

# A framework to ethically approach incidental findings in genetic research

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## ARTICLE INFO

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## ABSTRACT

With the advancement of science in the area of genetics and genomics, special ethical considerations should be taken in addition to the general ethical framework followed in research.

Genetic research can reveal information about the susceptibility of an individual to disease and hence about his/her future health. Such information may be of interest and benefit to research participants, especially if preventive strategies exist. It may also expose them to other risks or anxieties when incidental findings that were not the primary scope of the study are found. Ethical guidelines acknowledge the duty of researchers to disclose incidental findings (IFs) to participants. In this review, we recommend four steps approach that researchers can use to disclose incidental findings: plan for IFs, discuss IFs in informed consent, identify and disclose IFs. Verification and identification of IFs should follow a categorical stratification based on the importance of the findings and the presence of a beneficial intervention to the participants.

## INTRODUCTION

Genetic testing is “a (laboratory) procedure to detect the presence or absence of, or change in, a particular gene or chromosome, including an indirect test for a gene product or another specific metabolite that is primarily indicative of a specific genetic change”(1). It is the analysis of human DNA, RNA, genes and/or chromosomes, or the analysis of human proteins or certain metabolites, with the primary purpose of detecting a heritable genotype, gene mutation, phenotype or karyotype. Next generation sequencing (NGS) has revolutionized clinical genomics by enabling the detection of large genetic variations in patients. This new type of advanced DNA analysis may fundamentally alter medicine and be used as genetic health screening tool. The knowledge of genomic information may allow healthy individuals to explore their susceptibility to certain gene disorders. Consequently, this knowledge provides an interventional opportunity for screening programs, prevention and personalized medicine.

Genetic research should not be conducted with the primary aim to provide research subjects with specific medical information about their genetic status or overall wellbeing. However, if there is a possibility that the research may yield incidental findings of significance to their health, prior to the research, the participant should be informed of this possibility and offered the choice of whether he or she would like to receive such information.

An incidental finding (IF) can be defined 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).

The enhanced capacity, rapid pace of NGS technology advances along with the falling costs of the test allow new ethical and psychosocial

questions to be asked. Since the information contained in genome sequencing is vast, diagnostic NGS may not only provide information about the genetic basis of disease, but potentially further IFs of certain or uncertain significance. Unsolicited information can be generated from sequencing and there is still an active debate about which information should be disclosed to the patient.

In the first part of this paper, we examine the characteristics of genetic testing that pose additional risks and ethical issues compared to other types of research. The vulnerabilities caused by these risks imply that researchers have ancillary obligations towards their participants as they disclose IFs. We also discuss genotype/phenotype correlation to point towards the importance of interpreting IFs and their significance suggesting guidance from experts and clinical geneticists should be sought whenever required. Lastly, we examine the current guidelines and ethical debates and suggest a framework to deal with IFs.

## CHARACTERISTICS OF GENETIC/GENOMIC TESTING

**Table 1** The characteristics of genetic information

- Personal
- Permanent
- Predictive, pre-symptomatic
- Prejudicial
- Pedigree-sensitive

The unique characteristics of genetic/genomic testing gives rise to special ethical issues that have been increasingly identified and discussed by international guidelines (3). They should be taken holistically in risk-benefits analysis and in guiding informed consent.

### 1. Personal

Genetic data is unique to each individual. Genetic variability between individuals is identified as .11% of 3.2 billion bases of nucleotides (4). Genetic databases can therefore be used to match individuals based on a small set of single nucleotide polymorphisms (5).

Most regulations have emphasized some additional safeguards to protect such type of information but the extent to how successful they are remains unclear (6).

### 2. Permanent

Individual genomes are immutable that is, they do not change throughout the person's life. Albeit, some somatic mutations that affect the DNA maybe acquired resulting in some alteration of some parts of the DNA. Therefore, researchers should consider that the genetic results are long lasting and have lifelong considerations when disclosed to the participants.

### 3. Predictive, pre-symptomatic

Some genetic testing may have predictive values in disease development. The accuracy in interpreting such predictability is a complex and critical subject. Therefore, careful interpretation of the results should be made by experts.

### 4. Prejudicial

Genetic testing may reveal private information that raises concerns of stigmatization and discrimination. Breach of confidentiality could result in financial risks such as loss of employment or insurance (7). Researchers, in particular epidemiologists, may wish to study genes in populations to determine their contribution to disease incidence and prevalence in the community. This information may result in social stigmatization of certain populations or ethnic groups such as the case of the Havasupai tribe (8).

### 5. Pedigree-sensitive

Genetic testing has the potential to reveal information about family members as in germline mutations. A lot of information may be revealed about individuals who have not consented to have their genetic material tested in the first instance.

It is widely known that individuals who carry a certain disease-causing mutation or a genotype may not exhibit all the pathological features or phenotype. This is a phenomenon known as reduced penetrance. This might be explained by allelic expression, modifier genes, digenic inheritance, imprinting, the influence of age, sex and environmental variants and epigenetics on gene expression and post-translational modification (9) (10). The type of mutation (e.g. missense, nonsense, frameshift, or deletion) would have an impact on the exhibited phenotype. In monogenic disorders, the presenting phenotype depends on the presence of a mutation in another gene. Somatic mosaicism also results in phenotypic variations. There is also a difference between loss of function and gain of function mutations. For instance, distinct mutations of STAT3 at the same position may cause either loss of function or gain of function. Loss of function may results in hyperimmunoglobulin E syndrome also known as Job's syndrome while gain of function may results in early onset lymphoproliferation, autoimmunity and myelodysplastic syndromes (11)(12)(13). In some instances, complete penetrance may require the presence of mutation variants at other loci.

Autosomal recessive conditions are known to have reduced penetrance with varying clinical implications since depending on the function of the second allele. Autosomal dominant conditions were previously thought to be penetrant. However, it is now increasingly described that the alleles that are not completely

penetrant may act in a recessive fashion such as PKD1 alleles in renal manifestations (14) (15). Penetrance should be distinguished from the expressivity. Expressivity refers to the phenotypical variations among the same genotype (10). Although used in an inter-related manner, making a distinction between the two phenomena is important when informing research subjects regarding what the results imply.

Although a discussion of genotype/phenotype correlation is not the purpose of this article, it is important to highlight the importance of understanding individual results in genetic research in the presence of such uncertainties. A careful interpretation of such genetic variants should be made and discussed with geneticists prior to reaching a conclusion. Sometimes, giving a black or white answer to whether a specific phenotype will be manifested as a result of a certain mutation is not always feasible. It is also of importance to highlight these inevitable risks and uncertainties within the process of informed consent.

## CURRENT GUIDELINE RECOMMENDATIONS

Incidental findings are becoming the most pressing issue in genetic research today and are increasingly recognized by guidelines and research ethics committees. The issue raises a fundamental question regarding whether researchers have an ethical obligation to disclose incidental or unsolicited findings to participants, guidelines recognize the need to do so. The National Bioethics Advisory Commission (NBAC) recommended that when the risks identified in the study are both valid and associated with a proven intervention for risk reduction, disclosure may be appropriate (17). The Council for International Organizations of Medical Sciences (CIOMS) also recommends that a prior informed plan on how to manage unsolicited findings

should be disclosed to research participants “a procedure for determining whether unsolicited findings should be disclosed, and if so, how they should be managed; how the quality of the material is controlled; how confidentiality of the link between biological specimens and personal identifiers is maintained” (3). The National Heart, Lung, and Blood Institute conditions the return of genetic research results on a significant risk of disease (specific relative risk >2.0). The disease should have fatal or debilitating morbidity or reproductive implications, and the availability of therapeutic or preventive interventions (16).

These established ethical justifications to disclose IFs have not identified a specific implementation approach. Given the characteristics of genetic information and the implications of results in relevance to genotype/ phenotype correlation, it is important to be careful in determining the significance and validity of tests prior to interpretation.

## A FRAMEWORK TO DISCLOSE IFs

### 1. Planning for IFs

The possibility of obtaining IFs should be included in the study plan. The plan should include a procedure to verify IFs, interpret and evaluate their implications taking into consideration genotype, phenotype correlation, and reproductive importance. The plan should explain the possibility of IFs whether foreseeable or not in their informed consent and include the intent of researchers to disclose these findings should they arise.

There should be a process to ensure data validity and quality to avoid any false positives that may result from data mistakes. Research ethics committees (RECs) should review this plan and ensure it is satisfactory to minimize risks and safeguard participants and their autonomy.

## 2. Discussing IFs in the process of informed consent

Research ethics guidelines consider informed consent a cornerstone document in maintaining the autonomy of research participants. The informed consent should explain the genetic test that will be conducted in research and the characteristic of the data produced from it. This lays the foundation to discuss and explain the potential IFs whether anticipated or unanticipated. IFs may result in psychological, social, and financial risks. The prejudicial nature described earlier recognizes risks of stigmatization, loss of employment or insurance as a result of disclosure. Researchers should allow subjects to ask questions, verify any queries and understand the scope of the research and resultant risks in order to make an informed decision.

## 3. Verifying and identifying IFs as they arise

An old generic framework by Reilly suggests that investigators should differentiate three categories of findings in research: those “of such potential importance ... that they *must* be disclosed immediately”; those that “are of importance to subjects ... but about which ... [the investigator] should exercise judgment” on disclosure; and those “that do *not* require special disclosure.” (17). This article similarly recommends a three categories stratification framework in which the investigator initially carries an assessment and interpretation of the findings after consulting with genetic experts – should this be of need – to determine the implication of a genetic variant on an individual’s health. Currently, many analysts place only findings of health importance in the “should return” category, even though individuals may assign high importance to findings with major reproductive implications. Although, most recommendations to date have conditioned “should return” on the “actionability” of findings, this remains ambiguous. It is under

debate whether the utility of findings should be viewed from the standpoint of clinicians, the standpoint of individual participants, or some combination (17) (18). For instance, in the case of identifying a colorectal cancer gene, actionability from the standpoint of a physician is undertaking yearly colonoscopy, while from a participant’s standpoint it could mean making different choices in life.

## 4. Disclosure of IFs

A compassionate subject-centered approach should be used to disclose IFs. The plan to disclose should take into consideration the autonomy of individuals and their preferences as well as the ancillary care obligations of researchers. Current models perhaps stratify IFs to inform the appropriate decision of action but it is still debatable what kind of action should be taken exactly. What is it that is owed to the participants by researchers? To what extent are researchers obliged to minimize the risks resulting from the vulnerabilities created from IFs, even though they have not been created by them.

Offering genetic counseling with disclosure contributes to risk minimization. The OHRP IRB Guidebook states that “[a]ppropriate counseling should be provided to educate subjects about the meaning of the genetic information they have received, and to assist them in coping with any psychosocial effects of participation.” (18).

There has been a debate whether researchers have the duty to provide further clinical work-up and care as a result of these IFs. Researchers may also be requested to share information with the participant’s treating physician, which should not be denied (20).

This positive moral duty in the disclosure of IFs has been emphasized by ancillary care frameworks discussed by Beskow et al (19). The ancillary approach supports the notion the researchers and

RECs should take into consideration the degree of entrustment in genetic research that individuals put into researchers that creates participants' vulnerabilities. This vulnerability becomes more complex when it is combined with medical, financial and social vulnerabilities. Therefore, they are ought to contribute to addressing the consequences of IFs. Such ancillary obligation needs to be considered when planning and budgeting research.

Research differs from clinical care that it is conducted with the motivation to advance generalizable knowledge rather than create individualistic benefits. Despite the pluralistic nature of the research enterprise, it is advocated that researchers are motivated by some fiduciary obligations to maintain public entrustment especially in the context of genomic research and biobanking.

## OTHER ISSUES

### *Incorporating participants' preferences to guide the decision of disclosure*

An outstanding question is whether patients' preferences should be considered in the decision-making process regarding the disclosure of IFs. Although guidelines have emphasized on the principle of respect for persons and the exercise of autonomy (20)(21), it remains unclear how to incorporate that. Just like physicians who tend to overestimate potential benefits of testing over the unanticipated harms, researchers are not an exception. Similarly, research subjects may have an underestimation of the risks arising from disclosure. This may possibly be due to the lack of information regarding the nature of genetic testing and the disease implication of discovered mutations or genetic variants. If a participant states that they do not wish to have IFs returned, and their results come back with potentially important information such as the presence of BRCA1/BRCA2 gene,

does the researcher have a "duty to rescue"? Will ignoring the person's autonomy driven by beneficence be considered undue paternalism? It is best to use a planning approach that considers both participants' preferences and current recommendations from ethics guidelines. Emphasis should be put on the process of informed consent where researchers take the time to provide information, resources and examples of the foreseeable and unforeseeable risks associated with IFs.

It should be reiterated that research ethics have evolved into a model of collaborative partnership between researchers and research subjects that are now increasingly referred to as participants to imply this collaborative nature. Guidelines encourage community representative groups to develop guidelines on evidence-based best practices for managing incidental in genetic research. The characterization of preferences about the disclosure and management of these IFs is yet to be understood (20). Many commentators are recognizing the importance of the public's view to understand community norms. As these become available to researchers and RECs, they can take it into considerations to inform plans to deal with IFs.

### *Access to results*

Another question is whether participants have the right to access their results. The National Human Genome Research Institute recommends the allowance of this: Upon their request, "research participants should have access to experimental research data except when the research results are of unproven clinical validity, and the IRB has judged that there is no benefit to the research subjects" (22). Even though the access to results of benefit to participants is advocated, it is subject to logistical arrangements by researchers. Researchers must specify whether they intend to send results upon request while maintaining the privacy and confidentiality of

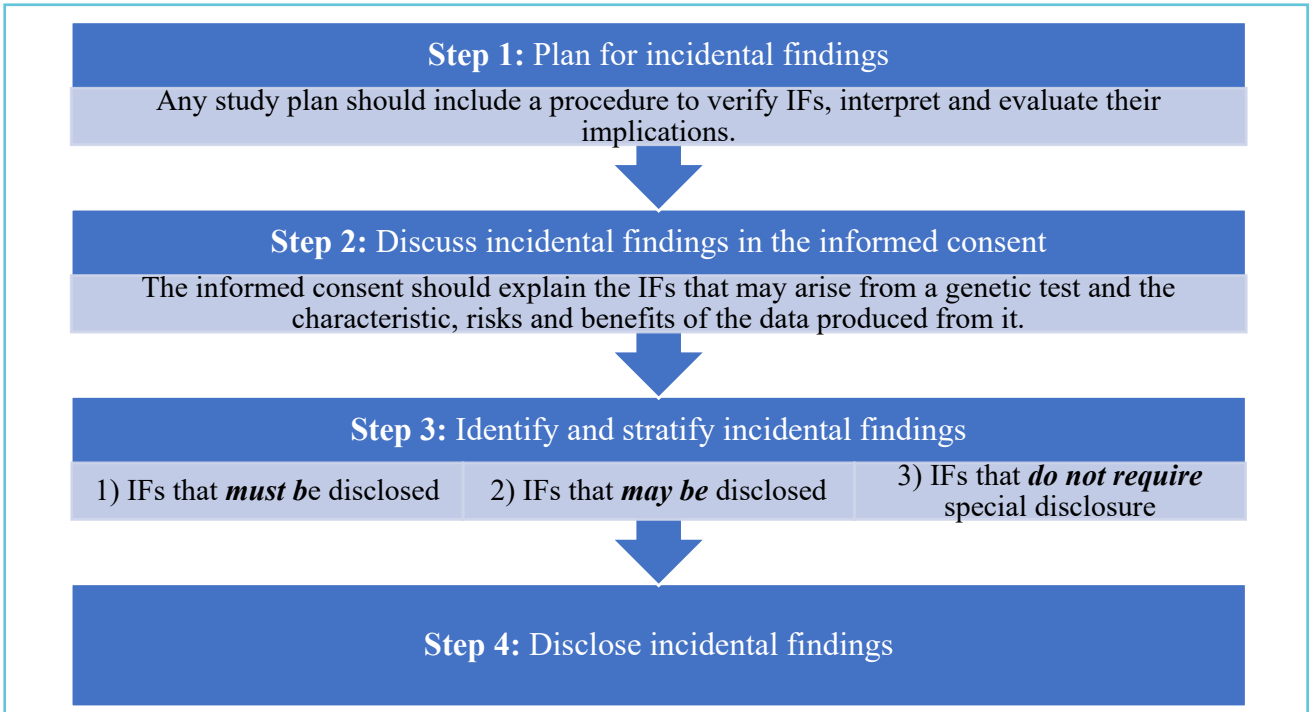
participants, time frame to do so and other details they think are worth highlighting. Discussing this in the process of informed consent ensures participants' expectations are met.

Biobanks are a research resource rather than a research project. Therefore, it is difficult to determine what an IF is when no clear objectives of the research is available. Researchers should have a policy for returning IFs that are preventable or treatable conditions of early onset to participants. Details of this should be included in the consent forms (Figure 1).

### KEY POINTS

- Guidelines have acknowledged the duty of researchers to disclose IFs.
- Researchers should have a plan to address IFs in their protocol and informed consent.
- Informed consent should explain potential risks from genetic research in general and IFs specifically including the researchers' approach to disclose them.
- Researchers should verify and interpret these results carefully. Experts and geneticists should be consulted to determine their clinical and reproductive implications. Emphasis on the quality and validity of data should be made.
- Stratification of the IFs using a **three categories approach**:
  1. Important findings with strong net benefit of disclosure
  2. Potentially important with possible net benefit if disclosed
  3. Unknown variants with no benefit

**Figure 1** A framework to ethically address incidental findings in genetic research



*This framework suggests a 4-step approach where IFs are initially planned for, discussed, stratified following identification and finally disclosed to research participants. The IFs may be stratified into three categories based on the significance of those results and their health implications. These include IFs that must be disclosed, those that may be disclosed based on the researchers' judgement and those that do not require disclosure because of their insignificance. Such stratification may need the expertise of a geneticist.*

- A compassionate participant-centered approach should be opted for.
- The autonomy and preferences of participants should always be respected.

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