Jackie: Welcome to our live webcast brought to you by the American Society of Human Genetics. Thank you for joining us. My name is Jackie and I will be the operator for the presentation today. Before we get started, I would like to take a moment to acquaint you with a few features of this web event technology. At any time, you may adjust your audio using any computer volume settings you may have. On the right hand side of your screen, you will see a text window for questions. There is a large window that holds all of your sent messages, and a smaller text box at the bottom where you will type in your question.

Jackie: To send a question, click in the text box and type your text. When finished, click the send button. All questions that you submit are seen only by today's moderator. The moderator will present your questions to the speaker, and we will attempt to answer as many questions as possible at the end of the presentation. At the conclusion of today's program, we ask that you complete a brief post event survey. Please take a moment to complete this survey as it will help ASHT plan future web events. We are joined today by our moderator, Leila Jamal ScM PhD.

Jackie: She is a certified genetic counselor at the National Institute of Allergy and Infectious Diseases and an affiliated scholar with the NIH Bioethics Department. At NIAID, she is a co-investigator on the Centralized Sequencing Initiative, a program that uses genomic sequencing to better understand the human immune system. The CSI has developed the first scalable pipeline for returning clinical grade research results to NIAID research participants. Her research interests include the return of results from genomic sequencing studies in settings where research and clinical responsibilities overlap. At this time, I'd like to turn things over to our moderator, Dr Jamal.

Leila Jamal: Hello and welcome to this webinar hosted by the American Society of Human Genetics. As our introducer mentioned, my name is Leila Jamal. As a genetic counselor who spends a lot of time thinking about the ethical, and the practical issues involved in returning research results to study participants. I was very pleased to be part of the ASHG work group that examined the nature and scope of researchers responsibilities in the area of variant reclassification and recontact. I and my colleagues are looking forward to participating in the discussion generated by the ASHG joint position statement and today's webinar.

Leila Jamal: Without further ado, let me introduce our speakers today. We will hear first from Dr Yvonne Bombard. Dr. Bombard is a genomics health services researcher and scientist at the Li Shing Knowledge Institute of St Michael's Hospital. She's also an associate professor at the University of Toronto in the Institute of Health Policy Management and Evaluation. Her research focuses on evaluating the adoption of new genomic technologies in clinical practice. She conducts public and patient engagement research to advance health technology assessment and health service delivery.

Leila Jamal: Dr. Bombard has acted in numerous international policy advisory committees and her research informs policy of development in several areas. Today we will also hear from Dr. Howard Levy. Dr. Levy is an associate professor of medicine at the Johns Hopkins University School of Medicine, and the co-chair of the Johns Hopkins Medicine patient and family centered design team. His areas of clinical expertise include routine primary care, pharmacogenetics, cancer genetics, clinical genetics and Ehlers-Danlos Syndrome.

Leila Jamal: His research interests include genetic education, heritable disorders of connective tissue, electronic health records and patient portal. Before we begin, I'd like to remind members of our audience to ask questions throughout the presentation today. I'll be keeping track of them and we'll answer them during our Q and A session at the end. I'll now turn it over to our first speaker, Dr Yvonne Bombard.

Dr. Yvonne B.: Thanks Leila. Thanks everyone for joining today. Howard and I are grateful for the opportunity to present this work on behalf of the larger ASHT recontact work group. The numbers are listed here on the slide and are drawn from various countries and jurisdictions including the US, Canada and Australia. Our work group members offer a range of expertise including laboratory and clinical scientists, laboratory directors, medical geneticists, primary care providers, bioethicist, health services researchers, lawyers and genetic counselors.

Dr. Yvonne B.: In addition to ASHT members as well as social issues committee members. We were also fortunate to partner with members from the National Society of Genetic Counselors, Canadian College of Medical Genetics and the Canadian Association of Genetic Counselors. Next slide please. We're also fortunate to have the support and endorsement from the following organizations including genetic patient groups such as the Genetics Alliance and professional societies internationally, including the European Society of Human Genetics, Human Genetic Society of Australasia and various others listed on the slide.

Dr. Yvonne B.: Next slide please. Ultimately, we came together to address an increasingly pro-common scenario which might look something like this. Your IRB approved protocol allows you to release VUS results to participants who are asymptomatic for a particular disease condition to your awareness. However, you happen to discover that a previously returned VUS has now been reclassified as pathogenic, either because you came across that reclassification yourself or perhaps the patient was asymptomatic at time of initial return of results has now come back with symptoms. What should you do now? What is your responsibility as a researcher to recontact those participants with that VUS results, to update them on their reclassified result.

Dr. Yvonne B.: Next slide please. The scenario may become increasingly common since VUS get reclassified at a relatively high rates. Up to half of such variants have been reclassified in the past decade and a majority of these are downgraded to benign. Of course, reclassification rates vary across clinical indication ethnicity, but importantly some reclassification can impact clinical management through screening, treatment or familial testing recommendation. One paper found that, 12% of these way classifications had the potential to alter clinical management. So this raises critical questions about whether researchers have a responsibility to communicate new knowledge on previously reported genetic variance.

Dr. Yvonne B.: Next slide please. The question of recontact is challenging. On the one hand there is a basic but important recognition that recontacting individuals, keep them abreast of new knowledge. Is it ethically desirable and important goal? The problem is that we live in a world of limited resources and the cost of achieving this goal can be onerous, especially for research that often is time limited and has limited budgets. In the research setting, the analysis is inherently a bit different, because the goals of research are not the same as delivering clinical care. The goal of research is not to deliver medically important information, but it's to produce new information, new knowledge to benefit society as a whole.

Dr. Yvonne B.: Of course direct benefit to an individual research participant is wonderful if it can occur, but it is not the primary purpose of research. So one could legitimately argue that the benefit to the individual by recontacting them, for example, is somewhat lower in a research setting, and very importantly, anything that takes away from resources of promoting the actual research goals is getting in the way of achieving those goals. So there's an opportunity cost here. There are limited resources and if they aren't used appropriately, and that unpacks the success of the research. So what ought scientists do?

Dr. Yvonne B.: Next slide please. This is where guidance help, but the only research guidance that exists relates to the initial return of results, not recontact, and this is by Gail et al as part of the CSER emerge consortium which recommended that at minimum, researchers should offer actionable results, that there is no duty to hunt to return these results, that the return of results is limited to the active period of funding, and the participants must be identifiable and may actually opt out of receiving these return of results. But again, these recommendations do not address the contacting participants who variants might have been reclassified since their initial return of results.

Dr. Yvonne B.: Next slide. So after return of results, is there an actual duty recontact? Existing guidance that has been recently published in this domain has actually come from the clinical setting, for example, by a CMG and ASHG. But there is no existing policy that addresses whether and when researchers ought to recontact their research participants after reinterpretations genomic test results. I'll hand it over now to Howard to explain how we fill this gap.

Dr. Howard L.: Thanks Yvonne. So back in the fall of 2017, several of us on the social issues committee started talking about this issue largely at Yvonne's initial astute observation of a gap year. We actually, some of you may have recalled or even attended a small colab at the ASHT meeting in October, 2017, on the exhibit floor where there was a small but lively group that attended and there was a very robust discussion about this issue, and really it came back to what Yvonne has reviewed and what's in the literature that yes, recontact is ethically desirable but sometimes very challenging resource intensive and a need for guidance around what is the responsibility and how best to approach it.

Dr. Howard L.: So we went to the ASHG board of directors and got approval to tackle this issue, convene the work group that you've already heard described by the end of 2017. Spent most of 2018 working through literature review, having our own lively discussions about pros and cons, bringing in additional work group members as we evolve and eventually got to last fall where we were able to present a draft statement to the board of directors. We then for those who were fortunate to attend, had another an invited session at last year's ASHG meeting where we heard from the American College of Medical Genetics and the European Society of Human Genetics on their policy statements as well as presenting the draft of this statement that we're here to talk about today, and then had a very nice discussion after that.

Dr. Howard L.: With the input from the board of directors, and the input from that session last fall, we made additional adjustments to the position statements that we're here to discuss today. Submit that back to the board of directors, and that got approved by ASHG board in November of last year. Then we took it back to our partner organizations as you saw on the prior acknowledgements live and got their endorsement as well. So this really was a multinational multi-specialty efforts that was ... I think a wonderful experience for all of us involved and hopefully we've arrived at something that all of you will find workable and helpful.

Dr. Howard L.: The way we approached it was first to lay up a scope, and you've already heard much of this already, but basically we felt that the needs here and the guidance from our board of directors was to focus on the research setting. But of course recognizing that there's a blurry line between research and clinical care, so there will always be crossover, and then of course recontact can only happen if there has been an initial return of results. So this second bullet here of course is that there is no recontact if there hasn't been an initial return, and certain areas excluded from the scope would be anything that is purely clinical with no research component that belongs in the clinical realm.

Dr. Howard L.: We expressly excluded issues about people who have died. There are other publications addressing release of information, return of results and recontact and those settings. We stayed away from pediatric and transitioned to adulthood. But essentially all guidance for handling information for children and their transition to adulthood would still apply. We believe to everything that we've produced in this guidance and recommendations statement. Again, we are not addressing in this return of results, but rather focusing on recontact after initial return has occurred, and the Jarvik paper that you've already seen referenced really is the Go To Source for initial return of results even in the research setting.

Dr. Howard L.: Another important thing to highlight is our word choice in this entire statement. We set out very carefully to not establish legal standards or legal precedent. This is not meant to obligate anybody to do anything. This whole purpose was to provide guidance where there had not previously been any. So our word choice is very careful and intentional using words such as desirable and recommendation. Despite the word duty being discussed throughout the last year and a half as all of this as being massaged. We've stayed away from words such as duty or obligation in any of the recommendations statements, and even the word responsibility is used primarily to clarify or limit what one might be expected to do rather than to expand anybody's obligation. So no responsibility in certain settings or when there was responsibility, there are certain limitations to whatever that responsibilities might be.

Dr. Howard L.: Our framework, the first words here on the slide is more than just a fancy word to show up proactive. Inherently anything that you do when you jump into the middle is hard to turn around and apply retroactively, but of course many of us find ourselves in those situations. So the guidance and the recommendations in this policy statements are necessarily going to be challenging retrospectively. But the main idea is with your next research project, the one that you're designing right now. Hopefully you're thinking about the issues that we're discussing today, now building that into your research design.

Dr. Howard L.: So the proactively and prospectively we are all moving forward in an environment where this kind of thing is being thought about and we're moving in the right direction, and indeed we are not just coming up with a consensus statement here, but we spend a lot of time and effort looking through the research, looking at ethical principles and previously published position statements, philosophies, ethical principles, and research outcomes to help guide what makes the most sense.

Dr. Howard L.: With that in mind, if one goes back and looks at the original Belmont report and the four pillars of ethical principles. The first one that really dominates in all of this is respect for persons and within respect for persons as you see on the slide here, there are two main components. The first being autonomy, and autonomy requires ... we feel deserves some additional thought as well. It's more than informed consent, it's more than a onetime, here's what's going to happen, are you okay with it? Good, I'm done with that.

Dr. Howard L.: It really is an ongoing naturally maturing process of providing information and asking for feedback. So this idea of autonomy, informed participation is a constant communication two way street. The second aspect of respect for persons is the concept of veracity or truth telling. The really important nuance to all of this is the idea that one could make an argument that if one release some information, when one have it, and at a future time period that information changes, then what was released to a participant previously would no longer technically be true. That with this new knowledge, the concept of truth telling would lead to some sense of ethical drive or desire to keep that participant, that recipient of information updated on the newer truth in this period of ongoing two way street autonomy.

Dr. Howard L.: So you start to see where there's some conflict here, that there's the desire, the need to respect people and maintain this truth telling. But again, limited resources. We have a two big pillars or big pieces of the Belmont report or the concepts of beneficence and justice, and really what we're getting at here as Yvonne has already highlighted, is on one side of this balance beam is the benefit to individuals, which in clinical care is always paramount first and foremost. But in research benefits to individuals is secondary. It's great when it happens, but not the goal of research.

Dr. Howard L.: But conversely, there's a justice risk here. If the research itself does not come to fruition, if the expenses that are expended, and if the risks that the research participants take do not result in generating the new knowledge, then a strong ethical argument can be made that those risks and costs were not justified and therefore should not have occurred. So beneficence and justice really have a different analysis in the research setting than they do in clinical care, and that again complicates the whole thing.

Dr. Howard L.: So how do you actually make this into something you can produce a guideline out of? The answer to that, we came up with the concept of practicability, which is essentially to look at all of these competing needs. You can't always do all of it. The idea though is to try to maximize individual engagement and benefit, while at the same time preserving the justice, making sure that every opportunity is maximized for the research to reach its goals of generating new knowledge and benefiting society.

Dr. Howard L.: Acknowledging that again, if individuals are taking risk to participate in research, those research goals need to be met or that risk can't be justified. Now this analysis is inherently subjective, so if it was just left to principal investigators and other research staff, it could be very easy for them to just say, “Sorry, too expensive, resource costs are too high. We can't justify recontact.” On the converse side though, it would also be biased for an information advocate to say you must always recontact.

Dr. Howard L.: So this kind of decision making we think is always going to need support from independent bodies, which can be IRB, can be Ethics Panels, can be other advisory boards, but no one should feel that they have to go this alone. This is the kind of thing that really does require analysis and fought on a case by case level, whether that's research project by research project, or even extenuating circumstances for an individual participant in a specific research project.

Dr. Howard L.: So with that in mind, that's the background of how we got to where we are. Now we'll dive into what you're probably all here for, which is the actual recommendations. I'm going to pause for a second because unfortunately we've had some technical difficulties, which is what the latest getting started. So our original plan was for Yvonne to take back over. Yvonne, I can advance the slides and you walk through this part if you'd like or I can keep going and you jump in wherever you feel like you want to add something. How do you best want to approach this?

Dr. Yvonne B.: Why don't you keep going Howard, since that's easiest for everybody participating, thanks.

Dr. Howard L.: Yes. Unfortunately not able to be on the Adobe. She's following along on the slides and jump right in at any point that I miss something that you had meant to emphasize here. So our basic point here is that, we want to be proactive. The ASHG is recommending, and our partner organizations recommending that when you're designing a research project, plan ahead, develop that plan for whether or not you're going to return results and whether or not you're going to return reinterpretations of those results.

Dr. Howard L.: Yet ongoing informed consents and asset and participation of your research participants so that they understand that these interpretations of genomic variants will change over time, may change over time, and they need to know that they have the opportunity to get those results back, get the initial results, get reinterpreted results, and just be prepared for it and give them the opportunity to accept or not accept that information.

Dr. Howard L.: Then again, as we stated earlier with the Jarvik paper and in the recontact principal as well, this last sentence is important that, there is no obligation for a researcher to proactively hunt or scan the literature for new interpretations. We're more thinking about situations here where you happen upon the information by whatever means you might get it, but certainly no duty, no obligation or responsibility to go perusing literature on a recurrent basis to try to find these changes. Great, if it can be done, not a requirement, not a responsibility.

Dr. Howard L.: When one does find a re-interpretation, then we get into this framework and this algorithm of how to approach it. The first question, of course is, did the initial study involve return of results? Right? Because you can't recontact if you didn't initially release. If the answer is no, then very simply there is no responsibility for recontact and there's nothing else that needs to be done. If the answer is yes, that the study did return results, then your next question is, has the purchase been consented to that return of results and presumably also to recontact in the setting of initial return? If the answer was no, that the patient or participant rather did not consent to return of results. Again, there's no responsibility for recontact because nothing was released. If they did, then our next question is, okay, is your protocol still open? Is the IRB protocol open? Is the research still ongoing in some way?

Dr. Howard L.: Because the presumption is that if you're not, if your project is not ongoing, you probably lack resources to do the recontact. So if the answer is no, the protocol is closed. Again, no responsibility for recontact. If your protocol is still open, then the next question is, is it feasible to reach back out to somebody? So if your data is completely anonymized, you don't know to whom a particular variant belongs, again, it would be unreasonable to ask you to work backwards and re identify those participants. So if the data is not linked to identifiers, again, no responsibility for recontact. If you do have identifiers link to the data, then the question of course is, all right? Has there actually been a reinterpretation of those initial results? That re-interpretation leads to new findings.

Dr. Howard L.: Again, as Yvonne outlined earlier, that re-interpretation could be a reclassification of a previously identified variant. It could be re-analysis of original data. It could be that that area of the genome hadn't been looked at before and now you're looking at it for some reason or could be that you looked at it, but it was not previously recognized to have clinical importance, and now some new publication has come out showing that that particular variant or that particular segment of the genome now is believed to have some interpretation. So really any, in a broad definition, any re-interpretation that might lead to new findings that could be relevant to somebody, that would be something where you'd consider recontact.

Dr. Howard L.: If the answer was no, again, there's no responsibility. If the answer is yes, then we've run out of room on the slide. So we jumped to the next slide. So if the answer to all of the previous questions was yes, then we get to, okay, how critical is this re-interpretation? Do these findings involve a change to or from pathogenic or likely pathogenic? So for most of us, I would venture to say almost all of us, we consider the medical and clinical applications of P and LP to be essentially the same. Certainly benign and likely benign are generally considered, have no real consequence, usually not reported out at all, and variants of uncertain significance in truth are neither benign nor pathogenic, but they're often treated the same way as benign or likely benign, which is to say no action is typically taken, although it's done with more uncertainty, hopefully communicated to that recipient of the knowledge.

Dr. Howard L.: So the first question we're asking here is, has this re-interpretation moved up from anything below PLP into PLP or vice versa from PLP back down to VUS or benign or likely benign? If the answer to that question is no, that you stayed within pathogenic, likely pathogenic or you've stayed in the spectrum of VUS or benign or likely benign, then the feeling is, recontact is still desirable, but the resource cost, the opportunity cost may not be worth it. So it is really more of a weak recommendation if feasible, if simple enough to do, yes, go ahead and do it, but it's a weaker recommendation.

Dr. Howard L.: Conversely, if yes, it is a move between PLP and anything else, then the next question is, is this directly related to the phenotype under study or is it reasonably expected to effect the participants medical management? The simplest way to think about this, although it's not an absolute definition, is if you're using the ACNG list of secondary findings or something similar. Then if it's among that category of genes and variants that are considered medically significance, then we're probably answering yes to this question. If your answer was no, it's not the phenotype under study and it's not expected to affect medical management, but it was a change between pathogenic and not pathogenic, then there's still a stronger recommendation. So much as to advise it, so stronger than that desirable but not the strongest recommendation.

Dr. Howard L.: If the answer to this question is yes, this is actually under study and or is felt to be medically significance, then we come back to the question of, okay, not only is your protocol open, but you still have active funding. Do you have the resources available to actually accomplish this recontact? If the answer to that question is no, then we're back to, okay, it's desirable, but it's really limited by the resources. Actually in our preparation for this presentation, we realized that in our algorithm we left something out here. So in this section here, if you're still under no for affecting the condition under study and no it's not a medically significant condition, we said it advised, but not strongly recommended.

Dr. Howard L.: But again, if you don't have active funding then you're probably really back in this desirable category. So a little bit of an oversight that we've only just realized and we're going to work on some sort of an addendum to the publication now that we've realized that. But if your final answer to all this is yes, it's a medically significant re-interpretation or to the phenotype under study, your project is still open, still funded, you have resources. Then we come to this final strong recommendation. In this circumstance, yes, it is strongly recommended to attempt that recontact to offer those updated results and it should be done relatively promptly, ideally within six months of coming upon that new information.

Dr. Howard L.: Of course like any other clinical or semi clinical care, those attempts to recontact should be well documented, but you don't have to go to the ends of the earth. If you can't reach that participants, a good faith effort is good enough and there's room for understanding what is logical and reasonable. Then whatever channel of communication you use for the initial return of results would probably be the most advisable channel for use for that recontact as well.

Dr. Howard L.: That in a nutshell summarizes everything that is in this publication. I highly recommend that you read the publication if you've not yet done so. We do have a box in the publication with 12 specific recommendations statements that essentially cover all of what we just walked through here in this algorithm. I think that brings us to the end of the slides, this is just to remind you of the reference for the paper and our participating organizations and I should turn it back to Yvonne for her to fill in anything that I might've missed in walking through the algorithm.

Dr. Yvonne B.: Howard, great job, and in lieu of the fact that we started late. Let's turn it over to Leila and we can get into the question answer period. Thank you Howard, for taking over at the last second.

Dr. Howard L.: Of course. Good plan. So Leila, back to you.

Leila Jamal: Sounds good. Thank you both. I also want to thank members of the audience who's been submitting questions as the presentation was going along. Please continue to feel free to submit questions. I'll say just as a clarification point, there are some questions that have been submitted which pertain a little bit more generally to the issue of return of results, which certainly is relevant, but I want to be clear that this position statement really quite specifically addresses the issue of whether there's a duty to recontact once a project has returned results. As such, I'm going to prioritize the questions that address that scenario first, and then certainly since this issue builds upon prior work in the return of results space generally, I will move on to some of those other questions if we have time.

Leila Jamal: So the first question from the audience I'd like us to think about is, a participant has asked a question. Basically, the people enrolled in a study may not have initially consented to return of results. Let's say perhaps later on they've changed their minds and if a researcher founds something new that's clinically actionable, is there any duty to recontact the study participants to get a renewed consent, to see if they want to receive results that they may not have opted to receive in the past? In general, the participant is just interested to hear how you view this issue. Howard and Yvonne.

Dr. Howard L.: I think that is best answered on ... Where was it now? We had an earlier slide. Oh, right here, yes. In this slide, hopefully I've correctly moved the slide back to our framework, under respect for persons in autonomy, this idea of ongoing informed participation. So I'm curious what others think, but to me, this really comes back to the idea of informed consent is not a onetime thing, but an ongoing two way communication. So if a participant initially did not want return of results but changed their mind, I would hope that the research protocol had the ability to hear back from that participant who said, “Yes, I've changed my mind, I now want to know.” That should be appropriately documented. Then once that is who wants that discussion has occurred, then return those results and if there's a recontact downstream from there, act upon that, that latest version of informed consent.

Dr. Yvonne B.: Yeah, I would just add to that, that how we thought about informed consent and try to operationalize that within this statement was to really mirror the informed consent that was communicated and received for the initial return of results. In a very basic way, we applied and extended the consent that would have been obtained from the participants about the initial return of results to any future recontact. So in the initial return of results in the protocol, if that person or participants had consented to receive initial return of results, then that would apply and extend to recontact, and vice versa.

Dr. Yvonne B.: If there was no return initial informed consent about the initial return of results and that would again apply and extend to the recontact. But if there is, as Howard says, if there is a living ongoing and foreign participation where there's the opportunity to reconsent that person and explain what return of results and recontact involved, it presents a wonderful opportunity to open up that I have a new communication and recontact them in future.

Dr. Howard L.: I've got two other thoughts, it just dawned on me. One is that, if the intent of the question was, that I might think there's something important here, should I recontact that person despite not having their consent? My answer would be no, because the very act of reaching out and asking, “Have you changed your mind? May I recontact you?” That might convey a suspicion that, “Oh my goodness, there's something new here.” That is now not respecting that person's autonomy and right to not share the information.

Dr. Howard L.: The other thought that I realized may be relevant here is what if the protocol is already closed, how would a participant later find out? The answer to that in today's world is we don't have a good infrastructure for that. My biggest excitement about this whole project, there were many good things that I enjoy participating on this project, but I'm very enthusiastic about the future of information technology to manage some of this. So in my utopian view, participants who receive their data, get it in some electronic form where they can maintain it and hopefully in the relatively near future measured in years, not decades, we will have good infrastructure to allow people to bank their data, hook it up to information sources such as ClinVar and other data sources that will allow people to simply register to be notified when something has changed.

Dr. Howard L.: That not only helps participants stay informed downstream when the protocol has closed, but it could also take some of the burden off of researchers by making more of a self service model where participants get their own information when appropriate, and of course seek researcher or clinician help when they've got an important question to get answered. But I think I've made a lot more of the question than the originally was. I should shut up here and let Leila take back over.

Leila Jamal: All right. Thank you both. The next question comes from a webinar participant who's interested in your statement that there's no duty to hunt for new interpretations of variants. The participant wanted to know if you think it's anyone's job to hunt for new interpretations of variants, like they'd been reported back to patients and if so, who's job is it? Or if not explain.

Dr. Yvonne B.: So I'll take a first stab at my initial [inaudible 00:36:31] which is that I wish that it was the job of every research study, but I think that we all in reality work with very constrained budgets and very constrained resources and time. So unless if that job is part of the research objectives, the specific aims, and as part of the protocol, then it might not necessarily be the job of that individual researcher, but it could be a collective question as to us as a research community. To what extent that needs to be an ongoing job and what is the data source from which we prioritize those re-classifications and how do we share that? So I think it's a larger almost institutional or society wide question. I'll turn it over to Howard for additional thoughts.

Dr. Howard L.: Yeah, it's a huge problem. I think it's fascinating to look back at the last time ASHG published anything on this issue. It wasn't ASHG published, I'm sorry, but there was a survey of ASHG team members in 1999 asking their opinions on recontact, and this is cited in our publication as well in the policy statement. Interestingly in that survey, ASHG membership felt that it was overwhelming. The majority of folks felt that it was a really good idea to recontact folks when there's been a reinterpretation. But when asked, who's responsibility is it? That's where things started varying a little bit more and oftentimes the finger was pointed at the clinician, but sometimes at the participant or the patient as well.

Dr. Howard L.: Even more interestingly, when you broke down the respondence, researchers were much more likely to put the responsibility on clinicians, then clinicians were to put responsibility on themselves. So my honest human answer is, we all think it's a good idea, but we all find it daunting and hard to do. So we're hoping somebody else will do it, and my hope is again, that computers and information technology will do it, that IBM's Watson or some other really sophisticated artificial intelligence software can come to our rescue and make this much easier. But again, that's future hoping.

Leila Jamal: Okay, that's very helpful. Thank you. There's a series of questions that I'm going to bundle together next because it seems like many people are asking for practical guidance about the type of language you recommend, should go in a consent form in order to make sure that people who are writing protocols today are compliant with these recommendations if they feel they have the wherewithal to do this.

Dr. Yvonne B.: So, this is Yvonne. I'll take the first stab. We didn't actually have any wordsmithing advice produced in the publication itself. But again, here is where we again rest on the initial return of results in the consent or the language that was formulated in those documents and conveyed to participants to begin with. So again, we would probably advise, and this is not again something that was necessarily discussed or suggested in any practical way or language that was provided.

Dr. Yvonne B.: But it would probably mirror the same kind of language that was used around the initial return of results and where there would be any changes to those initial return of results in terms of the way that those texts would be understood to impact yourself, as you participate in those and that would be an invitation to have a participant permission to re contacted about that. So again, I'm trying to suggest that you'd be essentially mirroring the same kind of language that's used in the consent form around the initial return of results to convey any obligations or permission to convey new updates on that information that was initially returned.

Dr. Howard L.: I completely agree. Again, we're not in this case speaking for the American Society of Human Genetics. The best practical advice is, we probably all recognize that most of our informed consent documents are way too wordy and are to some extent written for the lawyers more than for the participants. So I would try to frame it and state it in the simplest possible English. Question one, would you like to be informed of the results that we find and which one's? Right? Then just explain in plain English what is a VUS. Questioned two, if our understanding changes in the future, do you want to hear from us about that new understanding? Simple, plain English.

Leila Jamal: Great. Thank you. There's another series of questions that ask about the nature of the classification and question. I guess there are several participants online today who just liked to hear you guys talk a little bit more about, whether or not if the variant reclassification is from VUS to benign or VUS to likely pass, how should people think about that?

Dr. Howard L.: We struggled a lot with this one, we eventually landed on is, because people will take medical action based on their belief that they either are or are not at risk for a particular condition and then effort to keep it relatively simple. We drew that line at the border between VUS and likely pathogenic. If the reinterpretation crosses that line because that's a major change and that's the highest recommendation. The reality that I think we all recognize is that, most lay people and probably a lot of us geneticists struggle with truly grasping and coping with the uncertainty of the VUS. It is right smack in the middle and we truly don't know if it's causing a problem or not causing a problem.

Dr. Howard L.: So it's a great question to ask. What about a VUS, especially if someone has over interpreted that as being either benign or likely pathogenic and taking some actions, shouldn't at also require recontact or shouldn't it be a higher standard for recontact? Again, there's no official policy from American Society of Human Genetics based on this statement. My personal feeling is, this is a great example of why at best this publication can only be guidelines and recommendations. It's always going to be case by case. It's going to depend on the severity of the medical condition under question, it's going to depend on the specific case of that individual participants and how they had perceived their VUS and how they would now perceive the change.

Dr. Howard L.: So if it's someone who considered a VUS to essentially be pathogenic, now we're just saying, "Okay, guess what? It's pathogenic. Maybe that's not such a big deal, but it might be psychologically reassuring to just finally answer it. Conversely, if someone was considering that VUS pathogenic and now we believe it's benign, that's a much bigger deal and then of course there's a greater ethical desire to update that information until the new truth.

Dr. Yvonne B.: Yeah, the only thing I'd add because I agree fully with the nuance that Howard tried to illustrate is that these are meant to be, these recommendations are meant to be floor recommendations, not what you cannot do if you choose to do, and if you don't have any more resources, if you have more resources than what we expect to be finite budgets for research. That's why the recontact was still desirable in the case that VUS gets reclassified, for example, to the benign or likely benign. It's still desirable to recontact if you have sufficient resources.

Dr. Yvonne B.: Again, that's just the floor recommendation if you can, and want to do so then please go ahead. It's not something that we advise you can't, so I just wanted to find that, provide that extra clarification.

Leila Jamal: Okay, great. That's very helpful. Thank you both. Our next question, I think is quite interesting. There's a participant who'd like us to consider whether any responsibility lies with the research participants to contact the researcher to request and whether any results have been reclassified. I'm wondering what you guys think about that.

Dr. Yvonne B.: So that would certainly mirror the clinical arena where there is an expectation on clinical patients remain in contact with their clinician to learn of any updates that might be relevant to their results or certainly recontact at certain points in the life cycle that would be pertinent for them to learn new information such as planning a route that needs family planning, et Cetera. But that is not something that we address specifically in the statement, but certainly the ASHG, the ACM gene, the ASHG have language that ... and we've mirrored that language in our statement in this particular recent statement, that there is a shared responsibility among all of our communities, both as scientists, researchers, clinicians, and patients to play a role in this space and try to all remain in contact if you will.

Dr. Yvonne B.: But ultimately what we try to articulate and operationalize with our recommendations is what is that the role of the researcher, first and foremost to actually initiate that recontact. So certainly again with the idea that this is reflecting the floor recommendations and should patients and others choose to have open participation on engagement, then that would be a wonderful scenario whether that's feasible and available and there's sufficient resources to do though. Did you sell within a larger question but again, this is a shared responsibility about primarily one that rests at first last year with the researcher. Howard, do you want to add anything?

Dr. Howard L.: I think I would just draw an analogy that hopefully will resonate. I'd like to believe that every single person on this call would agree that it is ludicrous to ask the question, gene or environment? That our answer is gene and environment for any particular phenotyping question. But some phenotypes are more related to the gene and some more related to the environment, but it's never, almost never one or the other. I think the same concept applies here, it's not the researcher's responsibility and it's not the participants responsibility, it's both. It's shared and in different situations it might be more on one and more on the other, but I think all both rise and more people benefit if everybody shares that responsibility.

Leila Jamal: Okay, great. Our next question seems to come from more of an IRB perspective, for some research projects go on for years or even decades, and some feel that if there has not been any ongoing relationship with the research participants, recontact would be intrusive or even inappropriate after a significant period of time has lapsed. What do you think about that?

Dr. Howard L.: Again, personal opinion. I think that if the participant said, “I'm interested in recontact.” Five years, 10 years down the road, I as a researcher learn something that I believe is medically relevant. I am ethically, I don't want to say bound or duty bound but the ethical principle is honored. The last piece of information I got from that participant, if they said they wanted to be contacted, I should try to contact them. If they don't return my phone call and I've made a good faith effort, then maybe they've been not returning my call, told me that they're no longer interested, but I think I owe it to that participant to honor the last guidance that I got from him or her regardless of how long it has been. If my research protocol is still open and I'm still funded.

Dr. Yvonne B.: Yeah-

Leila Jamal: Yvonne and Howard.

Dr. Yvonne B.: ... I tend to agree with Howard.

Leila Jamal: Okay, great. I'm mindful that we're coming up on a time here, but I'm also mindful that we started late, so I think maybe we'll have time for one more question, and then after that I believe we are going to make a good faith attempt to go through some of these ones we haven't answered and find some way of getting back to our audience with, if not granular one by one answers and some kind of overall summary statements that addresses many of these questions as possible. So my apologies to those of you whose questions we did not get to address. But do you agree that we have time for one more, Howard and Yvonne?

Dr. Howard L.: [crosstalk 00:50:34]

Leila Jamal: Okay. So the last question is, just noting that a lot of our discussion today has focused on re-interpretation, but our participants interested in this scenario where exome information is acquired. An initial curation is limited to just a few genes, which are then looked at and returned to the participants, however, if the remaining exome sequences made available to the broader research community and then medical relevant variants come up through that research, is there any a responsibility to recontact if the initial researchers made aware of those variants?

Dr. Howard L.: Wow. Thanks for saving that for last. So we should answer [inaudible 00:51:17]

Leila Jamal: Why?

Dr. Howard L.: I love the problem. It's a great example of how we need better interoperability. If we're moving in that direction and it raises new ethical questions. I think the basic ethical principles still holds, that if new knowledge is gained and a participant wants to be informed, then yes, it is ethically desirable to provide that information. But this scenario really just pours the salt in that wound of whose responsibility and how best to do it. I can't answer that in the time we have left. That's a great question that I think needs a lot more thought.

Dr. Yvonne B.: Yeah, and I wonder if actually that would still be in captured by our definition of reinterpretation, which actually refers both to reclassification of variance and re analysis of the original data. So that renounced with the original data might be where that scenario fit, and if that's the case again because it's requires subjective interpretation of these guidance, endless guidance, then these recommendations might hold. But again, under the larger principle and rubric that these are meant to provide guidance that are intended to be operationalized on a case by case basis, we would probably advise, and this is not an ASHG speaking, but a personal opinions to consult with the local IRB and ethics board for a more specific guidance and advise.

Leila Jamal: All right. Thank you again to the audience for submitting such thoughtful and detailed questions. We will certainly look through them and apologies again to those we didn't get to. I think at this point. That concludes the Q and A section of this webinar and I'll now hand back to the FSHD team to close us out.

Jackie: All right. On behalf of the Society of human genetics, I would like to thank you for your participation in today's event. A post event survey will appear requesting your feedback. Please take a moment to complete the survey as it will help ASHG plan future web events. This concludes today's program. Thank you and have a great day.