Secondary Genomic Findings Consultation Service (SGFS)

Introduction

Human exome sequencing and genome sequencing (ES/GS) are powerful research tools that can generate secondary findings beyond the scope of the research. Most secondary ES/GS findings are of low importance, but some (currently estimated at 1-3% of individuals) confer an elevated risk of a serious disease that could be reduced by timely medical intervention. These have been termed actionable secondary findings. The impact and scope of impact of secondary findings in genome and exome sequencing is likely to increase in the future. There is considerable agreement that high impact findings should be returned to research participants, but many researchers performing genomic research studies do not have the background, skills, or resources to identify, verify, interpret, and return such variants. Here we outline a resource for intramural investigators, the NIH IRP Secondary Genomic Findings Service (SGFS). This service would support researchers by enabling the analysis, validation and return of clinically actionable sequencing results to research participants in a standardized manner. This document describes a proposed structure for this service so that Principal Investigators (PIs) and Institutional Review Boards (IRBs) can consider adoption of this approach for research protocols that include germline ES/GS. Groups interested in the SGFS should note that as the SGFS is an evolving service, changes may be made to some of the procedures outlined here. As well the SGFS website, which aims to be a helpful resource to investigators interested in this service, is currently under development. Investigators are welcome to apply to this service and will be updated as additional information, such as training documents and videos, become available.

Brief Background and Rationale

This section briefly summarizes the background and rationale for this program. Readers who wish to review more detailed descriptions of the background and rationale may refer to the report issued by the NIH Intramural Secondary Findings Working Group (Appendix 1) the preprint describing this approach to secondary genomic findings that has been published in the *American Journal of Human Genetics* [Darnell et al., 2016], and the original recommendations regarding secondary findings from the American College of Medical Genetics. [Kalia et al., 2017; Green et al., 2013]

ES/GS has the potential to identify variants that can be considered to be secondary findings (previously referred to as incidental findings). The implications of secondary genomic findings from clinical ES/GS have been extensively debated and current practice has settled on an approach that includes pretest counseling to inform about the potential to identify secondary findings with an opt out provision for patients who desire not to receive such findings. The potential for research ES/GS

sequencing is less settled. For the purposes of this program, research ES/GS sequencing is defined as germline sequencing that is not performed in a CLIA-certified testing environment and was done with the primary purpose of addressing a biomedical research question under an IRB-approved research protocol. There is wide variation in practice in the research community regarding secondary genomic findings, which leaves institutions, IRBs, and PIs unclear about their obligations to their research participants.

A working group of NIH intramural scientists assembled to address this challenge. This group reviewed current practices regarding secondary ES/GS findings and determined that at least some secondary genomic findings should be returned. The working group enumerated considerations that IRBs may take into account when reviewing ES/GS research studies and the decision whether to return secondary genomic findings, how this activity should be supported within the NIH Intramural Research program (IRP), and how this information should be disclosed. The working group recognized that it was critical for the IRP to support this activity by providing a service that would screen research ES/GS data for potential secondary variants, validate such variants in a CLIA testing environment, and provide medical and genetic counseling to research participants who are found to harbor such variants.

Currently, there is a disconnect between what both researchers and research participants say they prefer with respect to secondary genomic findings and what is actually occurring, which is reflected in survey data of relevant stakeholders. According to one study, only 28% of researchers report they are either already returning a subset of secondary genomic findings or plan to do so in the future. In contrast to this small fraction of researchers who actually are returning results or planning to do so, 95% of researchers agreed that secondary genomic findings should be returned to participants. [Klitzman et al., 2013] A wide range of genetic professionals hold the view that returning some secondary genomic findings from some types of studies is appropriate.[Fernandez et al., 2013; Lemke et al., 2013; Yu et al., 2014] IRBs are beginning to recognize that such results should be returned.[Gliwa et al., 2015] Furthermore, a substantial majority of research participants also consistently express a strong interest in receiving at least a subset of secondary genomic findings.[Bollinger et al., 2012; Daack-Hirsch et al., 2013; Haga et al., 2012] These data show a gap between researchers' desires and preferences to return secondary genomic findings and their current practice, and that participants generally expect the return of secondary genomic findings. We anticipate that creating the capability to validate and return secondary genomic findings will alleviate a major concern about responsibly informing research participants about them, and in turn shift the decision-making process toward favoring this approach. To address these gaps in capability, we propose a novel mechanism that will allow researchers to fulfill their expressed preference to return such results and to meet the expectations of participants to receive secondary genomic findings.

Initial design and implementation for the NIH IRP Secondary Genomic Findings Service (SGFS)

- The SGFS will be managed and operated by NHGRI with an advisory committee that will be comprised of up to one member from each institute that has an IRP.
- NHGRI will support the SGFS to accept and manage up to 2,000 ES/GS sequence files per year total on a first come, first served basis, with a limit of 250 per year from any one study. There will be no cost to the researchers until the service exceeds the 2,000 analyses per year. Requests above this ceiling will be addressed on a case-by-case basis and will likely necessitate support from the requesting institutes.
- The SGFS will develop, curate, and update a list of genes for which they would provide interpretation and return of variants therein. This list will initially be based on the genes and variant types specified by the ACMG clinical ES/GS secondary findings report.[Green et al., 2013] This list will be re-evaluated and updated at least annually by the SGFS with notification of any changes in the list to currently participating PIs and all IRP IRBs.
- Samples analyzed with prior versions of the gene list will not be re-analyzed for the newer lists.
- The SGFS will not analyze nor CLIA confirm any variants in any genes not on the secondary findings list (i.e., neither primary nor secondary variants). Participants or PIs may not choose to have subsets of the gene list analysis performed.
- PIs and IRBs are encouraged to submit requests for expanding or contracting the SGFS gene list to the SGFS, which will be considered during the periodic gene list re-evaluation.
- Eligibility is limited to research protocols with PIs from the IRP that are reviewed and approved by one of the IRP IRBs.
- Requests for SGFS support of a protocol should be made by the PI to the SGFS, using the attached application found on the SGFS website (SGFS Application). The PI should consult with her/his IRB throughout the process. The SGFS staff offers guidance and support for investigators seeking to obtain approval from their IRBs for the process engaging the SGFS, through written materials and the web site.
- The protocol and informed consent documents should include an adequate description of the SGFS process and the potential for follow-up contact (see below). In Appendix 3 we provide suggested language for protocols and consent forms, but this specific language is not required or mandated. PIs and IRB members should familiarize themselves with the recommended language so that they can make a determination that the language used in the approved protocol and consent form adequately addresses all of the issues addressed in the recommended language. PIs and IRBs may modify the language in these documents as they see fit, but the SGFS reserves the option to decline participation of a project if the SGFS (in

consultation with the advisory committee) concludes that the protocol or consent form are insufficient or contradictory to the goals and objectives of the program.

- The PI is responsible for providing staff who are adequately trained to perform the informed consent for secondary findings. These staff should be familiar with issues surrounding secondary findings, the range of disorders currently included in the SGFS analysis, and be able to answer participant questions. Training documents regarding consent for return of secondary variants may be accessed via the SGFS website. The SGFS team is available to address any questions that remain.
- The PI and IRB will jointly provide to the SGFS written assurance that the IRB review and consent process adequately informs research participants that a secondary findings analysis will be performed, that the participant may be contacted by a member of the SGFS team for sampling and other follow-up, and that the participants are also consented for requests for follow-up regarding the effectiveness and utility of the SGFS program. The PI and IRB should review the considerations in Darnell, et al, 2016 regarding considerations for the return of secondary findings.
- The relevant text from the IRB protocol and consent form should be provided to the SGFS prior to final IRB approval.
- The PI and IRB may determine that secondary findings analysis will be routine, in which case participants who do not wish to potentially receive secondary findings should not be enrolled in that study. The PI, with the concurrence of the IRB, may include an opt-out provision in their protocol and consent process (e.g., complete opt out) for secondary findings analysis for individual research participants. PIs and IRBs should be aware that this opt-out provision incurs an obligation to adequately inform individuals of the results they may be foregoing for themselves and potentially for their relatives. IRBs should consider mechanisms to document understanding of this process. This issue is discussed in more detail in the attached documents. ES/GS data from participants who do opt out should not be submitted to the SGFS.
- The SGFS will accept ES/GS data files from the research team and screen these data for potential secondary variants. These data files should be limited to those generated by standard exome or genome sequencing methodologies from genomic DNA from non-malignant tissues. If a participant has had ES/GS sequencing performed on both malignant and non-malignant tissue DNA, then only the latter should be submitted to the SGFS for analysis. Data from transcriptome sequencing, SNP chip, ChIP-seq, or other types of genomic analysis should not be submitted.
- The SGFS is currently working with our NHGRI Bioinformatics Core to develop methods for data transfer and will keep SGFS applicants updated on this process as it evolves.
- The formatting and other attributes of the ES/GS data files and the source of the sequence data will be specified in the application and negotiated with the SGFS as part of the

application process. The SGFS may require that the sequencing laboratory or PI reformat the data; VarSifter and VCF files are currently the only file formats supported by the SGFS. The files must include a widely recognized genotype quality metric for every variant. The PI may submit a file that is limited to variants within regions of the genome known to potentially harbor secondary findings (based on a BED file with GRCh37/hg19_2 coordinates provided by the SGFS) or a complete ES variant file. The service may not accept complete GS variant files, due to data storage limitations and GS files may need to be processed by the research team to limit variants to those relevant to the then-current SGFS gene list.

- Most samples will not have any variants that warrant reporting by the SGFS. The SGFS cannot return an individual clinical test report for participants with a negative result, because the ES/GS data are likely to be incomplete and CLIA testing to confirm the absence of findings cannot be performed. The SGFS will submit to the PI, at periodic intervals, a report that lists all of the participants whose research data files have undergone the secondary findings analysis process to date and an indication of which participants' results were positive for secondary findings. The PI is responsible for insuring that this list of participants who have undergone analysis is complete and correct (i.e., that all samples that were submitted by the PI were in fact analyzed). The communication to the participants regarding this process is nuanced and important for those (97-99% of participants) who do not have a secondary finding. The PI is responsible for a communication that conveys that the analysis has been completed and that, while no secondary findings were identified by the SGFS, this must not be misconstrued as any assurance that such findings are in fact absent, either in the analyzed genes or in other genes. This communication should also make clear that, if clinical testing for a secondary findings gene was currently indicated (or were to be indicated in the future), that the absence of a secondary finding from the research testing is no substitute for the indicated testing should not deter such testing. Specific training on how to address this issue can be found on the SGFS website.
- The SGFS will notify the PI if secondary variants are identified. The PI will provide the participant's name and contact information to the SGFS and the SGFS will begin the results return protocol outlined below:
    1. The PI (or designee) will enter a CRIS order for PCR/Sanger replication of a potential research finding for the participant. This CRIS order is currently in the process of development and SGFS applicants will be informed when it becomes available. The PI (or designee) is responsible for registering or activating any participants who are not currently as active NIHCC patients so that this CRIS order can be entered.

2. SGFS staff will contact the participant and inform them that there is a potential genetic finding that requires provision of a DNA sample for confirmation*.
3. SGFS staff will coordinate collection and shipment of the confirmatory sample, which will generally be a saliva sample collected in an Oragene collection kit. Please see the SGFS website for more information about what types of samples are acceptable for confirmation testing.
4. The SGFS will process the confirmatory sample in a CLIA-compliant environment to validate (or refute) the research finding.
5. The SGFS will generate a clinical test report and upload that report into CRIS.
6. The SGFS genetic counselor (Julie Sapp) will inform the research participant that a confirmation report is ready for the research secondary findings and provide medical and genetic counseling and referrals to appropriate care providers for further evaluation.
7. If the secondary finding is refuted by the confirmatory analysis, then a CLIA report will be issued that explains that the research data showed a variant that was not confirmed by clinical testing (e.g., was a false alarm) and the SGFS genetic counselor will communicate this to the participant.
8. The return of results will generally be done via telephone. If the research team prefers that these visits take place in person at the NIHCC, the research team is responsible for arranging and/or supporting the travel of the participant to the NIHCC at a time that is coordinated with the SGFS.

- The PI or his/her designate may elect for a health care professional other than the SGFS team to return the result to the participant and coordinate provision of the confirmatory sample.
- The PI agrees to support reasonable requests for follow-up surveys to evaluate the effectiveness and utility of the program. These requests may include provision of contact information for the participants, sending out requests for their participants to complete surveys or talk with a SGFS staff member about their experience with the process, their understanding of the results, what follow up evaluations were undertaken for the secondary finding, etc. Language to allow for informed consent for these follow up surveys must be included in the consent form and the protocol.

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* It is our experience that the wait between being informed that there is a potential secondary finding and having that finding confirmed with a second sample can provoke anxiety in research participants. To allay this anxiety, we strongly recommend that research teams inform their participants that they may be asked to provide confirmatory samples for any variety of reasons, not solely for the confirmation of potential secondary findings. See the SGFS Website for more information on this topic.

- Neither the SGFS nor the NIHCC agrees to provide further evaluation or ongoing care regarding the secondary finding. The PI may identify an appropriate research protocol that may choose to enroll the participant and provide such evaluation or care, but in general, it is expected that this care will be provided outside of the NIHCC.
- The SGFS will only provide CLIA-validated testing and counseling for secondary findings for individuals who have undergone research ES/GS and are enrolled in the SGFS-approved primary research protocol. Testing and counseling for other at-risk family members may be pursued by the family's outside health care team or the NIH PI through outside clinical testing laboratories at the expense of the PI or the family, as specified in the IRB-approved protocol.
- NHGRI may amend, modify, or limit the availability of this service as it evolves. The PI's whose studies are supported by this service are responsible for amending their protocols to reflect those changes.

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