Flinders UNIVERSITY

ASHG Position Statement

The Responsibility to Recontact Research Participants After Reinterpretation of Genetic and Genomic Research Results

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ABSTRACT

The evidence base supporting genetic and genomic sequence variant interpretations is continuously evolving. An inherent consequence is that a variant's clinical significance might be reinterpreted over time as new evidence emerges regarding its pathogenicity or lack thereof. This raises ethical, legal and financial issues as to whether there is a responsibility to recontact research participants to provide updates on reinterpretations of variants after the initial analysis. There has been discussion concerning the extent of this obligation in the context of both research and clinical care. While clinical recommendations have begun to emerge, guidance is lacking on the responsibilities of researchers to inform participants of reinterpreted results. To respond, an American Society of Human Genetics (ASHG) workgroup developed this position statement, which was approved by the ASHG Board in November 2018. The workgroup included representatives from the National Society of Genetic Counsellors, the Canadian College of Medical Genetics and the Canadian Association of Genetic Counsellors. The final statement includes twelve position statements that were endorsed or supported by the following organizations: Genetic Alliance, European Society of Human Genetics, Canadian Association of Genetic Counsellors, American Association of Anthropological Genetics, Executive Committee of the American Association of Physical Anthropologists, Canadian College of Medical Genetics, Human Genetics Society of Australasia, and National Society of Genetic Counselors.

INTRODUCTION

The American Society of Human Genetics (ASHG) workgroup developed this position statement with evidence-based justifications between January 2018 and November 2018. The workgroup is composed of a combination of laboratory and clinical scientists, laboratory directors, medical geneticists, primary care providers, bioethicists, health services researchers, lawyers, and genetic counsellors. The workgroup included representatives from the National Society of Genetic Counselors, the Canadian College of Medical Genetics and the Canadian Association of Genetic Counsellors. The workgroup has reviewed the literature in order to develop evidence-based recommendations with accompanied justifications, presented herein. Our analysis aligns with a previously published return of results consensus statement,[1] expanding the discussion to recontact for return of updated results from reanalysed genetic data.

The group met regularly through a series of bi-weekly conference calls and email discussions, proposed a draft outline of the statement to the ASHG Board of Directors in April 2018. A draft of this statement was reviewed by the ASHG Board of Directors on October 15, 2018. The Board requested revisions, which were reviewed by the committee and incorporated in the current statement. A consultation with the broader membership occurred during an invited session at the ASHG annual conference on October 19, 2018. There was a lively discussion and additional comments were invited via email. The Executive Committee of the Board reviewed and approved the current, revised statement on November 15, 2018.

The final statement includes twelve position statements that were endorsed or supported by the following organizations: Genetic Alliance, European Society of Human Genetics, Canadian

Association of Genetic Counsellors, American Association of Anthropological Genetics, Executive Committee of the American Association of Physical Anthropologists, Canadian College of Medical Genetics, Human Genetics Society of Australasia, and National Society of Genetic Counselors.

Currently research-related recontact typically happens on an *ad hoc* basis, which can lead to inequitable information provision and outcomes. Guidance is needed on how recontact should be operationalized in both clinical and research settings. This position statement addresses this critical policy gap in order to provide necessary guidance to our research communities. We recognize that not all research studies return results; these recommendations pertain to situations where the return of results has already occurred with the approval of the institution's IRB. These recommendations are intended to provide a set of principles; ultimately it is up to institutional review boards and advisory boards as to how these principles are operationalized.

Our statement acknowledges that the responsibility to recontact a research participant could occur in *some* instances when a researcher finds evidence to support the reclassification of a variant according to professional standards.[2] New knowledge might be learned about a variant that was previously returned to a study participant, or a medically relevant variant might be newly identified. In either case, a strong responsibility is limited to situations in which there are adequate resources to support such recontact (e.g. the research project is ongoing and has active funding). ASHG acknowledges any participant's right to decline return of results at the time of recontact. Further instances of recontact in this document imply that return is offered, not that return is made without participant agreement. Finally, the absence of an ASHG recommendation

to recontact in situations other than those enumerated below should not be interpreted as ASHG opposition to recontact in other situations. Rather, such omission indicates only that there is insufficient evidence available at this time for ASHG to issue a recommendation, and that in such situations the determination regarding recontact should be made on a case-by-case basis.

SCIENTIFIC BACKGROUND

The evidence base supporting genetic and genomic sequence variant interpretations is continuously evolving. An inherent consequence is that a variant's clinical significance might be reinterpreted over time as new evidence emerges regarding its pathogenicity or lack thereof. This raises ethical, legal and financial issues as to whether there is a responsibility to recontact research participants to provide updates on reinterpretations of variants after the initial analysis. There has been discussion concerning the extent of this obligation in the context of both research and clinical care.[3] While clinical guidance has begun to emerge,[4,5] guidance is lacking on the responsibilities of researchers to inform participants of reinterpreted results.

What does it mean to reinterpret results?

Reinterpretation of genetic and genomic results might occur at multiple levels. Most frequently, there is reinterpretation of the implications of one or more validated sequence variants. This might occur as a revision of an interpretation of the significance of a previously analysed variant, changing the status among the common categories of Pathogenic (P), Likely Pathogenic (LP), Variant of Uncertain Significance (VUS), Likely Benign (LB) and Benign (B), effectively reclassifying the variant. Such reinterpretation might be the result of reanalysis within a given laboratory after observation in another individual, or might be based upon new or revised data published elsewhere about a particular variant or gene. Clinically, P and LP are generally treated

the same, and typically VUS are not acted upon.[6] Thus, changes between P and LP may not have great consequence to participants, while changes from P/LP to VUS/LB/B or *vice versa* may.

New interpretations might emerge from sequence data that had not previously been analysed. This could be due to the recognition of a gene or sequence of interest that was not previously known to be relevant, changes in lists of genes and sequences recommended for routine analysis (e.g. the ACMG secondary findings list[4]), or revisions of the scope and/or goals of a research project.

Due to ongoing improvements in analytical methods and bioinformatic analyses, resequencing of an original specimen or reanalysis of raw sequence data might lead to a newly detected variant that was missed based on factors such as poor coverage or limitations in variant detection algorithms and filtration.[7–17]

The above situations may or may not justify an effort on the part of the research team to recontact a participant to disclose new information. In addition, recontact might be considered appropriate if there is a change in a research project's threshold of what types of variants should be disclosed at all, such that variants that were uniformly not disclosed in the past later meet criteria for disclosure after a participant had originally received his or her results.

How often does reinterpretation occur?

There is a relatively high rate of reclassification of variants, although the estimated rates vary across clinical indications for testing. In two early publications, Murray et al. (2011) found that

over half of *BRCA1/BRCA2* VUS (60/107) were reclassified, the majority of these (39/60) downgraded to benign. Aronson et al. (2012) reported on 214 variant classification changes in 11 hypertrophic cardiomyopathy genes over six years. The majority (56 variants) were upgraded from VUS to LP, 26 reclassified from LP to VUS, 32 from VUS to LB, another 25 variants changed between LB and B, and 62 changed between LP and P. More recent reclassification reports in both clinical and research settings demonstrate that the majority of reclassifications are downgrades,[18–21] largely due to the emergence of resources to document allele frequencies in diverse populations[22] as well as more rigorous criteria for classifying pathogenic sequence variants.[2] For example, Kast et al. (2018)[18] found 18/40 VUS downgraded to LB/B.

Importantly, a subset of cases of reclassifications can impact clinical management through screening, treatment or familial testing recommendations.[20,21,23] For example, Turner et al (2018)[20] reported that 12% of reclassifications (16/142) had the potential to alter clinical management: 6 of these were downgrades from P/LP to VUS (in *BRCA1, BRCA2, TP53,* and *CHEK2*) and 10 were upgrades from VUS to P/LP (in *HNF1A, MSH6, BRCA1, SDHD,* and *PMS2*). Because surgery is often considered at the time of diagnosis, in some cases individuals might have undergone unnecessary surgeries by the time reclassification occurs. Indeed, Murray et al. (2011)[19] report on four women whose VUS was later reclassified to benign who underwent risk-reducing mastectomy or oophorectomy. In two cases, the documented main reason was "strong family history of breast cancer."

These issues are further challenged by discordant (re)classification of variants and uncertainty of variant interpretations. Several studies have reported discrepancy rates in variant interpretation

between laboratories ranging from 39% to 66%.[24–28] Bland et al. (2017)[29] demonstrated that clinician experts' classifications of variants differed from laboratories' 18% of time, and differences were generally clinically significant. They found that clinicians tended to be more conservative in their classifications. Shah et al. (2018)[30] analysed the dynamics of re-classification of variant pathogenicity in ClinVar over time, which indicated progressive improvement in variant classification, favoring a general direction away from P/LPLB/B. However, the bulk of reclassified variants are reassigned to the "conflicting interpretation" category. More recent analyses have shown a more even distribution of upgrades and downgrades as laboratories continue to resolve discrepancies in variant classification.[31,32] Finally, reclassification rates also vary by ancestry/ethnicity,[33] highlighting potential disparities in the rate of recontact among participant communities.

Stakeholder perspectives

With the exception of a few studies,[18,33–35] the evidence base on stakeholder perspectives on recontact predominately originates from the clinical setting. Most of the literature focuses on patient and professional preferences, with some recent evidence emerging on the experience and feasibility of recontact (albeit in the clinical setting). Thus, there is a relative paucity of data on the most relevant population for the purpose of this statement.

In the clinical setting, research addressing patients' and research participants' *perspectives* on recontact indicates that majorities of patients and participants surveyed (69-97%) across various disease groups felt that the physicians are responsible for recontacting patients about new developments that could improve their or their family's care.[35–38] One clinical study found that some patients favor a "joint venture" of recontact, where patients and healthcare providers share

the responsibility for recontact.[39] However, patients appreciate the tension between the desirability of recontact and a perceived lack of feasibility.[38] To this end, in at least some jurisdictions, patients have recommended that health professionals ask patients during their visits whether they want to be recontacted, and do so using personalized letters either annually or "when new discoveries are made".[35]

Fewer studies have assessed professionals' *perspectives* on recontact. A 1999 survey of the ASHG membership found that the community was divided on whether recontacting clinical patients should be the 'standard of care'.[40] Interestingly, scientists were more likely to perceive a responsibility to recontact compared to clinicians (54% vs. 43%).[40] A Canadian survey of researchers found that large majorities agreed that, in general and in a variety of hypothetical research contexts, research teams that report results should ensure that research participants gain subsequent access to updated information (74–83%).[41] Carrieri et al. surveyed clinical genetics service providers in the UK and found that while the vast majority (95%) reported that they recontact patients and their family members, there are no standardized practices and the majority of services recontact on an occasional, not systematic, basis.[42] Later the same authors interviewed 30 healthcare professionals and clinical laboratory scientists and found that recontact was a concern, with no standard practices and unclear lines of responsibility in the clinical context.[38] These clinicians and clinical scientists acknowledged that recontact requires multidisciplinary collaboration, and that patients should sometimes take on some of the responsibility. Participants also expressed a need for consensus about recontact, and concerns about infrastructure and resources required.[38]

Recent evidence has begun to emerge about patients' and research participants' *experiences* with recontact. Taber et al. (2018)[34] surveyed ClinSeq research participants who had been recontacted about new information pertaining to their Duarte galactosemia variant, which had been reclassified from pathogenic to benign. They found that research participants were able to understand variant reinterpretations of either a neutral change or a change from carrier to non-carrier of a low risk condition, and that there were minimal adverse effects (though all participants were of high socioeconomic status). However, this change in classification would not have immediate impacts for these research participants' health; there is a need for more research among research participants recontacted about changes with greater personal health impacts. Romero (2018)[37] surveyed clinical adult patients who had been recontacted to inform them of new genetic tests related to their medullary thyroid carcinoma or pheochromocytoma/ paraganglioma. Only a minority of patients (29%, n=28) discussed genetic testing with their doctor or genetic counselor (9.5%), and 8.5% had genetic testing. Beunders et al. (2018)[36] surveyed parents of children who had received genetic testing for Fragile X syndrome or intellectual disability, who were recontacted and offered new tests (array CGH or whole exome sequencing) that might inform their child's diagnosis, and for the most part parents reported positive experiences in the clinical setting (83% were pleased to be recontacted, n=47).

Professionals' *experiences* with recontacting offers another perspective. The 1999 ASHG survey of the ASHG membership indicated that while 61% of genetics professionals have recontacted patients or research participants in the past, only 13% had formal system in place to do so.[40] This was consistent in a recent survey of 8 Canadian diagnostic labs, where none had a protocol for systematically reinterpreting previously analysed variants.[43] A European survey of 105 genetics

centers demonstrated that 95% (100/105) of clinical centers have recontacted patients; of these, 37 centers did so routinely, whereas 63 recontacted occasionally.[44] Common reasons justifying recontact efforts ranged from: availability of a new test (n=55), new clinical guidance (n=33), reclassification of a VUS (n=26) to new results from prior test (n=17).[44] Many European centers (41 of 105) have a formal system in place for recontacting patients, including: seeking consent at first visit, patients request or agree to future contact, or recontact occurs without prior consent (this was usually done when results are clinically actionable [n=44] or are medically relevant to a relative [n=16]).[44] Interestingly, Beunders et al. (2018)[36] compared the feasibility and yield from recontacting their patients by telephone versus letters. Total yield of parents who made appointments for re-evaluation was 36% of the 151 parents who were informed by telephone, and 4% of the 52 parents who were informed about recontact by letter. They also concluded that recontact was very time consuming, especially in selecting appropriate patients.

Overall, the evidence indicates that most stakeholders, primarily representing the clinical setting, consider recontacting patients or research participants to be ethically desirable though practically difficult,[45] and all point to a need for greater guidance on this issue.

Current guidance on recontact

Currently, guidelines addressing recontact are sparse and focus exclusively on the clinical context and not on the research setting. Only two clinical guidelines exist that explicitly address recontact: a 1999 position statement from the American College of Medical Genetics and Genomics (ACMG) and a recently published guideline from the European Society of Human Genetics (ESHG[5]). The 1999 ACMG guidelines suggest that recontact might be merited if new information is learned about a condition, but recommend that this be the responsibility of

primary care physicians who have more regular contact with patients than genetics specialists. The ACMG guidance also recommend that patients keep their primary care physician informed, or ask for updates about their results, suggesting a dual responsibility for recontacting. As of the writing of this statement, the ACMG was in the process of updating their guidelines. The ESHG recently recommended that clinicians should recontact patients regarding findings with clinical or established personal utility yet there is no legal or professional responsibility to do so.[5] They add that recontacting is a shared responsibility with patients and laboratories, where requests for reanalysis should be initiated by the patient, clinical laboratory or their clinician.[5]

Additional policy statements on other topics from the Canadian College of Medical Genetics (CCMG) and ACMG/American Association of Pediatrics (AAP) have briefly addressed clinical recontact, but it has not been the sole focus of any one recommendation. ESHG and EuroGentest previously concluded that clinical laboratories do not have a responsibility to routinely re-analyse data, but that if a variant is reclassified the clinical laboratory should identify patients affected by the change and report this to their clinicians. [46,47] Whereas the CCMG state that re-analysis should be initiated by the clinician.[48] ACMG/AAP encourage recontact if a variant is reclassified, but leave it to the discretion of clinical laboratories to determine when to re-analyse and when to recontact.[2] All statements point to a need for policies that specifically address when and how recontact should occur in the clinical setting. There is a paucity of guidance about recontacting in the research setting.

Scope of statement

Recontact after reinterpretation of genetic and genomic research results is a complex issue in which both clinical and research laboratories, clinicians and researchers across specialities and research participants all have potential roles to play. Currently, research-related recontact typically happens on an *ad hoc* basis – this might cause inequitable information provision and outcomes. There is a need for guidance on how recontact should be operationalized, and when and how it should occur, especially in the research setting – a setting where no guidance currently exists.

This position statement addresses this critical policy gap in order to provide necessary guidance to our research communities. It limits its recommendations to primarily research settings, while recognizing that genetic and genomic research results often impact clinical and other contexts. Indeed, even within a given research study or registry, there are varying degrees of crossover into the clinical realm (e.g. MyCode® Community Health Initiative at Geisinger). This statement attempts to address these research/clinical "grey zones" but recognizes that additional input from other stakeholders will be important as the experience with, and evidence base of, recontacting research participants grows.

Exclusively clinical contexts are outside the scope of this position statement, given the existing guidance on the topic. The position statement also avoids discussions related to researchers' obligations to recontact decedents when the proband/research participant is deceased, since this is the focus of separate guidance recommending that researchers have no obligation to return results to relatives (when proband is deceased) and no "duty to hunt" for such results.[49] This

position statement also excludes the cases where initial consent was received while a participant was a minor and related discussion as to what happens when such individuals reach adulthood, since this is beyond the scope and intent of this statement.

This document focuses exclusively on the recontact of study participants following the initial return of research results and does not address the issues relevant to initial return of a result. In other words, should reinterpretation occur in the context of interpretation of a gene not previously analysed, or similar, then study protocols should be followed; this document instead focuses on the recontact of participants when a variant has already been returned and, subsequently, a reinterpretation of that variant is made. The ASHG endorses a prior consensus statement on the initial return of genomic results to research participants.[1]

Ethical principles

It is important to ground this guidance in an appropriate set of ethical principles because policies addressing these issues should strive to reflect the same principles applied across all types of research ethics questions. It is appropriate, then, to start with the principles proposed in the Belmont Report, the document that provided the ethical foundation for modern research regulations in the U.S.[50] The Belmont Report suggests that three principles provide the foundation for ethically appropriate research with human participants: respect for persons, beneficence, and justice. Overlapping principles grounded in medical ethics commonly cited come from Beauchamp and Childress: beneficence, non-maleficence, respect for persons/autonomy, and justice.[51]

Among these three principles, respect for persons is potentially the most expansive. The framers of the Belmont Report interpreted this principle primarily from the perspective of autonomy: researchers are obligated to demonstrate respect for research participants by ensuring that participants have the opportunity to consider the risks and benefits of the research and voluntarily agree (via an informed consent process) to participate in the research. By emphasizing autonomy, this principle emphasizes that a broad range of approaches to returning genetic and genomic results revealed through reanalysis can potentially be ethically acceptable, assuming that this approach is made clear during the consent process to which the research participant has knowingly agreed. This is also, of course, why it is more difficult to deal with these issues when a plan has not been developed prospectively and included in the consent process.

It is also important to recognize that the obligation for researchers to demonstrate respect for the participants could entail a number of other important ethical principles.[52,53] Chief among these is the ethical principle of veracity or truth telling. In general terms, this aspect of the principle of respect for persons holds that researchers should not lie to participants unless there is scientific reason to do so (such as in psychological research that involves misdirection).[54] The ethical principle of veracity supports a limited obligation to return reinterpreted results, as the communication of the original research results to a participant could be seen as information that is now known not to be true, thus creating a limited obligation to correct this. As always, this interpretation of veracity would need to be weighed along with a range of other ethical principles.

In the research context, the principle of beneficence functions slightly differently from the way it is applied to clinical care.[55] In the clinical context, beneficence holds that healthcare providers have a fiduciary duty to pursue the best interests of their patients. In the research context, maximizing benefits and minimizing risks to research participants needs to be weighed against the overall aim of research: to generate new important scientific knowledge. It is necessary for researchers to carefully consider how to pursue scientific knowledge using an approach that confers the best possible balance of risks and benefits while still generating the benefits of high-quality research. In other words, any responsibility that researchers have to provide benefits to their research participants (also known as an ancillary care responsibility) is necessarily a limited responsibility.[56]

Justice, when applied to human research, can be operationalized in three ways in the context of the scientific value of research. First, researchers should be just in recruiting and enrolling participants in research studies. Except where justified by the scientific goal of the research, participants should have both equal access to the benefits of the research and equal exposure to its risks.[57] Second, decisions about the funding of research also need to be guided by the principle of justice. Third, since the risks associated with human research are justified largely by the potential benefit of research to generate scientific knowledge and provide benefit to society at large, both researchers and funders might need to prioritize scientific aims over other aims. For example, imagine that a psychological study is being conducted in a primary care clinic to answer an important scientific question, but the study also provides a mechanism for patients to receive psychological treatment. If that psychological treatment ends up being more expensive than originally anticipated (i.e. because participants need more intensive therapy than expected),

then researchers might need to curtail this ancillary care in order to ensure that enough budget is available for the study to achieve its scientific aims. The principle of justice dictates that the scientific aims of a research study must be protected, or else the risks assumed by participants would not have been justified.

These related aspects of beneficence and justice highlight the importance of practicability in applying ethical principles to the conduct of scientific research. There are a wide range of practices that researchers might want to adopt that would not be absolutely necessary for a research study to achieve its goals. For example, clinical study personnel sometimes send birthday cards or newsletters as a way to maintain participants' engagement with a research study. Biorepositories sometimes choose to return individual research results to participants to help prevent participants from experiencing adverse health events. If it is possible to successfully carry out these practices, and to do so without threatening the overall ability of the study to achieve its scientific aims, then these practices can be said to be practicable - they are capable of being done while not threatening the goals specific to a research study, i.e. to generate scientific knowledge and provide societal benefits.[1]

Practicability, then, provides a way to ethically weigh the potential conflicts that might arise in trying to balance ethical principles. The efforts of biorepositories to return individual research results to participants can be seen as a way to express respect for the contributions that participants have made to research.[52] While this expression of respect can be seen as an ethical good, this good must be weighed against other ethical goods. As we have seen, the principle of justice could limit this particular expression of respect for persons if, in fact, an effort to return

individual research results would prevent the biorepository from achieving its scientific aims (i.e. because it costs too much or because it requires too much effort from research staff).

In thinking about potential reasons that a researcher might need to return reinterpreted findings to participants, practicability provides a valuable framework for thinking about when this might or might not amount to an ethical obligation. Assuming that researchers utilize criteria that ensure the potential benefits of returning updated findings are maximized, taking on this additional effort would clearly provide an ethical good. However, whether there would be an ethical obligation to provide this good depends on a number of contextual factors. Practicability requires that the primary obligation of the researcher is to justify the risks that participants have assumed by ensuring that the research being conducted is completed successfully and is used to provide the scientific knowledge and societal benefit that it was designed to provide. Where this aim can be achieved while at the same time providing the service of reanalysis and return of updated results, making this effort clearly could provide additional benefit to research participants. However, where there are no resources at all to carry out this extra effort (e.g. after the funding for a research study has ended) or where it cannot be carried out without interfering with the study's scientific aims (e.g. when it would consume grant funds that are required to complete the study), then a case could be made that it would be unethical or impossible to pursue the return of reinterpreted results.

The use of practicability as a standard for deciding when there might be a responsibility to return reinterpreted results creates an obvious challenge: How should decisions be made about what is practicable? An important concern, of course, is that if the decision is left to researchers alone

the researcher might determine that an effort to return reinterpreted results is not practicable, when in fact it is practicable but inconvenient. From a pragmatic perspective, then, it is important that such decisions not be left solely to researchers. Typically, these types of evaluations are made by allowing researchers to present justification to the IRB, with the IRB making a final decision. However, other models of research governance are possible, and IRBs might approve plans to use advisory boards (such as groups of internal stakeholders or community advisory boards) to make these types of decisions.

With all of this in mind, however, it is worth re-emphasizing that a broad range of approaches to returning updated results can be permissible. Assuming these plans are developed prospectively, these need to be evaluated by an IRB to ensure that the principles of respect for persons, beneficence, and justice are being respected to the extent possible, and then included in a thorough informed consent process so that participants have enough information to voluntarily agree to the plan.

In summary, then, based on these ethical principles, the obligation to recontact is stronger when:

a. The research is active, ongoing, has funding and participant's contact information is up to date (practicability)
b. Informed consent set the expectation for potential recontact (respect for persons/autonomy)
c. There is a high degree of certainty about the new interpretation and/or implications of a changed interpretation, as judged by both investigator and IRB/governance structure ("non-maleficence")

d. The reinterpretation would be relevant to the condition under study or, in the case of an actionable incidental finding, likely to change medical management (beneficence)

Legal implications[45,49,58,60,62,64,66,68–70,72,74,76,78,80,82,84,86,88,90]

It is also important to ground this guidance in an appropriate set of legal principles, the first of which is consideration of fiduciary relationships. Fiduciary relationships are ones in which a person in a position of greater power is under an obligation to act for the benefit of another within the scope of the relationship. In other words, the fiduciary is to have undivided loyalties to the beneficiary. Fiduciary relationships might rise from contractual agreement, and it is important to recognize that fiduciary duties do not arise simply by virtue of an imbalance of expertise. A fiduciary duty is based in trust and is highly contextual. Absent explicit legislative authority establishing affirmative duties on researchers, courts in the United States have generally been unwilling to find that a researcher has fiduciary duties to research participants unless the researcher is also the participants' treating physician. While the physician-patient relationship has been described as a fiduciary one, this characterization has been framed distinctly from general tort duties related to fulfilling the standard of care. One rationale for maintaining a false dichotomy between care and research is based on the notion of conflicts of interest. A treating physician's primary duty of loyalty is to the individual patient to ensure the improvement or maintenance of the health and wellbeing of that individual patient; however, a researcher's primary duty of loyalty is to scientific enterprise itself and the production of generalizable knowledge rather than the provision of any direct benefit to an individual participant. Another basis for the dichotomy has been the now fading conceptualization of participation in research as a transactional activity (requiring informed discussion and consent only at the time of initial enrolment in the research) rather than a participatory one (with ongoing

communication and interaction as appropriate). Courts have been unwilling to extend fiduciary duties to researchers and have noted the countless questions such an extension would raise (e.g., how long such a fiduciary duty would last, whether the duties would persist beyond the participation in the research, and how to determine the scope of institutional duties that would arise vicariously).

Researchers could have duties arising from other theories, including general negligence (that is, failing to perform responsibilities according to the prevailing professional standard). As norms for the profession shift to accommodate more equitable and participatory approaches to research, genetics researchers could be required to stay current with technologies and methods as well as to provide participants with updated disclosures related to information previously disclosed or after-acquired information. The prevailing professional standard for the conduct of genetics research is set, in part, by issuance of position statements and recommendations by professional organizations, such as the ASHG. The recommendations provided in the present statement are not intended to establish a legal duty, although courts might find these recommendations useful if called upon to establish, define, or otherwise delineate the scope of a responsibility to recontact research participants.

In addition to agencies and oversight authorities that might establish and occasionally revise codes of conduct and set performance obligations that researchers owe to their participants, research institutions and research sponsors might also have their own policies that relate to a responsibility to recontact participants. The recommendations provided in the present statement are not intended to supersede other policies. Researchers should consult their attorney and

relevant administrators to reconcile any discrepancies between these recommendations and any and all applicable laws and policies for the situation.

RECOMMENDATIONS

What – Nature of results

The responsibility to recontact a research participant could occur in *some* instances when a researcher finds evidence to support the reclassification of a variant according to professional standards.[2] New knowledge might be learned about a variant that was previously returned to a study participant, or a medically relevant variant might be newly identified. In either case, a strong responsibility is limited to situations in which there are adequate resources to support such recontact (e.g. the research project is ongoing and has active funding). ASHG acknowledges any participant's right to decline return of results at the time of recontact. Further instances of recontact in this document imply that return is offered, not that return is made without participant agreement. Finally, the absence of an ASHG recommendation to recontact in situations other than those enumerated below should not be interpreted as ASHG's opposition to recontact in other situations. Rather, such omission indicates only that there is insufficient evidence available at this time for ASHG to issue a recommendation. In such situations, the determination regarding recontact should be made on a case-by-case basis.

Given these considerations, the ASHG offers the following recommendations:

1. ASHG *strongly recommends* attempting to recontact participants to offer updated results if the reinterpretation is related to the phenotype under study or reasonably expected to affect a research participant's *medical management.*

2. If the reinterpretation is *not expected* to affect management, recontact is advised, rather than strongly recommended, for correction of the classification of variant previously reported to the participant whose pathogenicity classification has changed from or to Pathogenic/Likely Pathogenic.

The strength of ASHG's recommendations to recontact diminishes when the evidence for medical benefit is less definitive. Clinical criteria for 'affecting medical management' are defined elsewhere by the ACMG and could serve as a resource for researchers[4,59]:

- Serious conditions
- Highly penetrant
- Effective intervention available (screening or treatment)
- Risk/benefit profile of intervention is favorable
- Strong knowledge base about condition overall

All of the above applies to disclosure of both primary and additional,[61] also called secondary or incidental, findings. For primary findings, related to the participant's phenotype under study, changes of clinical consequence (P/LP to B/LB/VUS or from B/LB/VUS to P/LP) recontact is advised, even in the case where medical management of the individual being tested will not clearly change, for example in most patients with already diagnosed cardiomyopathy.

It is acknowledged that expectations and decisions about medical management are appropriately shared between health care providers and patients, and that there are situations in which expectations between patients and health care providers are not aligned. For purposes of recommendation #1, the determination of what is 'reasonably expected to affect medical management' is to be considered from the perspective of the researcher but should be informed by clinical guidelines and, when practical, consultation with clinicians.

What – Threshold considerations

In general, thresholds should be considered relative to what a research participant has been led to believe based on results that either have (or have not) been disclosed to them already[63] and what was stated in the research consent if it was addressed.

The rationale for recontacting participants is *strongest* when:

- A participant has been notified of a LP/P variant, which is later downgraded to VUS/LB/B
- Researchers have told a study participant that no detectable variants of clinical significance have been identified, and a LP/P variant that might impact medical management is subsequently identified, or reclassified from VUS/LB/B.
- Researchers have <u>implied</u> that a study participant harbors no detectable variants of clinical significance because no results have been returned and a LP/P variant is subsequently identified that might impact medical management.

Recontact is advised when VUS were returned and are reclassified as LP/P. However, recontact in these situations falls short of a strong responsibility because:

- By definition, VUS are subject to revision based on changing evidence. Research participants who have VUS returned to them as part of research are (ideally) encouraged to seek clinical follow-up testing and counselling in the future.
- There is even less responsibility if reclassification of a VUS to LP/P is not believed to impact medical management.
- Recontact for reinterpretations from B/LB to VUS should be made on a case by case basis when there is anticipated benefit.

Researchers have no *responsibility* to hunt/scan genetic and genomic data or literature for changes in variant interpretation, or to identify new genetic causes of disease, if not part of the original study.[1,65,67] To do so would be outside the scope of what a researcher owes a study participant and might detract from the primary goals of research. This position is consistent with consensus that exists among clinical diagnostic laboratories, which also do not have a duty to hunt for variant reclassifications [46] and our endorsement of a prior consensus statement on return of genomic research results.[1] However, evidence to support variant reclassification might arise as part of a researcher's work (e.g. via functional studies, literature searching, or data sharing). Researchers are responsible for the validity of variant classification and are urged to critically evaluate the source of and evidence supporting each classification.

Given these considerations, the ASHG offers the following recommendation concerning the responsibility to hunt:

3. ASHG recommends that there is no responsibility for researchers to hunt or scan genetic and genomic data or literature for changes in variant interpretation.

When – Temporal considerations

Consistent with related guidelines,[1] no return of results should be expected after the close of study funding.

4. The ASHG recommends that any *responsibility* to recontact is limited to the duration of research funding. Recontact after the conclusion of funding may be *desirable* if sufficient resources exist.

It is important to distinguish temporal issues that need to be considered prospectively when planning a study versus those for ongoing studies, where the question of recontact emerges after study initiation.

For prospective studies researchers should plan to complete any recontact for interpretations of variants related to the phenotype under study and/or reasonably expected to affect a research participant's *medical management.*

For ongoing studies in which there is no existing plan for recontact, researchers are encouraged to consider whether any recontact related to reinterpretations of variants related to the phenotype under study and/or reasonably expected to affect a research participant's *medical management* (as defined in sections *"What – Nature of results"* and *"What – Threshold Considerations"*) is indicated prior to the end of study funding. The need for clinical confirmation of a research result might influence the process of recontact but is not expected to influence the timing. Funding for recontact might be challenging when not planned in the budget of an ongoing study. However, as

reviewed in section "*How often does reinterpretation occur?"*, the proportion of cases with variants whose reclassification has both strong scientific evidence and implications for medical management is likely to be modest.[20,21] In some cases, especially large-scale sequencing studies that choose to recontact for variants beyond those related to the phenotype under study and/or those reasonably expected to affect a research participant's *medical management*, supplemental funding might be necessary.

5. The ASHG recommends that no responsibility to recontact exists when the IRB protocol associated with the study closes or identifiers are stripped, rendering further recontact infeasible.

When the study protocol to which the participant consented closes, and IRB oversight ceases, the researchers' responsibility for recontact ends. Should the study Principal Investigator change in an ongoing study (such as a longitudinal study), ultimate responsibility for recontact is transferred in the same way as for responsibility of other study functions.

6. **The ASHG recommends that, when there is a strong recommendation for recontact, the recontact should occur within 6 months of the reinterpretation.**

When the certainty of the reinterpretation, the gene/disease association, and/or the medical relevance is less definitive, a longer duration for recontact is reasonable or even desirable, so as to allow more time to establish more certainty. A longer duration is also reasonable when recontact is pursued for reasons related to personal utility rather than medical management

(where personal utility refers to non-clinical benefits endorsed by patients, such as [but not limited to] family/ reproductive planning, life preparation, empowerment and advanced knowledge[92]). Such delay should balance against the risk that study funding or other resources may not be sufficient to support recontact in the future.

As previously established, there is no "duty to hunt" or duty to re-analyse unless otherwise specified in the research consent or protocol. Likewise, there is no predetermined time frame for a frequency of reanalysis. The timeframes relate to the time since discovery of new evidence during the course of research. An example would be a researcher reclassifying disease-specific variants per the 2015 ACMG/AMP criteria[2] prior to publication and in the course of this process, realizes that some variants previously adjudicated and returned as LP/P are now classified as VUS/LB/B.

How – Operational issues

The ASHG offers the following recommendations concerning operationalizing the responsibility to recontact:

7. **ASHG recommends that instances of recontact be documented.**
8. **ASHG recommends that any responsibility for recontact is limited to a "good faith effort" to reach the participant within the limits of existing constraints, including (but not limited to) financial and personnel resources, the existence of accurate contact information for the participant and willingness of the participant to accept recontact.**

For variant reinterpretation related to the phenotype under study and/or reasonably expected to affect a research participant's *medical management* and a high certainty of evidence supporting reclassification (as defined in section *"What – Nature of results"* and *"What – Threshold Considerations"*) it is reasonable for researchers to make this information available to participants through direct individual contact if consistent with the overall study return of results policy. For reinterpretations of variants unrelated to the phenotype under study and/or not expected to affect a research participant's *medical management* where individual results had already been returned, a broad-based notification (such as a newsletter or generic mailing) to study participants will likely suffice.

It is important to distinguish operational issues that need to be considered prospectively when planning a study versus those for ongoing studies, where the question of recontact emerges after study initiation.

For prospective studies, as part of an overall return of results plan, researchers should anticipate the possibility of needing to recontact participants following reclassification of variants and design the study protocol accordingly. This includes developing a process for maintaining communication with participants as well as ensuring necessary funding and staffing. Considerations for recontact for updating genetic and genomic results are similar to operational issues of best practices for return of initial genetic and genomic study results.[4]

For ongoing studies that did not consider recontact in an initial return of results plan, but where variant reclassification has prompted consideration of recontact, initial policies for release/disclosure of original genetic findings should be followed to the extent possible following IRB / ethics approval as needed. This includes decisions related to return of only clinically validated results vs. research results, actual form of recontact (mail, electronic, web-based, etc.), security considerations, notification of relatives of deceased participants, documentation, etc. For instance, in some circumstances documentation of reclassification within a report addendum in the medical record is warranted if the initial return of results protocol included deposition of genetic results into the medical record, but not if initial return of results included a personalized results letter to the study participant.

How - Issues of Consent

Informed consent and recontact first requires taking note of the informed consent and basic return of individual research results. It is important to distinguish consent issues that need to be considered prospectively when planning a study versus those for ongoing studies, where the question of recontact emerges after study initiation.

For prospective studies:

9. ASHG recommends that research projects develop a plan not only for initial return of results, but also for return (or not) of reinterpretations of those results. As part of that plan, research participants should be alerted to the likelihood that interpretations of results may change over time and be given the opportunity to provide informed

consent regarding the plan for return of results, including initial and reinterpreted results.

This position is consistent with numerous recommendations that have stated that researchers should anticipate the possibility of return of individual genetic research results.[1,67,69,71,73] Fabsitz et al. (2010)[71] state: "Researchers should consider prospectively whether their study has potential to yield individual research results of clinical importance and describe plans for return of results in consent forms and processes." As such, researchers should either state in the consent document that the participant might be contacted in the future and offered a research result or ask the participant in the consent document whether or not he/she would want to be contacted in the future to learn about a research result. Jarvik et al. (2014)[1] further expound on this saying "The consent process and form should address the possibility that there might be both research results related to the primary intent of the research and findings that are incidentally discovered in the course of research, and participants should be able to clearly opt in or out of receiving these types of results either at the time of initial consent or at a later point in the study when the specific types of results the participants might receive can be best defined. […] Ideally, the original consent form would include the possibility for, or an option of, future contact to offer results not anticipated at the time of consenting."

Limitations include the fact that technologies, and therefore responsibilities, are rapidly changing and many studies have consent forms developed (and signed) when the breath of findings and possibility for reinterpretations was poorly anticipated. Researchers should develop a plan for

recontacting research participants in the future and include it in the consent form, including an option to decline future recontact entirely.[1,75]

For ongoing studies, the original research consent documents are relevant in defining what will/will not be analysed, re-analysed and disclosed to research participants in the present and in the future. Original research consent documents are also relevant in determining how to approach whether or not to recontact participants.[1,67,69,71,73] A consent document that explicitly addresses the issue (either stating or requesting permission) is a different situation than a consent document that ignores the issue (i.e. not stating either way whether recontact may or may not occur).

If the research consent documents address the issue of recontact, the situation is fairly clear-cut and recontact can be initiated. If participants agreed to have individual results returned, it implies recontact for the same type of results has also been agreed to by the participant.

10. ASHG recommends that, if the participant consented to any return of results at the time of original research consent, then consent to recontact for the same type of results is implied and therefore appropriate subject to the other recommendations in this policy statement.

If the research consent documents do not address the issue of recontact or of return of research results, then depending on the nature of the information, researchers can and should turn to research ethics consultation service (e.g. the Clinical Research Ethics Consultation Collaborative

[RECs]) and/or IRB for guidance.[71,77,79,81] In addition, a *formal determination* will likely need to be made through a conversation between the researcher and the local IRB. This discussion must take into account the specific details of each case in question.

Of note, some institutions might have a local policy requiring return of any research finding (regardless of whether it is the initial return or a recontact to return reclassified results) to be approved by the IRB, even if it was stated in the protocol these might happen. That is, the local IRB might want to see the list of variants being returned (initially or as part of a recontact to return reclassified results) and justification for their return.

Participants may change their minds regarding return of results overtime. In situations where researchers feel a strong desire to overrule participants' initial consent to return initial results in order to recontact participants with reinterpreted variants, researchers should seek RECs guidance.

Who - Professional roles

Ideally, recontact protocols should be part of the initial research study design, with consideration for protocols that take into account the context and limitations of specific jurisdictions, in consultation with the IRB approving the study. In cases where no protocol or procedure for recontact was previously put in place, and recontact is warranted according to the specifications outlined earlier in this document, the points below should be considered. When in doubt, consultation should occur with the IRB under which the research study was approved.

The ASHG offers the following recommendation to operationalize the responsibility to recontact:

11. ASHG recommends that, ideally, the same individuals and communication methods should be used for recontact as were used for the initial return of results.

Since recontact implies that an initial contact took place, ideally the same channels should be used for recontact as for the initial contact for the type of result. For example, a research protocol can suggest that negative and uncertain results are returned by letter, whereas detection of the P/LP variants or medically actionable incidental findings are returned by telephone or personal meeting. Ideally, the same individuals involved in the prior contact should be involved with recontact. If the individuals initially involved left the institution, then ideally the individual(s) who assumed their professional role will carry out the recontact. In cases where no designated individual assumed this professional role, another member of the same team with similar credentials would be the preferred individual to carry on the recontact. If none of these options is available, the research team should notify research participants according to the mechanisms outlined earlier in this document. If a clinician was initially involved in referring a patient-participant to the study and/or managing study results, the research team should alert him/her to the new results.

It is recognized that participant clinical access might be limited by funding considerations and/or limited specialized human resources. As such, while the information might be made available to

clinicians, clinicians should act according to the clinical guidelines/protocols that apply in the jurisdiction.

There is a paucity of literature on duality of roles (clinician researchers) with the exception that perceived or real conflicts of interests should always be considered in the context of recontact, and a result conveyed by a healthcare provider who is actively treating the patient/participant is less likely to be perceived as value neutral by the participant, even if that provider is acting as a researcher at the time of conveying that result. A therapeutic intention is often assumed in such situations, even when patients are told otherwise.[1,83,85]

As noted above, the absence of an ASHG recommendation to recontact in situations other than those enumerated above should not be interpreted as ASHG opposition to recontact in other situations. Rather, such omission indicates only that there is insufficient evidence available at this time for ASHG to issue a recommendation. In such situations, the determination regarding recontact should be made on a case-by-case basis. However, as noted elsewhere[1], "researchers might be ethically and scientifically justified in returning all genomic information." If they are returning broader classes of information, they may be justified in recontacting for broader types of reinterpreted results.

12. **ASHG acknowledges that in the research context, participants may be consented for initial return of a much wider range of results. Thus, reinterpretations derived from reanalysis broader than those addressed in this statement are appropriate to return when that is consistent with study design and consent documents.**

DISCUSSION

It is now well-recognized that researchers should anticipate situations in which return of study findings might become appropriate.[1,4,49,87] With recent data documenting the relatively high rate of reclassification of variants, researchers planning a study should likewise anticipate and plan for recontacting study participants during the life of their funded studies. Herein, the ASHG sets the minimum principles underpinning researchers' responsibilities to recontact their research participants about variant reclassifications.

A common theme in most critical evaluations of recontact is the inherent tension between the desire to keep research participants as informed as possible and the opportunity costs and practical challenges of actually accomplishing that goal. Depending upon the details of a given situation, the degree of ethical imperative for recontact and the associated obstacles might vary. There are different types of utility as well as potential harm, some of which are clearly medically actionable with quantitatively measurable effects on morbidity and mortality, while others are more personal, intangible and qualitative. The resource costs of recontact depend on multiple factors, including accessibility of the intended recipient of the recontact, the experience of the clinical/researcher, and the nature of the revised interpretation. Funding for those resource costs might be uncertain, especially after a study has closed, and any budget devoted to recontact necessarily represents resources that were not dedicated to some other purpose.

These recommendations have been developed amidst an evolving landscape of related policies and guidance documents. For example, the recent report issued by the National Academy of

Sciences (titled, "Returning Individual Research Results to Participants: Guidance for a New Research Paradigm[89]") included an entire chapter devoted to the issue of "reshaping" the legal landscape to make it more conducive to the return of individualized research results (see Chapter 6). While NASEM concluded that there was not yet legal consensus on whether there is a right to access individualized research results and highlighted some regulatory challenges for doing so (such as *perceived* regulatory conflicts between HIPAA's right to access and CLIA-certification requirements wherein some, but notably not all legal experts, interpret a non-CLIA-certified laboratory's provision of access to individual research results in effort to comply with the civil right to access under HIPAA would necessitate the laboratory becoming CLIA-certified), NASEM underscored ethical and practical reasons for providing such access to individual research participants and advocated for harmonization and clarification of regulatory authorities (including OCR, CMS, and FDA). NASEM noted among the many liability concerns is the potential tort liability that might arise from a "[f]ailure to update previously disclosed results and to return the updated results." Liability concerns, NASEM notably concluded, could be alleviated through the issuance of standards for reporting individual research results. Among the areas in which clarity could emerge (see NASEM Table 6-3) is if there would be a more specific articulation of what individual research data is (or should be) considered as belonging to the HIPAA designated record set (DRS) for mandatory disclosure.

These recommendations could also be informed and updated in light of some much needed evidence. For example, data concerning the benefits, risks, costs, procedures and outcomes of recontacting participants about reinterpreted variants is limited as is researchers' experiences with return of results and being recontacted about reinterpreted results. Reanalysing variant calls

and recontacting requires resources and funding, both of which are limited, or even non-existent, in ongoing studies. Dedicated funding is required to supplement researchers' budgets to recontact participants, through institutional mechanisms or built in as part of future grant proposals. We urge funding agencies to encourage and financially support researchers' efforts to recontact participants in light of re-classified variants.

Enhancements in information technology (IT) will likely further reduce the opportunity costs of recontact, and open up new avenues of keeping patients and research participants informed. Most electronic medical record systems and many clinical laboratories now offer portals through which patients might see their data, interact with clinical, laboratory, and support staff, and access educational material. Databases can be interfaced and cross-referenced, enabling more of a self-service model of education. Some patients and participants are already being provided with some or all of their raw genetic test result data, in addition to the interpretation of that data. As our IT resources and our databases continue to evolve, it is plausible that much of the effort of recontact could become automated. When a variant is reclassified, an automated notification could be sent to all patients and subjects known to harbor that variant, alerting them of the revised interpretation and prompting them to log into the portal to view the new information and associated education. This future vision depends upon well-developed and interoperable databases, including both the interpretations of the variants and the lists of who has each variant. Effort will be required to identify which databases to include (or exclude), as well as how to manage conflicting data. Some laboratories have proposed databases or information technology approaches to recontact, some of which is used to track variant and patient data, and reclassifications, and could send updated reports directly to patients' electronic medical

records.[63,91] Potentially difficult questions about identity and privacy will need to be answered. There are also significant concerns about the "digital divide" and economic disparities; increasing reliance on IT solutions has the potential to discriminate against people who are unable to or choose not to utilize such resources. There will always be situations that require more nuance and explanation than an automated algorithm can achieve. But there is hope that IT enhancements can significantly lower the costs and barriers to recontacting research participants when it is considered desirable to do so.

CONCLUSION

Recontact after reinterpretation of genetic and genomic research results is a complex issue in which both clinical and research laboratories, clinicians and researchers across specialities and research participants all have potential roles to play. Currently, research-related recontact typically happens on an *ad hoc* basis, which can lead to inequitable information provision and outcomes. Guidance is needed on how recontact should be operationalized, and when and how it should occur, especially in the research setting – a setting where no guidance currently exists. This position statement addresses this critical policy gap in order to provide necessary guidance to our research communities. These recommendations are intended to provide a set of principles; ultimately it is up to institutional review boards and advisory boards as to how these principles are operationalized.

These recommendations have been developed amidst an evolving landscape of related policies and might need to be updated in light of the paucity of evidence on the burden and outcomes of recontacting research participants. Future research and changes in both IT and social values will likely impact our society's approach to applying ethical principles in conducting research and

keeping research participants as informed as possible about their genetic test results, even as our understanding of those test results evolves over time. Development of the evidence base along with ongoing stakeholder consultation is thus warranted to ensure the equitable and effective delivery of high quality research results to those who participate in research.

DECLARATION OF INTERESTS:

The workgroup* authors declare the following competing interests:

JLV is an employee of the US Department of Veterans Affairs (VA); this work does not necessarily represent the views of the US government or the VA.

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FIGURE TITLES & LEGENDS

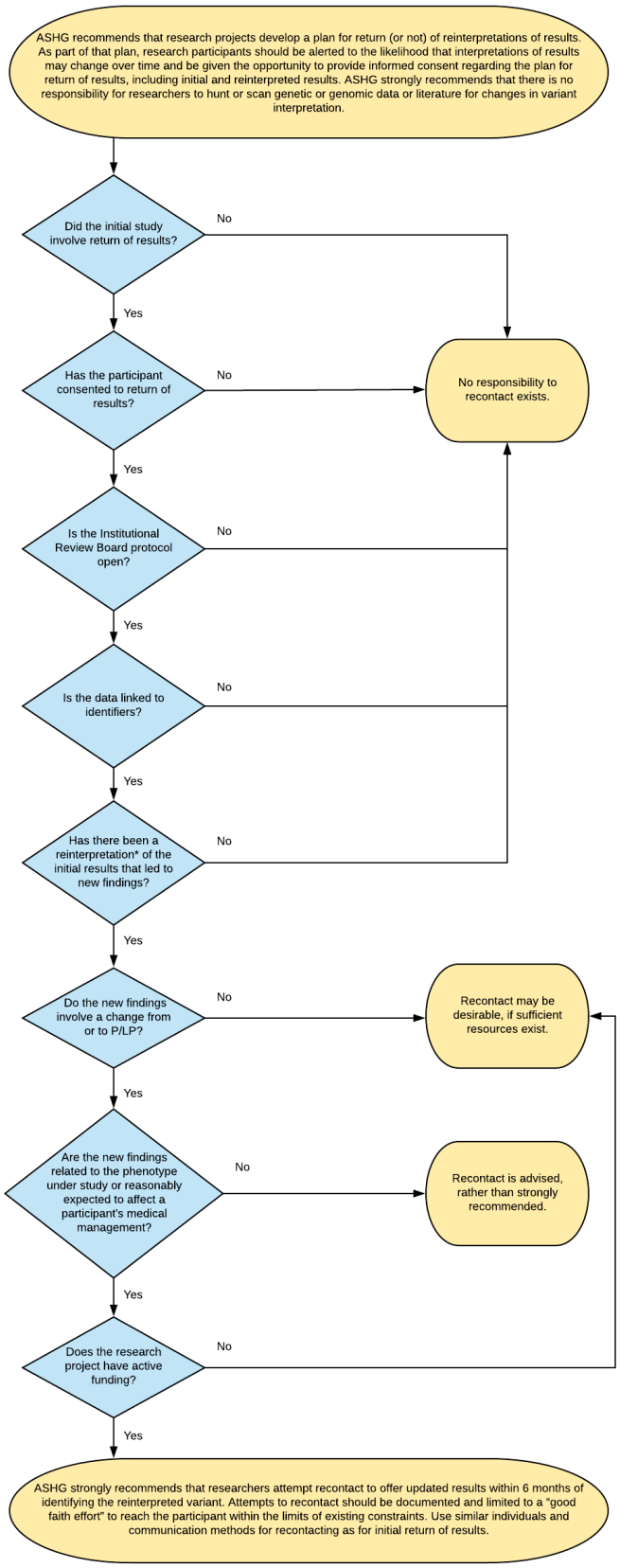
Figure 1: Recommended pathway for considering recontacting participants after reinterpretation of genetic and genomic research results

[To be used in conjunction with recommendations listed in Box 1]

Figure 1 Legend: Reinterpretation refers to both reclassification of variants and reanalysis of original data (per section "*what does it mean to reinterpret results*?")

Box 1: Recommendations for recontacting participants after reinterpretation of genetic and genomic research results

FIGURES & TABLES



*Reinterpretation refers to both reclassification of variants and reanalysis of original data (per section *What does it mean to reinterpret results?*)

Figure 1: Recommended pathway for considering recontacting participants after reinterpretation of genetic and genomic research results.

Box 1: Recommendations for recontacting participants after reinterpretation of genetic and genomic research results

1. ASHG *strongly recommends* attempting to recontact participants to offer updated results if the reinterpretation is related to the phenotype under study or reasonably expected to affect a research participant's *medical management*.

2. If the reinterpretation is *not expected* to affect management, recontact is advised, rather than strongly recommended, for correction of the classification of variants previously reported to the participant whose pathogenicity classification has changed from or to Pathogenic/Likely Pathogenic.

3. ASHG strongly recommends that there is no responsibility for researchers to hunt or scan genetic and genomic data or literature for changes in variant interpretation.

4. ASHG recommends that any *responsibility* to recontact is limited to the duration of research funding. Recontact after the conclusion of funding may be *desirable* if sufficient resources exist.

5. ASHG recommends that no responsibility to recontact exists when the IRB protocol associated with the study closes or identifiers are stripped, rendering further recontact infeasible.

6. ASHG recommends that, when there is a strong recommendation for recontact, the recontact should occur within 6 months of the reinterpretation.

7. ASHG recommends that attempts at recontact be documented.

8. ASHG recommends that any responsibility for recontact is limited to a "good faith effort" to reach the participant within the limits of existing constraints, including (but not limited to)

financial and personnel resources, the existence of accurate contact information for the participant and willingness of the participant to accept recontact.

9. ASHG recommends that research projects develop a plan not only for initial return of results, but also for return (or not) of reinterpretations of those results. As part of that plan, research participants should be alerted to the likelihood that interpretations of results may change over time and be given the opportunity to provide informed consent regarding the plan for return of results, including initial and reinterpreted results.

10. ASHG recommends that, if the participant consented to any return of results at the time of original research consent, then consent to recontact for the same type of results is implied and therefore appropriate subject to the other recommendations in this policy statement.

11. ASHG recommends that, ideally, the same individuals and communication methods should be used for recontact as were used for the initial return of results.

12. ASHG acknowledges that in the research context, participants may be consented for initial return of a much wider range of results. Thus, reinterpretations derived from reanalysis broader than those addressed in this statement are appropriate to return when that is consistent with study design and consent documents.