Impact of Genomic Variation on Function (IGVF) Pre-Application Webinar

Mike Pazin, Stephanie Morris, and Dan Gilchrist

National Human Genome Research Institute, Division of Genome Sciences

September 2020

National Human Genome Research Institute

The Forefront of Genomics

Agenda

- **Webinar Logistics** – 2 min
- **NHGRI and IGVF Overview** – 10 min
- **Application Guidelines and Cooperative Agreements**– 10 min
- **Individual Funding Announcements** – 25 min (5 min each)
- **Q&A Session** – Until we run out of questions or time, whichever comes first

Webinar Logistics

- These slides will be available on the NHGRI IGVF website after the second webinar: https://www.genome.gov/Funded-Programs-Projects/Impact-of-Genomic-Variation-on-Function-Consortium
- A list of frequently asked questions and answers (FAQs) will be posted on the NHGRI IGVF website
- All attendees will be muted for the entire webinar
- We will answer questions during the Q&A session at the end of webinar
- Please send your questions at any time during this webinar via Q&A (not chat) or via webform/email to https://forms.gle/DrgqfDCd2p71Cw47A or briana.nunez@nih.gov

NHGRI Overview

- Genomics
- Comprehensive, unbiased approaches
- Generalizable methods and knowledge
  - ❖NOT particular diseases or biological systems
  - ❖NOT particular genes
  - ❖NOT mechanistic studies

IGVF Significance

Challenge/ Opportunity	Interpreting variants Interpreting candidate genotype/phenotype associations
Objective	Understanding how genetic variation impacts genome function, phenotypes (including disease)
Implementation	Data collection, community data resource, integrative data analysis, and predictive modeling

IGVF Goal

- Systematic understanding of the effects of genomic variation on genome function and how these effects shape phenotypes

- Not expected to have all answers at the end of 5 years, but will have a framework to address these questions

IGVF Program Objectives

Transform our understanding of how variation impacts function and leads to phenotypes in health and disease

1. Assess genome function using systematic perturbation
2. High-resolution identification of where and when genes and regulatory elements function
3. Network-level understanding of genome function
4. Develop predictive models of genome function
5. Generation of a catalog of elements, variant and phenotypes; share data, tools, and models
6. Enabling others to apply these approaches

NIH NHGRI

Key IGVF Consortium Outcomes

Key Outcome: Resource

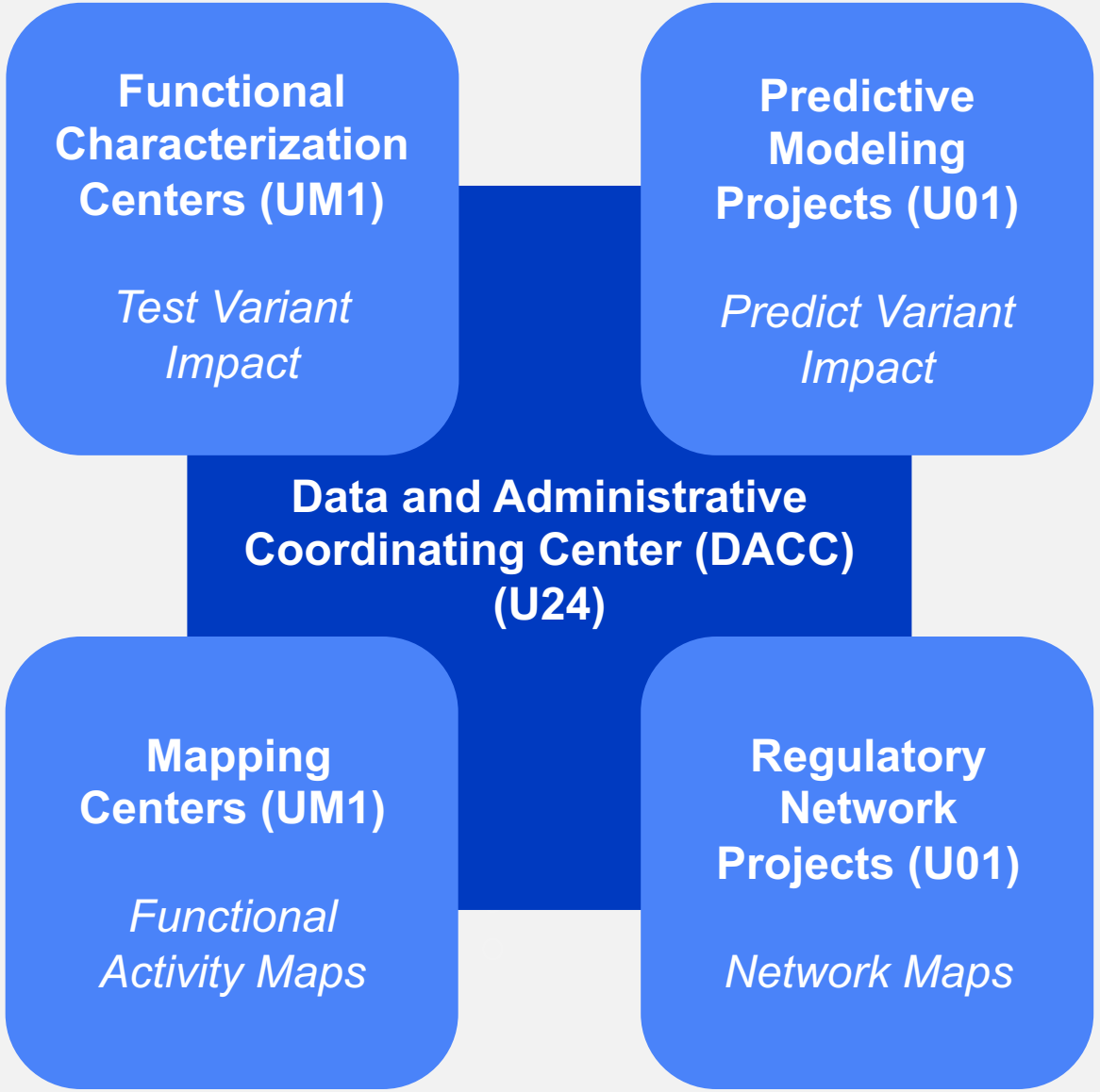
- Data on elements, variants, and phenotype
- Tools, models, methods, standards, technologies

Key Outcome: Understanding how genomic variation impacts genome function

- Catalog of variant impact
- Models predicting effects of untested variants
- Model variants and elements in networks and pathways

NIH
NHGRI

IGVF Consortium Structure



Organized as a multi-component research consortium that brings investigators together in a highly collaborative effort

Five interrelated funding opportunity announcements (FOAs)

NIH NHGRI

IGVF Applicants

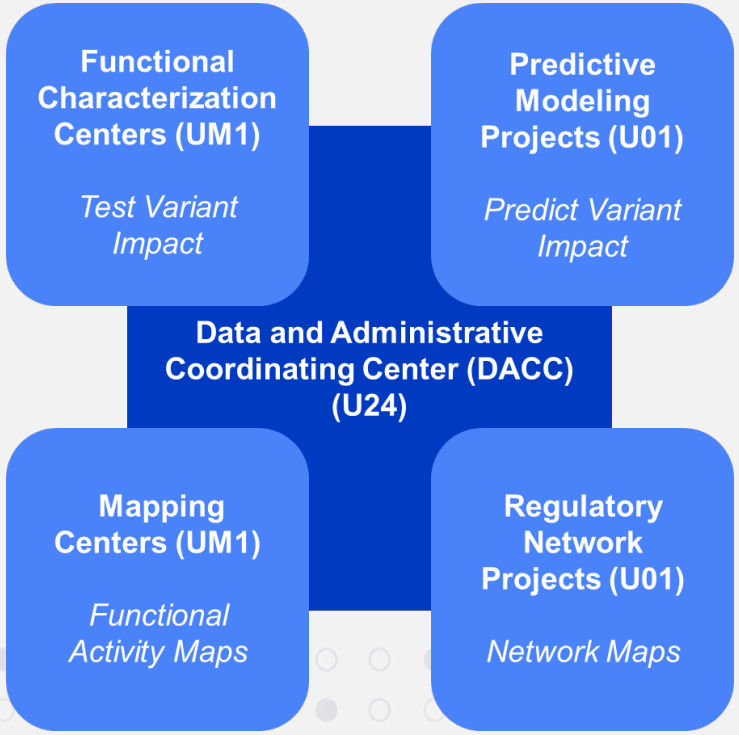
- IGVF is seeking applicants with diverse expertise including at least genomics and data science
- NHGRI encourages all investigators with ideas aligned with IGVF to submit applications, especially:
  - Investigators from demographic groups or institutions generally underrepresented in genomic science
  - New and early stage investigators
  - Experienced investigators who are new to genomic science
  - Investigators that have not previously participated in a NHGRI-consortium or program

First Year: Focus on Scientific Planning

- To plan consortium-wide and component-specific strategies for data collection and analyses
- To plan tests to characterize strengths, synergies, and weaknesses of proposed approaches
- Activities to be ramped up in years 2-5
- All funded teams will participate in kickoff meeting at start of year 1

IGVF Consortium: Shared Activities

This is a consortium effort—funded projects and centers will work collaboratively with each other, including the DACC and will:



- Contribute data, metadata, analyses, and software to the DACC and appropriate repositories
- Participate in planning, implementation, and analysis of consortium-wide or component-wide projects
- Develop standards and establish data quality metrics
- Share best practices and lessons learned
- Contribute to outreach efforts

Collaborative projects across the consortium will be encouraged

Application Guidelines for All FOAs

- Read FOAs carefully; know what to include in your application
- Non-responsive applications are neither reviewed nor considered for funding
- Contact NHGRI about your ideas *before* submitting your application
- Submit a couple days early, do not wait until the last minute

Application Guidelines for All FOAs

- Applicants are eligible to apply to multiple FOAs
- Provide timeline and annual milestones spanning funding period
- Key personnel/consultants/team should demonstrate strong scientific expertise
- What makes your approach different, and better? What will put your application into the reviewer's top applications?

Cooperative Agreements

- Used when substantial programmatic involvement is anticipated between NIH and the recipient
- For roles and expectations see Cooperative Agreement “Terms and Conditions of Award” in FOA
  - Work collaboratively within the consortium
  - Participate in IGVF annual meeting, working groups, and in regular conference calls
  - Make satisfactory progress towards proposed scientific milestones

Application Guidelines for All FOAs

- Please review Terms and Conditions, as well as Resource Sharing
- All applications should have a Resource Sharing Plan and should address data sharing
- Awardee responsibilities include complying with IGVF policies, including any data release policies, publication policies or software sharing policies
- Applicants should explicitly state their willingness to cooperate with the IGVF consortium, NIH staff, and other stakeholders in the development and implementation of standardized formats, metadata, and quality control metrics.
- Biological samples from humans are expected to be consented for future research use and broad data sharing
- Sources with participant consent for unrestricted access are strongly encouraged

Application Guidelines for All FOAs

Please read Budget Instructions, Section IV

- Budget in first year is different from following years (RFA-HG-20-043, RFA-HG-20-045, RFA-HG-20-046, RFA-HG-20-047) (See Section II)
- 20% of the direct costs from years 2-5 of the award must be allocated to support shared work (RFA-HG-20-043, RFA-HG-20-045, RFA-HG-20-047)
  - Applicants are encouraged to include a paragraph about a project(s) that may be proposed in the future
  - The common projects will be chosen by awardees in consultation with NIH staff
- Budget must include funds to support investigator travel to initial in-person IGVF kickoff meeting, year 1 and 2 Steering Committee meetings, and to attend the annual IGVF Consortium meetings within the continental U.S.
- Budget must include funds for project manager (RFA-HG-20-043, RFA-HG-20-045, RFA-HG-20-046) and appropriate effort for PI/MPI

Application Guidelines for All FOAs

Review Criteria, Section V.1

- Look for non-standard review criteria flagged by “Specific to this FOA”

Section V.2—will be considered in making funding decisions

- Relevance to program priorities
- Programmatic balance, synergy…
- Potential to work effectively in large collaborative efforts or research consortia…
- Data sharing, software and analysis sharing and resource sharing plans
- Expansion of the community of genomic science…
- Inclusion of investigators that are new to NHGRI consortia
- Whether an applicant will be funded as a PD/PI through the other IGVF FOAs

Five Interrelated IGVF FOAs

- Characterization: RFA-HG-20-043: Systematic Characterization of Genomic Variation on Genome Function and Phenotype (UM1)
- Mapping: RFA-HG-20-045: Single-cell Profiling of Regulatory Element and Gene Activity in Relationship to Genome Function (UM1)
- Modeling: RFA-HG-20-047: Developing Predictive Models of the Impact of Genomic Variation on Function (U01)
- Networks: RFA-HG-20-044: Defining Genomic Influence on Gene Network Regulation (U01)
- DACC: RFA-HG-20-046: Genomic Variation and Function Data and Administrative Coordinating Center (U24)

RFA-HG-20-043: Systematic Characterization of Genomic Variation on Genome Function and Phenotype (UM1)

Purpose: to experimentally correlate genomic variants with their effects on genomic function

Contact: Mike Pazin, michael.pazin@nih.gov

RFA-HG-20-043: Systematic Characterization of Genomic Variation on Genome Function and Phenotype (UM1)

Objectives:

- Select genomic variants and/or elements for systematic testing
- Apply genomic perturbation methods and assay the impact on biologically relevant phenotypes
- Generate a variant/element/phenotype catalog for the community

Contact: Mike Pazin, michael.pazin@nih.gov

RFA-HG-20-043: Systematic Characterization of Genomic Variation on Genome Function and Phenotype (UM1)

Scope also includes:

- Enable others to perform related studies using these approaches
- Define a data collection strategy for characterization centers and predictive modeling
- Assist in generating predictive models for the community
- Improve generalizable approaches or technologies for high-throughput assays (optional)

Contact: Mike Pazin, michael.pazin@nih.gov

RFA-HG-20-043: Systematic Characterization of Genomic Variation on Genome Function and Phenotype (UM1)

Budget:

- In FY21 application budgets are limited to $700,000 direct costs
- In FY22-FY25 application budgets are limited to $1.4M direct costs per year

Contact: Mike Pazin, michael.pazin@nih.gov

RFA-HG-20-043: Systematic Characterization of Genomic Variation on Genome Function and Phenotype (UM1)

Make sure to adhere to all Instructions for Applicant Submission, including addressing the following:

- Plan for variant/element/phenotype catalog for the community
- Planning year, first year
- Consortium data collection plan

Contact: Mike Pazin, michael.pazin@nih.gov

RFA-HG-20-043: Systematic Characterization of Genomic Variation on Genome Function and Phenotype (UM1)

Examples of approaches: massively parallel reporter assays, genome editing, epigenome editing, high-throughput protein mutagenesis

Examples of biological systems: human and/or mouse

May test variants and/or elements

Contact: Mike Pazin, michael.pazin@nih.gov

RFA-HG-20-043: Systematic Characterization of Genomic Variation on Genome Function and Phenotype (UM1)

Considered non-responsive:

- Projects that do not test the function of genomic elements or variants
- Projects that are primarily developing new experimental methods
- Projects that do not use biological systems relevant to human health and disease
- Mechanistic studies or projects focused on a single disease
- Proposed work that does not indicate plans to participate in the ramp-up year and to collaborate with and contribute to consortium-wide, collaborative activities and analyses throughout the course of the project

Contact: Mike Pazin, michael.pazin@nih.gov

RFA-HG-20-045: Single-cell Profiling of Regulatory Element and Gene Activity in Relationship to Genome Function (UM1)

Purpose: to generate single-cell, multi-omic maps of elements in the human and mouse genomes

Contact: Stephanie Morris, morriss2@mail.nih.gov

RFA-HG-20-045: Single-cell Profiling of Regulatory Element and Gene Activity in Relationship to Genome Function (UM1)

Objectives:

- Use state-of-the-art, high-throughput genomics methods to map genes and regulatory elements at single-cell resolution
  - Identify candidate functional elements in distinct cell types and states (i.e., particular biological and spatial contexts)

- Produce durable datasets of annotated candidate functional elements accessible to the broader research community

Contact: Stephanie Morris, morriss2@mail.nih.gov

RFA-HG-20-045: Single-cell Profiling of Regulatory Element and Gene Activity in Relationship to Genome Function (UM1)

Scope of this FOA also includes:

- Enable others to perform related studies using these approaches
- Contribute to defining a strategy for data collection and analyses for Mapping Centers and the consortium
- Contribute to generating a variant/element/phenotype catalog for the community

Contact: Stephanie Morris, morriss2@mail.nih.gov

RFA-HG-20-045: Single-cell Profiling of Regulatory Element and Gene Activity in Relationship to Genome Function (UM1)

Budget:

- In FY21 application budgets are limited to $900,000 direct costs
- In FY22-FY25 application budgets are limited to $1.8M direct costs per year

Contact: Stephanie Morris, morriss2@mail.nih.gov

RFA-HG-20-045: Single-cell Profiling of Regulatory Element and Gene Activity in Relationship to Genome Function (UM1)

Some Key Points

- **Experimental Assays:**
  - Initiative will support generation of multiple data types
  - Must be able to support data generation utilizing 2-3 distinct, robust assays
  - One of these assays must be single cell transcriptomics
  - Assays/approaches that generate complementary information are encouraged
  - Multi-modal, single-cell assays/approaches are encouraged
- **Biological Samples:**
  - Propose study of samples derived from human and/or mouse
  - Propose study of specific cell types, fates, or states with focus on those important in development, differentiation, or to human diseases associated with known genomic variants

Contact: Stephanie Morris, morriss2@mail.nih.gov

RFA-HG-20-045: Single-cell Profiling of Regulatory Element and Gene Activity in Relationship to Genome Function (UM1)

Some Key Points

- **Mapping Centers will work together to prioritize assays and biological samples**
  - Centers may need to adjust samples or add samples
  - For this reason, technologies must have demonstrated ability to produce high quality data in diverse tissues and cell types

Contact: Stephanie Morris, morriss2@mail.nih.gov

RFA-HG-20-045: Single-cell Profiling of Regulatory Element and Gene Activity in Relationship to Genome Function (UM1)

Make sure to adhere to all Instructions for Applicant Submission, including addressing the following:

- Planning year/first year
- Consortium strategies for data collection and analyses
- How you will work with the consortium

Contact: Stephanie Morris, morriss2@mail.nih.gov

RFA-HG-20-045: Single-cell Profiling of Regulatory Element and Gene Activity in Relationship to Genome Function (UM1)

Considered Non-responsive:

- Exclusion of transcriptomics as one of the generated data types
- Research proposed in model systems that are not of human or mouse origin
- Studies proposed that are primarily computational
- Studies proposed to test and characterize the specific biological function of genes and regulatory elements
- Proposed work that does not indicate plans to participate in the ramp-up year and to collaborate with and contribute to consortium-wide, collaborative activities and analyses throughout the course of the project

Contact: Stephanie Morris, morriss2@mail.nih.gov

RFA-HG-20-047: Developing Predictive Models of the Impact of Genomic Variation on Function (U01)

Purpose: Develop innovative computational models to predict the impact of genomic variation on genome function and/or phenotype

Contact: Dan Gilchrist, daniel.gilchrist@nih.gov

RFA-HG-20-047: Developing Predictive Models of the Impact of Genomic Variation on Function (U01)

Objectives:

- Develop computational approaches to model/predict relationships among variation/function/phenotype
- Collaborate to define IGVF data collection/analysis strategies
- Generate a variant/element/phenotype catalog for the community
- Contribute analytical expertise to the consortium

Contact: Dan Gilchrist, daniel.gilchrist@nih.gov

RFA-HG-20-047: Developing Predictive Models of the Impact of Genomic Variation on Function (U01)

Scope of this FOA also includes:

- Enable others to perform related studies using these approaches
- Create tools to enable inferences about genome function (optional)

Contact: Dan Gilchrist, daniel.gilchrist@nih.gov

RFA-HG-20-047: Developing Predictive Models of the Impact of Genomic Variation on Function (U01)

Budget:

- In FY21 budgets are limited to $275K direct costs
- In FY22-FY25 budgets are limited to $550K direct costs

Contact: Dan Gilchrist, daniel.gilchrist@nih.gov

RFA-HG-20-047: Developing Predictive Models of the Impact of Genomic Variation on Function (U01)

Make sure to adhere to all Instructions for Applicant Submission, including addressing the following:

- Plan for variant/element/phenotype catalog for the community
- Consortium data collection plan
- Plan to contribute analytical expertise to consortium
- Planning year/first year

Contact: Dan Gilchrist, daniel.gilchrist@nih.gov

RFA-HG-20-047: Developing Predictive Models of the Impact of Genomic Variation on Function (U01)

Considered non-responsive:

- Projects proposing extensive wet-lab data generation. Limited (<10% annual direct costs) wet-lab work to inform modeling efforts OK
- Projects proposing models that are not comprehensive in scope (e.g., applicable to only one or a small set of genomic loci/sequences/elements)
- Projects proposing models that are not generalizable (e.g., applicable to one or a small number of diseases)
- Projects not proposing plans to help design experimental strategies generating data useful for predictive modeling
- Projects not proposing contributing analytical expertise to consortium
- Projects not proposing participation in the ramp-up year and collaboration/contribution to consortium-wide, collaborative activities and analyses throughout the project

Contact: Dan Gilchrist, daniel.gilchrist@nih.gov

RFA-HG-20-044: Defining Genomic Influence on Gene Network Regulation (U01)

Purpose: Explore the effects of genomic variation on phenotypes at the network level

NIH NHGRI

Contact: Dan Gilchrist, daniel.gilchrist@nih.gov

RFA-HG-20-044: Defining Genomic Influence on Gene Network Regulation (U01)

Objectives:

- Apply systematic genomic/multi-omic data collection methods
- Measure changes in gene/regulatory element activity during biological changes
- Develop/refine approaches to model gene-regulatory networks using collected data
- Identify, test network-level relationships among variants, elements, genes, phenotypes

Contact: Dan Gilchrist, daniel.gilchrist@nih.gov

RFA-HG-20-044: Defining Genomic Influence on Gene Network Regulation (U01)

Scope of this FOA also includes:

- Collaborate to define the IGVF consortium data collection and analysis strategies
- Enable others to perform related studies using these approaches

Contact: Dan Gilchrist, daniel.gilchrist@nih.gov

RFA-HG-20-044: Defining Genomic Influence on Gene Network Regulation (U01)

Make sure to adhere to all Instructions for Applicant Submission, including addressing the following:

- If applicable, rationale for selecting any non-human system(s), including transferability of findings to studies of human health and disease
- If applicable, rationale for selecting disease system(s), including generalizability of approaches/findings to other systems

Contact: Dan Gilchrist, daniel.gilchrist@nih.gov

RFA-HG-20-044: Defining Genomic Influence on Gene Network Regulation (U01)

Budget:

- Application budgets are limited to $900K direct costs per year

Contact: Dan Gilchrist, daniel.gilchrist@nih.gov

RFA-HG-20-044: Defining Genomic Influence on Gene Network Regulation (U01)

Considered non-responsive:

- Projects focused on specific biological or disease systems that are unlikely to lead to generalizable approaches and paradigms
- Projects that do not propose systematic collection of multi-modal genomic data
- Projects that focus on a single gene or functional element, or small number of genes or functional elements
- Projects that do not propose to develop network models or do not use models to predict impacts of genomic variation
- Projects that do not propose experimental tests of model predictions
- Projects that do not indicate plans to participate in collaborative activities and analyses throughout the course of the project

Contact: Dan Gilchrist, daniel.gilchrist@nih.gov

RFA-20-046: Genomic Variation and Function Data and Administrative Coordinating Center (DACC) (U24)

Purpose: serve as coordinating center for the IGVF consortium

NIH NHGRI

Contact: Stephanie Morris, morriss2@mail.nih.gov

RFA-20-046: Genomic Variation and Function Data and Administrative Coordinating Center (DACC) (U24)

Objectives:

- Coordinate submission and uniform processing of data, metadata, protocols and tools
- Develop a database and portal for housing and sharing of consortium resources
- Serve as an administrative and coordinating center for the consortium
- Coordinate consortium-led analyses and lead outreach efforts

Contact: Stephanie Morris, morriss2@mail.nih.gov

RFA-20-046: Genomic Variation and Function Data and Administrative Coordinating Center (DACC) (U24)

Scope of this FOA also includes:

- Enable others to perform related studies using consortium approaches
- Contribute to defining a strategy for data collection and analyses for the consortium
- Contribute to generating a variant/element/phenotype catalog as part of the consortium's community data resource

Contact: Stephanie Morris, morriss2@mail.nih.gov

RFA-20-046: Genomic Variation and Function Data and Administrative Coordinating Center (DACC) (U24)

Budget:

- In FY21 application budgets are limited to $2.5M direct costs
- In FY22-FY25 application budgets are limited to $3.5M direct costs per year

Contact: Stephanie Morris, morriss2@mail.nih.gov

RFA-20-046: Genomic Variation and Function Data and Administrative Coordinating Center (DACC) (U24)

Some Key Points:

- Division of center's activities into two components: (1) Data Coordination and (2) Administrative Coordination is encouraged
  - Each should be managed by a team with appropriate expertise and leadership
- Center must be prepared to work with metadata and data from a range of experimental and computational genomics research; review of companion FOAs is encouraged
- Center should have experience with, and plans for, working with data consented for unrestricted access and controlled-access
- Propose a transition plan for the consortium-generated resource that addresses sustainability
- Center will be responsible for facilitating consortium coordination and communication; propose budget that addresses meeting logistics and communication platforms

Contact: Stephanie Morris, morriss2@mail.nih.gov

RFA-20-046: Genomic Variation and Function Data and Administrative Coordinating Center (U24)

Make sure to adhere to all Instructions for Applicant Submission, including addressing the following:

- Planning year/first year
- Consortium strategies for data collection and analyses
- How you will work with the consortium

Contact: Stephanie Morris, morriss2@mail.nih.gov

Timeline for FOAs

- Contact NHGRI about your ideas
- Letter of intent due: 4 October 2020
- Receipt date: 4 November 2020
- Review: March 2021
- Council: May 2021
- Earliest start date: July 2021

NHGRI Contacts for IGVF

RFA	Program	Grants	Review
RFA-HG-20-043 Characterization	Mike Pazin michael.pazin@nih.gov	Anneliese Galczynski anneliese.galczynski@mail.nih.gov	Rudy Pozzatti pozzattr@exchange.nih.gov
RFA-HG-20-044 Networks	Daniel Gilchrist daniel.gilchrist@nih.gov	Lisa Oken loken@nih.gov	Rudy Pozzatti pozzattr@exchange.nih.gov
RFA-HG-20-045 Mapping	Stephanie Morris morriss2@mail.nih.gov	Devon Bumbray-Quarles db400w@nih.gov	Rudy Pozzatti pozzattr@exchange.nih.gov
RFA-HG-20-046 DACC	Stephanie Morris morriss2@mail.nih.gov	Devon Bumbray-Quarles db400w@nih.gov	Rudy Pozzatti pozzattr@exchange.nih.gov
RFA-HG-20-047 Modeling	Daniel Gilchrist daniel.gilchrist@nih.gov	Lisa Oken loken@nih.gov	Rudy Pozzatti pozzattr@exchange.nih.gov

Question and Answer Session

- Please ask your questions via Q&A (not chat), webform https://forms.gle/DrggfDCd2p71Cw47A or via email to briana.nunez@nih.gov
- All attendees will be muted
- These slides will be available on the NHGRI IGVF website after the second webinar: https://www.genome.gov/Funded-Programs-Projects/Impact-of-Genomic-Variation-on-Function-Consortium
- A list of frequently asked questions and answers (FAQs) will be posted on the NHGRI IGVF website
- We are focusing on general questions in today's Q&A. If specific questions remain please follow-up with the appropriate contact


The Forefront
of Genomics

IGVF: Resource and Research

Mapping Centers

Data Coord. Center

Functional Char. Centers

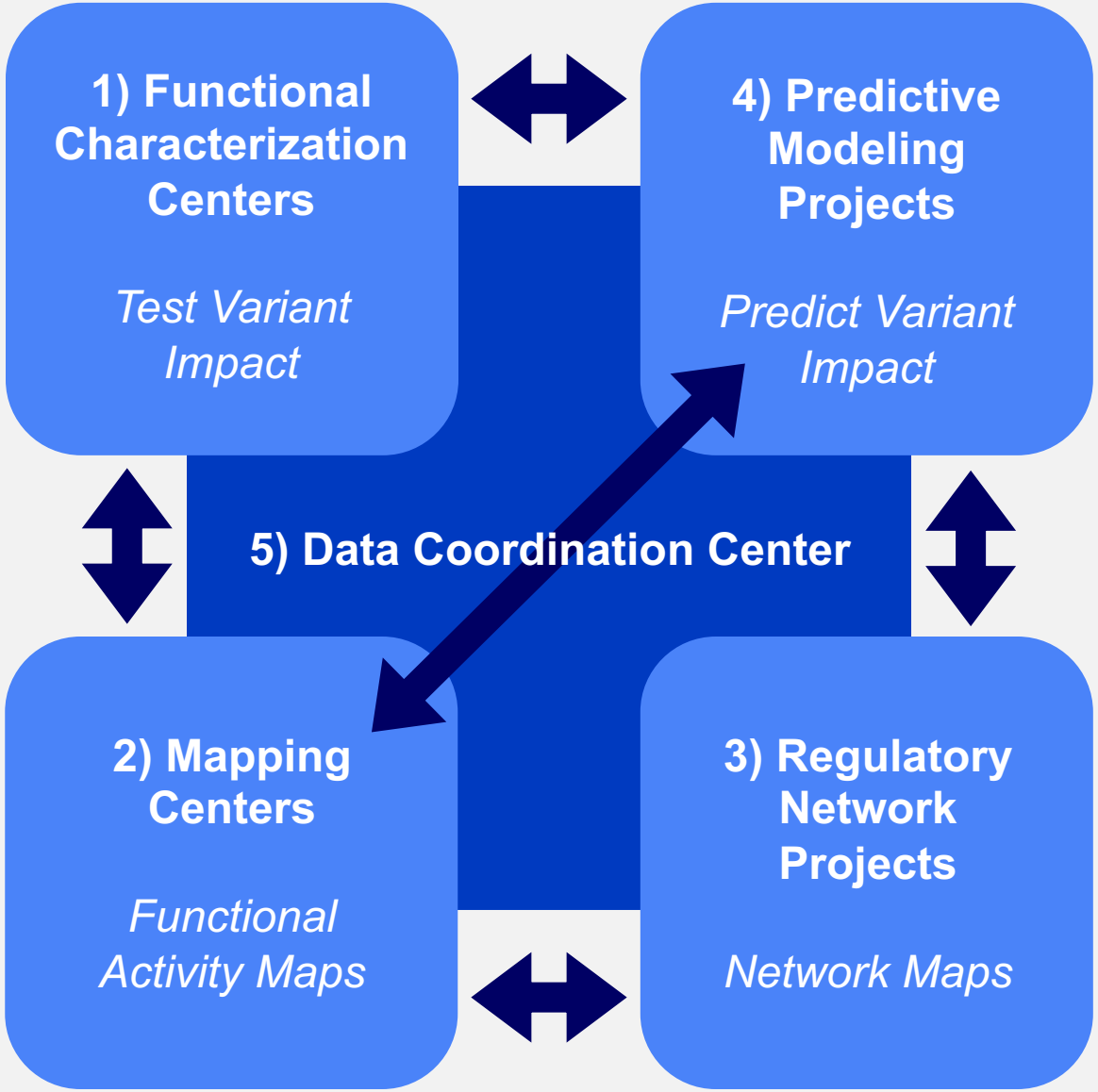
Predictive Modeling Projects

Regulatory Network Projects

NIH
NHGRI

Synergies Within The IGVF Consortium

Characterization centers help prioritize samples to be mapped; element maps inform testing by systematic perturbation



Characterization and mapping data inform predictive models; models help prioritize variants to test, samples to map

NIH NHGRI