



ORIGINAL ARTICLES AND REVIEWS

Incidental findings, genetic screening and the challenge of personalisation

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Abstract

Genetic tests frequently produce more information than is initially expected. Several documents have addressed this issue and offer suggestions regarding how this information should be managed and, in particular, concerning the expedience of revealing (or not revealing) it to the persons concerned. While the approaches to the management of these incidental findings (IFs) vary, it is usually recommended that the information be disclosed if there is confirmed clinical utility and the possibility of treatment or prevention. However, this leaves unsolved some fundamental issues such as the different ways of interpreting “clinical utility”, countless sources of uncertainty and varying ways of defining the notion of “incidental”. Guidelines and other reference documents can offer indications to those responsible for managing IFs but should not be allowed to relieve researchers and healthcare professionals of their responsibilities.

Key words

- bioethics
- genetic screening
- incidental findings
- research

DEFINITIONS

Recent years have seen steadily mounting interest in the issue of “incidental findings” (IFs), their management and (possible) disclosure, fuelled partly by the convulsive evolution of a wide variety of genetic tests and the ensuing increased probability of obtaining unexpected abnormal results.

So far as large-scale genomics studies are concerned, the question of IFs has been debated above all over the last ten years, in parallel with an emerging trend within the international research community to disclose certain single genetic results to research participants [1].

In 2008 Wolf *et al.* defined IFs as “a finding concerning an individual research participant that has potential health or reproductive importance and is discovered in the course of conducting research but is beyond the aims of the study” [2].

Other similar definitions followed, such as that contained in an important article published five years later, which noted that IFs “have been defined as findings having potential health or reproductive importance for an individual, discovered in the course of conducting a particular study (in research, clinical care or screening) but beyond the aims of that study” [3]. In the same year the Public Health Genetics Foundation defined IFs as “additional findings concerning a patient or research participant that may, or may not, have potential health implications and clinical significance, that are discovered during the course of a clinical or research investigation, but are beyond the aims of the original test or investigation” [4]. Kohane *et al.* even suggested the term “incidentalomes”

in the particular setting of medical genomics [5]. The term has been adopted by other authors, including Solomon, who used it when proposing an analogy between IFs in genomics and in radiology [6].

The earliest definitions of IFs made no clear distinction between the problems involved in the return of unexpected results and those involved in the return of research results in general [7]. One of the few exceptions was the Statement on the Principled Conduct of Genetics Research of the Human Genome Organisation [8]. A distinction between the research and practical settings gradually gained usage and has been widely adopted in recent articles. The US Presidential Commission for the Study of Bioethical Issues (“Bioethics Commission”), which had already partially addressed the issue in its report “Privacy and progress in whole genome sequencing” [9] (with particular reference to large-scale genetic sequencing), published an ample report entitled “Anticipate and communicate: Ethical management of incidental and secondary findings in the clinical, research, and direct-to-consumer contexts” [10], which defined IFs as “results that arise that are outside the original purpose for which the test or procedure was conducted”. The Bioethics Commission “divides the term ‘incidental finding’ into two categories: incidental findings that are ‘anticipatable’ and those that are ‘unanticipatable’. An anticipatable IF is a finding that is known to be associated with a test or procedure, while an unanticipatable IF includes a finding that could not have been anticipated given the current state of scientific knowledge”. The Commission also draws a distinction between primary, secondary and

discovery IFs. Primary findings are results that are actively sought using a test or procedure designed to find that result. Secondary findings are those “actively sought by a practitioner” but that are not the primary target, and discovery findings are those of a “broad or wide-ranging test that was intended to reveal anything of interest” [10].

A BRIEF OVERVIEW

Several influential documents recognise the duty to advise participants in research of any information that concerns their health. The Council for International Organizations of Medical Sciences (CIOMS), for instance, already in 1991 and again in 2002, in its “International Guidelines for Ethical Review of Epidemiological Studies” recommended that “individual subjects (...) be informed of any finding that relates to their health status” [11]. The same guidelines also recognised the subject’s “right not to know”. Similar recommendations have been issued by the World Health Organisation (WHO) [12]. In 2005 the Council of Europe, in Article 27 of the “Additional Protocol to the Convention on Human Rights and Biomedicine, Concerning Biomedical Research” [13, 14], recommended that “If research gives rise to information of relevance to the current or future health or quality of life of research participants, this information must be offered to them. That shall be done within a framework of health care or counselling. In communication of such information, due care must be taken in order to protect confidentiality and to respect any wish of a participant not to receive such information”.

The rapid growth of genomic data over the last decade has led several national and international groups to draw up guidelines on the procedures for informing research participants of their individual research results and, in particular, of IFs [1]. The report of the US Bioethics Commission [10] includes two lengthy appendices of lists and brief descriptions of national and international reports concerning the issue. The literature also contains reviews and summaries of key recommendations [3]. These documents often divide IFs into three categories: results that must be communicated; results that may be communicated; and results that should be withheld.

However, these categories can be interpreted in different ways. There is general consensus that clinically useful results should be communicated (but that information concerning pathologies for which no treatment is currently available and whose disclosure would only give rise to apprehension should not be disclosed) [15]. One typical approach for communicating research results that may serve as an example was adopted in 2004 by a working group from the National Heart, Lung and Blood Institute (NHLBI) of the National Institutes of Health. The group agreed on the conditions that should be met for genetic results to be disclosed to research participants [16]: briefly, these are that (1) the risk for disease should be significant; (2) the disease should have important health implications; (3) there should be a proven therapeutic or preventative intervention [15].

As we shall see from the broader discussion in the next section (“Some of the problems”), the notion of “clinical utility” can be interpreted in more than one way. One interpretation holds that clinical utility applies to IFs for

which there exists a potentially useful intervention that can improve the individual’s health status [17]. Another adopts a broader view and attributes “clinical utility” to information that would “facilitate life” [18] and which should therefore also be disclosed. Yet other scholars propose an even broader approach, holding that IFs should always be communicated out of respect for the person and regardless of their actionability [19].

These divergent positions are partly due to the different ways in which researchers and healthcare professionals interpret personal preferences [20]. Some assume a paternalistic attitude and consider that certain information should be withheld, even when patients would wish to know it [21]; others attribute a strong normative role to subjects’ preferences [22] and believe that all information should be disclosed, in accordance with the principle of respect for the person [23].

Whatever the approach, there is general agreement that all due caution should be used in disclosing information and that individual circumstances should be taken into account, particularly, for instance, when communicating information concerning minors [24] or genetic information that also affects other family members [25].

There is also agreement concerning the crucial role of informed consent [26]; it is advisable to include information on the procedures for managing eventual IFs in the forms submitted to subjects participating in research or clinical tests and to acknowledge the right not to be informed, except in specific circumstances [5].

INCIDENTAL FINDINGS: SOME OF THE PROBLEMS

Incidental findings pose a number of problems and intrinsically present certain weak points. These weaknesses are particularly significant when IFs involve genetic data derived from screening or other research. The following paragraphs mention a few of them.

The distinction between research and current practice and the notion of “incidental”

The debate over where to draw the line between research and current practice has never been satisfactorily resolved and the differences of opinion (which date back many years, as is evident from the debate shown in the appendices [27, 28] to the “Belmont Report” [29]) are still in evidence [30]. One cause of the problem is that the confines between the two settings are inevitably blurred [31]. And it is not only IFs that are affected; a distinction is crucial, for instance, in order to establish the bureaucratic course that any procedure should follow. In the case of IFs, however, the problem of distinguishing between the two settings is particularly delicate because the procedures for their management may vary according to the specific context. In order to decide whether a particular activity constitutes clinical care or research it may be helpful to refer first of all to the underlying motivations. As a general rule, interventions in a clinical care setting are personalised, whereas research is hypothesis- rather than needs-driven. To establish whether the setting is one of clinical care or research, it may thus be useful to ask whether the rationale for the intervention concerns the benefit of the patient or the broader category to which the patient belongs [4].

Yet even the criterion of motivation leaves some issues unsolved, as is illustrated by the fact that in 2012 Wolf *et al.* [18] re-considered the notion of IFs that some of them had proposed four years earlier [2]. The authors recognised that while the expression “IFs” was appropriate in the context of genetics research procedures that had in the meantime become obsolete, it is not always appropriate where more advanced techniques are being used, particularly genome screening. They consequently acknowledged that the expression itself may hamper the process of agreeing an unambiguous definition of the circumstances in which researchers are duty-bound to disclose their findings to research participants. They noted that “in large-scale discovery research (...) it is difficult to identify what is ‘beyond the aims of the study’ because the entire genome is under scrutiny and the research is inductive discovery research rather than research driven by discrete hypotheses” [18]. Despite these misgivings the authors maintained that the expression “IFs” was still valid, and provided examples to support their position. One example is the case of a genomics researcher who, during the enrolment phase of a study, discovers that a potential participant has elevated blood pressure. Wolf *et al.* proposed distinguishing IFs from what they call “individual research results”, *i.e.* a finding “discovered in the course of the research, when the finding is on the focal variables under study in meeting the stated aims of the study” [18]. This distinction thus focuses on the intentions: if the researcher was not looking for the finding, then it is an incidental finding; if, on the other hand, the researcher was looking for it, then it is an individual research result. This brings us back to the distinction between research and clinical practice mentioned earlier. Even if it were possible to make a clear distinction between the two settings, the fact remains that the motivation (focusing on the patient or even embracing the broader category to which the patient belongs) does not help to decide how to manage the results: “If researchers are obliged to return data indicating the presence of a mutation that markedly increases the risk of disease, that duty applies whenever such information is in their hands, whether they intended to find it or not. Unfortunately, however, the complicated conversation about which results to return to subjects risks becoming still more complicated if we use a term that gives unwarranted attention to just that: the researcher’s original intention” [32]. To address this problem Parens *et al.* “suggest ‘individual genomic result’. The term avoids the problem of giving undue attention to the researcher’s or clinician’s intentions. To the extent that the term is vague, the vagueness may be a virtue. It reminds us of the real, difficult work that remains: articulating criteria to distinguish between individual genomic results that do – and do not – warrant an offer to return to research participants or patients” [32]. In the case of genome screening, the already difficult search for an appropriate term is compounded by the fact that it is difficult “to identify what might be an [incidental finding], as any genomic pattern correlating with pathology may be captured and studied” [32]. Thus the notion of “incidental” remains controversial [33] “It could be said that nearly nothing is ‘incidental’ because very little is outside the scope of the research question” [34].

Clinical utility

Recommendations often refer to notions or concepts without offering a precise definition of them. This may give rise to difficulties, whether the notion is a broad one (such as “health status”) or more specific (such as “reliable” or “potential benefit”), and the interpretations of these concepts are left to professional judgment.

As noted above, one of the notions that, in the absence of clear definitions, lends itself to subjective interpretations is the term “clinical utility”: the term “actionability” is similarly problematic. Yet some documents consider these concepts to be crucial when it comes to deciding the procedures for managing IFs. The margins of subjectivity for interpreting “utility” are also to be found in guidelines concerned mostly with practical aspects. For instance, a document published by the Public Health Genetics Foundation, which takes a very pragmatic approach, recommends that the “100 000 Genomes Project” (100kGP) “should adopt a policy of disclosing only research findings that are scientifically significant and have been assessed by a competent individual that are clinically significant AND severely or moderately life threatening AND clinically actionable. The operationalization of these terms will need to be determined for individual research projects. The consent procedure should also include a description of what types of findings will be disclosed, why these and not others; and also that any findings disclosed from research studies may need to be validated in a clinical laboratory” [4] (author’s note: capitalised in the original). In the absence of an accepted interpretation of “actionability” this recommendation is subject to a number of interpretations (particularly if the concepts of “life threatening” and “clinically actionable” are applied to pathologies rather than findings!).

Pleiotropy

It is often pointed out that reliable information and data management systems need to be established that clearly identify the risks associated with each genetic variant included in research studies [35]. One of the reasons for the difficulty of positively identifying these risks is pleiotropy, a factor that is insufficiently addressed in several of the guidelines and recommendations concerning IFs. Pleiotropy – or the phenomenon of a single gene or genetic variant affecting multiple phenotypes – can considerably complicate the decision as to whether or not to disclose a finding.

The $\epsilon 4$ variant of the APOE gene may be associated with a (treatable) cardiovascular risk and with a risk of developing (untreatable) Alzheimer’s disease [36]. The recommendations included in some guidelines are that information regarding the former risk be disclosed and information regarding the latter withheld. This poses problems for both the researcher and the clinician who must disclose the information [37].

The question of pleiotropy arises fairly frequently in the management of IFs. One significant example of this is the list of 57 genes for which the American College of Medical Genetics and Genomics (ACMG) believes that incidental findings should be sought and reported in clinical exome and genome sequencing [38]. As Kocarnick and Fullerton observed in the Online Mendelian Inherit-

ance in Man resource, 43 of these 57 genes have multiple associated phenotypes listed: thus, even if the disclosure of IFs is limited only to the genes identified in carefully chosen lists, considerable problems still remain [39].

IFs, uncertainty, the problems for researchers: some general considerations

One of the key problems in the management of IFs is the uncertainty that surrounds them. This uncertainty can be associated with a number of factors: it is particularly important in the early stages of research and in the genetics setting, where most disease predictions based on genetics are probability estimates [35] and the significance of IFs may vary between ethnic groups [5]. The uncertainty factor in IFs is further compounded by the fact that they are generally unconfirmed.

This uncertainty is one of the key elements complicating the task of researchers when managing IFs, to the extent that "most genetics researchers, while aware of the potential for incidental findings, simply do not want to deal with them" [34]. This reluctance has been recognised in several documents. Even before the expression "incidental findings" became established, both the American Society of Human Genetics [40] and the Canadian College of Medical Geneticists [41] acknowl-

edged that researchers have limited expertise in handling medically relevant information and recommended that the results of DNA tests should first be communicated to an appropriate healthcare professional, who in turn can decide whether or not to disclose the information to the individual concerned. Other documents recommend that researchers should be trained specifically to manage IFs and that their training should cover not only the technical aspects but also the procedures for dealing with them. This points to a need: the various documents – and guidelines, in particular – undoubtedly provide fundamental guidance for the management of IFs, but they cannot replace the individual responsibility of researchers and healthcare professionals, who must consider each case on its merits, bearing in mind the peculiar circumstances of each individual [42, 43].

Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

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