

Information Session for Applicants
to NHGRI Sequencing and Ethical,
Legal, and Social Implications (ELSI)
FOAs

January 28, 2011

Call Logistics

- See Logistics write up
- Send questions in to Webinar host (throughout) or just ask when we open up each session to questions (otherwise lines will be on mute).

RFA List

- Genome Sequencing and Analysis Centers (U54) (RFA-HG-10-015)
- Mendelian Disorders Genome Centers (U54) (RFA-HG-10-016)
- Clinical Sequencing Exploratory Research (U01) (RFA-HG-10-017)
- Development of a Preliminary Evidence Base to Inform Decision-making about Returning Research Results to Participants in Genomics Studies (R01) (RFA-HG-11-003)
- Ethical, Legal, and Social Implications of Returning Research Results to Genomic Research Participants (R21) (RFA-HG-11-004)

NHGRI Sequencing and Ethical, Legal, and Social Implications (ELSI) FOAs

	Main Objectives	Sequence Data Production & Data Analysis	Understanding the Genetic Basis of Disease	Interpretation & Returning of Sequence Data for Patient Care	ELSI in Clinical Context	ELSI in Research Context
Genome Sequencing and Analysis Centers (U54), RFA-HG-10-015, \$90 M/year	Large-scale sequencing and data analysis; Driving the state-of-the-art in sequencing and data analysis.			Perhaps some		
Mendelian Disorders Genome Centers (U54), RFA-HG-10-016, \$10 M/year	Discovering the genetic basis of Mendelian disorders			Perhaps some		
Clinical Sequencing Exploratory Research (U01), RFA-HG-10-017, \$5.5 M/year	Exploring the challenges in using genomic data in the routine clinical care of individual patients					
Development of Evidence Base for Return of Research Results (R01), RFA-HG-11-003, \$2 M/year	Behavioral or social science research on returning individual research results to participants in genomic research studies			Perhaps some	Perhaps some	
ELSI of Returning Research Results to Genomic Research Participants (R21), RFA-HG-11-004, \$750K/year	Analytical research on normative and legal issues involved in returning individual research results to participants in genomic research studies					

Genome Sequencing and Analysis Centers (U54) (RFA-HG-10-015)

<http://grants.nih.gov/grants/guide/rfa-files/RFA-HG-10-015.html>

FY 2012 – FY 2016

Contact: Adam Felsenfeld 301-496-7531 adam_felsenfeld@nih.gov

Similar to Previous Program

- Large, flexible centers
- State-of-the-art high throughput
- Capable of multiple project types, designs (not just doing but inventing)
- Integrated: drive state of art in multiple areas of expertise: sequencing, informatics, analysis, biology
- Highly collaborative; disseminate knowledge

HG 10-015

- Large, state-of-the-art
 - Current total capacity: 50Tb/quarter
 - Expect state-of-the-art to improve—quality, cost, throughput. Expect centers to drive this over time

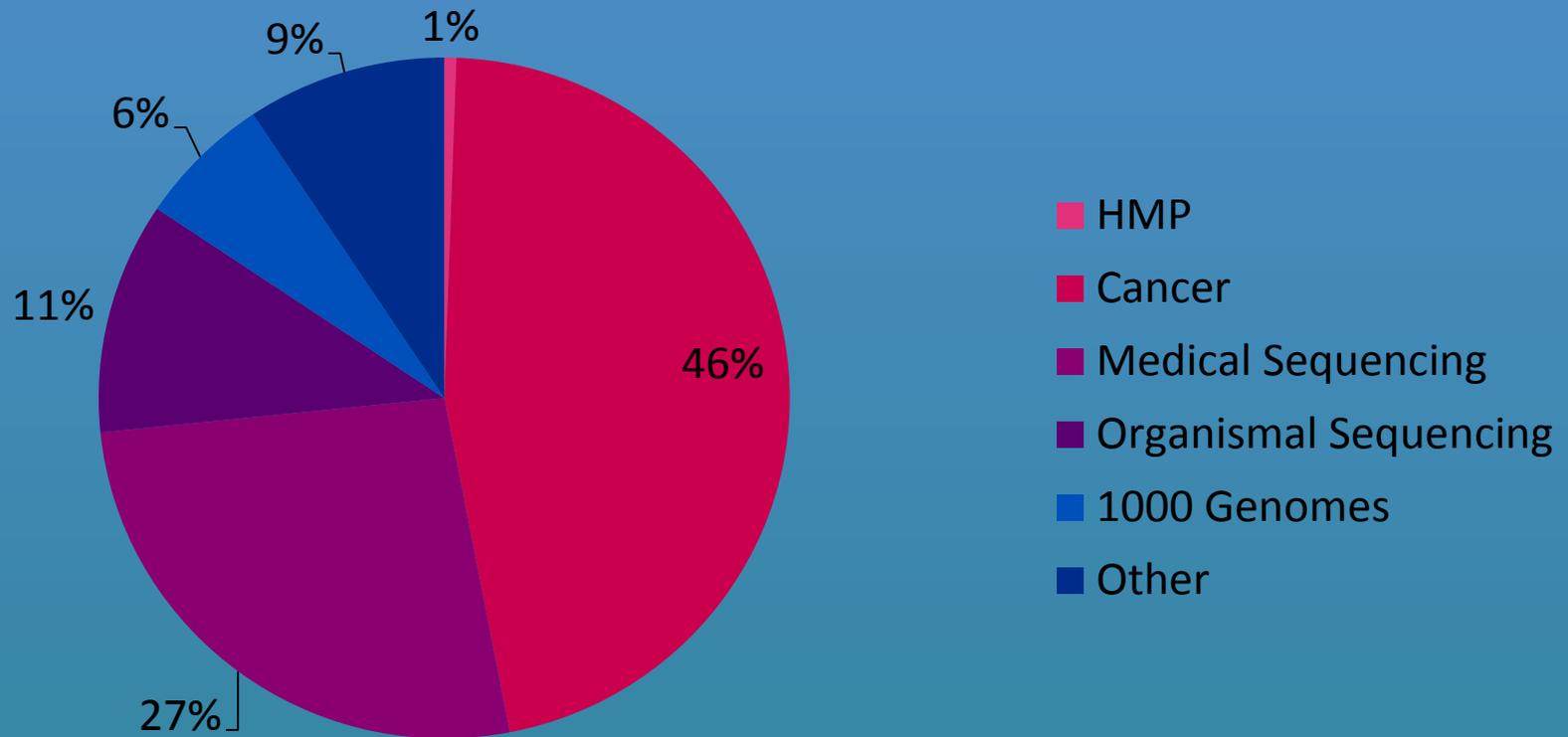
HG 10-015

Flexible, capable of multiple project types, designs - not just doing but inventing. Current range includes:

- Med seq: whole genomes, exomes, targeted sequencing. Complex/ Mendelian/ Cancer. Flexibility to real project demands (designs, small amounts of sample, etc.)
- Human and model system variation
- Organismal seq: vertebrates, protists
- RNA seq
- Others?

NHGRI Last Quarter Production - Across three platforms

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HG 10-015

Flexible...

- Capable of completing/designing projects chosen by NHGRI/collaborators AND identifying compelling Center Initiated Projects
- From the RFA: “...identifying and designing new project types that address the most compelling new questions that can be answered as high throughput sequencing continues to evolve, and also the increasingly challenging bioinformatics and integration issues that attend such studies”

HG 10-015

Highly collaborative; disseminate knowledge

- Collaborations with communities (disease, organismal—samples!); analysis; design; publication
- Dissemination: data (NCBI); now also software, project design, “know-how”—more emphasis this time
- Can deal with human samples

Key Dates: HG 10-015

- Letters of Intent Due Date: February 3, 2011
- Application Due Date: March 3, 2011
(rec'd, not postmarked)
- Scientific Merit Review: July 2011
- Advisory Council Review: October 2011
- Earliest Start Date: December 2011

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HG 10-015: Three Research Plan Sections

I. Overall “Center Management Plan” (30 pages)

Two elements:

- a. brief general intro, previous contributions to field; retrospective information on all aspects of an integrated sequencing center (progress) including costs. 20 pages (or less).
 - b. center management plan. 10 pages (or less).
- *Cost Reporting*: links to spreadsheet for retrospective cost reporting. Not strictly required to use, but if you don't break out costs along those lines, reviewers will not be able to assess

HG 10-015: Research Plan Sections, Continued

- II. Large-Scale Sequencing plan (30 pages)
 - a. aims and introduction, areas of emphasis, opportunities, general justification
 - b. Technical plans for the center, all aspects of an integrated center (as detailed in RFA), plans for outreach/dissemination; plans for involvement in specific ongoing NHGRI projects (eg TCGA).

HG 10-015 Research Plan Sections, Continued

III. Center Initiated Projects (10 pages)

- Centers should propose projects to fill about half of their capacity for the first year to 18 mos
- CIP's will be evaluated according to their overall demonstration of state-of-the art applications of large-scale sequencing, including significance, appropriateness for application at high-throughput, potential for demonstrating or refining a new project type, etc.

HG 10-015: Other Essentials

- Data Sharing Plan (separate). We expect all awardees will comply with institute policies. Note that technical aspects of data deposition (those which will cost \$ to do; mostly informatics) may be covered in the research plan section.
- Separate Diversity Action Plan application. Applicants are required to submit a simultaneous, parallel application to the “Initiative to Maximize Research Education in Genomics (R25)”
<http://grants.nih.gov/grants/guide/pa-files/PAR-09-245.html> *May 25th receipt date*

HG 10-015: Cooperative Agreements

- These awards will be closely managed: projects, throughput, costs; quarterly goals and reporting according to an agreed format; Scientific Advisors to the program (SAP).
- Research Network: At least one annual face-to-face meeting with SAP. Other calls/meetings to coordinate specific large projects. Cooperation between centers on e.g. deposition policies/standards; quality; etc. NHGRI will look for any opportunities for useful coordination between all grantees funded under the sequencing RFA's.

HG 10-015: Clarifications

- Number of Awards: 2 or 3 *does not bind us*. But: no applicant should request more than about \$65M of the \$90M total for this RFA. Within that, we intend that applicants have maximum flexibility to address the goals of the RFA as efficiently as possible.
- Please check <http://grants.nih.gov/grants/guide/> for any Notices that update this RFA. One will be published very soon regarding this point.

Mendelian Disorders Genome Centers (U54)

<http://grants.nih.gov/grants/guide/rfa-files/RFA-HG-10-016.html>

FY 2012 – FY 2016

FOA Objectives

- Discover the genetic basis for as many Mendelian disorders/phenotypes as possible during the funding period;
- Provide a foundation for reaching a comprehensive understanding of the genetic basis of Mendelian disorders;
 - Establish and refine effective and efficient study designs, technologies, and analysis methods that balance cost, efficiency, and quality; gain insight about the range of tractability of Mendelian phenotypes to state-of-the-art genomic approaches;
 - Disseminate the “know-how”;
 - Create a public sample list.

Award Information

- Up to two Centers
- A budget of \$10M per year in total costs
- Domestic Eligible Organizations can apply (Part 2: Section III - Eligibility Information)
- Four-year funding period (FY 2012 -- FY 2016)
- U54 - Cooperative agreements

Key Dates: HG 10-015

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Research Plan (30-page limit)

- Description of relevant past experience and current capacity;
 - Acquisition of human samples;
 - Production of next-generation sequence data and subsequent identification of genetic variants of interest;
 - Public release of genomic data;
 - Development and dissemination of community resource data or tools;
 - Management of scientific collaborations;
- Proposed research objectives and plans to fulfill them.

Research Objectives

- Sample availability, acquisition and prioritization
- Genome sequencing and identification of genetic variants
- Public sample list
- Center management
- Data release
- Dissemination of genomic “know-how”
- Scientific collaborations

Research Objectives

- Sample availability, acquisition and prioritization
 - Samples for at least the first six months of operation;
 - Milestones for sample acquisition and allocation plan for the funding period;
 - Samples should be properly consented for data release into a public “controlled access” repository.

Research Objectives

- Genome sequencing and identification of genetic variants
 - Milestones (number and types of disorders)
 - Cost reduction: per exome and range of costs per disorder
 - Throughput improvement
 - Technology, tool, and method improvement for data generation and analyses
 - Contingency plans
- Described in relation to the main features of the current state-of-the-art.

Research Objectives

- Genome sequencing and identification of genetic variants
 - Applications are not limited to the whole exome sequencing approach;
 - Proposals for alternative strategies should provide justifications;
 - The most competitive applications will be those that can demonstrate the highest potential to meet the research objectives with the available funds.

Research Objectives

- Public Sample List - point of coordination for genetic variant discovery efforts that will be carried out by many groups
 - Information that the sample list will be annotated with;
 - Functions (downloadability, e.g.) that will be built into the sample list;
 - How the list will be maintained;
 - Plan to publicize the sample list.

Research Objectives

- Center organization and management plan
 - Organization and reporting structure
 - Recruitment and training of personnel
 - Plans for inter-center coordination

Research Objectives

Data release (Appendix)

- In general, the NHGRI expects that the sequence and genetic variant data generated by the Centers will be released into a public “controlled access” repository.
- The plan for releasing genomic data should be described in the Appendix section.

Research Objectives

- Dissemination of genomic “know-how”
 - Study design
 - Sequencing strategy
 - Pipeline management
 - Quality control
 - Data analyses and variant identification
 - Tractability of Mendelian disorders to state-of-the-art genomic approaches
 - Standard practice in data release
- Managing scientific collaborations

Funding Criteria

- Scientific and technical merit of the proposed project as reflected in Impact Scores;
- Availability of funds;
- Program priorities;
- The likelihood that the proposed effort will contribute to and accelerate the discovery of the genetic basis of Mendelian disorders in human;
- The quality of the plan to share research data and materials with the research community.

Clinical Sequencing Exploratory Research (U01)

<http://grants.nih.gov/grants/guide/rfa-files/RFA-HG-10-017.html>

Receipt Date - March 3, 2011

RFA Objectives

- Research the challenges and solutions to applying comprehensive genomic sequence data to the care of patients:
 - generation and application of genomic sequence data in the clinical workflow,
 - interpretation and translation of the data for the physician,
 - communication to the patient.
- Examine the ethical and psychosocial implications of bringing broad genomic data into the clinic.
- Variant discovery is secondary to these primary aims.

Research Plan

- Three highly integrated research projects:
 1. Clinical Study
 2. Sequence analysis and interpretation
 3. Ethical and psychosocial implications
- And Management Core

Research Plan: Project 1 - Clinical Study and Rationale (12 page limit)

- Medical objectives
- Dissemination of sequence findings
 - description of measurable outcomes relevant to the integration of sequence information in clinical care,
 - discussion of how potentially actionable research findings will be identified and replicated in a laboratory certified under CLIA,
 - description of the human subjects research protections that will be employed.

Research Plan: Project 2 – Analysis and Interpretation of Sequence Data (12 page limit)

- Plan for sequence generation
- Sequence analysis
- Interpretation and transmission to clinician

Research Plan: Project 3 – Ethical and Psychosocial Implications (12 page limit)

- Description of specific empirical research relating to the return of results to patients
- Description of methodologies

Management Core

(6 page limit)

- Description of the integration of and interdependent associations between Projects 1, 2, and 3,
- Description of management structure, leadership roles, and mechanisms of communication; note that the senior investigator for each project is required to devote at least 1.2 person months of effort to this project,
- Description of institutional human subjects protections oversight, and
- Specific Aims for the overall project.

Grant Information

- U01 - Cooperative agreements
- Four-year funding period (2012-2016)
- A budget of \$1.5M per year in direct costs
- Information on eligibility
 - Foreign institutions may apply
 - Multiple applications from an institution are allowed

Informed Consent and Data Sharing

- Given the significant ethical complexities involved in generating large amounts of genomic sequence data relating to identified patients, in deciding which individual findings to offer to communicate to patients, and in deciding when and how to communicate such findings, it is expected that all patients recruited for these studies—even those who have previously provided consent to participate in genomic research--will need to provide a new informed consent for participation. Plans for consent or reconsent will be reviewed.

Informed Consent and Data Sharing

- Genomic data may become part of a patient's medical record and may, therefore, be considered for exemption from NHGRI's long-standing rapid data release principles.
- However, sequence and phenotype data resulting from this research may have value beyond that intended by the submitting investigators. Therefore, submission of data sets to dbGaP, while not required before publication, is encouraged, and should be released at the time of publication, within the rules and regulations of the controlling IRB and local jurisdiction and with informed consent to permit broad data release via an NIH database.

Two ELSI RFAs:

RFA-HG-11-003 (R01)

RFA-HG-11-004 (R21)

Jean E. McEwen, J.D., Ph.D.

Applicant Information Session

January 28, 2011

RFA-HG-11-003

Development of a Preliminary
Evidence Base to Inform Decision-
making about Returning Research
Results to Participants in Genomic
Studies

RFA-HG-10-003

RFA-HG-10-004

Purpose

To stimulate *empirical research* to inform decision-making about whether, when, and how to offer to return individual research results to participants in genomic research studies or to those who have provided samples or data for genomic repositories

Aimed primarily at investigators who propose *behavioral or social science research* involving *direct interaction* with research participants or others in current, ongoing genomics projects (*esp. whole exome or whole genome sequencing projects*)

RFA-HG-10-003

RFA-HG-10-004

RFA-HG-11-004

**Ethical, Legal, and Social Implications
of Returning Research Results to
Genomic Research Participants**

RFA-HG-10-003

RFA-HG-10-004

Purpose

To stimulate *analytical research* on the *normative and legal issues* involved in deciding whether, when, and how to offer to return individual research results to participants in genomic research studies or to those who have provided samples or data for genomic repositories

Aimed primarily at *sole investigators or small teams of investigators* who propose modest *legal and normative* research projects

RFA-HG-10-003

RFA-HG-10-004

Budget Caps and Project Periods

- R01
 - Up to \$500,000/year (direct costs)
 - Up to 3 years
 - Do NOT feel compelled to come in for the maximum budget!
- R21
 - Up to \$275,000 (direct costs) over 2-year period
 - No more than \$200,000 (direct costs) in any single year
 - Do NOT feel compelled to come in for the maximum budget!

RFA-HG-10-003

RFA-HG-10-004

Available Funds

- R01
 - Approx \$2 million/year
 - Hope to made 3-4 awards
- R21
 - Approx \$750,000/year
 - Hope to make 3-5 awards
- NCI, NIDCD also participating
- *May* be able to secure additional funding from other interested institutes

RFA-HG-10-003

RFA-HG-10-004

Consortium

- Goals
 - Address common issues
 - Explore opportunities for synergy among studies
 - Identify areas of possible consensus that can form basis for policy recommendations
- Will also include ELSI investigators funded under RFA-HG-10-017 (U01) and under standing ELSI program announcements
- Need to include funds for approx 1x/year travel to consortium meetings in budgets

RFA-HG-10-003

RFA-HG-10-004

Letters of Intent

- Deadline: February 10, 2011
- Not required, but greatly appreciated (helps in planning)
- Please send LOI even if you have already contacted us

RFA-HG-10-003

RFA-HG-10-004

Review of Applications

- Applications for both R01s and R21s reviewed by a Special Emphasis Panel (convened especially for these RFAs)
- Standard review criteria apply (as listed in RFAs)
- Description of human subjects protections especially important (especially for R01s that include plans for actual return of results)

RFA-HG-10-003

RFA-HG-10-004

Timelines for Submission, Review, and Funding

- Applications for R01s and R21 due March 10, 2011
- Review in Summer 2011
- Council review in September 2011
- Awards made by September 2011

RFA-HG-10-003

RFA-HG-10-004

For additional information:

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RFA-HG-10-003

RFA-HG-10-004

