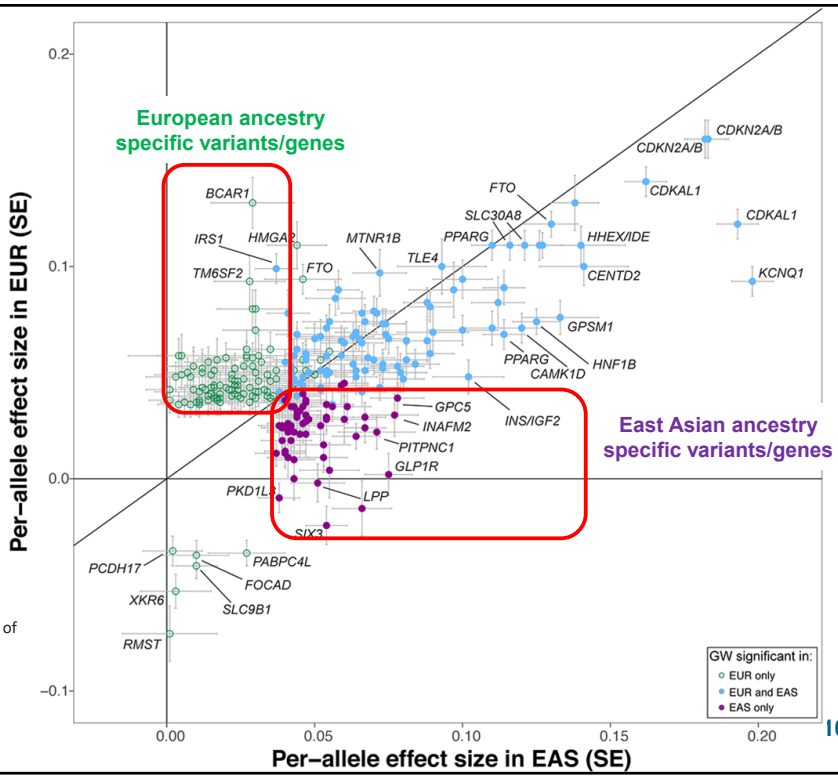
Leveraging PheWAS and tissue-specific epigenetic marks to define independent causal mechanisms and pathways contributing to traits of interest



Øyvind Helgeland et al (2021) *Characterization of the genetic architecture of BMI in infancy and early childhood reveals age-specific effects and implicates pathways involved in Mendelian obesity.* medRxiv 2021.05.04.21256508

Future directions:

Sampling multiple independent populations to help fill out information on disease-relevant pathways, mechanisms and targets



Spracklen, C.N., Horikoshi, M., Kim, Y.J. *et al.* Identification of type 2 diabetes loci in 433,540 East Asian individuals. *Nature* **582,** 240–245 (2020).

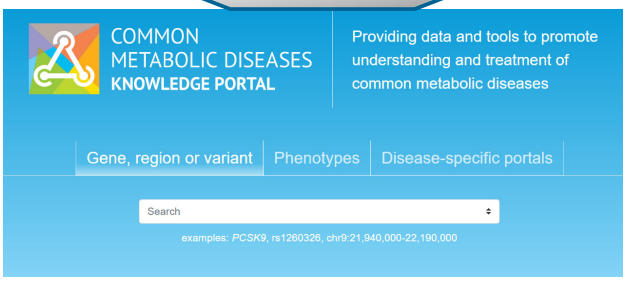
Together we will:

Identify, generate and collect the information necessary to enable “super powered human genetics”

Develop the tools and methods to turn that data into actionable hypotheses for common metabolic diseases

Keeping in mind the two key groups of users of this information:

GWAS scRNAseq H3K27ac ExWAS snATACseq WES WGS phenotypes functional genomics genomic screens



Casual user, bench biologist
“biology first”
What can human genetics tell me about my favorite gene

Expert user, Computational biologist
“genetics first”
What can human genetics tell me the best genes and pathways to pursue for a specific indication

FNIH


Partner's Vision
FNIH
AMGEN®

ACCELERATING MEDICINES PARTNERSHIP

COMMON METABOLIC DISEASES

A Shared Vision

FNIH 25
Foundation for the National Institutes of Health

Accelerated Medicines Partnership

Common Metabolic Diseases

Stakeholders

Confidential

Beena Akolkar, Ph.D.

Program Director, Division of Diabetes, Endocrinology, and Metabolic Diseases, NIDDK

Dr. Beena Akolkar, Senior Advisor, Immunopathogenesis and Genetics of Diabetes at DDEMD, NIDDK is an expert on autoimmune diseases such as type 1 diabetes and celiac disease. She coordinates several major international, NIH-sponsored clinical networks such as TEDDY (The Environmental Determinants of Diabetes in the Young) that conducts studies to identify environmental triggers of T1D in genetically susceptible individuals. She is also the project scientist for the NIH portion of the AMP-CMD consortium. It aims to elucidate the mechanisms of metabolic disease, through generation and integration of novel genomic datasets. She received her PhD from Bombay University, India in 1984. She was an Assistant Professor, Medicine and Pathology, NYU School of Medicine, Division of Molecular Medicine, Department of Medicine, North Shore University Hospital, 1996-2000 before joining NIDDK.

Michael Boehnke, Ph.D.

Michael Boehnke is the Richard G. Cornell Distinguished University Professor of Biostatistics. He is Director of the University of Michigan Center for Statistical Genetics and Genome Science Training Program, a member of the National Academy of Medicine, and a Fellow of the American Statistical Association and of the American Association for the Advancement of Science. Dr. Boehnke's research focuses on problems of study design and statistical analysis of human genetic data with a particular emphasis on development and application of statistical methods for human gene mapping, and a current focus on disease and trait association studies based on genome sequence and genotype-array data. He is a principal investigator of the FUSION study of the genetics of type 2 diabetes and a founder and steering committee member of the DIAGRAM (type 2 diabetes), DIAMANTE (type 2 diabetes), MAGIC (glucose and insulin traits), GIANT (anthropometric traits), and Global Lipids genome-wide association meta-analysis consortia. He was previously chair of the T2D-GENES steering committee and currently is a PI of the NIH AMP CMD portal project.

Nöel Burtt, M.S.

Noël Burtt is the Director of Operations and Development for Knowledge Portals and Diabetes Research at the Broad Institute and a Principal Investigator for the AMP CMD Portal award. Trained in molecular biology and human genetics, for the last 15 years, she provided operational and organizational leadership to large-scale, international consortia and public/private partnerships for human genetics, with a focus on type 2 diabetes and cardio-metabolic diseases. She directs operations and data coordination for the AMP T2D Data Coordinating Center at Broad Institute. She also leads outreach, user experience, external partnerships, and community engagement for the AMP T2D Knowledge Portal and now the AMP Common Metabolic Disease Knowledge Portal.

Karin Conde-Knape, Ph.D.

Senior Vice President, Global Drug Discovery, Novo Nordisk

Karin Conde-Knape is a Senior Vice President for Global Drug Discovery/GDD within Novo Nordisk. She is involved in driving the early pipeline and innovation within the areas of Diabetes, Obesity, Cardiovascular, Renal, Rare endocrine and metabolic diseases. She is an experienced executive within the pharmaceutical industry for the last 19 years with different areas of responsibility, including project leadership, line management, strategic planning and execution as well as business development. Karin spent 11 years at Hoffman-La Roche in the Cardiovascular and Metabolism Discovery and early development areas, responsible for pharmacology teams as well as discovery and biomarker teams. Before joining NN she spent 4 years at Johnson and Johnson, responsible for external innovation in Europe and Asia Pacific in the area of Cardiovascular and Metabolism. During these years she led cross functional teams in the evaluation for external opportunities and creating the business cases to support deal making for different external opportunities.

Oona Dierickx, M.A., MIS

Public-Private Partnership Manager, Global Chief Medical Office, Novo Nordisk A/S, Denmark

Oona Dierickx is an alliance project manager who drives Novo Nordisk's participation in public-private partnership projects like IMI SOPHIA and NASH consortia such as Liver Forum and NIMBLE. Oona, who is originally from Belgium, joined the Novo Nordisk R&D Innovation sourcing team in 2014, after having worked in South East Asia for the European Chamber of Commerce. She brings extensive

knowledge in multilateral and public-private partnerships thanks to her academic background and professional experience with associations such as PCDE (Primary Care Diabetes Europe).

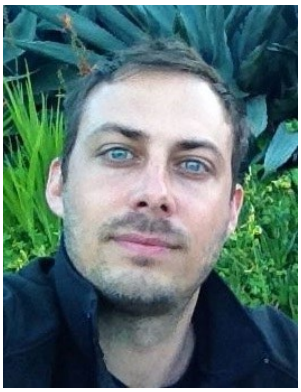
Oona has a specialist degree in Development Aid Projects and holds a Master of International Studies and Conflict Management as well a Master of Arts & Humanities.

Eric Fauman, Ph.D.
Senior Scientific Director, Pfizer

Eric Fauman, PhD, is a Senior Scientific Director of Integrative Biology in the Internal Medicine Research Unit at Pfizer. Eric's team uses and develops computational methods to evaluate genetic, multi-omics and imaging data to support the discovery of new medicines to address unmet medical needs in cardiovascular and metabolic diseases. Eric joined Pfizer in 1998. Prior to Pfizer, Eric completed graduate and post-doctoral work in protein structure and X-ray crystallography at UC San Francisco and the University of Michigan.

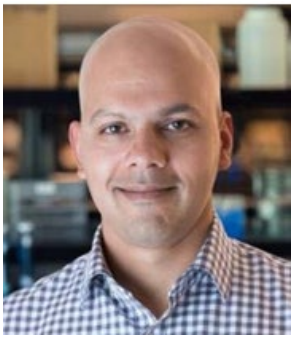
Jason Flannick, Ph.D.

Jason Flannick is an Assistant Professor in the Division of Genetics and Genomics at Boston Children's Hospital and the Broad Institute. He received his PhD in Computer Science from Stanford University and trained as a postdoctoral scholar in human genetics at Massachusetts General Hospital and the Broad Institute. He has published numerous discoveries on the genetic basis of type 2 diabetes, particularly with respect to the role of rare coding variation in disease, and his group has developed and maintains the type 2 diabetes knowledge portal, a public resource of genetic and genomic data for type 2 diabetes and its complications. His current research interests are on the use of rare coding variants to learn about rare and common diseases and their clinical subtypes, as well as on methods to integrate genetic and genomic data to translate genetic associations to biological insights.



Kyle Gaulton, Ph.D.

Kyle J Gaulton, PhD is an assistant professor at the University of California San Diego. He has a BAS in computer science from the University of Pennsylvania, a PhD in molecular biology and genetics from UNC Chapel Hill and did postdoctoral training at the University of Oxford. The primary focus of his research group is mapping the epigenome and gene regulatory programs in human cell types, defining changes in the epigenome and gene regulation across phenotype and genotype, and determining the role of genetic variants affecting cell type-specific gene regulation in complex traits and disease. This research has recently generated single cell epigenome maps in the human pancreas, lung, heart, peripheral blood and other tissues, and through integration of genetic association and functional genomics data uncovered novel insight into the biological mechanisms of complex metabolic, autoimmune, respiratory and cardiovascular disease. His group has also developed multiple collaborative platforms and visualizations for epigenomic data (lungepigenome.org, diabetesepigenome.org).



Saptarsi M. Haldar, M.D., FAHA

Vice President, Research Head, Cardiometabolic Disorders, Amgen

Saptarsi (Sap) Haldar joined Amgen as Vice President of Research in August 2018, overseeing the Cardiometabolic Disease Therapeutic Area. He joined Amgen from the Gladstone Institute of Cardiovascular Disease and University of California San Francisco, where he was a Professor of Medicine. In that role, he ran a laboratory focused on how cells in the cardiovascular and metabolic system control gene expression and how these gene control mechanisms go awry during disease. His lab had a major interest in congestive heart failure, a very common and deadly condition that affects a large number of adults. More specifically, he has developed therapeutic approaches that target gene-control mechanisms in the stressed and failing heart, a process that has striking similarities to uncontrolled growth in cancers. Sap received his B.S. from Cornell University and M.D. from Johns Hopkins University. He trained in internal medicine at Johns Hopkins followed by Fellowship training in Cardiovascular Disease at Brigham and Women's Hospital, Harvard Medical School. He has had continuous funding from the National Institutes of Health and has been the recipient of several awards including the Jeremiah Stamler Distinguished Young Investigator Prize, appointment to the board of Associate Scientific Advisors to Science Translational Medicine, election as a Fellow of the American Heart Association, and induction into the American Society for Clinical Investigation. He has also chaired major research symposia, served on several scientific advisory boards for academic and non-profit organizations in biomedical research and is deeply committed to mentorship of junior colleagues, including those on a physician-scientist pathway. In addition to his lab's research, Sap co-founded Tenaya Therapeutics, which is focused on developing therapies for heart failure. Sap is also a board-certified cardiologist who continues to actively see patients while conducting basic research and leading cardiometabolic drug discovery.

Narimon Honarpour, M.D., Ph.D.
Vice President of Translational Medicine, Amgen

In leading Translational Medicine, Narimon oversees the integration of and collaboration between four core functions: Early Development, Clinical Biomarkers & Diagnostics, Clinical Pharmacology Modeling & Simulation, and Clinical Immunology. Each function has a critical role in advancing therapeutics from Research to Global Development. Together, these teams generate the evidence base necessary to support progression of Amgen's pipeline assets into late phase clinical trials.

Narimon joined Amgen in 2011 and has held diverse leadership roles supporting both Cardiovascular and Inflammation Therapeutic Areas. Prior to joining Amgen, Narimon was at UCLA where he completed his clinical training in Internal Medicine and Cardiology. His postdoctoral work at Caltech focused on the role of the ubiquitin proteasome system in mediating stem cell differentiation into cardiovascular tissue.

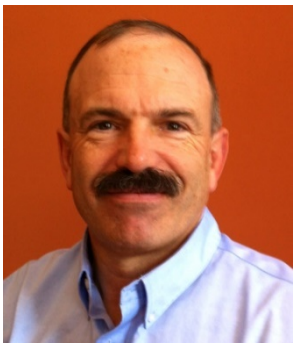
Corey James, M.S.
Bioinformation Scientist, Eli Lilly

I am a scientist in the Bioinformatics and Genetics group within the Diabetics and Complications Therapeutic Area of Lilly Research Labs. I have a broad computational background that started in healthcare informatics and has moved into a more traditional bioinformatics role during my time at Lilly. My experience has ranged from data engineering and capabilities focused roles within the bioinformatics core supporting cross functional teams and therapeutic areas, to more recently a translational bioinformatics role within Diabetes supporting early discovery research through data analysis and algorithm design and implementation.

Tania Kamphaus, Ph.D., M.Sc.

Scientific Program Manager, Metabolic Disorders Portfolio of Research Partnerships, FNIH

Tania Kamphaus is the Scientific Program Manager for Metabolic Disorders at the FNIH. In her role, she leads the Metabolic Disorders Research Partnership programs and manages the Steering Committee for Metabolic Disorders Biomarkers Consortium including projects on non-alcoholic steatohepatitis, heart failure, cachexia and bone health as well as the Type 2 Diabetes Accelerated Medicines Partnerships (AMP T2D) program in coordination with the NIH, non-profit and industry leaders. Dr. Kamphaus is trained in molecular genetics, molecular and cell biology and skilled in strategic planning and collaborative program development across basic, translational and clinical research. Prior to joining the FNIH, Dr. Kamphaus was the Director of the Office of Clinical Protocol Development at the University of Wisconsin-Madison, where she supported development of large clinical trial protocols ranging from interventional and observational studies to implementation and dissemination studies. She also served as a key member of the Trial Initiation Network (TIC). Before her work in clinical trials, Dr. Kamphaus was Director of Collaborative Research at the Crohn's and Colitis Foundation. Dr. Kamphaus conducted her postdoctoral fellowship at Columbia University at the department of Pathology and Cell Biology. She earned her PhD in Molecular Genetics from The Ohio State University and her Masters in Biotechnology from Madurai Kamaraj University, India.



James B. Meigs, M.D., M.P.H.

James B. Meigs is Professor of Medicine at Harvard Medical School, a primary care internist at Massachusetts General Hospital, the Director, MGH Division of Clinical Research's Clinical Effectiveness Research Unit and an Associate Member, Broad Institute. His research interest is the cause and prevention of type 2 diabetes and cardiovascular disease using biochemical and genetic epidemiology and health services translational research approaches. In 2009 he was awarded the ADA's prestigious Kelly West Award for Outstanding Achievement in Diabetes Epidemiology. He is a senior leader of many major large international T2D genomics consortia, including MAGIC, DIAGRAM, AAGILE, CHARGE- and TOPMed-diabetes, NIDDK T2D AMP/CMD and the VA's MVP cardiometabolic work group, and is the PI, co-PI or co-investigator on many NIH grants, currently including UM1 DK078616-13 TOPMed Omics of T2D and Quantitative traits and R01 HL151855-01 TOPMed Omics of CVD in T2D and Quantitative traits. He has formally mentored over 50 early career investigators, most of whom have remained in academic medicine, and is an MGH Institutional Research Mentor.

Joseph P. Menetski, Ph.D.
Vice President of Research Partnerships, FNIH

Joseph Menetski received his Ph.D. from Northwestern University Medical School with Dr. Stephen Kowalczykowski and completed his post-doctoral training at the Laboratory of Molecular Biology, National Institutes of Health (NIH/NIDDK) with Dr. Martin Gellert. He started his career in industry in 1993 in the Immunopathology Department at Parke-Davis (later Pfizer), where he established a discovery research program in cellular inflammation that eventually transitioned to the molecular study of osteoarthritis. Joseph moved to Merck in 2004 where he continued his work in osteoarthritis in the Department of Immunology. He held positions in several groups primarily focusing on large data set analysis and competitive intelligence. Currently, Joseph manages the Research Partnerships department and guides the work of several large public-private partnerships (including the Alzheimer's Disease Neuroimaging Initiative, the Biomarkers Consortium, the Accelerating Medicines Partnership and the Accelerating COVID19 Therapeutic Interventions and Vaccines).

Melissa R. Miller, Ph.D.
Director of Human Genetics, Pfizer

Melissa R. Miller, PhD, is a Director of Human Genetics in the Internal Medicine Research Unit at Pfizer. Melissa and her team use human genetics and statistical genetics methods to help identify and prioritize targets to support the discovery of new medicines to address unmet medical needs in cardiovascular and metabolic diseases. In addition to serving on the AMP-T2D steering committee, Melissa has also been involved in other pre-competitive consortia including the UK Biobank whole exome sequencing consortium and the IMI Liver Investigation: Testing Marker Utility in Steatohepatitis (LITMUS) project. Melissa joined Pfizer in 2014. Before joining Pfizer, Melissa completed her PhD in Epidemiology at the University of Colorado and completed a post-doctoral fellowship in statistical genetics and genetic epidemiology at the Hospital for Sick Children in Toronto.

Karen L. Mohlke, Ph.D.

Karen Mohlke is a human geneticist from the University of North Carolina in Chapel Hill, where she is currently Professor, Oliver Smithies Investigator, and Associate Chair for Research in the Department of Genetics.

Karen's research focuses on genetic susceptibility to type 2 diabetes, obesity, and variation in related quantitative traits. Her lab uses genetic association studies and fine-mapping to identify susceptibility variants; transcriptome and epigenome analyses to characterize variants, and molecular and cellular assays to determine the functional consequences of variants on disease processes.

Lynette Nguyen, Ph.D., PMP

Lynette Nguyen is a Scientific Project Manager for Metabolic Disorders projects at the FNIH. In her role, she collaborates with NIH, industry leaders, academics and non-profit organizations to support the Accelerating Medicines Partnership Type 2 Diabetes. Prior to joining the FNIH, she was a project manager for seven years at the United States Pharmacopeia, managing the work of expert committees for small molecules. Lynette received her Ph.D. from the Medical College of Virginia in neuroanatomy and completed her post-doctoral training at the Smith Kettlewell Eye Research Institute in San Francisco, California.

Afshin Parsa, M.D., M.P.H.
Program Director, Division of Kidney, Urologic, and Hematologic Diseases, NIDDK

Rasmus Rabøl, M.D., Ph.D.
Corporate Vice President, Translational Science and Medicine, Novo Nordisk

Rasmus Rabøl has several years of experience in drug development within diabetes and obesity. During his ten years with Novo Nordisk he has held positions within clinical development and project management and is currently head of the area of Translational Science and Medicine.

Prior to joining Novo Nordisk, Dr. Rabøl worked in internal medicine, and he earned his PhD in endocrinology from the University of Copenhagen while working part time for the Danish Medicines Agency.

Griffin P. Rogers, M.D., M.A.C.P.
Director NIDDK

Dr. Griffin P. Rodgers was named Director of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)--one of the National Institutes of Health (NIH)--on April 1, 2007. He had served as NIDDK's Acting Director since March 2006 and had been the Institute's Deputy Director since January 2001. As the Director of NIDDK, Dr. Rodgers provides scientific leadership and manages a staff of over 600 employees and a budget of ~$2.3 billion.

Dr. Rodgers received his undergraduate, graduate and medical degrees from Brown University in Providence, R.I. He performed his residency and chief residency in internal medicine at Barnes Hospital and the John Cochran VA, respectively, at Washington University in St. Louis, MO. His fellowship training in hematology was in a joint program of the NIH with George Washington University. In addition to his medical and research training, he earned an MBA, with a focus on the business of medicine/science, from Johns Hopkins University in 2005, and a Masters in Legal Studies in 2017.

Dr. Rodgers is a member of the American Society of Hematology, the American Society of Clinical Investigation, the Association of American Physicians, the American Academy of Arts and Sciences, the American Association for the Advancement of Science, and the National Academy of Medicine, among others.

Patrick Seale, Ph.D.

Patrick Seale is an Associate Professor of Cell and Developmental Biology in the Institute for Diabetes, Obesity and Metabolism at the University of Pennsylvania. He obtained his Ph.D. from McMaster University, Canada where he studied skeletal muscle stem cells and regeneration. He conducted postdoctoral research in Dr. Bruce Spiegelman's lab at Harvard Medical School. His research program focuses on adipocyte biology and obesity pathogenesis, with an emphasis on the mechanisms that control the fate and function of adipocytes under various contexts, including development, cold exposure, and obesity. He has discovered several key transcriptional regulators of brown fat cells, including PRDM16 and EBF2. Recent studies in his lab have focused on the regulation of adipose tissue progenitor cells and fibrosis responses.

Philip Smith, Ph.D.
Deputy Director, NIDDK, Co-Director, Office of Obesity Research

Melissa Thomas, M.D., Ph.D.

Melissa Thomas is a physician scientist who received her MD and PhD in Molecular Physiology and Biophysics from Vanderbilt University and completed clinical postgraduate training in Internal Medicine and Endocrinology at Massachusetts General Hospital. Before joining Lilly Research Laboratories, Dr. Thomas served as Associate Chief of the Laboratory of Molecular Endocrinology at Massachusetts General Hospital, where she led a basic diabetes research program focused on pancreatic islet cell biology and served on faculty of Harvard Medical School and affiliated faculty with the Harvard Stem Cell Institute.

Dr. Thomas is a Senior Medical Fellow in Diabetes Discovery and Clinical Investigation at Lilly Research Laboratories where she applies expertise in translational science and medicine to support diabetes and complications discovery and clinical research portfolios. Her contributions include advancing target identification and validation, developing and translating innovative human cellular disease models, discovering and translating mechanistic biomarkers, advancing novel therapeutic modalities, and leading and building international collaborations and private-public partnerships. Melissa was a founding co-chair of the Innovative Medicines Initiative (IMI) Strategic Governing Group for Diabetes and Metabolic Disorders that framed strategic direction to build multiple diabetes and complications-related private-public partnerships between pharma and the European Commission. Dr. Thomas represented Lilly in the Target Validation Consortium team that framed the original Accelerating Medicines Partnership (AMP)-Type 2 Diabetes project plan, has served on its Steering Committee since its inception, and currently is industry chair. Dr. Thomas co-led design and framing of the AMP-Common Metabolic Diseases project.

Erin Whalen, Ph.D.

Executive Director, Research Cardiometabolic Disorders, Amgen

Erin Whalen, Ph.D., joined Amgen on March 1, 2021, as Executive Director in Cardiometabolic Disorders, Amgen Research.

Erin has a broad scientific background in cardiometabolic biology and extensive experience in drug discovery. He received his PhD from the University of Iowa and postdoctoral training in the lab of Robert (Bob) J. Lefkowitz (2012 Nobel Prize for Chemistry) at Duke University, where he made fundamental contributions to our understanding of G-protein coupled receptor signaling and trafficking. Erin was a co-founder of Trevena Inc. (TRVN), a biotech company focused on the discovery and development of G-protein coupled receptor biased ligand therapeutics. Trevena has taken multiple compounds into clinical trials for acute heart failure and pain. After Trevena, Erin spent 5 years at the Novartis Institutes for Biomedical Research in Cambridge, Massachusetts as a Senior Investigator in the Cardiovascular and Metabolic Disease group. Most recently he was the Director of *in vitro* Pharmacology and subsequently External Evaluation and Diligence for Obesity Research at Novo Nordisk in Seattle, Washington. He has published 45 articles in highly respected scientific journals and is also recognized for his collaborative ethos and dedication to mentorship.

David Wholley, M.Phil.

Senior Vice President of Research Partnerships, FNIH

David Wholley manages the Research Partnerships Division of the Foundation, which is responsible for major research collaborations including the Accelerating Medicines Partnership (AMP), the Biomarkers Consortium, the Partnership for Accelerating Cancer Therapies (PACT), the LungMAP precision medicine trial in lung cancer, and the Alzheimer's Disease Neuroimaging Initiative (ADNI). Mr. Wholley has also served as Director of the Genetic Association Information Network (GAIN), a public-private partnership dedicated to helping discover the genetic basis of common diseases, and led the development of a major public-private partnership in drug safety with the biopharmaceutical industry and FDA. Prior to joining the Foundation in 2006, Mr. Wholley's career spanned nearly 25 years in healthcare technology business management, including extensive experience in product development, sales, marketing, corporate strategy and partnership and project development. Mr. Wholley has held senior management roles in several venture-funded technology startup companies, including head of Global Marketing and Development for First Genetic Trust, Inc., which developed software for large-scale collaborative genetic research and personalized medicine. During a 16-year career at IBM, he co-led the corporate strategy team that guided IBM's formation of its Life Sciences industry organization. Mr. Wholley holds an M.Phil from Rutgers University and a Certificate in Business Administration from the Stern School of Business at New York University.

Norann Zaghloul, Ph.D., M.S.

Norann Zaghloul currently serves as a Program Director in NIDDK within the Division of Diabetes, Endocrinology, and Metabolism where she is overseeing portfolios in type 2 diabetes genetics and genomics and functional genomic modeling of diabetes and related metabolic conditions. As part of her responsibilities, she is the Program Official for the Accelerating Medicines Partnership (AMP) in T2D and the newly formed AMP in Common Metabolic Diseases. Prior to joining NIDDK, she was an Associate Professor at the University of Maryland School of Medicine where she ran a research laboratory focused on functional genomics of diabetes and related cardiometabolic conditions in both common and rare disease. Dr. Zaghloul's research interests focused on understanding genetic regulation of metabolic diseases using a combination of human genetics and functional modeling approaches in animal and cell-based systems to understand gene function in relevant tissues and cell types. These interests have evolved over her career starting with my training that included an undergraduate degree in Public Health from the Johns Hopkins University, followed by graduate degrees in Genetics from The George Washington University, and postdoctoral training at the Johns Hopkins University School of Medicine.