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Supplemental Data

Evaluation of Recipients of Positive and Negative Secondary Findings Evaluations in a Hybrid CLIA-Research Sequencing Pilot

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Table S3: Pathogenic or likely pathogenic variants not returned to participants as part of this sub-study either because they were monoallelic (*MUTYH*) or primary variants					
Variant Genomic Position GRCh37	**Gene Name & MIM**	**Variant cDNA**	**Predicted Protein Change**	**ACMG Scoring**	**Pathogenicity Assessment, Clinical Action**
chr1:g.45797228C>T	*MUTYH* 604933	NM_001128425.1:c.1187G>A	p.(Gly396Asp)	PS3, PS4, PM3, PP1, PP3, PP5	ACMG: Pathogenic Not Returned, monoallelic
chr1:g.45797230T>C	*MUTYH*	NM_001128425.1:c.1187-2A>G	p.?	PVS1, PM3, PS4_Supporting, PP5	ACMG: Pathogenic Not Returned, monoallelic
chr1:g.45798466C>T	*MUTYH*	NM_001128425.1:c.545G>A	p.(Arg182His)	PS3, PM3, PM5, PS4_Supporting, PM2_Supporting, PP3, PP5	ACMG: Pathogenic Not Returned, monoallelic
chr1:g.45798475T>C	*MUTYH*	NM_001128425.1:c.536A>G	p.(Tyr179Cys)	PS3, PS4, PM3, PP1, PP3, PP5	ACMG: Pathogenic Not Returned, monoallelic
chr7:g.6048649A>C	*PMS2* 600259	NM_000535.5:c.2T>G	p.(Met1?)	PVS1, PM2_Supporting, PP5	ACMG: Pathogenic Returned: Pathogenic Primary Finding
chr13:g.32953959_32953963del	*BRCA2* 600185	NM_000059.3:c.9026_9030del	p.(Tyr3009Serfs*7)	PVS1, PS4, PM2_Supporting, PP5	ACMG: Pathogenic Returned: Pathogenic Primary Finding
chr16:g.2138118G>A	*TSC2* 191092	NM_000548.3:c.5138G>A	p.(Arg1713His)	PS3_Moderate, PS4_Moderate PM2_Supporting, PP3, PP5	ACMG: Likely Pathogenic Returned: Likely Pathogenic Primary Finding
chr17:g.41276047_41276048del	*BRCA1* 113705	NM_007294.3:c.68_69del	p.(Glu23Valfs*17)	PVS1, PS4, PS3_Moderate, PP1, PP5	ACMG: Pathogenic Returned: Pathogenic Primary Finding
chr19:g.11200230del	*LDLR* 606945	NM_000527.4:c.6del	p.(Trp4Glyfs*202)	PVS1, PS4_Moderate, PM2	ACMG: Pathogenic Returned: Pathogenic Primary Finding

Table S3 (cont.): Pathogenic or likely pathogenic variants not returned to participants as part of this sub-study either because they were monoallelic (*MUTYH*) or primary variants

Variant Genomic Position GRCh37	Gene Name & MIM	Variant cDNA	Predicted Protein Change	ACMG Scoring	Pathogenicity Assessment, Clinical Action
chr19:g.11213445C>G	*LDLR*	NM_000527.4:c.296C>G	p.(Ser99*)	PVS1, PS4, PM2_Supporting	ACMG: Pathogenic Returned: Pathogenic Primary Finding
chr19:g.11216024T>C	*LDLR*	NM_000527.4:c.442T>C	p.(Cys148Arg)	PM2, PM5, PS4_Moderate, PP3	ACMG: Likely Pathogenic Returned: Upgraded, not included in results of study Primary Finding
chr19:g.11216096G>A	*LDLR*	NM_000527.4:c.514G>A	p.(Asp172Asn)	PS3_Moderate, PM5, PS4_Supporting, PM2_Supporting, PP5	ACMG: Likely Pathogenic Returned: Likely Pathogenic Primary Finding
chr19:g.11216171T>G	*LDLR*	NM_000527.2:c.589T>G	p.(Cys197Gly)	PM2, PM5, PS4_Supporting, PP3	ACMG: Likely Pathogenic Returned: Likely Pathogenic Primary Finding
chr19:g.11216236_11216238del	*LDLR*	NM_000527.4:c.655_657del	p.(Gly219del)	PS4, PS3_Moderate, PM4, PM2_Supporting, PP5	ACMG: Pathogenic Returned: Pathogenic Primary Finding
chr19:g.11218160G>A	*LDLR*	NM_000527.4:c.910G>A	p.(Asp304Asn)	PS3_Moderate, PM5, PS4_Supporting, PP3, PP5	ACMG: Likely Pathogenic Returned: Likely Pathogenic Primary Finding

[a.] ACMG refers to pathogenicity assessments per the ACMG/AMP criteria of Richards et al. The evidence codes are as specified in that manuscript, with the modification codes as per the ClinGen web site (https://www.clinicalgenome.org/working-groups/sequence-variant-interpretation/)

Table S4 – Selected quotations from interviewed/surveyed participants

Quotes from interviews[a] with recipients of secondary findings		
Participant Characteristics	**Quote**	**Code**
61-year-old female recipient of a secondary *BRCA2* result enrolled in an NIDCR study	*"It was totally a shock for me. One, not knowing how to communicate to my family, because we never knew -- I never knew we had that. And two, […] how do I cope with it now? That is the only downfall, I would say, that it is the surprise. We were not expecting anything. It was a total shock, a surprise. You know, it was not a pleasant surprise."*	Initial reactions
	"I think I'm more at ease now, and I […] really thank God for having to go through the other protocol that I was going [through] if it wasn't for that, I don't think I would have ever found out."	Feelings changing over time
61-year-old female recipient of a secondary *BRCA2* result enrolled in an NCI study	*"So, honestly all of this has been positive. I'm very glad that I did the study and that we found this [secondary finding] at the point where [the researchers] did find it. So, yes, it was a surprise, but it was okay I guess this is a good thing to know about."*	
61-year-old male recipient of a secondary *DSG2* result enrolled in an NICHD study	*"I think it's useful enough that I need to take action on it. […] bad things can happen to you and [you] go, "Oh my God, I didn't know that." But, in this case I have some warning that I do.* *[…] You never know when something like that's going to pop up and cause you a serious problem. Or it could even kill you, I guess. […] Well, it gives me a chance to do something about it."*	Reassured/grateful for knowledge

Example responses[b] from surveyed participants who received negative secondary findings reports			
Question text	**Participant Characteristics**	**Quote**	**Code**
"In what ways do you think learning a secondary finding may have been useful to you?"	22-year-old male recipient of a negative SF report enrolled in an NINDS study	*"I think it's very beneficial because at the end of the day I go to sleep knowing we are one step closer to a diagnosis."*	Better understanding of current/primary condition
	55-year-old female recipient of a negative SF report enrolled in an NIDCR study	*"…could have helped me understand where any pain, soreness, or lack of energy issues i have may have been coming from."*	

	70-year-old female recipient of a negative SF report enrolled in an NINDS study	*"Knowing how to manage or watch for particular signs or symptoms related to the findings"*	Seek follow-up care related to secondary finding
"If you had received a secondary finding, what would it have meant for your health and well-being?"	20-year-old female recipient of a negative SF report enrolled in an NIAMS study	*"If the second finding revealed that my lupus had gotten worse, I would seek out more help."*	Better understanding of current/primary condition
	41-year-old male recipient of a negative SF report enrolled in an NINDS study	*"…it means I can more properly and accurately deal with the issues I am having."*	
	25-year-old male recipient of a negative SF report enrolled in an NCI study	*"It would have meant that I would take precautions in my life to prevent it from developing if possible or make regular check ups to see if something develops from it."*	Seek followup care related to secondary finding
"How valuable do you believe this information may have been to you and your family?"	56-year-old male recipient of a negative SF report enrolled in in an NCI study	*"…this disease affects not just me, it affects the whole family support system. information gives us power and hope to proceed in the right direction."*	Valuable/useful
	64-year-old male recipient of a negative SF report enrolled in in an NCI study	*"Very valuable. If I can help my family live a healthier life it is definitely worth it."*	Valuable/useful

[a.] Quotes selected from various portions of interview

[b.] Question prompts from survey provided for each quote

Table S5: Protocol titles and NIH Institutes supported by CCGO

NIH Institute	Protocol title(s)
National Institute of Dental and Craniofacial Research (NIDCR)	Characterization of Diseases With Salivary Gland Involvement (NCT02327884)
Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)	Genetic Causes of Growth Disorders (NCT02311322)
National Heart, Lung, and Blood Institute (NHLBI)	Characterization of the Pathogenesis of Primary and Secondary Lymphatic Disorders (NCT02156115)
National Institute of Neurological Disorders and Stroke (NINDS)	Genetic and Physical Study of Childhood Nerve and Muscle Disorders (NCT01568658)
National Heart, Lung, and Blood Institute (NHLBI)	Genes Involved in Lipid Disorders (NCT02311335)
National Institute of Allergy and Infectious Diseases (NIAID)	NIAID Clinical Center Genomics Opportunity Protocol (NCT02417766)
National Eye Institute (NEI)	Whole Exome and Whole Genome Sequencing for Genotyping of Inherited and Congenital Eye Conditions (NCT02077894)
National Institute of Mental Health (NIMH)	Evaluation of the Genetics of Bipolar Disorder (NCT00001174)
National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)	Study of Systemic Lupus Erythematosus (NCT00001372) Natural History and Development of Spondyloarthritis (NCT01422694)
National Cancer Institute (NCI)	Collection of Serum and Tissue Samples From Patients With Biopsy-Proved or Suspected Malignant Disease (NCT00026884)
National Human Genome Research Institute (NHGRI)	Genetic, Brain Structure, and Environmental Effects on ADHD (NCT01721720)

S1. Cover letter sent with negative findings

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Social and Behavioral Research Branch
National Human Genome Research Institute
National Institutes of Health
31 Center Drive (31/B1B36) – MSC 2073
Bethesda, MD 20892-2030
(301) 443-0283

Date

Dear

As you know, you recently participated in a research study at the National Institutes of Health (NIH) whose goal was to learn the genetic cause of a health condition that affects you or a family member. This study uses extensive genetic testing technology that allows researchers to "read through" most of a person's genes. This technology is called "genome sequencing."

In addition to helping NIH investigators understand more about the genetics of a particular health condition, genome sequencing can tell us about other genetic differences that a person may have that are unrelated to the reason why they had the testing done. We call these differences "secondary variants." In the NIH study you participated in we routinely screen for secondary variants. If we identify one or more secondary variants that could be very important for a person's health we notify the participant.

We have about 20,000 genes and in this study we look carefully for secondary variants that could be important for a person's health in only 56 of them. The American College of Medical Genetics endorses these genes as medically actionable because we can interpret the risk to a person's health and we have experience in helping people manage the risk to reduce disease. Variants in these genes are rare (about 2-3%) so most people do not have one.

The attached report indicates that we **did not find** any highly significant secondary variants in in this limited set of genes. Stated another way, when looking at a very limited group of genes that, when altered, can cause significant and treatable health problems, we did not find any genetic variants that we think would be very important for you to know about. It is important to remember that genome sequencing technology is not perfect. Also, the attached report is relevant to only a very small fraction of your genes – it is very likely that there are other genetic variants present that are not covered by this report.

Through participation in this study, we would like to ask you to complete an online follow-up survey in three months. You will be contacted by the research team at that time with a web-link to complete the survey. Thank you very much for participating in our study.

Sincerely,

Name of Research Assistant
NIH/NHGRI/SBRB
CCGO 0017 Research Assistant

S2. Genetic counseling outline for positive disclosure sessions

1. Introduction
    a. Review of goal of primary research study
    b. Definition/review of primary and secondary genetic variants
2. Contracting
    a. Goal of session is to disclose a positive secondary variant
    b. Provide participant with information and support necessary so that they can initiate
        i. Specific healthcare actions
        ii. Familial conversations
        iii. Psychosocial adaptation
3. Disclosure of result
    a. Basic and brief genetics review
    b. Gene and mutation disclosure
        i. Evidence for pathogenicity
        ii. Who carries mutation (proband only or parent as well)
    c. Phenotype associated with mutation
    d. Inheritance pattern of associated disorder
    e. Overview of clinical recommendations specific to finding
4. Risk assessment
    a. Targeted medical history
    b. Targeted family history
5. Psychosocial assessment
    a. Psychological impact of variant receipt
    b. Limited psychosocial intervention
    c. Referral if needed
6. Plan
    a. Documentation of finding
        i. Logistics of report receipt (overnight FedEx)
        ii. CRIS Genetic Counseling Note
    b. Recommendations regarding additional validation if needed
    c. Referrals
        i. Local genetics services
        ii. Specific support group/disease information websites/resources
    d. Questions/concerns
        i. Understanding/clarification
        ii. Familial communication/testing
        iii. Barriers to referrals
    e. Communication with primary team
        i. Result disclosure summary
        ii. Referral back to primary team for questions regarding primary variant