## Content

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Page(s)</th>
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<tbody>
<tr>
<td>10:00 AM</td>
<td>Opening Remarks</td>
<td>Page 5</td>
</tr>
<tr>
<td>10:15 AM</td>
<td>Meeting Overview</td>
<td>Page 6</td>
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<td>10:20 AM</td>
<td>AMP CMD Organizational Overview and Project Governance (Kamphaus)</td>
<td>Pages 7-8</td>
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<tr>
<td>10:25 AM</td>
<td>Introducing Private Partners</td>
<td>Pages 9-12</td>
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<tr>
<td>10:40 AM</td>
<td>AMP CMD Research Plan (Thomas)</td>
<td>Pages 13</td>
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<td>10:50 AM</td>
<td>Introduction to NIDDK Foundational Grants and Projects (Zaghloul)</td>
<td>Pages 18-21</td>
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<td>11:00 AM</td>
<td>Evolution of AMP Knowledge Portal and Plans for AMP CMD (Burtt &amp; Flannick)</td>
<td>Pages 22-36</td>
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<td>11:10 AM</td>
<td>Evolution of Analytical Tools and Plans for AMP CMD (Boehnke)</td>
<td>Pages 37-44</td>
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<td>11:20 AM</td>
<td>Diabetes Epigenome Atlas (Gaulton)</td>
<td>Pages 45-53</td>
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<td>11:30 AM</td>
<td>Bridging the Gap Between GWAS and Therapeutic Targets (Mohlke)</td>
<td>Pages 54-60</td>
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<tr>
<td>11:40 AM</td>
<td>Functional Interrogation of Disease-associated Genes in Human Stem Cell-derived Models and Mice (Seale)</td>
<td>Pages 61-67</td>
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<tr>
<td>11:50 AM</td>
<td>TOPMed ‘Omics of Type 2 Diabetes and Quantitative Traits (Meigs)</td>
<td>Pages 68-73</td>
</tr>
<tr>
<td>12:10 - 12:40 PM</td>
<td>Partnership Vision and Deliverables</td>
<td>Page 74</td>
</tr>
<tr>
<td></td>
<td>- Eli Lilly</td>
<td>Pages 75-85</td>
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<td>- Novo Nordisk</td>
<td>Pages 86-89</td>
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<td>- Pfizer</td>
<td>Page 90</td>
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<td>- Amgen</td>
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<tr>
<td>12:40 PM</td>
<td>A Shared Vision</td>
<td>Page 91</td>
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## Appendix

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<th>Time</th>
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<tbody>
<tr>
<td></td>
<td>AMP CMD Bio</td>
<td>Pages 92-103</td>
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AMP CMD
Inaugural Meeting
Thursday, May 27, 2021
10:00 a.m. – 1:00 p.m. EDT

Join Zoom Meeting
https://fnih.zoom.us/j/94951042134?pwd=cS9PRFJWV2YzZlBxbnJ3SVJrUTlyQT09

Meeting ID: 949 5104 2134
Passcode: 302367
One tap mobile
+13017158592,,94951042134#,,,,*302367# US (Washington DC)
+13126266799,,94951042134#,,,,*302367# US (Chicago)

Dial by your location
+1 301 715 8592 US (Washington DC)
+1 312 626 6799 US (Chicago)
+1 646 876 9923 US (New York)
+1 408 638 0968 US (San Jose)
+1 669 900 6833 US (San Jose)
+1 253 215 8782 US (Tacoma)
+1 346 248 7799 US (Houston)

Meeting ID: 949 5104 2134
Passcode: 302367
Find your local number: https://fnih.zoom.us/u/adgl2mT8mQ
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

11:10 AM  Evolution of Analytical Tools and Plans for AMP CMD
Mike Boehnke, University of Michigan

11:20 AM  Diabetes Epigenome Atlas
Kyle Gaulton, University of California, San Diego

11:30 AM  Bridging the Gap Between GWAS and Therapeutic Targets
Karen Mohlke, University of North Carolina

11:40 AM  Functional Interrogation of Disease-associated Genes in Human Stem Cell-derived Models and Mice
Patrick Seale, University of Pennsylvania

11:50 AM  TOPMed’Omics of Type 2 Diabetes and Quantitative Traits
James Meigs, Massachusetts General Hospital

12:00 PM  Break

SESSION III: PARTNERSHIP VISION AND DELIVERABLES

12:10 – 12:40 PM  A Shared Vision
Phil Smith, NIDDK

12:40 – 12:50 PM  Next Steps and Adjournment
Tania Kamphaus, FNIH
Welcome and Introduction to AMP Common Metabolic Diseases
Meeting Overview

Phil Smith, NIDDK
AMP CMD Program Management

- Extended Executive Committee
- AMP Executive Committee
- AMP CMD Steering Committee (NIDDK + Partner Companies + FNIH)
- Joint Leadership and shared scientific vision
- NIDDK-Academic Steering Committee (NIDDK + leadership from foundational awards)

RFPs

AMP CMD Consortium – Shared Vision, Independent Funding Streams

- AMP Executive Committee
- AMP CMD Steering Committee
- Joint Working Groups
- Scientific discoveries to validate targets for common metabolic diseases

RFPs

NIDDK/Academic PI managed OPs

FNIH Managed RFPs

FNIH

NIDDK Managed
Accelerating Medicines Partnership
Common Metabolic Diseases
Research Plan

Melissa Thomas, MD, PhD

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

Nature Reviews Drug Discovery - February 27, 2019
https://www.nature.com/articles/d41573-019-00333-8
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

---

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

Maximize Value, Community
Maintain Focus, Feasibility

NIH Prioritized Value

Co 1 Value

Shared Core Project Value

Industry Prioritized Value

Co 2 Value

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

AMP Metabolic Diseases: Program Overview

Part A: Knowledge Portal Expansion Module

<table>
<thead>
<tr>
<th>Clinical Data Expansion</th>
<th>Human Genomic Data Expansion</th>
<th>Enhanced Data Harmonization and Integration</th>
<th>New Advanced Analytic Tools</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenotypes, Traits, Endotypes, Clusters, Biomarkers</td>
<td>Genetic data, Genomic, epigenetic data, Tissue and single cell data, Perturbation data, Genome wide screens</td>
<td>Genetic with genomic, Multi trait analyses, Endotypes and clusters, Biobank data scaling</td>
<td>Target prioritization, Functional annotation (noncoding variants), Cluster analyses, Pathways/networks</td>
</tr>
</tbody>
</table>

Part B: Disease-Focused Modules

<table>
<thead>
<tr>
<th>NASH</th>
<th>KIDNEY DISEASE</th>
<th>CARDIOVASCULAR</th>
<th>OBESITY</th>
<th>DIABETES PRE-DIABETES</th>
<th>INFLAMMATORY DRIVERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prioritize, acquire, harmonize, and integrate existing high value genetic and genomic data in portal</td>
<td>Enhance mechanistic understanding of disease</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Generate new disease-related data to address prioritized gaps for target identification</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td>Prioritize new therapeutic targets and elucidate their mechanism of action</td>
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</table>
### 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!*
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

260 datasets, 309 traits
Translating variants to knowledge

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
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

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
Section I: Disease context and care for action 1
- Establish why this disease is relevant for the T2D
- Relate the current "state of the science" for the disease
- Outline the "problem statement" to address

Section II: Project Overview 2
- Provide a summary of the proposed research objectives and agenda (similar to an abstract)
- Outlining hypotheses to test
- Convey the value proposition & why via a consortium

Section III: Scientific Design 6
- Define the scientific research strategy and design
- Describe relevant experimental context, populations studied, key approaches / methodologies, & analyses

Section IV: Project Management 10
- Identify individuals likely to be involved in the project
- Identify potential institutional partnerships
- Identify potential sources of support and solicitations

Section V: Timeline, Milestones and Deliverables 10

How it’s going:

Program
How it started:

18 Awardees

140+ investigators & full time staff

2 Portal staff members

How it's going:

26 Awardees

Matrixed team with alumni
How it started:  

9 Datasets  
25 traits  

How it’s going:  

315 datasets  
379 traits  

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:

We will miss you, Phil!
How did we do this?

Built a data & software platform

AMP - Accelerating Medicines Partnership
Common Metabolic Disease
The product

- 77M variants
- 315 genetic datasets
- 40 Curated credible sets
- 3920 Genomic annotations
- 11 Bioinformatic methods
- 3 gene predictions approaches

Data & Software platform

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

AMP
Accelerating Medicines Partnership
Common Metabolic Disease

DCC
EBI
LoamStream
Aggregator
Knowledgebase
Portal
Visualizations
Collaborators
Euro genetic
US genetic
Func genomic
Individual level data

D.1, D.2, D.4
B.3
B.1
C.3
C.4
C.5
B.2
D.5
B.1
D.2
B.3
B.2
B.1
C.2
B.3
C.2
B.1
D.3
B.1
D.1
D.2
B.1
B.3
B.3
B.4
C.1
C.5
C.1
C.5
C.5

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

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

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Variants</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>Fasting glucose</td>
<td>19</td>
<td>-3.562937 0.0003279 -0.1107 0.0086279 26,807</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>24</td>
<td>-2.983776 0.0028471 0.7030 0.1183989 44,083</td>
</tr>
</tbody>
</table>

Implementation of GAIT

Individual-level data
LD server
Covariance matrices

Portal
Visualizations

Users
Next extension: TOPMed + BioData catalyst
Aim 2: one area of focus

- Representing functional genomic data

![Diagram showing causal variant, tissue, gene, pathway, and disease]

- Association statistics
- Transcription factor binding sites
- eQTLs
- Reference chromatin state
- Meta-analysis
- Fine mapping
- Variant effect predictors
- Regulatory element prediction
- Tissue-specific enrichment
- Chromatin capture
- Gene expression
- Gene function
- Gene prioritization
- eQTL colocalization
- Chromosome contact prediction
- Networks
- Pathways
- Gene set enrichment
- Cellular models
- Animal models

---

Standard browser view

![Browser view showing GenePrediction, DNASE, AccessibleChromatin MACS2, and other annotations]
Another model: relationships

Alternative visualizations

Emphasize relationships rather than genomic coordinates
Leverage integrated data
Evolution of analytical tools and plans for AMP CMD

Michael Boehnke for the Michigan team

AMP CMD Inaugural Meeting, May 27, 2021

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)

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

Select variants of interest

Select individual covariates via tooltip

List of covariates in dropdown menu: synchronized with plot

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

ACCELERATING MEDICINES PARTNERSHIP (AMP)
TYPE 2 DIABETES
**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
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

https://eqtl.pheweb.org/
**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

https://www.diabetesepigenome.org

Diabetes Epigenome Atlas

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

<table>
<thead>
<tr>
<th>Sources</th>
<th>Data types</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENCODE, GTEx and other resources</td>
<td>Experiments</td>
<td>DGA</td>
</tr>
<tr>
<td>GEO/EGA for published studies</td>
<td>e.g. ATAC-seq, RNA-seq, Hi-C, snRNA-seq, Perturb-seq</td>
<td>Web interface, API</td>
</tr>
<tr>
<td>AMP-CMD consortium</td>
<td>Annotations (derived from experiments)</td>
<td>Custom API</td>
</tr>
<tr>
<td>Other consortia (e.g. HPAP)</td>
<td>e.g. chromatin state, cCREs, gene expression, ABC predictions</td>
<td>CMD KP</td>
</tr>
</tbody>
</table>
Data currently in DGA

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

Annotations: 4,193

Experiments: 4,955

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

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

Annotations broken down by tissue category

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

- Genes linked to cCREs
- Chromatin interactions (Hi-C/pcHi-C)
- Co-accessibility (ATAC-seq)
- ABC predictions (ATAC-seq/Hi-C/ChIP-seq)
Types of data in DGA

Cis-regulatory elements
Gene target predictions
Variant allelic effects

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

Variant effects on cCREs
eQTLs (RNA-seq)

caQTL/hQTL (ATAC-seq/ChIP-seq)
eSNP/pbSNP (STARR-seq/SELEX-seq)
Predicted effects (dSVM, Bassett)

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?
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

---

**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

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
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
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/isof orm 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

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

GWAS colocalization with molecular QTLs

QTL data available or in process

<table>
<thead>
<tr>
<th>QTL &amp; Tissue</th>
<th>n</th>
<th>QTL &amp; Tissue</th>
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</tr>
</thead>
<tbody>
<tr>
<td>eQTL-inlet</td>
<td>420</td>
<td>caQTL-inlet</td>
<td>228</td>
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<tr>
<td>eQTL-inlet</td>
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<td>caQTL-adipose</td>
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<td>methylQTL-adipose</td>
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<td>methylQTL-blood</td>
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<td>eQTL-inlet</td>
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<td>miQTL-adipose</td>
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<tr>
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<td>metabolQTL-blood</td>
<td>184</td>
</tr>
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</table>

Arushi Varshney, Steve Parker, Swarooparani Vadlamudi
**Perturb variants: STARR-seq**

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

**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.
**Integrative analysis**

Activity-by-contact (ABC)

Epigenome maps in 131 cell types

Enhancer-promoter maps

Fine-mapped T2D variants

**Systematic evaluation of transcripts**

Models and Assays Working Group

Screen in doxycycline-inducible dCas9-KRAB-expressing human cell lines
Targeted arrayed screens

From Potential Effector Transcript → Function → Mechanism → Therapeutic Hypotheses

Targeted metabolic readouts

High-dimensional feature analyses

Selected genes – detailed mechanistic studies

Sharing of IPS cell resources across groups with domain expertise

Loss of ZnT8 function protects against diabetes by enhanced insulin secretion

Drosophila models

Recruit by genotype
Map multi-omic gene networks and modules

Data Integration → Network Analysis → Target Prioritization

Network visualization

Network hubs & modules containing effector transcripts

Differential network module activity across cell types & conditions

Individual disease heterogeneity

Core T2D Pathways

Pathway-Specific Precision Risk

Clustering individuals based on risk

Pathways

T2D Risk

Jose Florez
Summary

Variant ⇒ Element ⇒ Tissue ⇒ Potential effector transcript
- e/caQTL Colocalization
- STARR-seq

Transcript ⇒ Function ⇒ Mechanism ⇒ Therapeutic hypotheses
- Targeted screens
- Mechanistic studies
- CRISPRi screens
- Activity By Contact
- Drosophila models
- Allelic series

Data integration ⇒ Network analysis ⇒ Target prioritization
- Gene networks and modules
- Cell-specific regulators
- Network visualization
- Individual disease heterogeneity

The NEWS Team

Alina Aimbinder
Romi Bevacqua
Marci Brandenburg
K. Alaine Broadaway
Ines Cebola
Melina Claussnitzer
Kevin Currin
Hesam Deshtai
Marcel den Hoed
Ahmed El-hossiny
Jesse Engreitz
Michael Erdos
Jose Florez
Jimena Giudice
Anna Gloyn
Yan Hang
Aly Harney
Suzanne Jacobs
Alokumar Jha
Seung Kim
Nicole Krentz
Anshul Kundaje
Soumya Kundu
Samantha Laber
Seunggeun Lee
Nandini Manickam
Mark McCarthy
Elizabeth McGonagle
Josep Mercader
Karen Mohlke
A. Shelley Moxley
Surag Nair
Marcelo Nobrega
Peter Orchard
Gautam Pandey
Vishal Parekh
Stephen Parker
Victoria Parsons
Alina Virginia Pollner
Vivek Rai
Varsha Rajesh
Vivekanandan Ramalingam
Arvind Rao
Alham Saadat
Sarah Schoenrock
Laura Scott
Anand Shankar
Seth Sharp
Adam Stefek
Han Sun
Lakshman Sundaram
Jason Torres
Adelaide Tovar
Miriam Udler
Swarooparani Vadlamudi
Arushi Varshney
Christa Ventresca
Amedeo Vetere
Bridget Wagner
Robert Whitener
Yingying Ye
Grace Yu
Cynthia Zajac
Weichen Zhao
Functional Interrogation of T2D-associated genes in human stem cell-derived models and mice

FNIH AMP CMD Inaugural Meeting • May 27, 2021

Project Workflow

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

Computational Genetics
Variant-to-Gene Mapping

Physiological Assessment of Effector Transcripts
Mechanistic/Pathway Analyses

Primary cell & iPSC-models
Disease Modeling
Mechanistic Studies

Mouse models of obesity
& diabetes
- Integrated Physiology
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)

---

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

200 kb

- q31.31 chr7
- rs1861000
- rs3068006
- rs13245690

**Knockdown of ING3 expression**
- Impairs osteoblast differentiation
- But not WNT16 or CPED1

Ches,..,Wells, Grant et al. Nature Commun. 2019

---

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

1. **Identify Mutations/Variants**
   - From whole-exome sequencing of diabetic patients or large-scale genetic studies, identify 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 mutations into WT IPS or ES cell line.

4. **Differentiation beta cells**
   - Using genetically matched isoform-stem cell lines harboring various genetic lesions, differentiate into pancreatic beta cells.

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

6. **ER stress reporter**
   - Various cell stressors, such as ER stress, induce splicing of XPB1 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 RBP only upon cell stress.

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

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

**INS-GFP+ beta-like cells**

---

Paul Gadue
Human stem cell models, β-cell biology
Assoc. Director, CHOP ES cell Core
**iPSC-derived cell and disease models**

**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

**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)
Pancreatic Islet Biology

Assessment of Islet Function in Genetically Modified Mice

High efficiency, high specificity alpha cell CreER line

Liver Biology and Disease

Hepatic Metabolism

Lipogenesis

Glucose Output

Primary hepatocytes

3D hPSC-differentiation

Abbey et al., Hepatol Commun, 2020
Skeletal Muscle Biology

Muscle Metabolism and Function

- Ex vivo physiology (Jaiswal et al. Mol Met 2019)
- In vivo glucose uptake & flux analysis

In vivo experiment

- Control
- M-AktDKO

- Soleus

Glucose Uptake

- Ex vivo physiology (Jaiswal et al. Mol Met 2019)
- Insulin-stimulated glucose uptake
- Human primary muscle cells

- Insulin resistance in Akt-KO mice

- hPSC-derived muscle cells for functional analyses

Adipose tissue and obesity pathogenesis

Pathologic Expansion

- Hypertrophy
- Insulin resistance
- Inflammation
- Hypoxia
- Fas-mediated apoptosis
- Adipogenesis

Healthy Expansion

- Adipocyte biology
- 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
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**

Wenli Yang, PhD  
Ben Voight, PhD  
Struan Grant, PhD  
Klaus Kaestner, PhD  
Dan Rader, MD  
Patrick Seale, PhD  
Paul Titchenell, PhD  
Paul Gadue, PhD  
Andrew Wells, PhD  
Casey Brown, PhD

**Collaborators**

Doris Stoffers, MD, PhD  
Mitch Lazar, MD, PhD  
Joe Baur, PhD  
Ray Soccio, MD, PhD  
Josh Rabinowitz, PhD

**Team Members**

Yang Chen, PhD  
Mary Ann Hazuga  
Jim Pippin  
Nick Hand, PhD  
Kate Creasy, PhD  
Kim Lorenz, PhD  
Dominic Santoleri  
Donna Conlon, PhD  
Natasha Jaiswal, PhD  
Subhshri Sahu, PhD  
Karima Drareni, PhD  
Dawn Marchadier  
Carolin Schneider  
Long Gao, PhD  
John Millar, PhD  
Rachel Stine, PhD  
Nick Hand, PhD  
Matt Pahl, PhD  
Marijana Vujkovic, PhD  
Joe Park  
Jaclyn Welles
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

UM1 DK078616 – TOPMed Team

1. MGH: James Meigs (PI), Alisa Manning, Jose Florez, Aaron Leong
2. Broad Institute: Josep Mercader, Jason Flannick
3. Boston University: Josée Dupuis, Ching-Ti Liu
4. U of North Carolina: Laura Raffield
5. U of Indiana: Jennifer Wessel
6. U Colorado-Denver VA: Sridharan Raghavan
7. U of Texas Houston: Paul De Vries, Alanna Morrison
8. U of Washington: Susan Heckbert, Jen Brody
9. Fred Hutchinson Cancer Research Center: Charles Kooperberg
10. Lundquist Institute: Jerry Rotter, Kent Taylor
11. Cedars Sinai: Mark Goodarzi
12. McGill University, Montreal, QC: Rob Sladek
AMP CMD - TOPMed Steering Committee Members

James Meigs  
Harvard  
MGH  
Broad

Alisa Manning  
Harvard  
MGH  
Broad

Jerry Rotter  
Lundquist Institute

Rob Sladek  
McGill University

Laura Raffield  
University of North Carolina

Sridharan Raghavan  
University of Colorado 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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Sample</th>
<th>Manuscript Status</th>
<th>Reference</th>
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<tbody>
<tr>
<td><strong>Type 2 Diabetes</strong></td>
<td>9,639 T2D cases and 34,994 T2D controls from 16 studies and 5 ancestries</td>
<td>Submitted and in preprint</td>
<td>Wessel, J. et al. Rare Non-coding Variation Identified by Large Scale Whole Genome Sequencing Reveals Unexplained Heritability of Type 2 Diabetes. Medrxiv 2020. <a href="https://dx.doi.org/10.1101/2020.11.13.20221812">https://dx.doi.org/10.1101/2020.11.13.20221812</a></td>
</tr>
<tr>
<td><strong>HbA1c</strong></td>
<td>10,338 non-diabetic individuals from 5 studies and 4 ancestries</td>
<td>Published AJHG</td>
<td>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. <a href="https://dx.doi.org/10.1016/j.ajhg.2019.08.010">https://dx.doi.org/10.1016/j.ajhg.2019.08.010</a></td>
</tr>
</tbody>
</table>

### TOPMed WGS Variant Frequency Spectrum by Islet Functional Annotation

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

<table>
<thead>
<tr>
<th>Islet interaction and chromatin structure</th>
<th>Proportion of variants</th>
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</thead>
<tbody>
<tr>
<td>Enhancer (0.41%) - Promoter (0.95%) -</td>
<td></td>
</tr>
<tr>
<td>Enhancer (1.69%) - Promoter (0.59%) -</td>
<td></td>
</tr>
<tr>
<td>Enhancer (1.69%) - Promoter (0.59%) -</td>
<td></td>
</tr>
<tr>
<td>Loss of function (0.01%) - Exonic (1.40%)</td>
<td></td>
</tr>
<tr>
<td>All missense (0.38%) - Deleterious missense (0.02%) - Loss of function (0.04%) - Exonic (3.56%) -</td>
<td></td>
</tr>
<tr>
<td>All (100.00%) -</td>
<td></td>
</tr>
</tbody>
</table>

Legend:
- Singleton
- 2<=MAC<20
- MAC>=20, MAF<0.1%
- 0.1%<=MAF<1%
- 1%<=MAF<5%
- MAF>=5%
- Rare
- Common
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%

Fasting Glucose (mmol/L)

<table>
<thead>
<tr>
<th>Self Reported Race / Ethnicity</th>
<th>Count</th>
<th>Mean (SD)</th>
</tr>
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<tbody>
<tr>
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<td>Asian</td>
<td>4,799</td>
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<td>European</td>
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<td>Hispanic American</td>
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<td>5.52 (2.60)</td>
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<tr>
<td>Samoan</td>
<td>987</td>
<td>4.94 (0.75)</td>
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<tr>
<td>Other</td>
<td>8</td>
<td>5.61 (0.60)</td>
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<tr>
<td>Total</td>
<td>52,784</td>
<td>5.22 (1.42)</td>
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</tbody>
</table>

Fasting Insulin (mIU/L), Log Transformed

<table>
<thead>
<tr>
<th>Self Reported Race / Ethnicity</th>
<th>Count</th>
<th>Mean (SD)</th>
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<tbody>
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<td>African</td>
<td>8,819</td>
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<td>European</td>
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<td>Hispanic American</td>
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<td>Hispanic</td>
<td>1,998</td>
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<td>Samoan</td>
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<td>Other</td>
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<td>2.68 (0.40)</td>
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TOPMed Freeze 9 Glycemic Traits

<table>
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<tbody>
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<td>2.14 (1.09)</td>
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<tr>
<td>Asian</td>
<td>2,062</td>
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<tr>
<td>European</td>
<td>2,062</td>
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<td>2,062</td>
<td>2.14 (1.09)</td>
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<tr>
<td>Samoan</td>
<td>2,062</td>
<td>2.14 (1.09)</td>
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<tr>
<td>Other</td>
<td>2,062</td>
<td>2.14 (1.09)</td>
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<tr>
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<td>2,062</td>
<td>2.14 (1.09)</td>
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TOPMed Omics Resources May 2021

<table>
<thead>
<tr>
<th>Studies with prevalent T2D harmonized data</th>
<th>Sample size</th>
<th>Platform</th>
<th>Generated through TOPMed?</th>
<th>Currently available?</th>
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<td>LC/MS</td>
<td>TOPMed and other</td>
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<tr>
<td>MESA</td>
<td>982</td>
<td>LC/MS</td>
<td>TOPMed</td>
<td>yes</td>
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<tr>
<td>WHI</td>
<td>1400</td>
<td>LC/MS</td>
<td>TOPMed</td>
<td>yes</td>
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<tr>
<td>Total</td>
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<td>SOMAscan</td>
<td>TOPMed and other</td>
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<td>Olink</td>
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<td>TrueSeq</td>
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<td>EPIC</td>
<td>Other/TopMed</td>
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<td>MESA</td>
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<td>EPIC</td>
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<td>yes</td>
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<tr>
<td>Total</td>
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</table>

*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
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
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
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**

**About**
- **45,300 employees**

**Diabetes**

- **10 largest pharma companies measured by market value**

**Growth disorders**

- **126.9 billion DKK**

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

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

**Affiliates in** 80 countries

**Obesity**

- **80**

**Haemophilia**

- **45,300 employees**
Chronic diseases are an urgent global health challenge.
Our heritage enables us to defeat diabetes and other serious chronic diseases.
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

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
### Diabetes care

<table>
<thead>
<tr>
<th>Project</th>
<th>Indication</th>
<th>Description</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semaglutide 2.0 mg NN9535</td>
<td>Type 2 diabetes</td>
<td>A long-acting GLP-1 analogue for once-weekly treatment.</td>
<td>● ● ● ●</td>
</tr>
<tr>
<td>Oral semaglutide HD NN9926</td>
<td>Type 2 diabetes</td>
<td>A long-acting oral GLP-1 analogue, 25 and 50 mg, intended for once- and daily oral treatment.</td>
<td>● ● ● ○</td>
</tr>
<tr>
<td>Icodec NN1436</td>
<td>Type 1 and 2 diabetes</td>
<td>A long-acting basal insulin analogue intended for once-daily treatment.</td>
<td>● ● ● ○</td>
</tr>
<tr>
<td>Insulin 965 NN1965</td>
<td>Type 1 and 2 diabetes</td>
<td>A novel basal insulin analogue intended for once-daily treatment.</td>
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<tr>
<td>Iloseme NN1535</td>
<td>Type 2 diabetes</td>
<td>A combination of GLP-1 analogue semaglutide and insulin icdec intended for once-weekly treatment.</td>
<td>● ○ ○ ○</td>
</tr>
<tr>
<td>PDC-Sama -- OW GIP NN9389</td>
<td>Type 2 diabetes</td>
<td>A combination of semaglutide and novel GIP analogue for once-weekly treatment.</td>
<td>● ○ ○ ○</td>
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<tr>
<td>Glucose-sensitive insulin NN1845</td>
<td>Type 1 and 2 diabetes</td>
<td>A glucose-sensitive insulin analogue intended for once-daily treatment.</td>
<td>● ○ ○ ○</td>
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<tr>
<td>Iodeal Pump Insulin NN1471</td>
<td>Type 1 diabetes</td>
<td>A novel insulin analogue ideal for use in a closed loop pump device as delivery.</td>
<td>● ○ ○ ○</td>
</tr>
<tr>
<td>DNA immunotherapy NN9041</td>
<td>Type 1 Diabetes</td>
<td>A novel plasmid encoding pre- and pro-insulin intended for preservation of beta cell function.</td>
<td>● ○ ○ ○</td>
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</table>

### Obesity care

<table>
<thead>
<tr>
<th>Project</th>
<th>Indication</th>
<th>Description</th>
<th>Phase</th>
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</thead>
<tbody>
<tr>
<td>Semaglutide 2.4 mg NN9536</td>
<td>Obesity</td>
<td>A long-acting GLP-1 analogue intended for once-weekly treatment.</td>
<td>● ● ● ●</td>
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<tr>
<td>AM833 + semaglutide NN8933</td>
<td>Obesity</td>
<td>A combination of amylin analogue and GLP-1 analogue semaglutide intended for once-weekly treatment.</td>
<td>● ● ● ○</td>
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<tr>
<td>LA-GDF15 NN9215</td>
<td>Obesity</td>
<td>A long-acting GDF-15 analogue intended for appetite regulation leading to weight loss.</td>
<td>● ○ ○ ○</td>
</tr>
<tr>
<td>PY1875 NN9715</td>
<td>Obesity</td>
<td>A novel analogue of the appetite hormone, PY1, intended for once-weekly treatment.</td>
<td>● ○ ○ ○</td>
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</table>

### Biopharm

<table>
<thead>
<tr>
<th>Project</th>
<th>Indication</th>
<th>Description</th>
<th>Phase</th>
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</thead>
<tbody>
<tr>
<td>Sogroya ® NN8540</td>
<td>Adult GHD</td>
<td>A long-acting HGH 1 derivative intended for once-weekly subcutaneous administration in adults.</td>
<td>● ● ● ●</td>
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<tr>
<td>Semapodan NN8640</td>
<td>GHD</td>
<td>A long-acting HGH 1 analogue intended for once-weekly subcutaneous administration in children.</td>
<td>● ● ○ ○</td>
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<tr>
<td>Conculizumab NN7415</td>
<td>Haemophilia A and B w/o inhibitors</td>
<td>A monoclonal antibody against tissue factor pathway inhibitor intended for subcutaneous prophylaxis treatment.</td>
<td>● ● ○ ○</td>
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<tr>
<td>Macrin/TM EX2020</td>
<td>GHD</td>
<td>An oral diagnostic agent used for the diagnosis of GHD in adolescents and children.</td>
<td>● ● ○ ○</td>
</tr>
<tr>
<td>Mm8 NN7769</td>
<td>Haemophilia A with or without inhibitors</td>
<td>A next generation FVIII mimetic bispecific antibody for subcutaneous prophylaxis of haemophilia A regardless of inhibitor status.</td>
<td>● ● ○ ○</td>
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<tr>
<td>Eclipse NN7533</td>
<td>Sickle cell disease</td>
<td>An oral combination treatment of sickle cell disease and beta thalassaemia. Project is developed in collaboration with EpiDestiny.</td>
<td>● ○ ○ ○</td>
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</table>

### Other serious chronic diseases

<table>
<thead>
<tr>
<th>Project</th>
<th>Indication</th>
<th>Description</th>
<th>Phase</th>
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<tbody>
<tr>
<td>Semaglutide NN9931</td>
<td>NASH</td>
<td>A long-acting GLP-1 analogue for once-weekly treatment of NASH.</td>
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<tr>
<td>Ziltivekimab NN6518</td>
<td>CVD</td>
<td>A novel once-monthly monoclonal antibody intended for inhibition of IL-6 activity.</td>
<td>● ● ○ ○</td>
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<tr>
<td>PCSK9i peptide NN6434</td>
<td>CVD</td>
<td>A long-acting PCSK9 inhibitor for subcutaneous treatment.</td>
<td>● ● ○ ○</td>
</tr>
<tr>
<td>Anti-ApoC3 NN5506</td>
<td>CVD</td>
<td>A novel monoclonal antibody intended for inhibition of ApoCIII activity. Project is developed in collaboration with STATEN.</td>
<td>● ○ ○ ○</td>
</tr>
</tbody>
</table>

Source: Adapted from Novo Nordisk Annual Report 2020

1. GHD = Growth hormone deficiency 2. HGH = Human growth hormone 3. NASH = Non-alcoholic steatohepatitis 4. CVD = Cardiovascular disease
AMP-CMD & Novo Nordisk: 
<em>because in union there is strength</em>

**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
Chronic diseases are an urgent global health challenge.
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


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

74% of global deaths in 2019 were due to NCDs \(^1\)

---

Partner’s Aspirations for AMP CMD

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

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.
Evolve from: rs646776 has a p-value of $5 \times 10^{-241}$ 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?

Future directions:

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

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:

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
Partner’s Vision
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.
Noël 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.