Patient Education and Counseling 90 (2013) 133–138

Contents lists available at SciVerse ScienceDirect

Patient Education and Counseling

journal homepage: www.elsevier.com/locate/pateducou

Provider Perspectives

Genetics specialists' perspectives on disclosure of genomic incidental findings in the clinical setting☆

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ARTICLE INFO

Article history:
Received 16 January 2012
Received in revised form 31 August 2012
Accepted 23 September 2012

Keywords:
Genomics
Incidental findings
Clinical genetics
Disclosure

ABSTRACT

Objective: Evidence documenting management of incidental findings (IFs) from clinical genomic testing is limited. The aim of this study was to examine genetics specialists' perspectives regarding current and preferred disclosure of clinical genomic IFs.
Methods: 50 genetics specialists, including medical geneticists, laboratory professionals, genetic counselors, and nurses participated in structured telephone interviews. Data were analyzed using qualitative content analysis and descriptive statistics.
Results: Most specialists had encountered IFs, but definitions of IFs varied. They discussed challenges with informing patients about the prospect of IFs and disclosing IFs to patients. Causing psychological harm to patients was a concern. Participants were divided on whether IFs needed to be clinically significant and/or actionable in order to be disclosed to patients. Creating formal disclosure guidelines was considered useful, but only if they were flexible. Additional counseling, more interdisciplinary communication, maintaining contact with patients, and a centralized database to interpret IFs were also proposed.
Conclusion: Genetics specialists offer insights into the challenges of defining IFs, knowing when and how to disclose them, and the potential need for flexible disclosure guidelines.
Practice implications: Further discussion between practicing genetics specialists is needed to develop consensus on the development of best-practice guidelines for IF management.

1. Introduction

The rapidly increasing number and use of genetic and genomic tests in clinical practice are raising new dilemmas with respect to management of incidental findings (IFs). Sequencing technologies, including whole genome sequencing (WGS) and whole exome sequencing (WES) increase the possibility of encountering variants known to cause disease, suspected to cause disease, or of uncertain significance that are outside the original intent of testing [1]. Although WGS and WES can reveal findings beyond those related to the purpose of the test, they may be unanticipated and thus still considered IFs [2].

Ethical management of IFs is debated in the research setting [3]. Some members of the public say that they would like to receive individual research results from genomic research [4,5], which may include IFs [4]. While some issues related to disclosure of IFs in research are similar to those in the clinical setting [3,6,7], clinicians typically have a more personal relationship with their patients than researchers, and the clinician role may extend to the duty to warn patients' family members about future health risks indicated by genomic IFs [8].

Genomic IFs may have direct clinical implications for patients and their families' health, have personal utility, be useful for future reproductive decisions or for life planning, or be of personal interest [9]. While the discovery of IFs is a component of clinical practice, the amount of data that can potentially be generated from genomic testing creates new challenges [10].

1.1. Genetic and genomic tests and IFs

While genetics specialists are likely to have some experience managing IFs, the increased volume of IFs due to the increase in the number of tests and genome-scanning technology may mean that more time will be devoted to validating, interpreting, and

☆ *Funding*: NHGRI RC1 HG005786.
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http://dx.doi.org/10.1016/j.pec.2012.09.010

communicating IFs to patients. Furthermore, primary care physicians may ultimately be responsible for implementing follow-up procedures with respect to IFs that enter into patient records [11]. Ethical issues that arise when entire or extensive segments of a patient's genome are interrogated include the risk of providing patients with incomplete or incorrect information; providing information for which patients are not prepared; exposing patients to unnecessary and potentially harmful or ineffective treatment; and determining whether or not to report misattributed paternity, consanguinity, or carrier status [1,12–14].

There is no consensus regarding how to minimize these risks in the clinical setting. One proposal recommends limiting disclosure to IFs with clinical utility, although patients and clinicians may agree to disclose IFs without clinical utility [15]. The proponents of this proposal argue that limiting disclosure to IFs with clinical utility reduces the potential for reporting false positive findings [16] or overwhelming patients and clinicians with currently uninterpretable information [15]. Other recommendations range from offering menu-type options on informed consent documents [17], to a 'blanket' disclosure policy to return all genomic findings, regardless of their significance [12]. Associated issues include whether written informed consent should be required that addresses both the possibility of IFs and whether they will be disclosed to patients and/or family [18].

To our knowledge, there is no empiric research regarding genetic specialists' perspectives concerning disclosure of IFs from clinical genetic or genomic testing. The purpose of this study was to examine the perspectives of clinical genetics specialists regarding the management of IFs.

2. Methods

2.1. Approach

This paper presents one component of a larger study examining the management of genomic IFs from the perspectives of numerous stakeholders (Williams and Simon, NHGRI RC1 HG005786). This report focuses on the perspectives of genetics specialists in the clinical setting. This includes medical geneticists, laboratory professionals, genetic counselors, and genetics nurses. The Institutional Review Boards at The University of Iowa and The University of Northern Iowa approved this study.

2.2. Participant selection

We used purposeful sampling [19] to identify genetics specialists involved in clinical genomic testing. Participants were invited through collaboration with the Heartland Regional Genetics and Newborn Screening Collaborative, the American College of Medical Genetics, the National Society of Genetic Counselors, and the International Society of Genetics Nurses. Potential participants were directed to contact the University of Northern Iowa Center for Social and Behavioral Research (UNICSBR) who screened them for eligibility.

2.3. Interview guide development and pilot interviews

The interview guide (Table 1) was developed by the research team following an extensive review of the literature on the issues related to IFs in clinical practice and research contexts [7,10,20,21] and consultation with clinical experts, including a medical geneticist and a genetic counselor. For this study, we defined IFs as "test results unrelated to the reason or purpose for which a person is being tested; sometimes the health significance of IFs is known, but often their significance is ambiguous" [10,22]. This definition was provided to participants if they asked for clarification of the use of this term in the study. Questions were refined in a one day workshop with PIs, interviewers, and survey methodologists from UNICSBR.

The interview guide was piloted in three phases. In the first phase, members of the research team interviewed a medical geneticist and a genetic counselor with clinical experience in genetic and genomic testing. In the second phase, three members of the research team took the role of genetic specialists in interviews conducted by the UNICSBR interviewers. Minor wording changes were made as a result of these first two piloting phases. The third phase involved the administration of the interview by a UNICSBR interviewer to a medical geneticist and a laboratory director who contacted the interviewing center to participate in the study. No changes were identified upon completion of this last component of the pilot process.

2.4. Data collection and management

Trained interviewers conducted telephone interviews with participants who met eligibility criteria. Interviews were

Table 1
Structured interview guide questions.

1.	When you hear the words, "incidental finding," what comes to mind?
2.	Can you give me an example of an incidental finding that has occurred in your work?
3.	What information about incidental findings, if any, are you able to provide your patients before they undergo a genetic or genomic test?
4.	In what format do you provide this information to your patients?
5.	Apart from any of the information that is already shared with your patients, what additional information about incidental findings do you think should ideally be shared with them?
6.	How do you feel about giving your patients the option of indicating whether or not they want to be contacted if an incidental finding is found?
7.	Next, I would like to get an idea of how many IFs you encounter in your work. Thinking back over the last 12 months, how many genetic or genomic IFs have you encountered?
8.	Is this number more or less typical of most years?
9.	Approximately what percentage of these IFs did/do you contact the patient about?
10.	How much of the detailed information about an incidental finding do you provide to a typical patient?
11.	How did/do you contact (or, "are you likely to contact" for respondents who have not yet done so) a patient with the news that an incidental finding has been discovered?
12.	Do you have specific procedures in place for dealing with or managing incidental findings? If not, would you find such procedures useful in any way? Why? Why not?
13.	Who developed these procedures?
14.	Whose policies or guidelines, if any, are these procedures based on?
15.	What do these procedures require you to do?
16.	How well have these procedures worked for you so far? [*If respondent has not needed to use the plan yet*] How well do you think they are likely to work for you?
17.	Have you personally discussed with patients any incidental findings that you have found?
18.	Approximately how many such discussions have you had over the last 12 months?
19.	How well do you think patients understand the information you typically share with them?

audio-recorded and transcribed verbatim. Transcripts were downloaded into NVivo8 [23], a software program for qualitative data management.

2.5. Data analysis

Demographic items were analyzed using descriptive statistics including frequencies, measures of central tendency, and dispersion, depending on the level of data. Medians are provided when data are skewed. Narrative data from open-ended questions were analyzed using response frequencies and qualitative content analysis [24]. Two research team members conducted the initial coding of transcripts. Coders discussed coding until 100% agreement was reached between them. A third member of the research team participated in early coding discussions to resolve discrepancies between the two primary coders. Data analysis was ongoing and recruitment of new participants stopped when data reached saturation.

3. Results

3.1. Participant characteristics and encounters with IFs

The sample of 50 genetics specialists included clinicians and laboratory professionals from 43 institutions (Table 2). All participants were involved with clinical genetic and/or genomic testing, including karyo typing ($n = 43$), CMA ($n = 41$), molecular genetics ($n = 41$), prenatal diagnosis ($n = 27$), cancer genetics ($n = 5$), newborn screening ($n = 3$), and miscellaneous genetic tests ($n = 8$). Clinicians included 13 medical geneticists, 13 genetic counselors, and four genetics nurses. Genetic counselors and genetic nurses were grouped together in analyses because they returned test results to patients. The majority of medical geneticists were male (62%). Genetic counselors and nurses were primarily female (76%). Laboratory professionals included 18 laboratory directors and two lab-based genetic counselors, 60% of whom were male. Most participants were white (80%) and worked at non-profit institutions (80%). Participants had a median three years of experience with genetic and genomic testing.

Most participants (94%) reported that they had encountered at least one IF including misattributed paternity, consanguinity, chromosomal anomalies, variants assumed to be benign, and variants whose significance were unknown. Participants were asked if they had specific procedures in place for dealing with or managing IFs and, if so, what these procedures required them to do. Responses ranged from avoidance of encountering, reporting, or disclosing IFs; determining which IFs warranted reporting by laboratory professionals or disclosure by clinicians; and relaying all IFs.

Note: In the following sections, participants are identified by profession – medical geneticists (MG), genetic counselors/genetics nurses (GC/GN), and laboratory professionals (LP).

3.2. Definition of IFs

Participants were asked, "When you hear the words, 'incidental finding,' what comes to mind?" and to provide an example of an IF that had occurred in their work. There was general agreement that IFs were unexpected and unrelated to the purpose for which the test was ordered. However, participants varied as to whether they considered IFs to be only findings that could be interpreted, only variants that were known to be normal or benign, only findings whose significance was uncertain, or a combination of these elements: "*[I]t is a DNA change that we're unable to interpre*t" [GC/GN24]; "*I don't think of incidental findings as things like variants of uncertain significance, but that's a different issue altogether, but they sort of get jumbled in my head*" [GC/GN51];

> *When I hear 'incidental finding' I generally think of a possible abnormality that could be clinically significant. That's one way that I hear it. But incidental findings can be variants that have no real clinical significance or might be variants of unknown significance* [LP47].

3.3. Informing patients about the prospect of IFs

Participants were asked what information, if any, about IFs they provided to patients prior to genetic and genomic testing. Responses varied according to the volume and scope of information provided prior to testing: "*As part of our consent process we discuss the possibility of incidental findings, and discuss that the results could be positive, negative, or have a variant of uncertain significance*" [GC/GN44]; "*In general, I do not provide information about incidental findings or the possibility of incidental findings in the clinical setting*" [MG15].

Participants expressed concern that there was the possibility of providing too much information about IFs: "*From a prenatal standpoint, sometimes giving them too much is maybe overwhelming*" [GC/GN52]. Some said it was impractical to address the topic of IFs prospectively: "*I mean, you'd have to have a 10-hour counseling*

Table 2
Participant characteristics and demographics.

Genetics specialist $N = 50$	Mean age (range)	Gender	Race/ethnicity	Highest degree	Avg. yrs genetic testing	Avg. no. IFs encountered in past 12 months (range)	Institution type	Profit/non-profit
Medical geneticists $n = 13$	52.0 (36–65)	M = 8 F = 5	White = 12 Other = 1 Hispanic = 0	MD = 10 MD/PhD = 2 Doctorate = 1	19.34 (<1–25+) Median = 3	12.92 (0–75)	State uni = 11 Private uni = 1 Not a uni = 1	Profit = 0 Non = 10 Unclear = 3
GC/RNs $n = 17$	45.75 (33–69)	M = 4 F = 13	White = 15 Black = 2 Hispanic = 0	Master's = 14 Doctorate = 3	15 (<1–25+) Median = 2	8.21 (0–30)	State uni = 8 Private uni = 3 Not a uni = 6	Profit = 2 Non = 15
Lab professionals $n = 20$	49.44 (34–63)	M = 10 F = 10	White = 13 Asian = 7 Hispanic = 0	Master's = 2 Doctorate = 14 MD-PhD = 2 MD = 2	16.79 (<1–25+) Median = 3	13.42 (0–100+)	State uni = 7 Private uni = 5 Not a uni = 9	Profit = 5 Non = 15
Total clinician group	48.2 (33–69)	M = 22 F = 28	White = 40 Black = 2 Asian = 7 Other = 1 Hispanic = 0	MD = 14 Doctorate = 18 Masters = 16 MD/PhD = 4	16.76 Median = 3	22.9	State uni = 26 Private uni = 9 Not a uni = 16	Profit = 7 Non = 40 Unclear = 3

session to talk about all the things that you might find" [GC/GN49]. Others stated they did not discuss the possibility of IFs prior to testing when they conducted testing that was not expected to encounter IFs: "*[T]he testing is quite targeted and the chance of finding something incidental is not that high*" [MG21]. Laboratory professionals stated the information provided to patients prior to testing was up to the ordering clinician. Those that did talk to patients provided a general written or verbal statement about the possibility of IFs: "*I talk about finding things that we don't know the implications about*" [LP46].

3.4. Disclosure experience and practices

Sixty-two percent of participants stated they had personally disclosed and/or discussed IFs to patients, with lab professionals stating they generally reported them to the ordering clinicians and not directly to patients. Participants volunteered information regarding feelings of discomfort about disclosing IFs of uncertain significance when no definitive results related to the reason for testing were found: "*If there is a copy number. . .variant . . . I will of course decide to disclose that, but, it's hard for people to understand what that means, and it's hard for me to explain the uncertainty around it. So those are relatively unsatisfactory discussions sometimes. The more relevant it is, the more satisfactory it is*" [MG21].

Participants expressed concern over the possibility of causing psychological harm to patients: "[W]hen these incidental findings come up in a prenatal setting, the anxiety, the turmoil, that I see out of this is tremendous. . ." [MG55]. When participants were asked how well they thought patients understood the information that was shared with them, over half (63%) of the genetics specialists who had experience disclosing IF information stated patients did not understood the information well: "[I]f they find out that they have [an IF] often you find out that they wonder, 'Well what's wrong with me?' Or, 'How am I fine if I have this lab difference?'" [MG17].

Participants who had personally discussed IFs with patients ranged from reporting all IFs to reporting only some types of IFs. For example, misattributed paternity and consanguinity were IFs participants stated they would not necessarily disclose to patients or report to clinicians:

> *Well, some incidental findings are not disease-related, like the paternity cases. . .and in those cases we really weighed whether the knowledge of the mistaken paternity would have any effect on the result of the test. And if it didn't. . .we generally did not disclose that information* [LP19];

Others acknowledged that it was important to disclose accurate information regarding genetic relationships: "*If that gentleman thinks he's the carrier for something and he's not, he needs to know that*" [GC/GN49].

3.5. Opting out of disclosure

When asked how they felt about giving patients the option of indicating whether or not they wanted to be contacted about IFs, some stated they either did not think opting-out was a good idea (40%), or that they were conflicted about it (30%). Responses were related to the type of genetic or genomic testing involved: "*Well the kind of incidental finding that I'm talking about isn't an option really. . .people have consented to have the [CMA] done and that's part of the kind of test results*" [MG67]. Respondents expressed more conflict about the choice for patients to opt out of receiving information about IFs when the IFs had known clinical significance: "*It is absolutely their right to choose. . .but I think it would be really difficult if we knew something that was medically important, possibly treatable. . .*" [GC/GN43].

3.6. Formal IF disclosure procedures

Only 14% of participants stated definitively that they had IF procedures; 48% stated definitively that they had no procedures for managing IFs. Some participants stated they managed IFs on a case-by-case basis (10%), or treated IFs the same way they treated other test results (14%): "*[W]e put in a policy, not in any written form, but in our divisional discussions, that every family should be told* a priori, *when the test is being done, that something might surface*" [MG65]. Laboratory professionals were the most likely to state they had specific procedures for managing IFs. Four laboratory professionals referenced ACMG guidelines on reporting sequence variations; two stated they had specific procedures only for selected tests.

3.7. Preferred IF management

Thirty-eight participants who stated they had no specific procedures were asked whether they thought specific procedures would be useful. Most of these participants (76%) stated that they thought procedures would or may be useful and some (21%) added that procedures should be flexible, allowing for professional judgment: "*I think I would find loose guidelines useful, you know, to kind of know what the standards or what the norm is, with the ability to mold that to your specific practice*" [GC/GN09].

3.8. Suggestions for IF management

In the course of the interviews, some participants volunteered suggestions for improving management of IFs: "Having a good database, and having relevant clinical information [that] people as a community can [use to] share our experiences . . .would be very helpful" [LP48];

> *I think having an additional. . .counseling session, and a period of time farther out from the review results, [so patients] could have had time to think through what that means to them, and what questions they would have* [GC44].

Clinicians and lab professionals expressed the desire for clearer communication between these two groups to assist with IF interpretation:

> *[T]he clinician that's ordering the tests and the laboratorian that's performing the test analytically and interpreting the significance of that test result—those two people need to have a conversation. . .. And often, neither side has the time or the ability to make that happen* [MG69].

4. Discussion and conclusion

These study results indicate there is a continued reliance on case-by-case management of genomic IFs in the clinical setting. However, there are significant ethical and practical issues regarding management of genomic IFs that may not be sufficiently addressed without formal guidelines. Findings from this study raise four specific issues that require further examination.

4.1. Inconsistent definition of incidental findings

The first issue is the lack of a common understanding of the term "incidental findings." While the definition of IFs used in this study included unanticipated findings whose significance was known or ambiguous, not all participants defined IFs in this way. Part of the variation in definitions may be related to the word "incidental," which appeared to have two different meanings – "unrelated" or "unimportant," which is consistent with the lay

definition of incidental. The "unexpected" nature of IFs may mean different things to different people. For example, while genetics specialists may expect to discover findings unrelated to the reason for testing, these discoveries, if disclosed, may be wholly unexpected for patients and their families. Biesecker reports that some research participants experienced "shock and incredulity" [1] (p. 396) regarding results that were not expected in light of their family medical histories. It is important to clarify the definition before making recommendations for IF management in the clinical setting to ensure all stakeholders, including the patient, are talking about the same thing.

4.2. Informing patients and determining their preferences for IF disclosure

The second issue involves the extent to which and how patients should be informed about the prospect of clinical genomic IFs, and whether they should be asked for their permission to disclose IFs. Clinical informed consent is one context in which patients can be asked to state their (non)disclosure preference with respect to IFs. Participants echoed the concerns of experts who recognize the challenges of obtaining meaningful informed consent with respect to IFs that have yet to be discovered [9,17]. These challenges include the limited amount and speculative nature of information that may be available for describing future IFs. In the case of IFs resulting from CMA, Netzer and colleagues [17] proposed an informed consent document with menu-like options, including whether patients want to be informed about findings with health implications that are unrelated to the reason for testing, or findings for which there is an available treatment or surveillance regimen, or whether they want to be informed about carrier status related to these findings. This 'tiered' approach to consent potentially enhances patient choice and control, but may also lengthen and complicate the consent process.

While some have argued there are unique ethical challenges in the management of genomic information that necessitate use of documented informed consent procedures [11], others argue for non-exceptionalism, i.e., the issues are not unique and should be treated similarly to other sensitive health information [25–27]. Our findings suggest that the need to obtain patients' permission prior to IF disclosure is not clear-cut. Genetics specialists in this study were uncomfortable with the idea of allowing patients to opt out of receiving IFs with known clinical significance, a perspective shared by some in the literature [28]. Assessing patients' educational backgrounds, expectations, and contextual issues before disclosing IFs may be necessary when determining how to facilitate comprehension of genomic information [29].

4.3. Minimizing harm

A third issue raised by participants in this study is the risk of causing psychological harm when disclosing IFs. For example, some participants did not disclose IFs related to misattributed paternity due to the risk of psychological harm. However, our findings indicate there was also increased recognition of the importance of having accurate personal genomic information, including misattributed paternity [30]. This may represent a shifting perspective on this issue in the era of personal genomic medicine [31].

Participants were concerned that disclosing IFs they could not currently interpret would cause undue anxiety to patients, as well as frustration to themselves. This frustration was compounded when there were no findings that explained the phenotype for which patients sought testing. While this appears to support the recommendation to limit disclosure of IFs to those findings with known clinical utility [15], participants in our study also recognized that new information regarding the interpretation of IFs with uncertain significance is being updated constantly. This contributes to the dilemmas regarding how to present these findings to patients, how to manage implications for patients' relatives, and who should be responsible for following up when new information about IFs becomes available [11,28,32]. Free access to centralized databases with information on phenotype-genotype information, such as db GaP [33], facilitates the interpretation of these IFs. However, issues that still need to be addressed include: the time it takes to search multiple existing databases; the amount of time after testing that genetics specialists are responsible for searching databases; how to maintain contact with patients; and who is responsible for following up when new information becomes available.

4.4. What and how to disclose

In the current study, participants' responses were divided on whether IFs needed to be clinically significant and/or actionable in order to be disclosed to patients. This viewpoint parallels discussions regarding individuals' rights to their personal genomic information [34–42]. Genomic IFs might have personal value to patients, regardless of their clinical value [43], and patients may use genomic information to change behaviors even when no clinical treatment is available [44]. The differing views of genetics specialists presented in the current study indicate a need for further discussion in order to develop guidelines that are acceptable to all stakeholders.

Participants seldom discussed IFs from the viewpoint of patients, other than the concern for causing psychological harm. More data are needed regarding the patients' perspectives on whether and how they would like to receive information regarding IFs following clinical genetic and genomic testing.

4.5. Limitations

A limitation of using a structured questionnaire to obtain the data for this study is that it did not allow for clarification of responses. For example, we were unable to clarify what participants meant when they stated they had specific procedures for managing IFs. While we designed this study using a definition of IFs, we did not anticipate the wide discrepancy in use of the term. Therefore, it is not always possible to determine whether participants interpreted questions similarly. For example, the large range in number of IFs encountered may in part be based on individual definition of IFs. Participants in this study were invited based on affiliation with organizations that include clinicians involved in clinical genetic and/or genomic testing. Participants who volunteered may not be representative of all clinicians involved with clinical genetic and/or genomic testing that might reveal IFs. We did not ask participants whether or not they owned stock in any genetic testing companies that might have biased their responses.

4.6. Conclusion

This study identifies practical and ethical issues in disclosing IFs to patients undergoing clinical genetic and genomic testing. Key issues include inconsistent definitions, when and how to inform patients, minimizing psychological harm, and having flexible disclosure guidelines. There is the risk of psychologically harming patients by over-emphasizing the possibility of IF discovery, or by disclosing IFs in an insensitive or inexperienced way [10,45]. On the other hand, withholding IFs may indirectly harm patients by denying them access to potentially actionable or personally meaningful health information. Navigating between these potential harms is a current challenge facing genetics specialists.

4.7. Practice implications

Patient education is needed. Obtaining patient preferences will likely be a component of disclosure decisions regarding some types of genomic IFs. Members of the health care workforce will need time and resources to achieve best practices for managing genomic IFs in the clinical setting.

Acknowledgements

This project was funded by a grant from NHGRI (RC1 HG005786) to Janet K. Williams, and Christian M. Simon, Principle Investigators. The American College of Medical Genetics, the Heartland Regional Genetics and Newborn Screening Collaborative, the National Society of Genetic Counselors and the International Society of Nurses in Genetics provided assistance in recruitment. The University of Northern Iowa Center for Social and Behavioural Research conducted the informed consent process and data collection procedure.

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