Author/s:
Vears, DF;Sénécal, K;Borry, P

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Reporting practices for unsolicited and secondary findings from next generation sequencing technologies: Perspectives of laboratory personnel

Running title: Laboratory reporting practices for unsolicited and secondary findings

Danya F Vears[1,2], Karine Sénécal[3], Pascal Borry[1,2]

[1] Centre for Biomedical Ethics and Law, Department of Public Health and Primary Care, KU Leuven, Leuven, Belgium.

[2] Leuven Institute for Human Genomics and Society, KU Leuven, Belgium.

[3] Centre of Genomics and Policy, McGill University, Montreal, Canada.

Corresponding author:

Danya F Vears

Center for Biomedical Ethics and Law
Department of Public Health and Primary Care
KU Leuven
Kapucijnenvoer 35, Box 7001
3000 Leuven
Belgium
Phone +32 16 37 46 85
Fax +32 16 33 69 52

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ABSTRACT

While next generation sequencing has enormous potential to identify genetic causes of disease, the nature of the technology means that it can also identify additional information about the individual receiving sequencing that is unrelated to the original rationale for testing. Reporting these unsolicited findings (UF) to clinicians, and subsequently to patients, could lead to potentially lifesaving interventions. Most international guidelines provide limited specific recommendations as to whether these UF should be reported. Little research has been conducted exploring which of these variants are reported in practice.

26 interviews were conducted with 27 laboratory personnel, representing 24 laboratories in Europe (12), Canada (5) and Australasia (7) to explore their reporting practices. There is considerable variation between laboratories in the reporting of UF. While some limit their reporting to findings that are relevant to the clinical question, others report UF to varying degrees. In addition, most laboratory personnel interviewed said that their laboratories do not actively search for secondary findings in disease-causing genes unrelated to the clinical question, such as those suggested by the ACMG. Our study highlights that laboratories are still grappling with decisions about which UF to report from NGS and are calling for more guidance.

Keywords: genetic testing; genomic sequencing; incidental findings; genetic counseling; bioethics; diagnostic

INTRODUCTION

The introduction of next generation sequencing technologies (NGS) into both research and clinical settings has been instrumental in the detection of many new disease-causing genes, particularly for rare diseases and cancers (Guerreiro, et al., 2016; Rotunno, et al., 2016; Tetzlaff, et al., 2016). NGS, which encompasses targeted gene panels and whole exome/genome sequencing, is novel in that it allows analysis of numerous genes in a single test (Rabbani, et al., 2014). While NGS has enormous potential to identify genetic causes of disease, the nature of the technology means it can also identify additional information about the individual that is unrelated to the original rationale for sequencing, often referred to as *incidental findings* (Kohane, et al., 2006).

The inconsistent terminology around incidental findings has caused considerable confusion (Downing, et al., 2013). These findings have been referred to as unsolicited, iatrogenic, serendipitous, additional or secondary, to name several (Botkin, et al., 2015; Green, et al., 2013; Matthijs, et al., 2016; Tan, et al., 2016; van El, et al., 2013). In particular, the term "incidental" has received criticism as it may lead patients to perceive these types of variants as trivial (Tan, et al., 2016). For this reason, we will use *unsolicited findings* (UF), which refers to variants in disease-causing genes that are unrelated to the original rationale for testing and that are identified *inadvertently*. We differentiate this from *secondary findings* (SF), which refers to variants in disease-causing genes that are unrelated to the original rationale for testing but that are *actively sought* during the analysis. This term was recently recommended by the American College of Medical Genetics and Genomics (ACMG) (Kalia, et al., 2016) after their recognition that using *incidental findings* did not reflect their intention to actively search for these variants (Green, et al., 2013).

This concept of actively searching for secondary findings was first proposed by the ACMG in their frequently cited recommendations in 2013 (Green, et al., 2013). In this, they described a list of causative variants in 56 genes predicted to cause 24 conditions, such as hereditary cancers and cardiac conditions, which they recommended should be actively searched for and reported in both adults and children receiving diagnostic genomic sequencing (Green, et al., 2013). This list was reassessed in 2016 and now suggests 59 genes, with an intention for 6 monthly revisions (Kalia, et al., 2016). However, other professional bodies have suggested that this kind of opportunistic screening is inappropriate and instead recommend a more targeted approach, limiting analysis of NGS data to genes that are relevant to the phenotype of the patient (Boycott, et al., 2015).

Studies have explored patient and general public preferences regarding the return of UF (Daack-Hirsch, et al., 2013; Hufnagel, et al., 2016; Yu, et al., 2014a) and health professionals' views about whether these findings should be reported (Lemke, et al., 2013; Lohn, et al., 2013; Yu, et al., 2014b). In 2016, a US-based study conducted a survey of US laboratories to assess their reporting practices (O'Daniel, et al., 2016). However, aside from a brief survey of 9 European laboratories undertaken in 2013 (Hehir-Kwa, et al., 2015), no one has investigated the current practices, or perspectives, of laboratory personnel who are actually reporting results from NGS about the reporting of UF or SF outside the USA.

MATERIALS AND METHODS

This study used qualitative methods to explore the reporting practices of laboratories using NGS. Purposive sampling was used to recruit laboratory personnel who are analyzing/reporting data generated by NGS technologies, including targeted gene panels, clinical exomes, and whole exome or genome sequencing. Potential participants were identified using internet searches to identify laboratories using NGS and snowball sampling.

Semi-structured interviews were conducted by one member of the research team (DV). These interviews explored a range of different aspects relating to their use of NGS, including the types of technologies and analysis/filtering strategies used in their laboratory. Here we report the interview components relating to the reporting of UF, how they made decisions about reporting UF, and whether they actively search for SF. Interviews were audio-recorded, transcribed verbatim and analyzed using inductive content analysis in which content categories were derived from the data, rather than pre-determined (Downe-Wamboldt, 1992; Graneheim and Lundman, 2004; Schamber, 2000). Each transcript was coded into broad content categories. Sections of the data within the broad categories were compared and more specific subcategories were developed. All interviews were coded by DV; KS and PB coded a subset to confirm the coding scheme.

Verbal informed consent was obtained from all participants. This study was approved by the SMEC Review Board (Social and Societal Ethics Committee), KU Leuven, and the Research Ethics Board of the Faculty of Medicine, McGill University.

RESULTS

Participant characteristics

A total of 26 interviews were conducted with 27 laboratory personnel. This included participants from 24 different laboratories in Europe (12), Canada (5) and Australasia (7). Participants had a mean of 8.1 years (4 weeks – 24 years) experience in their current role and a mean of 17.4 years (6 – 32 years) in the field of genetics. Two of the participants also had training in clinical genetics. 19/24 laboratories operate in the diagnostic context with several also including research components to their laboratory. Five of the laboratories operate purely on a research level although they do issue reports to clinicians. At the time of the interviews, laboratories had between 1 and 10 years experience using NGS technologies. Twenty of the laboratories were using targeted panels, including five who were using a mendeliome-based panel (e.g. TruSight One). Twenty-two were using exome sequencing, with or without virtual panels, and four were using whole genome sequencing (3/4 are research laboratories).

[Insert Table 1 here]

Reporting practices for unsolicited findings

Some participants indicated that their laboratories do not report any UF, limiting their reporting to variants that are relevant to the clinical question and thought to be causative of the phenotype.

> *I think we had a discussion with our clinicians about this and because the question is specific for that disorder, I don't see why we should look at, I mean […] why should we*

report all those things? I think there's a differing view both from the European and the American guidelines, isn't there.

Participant 6

One participant said that when their team started performing sequencing using NGS they were initially reporting UF but have since changed their practices in response to discussions with clinicians.

So when we started to make next generation sequencing, at the beginning we were reporting them, because that's what we were doing for microarray. And when we started I would say the 30, 40 patients, we found far more <incidental findings> than we expected. We had almost as much incidental findings than diagnosis. So the clinicians were very upset by that […] And we had a meeting, specifically for discussing this, and at the end we chose to not report them.

Participant 24

Other laboratories do report UF although there is variation within this group as to which variants they would report. For some laboratories, the decision about which UF to report is based on the criterion of clinical actionability, as in whether some treatment or surveillance can be taken through the knowledge of that information.

[...] this depends on what disease it gives. For instance, we had a variant in the Factor VIII gene which gives haemophilia. And there we decided, because you can treat it, and it's good that you know it, there we decided to report it. So depends on [...] if you can treat it or not.

Participant 10

Respondents also acknowledged it may be difficult to define the extent to which a variant might be clinically actionable. Therefore, their decisions regarding the reporting of UF were often based on the potential medical relevance of the finding.

Sometimes it's not that clear cut whether it's actionable or not. Sometimes there is an expectation maybe that if the child is just like a few years old and there is an indication that it would only be like when they're 30 years old that there might be a problem, and that there are many options that could become available <in the future> [...] So, in those cases, sometimes also non-actionable in this moment might be reported.

Participant 8

In situations when carrier status is identified as a UF, some laboratories report carrier status, with this participant illustrating an example of where this reporting has been beneficial to a family in a founder population.

That's also driven by examples that it was good to know. We have a few consanguineous populations in <our country> and we just picked up a carrier because of this <use of NGS> and then the other parent appeared to be a carrier as well and then we prevent them from yeah, a bad pregnancy in the future. So we have a few examples on which it was very good for the family to know. And we do not really see the disadvantage of knowing.

Participant 5

The majority of laboratories interviewed do not currently report carrier status, often because it is not relevant to the current clinical question.

So, it's not uncommon, especially in things like limb girdle muscular dystrophy, to find single definite mutations […] So, does that mean that they're a carrier for that and it's not related to the disease or is it in fact that we haven't seen the second mutation? […] We don't report it because that's not the question that's being asked.

Participant 13

Notwithstanding, several of these laboratories indicated they are currently discussing whether to change their reporting practices on this point. This is because through their analysis, some carriers are being identified and there is some discomfort about their decision not to report this information. However, they raised that if they decide to report carrier status they would want to ensure this was

done in a systematic way and that all carriers of the conditions they chose to report on would be identified. The feasibility of this is being questioned as part of these discussions.

Some participants indicated that they discuss the decision about whether to report an UF or not with the referring clinician before a formal report is issued. Many of the laboratory personnel mentioned that they have team meetings, specific committees or expert panels in which they discuss the reporting of UF (and also variants of uncertain significance; VUS). These are often multidisciplinary in nature, comprising representatives from the laboratory and clinicians. Some committees also include ethicists and/or lawyers. Decisions about reporting of UF are often made on a case-by-case basis. Some mentioned that they draw on reporting guidelines or consider the preferences of patient, or their family, if these preferences are known.

Most participants indicated that there was no difference in their reporting practices for UF between children and adults. For some this was because they do not report *any* UF, regardless of age. Other participants indicated their laboratory reports UF both in adults and in children, regardless of the predicted age of onset of the condition caused by the variant.

> *That's also one of the recurring debates of course. Because now you get, for instance, these BRCA findings in children, where otherwise you would never do pre-symptomatic testing on children for these genes, at least not in our country. But now you find them in these children. But we think we should report them in children too because the chance*

that one of the parents is a carrier of this disease is very high and it has immediate actionable, how you say, relevance for one of the parents or the family involved.

Participant 2

Active searching for secondary findings

While the ACMG suggests that laboratories performing sequencing should actively search for and report a predetermined list of disease-causing variants, in addition to the variant that could explain the clinical question (Green, et al., 2013; Kalia, et al., 2016), most laboratories interviewed do not actively search for these SF.

If we find it, we will report it. But we are not searching for that. We are not doing like the American guidelines, just searching for all the actionable genes or mutations in the file. So it's just if we found it by chance or not.

Participant 25

In fact, many of the laboratories make decisions at the bioinformatics level in order to reduce the identification of UF. This is achieved by limiting their analysis to particular sets of genes relevant to the clinical question, either through gene panels or, if they are performing exome sequencing, using bioinformatics (virtual) panels. They may filter using inheritance patterns (if they have opted for a trio-based approach), or gene masking analysis strategies where they use a bioinformatics filter to hide a list of genes like those the ACMG recommends actively searching for.

I don't want to know about these genes, you know. Particularly if you've got a patient with developmental delay and you might go well, I don't really want to know about BRCAs and […] you know, the Long QT type ones. So you'd say look, let's keep those hidden away 'cos they're not clinically relevant to this patient.

Participant 16

Three laboratories actively search for SF. One of these laboratories routinely reports these variants to clinicians and leaves it to the discretion of the clinicians as to whether to disclose them to the family.

The other type of report we make is that we systematically analyse the variants that are pathogenic or likely pathogenic and affecting genes listed by the ACMG that are relevant for secondary findings. And so we propose to report these variants to the clinician. And after, the clinician will judge if the family is willing to know or not these variants. But the laboratory is reporting them.

Participant 18

The other two laboratories allow patients to "opt in" for this active searching to be performed and to receive these results, although one only allows this choice for competent, adult patients.

DISCUSSION

This is the first study to provide an in-depth exploration of the reporting practices of laboratories outside of the USA relating to unsolicited and secondary findings. Our research has identified that there is considerable variation between laboratories in the reporting of UF – while some limit their reporting to findings that are relevant to the clinical question, others will report UF to varying degrees. This corresponds with the brief survey of nine European laboratories which identified 5/9 laboratories did not return UF (Hehir-Kwa, et al., 2015). On consideration, this variation between laboratories is not surprising given the limited specific guidance provided in the published recommendations of the countries from which we recruited participants. For example, there are no clinical guidelines in Australia that give specific recommendations about the reporting of UF. In the guidelines published by the EuroGentest network (Matthijs, et al., 2016), and the Canadian College of Medical Geneticists (CCMG) (Boycott, et al., 2015), rather than specifically recommending whether UF should be reported, they a) recommend adopting a targeted approach to the analysis of genomic data in order to limit identification of UF, and/or b) suggest that laboratories should develop clear protocols about which UF they report which must be made explicit to referring clinicians (Boycott, et al., 2015; Matthijs, et al., 2016). While the European Society for Human Genetics (ESHG) recommendations (van El, et al., 2013) state that if UF are detected that are "[…] indicative of serious health problems (either in the person tested or his or her close relatives) that allow for treatment or prevention, in principle, a health-care professional should report such genetic variants", they also recommend development of a clear protocol, ultimately leaving the decision whether to report UF to the laboratory. This focus on the need to develop explicit reporting protocols, rather than providing recommendations on what they should report, implies that these professional bodies value transparency in reporting and that they trust in laboratories' abilities to make ethically sound decisions.

Within the group of participants who indicated their laboratories do report UF, different benchmarks are used between laboratories with some of our participants indicating they only report variants which are clinically actionable and others suggesting that actionability is not a requirement, provided the variant is medically relevant. In reality, the boundary between these two categories is blurred at best and is open to subjective interpretations. Whilst actionability may be limited to situations where some form of treatment, intervention, or surveillance is possible for the individual patient, it could also encompass these aspects in relation to family members (Green, et al., 2013). This could include carrier status where the actionability associated with reporting this type of variant extends to future pregnancies, rather than just existing family members. This shows that the interpretation of what is "actionable" and "medically relevant" is partly a value-based decision.

Our findings contrast with the results of the survey conducted by O'Daniel et al. who found reporting practices relating to SF were more consistent across laboratories in the USA with all of the 21 laboratories they surveyed indicating that they return SF (O'Daniel, et al., 2016). In their study, the SF reported were generally those considered to be medically actionable, whether or not they were part of the original 56 genes recommended by the ACMG (Green, et al., 2013). In addition, 57% (12/21) of laboratories in the US study said they report carrier status, 48% (10/21) report monogenic disease with childhood onset, and 57% (12/21) report monogenic disease with adult onset (O'Daniel, et al., 2016). However, 9/21 laboratories were Clinical Sequencing Exploratory Research program laboratories and reporting of these types of variants was more common in these research laboratories than those operating in a diagnostic capacity. One might hypothesize that in order to be in keeping with the ACMG recommendations that are explicit about the need to report these SF, the US laboratories are more likely to report SF than those we interviewed in Europe, Canada and Australia

as the European and Canadian guidelines are less explicit on this point.

Our interviews indicated that only 3 of the 24 laboratories we accessed actively search for SF. Again, this is perhaps unsurprising given the positions taken by the CCMG, ESHG and EuroGentest (Boycott, et al., 2015; Matthijs, et al., 2016; van El, et al., 2013). While the ESHG and EuroGentest Statements do not address active searching for disease-causing genes unrelated to the original rationale for testing specifically, their recommendation for a targeted approach to sequencing implies that they do not support it (Matthijs, et al., 2016; van El, et al., 2013). The CCMG specifically stress that they "[…] do not endorse the intentional clinical analysis of disease genes unrelated to the primary indication, even if the results might be medically actionable" (Boycott, et al., 2015). It is difficult to contrast this with the US-based study (O'Daniel, et al., 2016) as it is unclear which of the laboratories they surveyed limit their reporting to UF, meaning those that are identified during the original analysis, and which laboratories specifically search for SF using a separate bioinformatics panel. However, it seems that 20/21 laboratories surveyed are, at a minimum, reporting SF from the original 56 genes on the ACMG list (Green, et al., 2013), and although not specifically stated, there is a suggestion that at least some of these laboratories are actively searching for these variants (O'Daniel, et al., 2016). Authors have highlighted that there is insufficient evidence of clinical utility in testing the genes on the ACMG list (Boycott, et al., 2015; Burke, et al., 2013). In addition, the removal of one of the genes from the list in the ACMG's most recent publication, based on insufficient evidence of pathogenicity, suggests concerns about using this list for opportunistic screening are not unfounded (Kalia, et al., 2016). While the fact the ACMG intend to review and revise this list regularly is promising, it seems pertinent to stress that, according to our results, the majority of laboratories in our study are not actively searching for these SF.

We identified that most of the laboratories indicated no difference in their reporting practices for UF between children and adults; some participants indicated that their laboratories report UF in children, regardless of the age at which the condition is predicted to develop. Interestingly, although the ESHG and EuroGentest guidelines do not give specific recommendations regarding the reporting of UF in children (Matthijs, et al., 2016; van El, et al., 2013), the CCMG recommendations specify that "[…] incidental results that reveal risk for a highly penetrant condition that is medically actionable during childhood should be reported to the parents" (Boycott, et al., 2015). This is in line with guidelines for predictive testing for childhood onset conditions where testing would be deemed appropriate if it would provide medical benefit, in the form of treatment, prevention, or surveillance (Borry, et al., 2009; British Medical Association Ethics Department, 2012). The CCMG goes on to suggest that if variants for adult onset conditions are identified in children, these should not be communicated unless the parents request that these UF be disclosed *and* "disclosure of the information could prevent serious harm to the health of a parent or family member", which should be determined on a case-by-case basis (Boycott, et al., 2015). This contrasts with guidelines for predictive testing in childhood for adult onset conditions, as the CCMG recommendation would allow disclosure of a *BRCA1* result, for example, where performing genetic testing for this in childhood would normally be refused (Borry, et al., 2008). This highlights the challenge associated with balancing protecting the child's future right not to know genetic information about themselves, with disclosing information that could lead to lifesaving interventions for their parents, which would also benefit the child.

It is important to consider who should be making decisions about which UF should be reported. Interviews with our participants indicated that, in most cases, decisions about which UF should be reported were not made in isolation. Rather, decisions were made on a case-by-case basis and through careful deliberation, either with fellow laboratory specialists and/or in multidisciplinary teams.

Notably, the participants emphasized the expertise and critical input of clinicians, both those who are members of these expert panels and also the referring specialists. These clinicians play an important role in determining the clinical relevance or actionability of UF and therefore whether they were worthy of reporting. Although most participants seemed to agree with their laboratories' reporting practices for UF, they also felt laboratories would benefit from more guidance on this issue and that more detailed recommendations to help standardize procedures were warranted. This tension between standardizing reporting practices across laboratories and wanting to discuss UF with clinicians on a case-by-case basis was also made explicit by participants' desire to report carrier status in a systematic manner. This call for more guidance implies that laboratories do not find the current reporting recommendations adequate for their practice. While some have suggested reporting practices should be consistent across laboratories (O'Daniel, et al., 2016), we need to carefully consider whether uniformity in reporting is desirable, let alone feasible. Lack of consistency in the reporting of UF and SF means a lack of equity in access to potentially lifesaving interventions for patients and their families. Yet, even if more detailed recommendations are developed, laboratories will still need to be able to exercise some degree of professional autonomy around this issue, particularly in response to complicated variants where the combined expertise of the laboratory specialists and the clinical geneticists within their multidisciplinary teams, will be critical in determining what should be reported to the referring clinician.

CONCLUSION

In line with the recommendations by the ESHG, EuroGentest and CCMG, many of the laboratories studied have adopted a targeted approach to their analysis, using bioinformatics/virtual panels in order to limit the overall number of variants identified, including UF (van El, et al., 2013). In addition, a small subset of laboratories has adopted a masking technique where they "hide" an ACMG-like list to

avoid seeing these UF. Contrary to the ACMG recommendations (Kalia, et al., 2016), very few of the laboratories are actively searching for SF. Despite being relatively comfortable with the reporting practices of their laboratory, the calls from participants for more guidance on which UF to report suggest that current recommendations are inadequate and require further elaboration.

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Lab no.	Region	1^{o} activity	Technologies in use	Who can request?	Return of UF	Criteria	Patient Choice	Searching for SF
1	Europe	Diagnostic	CTP; WES	S	No[a]	NA	NA	No
2	Europe	Diagnostic	CTP; WES	CG; S	Yes (not CS)	MR	No[d]	No
3	Europe	Diagnostic	CTP; WES	CG	Yes (includes CS)	A	No[d]	No
4	Europe	Diagnostic	CTP; WES	S	No (perhaps CS)	RF	No	No
5	Europe	Research	CTP; MTP; WES	C	No[a]	NA	NA	No
6	Europe	Diagnostic	CTP; WES	CG; S	Yes (includes CS)	MR, PC + CA	Yes	No
7	Europe	Diagnostic	CTP; WES	S	No[a]	NA	NA	No
8	Europe	Diagnostic	CTP; WES	S	Yes[b]	A	Yes[e]	No
9	Australasia	Diagnostic	CTP; WES	S	Yes[c] (includes CS)[b]	MR + PC	Yes	No
10	Australasia	Research	CTP; WES; WGS	S	Yes (not CS)[a]	A	No	No
11	Australasia	Diagnostic	CTP; MTP; WES	S	No[a]	NA	NA	No
12	Australasia	Diagnostic	CTP; MTP; WES	S	Yes (not CS)	A + PC	Yes	No

13	Australasia	Diagnostic	CTP; WES; WGS	S*	Yes (not CS)[b]	MS	No[f]	No
14	Australasia	Diagnostic	CTP; MTP	S	Yes[a]	A	No	No
15	Canada	Diagnostic	WES	C	Yes (not CS)	A + PC	Yes[e]	Yes (with consent)
16	Europe	Diagnostic	WES	S	Yes (not CS)	A + PC	Yes	Yes (routinely)
17	Canada	Diagnostic	CTP; MTP	S	Yes (not CS)	PA	Yes	Yes (with consent)
18	Europe	Diagnostic	CTP; WES	CG	Yes (not CS[b]	PC	Yes	No
19	Europe	Diagnostic	MTP; WES	CG + GC	Yes (not CS)[a]	PA	No[d]	No
20	Australasia	Research	WES; WGS	S	Yes[b]	A	No[d]	No
21	Europe	Diagnostic	CTP; WES	S	No	NA	NA	No
22	Europe	Diagnostic	CTP; WES	CG	Yes (not CS)	A + PC	Yes	No
23	Canada	Research	CTP; WES; WGS	C; R	Yes (not CS)[b]	A	No[f]	No
24	Canada	Research	WES	C	Yes (includes CS)	PA	Yes	Yes (routinely)

Table 1. Summary of laboratory practices

CTP – Condition-specific Targeted Panels; MTP – Mendeliome-based Targeted Panels; WES – Whole Exome Sequencing; WGS – Whole Genome Sequencing. CG = clinical geneticists; CG+GC = clinical geneticists and genetic counselors; CG; S = any specialists for targeted analysis but CG for whole exome analysis; S = any specialists; S*= any specialists but with clinical geneticist involvement; C = any clinicians; R = researchers can also request. CS – carrier status. [a] Use a gene-based targeted analysis; [b] Filter using trios or gene masking to limit UF identification; [c] only in adults; NA – Not applicable; MR – Medical Relevance; MS – Medical Significance; A – Actionability; PA – Pathogenicity Alone; PC – Patient/parent Choice; RF – Relevance for family members; CA - potential for child to become autonomous; [d] if patient consents to WES, obliged to receive UF; [e] for WES analysis only; [f] laboratory does not have own consent forms.

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