RFP Title: Call for Genotypic and Phenotypic Data related to Nonalcoholic Steatohepatitis (NASH) for Incorporation into the Accelerating Medicines Partnership Type 2 Diabetes Knowledge Portal

Accelerating Medicines Partnership (AMP) Summary: The Accelerating Medicines Partnership (AMP) is a pre-competitive collaboration that aims to harness collective capabilities, scale and resources across multiple sectors to improve therapeutic development efforts against complex, heterogeneous diseases. The partnership’s goal is to understand such diseases more fully through research focused on identification of safe and effective novel therapeutic targets, and as a result, accelerate the process of bringing new medicines to patients.

AMP Research Plans for three therapeutic areas – 1) Type 2 Diabetes; 2) Alzheimer’s Disease; and 3) Rheumatoid Arthritis, Lupus & Related Autoimmune Disorders – were developed in 2013 through a series of Steering Committee meetings which included representatives from government, academia and private industry, including Biogen Idec Inc., Bristol-Meyers Squibb, GlaxoSmithKline, Janssen Research & Development LLC, Eli Lilly and Company, Merck Sharp & Dohme Corp., Pfizer Inc., Sanofi US Services, and Takeda Pharmaceuticals.

The Research Plan for Accelerating Medicines Partnership Type 2 Diabetes (AMP T2D) was developed with input from NIDDK/NIH, Eli Lilly and Company, Janssen Research and Development LLC, Merck Sharp & Dohme Corp., Pfizer Inc., Sanofi US Services and FNIH, whose representatives sit on the AMP T2D Steering Committee. The Steering Committee oversees, manages, provides expertise and ensures the integration of work streams supported by the public and private sector for the AMP T2D project.

AMP T2D Project Objective: AMP T2D aims to provide public access to interrogate high-quality human genetic and phenotypic data to allow evaluation of novel therapeutic targets for T2D and its complications. This effort is intended to identify safe and effective novel targets to inform the industrial drug development pipeline. The overall strategy is to integrate human genetics data through analysis of natural variations in human protein expression in order to identify and validate targets in vivo. Mutations of known molecular effect (e.g., loss of function) resulting in a desirable clinical outcome (e.g., protection from disease) without adverse consequences will be of special interest. Annotation of noncoding genetic variants associated with T2D, T2D-related quantitative traits, and T2D complications to enable identification of related gene targets will also be of importance. AMP T2D seeks to gather and annotate diverse human genetics data to allow identification, validation and characterization of gene(s) as potential T2D targets. Data will be collated from multiple studies, large or special collections of samples, multiple phenotype measurements, and investigation of multiple gene variants.

The work described in this RFP is part of the larger AMP T2D Project. For further information on additional funding opportunities for the AMP T2D Project, go to:
RFP Objective: The open access AMP T2D Knowledge Portal has been built to generate new biologic and disease state understanding by maximizing the ability to explore rare and common genetic variants across quantitative and qualitative phenotypes related to the many indications related to T2D and its complications. One such complication that has become of increasing interest is Nonalcoholic Steatohepatitis (NASH). As such, FNIH is seeking proposals from organizations to contribute high-quality human genome sequence, clinical, and molecular phenotypic data for NASH to the AMP T2D Knowledge Portal. Proposals to contribute existing data sets as well as proposals to derive new genotyping data from readily available and appropriately consented samples will be considered. The consortium is expanding the KP to federated sites outside the U.S. in order to facilitate inclusion of global data in order to accommodate regional requirements. By participating in this global collaborative effort, awardees will help advance translational science and help identify new treatments for T2D and its complications. Data of interest include those derived from whole exome sequencing, whole genome sequencing, exome chip, or genome wide association analyses of large cohorts with corresponding and relevant individual level phenotypic data. Data from any and all geographic regions, races, and ethnicities are of great value to the knowledge portal and will contribute toward building the single most powerful resource for understanding the genetics of Type 2 Diabetes and its complications. In the interest of attaining critical scale, applications from consortia representing multiple cohorts are encouraged. Awardees will become active members of a growing AMP T2D collaborative group, which includes experts from multiple private, public, and non-profit institutions. Awardees will benefit from access to state of the art computational tools facilitated by harmonization and integration with extensive, well-phenotyped data from other sources.

Expectations: RFP responses should include the following:

1. A description of the organization’s or collaboration team’s approach to addressing the needs of the RFP.
2. A discussion of data storage and protection - what capabilities does the organization have to store and protect confidential data?
3. A detailed budget, including FTEs, and travel to attend annual partnership meetings.

*Multiple awards are expected to be made through this RFP.

Full proposals including items 1-3 above are not to exceed 25 pages. Please provide your responses as an email attachment to Dr. Sanya Whitaker (swhitaker@fnih.org) and Ms. Nicole Spear (nspear@fnih.org) with “AMP T2D RFP 5 – NASH Data Solicitation” in the subject line.

Issued by: The Foundation for the National Institutes of Health (FNIH) Division of Research Partnerships on September 8, 2016
**Application Process:** Organizations that submit high-caliber, focused, and detailed responses to this RFP will be invited to meet by teleconference with the AMP T2D Steering Committee. The purpose of the meeting is to allow for appropriate discussion of possible next steps as well as provide the opportunity for the respondent to ask questions of the multi-stakeholder oversight group. An institution can submit more than one application for different data sets.

**Disclaimers:** The FNIH AMP T2D consortium reserves the right to suspend or terminate funding depending on demonstrable progression of the effort. The T2D AMP Steering Committee might choose to fund all or some of the given proposal.

**Responses:** Due on December 31, 2016

**Eligibility:** Any organization from the private and public sector is eligible to apply as long the requirements below are met. It is acceptable for more than one organization to collaborate and submit a joint response.

**Target Selection Date:** May 1, 2017

**For More Information:** Please contact Dr. Sanya Whitaker (swhitaker@fnih.org). Feel free to ask questions to enable preparation of your responses.

**The AMP T2D Knowledge Portal Project Overview**

The AMP T2D project has built and continues to develop the AMP T2D Knowledge Portal (KP) which researchers can publicly query to identify relationships between potential therapeutic target gene sequence variations and 1) T2D risk or protection; 2) T2D-related quantitative traits; 3) T2D-related microvascular, cardiovascular, renal, and eventually hepatic complications risk; 4) T2D complications-related intermediate metabolic endpoints; and 5) biochemical, genomic, and other molecular phenotypes. The KP includes an infrastructure to aggregate and render compatible available genome sequence and phenotype data across samples from multiple cohorts to enable large scale integrated analyses. Key features of the KP include automated analytical methods and query tools to provide clear and interpretable answers to questions about T2D gene function and related phenotype relationships. Since a major knowledge gap in current T2D knowledge exists around understanding T2D clinical phenotypes, the KP will also include such relevant data fields. The consortium is expanding the KP to federated sites in Europe in order to facilitate inclusion of globally sourced data in late 2016. Additionally, it is expected that the data content as well as the overall functionality and analytic capabilities of the KP will continue to grow and evolve.

The purpose of the KP is to allow academic researchers, clinicians, and pharmaceutical industry experts to utilize the database to test the following types of questions:
- **Phenotype-based queries:** Is genetic variation linked to T2D protection or risk associated with variability in T2D-related phenotypes or complications?
- **Gene- or pathway-based queries:** What genetic variation exists within a target or pathway of interest and is this variation associated with an increased or decreased risk of T2D, T2D-related quantitative traits, or T2D-related cardiovascular or kidney disease?
- **Variant-based queries:** What clinical, biochemical, expression quantitative trait loci (eQTL), and epigenetic phenotypes are associated with a given gene variant?
- **Subset queries:** Are results consistent across ancestry groups and across studies?

**Features of the KP include the following:**

- Exome sequencing data, exome chip data, genome-wide association studies (GWAS) from multiple consortia with phenotypic data related to T2D
- Large GWAS meta-analyses of many other traits including those related to chronic kidney disease, coronary artery disease, bipolar disorder, major depressive disorder, and schizophrenia.
- Current information on data that is contained in the KP is available [here](#).
- Ability to aggregate and harmonize data
- System to reproducibly automate data analysis, enabling continuous data updating
- User interface allowing users of varying technical and domain expertise to perform biologically motivated queries on full results of analyses

The AMP T2D KP is expected to incorporate an expanding range of genotype and phenotype data derived from an even broader collection of global cohorts of individuals with T2D and T2D complications, including diabetic nephropathy, NAFLD/NASH and diabetic cardiovascular disease. To this end, funding from FNIH and NIH has been awarded to support the incorporation of the additional data from studies such as BioME, EXTEND, FUSION, METSIM, Oxford Biobank, and SUMMIT, SAMAfs, Hong Kong Diabetes Registry, DNCRI, Singapore Protective Study Program, Living Biobank (Singapore), Diabetic Cohort (Singapore), SIMES, SINDI, SCES, AGEn, GoDARTS, and GoSHARE which will add GWAS, Exome Chip, Exome Sequences, and Metabochip data from thousands of subjects.

**In order to support contributions of data on a global scale, the AMP T2D project is developing the KP into a federated group of geographically distinct nodes that will allow researchers to submit their summary and individual level data in compliance with regional data privacy requirements.**

The U.S. hub of the KP is hosted at the Broad Institute in Cambridge, MA and the European hub will be hosted at the European Bioinformatics Institute in Cambridge, UK. Additional funding from NIH and from FNIH has been awarded to a growing collaborative team to enable further development and expansion of the AMP T2D KP.

The AMP T2D Consortium and AMP T2D Steering Committee will leverage analytic capabilities of the AMP T2D KP for prioritization of funding opportunities for additional AMP T2D related research.
Scope of Work

For this RFP, FNIH is accepting proposals to join the AMP T2D Consortium by contributing datasets focused on NASH to the AMP T2D KP according to the specifications described below. Proposals to contribute existing data sets as well as proposals to derive new genotyping data will be considered. This growing partnership will benefit researchers and patients alike by bringing together as much data and analytic capacity as possible to address the critical unmet medical need for new medications to treat patients with Type 2 Diabetes and complications related to NAFLD/NASH. Researchers who contribute data to the KP through any one of its federated sites will be able to leverage their own data by running analyses across broad, combined data sets. Awardees will provide access to high-quality human genotypic and individual level phenotypic data in large cohorts of T2D and its microvascular, cardiovascular, renal, and hepatic complications for incorporation in the open-access AMP T2D KP. Global NASH-related datasets, including large, deeply genotyped cohorts with robust individual level phenotyping data for NASH related quantitative and qualitative traits are of great interest. Cohorts with representation from specific geographic and ethnic subgroups (e.g., Finnish, Icelandic, Asian, Amish, others) and familial datasets are also of interest. Proposals to contribute individual level genotype and phenotype data from existing data sets as well as proposals to derive new individual level genotype and phenotype data from readily available and appropriately consented samples will be considered.

Such datasets are intended to be incorporated into the FNIH- and NIH- funded AMP T2D knowledge portal that is planned to be a collection of federated nodes in multiple global regions. Additional information regarding AMP T2D research objectives and development plans for the federated regional nodes of AMP T2D KP is available on the FNIH AMP T2D website.

In your proposal, please provide your approach to meeting the requirements below.

Assumptions

- All data will be incorporated into the AMP T2D knowledge portal through an appropriate federated node to comply with regional data privacy requirements within a specified time frame.
- All data provided will also be made available for public queries through the AMP T2D Knowledge Portal.
- Awardee(s) will use software and data harmonization approaches that are interoperable with the AMP T2D knowledge portal.
- Genotype data contributed through this funding mechanism are to originate from existing datasets associated with well phenotyped cohorts, or are to be newly generated from readily available and appropriately consented samples for which individual level genotype and phenotype data can be deposited in the KP.
- Data must be accessible for input into the KP and accessible for analytic output under informed consent.
- Data will be derived either from large single cohorts or from multiple cohorts whose data are collated and harmonized by the awardees prior to submission to the KP. In the interest of attaining critical scale, applications from consortia representing multiple cohorts are encouraged.
• The awardee(s) will accomplish all work described in collaboration with recipients of FNIH and of NIH funding for AMP-T2D KP development as members of the AMP T2D Consortium. As such, awardees will be invited to attend annual face to face consortium meetings as well as join consortium working groups and other teleconferences.

Requirements

1. Data Content: The AMP T2D project has specific interest in the individual level human genotypic data from well phenotyped NAFLD/NASH cohorts associated with the following:

• Whole exome sequencing, whole genome sequencing, genome-wide association studies, and/or exome chip corresponding with relevant individual level phenotype data including but not limited to one or more of the following parameters (or corresponding ICD9/10 codes) as possible:

  o Liver biopsies graded for degree/stage of fibrosis, inflammation, and hepatocyte ballooning, specifically with NAS score; longitudinal biopsy results
  o Fibrotic imaging (e.g., fibroscan, MR elastography)/ collagen proportional area (CAP)
  o Hepatic triglyceride content measured by techniques such as 1H MRS/MRI or CT imaging
  o Hepatic stiffness measured by techniques such as MRE
  o Transaminase and other liver function test measurements (AST, ALT, alkaline phosphatase, and bilirubin)
  o Incidence of cirrhosis by biopsy diagnosis; incidence of cirrhosis complications (e.g., diagnosis of varices, ascites, etc.), hepatocellular carcinoma, and/or liver transplant
  o Metabolic phenotypes (eg LDLc, TGs, TC, fasting glucose, fasting insulin, HOMA-IR, HOMA-B, BMI, 2-hr glucose, cIMT, CAC score)
  o Additional circulating biomarker data

• Longitudinal data are preferred (at least 2 years), but well characterized populations (e.g., with biopsy results or detailed imaging or other detailed phenotyping results) with cross-sectional data would also be desirable.

• Datasets should be of significant scale containing thousands of subjects either by including large individual cohorts or by combining and harmonizing multiple cohorts. Alternatively, large data sets from relevant familial studies may also be considered.

• Datasets from multiple geographic regions and ethnicities are highly desirable.

• Datasets from cohorts and studies with the capability to recall subject for follow up study are also desirable.

• Datasets that may enable identification of mutations of known molecular effect (e.g., loss of function) that result in a desirable clinical outcome (e.g., protection from disease) without adverse consequences. Examples of this approach include CXCR4/CCR5 and protection from HIV infection and PCSK9 and reduction in LDL to prevent coronary disease.
- **Data provided should be able to help answer the following types of questions:**

  o **Phenotype-based queries:** What genes, functional elements, or variants confer 1) increased or decreased NASH risk, 2) NASH-related quantitative trait variability, 3) increased or decreased risk of T2D related liver complications, or 4) a combination of risk or trait patterns?
  
  o **What expressed genes or coding or noncoding gene variants are associated with NASH risk and related traits (including tissue eQTLs in relevant tissues (e.g., liver, adipose)?**
  
  o **Gene- or pathway-based queries** – e.g., what genetic variation (of a specific annotation type: e.g. loss or gain of function) exists within a specific gene, gene set, gene region, or pathway? Are these variants associated with NASH risk, quantitative T2D-related traits (e.g., metabolic or lipid), or the risk of T2D subjects developing liver disease?
  
  o **Variant-based queries** – e.g., what clinical, biochemical, eQTL, and epigenetic phenotypes are associated with this variant?
  
  o **Subset queries** – e.g., are results consistent across ancestry groups, user-selected subsets of subjects, or studies?

2. **Data Integrity and Format**

- **Genomic and Phenotypic Data Quality Control (QC)** - data provided will have undergone full QC procedures as agreed upon by the AMP T2D Steering Committee. Data QC is the responsibility of the data provider and not the entity performing the database build. Data are expected to undergo QC by the data provider prior to incorporation into the KP, and awardee(s) should be able to provide evidence of QC. If additional resources would be needed to complete data QC, please include this in your proposal.

- **Awardee(s) will work with collaborators to agree upon a Data Sharing and Transfer Agreement prior to data transfer. Current policies around KP data use, citation, and user tracking can be found [here](#).**

- **Awardee(s) will harmonize all data to a format and template as agreed upon by the AMP T2D Steering Committee. Resources needed to enable data harmonization should be included in the submitted proposal.**

The AMP T2D Steering Committee will ensure the integration of work streams supported by the cross-sector project and determine criteria defining successful completion of milestones and functionality of the KP.

FNIH expects that award recipients will follow U.S. Department of Health and Human Services regulations at [45 CFR 46](#) and that data to be deposited into the knowledge portal will have been obtained under informed consent for broad research uses.
**Funding Mechanism:** milestones around the requirements above will be negotiated as a part of the FNIH grant or contract post-award announcement and overseen by the AMP T2D Steering Committee. The AMP T2D Steering Committee will also ensure the integration of work streams supported by the cross-sector project and determine criteria defining successful completion of milestones.

**Anticipated Duration of Work:** 1-2 years of milestone-driven research plans, with potential for competitive renewal applications for additional projects within the AMP T2D Consortium

**Budget Range:** Up to $200,000 per individual award for proposals to harmonize and transfer existing datasets; up to $500,000 per individual award for proposals that include the generation of new genotyping data. For proposals to contribute data from existing data sets and from new genotyping studies, budgets should be prepared so as to enable modular award funding as follows. Module 1: requests for funding for data harmonization and preparation to enable deposition of existing genotype and phenotype data in the knowledge portal. Module 2: requests for funding for the generation and harmonization of new genotyping data in deeply phenotyped cohorts for rapid deposition of individual level data in the knowledge portal. Award budgets will be based on the size of the data set, the types of genotypic and individual level phenotypic data provided, and timelines for milestone-driven work plans. Higher levels of funding may be considered for projects of significant complexity or involving large datasets where strong justification is provided. Applicant organizations are encouraged to include travel expenses for participation in AMP T2D Consortium meetings within their budget proposals. A proposal from a single organization could include multiple data sets.