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ARTICLE

To disclose, or not to disclose? Context matters

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Progress in understanding childhood disease using next-generation sequencing (NGS) portends vast improvements in the nature and quality of patient care. However, ethical questions surrounding the disclosure of incidental findings (IFs) persist, as NGS and other novel genomic technologies become the preferred tool for clinical genetic testing. Thus, the need for comprehensive management plans and multidisciplinary discussion on the return of IFs in pediatric research has never been more immediate. The aim of this study is to explore the views of investigators concerning the return of IFs in the pediatric oncology research context. Our findings reveal at least four contextual themes underlying the ethics of when, and how, IFs could be disclosed to participants and their families: clinical significance of the result, respect for individual, scope of professional responsibilities, and implications for the healthcare/research system. Moreover, the study proposes two action items toward anticipatory governance of IF in genetic research with children. The need to recognize the multiplicity of contextual factors in determining IF disclosure practices, particularly as NGS increasingly becomes a centerpiece in genetic research broadly, is heightened when children are involved. Sober thought should be given to the possibility of discovering IF, and to proactive discussions about disclosure considering the realities of young participants, their families, and the investigators who recruit them.
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INTRODUCTION

Progress in understanding childhood disease using next-generation sequencing (NGS) portends vast improvements in the nature and quality of patient care.[1–3] Advocates for widespread use of personal genomic profiling recommend that it is best done as early as possible in life,[4] underscoring the need for comprehensive management plans and multidisciplinary discussion on the return of incidental findings (IFs) in clinical research.

The ethics literature is rich with discussions regarding how to approach this.[5–11] Many of the prevailing ethical issues are accentuated in the pediatric research context, and render the technological innovations in genetics 'a blessing and a curse, a real Pandora's Box', as one respondent maintained. Indeed, a classic ethical tension remains. Although considered a population deserving of special protections, children should not be excluded from research expressly meant to better understand childhood disease. Thus, the child's vulnerability, conflicting views regarding their best interests, and the discordance between some ethical guidelines[12,13] are formidable challenges facing investigators in pediatric research generally. Furthermore, communication and disclosure procedures must take into account the scientific and ethical nuances of the finding itself, namely that it requires further clinical validation,[14–16] may carry uncertain implications for children and families,[17–19] and may conflate the distinctions between research and care.[20–23] Other concerns surround the method and timing for disclosure from legal and professional standpoints,[24] whereas some cite blurred duties to inform[25] and insufficient confidentiality safeguards.[26]

These continuing debates[27] testify to the diversity of opinions among both clinical and basic health science researchers – herein referred to as investigators – and reinforce the essential role that context imparts on the ethical analyses used to inform disclosure decisions. Beskow and Burke[28] were among the first to draw attention to contextual nuances in researcher perspectives. They argued any model to approach disclosure of IFs ethically 'will be facilitated by a more grounded understanding of researchers' obligations in different contexts.' It is in attempting a more grounded understanding of the pediatric research context that we provide qualitative evidence in support of a continuum of ethical disclosure practices.

To date, only a number of studies offer investigator perspectives, concerns, and hopes for policies guiding IF disclosure.[29–32] Therefore, the data in this paper are drawn from a qualitative study exploring the attitudes and perceptions of investigators concerning IFs in pediatric oncology research. In addition, the authors present two critical action items respondents identified in deriving maximum clinical utility from innovations in NGS and genetic diagnostics, while preserving the bioethical mandates for research participation. It is the opinion of the authors that the frameworks used to meet these challenges will dictate the continued progress of genomic applications in pediatric research.

MATERIALS AND METHODS

Study design

We conducted a qualitative study with purposeful sample of 16 investigators in pediatric oncology. The study protocol and consent procedures were reviewed and approved by the research ethics boards at McGill University and the Sainte-Justine Hospital University Health Center (SJUHC).

Participant recruitment

The inclusion criteria aimed to recruit basic health science researchers (ie, not involved in clinical care) and clinician researchers at various top pediatric research institutions across Canada. Potential participants were recruited by contacting genetic research teams at SJUHC and Montreal Children's Hospital in Quebec, and from within professional research societies such as the C17 Council.[33] We used a purposeful sampling strategy to collect a broad range of perspectives until we achieved data saturation. A total of 100 potential interviewees involved in pediatric oncology research were notified of the project to build awareness around its objectives. Interviews were then arranged for $N=16$ investigators (Table 1) at their convenience. All interviewees

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Table 1 Demographic information of participants involved in pediatric oncology research

	Clinician investigators (N = 11)		*Basic researchers* (N = 5)	
	N	%	N	%
Gender				
Male	6	54.5%	2	40%
Female	**5**	45%	**3**	60%
Age (years)				
21–40		9%	1	20%
41–55	4	36%	2	40%
>55	**5**	45%	**2**	40%
Experience (years)				
6–10	1	9%	1	20%
11–20	3	27%	2	40%
>20	**7**	64%	**2**	40%
Specialty				
Research nurse	3	27%	0	0%
Oncologist	7	64%	0	0%
Basic health science researcher	0	0%	4	80%
Other	1	9%	1	20%

received a consent form and detailed interview guide explaining the interview procedure and anticipated questions. We obtained verbal consent to record the interviews, and ensured participants were fully informed of the protocol before proceeding with the interview.

Data collection procedure

An interview guide was developed on the basis of the literature to address three main sections: (1) views and experiences returning incidental results in the context of pediatric genetic research, (2) the perceived challenges, both personal and professional, to disclosing genetic IFs, and (3) possible solutions to facilitate the communication of incidental genetic results to pediatric participants and their families. Principal Investigator (DA) conducted the semistructured telephone interviews from January to June 2013 that lasted between 30 and 45 min in the respondent's preferred language (either French or English). All interviews were audiotaped upon verbal consent and subsequently transcribed.

Data analysis

A thematic approach was used to analyzing the qualitative data. Codes were both predetermined from the literature and emerged from the 'grounded' analysis. One investigator (VR) prepared tables and other graphical indices to identify patterns and themes, whereas the interview guide categories served as a preliminary code-developing framework. Secondary codes and subcodes were created from subsequent review of the transcripts, and investigators (VR and DA) modified the codes as necessary in accordance with emerging themes.

RESULTS

Respondents identified four key considerations for determining when and under what circumstances disclosing IFs is ethically appropriate in pediatric oncology genetic research (Figure 1). The decision to disclose varied according to (1) clinical significance, (2) respect for individuals, (3) professional responsibilities, and (4) implications for the healthcare/research system.

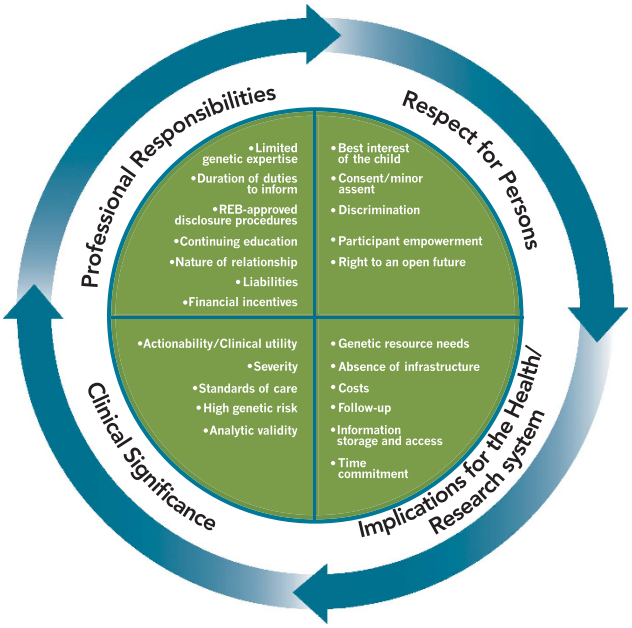

Figure 1 Overview of contextual factors informing decisions to disclose IFs.

Clinical significance

Attributing clinical significance (eg, clinical validity and utility) motivated the decision to inform participants and their families of particular results. Many felt only an IF replicated in an accredited clinical laboratory could be considered a 'true' result and therefore trustworthy to report:

'*—There definitely should be sufficient evidence out there that the result is really a* ***true*** *result, because another issue, of course, with genetic studies and with all the technologies is that there are some results out there that are not.*'

Investigators mentioned the impetus to report IF was commensurate with the degree of severity associated with the condition and its impact on the immediate or future health of the child.

'*—it can happen that someone is a carrier of a given mutation that I think, yes, they should know this is of some relevance of their health, but by saying all mutations that someone* ***carries I don't see that much point in that.***'

Relatedly, a majority of respondents regarded clinical actionability as one of the foremost reasons for disclosure. While popular pediatric standards define clinical utility as '[h]ow likely the test is to significantly improve patient outcomes,'[34] one respondent asserted,

'*—****Any*** *genetic finding that can influence one's health is clinically relevant whether it occurs short term or long term.*'

According to another researcher, the limited clinical actionability of an IF did not constitute respect for individuals:

'*—I've heard a school of thought that says, 'well, if you can't do anything about it, you shouldn't tell them about it.' I'm not sure I agree with that, and I'm pretty sure patients wouldn't either. The families* ***don't actually care*** *that we can't do anything about it. They want to know...it seems to me sort of* ***paternalistic to arbitrarily decide****, we can't do anything about that, so we're not going to tell you.*'

Respect for individuals

Underpinning decisions across the disclosure continuum was adherence to respect for individuals – and by association consent and informational privacy. When children are implicated in the discovery

of an IF, fulfilling the respect for individual mandate can grow exceedingly complex:

'Look, when you deal with children, it's not ***just the child****. You're often dealing with the* ***parents****, you know,* ***potentially siblings*** *if they're donors and that sort of thing.'*

One researcher concluded that moral obligations to ensure the future health and well-being of the child participant supersedes other barriers, such as lack of financial or patient resources, that are frequently cited as reasons against disclosure based on contextual considerations.

'—I don't look at [disclosing IF] as a ***funded piece of work*** *where, if money goes away I cannot provide that information because it was related to the money. I believe the obligation is* ***much stronger*** *than that. There's... in my mind,* ***a moral side to it which is beyond money.***'

Although respect for individuals is often operationalized through informed consent, an IF problematizes many of the elements intrinsic to the consent process, including the detailing of purposes and risks and benefits associated with participating in the study. Particular disclosure procedures can endanger respect for individuals if relevant contextual information is not taken into account, although researchers can unintentionally violate this mandate when they are called to make normative judgments about the informational value of the IF.

Multiple perspectives on the role and purpose of the consent form emerged as a source of varying concern. Some respondents brought into question the relative utility of the consent form itself:

'You know, [patients] are ***not reading*** *them and understanding, and you try to go over stuff with them but I think the* ***consent forms are ridiculous****.'*

Although some affirmed the consent process serves primarily as an informational tool to educate prospective participants on the study, others asserted that it absolved, or at least delegated, professional liability elsewhere in cases of IFs:

—'I think we have ***to draw a line*** *at a certain point and say 'You will not get results for this'; It's in the consent form, and I think there is a* ***responsibility of the ethics committees*** *to oversee that it's clear to the families.'*

Some researchers contended all procedures for handling IF should be disclosed in the consent forms:

—'It's got to ***be decided up front*** *what's in the consent form; and, as far as any data that's collected, it's got to be clearly decided whether the participants will receive or will want to receive the data….****And we got to respect that.****'*

In contrast, others questioned the ethicality of third-party researchers making sweeping decisions about disclosing IFs to families given the implications of receiving this information:

—'I know there are some people who ***definitely want to know*** *these results and there's other patients who do not want to know these results. And, as a researcher, I don't think it's* ***my place*** *to decide whether or not somebody in the family members should.'*

Professional responsibilities

Guiding much of the discussion with respondents was when and under what circumstances does a professional duty to inform necessitate IF disclosure. The notion of professional expertise, its limits, and potential for liability were specific challenges identified in the process of first determining actual clinical risk, and second explaining this risk to patient-participants.

In contrast, investigators not involved in clinical care challenged whether a duty to inform participants of clinically significant IFs was within their professional realm. Most basic health science researchers felt any professional obligation toward individual participants was ultimately presumptuous and misplaced. One basic health science researcher reasoned that care-driven initiatives were simply out of their professional scope:

—'I'm in research, and ***I cannot do diagnostic things because I am in research****; and no one is* ***paying me for the diagnostic things****, so I cannot stop everything and do diagnostics that I am not entitled to do.'*

Many clinician investigators agreed, assuming their professional obligations to their patients were not annulled simply because they are also involved in research concurrently with clinical practice:

'—A researcher who has a clinical background, I'd like to have a ***formal and explicit obligation*** *to find a resolution of clinical concerns that emerge. I'm not saying that they generally do it well. I'm not saying they necessarily even do it all. But, there is an obligation that their general clinical responsibilities aren't* ***shut off*** *just because they're involved in research. Whereas a PI who's a molecular biologist does not have that kind of* ***clinical-societal responsibility****...'*

Moreover, our findings reveal that investigators also appeal to personal morality in making disclosure decisions. Notions of professional duty, and ideas about what constitutes good medical practice, were often integrated in an investigator's own moral justifications to disclose (or not). As one interviewee claimed:

'—In clinical medicine, one of the mantras I believe is that you should ***never order a clinical test for a patient unless you have a reason to order the test*** *and unless you know what you're going to do with the result. Talking about incidental findings in research,* ***some things completely violate that whole tenet****, and the chance that a laboratory result will be used out of context or to the wrong conclusion inappropriately* ***skyrockets*** *when nobody asked for that test in the first place. So, I think it* ***flies in the face of good clinical medicine*** *to be sending patients' incidental results and tests nobody ever ordered.'*

Implications for health-care system

Professional competence in interpreting genetic risks has important system-wide implications for resource allocation. Most investigators regarded the genetic counselor as the most appropriate health professional to assist participants and other clinicians in making sense of genetic risk.

'—[Patients] need genetic counseling to put [the finding] ***in perspective with their other risks****. We have to decide first whose responsibility is that, can't be the researcher's responsibility; they're* ***not equipped*** *to do that. Primary care physicians are not properly equipped to deal with it, so I could probably send [the patient] to a genetic counselor.'*

There was a reverberating call for enhanced genetic resources to help mitigate the limited genetic expertise among clinician investigators, especially. One respondent argued supply was not meeting demand in this regard:

'—Well, very often there's not enough ***skilled people*** *to provide [genetic counseling]. A lot of times, the* ***knowledge just isn't available*** *or only available to a select few people.'*

Investigators additionally voiced concerns surrounding the consequences of a lack of genetic resources for patient care. The harms of feigning genetic expertise greatly outweighed the potential financial burdens to the health system if this need was neglected:

'—I think part of it is ***acknowledging what you don't know****. You know? I think part of the problem is if you* ***transmit incomplete information****, or give the impression of more is known than actually is known, that* ***can cause problems****.'*

Furthermore, many questioned whether investigators should still be held accountable for informing patient-participants of breakthrough

discoveries beyond the duration of any given study. As one researcher put it:

'—*In **an ideal world**, we would probably say, you know, anything that is of high relevance for the patient should be returned, even if it's a certain period of time. But, of course, the **longer time goes** on in terms of the feasibility of actually doing that, and also knowing the limitations of research studies – as a researcher I know that, as much as we would like to do that, there are **certain limitations in terms of resource**s that will **not really make it possible** to return findings to patients after five or... ten years.*'

Certainly, resource constraints remain a limiting factor to maintaining ties with participants beyond a study's duration. But whereas resource distribution can have a finite end, the continuation of professional responsibilities to patients may not be so linear. The clinical and analytical validity of a genetic diagnosis is proportional to technological innovation and time. Presumably as genetic technology becomes more ubiquitous in the clinical sphere, the validity of genetic findings discovered in previous years become subject to reevaluation. It is this issue that has at least one researcher worried:

'—*So that's the problem [with disclosing incidental findings], or at least one of the problems: **For how long**? If the results become available ten years later, really, we're opening such a huge box that's potentially **without boundaries**, and I'm **concerned** about the **responsibility** that that might put upon us.*'

In contrast, one clinician investigator argued if the participant can be traced and recontacted using stored information, the responsibility to inform extends beyond the duration of the study. Although this responsibility is believed to exist, the respondent identified that fulfilling it occurs in the absence of a framework or guideline:

'—*As long as the data has been stored in a way where it's possible to **retrieve and identify** the person where there is information of concern that relates to them, then I **don't think responsibility ends** because the study itself was terminated. But it is very **unclear** and I don't think right now the way research is structured there is a real clear way of designating how you **maintain that ongoing responsibility**.*'

Suggestions for improving infrastructure

Despite the many challenges and palpable worries delaying the formulation of ethical protocols for disclosing IFs, researchers are optimistic about the clinical futures that NGS and other genomic technologies chart for pediatric research in oncology. Deriving maximum utility from these innovations demands respect for the ethical principles governing research participation. In the next sections, we describe two critical action items and proposed solutions our respondents identified in achieving this goal in pediatric oncology.

First, ethical frameworks for disclosing IFs must shift from reactionary to anticipatory policy making. Only in treating the possibility of discovering IF as commonplace in NGS can investigators make this transition. According to one researcher, envisioning IFs as a well-planned event is one step toward adopting anticipatory approaches to policy making generally:

'—*The [approach] needs to be a **well-thought out exercise**; at end of the day what you want to do is give the patients the information and certainties they need **without disabling them; ideally, empowering them**.*'

One specific component of the 'well-thought out exercise' includes reorienting the ways in which the research community conceptualizes these issues:

—'*I mean... we are so used to, in oncology, working with algorithms, that sometimes it is difficult to work outside them; And algorithms sometimes make life easier. On a different note they... prevent us from, at times, thinking outside the box...*'

Second, adaptations in clinical infrastructure, including improved communication, are necessary to prepare participants and investigators for the inevitable integration of NGS into routine clinical care. As such, the proposed connection between advanced genetic testing and health prevention evokes both concern and optimism:

'—*There are both **growing concerns and growing excitement** at the same time. I mean, the potential for benefits seem to be huge for me in having this information accessible. But the concerns are around what are the ethical frameworks and considerations in place. I guess the one thing that is worrying is the fact that there **is no infrastructure in place** to really deal with these results.*'

Similarly, investigators identified the essential yet marked absence of follow-up services after IF disclosure:

'—*There's **no point** having a test unless you've got somebody in to **follow up on it**… Resource-wise, you don't really know whether you **actually have the infrastructure** or even the **funding to support** a follow-up on that.*

One respondent offered a sober reminder of how improving follow-up infrastructure has a rippling effect on the healthcare system as a whole:

'—*If our healthcare system says, 'We'll follow up on all these incidental results,' we've just **overwhelmed** the healthcare system…*'

DISCUSSION

What emerges from our study, and others to be sure, is the need for IF disclosure to be thought of as a dynamic process with special attention to the social and scientific values that investigators place on contextual information. Evaluating the decision to communicate IFs involves balancing practical, ethical, and risk-related factors. For this reason, the authors caution against a universal standard of care to IF disclosure called for by some.[35] Rather, the findings presented in this study demonstrate that respectful disclosure practices are those that reflect the primacy of the participant's well-being by acknowledging, 'what disclosure might mean in an individual's life context…'[36]

Although not asked to prioritize contextual factors explicitly, investigators rated clinical significance and respect for individuals as the leading factors atop a hierarchy of pressing considerations. Increasingly, genetic researchers are questioning whether an obligation exists to actively search for important, although secondary, clinical findings.[37] Our results further corroborate this marked heterogeneity in investigator opinions. There was no clear consensus regarding what constitutes a clinically significant finding, how standards of care should adapt to the emergence of an IF during research participation, and to what extent investigators should weigh familial preferences when notions of best interests for the child are in conflict.

To the latter point, we observed differences in framing discussions of professional responsibilities between basic health science researchers and clinicians, namely when referring to liability and the role of caring for patients. In line with this finding, the discovery of an IF engendered issues regarding the participant's right of not to know. As the European Society for Human Genetics[2] highlighted, guidelines need to be established as to what IF should be disclosed in order to balance the autonomy and interests of the child and the parental rights and needs (not) to receive information that may be in the interest of their (future) family. The Public Population Project in Genomics and Society (P^3G) International Paediatric Platform[38] suggested the possible return (or not) of IF in pediatric research should be discussed during the informed consent process. Any IFs that are 'scientifically valid, clinically useful, and reveal conditions that

are preventable and actionable during childhood' should be offered to parents. Although not explicitly referring to pediatric populations – where informed consent is of special interest – Ayuso *et al*[39] share the views of the P^{3}G in their suggestion 'that… clinically manageable disorders affecting the patient... must always be disclosed to the patient'…the possible disclosure of other types of information.... should be discussed and agreed upon in advance with the patient during the informed consent process.'

In general, there is consensus that results indicating a mutation that will affect the child when he/she reaches adulthood, or which predisposes the child to an adult-onset disorder, should not be returned. On a case-by-case basis, an exception could be made if disclosure of an IF detailing a highly penetrant gene, which poses serious risk to the health and well-being of the child's family member, is otherwise preventable and amenable to treatment.[38]

The recent ACMG Recommendations[40] continue to be at the center of these discussions, particularly the mandatory reporting of mutations in a panel of 56 identified gene loci irrespective of age. The ACMG recently released their intent to update these existing guidelines, however: 'While the ACMG Board still considers the IFs to be important medical information that can be a great value to families, it has voted to recommend that such an 'opt out' option be offered to patients who are considered candidates for clinical genome-scale sequencing'.[41] The authors have questioned their applicability in clinical settings, where it is recommended that IF should be delivered to the clinician who ordered the sequencing, and that this clinician may contextualize any IF for the patient in light of personal and family history, physical examination, and other relevant findings.[42] Others question whether the recommendations delegitimize patient/participant preference and invite genetic paternalism.[43] To this end, one respondent relayed a powerful anecdote bearing a cautionary tale:

'*—I treated a child who actually had a gene mismatch repair defect. And obviously the family was counseled and we needed to test the family. And I was in the situation of how to counsel them to go for testing.* ***It was a family that wasn't interested****. And at a certain point in that particular relationship, after making the point at least two or three times that testing was important, I stopped. And I said, "Well, I've given you the information.* ***You are now responsible for using it the way you deem appropriate****, and I have done my due diligence, so to speak." And why does that stick in my mind? Because this was the instance where the dad actually said to me, "Why should I get tested? And why should my children get tested?* ***Because right now I'm living a happy life. My children are living a happy life. The moment I get tested, I will start dying****." And that was very* ***powerful*** *for me...* ***Here's a perfect gene*** *that, if you have it, one would die of cancers in early age if it was homozygous, and if not, they would actually develop early colon cancers, some of which can* ***be prevented to some degree in terms of prolonging life****. You couldn't take them all away, but you could actually prevent them from causing death. And you could, you know, maybe buy five years, ten years, fifteen years, of life.*'

In turn, all the contextual considerations raised in this paper preclude establishing a universal IF disclosure policy across research and clinical institutions. They make clear a one-size-fits-all approach ignores many of the contextual elements that inevitably surface in the course of conducting genetic research involving children. The pressing need identified by our study respondents toward a context-oriented and anticipatory policy approach to IF disclosure is also endorsed in the recent report for the management of IF by the US Presidential Commission.[44] Through contributing the views of those at the frontlines of genetics and pediatric genetic research, we might better identify challenges that the literature has not yet addressed in the complex tripartite relationship between clinician, parent, and child[45] and the demand for collaborative dialog on forthcoming ethical guidelines of IF disclosure.

Study limitations

Although modest in scale because of challenges in recruiting physicians, our study nevertheless facilitates an in-depth analysis of issues that help illustrate the perceptions of Canadian pediatric investigators and those who work primarily in the field of pediatric oncology research. Our findings may not be representative of views from nonpediatric health professionals, or those from other countries. The use of volunteer participants resulted in views from those interested and aware of the issue of returning IF, although further research with larger groups of investigators may reveal differences in their reasoning. In addition, our study provides a temporal snapshot of opinions and attitudes in this complex field during a dynamic and ever-evolving era in genetics and genomics. It is likely that the mentality around, and approaches to, the disclosure of IFs will vary as new innovations emerge to alter the trajectory of WGS and clinical care.

CONCLUSION

Our study reveals several factors considered when returning IFs to the families of child participants and perhaps the children themselves commensurate with their ability to appreciate the implications of the proposed information. This theme has been widely debated in pediatric research ethics discourse, yet questions persist concerning at what age, in what context, and in what capacities should investigators consider direct disclosure to children. Regardless of the information recipient, the most pressing contextual factors guiding the decision to disclose an IF were clinical significance, respect for individuals, scope of professional responsibilities, and implications for the healthcare/research system. Given the technological innovations in NGS and other genetic diagnostics, investigators should be prepared for the inevitability of managing IFs in, among others, a pediatric oncology research setting. As one respondent astutely observed,

'*—The disclosure* of incidental findings *is not an incidental activity*.'

The first step toward drafting collaborative policies is to dispel the notion that a one-size-fits-all standard will best address the ethical tensions inherent to IF disclosure. Thoughtful discussion across clinical and research spheres is essential if guidelines for disclosure are to reflect the realities of both investigators and research participants. Finally, improvements in the clinical infrastructure and the transition to anticipatory policy making will enable investigators to prepare for the ethical exercise of IF disclosure. By fostering a culture of communication around the capacities of NGS, IFs will indeed cease to become an incidental activity. Rather, shared decision making and honest dialog with participants and their families will supplant professional dilemmas arising from IF disclosure at least in part.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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