Deriving Drug Discovery Value from Large-Scale Bioresources – an IOM Workshop

The Accelerating Medicines Partnership

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FNIH
Foundation for the
National Institutes of Health

About FNIH

PURPOSE

Support the mission of the NIH

Advance collaboration with biomedical researchers from universities, industry, not-for-profit organizations

STRUCTURE

501(c)(3) not-for profit foundation created by Congress

Independent Board of Directors with NIH Director and FDA Commissioner as *ex-officio* Board members

HIGHLIGHTS

Raised over $800 million since 1996

Supported nearly 500 projects

94 cents of every dollar spent directly funds programs

FNIH Research Partnerships

- **Grand Challenges in Global Health (GCGH)** — **$201 M**
  Partners: Bill & Melinda Gates Foundation
- **Accelerating Medicines Partnership** — **$187 M**
  Partner: NIH (OD), NIA, NIAMS, NIDDK, 10 companies, 9 non-profits
- **LungMAP: Master Lung Protocol Trial** — **$163 M**
  Partners: NCI (SWOG), FDA, Friends of Cancer Research, 5 companies to date
- **Alzheimer's Disease Neuroimaging Initiative (ADNI)** — **$148 M**
  Partners: NIA, NIBIB & 20 companies/2 non-profits
- **Vector-Based Control of Emission (VCTR)** — **$78 M**
  Partners: VRC/NIAID, Bill & Melinda Gates Foundation
- **The Biomarkers Consortium** — **$65 M**
  Partners: FDA, NIH, CMS, PhRMA, BIO, pharmaceutical and nutrition companies
- **Comprehensive T Cell Vaccine immune Monitoring Consortium (CT-VIMC)** — **$50 M**
  Partners: Bill & Melinda Gates Foundation, NIAID
- **MAL-ED: The Interactions of Malnutrition and Enteric Infections, Effect on Childhood Development** — **$46M**
  Partner: Bill & Melinda Gates Foundation, Fogarty Institute Center (NIH)

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The rationale: better targets = fewer late stage failures

Current targets

- Animal models
- Cell lines

AMP targets

- Emerging Technologies
  - DNA sequencing
  - Proteomics
  - Single-cell analysis
  - Bioengineered cells
  - Imaging
- Extensive Human Data
  - Tissue/blood samples
  - Clinical information
  - Demographics
- Big Data Tools

Lack of efficacy currently accounts for more than half of all drug failures in Phase II clinical studies

AMP's target validation efforts aimed at improving efficacy and increasing success rate

AMP Goals

If successful, AMP will:

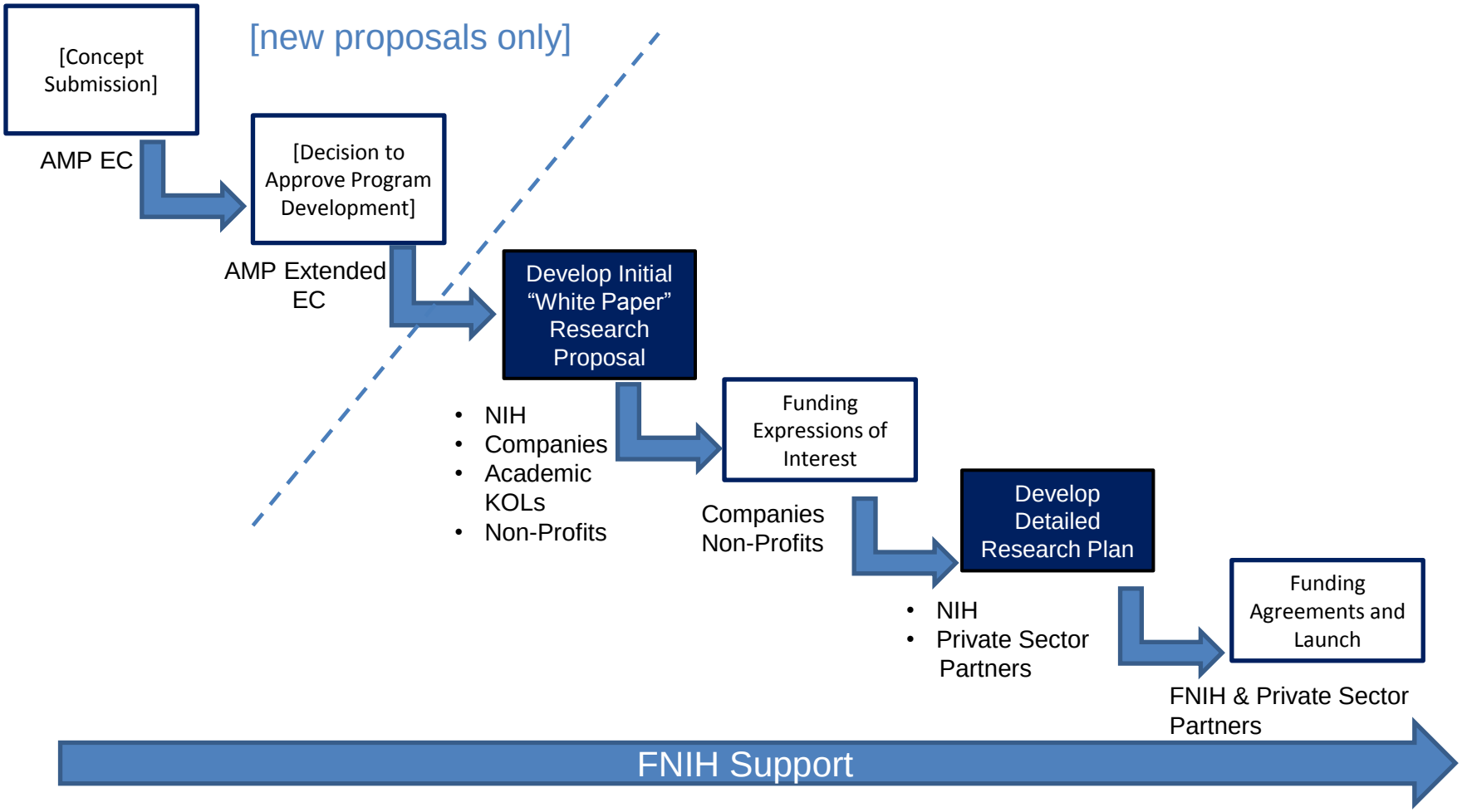
- Discover and validate new targets that companies can incorporate into their therapeutic development programs
- Provide new insights into known, existing targets
- Enable a significant increase in our knowledge of tractable disease biology and disease pathways
- Create a rich, comprehensive, integrated knowledgebase that is easy to use and available to the entire global research community

…for major common diseases.

AMP – IP & Data Sharing

- Research supported by AMP will be precompetitive
- Data will be shared broadly and quickly; AMP participants have access to data during assessment of data quality (up to 6 months)
- No pre-emptive patenting to ensure broadest possible opportunity for commercialization

AMP Program Development Process



AMP Research Topics

Disease area	Research plan topics	Deliverables and approach
Alzheimer's disease	Exploratory biomarker validation in clinical trials and network analysis on human tissue	• Embed tau imaging and exploratory liquid biomarkers in NIH-funded clinical trials to develop biomarkers of disease progression and surrogate endpoints • Conduct network analysis in human brain samples to identify genetic nodes & networks linked to AD to support target identification & validation
Type 2 Diabetes	Sequencing & phenotyping of targets of interest and a tool to enable easy interrogation of all available data	• Create a knowledge portal containing comprehensive T2DM (& diabetic complications) genotype/phenotype data sets – apply informatics to identify predictors of risk and potential drug targets • Conduct targeted sequencing/genotyping and explore additional methodologies to evaluate of high priority targets of interest (as defined by industry); phenotyping on patients with high priority variants
RA, SLE & related autoimmune diseases	Immune module deconstruction with blood/tissue and cross-disease comparisons	• Conduct extensive profiling of key immune modules in highly refined subsets of relevant cells in informative cohorts to establish pathway/network maps of RA & SLE • Identify high priority targets identified from pathway analysis to be validated via RNAi. Make all data available in a knowledge portal - Informative cohorts include: Early RA, Established RA (responder/non-responder), Lupus Nephritis, Skin Lupus

Current AMP Participation by Disease Area

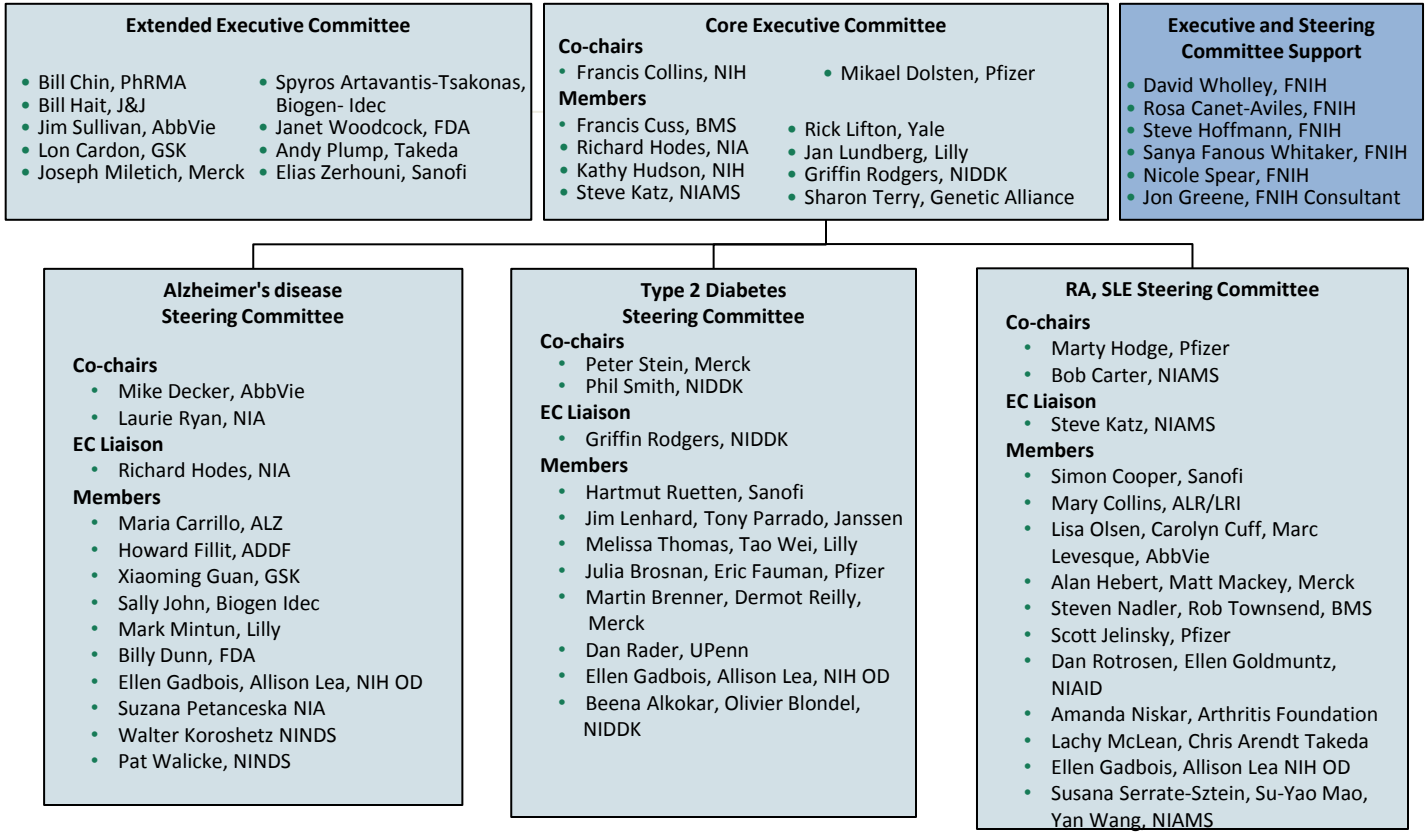
	Alzheimer's disease	Type 2 Diabetes	RA, SLE & related
Industry members	abbvie Biogen GlaxoSmithKline Lilly	janssen PHARMACEUTICAL COMPANIES OF Johnson & Johnson Lilly MERCK Pfizer SANOFI	abbvie Bristol-Myers Squibb MERCK Pfizer SANOFI Takeda
Government members	NIH National Institute on Aging NIH National Institute of Neurological Disorders and Stroke FDA	NIH National Institute of Diabetes and Digestive and Kidney Diseases	NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases NIH National Institute of Allergy and Infectious Diseases
Non-profit members	alzheimer's association Alzheimer's Drug Discovery Foundation GEOFFREY BEENE US Against Alzheimer's	American Diabetes Association. JDRF IMPROVING LIVES. CURING TYPE 1 DIABETES.	Lupus Research Institute Alliance for Lupus Research PREVENT. TREAT. CURE. LUPUS FOUNDATION OF AMERICA Arthritis Foundation Rheumatology Research Foundation Advancing Treatment | Finding Cures PhRMA RESEARCH + PROGRESS + HOPE FNIH Foundation for the National Institutes of Health

Current AMP Funding Commitments (total: 5 years)

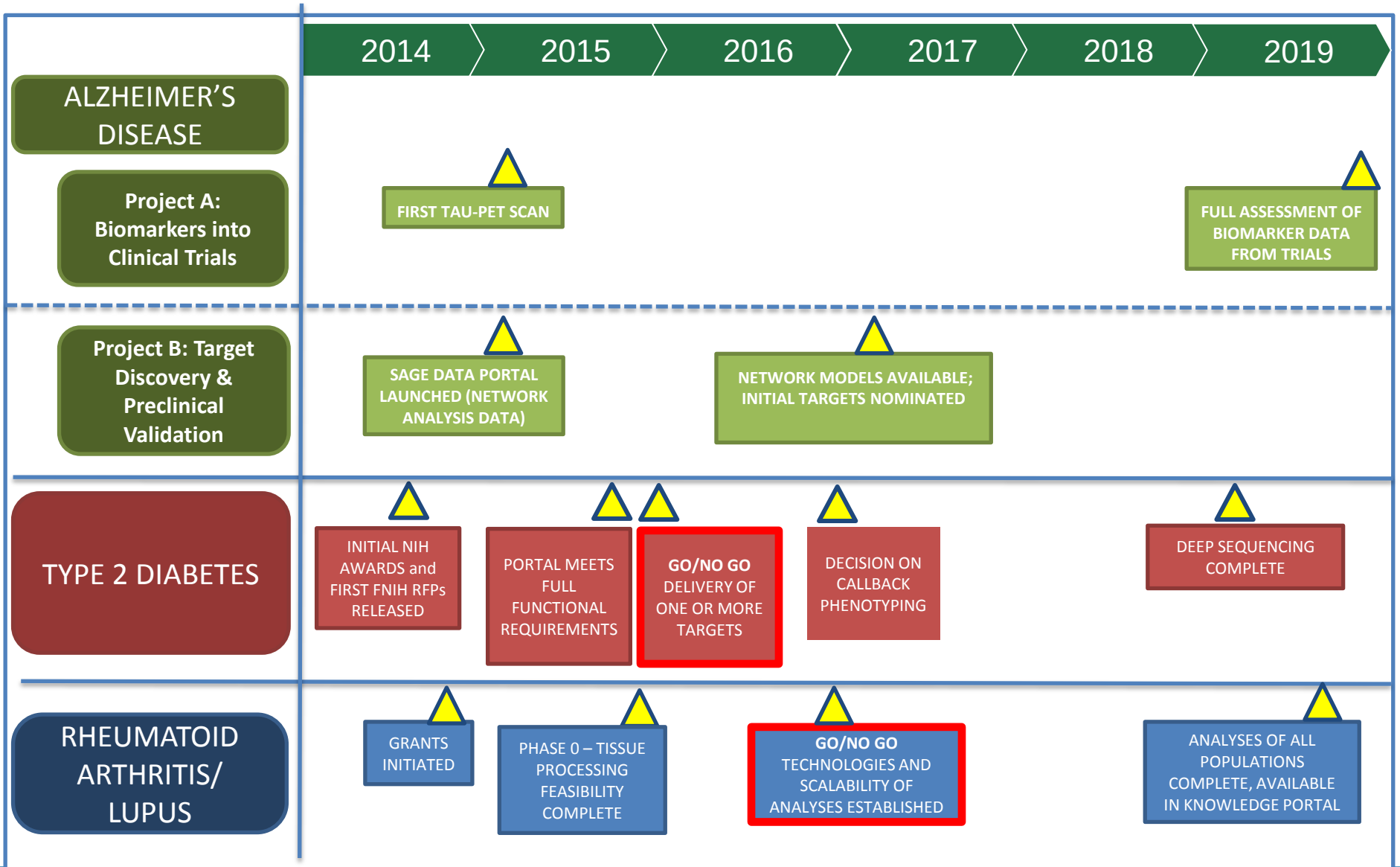
Disease area	Total project funding ($M)	Total NIH funding ($M)	Total industry funding ($M)	Total non-profit funding ($M)
AD	92. 5	69.6	21.9*	1.0
T2D	52.8	31 +**	21.5*	.3
RA/SLE	41.9	20.9	20.7	.3
Total	187. 2	121.5	64.1	1.6

* Does not include in-kind contributions of $40M to AD and $6.5M to T2D
** Additional funding anticipated

AMP Governance and Membership



Summary of AMP Timelines and Deliverables



Type 2 Diabetes AMP Program Overview

5-year program with focus on linking human genetic data on risk for T2D & phenotyping to identify novel drug targets by creating tools to allow easy, integrated interrogation

- **$40M + project with 3 specific aims:**
  - Create knowledge portal with broad genotype/phenotype T2D & diabetic vascular complications data sets allowing informatics approach to identify predictors of risk and potential drug targets
  - Conduct targeted sequencing/genotyping and explore other methodologies for areas of interest
  - Conduct hypothesis-driven phenotyping on patients with high- priority LoF/GoF variants to validate potential T2D/complications targets (NIH-funded)

- **Strategic decisions to date made for AMP T2D Project:**
  - Aggregate human genetic data from 200K+ individuals on risk/protection for T2D & its complications with phenotypic data in the knowledge portal
  - Create tools within the portal to allow easy, integrated interrogation across multiple datasets while maintaining individual level data privacy

Project Strategy: Phased Approach

The AMP T2D Partnership Currently has Two Phases:

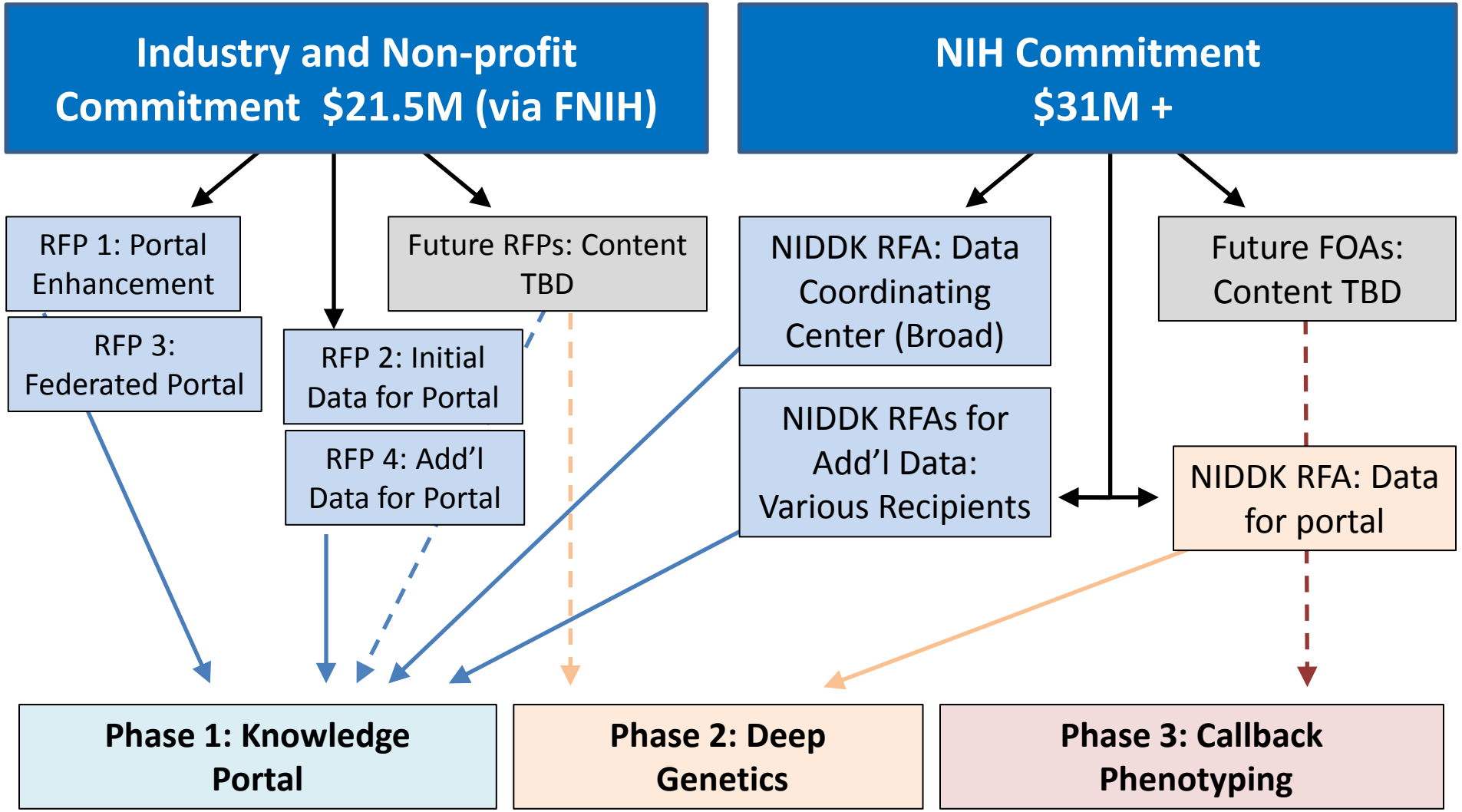
<u>Phase 1</u>: Create a public-access Knowledge Portal (KP) incorporating 150K+ individuals with capabilities to:

- Link phenotype data with genetic data on risk for or protection from T2D
- Interrogate all data in an integrated fashion to answer phenotype, gene, pathway, variant, or subset based queries on T2D and its complications using analytical tools

<u>Phase 2</u>: Use "deep" genetics and explore other techniques to generate new data for targets of particular interest

<u>Phase 3 (to be funded by NIH):</u> Calling back individuals with loss or gain of function mutations at novel loci for in depth clinical phenotyping

Project Background: Current Funding Streams



Key Accomplishments to Date

- Milestones:

Key Go No-Go Milestones	Status
Data in the portal (target: 200K GWAS, 100K Exome Chip, 10,000 Exome Sequencing) with sufficient diversity	• GWAS: >300K with summary; ~ 59K individual level by end of 2015 • Exome Chip: ~90K with summary; ~9K individual data by end 2015 • Exome Sequencing: ~26K with summary/individual level data in portal • Ethnic representation in portal: African-American, East Asian, South Asian, European, US, Mexican and Latin American
Complete functionality/ feature requirements for queries submitted to portal	As of June 2015 Knowledge Portal fully up and running/additional public rollout at Oct 2015 ASHG meeting
Results from initial SC specified research queries	Complete ("Proof of Concept" analyses)

- Awards to date:
  - Six NIDDK grants: portal infrastructure support and data generation
  - Six + FNIH grants: portal enhancement, new data for portal, and first federated hub expansion to the UK (EBI)

Data Areas of Interest

Ethnicities	Status
African American	Some represented in portal, soon to be represented in substantial numbers
East Asian	Some represented in portal, soon to be represented in substantial numbers
European	Well-represented in portal
Hispanic	Well-represented in portal
Native American	Possible representation in portal in coming years (discussions initiated)
South Asian	Soon to be represented in portal in substantial numbers
Complications	**In portal**
Cardiovascular	Represented in portal in substantial numbers, more incoming data
Diabetic Nephropathy	Little represented in portal, soon to be represented in more substantial numbers
Other	Little represented in portal, soon to be represented in more substantial numbers

Visit the AMP T2D Knowledge Portal at
http://www.type2diabetesgenetics.org/home/portalHome

AMP Challenges

- Data sharing
  - Incentivizing investigators
  - Dealing with data restrictions (consents, country restrictions)
- Data integration
  - Heterogeneous data, analysis needs, funding sources, legacy support = different data platforms
- Concerns about publications, authorship, and acknowledgement – publication policies are critical to address this
- Integrating different work/ funding streams to deliver functional product under aggressive timeline
- Making best use of limited funds
  - (No, there is never "enough"!)
- Cultural differences (Academic, Industry, Government)