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Processes and factors involved in decisions regarding return of incidental genomic findings in research

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Abstract

Purpose—Studies have begun exploring whether researchers should return incidental findings in genomic studies, and if so, which findings should be returned; however, how researchers make these decisions—the processes and factors involved—has remained largely unexplored.

Methods—We interviewed 28 genomics researchers in-depth about their experiences and views concerning the return of incidental findings.

Results—Researchers often struggle with questions concerning which incidental findings to return and how to make those decisions. Multiple factors shape their views, including information about the gene variant (e.g., pathogenicity and disease characteristics), concerns about participants' well-being and researcher responsibility, and input from external entities. Researchers weigh the evidence, yet they face conflicting pressures, with relevant data frequently being unavailable. Researchers vary in who they believe should decide: participants, principal investigators, institutional review boards, and/or professional organizations. Contextual factors can influence these decisions, including policies governing return of results by institutions and biobanks and the study design. Researchers vary in desires for: guidance from institutions and professional organizations, changes to current institutional processes, and community-wide genetics education.

Conclusion—These data, the first to examine the processes by which researchers make decisions regarding the return of genetic incidental findings, highlight several complexities involved and have important implications for future genetics research, policy, and examinations of these issues.

Keywords

benefits and risks; decision making; genome sequencing; incidental findings; return of results

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SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at <http://www.nature.com/gim>

DISCLOSURE

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INTRODUCTION

Studies have begun to explore whether researchers should return incidental findings (IFs) in genomic research, and if so, which findings should be returned; however, how researchers in fact make these decisions remains unclear. Thousands of genetic variants could potentially be returned,¹ presenting complex ethical decisions.² Many geneticists feel that “clinically actionable” findings should be returned to participants³ and that lists of such genes should be established.⁴ The American College of Medical Genetics and Genomics (ACMG) has enumerated so-called “medically actionable” secondary findings that clinical diagnostic laboratories performing genomic sequencing should return to all patients, regardless of preferences.⁵ However, in research settings, different considerations, leading to different conclusions, may apply. Theoretical analyses have suggested that researchers should consider relationships with, and vulnerabilities of, research participants⁶ and may have duties to look actively for IFs.^{7,8} Needs for federal guidelines have been articulated, and general recommendations and broad procedural guidelines for biobanks and institutions have been proposed.^{9,10}

Recently, a few studies have begun to probe genetics researchers’ attitudes regarding return of results (RoR).^{11,12} Researchers across a broad array of fields, considering hypothetical vignettes about returning IFs, cited information quality, adherence to rules, and participant welfare as important considerations.¹² Few researchers (4%) of genome-wide association studies reported returning results, but most thought doing so would be warranted in certain circumstances, recognizing a variety of conflicting concerns.¹³ Williams et al.¹³ found that researchers prefer case-by-case determinations concerning IFs, whereas institutional review board (IRB) chairs prefer preestablished policies.¹⁴ We have reported, based on in-depth interviews with researchers, that in deciding whether to report particular IFs, investigators may lack funds for Clinical Laboratory Improvement Amendments (CLIA) confirmation, expertise to interpret findings, and genetic counseling staff, or may have failed to obtain previous consent.¹⁵

Thus, crucial questions remain about how researchers resolve the tensions involved in RoR decisions. Published studies have not examined how researchers in fact do, or believe that they should, weigh the competing logistical and moral considerations that may arise—for example, what contextual and other processes and factors are involved. In this article, we report the interviews with researchers concerning these issues.

MATERIALS AND METHODS

Subjects

As reported elsewhere,¹⁵ we identified genetic researchers for the interviews (and for a parallel online survey) by searching the National Institutes of Health online RePORTER database and abstracts from the 2011 American Society of Human Genetics meeting for principal and coprincipal investigators of currently funded grants, using key words (e.g., human genetics). We included only those investigators who focused on human disease gene identification in the United States and for whom an e-mail address could be found.

From the 2011 American Society of Human Genetics meeting abstracts and the National Institutes of Health online RePORTER database, 88 researchers were identified and invited to participate in a telephone interview. Purposive sampling was used to ensure diversity of geographic regions of the United States, types of institutions (public and private academic medical centers, the National Institutes of Health), types of researchers (physician scientists, basic scientists, statistical geneticists, epidemiologists, genetic counselors, or study coordinators), and disease focus. Twenty-five agreed to be interviewed, 55 failed to respond,

6 declined, and 2 messages bounced. Respondents to the parallel survey who indicated that they had returned IFs ($n = 30$) were also asked whether they would be interested in participating in telephone interviews; four agreed and three were interviewed. Characteristics of the 28 researchers interviewed by phone are indicated in Table 1.

We developed the questionnaire based on an extensive literature search and input from several genetics researchers, identifying major issues to examine. During the 1-h semistructured telephone interviews, conducted in the period from June to December 2012, we asked participants broad sets of questions concerning whether they had faced decisions about return of IFs and how they made or believe they should make these decisions (Supplementary Appendix I online). All participants gave informed consent. The IRBs of the Columbia University Medical Center and the New York State Psychiatric Institute (New York, NY) approved the study.

Data analysis

Interviews were coded and analyzed using grounded theory.¹⁶ Two of us read each interview, using ATLAS to code blocks of text systematically, assigning “core” codes or categories (e.g., who respondents thought should make decisions about what IFs to return to a subject). While reading the interviews, a topic name (or code) was inserted beside each excerpt of the interview to indicate the themes being discussed. We reconciled these independently developed coding schemes into a single scheme through close discussion and prepared a coding manual, examining areas of disagreement, which were rare, until reaching a consensus, usually by further clarification or addition of codes. We then identified the principal subcategories (e.g., whether respondents thought decisions should be made by genomic study participants, researchers, or external “expert” committees). Codes and subcodes were then used in analysis of the interviews. Two coders analyzed all interviews, resolving discrepancies by consensus. Where necessary, we used multiple codes. We assessed similarities and differences among participants, examining categories that emerged, ranges of variation within categories, and variables that may be involved.

RESULTS

As summarized in Table 2, several key themes emerged across interviews. Researchers are aware of the national dialogue on these topics but are uncertain how to respond. They often take multiple factors into account simultaneously, weighing information about genetic variants, pathogenicity, associated diseases (e.g., penetrance, age of onset, and actionability), participants’ well-being, researcher responsibility, and input from institutional and other entities. Researchers vary in who they believe should make these decisions: participants, investigators, IRBs, and/or professional organizations. Several contextual factors can shape these decisions, including institutional and biobank RoR policies, study design, consent forms, and the law. These themes are presented in the following sections, illustrated by excerpts from the interviews.

Deciding whether to return IFs: dealing with uncertainty

When asked how they did or would determine whether to disclose an IF to a participant, respondents did not state awareness of published guidelines addressing these issues. Interviewees considered independent scientific publications implicating the gene in disease; data for pathogenicity of specific variants, including allele frequency, segregation data in families, or demonstration it was *de novo*; and medical actionability. Several respondents used fairly strict criteria, but determinations were not always straightforward, especially for rare or novel variants.

How do we adjudicate pathogenicity? If it's never been seen before, does that guarantee it's important? No. But it makes you lean towards reporting it because it has a higher chance of being problematic...Has it been observed to segregate with disease in families?...Is it affecting a highly evolutionary conserved nucleotide?... Prediction models...are just models. We don't know how to interpret them. I am very leery of putting a lot of weight on those...But none of these, with the exception of great family segregation data, is going to be determinative. (R26)

This investigator would also consider allele frequency to classify variants.

By the time you see something in 1% of the population in a gene that has a highly penetrant severe condition, it's starting to argue pretty strongly that it is inconsequential and would lead me away from the need to report it. (R26)

Many researchers are uncertain about the scientific validity of the standards they set. At times, researchers questioned the use of criteria, in the absence of national standards, to establish pathogenicity: "That's the kind of decision-making that's likely to come about. It might be classified as arbitrary. Being arbitrary is not exactly what we get paid to do as scientists." (R13) This interviewee concluded that researchers should thus return either "nothing or everything," because any other approach to establish cutoffs for pathogenicity would be "arbitrary."

Reflecting this lack of certainty, laboratories may reach different conclusions based on the same data, sometimes with significant and detrimental consequences for participants.

We found a variant that we felt was benign. Subsequently, a lab sequenced this gene in a pregnant mother, and came up with this variant...and reported it as pathogenic to the family, who terminated the pregnancy. They said, "We believe this is a partially penetrant variant." So, unfortunately there is a little bit of subjectivity. (R21)

The scientific literature itself may be misleading. For example, conclusions from studies based on participants selected because of disease status or family history may be inaccurate for other groups.

Are the data from the literature really generalizable to a patient like ours? Associations have been made in certain populations. Whether those findings have the same meaning in different ethnic backgrounds or populations not selected on the basis of phenotype may not always be clear. (R20)

The literature may contain errors, with benign variants misclassified as disease causing, "because of mistakes, partly due to the intense publishing pressure to be first." (R4)

Researchers may also consider participants' medical and family histories. To analyze variants' significance in context, several researchers considered whether participants were past the age of usual disease onset. Participants' health may also influence the likelihood of certain results being medically relevant. "A BRCA1 mutation in a 75-year-old with Alzheimer disease is probably irrelevant to their health care. But maybe their kids or grandkids should know *they* might have it." (R9)

Family segregation data can play a large role in decisions about pathogenicity but are often unavailable. ("It can be extraordinarily important and persuasive. The problem is you rarely have it." (R26))

Ultimately, in RoR decisions for a participant, researchers often analyzed multiple factors rather than relying only on judgments of pathogenicity. Researchers must frequently make

final “judgment calls,” assessing the information’s value and potential impact on the participant.

In the end, it’s a judgment call about the *bulk of the data*, and how comfortable you feel giving somebody this. You don’t want them over-interpreting it, taking it to another doctor who isn’t sufficiently circumspect, who then tests the daughter who ends up getting MRIs every year or a bilateral mastectomy, just because she has inherited what may well be totally innocuous. (R26)

In interpreting pathogenicity, most researchers erred on the conservative side due to concerns that participants might take aggressive medical actions that are not necessarily warranted.

With *BRCA1/2*, we sometimes get an incidental finding that says we found a variant. It’s been seen in 0.5% or 1% of the population, and looks very innocent. It’s just inconceivable that this causes the patient’s and the family’s cancer. On many occasions, I have just simply *not* told the patient... (R26)

Considering the need to weigh these various factors, some researchers like having “wiggle room,” rather than rigid, preset categories and thresholds dictating return or nonreturn of IFs. (“People’s definitions of what’s actionable and what’s not differ quite a bit, so there’s a lot of wiggle room within those categories.” (R8))

Yet the complex calculations involved in each participant’s case may make it very hard to return IFs on a large scale. Addressing all possible clinically actionable variants could also detract from the research itself. “If you talked about anything that *could* be actionable, there wouldn’t be time to do research.” (R18)

Who should decide?

Considering these ambiguities, researchers must determine who should ultimately decide. Overall, these decisions could be made by participants, researchers, external experts, or two or more of these parties.

Participants—Interviewees thought that one option would be to let participants choose but noted that participants’ understandings, preferences, and expectations vary widely. Researchers felt that many genomic study participants may state desires for results but may not understand or consider the implications of this information. When informed about these implications, participants may change their minds—especially regarding untreatable diseases (e.g., Huntington disease).

Still, researchers tend to think that individual participant preferences are important to elicit. If a variant caused disease 50% of the time, one researcher “would want to talk to whoever can go back to the patient, explain the situation, and find out how the patient wants to proceed.” (R10)

Researchers—Considering the potential limitations in participants’ understandings, some researchers felt that ultimately *they*, not the participants, should decide. A few researchers felt that they should be able to override participants’ preferences, if necessary.

You want to respect preferences, but worry that these are not always going to be well-informed. It’s not as simple as respecting their choice—if somebody says, “I’d rather not know about my risk of cancer,” and you’re now sitting on a result that says you’ve got an 80% risk of cancer. (R7)

Participants may not have fully considered all of the intricacies involved.

If somebody said, I don't want anything unless it's related to cancer, do I really believe they wouldn't want to know about their risk for sudden cardiovascular death? I'm not convinced they've really expressed a preference. They haven't really thought about it... (R20)

Researchers may thus rely on their own judgment, weighing their perceptions of the findings' value versus participants' preferences.

Preferences are not the only thing that should govern what goes back... We are leaving ourselves a *safety valve* to say, even though somebody indicated that they wouldn't want this back, that we can't go along with that—we feel we have to give it back. It's going to be hard for docs to sit on actionable high-impact findings. (R20)

Many researchers therefore prefer general rather than specific language in the informed consent (e.g., “We may contact you if we find something we think may help you.” (R6))

Researchers may seek standardized algorithms but end up having to decide on a case-by-case basis. Some may lean toward returning results (“I would always err on the side of trying to share information, if there's some reasonable possibility that one could look into it further and maybe do more.” (R6)) To do otherwise may be seen as “paternalistic.”

To avoid these problems, researchers may simply establish a “ground rule” that they will not look at data outside the target disease. “We typically would rather program a computer *so that we never see the data* if we're not going to report it.” (R6) However, some researchers are uncomfortable with this stance of “willful ignorance,” highlighting the ethical complexities involved.

External expertise—Rather than let either the participant or the researcher decide alone, researchers may also consult others, including external experts—for example, multidisciplinary committees or referring clinicians.

“[A]ctionable” information will be defined by an independent board of wise people not directly involved in the research—including geneticists, genetics counselors, some sector of the community-at-large, and others, depending on the gene. No one can have a deep knowledge of all 20,000 genes. (R14)

Such review committees may be standing or “*ad hoc*.” (“I'd consult with two colleagues not involved with the project, and essentially form kind of an *ad hoc* ethical review.” (R23))

Well-established studies may have several layers of governance: an executive committee, an ethics advisory panel, and one or more IRBs. Such committees may be multidisciplinary. Yet individuals with different training, although helpful, can also have varying, and sometimes conflicting, perspectives. In one research group, a statistical geneticist suggested returning genes associated with pancreatitis but was vetoed by “a specialist in pancreatitis.” (R16) In another case, “Five really smart people—clinical geneticists, genetic counselors—reviewed it. But there were gigantic disagreements of whether to report it or not to.” (R17) Nonetheless, in the end “more frequently than not, we decide to give patients the information.” (R17)

Details of how these committees will operate may also be left unspecified initially.

We didn't actually specify every detail, because we figured the committee should figure out its own procedures for itself. Who should be on it? How big? What disciplines? What are the data sources for annotating all of the mutations? (R20)

Moreover, although experts in a given disease can aid these decisions, they are not necessarily available, and consulting experts on each IF can be time consuming.

Institutional and other constraints

Researchers' decisions are often affected by larger contexts, including biobanks, IRBs, and governmental policies.

Biobanks—Biobanks and other repositories may have their own established policies, which may differ. “Repositories vary widely. There may be zero opportunity to re-contact the family, or considerable opportunity, and even a promise that you *will* report back to the family.” (R6) Some repositories may have been established before identification or return of IFs was possible.

The biobank was set up very explicitly not to return results. None of the samples were handled in a clinically certified manner. To do so would require re-consenting everybody. We should have thought a decade ahead, but didn't. (R19)

Such policies may be seen as precluding researcher discretion.

The repository may have a policy absolutely cast in stone, that there can be no communication back under any circumstances. The repository made every effort to destroy any information to make it possible. (R6)

IRBs—IRBs, too, can profoundly affect whether researchers return IFs but vary widely in genetics expertise and decisions concerning RoR. Researchers may not always agree with IRBs' decisions, but many found their IRBs open to learning and helpful in considering these issues.

In multicenter research consortia, IRBs can differ concerning whether to return even medically actionable results.

Investigators are currently facing an ethical dilemma, because they're sitting on *BRCA1* and 2 results, and cannot return these, because consents say results will not be returned. Their IRB will not let them re-approach and re-consent subjects. It puts the PI in a very bad spot. PIs in the same multi-site groups, with the same exact consent, were granted the ability by their IRBs to go back and re-consent. (R5)

IRBs may base their decisions in part on the ability to provide clinical care and support, including genetic counseling, to such participants.

IRBs at institutions that aren't with a large medical center aren't willing to go back and return results, because they're not very patient-oriented...with the infrastructure to do this. (R5)

IRB members' particular perspectives on genetics can also affect decisions that

very heavily reflect the local personalities of IRBs, and their preferred ways of operating, rather than any preferences of the scientists. I do many multi-center studies. IRBs are highly idiosyncratic. That annoys me. Few genomic scientists tend to be included—even fewer statistical geneticists. Such IRBs often make poorly informed decisions. (R10)

A few investigators worked effectively with their local IRBs to return medically actionable IFs, even if the initial consent had not included that option.

We could easily petition the IRB and say, “This is an exception. The family needs to know about this.” They would give us the permission to essentially step around the limits of the old consent form. (R21)

Other researchers sometimes disagree with their IRBs and may try unsuccessfully to change their decisions. One researcher’s IRB, for example, wanted her to use a generic consent form that would preclude depositing data into a repository and give participants only one opportunity to decide about IFs.

Our IRB was adamant that to go back when something is discovered and ask [participants] was not going to be logistically feasible. Therefore, the IRB wanted it to be an up-front—all or none. “You will get back information deemed important.” Or, “never be contacted again.” (R14)

She added, “Our IRB has been thoughtful, but very conservative... It’s very frustrating. We spent a lot of time talking to them about this.” (R14)

Other researchers may simply comply with their IRBs, even if not wholly agreeing, to obtain approval of their research. (“You do whatever the ethicist tells you...to get the study done.” (R10))

Researchers who may not want to return results can use IRB restraints to justify that decision. “If we could give back results...I would. But...my hands are tied.” (R5)

Governmental policies—In the United States, federally required CLIA confirmation can be costly; many research laboratories are not CLIA approved. Resources needed for CLIA approval can be prohibitive, swaying many researchers against RoR. Other researchers may return results without CLIA confirmation and simply explain the situation to subjects, although whether research participants grasp the distinctions is unclear.

I return information found on a research basis, because that’s what we said we’d do. We always indicate to families that they can have this confirmed; but most don’t. Yet the information has been placed in their chart and we aren’t CLIA-certified. We indicate that this is “only done on a research basis.” Whether families understand the difference... is a good question... (R27)

Several interviewees spontaneously mentioned additional complexities due to receiving samples from other countries—either developed or developing. Even among industrialized countries, health systems can vary in relevant ways:

In Australia and Canada, if the investigator is looking at Lynch [syndrome genes], but happens to find a BRCA [mutation], they can send that person...to a clinic to see a genetic counselor and geneticist, and it’s all free...In the U.S., it’s not that cut-and-dry.” (R5)

The United States is also more litigious, shaping practices, especially for prenatal genetic testing.

In Europe, if they have a finding of *unknown* significance, either research or clinical, they will not report it. In the States, the consensus has been the exact opposite: because of lawyers, the biggest fear here is, “Will I be responsible for not having told them?” (R17)

Differences may become even wider in the developing world, where medical resources are generally far scarcer. A mutation may realistically be actionable in the United States—because screening or intervention is available—but not in poor countries with limited health care, posing additional dilemmas.

DISCUSSION

These data—the first to examine the processes by which researchers make decisions about whether to return genomic IFs—indicate the complexities involved. Although recommendations favor RoRs with “important health implications,” or where potential benefits outweigh risks,¹² our data highlight the challenges in determining when variants meet these criteria. Researchers’ decisions may be constrained, too, by contextual factors—for example, biobank and IRB policies and regulatory requirements. Moreover, researchers often feel compelled to take into account the circumstances and clinical context of individual participants, adding additional complexity to their decisions.

To assist in the process, many investigators turn to expert committees assembled specifically for their projects or seek advice on an *ad hoc* basis. Although these committees can facilitate input from diverse perspectives, they do not necessarily make decisions easier, because definitive data establishing the pathogenicity of a variant or the value of prophylactic interventions may be lacking. In addition, committee meetings impose time and cost burdens of their own. IRBs are another source of guidance, though our respondents report variability in the expertise of IRBs about genomic research and the issues of IFs, and sometimes rigidity in dealing with the question of RoR, especially when it is unaddressed in an earlier consent process. Researchers’ preference for case-by-case decisions appear to conflict with the desire of many IRBs for fixed rules.¹⁴

Another potential source of guidance mentioned in our interviews is a national advisory committee, which others have recommended, too.¹² Existing guidelines, which were not referred to in our interviews, have generally been sufficiently vague as not to be of much assistance with specific RoR determinations. However, the recent recommendations of the ACMG on return of IFs in clinical contexts, published after these interviews were completed, offering more concrete guidance, have been controversial precisely because of the bright lines that were drawn.¹⁷ In addition, by their focus on a small number of genes, these guidelines highlight the fact that many uncertainties remain about other genes, involving more nuanced decisions of the sort that perplexed our interviewees. The research community may benefit from guidelines with a degree of specificity intermediate between the general recommendations of most groups that have addressed RoR issues and the very prescriptive approach of the ACMG.

The limitations of this study include those common to much qualitative research. It was designed to elucidate, in ways that quantitative data cannot, the variety of attitudes and beliefs that emerge from an in-depth discussion of issues related to IFs, in part to generate research questions and hypotheses that future investigations can probe with larger samples. Although the current sample size was sufficient for qualitative research, it was not designed to permit us to quantify responses or assess associations with other variables. Interviewees were selected to afford diversity along a number of relevant dimensions, but no sample of 28 researchers could possibly be representative of the entire genomic research community. Thus, some of the quotes cited reflect a clinical orientation, because 12 of the 28 interviewees were physicians, for whom research and clinical work can blur, especially when research is conducted with patient samples. A different mix of researcher backgrounds might have yielded somewhat different results. Future research using survey methods, however, can examine whether particular types of researchers (e.g., based on training or gender) vary in their views and experiences. Although the utility of studying researchers’ attitudes has been questioned,¹⁸ these data suggest their value in illuminating the details, circumstances, and contexts in which decisions about RoR to genomic research participants will need to be made.

Our data suggest several areas ripe for additional investigation. As genomic research becomes common, the identification of optimal procedures for making decisions about RoR will become more urgent. The practical utility of decisional aids such as decision trees and their appropriate degree of specificity will need to be determined. The added value of expert advisory committees should be assessed, along with the impact of varying membership (e.g., clinicians versus nonclinical researchers) and procedures (e.g., establishing study-specific procedures versus consulting on individual cases). As procedures develop, they should be described, shared, and compared, so that the field can converge on evidence-based best approaches. The specific types of “judgment calls” that researchers make should be studied to help develop case analyses and algorithms to assist other researchers who are confronting these decisions. Studies of research participants should assess not just their preferences, but their understandings of the implications of the choices with which they are faced, and their ways of handling uncertainty.

In summary, although many current discussions focus on developing categories of IFs for RoR, the present data underscore the importance of focusing on procedural issues in the decision-making process as well.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Background data on researchers interviewed

	<i>N</i>	%
Sex		
Female	11	40
Male	17	60
Education (academic degrees)		
MD	6	21
PhD	15	54
MD–PhD	5	18
MS	2	7
Researchers' affiliations		
Academic medical center	27	96
The NIH	1	4
Researchers' ranks		
Full professor	20	71
Associate professor	2	7
Assistant professor	3	11
Administrator	3	11
Genetic methods used		
WES	6	21
WGS	1	4
WES and WGS	12	43
Plans to do WES/WGS	3	11
No plans to do WES/WGS	4	14
Unreported	2	7
Genetic data generated in research		
IFs	11	39
Non-IFs	11	39
Attitudes of researchers interviewed		
Return everything	2	7
Return nothing	4	14
Return all or nothing	4	14
Unsure/mixed (support returning some results but not others)	18	64

IF, incidental finding; NIH, National Institutes of Health; WES, whole-exome sequencing; WGS, whole-genome sequencing.

Table 2

Themes concerning how researchers make decisions concerning return of incidental findings

Assessing multiple factors jointly

- Assessing “the bulk of the data”
- Providing uncertain results and explaining the uncertainty
- Making judgment calls

Interpretations may vary over time

Who should decide

- Leave it up to the participant
 - But they may decide without fully understanding the complexities
- Leave it to PI discretion
 - Override patient preferences?
 - Offer possibility, not promise of return
 - Err on side of giving results versus err on “conservative” side
 - Maintain “willful ignorance”
- Seek external expertise
 - Within study team
 - External to study team

Contextual factors/roles of institutions and other governing bodies

- Biobanks
 - Biobank has preestablished parameters or not
- IRBs
 - Experienced with this issue or not
 - In agreement with researcher or not
 - Can provide a rationale not to return results (“The IRB said no”)
- Governmental policies
 - In the United States, many laboratories are not CLIA-approved, and CLIA confirmation is costly
 - Policies differ in other countries
 - In the developed world
 - In the developing world

CLIA, Clinical Laboratory Improvement Amendments; IRB, institutional review board; PI, principal investigator.