Considerations in applying for the CCGO 1000exome project. These considerations are likely to evolve over time, so please watch the CCGO web site periodically for changes – we will highlight on the page the revision date for changes in this document so you can see that readily. If anything in this document contradicts what is on the powerpoint from the CCGO town hall meeting April 28, you should go with what is in this document.

Application considerations:

A. Participants:
    a. Disorder to be studied: The group of 50-300 samples should comprise a scientifically justifiable, coherent grouping. If they a single unitary and specific clinical entity, such as Chronic granulomatous disease, that is straightforward, and you should describe the precise definition of the disorder that you will use for eligibility. It may also be acceptable for the cohort to comprise a somewhat heterogeneous grouping of patients. Three examples of this might be non-syndromic deafness, or syndromic coloboma, or bone marrow failure syndrome patients negative for mutations in genes x,y, & z. You will need to scientifically justify this grouping and deal with the issue that the more heterogeneous the grouping, the more challenging it may be to identify pathogenic variants.
    b. NIHCC. We will strongly prioritize projects that design into the study phenotyping that makes use of the NIHCC. For example, a proposal to sequence a set of patients who have undergone functional MRI imaging in the NIHCC and have a particular imaging attribute. We also encourage applications to sequence patients who will be brought in for phenotyping as a part of this study. For example, an existing cohort of patients with a retinal disease that you wanted to bring back to the Clinical Center to phenotype for hearing and consent for the CCGO program at that time would be a higher priority than a cohort that didn't take advantage of other NIHCC resources.
    c. Samples: Given our objective to develop CLIA-compliant sample tracking, we will prioritize projects that use samples that are prospectively collected, peripheral blood from the NIHCC phlebotomy service to identify germline (non-mosaic) alterations. We will process these samples to isolate DNA and perform the phenol-chloroform extraction required by NISC. Any exceptions to this sampling approach should be discussed with Drs. Biesecker or Manolio prior to submission. Note that CCGO would readily

consider a project where participants were brought in to the NIHCC and underwent CLIA-compliant blood sampling and some other type of sampling (e.g., tumor biopsy), where CCGO processed the blood sample through its routine sequencing pipeline and the PI isolated DNA from the tumor and submitted that to NISC for research sequencing at their expense. Such projects should be discussed with Drs. Biesecker or Manolio, and Dr. Mullikin prior to submission.

B. Return of results

a. Primary findings. We will prioritize projects where the investigator is committed to the return of individual positive test results that meet standards for analytic and clinical validity. This aspect of the study must be reviewed and approved by the PI's IRB. We will provide suggested language for your protocol and consent. We recognize that a minority of participants may receive a result and for some projects, it may not be appropriate to return primary results (if this is anticipated to be the case, an explanation of this in the application would be helpful). Because of complex issues relating to recent policy changes at the FDA, it will be necessary for the investigator to seek CLIA validation of their primary variants beyond that of the CLIA exome. This can be done by CLIA validation in house or through clinical service laboratories. We will provide help in obtaining necessary clearances through the FDA.

b. Secondary findings. Developing infrastructure to do comprehensive clinical genomics in the NIHCC is a long-term goal of this program. We are starting small by performing secondary findings analysis (incidental findings) routinely on CCGO exomes. This will likely involve routine analysis of variants in a limited gene panel (most likely the ACMG list, see PMID 23788249) with generation of a clinical report that will be entered into CRIS. Participants with positive findings will be offered medical and genetic counseling for positive findings through the NHGRI genetics consult service. We will develop a mechanism for individual patients to opt out of this mechanism after Clinical Center ethics consultation; please note that we expect the proportion of opt-out participants to be less than 5%. It is important for the success of this program that this aspect be carried out for the great majority of the patients. To that end, researchers should only submit a CCGO application if they are supportive of this objective. This aspect of the study must also be reviewed and approved

by the PI's IRB. We will provide suggested language for your protocol and consent. As discussed at the town hall, we have no intent to appropriate your research participants into NHGRI studies. At the same time, it is essential that we learn how to do secondary findings analysis rigorously and we need to build the capability to address emerging issues, which includes the FDA IDE consideration (see below). To that end, we will need to administer brief surveys of the participants once or twice regarding secondary findings and we may also survey you on how having this analysis done has affected your research program – positively or negatively. If you are interested in participating actively (not just as sample contributors) in this research we would welcome your collaboration. .

C. Data sharing
    a. The IRP is developing a genomic data sharing plan. This plan is not yet finalized, but is very likely to include a requirement that the exome data and relevant associated phenotypic data are deposited into dbGaP and that the NIH IRP-wide rules for data sharing are followed. The PI will need to include in their application a description of the clinical data fields that will be submitted with the data deposition to dbGaP and the timeline for submission. This aspect of the study must also be reviewed and approved by the PI's IRB. We will provide suggested language for your protocol and consent.

D. IRB review
    a. PIs will be required to submit to the CCGO committee the IRB protocol and consent following review and approval by their IRB for the research relating to the primary research objective. As noted above, we will provide suggested language for your protocol and consent. Drs. Biesecker, Manolio, Hull, and Mr. Berkman are available to you for advice regarding this process. It is essential that the protocol and consent directly address the genomic research primary objectives, the return of results, the data sharing, and the FDA issues (see below).
    b. The FDA is seeking increased engagement in research studies that use genomic sequencing technology that have any significant effect on patient care or medical decision-making. This is being implemented through the FDA's authority to regulate medical devices used in research, and it considers the sequencing pipeline to be a medical device. Therefore,

investigators and their IRBs will need to address this issue by having in place either an IDE (investigational device exemption) or a waiver of the requirement for an IDE approved by their IRB. We are proposing a two-pronged approach.

i. For the primary findings, we anticipate that it is very likely that the FDA will grant a waiver of the IDE requirement if the PI agrees that any primary results returned to the participant will validated by Sanger in a CLIA environment. Investigators may do this by setting up a CLIA laboratory in their group, by having a CLIA lab on the NIH campus do this for them, or by paying a clinical testing lab to do the CLIA confirmation of the variant they wish to return. We will provide the PI with suggested language for their protocol to help the IRB to determine that a waiver of the IDE is appropriate.

ii. For the secondary findings analysis, we propose to initially perform Sanger validation but transition as rapidly as possible to a clinical research protocol with an IDE. To this end, the PI will need to agree to have all participants in CCGO sign a consent form for the secondary findings analysis. If the consent is not signed, the sample may not be sequenced by CCGO and the DNA may be returned to the investigator for research sequencing.

E. The completed application should be emailed to Dr. Biesecker by the deadline. Please ask in that email for a confirmation of receipt of the application.

F. Timelines

a. Round 1 application deadline: Midnight, Friday, June 20, 2014
b. Announcement of decisions for selected proposals: Wednesday, July 16, 2014
c. Samples accepted beginning Tuesday, Sept. 2, 2014
d. First progress report due Monday, March 2, 2015