

Appendix 3: Suggested protocol and consent language for SGFS

Suggested text for protocols and consent forms that will take advantage of the Secondary Genomic Findings Service:

It is a required component of the SGFS program that the protocol includes appropriate language for the evaluation and return of secondary findings and that the participants are available for follow-up surveys to assess the quality and utility of the program. This suggested text is offered to support protocols using the SGFS and serve as a starting point for the PI and their IRB. It is not a requirement of the SGFS program that the precise language suggested here is adopted, either in the protocol or in the consent form. However, the SGFS advisory committee may request changes or additions to the language, or decline a proposal if it determines that the language of the consent form and protocol are not consistent with the policies and objectives of the SGFS.

PROTOCOL LANGUAGE

Informed Consent

The PI or her/his clinical designee on the protocol will perform the informed consent for the exome sequencing, which includes consent for the secondary findings analysis process and follow-up evaluation thereof. NHGRI offers a number of training resources on their [website](#) with the option for in-person training sessions. NHGRI has offered to the PI suggested consent language.

Secondary (incidental) findings

Secondary (incidental) findings analysis will be performed by the NHGRI-NIHCC-SGFS team under its CLIA license. The exomes or genomes will be analyzed for a particular set of variants or genes that will be determined by the SGFS team. This gene or mutation list may change periodically and will be initially based on published recommendations for clinical sequencing (which currently includes 59 genes)[Kalia et al., 2017], but is expected to evolve over time. Although that list may evolve over time, we currently propose to perform this analysis once for a given exome/genome, for the then current set of recommended variants. However, we do not wish to exclude the possibility that these exomes may be evaluated for variants relevant to other incidental findings in the future. These variants will be filtered to exclude variants that meet quality and coverage criteria. Remaining variants will be evaluated by using general, and in some cases, locus-specific databases, primary literature, and other sources to make a clinical determination of the predicted pathogenicity of the variant(s). It is critical to recognize that this evaluation is deliberately designed to have a high positive predictive analytic validity (high likelihood that the variant is truly present in the participant and

is pathogenic) and poor sensitivity. This evaluation is also deliberately designed to have very high thresholds for pathogenicity (clinical validity) and therefore variants with less than very strong data supporting pathogenicity will not be reported. This tradeoff is intended to minimize false positive results of such findings, recognizing that the participants have a low likelihood of having the disease. These filtering criteria are modifications of published methods [Gonsalves et al., 2013; Johnston et al., 2012; Ng et al., 2013; Richards et al., 2015].

If some of the primary genes for the disease under study overlap with the secondary gene list, they will be considered as primary genes for the purpose of this project. In this case, the PI will be informed of the identification of the finding but the result may not be validated, pending agreement between the PI and the SGFS.

Validation and return of secondary results

The SGFS process will evaluate exomes/genomes for secondary findings for each submitted exome or genome file. The PI will submit to the SGFS periodic datasets comprising either full exome files or exome or genome variant files that encompass only the coding regions of the then current genes for which the SGFS provides analysis (e.g., the ACMG 59 gene list). These files will be configured per the specification of the NHGRI Bioinformatics Core and each file will include a coded individual identifier (no personally identifiable information) for which the PI retains the key.

If there is a secondary variant identified (current, 2014 estimated yield is that 2-3% of participants will have such a finding), the SGFS will contact the PI to inform them of the finding and the PI will provide the PII (Name and contact information) of the individual with the finding. The typical approach will be that the research participant will then be contacted by the SGFS team to inform them that a genetic finding that requires confirmation with a second sample has been found and that it is recommended that the participant submit a follow up sample (typically Oragene saliva DNA kit) to allow confirmation and clinical validation of this finding. The nature of the disease and the putatively mutated gene will not be disclosed in this call. In the experience of the SGFS staff, explicitly informing participants that a second sample is required to validate a secondary finding can provoke needless anxiety in participants as the finding may not validate. The SGFS instead recommends that participants are informed that they may be asked to supply a second sample for any variety of reasons, not solely to validate a potential secondary variant. The participant will be encouraged to register as a patient with the Clinical Center (if not already registered). The primary team will take the lead on this registration process and enter a CRIS order for "Secondary Genomic Finding Confirmation Testing" and the SGFS will send an Oragene collection kit to the participant. Upon return of the sample, the SGFS will perform CLIA-valid Sanger PCR testing for the variant and a clinical report will be generated that either confirms or refutes the research finding. If positive, the NHGRI

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consult attending and genetic counselor will review the variant, disclose the finding to the participant, provide medical and genetic counseling for that variant, and provide referrals for further evaluation and follow-up for the proband and recommendations for testing for his/her family members. These counseling sessions will generally be conducted by telephone. The clinical testing report will be uploaded into CRIS.

Individual negative secondary findings analysis reports will not be returned to the participant or PI, instead, the service will return to the PI a list of all exomes/genomes that were analyzed, and an indication of which (if any) were positive.

Opt out

The IRB and PI may determine that individual participants in the study can opt out of the SGFS evaluation. The informed consent process must clearly explain the nature of the disorders that would be screened and the possible consequences of declining such testing. For any individuals who opt out, their exome/genome files should not be submitted to the SGFS.

NIH SGFS SEQUENCING CONSENT ELEMENTS

What is involved in the study?

- In this study we will use a test that looks at all or most of your genes or DNA. This testing is done on a research basis and this means that we may ask you for a second sample to confirm any of our findings before sharing them with you.
- We are working with the genetics service to review your sequence data for unexpected gene changes that do not explain your [Condition(s)] but tell us other important information about your health. We expect to find these changes in 2-4% of people in the study.
- These changes are called unexpected because they are not related to [name of condition(s)] and not the primary reason for the study.
- The genetics service will look for changes in a limited set of genes unrelated to [Condition(s)] in everyone in the study. These gene changes can cause disorders such as rare forms of cancer or heart disease.
- The genetics service may also contact you to ask some questions about their evaluation for unexpected gene changes to help them better understand and improve that service.

What kind of results can I expect to get from this study?

- If we find an unexpected gene change that we believe to be medically useful, we will ask you to submit a follow up specimen to the genetics service to confirm it. The genetics service will contact you with these results. They will provide medical advice that will help you to initiate care with your healthcare providers. The NIH will not generally provide any further follow-up testing or care for this condition for you or your family.

What are the risks of participating in the study?

- The evaluation for unexpected gene changes is limited and is not a substitute for clinical genetic testing.
- If an unexpected gene change result is confirmed, that test result will go into your NIH medical record. These documents are considered confidential but other investigators can see them.
- The genetics service may return to you an unexpected gene change that turns out not to cause that disorder. This may cause you unnecessary distress or lead to unnecessary medical testing risks and costs.

Are there benefits to taking part in the study?

- An unexpected gene change result may be useful because you can do something about it to protect your health.

What if I change my mind about being in this study?

- You may choose to not submit a follow-up sample to confirm an unexpected gene change.
- You may choose not to meet with the genetics service to learn about an unexpected gene change.
- You may choose not to answer questions from the genetics service about their evaluation for unexpected gene changes.

REFERENCES

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