Frequently Asked Questions – Human Genome Reference Program (HGRP)

Funding Announcements
- RFA-HG-19-002: High Quality Human Reference Genomes (HQRG)
- RFA-HG-19-003: Research and Development for Genome Reference Representations (GRR)
- RFA-HG-19-004: Human Genome Reference Center (HGRC)
- NOT-HG-19-011: Emphasizing Opportunity for Developing Comprehensive Human Genome Sequencing Methodologies

Concept Clearance Slides
https://www.genome.gov/pages/about/nachgr/september2018agendadocuments/sept2018council_hg_reference_program.pdf.
Note that this presentation includes a Concept for a fifth HGRP component seeking development of informatics tools for the pan-genome.

Eligibility Questions
1. **Are for-profit entities eligible to apply?**
   a. Only higher education institutes, governments, and non-profits are eligible to apply for the HGRC (RFA-HG-19-004).
   b. For-profit entities are eligible to apply for HQRG and GRR (RFA-HG-19-002 and 003), and for the Notice for Comprehensive Human Genome Sequencing Methodologies (NOT-HG-19-011). The Notice also allows SBIR applications.
2. **Can foreign institutions apply or receive subcontracts?**
   a. Foreign institutions are eligible to apply to the HQRG and GRR announcements, and Developing Comprehensive Sequencing Methodologies Notice.
   b. Foreign institutions, including non-domestic (U.S.) components of U.S. organizations, are not eligible for HGRC. However, the FOA does allow foreign components.
   c. For more information, please see the NIH Grants Policy Statement.
3. **Will applications with multiple sites be considered?**
   Yes, applications with multiple sites, providing they are eligible institutions, will be considered.

Application Questions
1. **How much funding is available for this program?**
   NHGRI has set aside ~$10M total costs per year for the Human Genome Reference Program. NHGRI expects to award one Human Genome Reference Center for $2.5M/year, total costs, for five years; one High Quality Reference Genomes for $3.5M/year, total costs, for five years; 2-4 awards for R&D for Reference Representations at $1.25M/year (total costs for all awards combined); and 2-4 awards for the Notice for Comprehensive Human Genome Sequencing Methodologies at $1.5M/year (total costs for all awards combined). Please note that applications responsive to the Notice would also likely be responsive to the general NHGRI Technology Development Notices; therefore, total funding of this component could exceed $1.5M per year if sufficient meritorious applications are submitted.
2. **What are the allowed direct and indirect costs?**
   Please see the NIH Grants Policy Statement and applicable cost principles found in 2 CFR Part 200.

3. **What are the submission deadlines?**
   a. The Human Genome Reference Center; High Quality Human Reference Genomes; and R&D for Genome Reference Representations are all due by April 2, 2019 by 5PM local time
   b. Comprehensive Human Genome Sequencing Methodologies (a NIH Guide Notice pertaining to the Novel Nucleic Acid Sequencing Technology Development R01/R21/R43/R44) will be due on June 27, 2019, by 5PM local time
4. **How will these applications be reviewed?**
   a. NHGRI will convene a special emphasis review panel for joint review of the HGRC and HQRG applications.
   b. The Genome Reference Representations applications will go to an NHGRI special emphasis panel.
   c. The R&D for Comprehensive Sequencing applications will go to a separate NHGRI special emphasis panel.
5. **When will the program begin?**
   NHGRI plans to fund the HGR and HQRG at the end of fiscal year 2019. The remaining components are planned to be funded in FY2020 and onward.
6. **Are other NIH institutes co-funding the program?**
   The Office of Research on Women's Health (ORWH) has indicated its potential interest in supporting the Human Genome Reference Center. See NOT-OD-19-068.

Scientific Questions
1. **How will this program relate to the existing Genome Reference Consortium (GRC)?**
   The HGRP represents NHGRI's continued investment in developing and maintaining human reference genome resources. NHGRI provided past and ongoing support for activities currently undertaken by the GRC, including high quality human genome assemblies, resolution of error reports, development of new reference "builds", and outreach. At the same time, complementary GRC activities have been and will continue to be supported by other entities, including NCBI and EBI. NHGRI's support largely ended in FY18; this new program is intended to re-focus and increase funding for NHGRI's portion of efforts in this area, in consideration of better technologies for genome references and an expanding and more diverse (expertise, basic vs clinical, etc.) user base. NHGRI expects that the new HGRP program will build upon the existing work of the Genome Reference Consortium and continue to work closely with GRC participants and stakeholders.
2. **How will this program interact with National Center for Biotechnology Information (NCBI) and the European Bioinformatics Institute (EBI)?**
   In previous iterations of NHGRI support for the human reference, the Wellcome Trust partnered with NHGRI and funded EBI and the Sanger Center for work on the reference as part of the Genome Reference Consortium. NCBI currently supports the data management associated with the GRC curation effort for all users: https://www.ncbi.nlm.nih.gov/grc; EBI contributes to GRC computational analyses. NHGRI expects that HGRP grantees will collaborate with other funders and resources that have a direct role in genome references, especially NCBI, EBI, and the Wellcome Trust. This will be an essential component of their work.
3. **Will this program build/improve GRCh38 or will it design a new reference build, i.e.,"GRCh39"?**

This program intends to improve the current reference by adding additional high-quality genomes and reference representations that are easier for users to understand and navigate. Applicants should propose the appropriate scope for the project, given the budget and timing of the award. As noted in the RFA for the HGRC: Plans should account for the near-term needs to serve the reference in its current assembly model (e.g. GRCh38), as well as a transition to improved representations that may adopt new models.

4. **Will GRR applications be considered if they do not propose graph-based assemblies?**

Yes, this FOA is open to other approaches, provided the applications otherwise address key FOA points, for example proposing reference formats that address the need to represent human haplotype variation, support scalable analyses, and be consistent with open science. As always, scientific choices should be well-justified in the application.

5. **How will the HGRP do annotation?**

Annotation is not stated as an explicit component in either the HGRQ or the HGRC FOAs. If applicants believe annotation is critical for reference quality, and/or representation, presentation or use of the reference or for other reasons directly related to the stated goals of these FOAs, then it may be included and justified in the application. In general, applicants may include, with justification, any other activity that they believe is critical for attaining the major FOA goals. Applicants should however be cautious about including activities that are not directly related to the major FOA goals, even if they would advance genomic science in general.

6. **How are the products of the HGRP intended to benefit the clinical and basic research community?**

The HGRP is intended to provide products for both the basic research and clinical communities. We anticipate that applications (and the program, once established) will consider these communities in making decisions about e.g., priorities for adding new genomes, or developing representations of the reference. The HGRC is expected to have an outreach/education component that considers the range of reference users.

7. **Will this program fund new sample collection? Should HQGR applicants propose samples from additional sample populations to sequence in their applications?**

Yes, the HGRP will fund new sample collection if needed through the HQRG grants. HQRG applicants should propose a plan for any new samples that may be needed. Once the program is funded, we expect that the consortium will continue the discussion about prioritizing additional samples that have the most value.

8. **Will the HGRP support non-human references?**

The new program will support only human references in the HGRP, but applicants should be aware that the larger GRC effort has also supported references for other organisms.

9. **How will the various components interact in the HGRP?**
   a. Once awards are made, NHGRI will manage the program as a consortium. It is highly likely that awardees will be convened to help establish the details of how the consortium will operate, beyond what is already stated in the FOA Terms and Conditions.
   b. We expect that grantees for the HGRC, HQGR and GRR components will interact closely on several aspects of the program, for example for prioritizing new samples, for resolving reference errors or ambiguities, for establishing quality metrics, for transitioning to graph representations or new reference "builds", and others. Applicants

are encouraged to identify key areas of interaction for their proposed activities that will be important for attaining program goals.

    c. The technology development grantees will be expected to attend consortium meetings and some teleconferences, although they will likely operate more independently than the HGRC, HQGR, and GRR grantees.

10. **How will this program interact with other communities and organizations (i.e., GA4GH, Genomes in a Bottle)?**

NHGRI expects that the HGRP will communicate with these groups that set standards in genomics and consider their feedback when developing the new reference and making it accessible for all users.

11. **How will this program interact with existing databases/resources (i.e. ClinVar, EGA, Human Genome Structural Variation Consortium, gnomAD, Bravo, etc.)**

NHGRI believes that that the human reference will be more broadly useful if it can be integrated with, or is part of an effective ecosystem with, other existing databases and resources that present human variation information in different contexts. Applicants are expected to work with these existing databases and resources to foster maximum reference utility. The HGRC will likely need to consider how to effectively interact with these other resources, e.g., to establish communications, and to consider boundaries and synergies. HGRC applicants may wish to identify some of these potential interactions where they will benefit the community the most.

12. **Where will the sequence data, assemblies, tools, etc. be shared and deposited?**

NHGRI expects that the high quality sequence data and assemblies will be deposited in AnVIL. Other program products will be made available in AnVIL, though NCBI, or through other platforms that are open and accessible. Applications should include information about how their products will be made available.

13. **Is a data sharing plan required?**

A Genomic Data Sharing Plan is required for all applications that will produce genomic data (sequence, variants, assemblies, etc.). For more information, please see the NIH Genomic Data Sharing Policy.

14. **What should be included in the HGRC outreach and dissemination plan?**

For more information, please see "Project 2: Community Outreach" in the HGRC FOA.

NHGRI Staff Contacts

- For questions related to the High Quality Human Reference Genomes (HQRG) and Human Genome Reference Center (HGRC), please contact Adam Felsenfeld.
- For questions related to the Research and Development for Genome Reference Representations (GRR), please contact Heidi Sofia.
- For questions related to the R&D for Comprehensive Genome Sequencing, please contact Michael Smith.
- For questions related to financial and administrative aspects of all FOAs, please contact Deanna Ingersoll.