Research Ethics: Incidental findings in genetic and genomic clinical research studies

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Abstract

In a clinical care setting, if unexpected abnormalities occur in a manner unrelated to the patient’s complaint, it is the physician’s duty to act in the “best interest of the patient.” This policy differs from that of a clinical research setting. The ethics of incidental findings in clinical research are complex, especially in settings involved in genetics and genomics research. In performing genetics research concerning families, misattributed paternity or other misattributed lineage is sometimes discovered by the investigator. The most compelling question facing clinical genomic research is what constitutes an incidental finding. There are currently no federal or state statutes that directly address the responsibilities of researchers to disclose incidental information to their participants. Problems such as lawsuits and unintentional harm may occur. As a result, researchers should communicate in advance about whether or not to disclose incidental findings in their informed consent to show respect for the individual’s autonomy. Incidental findings should not be disclosed if the individual does not wish to know. Even though researchers are not clinical care physicians, they have a professional relationship with their participants. The participants entrust the researcher with their own private information and trust that their samples are used for beneficent and not maleficent purposes. The principle of justice and fairness in incidental findings can make a positive impact for those with serious, urgent, and unmet needs. Incidental findings should be held at the maximum standard that is most fair between the researcher and the participant.

Keywords: incidental finding, participant, research, researcher
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To investigate the ethics of incidental findings, the idea of clinical context must be understood. In a clinical setting, ethical standards tend to be well-established. The patient is there because he or she intends to get help (Miller, Mello, & Joffe, 2008). He or she seeks a cure or a treatment to improve their health, while the physician is there for the “best interest of the patient.” The physician has the will and obligation to diagnose, and the duty to heal the patient in the best possible way (Miller, 2008).

When the physician and the patient meet, there is a doctor-patient relationship. This relationship is filled with ethical inclinations endorsed by juridical norms: respect, trust, empathy, and openness (Abdul-Karim et al., 2008). The physician has the duty to inform the patient about his or her condition, and the patient has the right to know. The patient expects that the physician will inform him or her about all health problems, including incidental findings. The doctor’s duty to inform also stems from the principle of non-maleficence, as informing or failing to inform the patient could harm the patient’s autonomy (Miller, 2008).

If there is an incidental finding during a clinical setting, it is the physician’s duty to act in the “best interest of the patient.” This policy differs from that of a clinical research setting (Solberg & Steinsbekk, 2012). In a research-based setting, the doctor-patient relationship is absent. Is the researcher obligated to inform the participant of results or incidental findings that may pose harm to the life of the participant, and if so, which results should they disclose? Incidental findings force the human subject research field to rethink the long-accepted division between the research and clinical settings, along with the question of what is appropriate to disclose (Wolf, 2012). The researcher
should do what is best for the goals of research, but should they also consider the participant’s autonomy and rights? Even though physicians may be involved, a research setting implies that the doctor is primarily a researcher and the participant is a subject of the research study (Solberg & Steinsbekk, 2012). Unlike physicians in care settings, the researcher does not have an established duty to act in the best interest of the patient. Instead, the investigator agrees to minimize hazardous risk to their subjects and at the same time maximize the benefits for their research to answer their study question (Solberg & Steinsbekk, 2012). Researchers may not have a doctor-patient relationship, but they should still practice a high standard of care in order to uphold ethical research standards. There are currently no federal or state statutes that directly address the responsibilities of researchers to disclose incidental information to their participants (Presidential Commission for the Study of Bioethical Issues, 2013). Even if investigators are not required by law to disclose information, do they have a moral duty to do so? The ethics of incidental findings in clinical research are complex, especially in settings that are involved in genetics and genomics research.

In the media, the words “genomic” and “genetic” are often used interchangeably. However, to geneticists, bioinformatics researchers, and biologists, there is a significant difference (Cho, 2008). In genetics research, one gene or a small number of genes are studied; whereas genomics research, many genes are studied, along with their interactions. Genomics research generally has a bigger cohort and involves large population-based subject investigation. Through these distinctions there are different yet similar ethical dilemmas faced in each respective field (Cho, 2008).
Genetic versus Genomic Clinical Research Studies

Genetics researchers may identify or discover a genetic or chromosomal variant that could increase susceptibility or cause a certain disability or phenotypic disease (Wolf et al., 2008). Researchers may then screen for affected families to understand the basis for variation. Analyzing family pedigrees and patterns can increase understanding of genetic diseases. In performing genetics research concerning families, misattributed paternity or other misattributed lineage is sometimes discovered by the investigator (Wolf et al., 2008). For example, research on germline mutations (any heritable gene variant passed from parent to offspring) can incidentally uncover misattributed paternity. For example, if a child has a disorder that requires a specific variant to be passed on from both parents, research on a germline showing that the father does not carry that particular variant would suggest misattributed paternity (Abdul-Karim et al., 2013). If neither parent is a carrier, then this could disclose adoption, embryo donation, or any other scenario in which the parents are not the biological parents (Wolf et al., 2008). In rare cases, investigators could incidentally find incest in the process of genetics research (Wolf et al., 2008). Such cases can pose ethical dilemmas for researchers, particularly when participants do not want to be made aware of the incidental findings.

Although genomics research differs from genetic by applying a holistic view of the entire genome, it can implicate similar ethical dilemmas in terms of misattributed paternity, embryo donation, adoption, rape, and incest. The most compelling question for genomics research that is more questionable than genetics research is: What might constitute an “incidental finding?” Any genomic pattern that correlates with pathology could potentially be captured and studied (Parens. Appelbaum, & Chung, 2013). In large-
population-based genomics research such as biobanking, the researcher is investigating large quantities of genes and their interactions with each other (Wolf et al., 2012). Some research teams may have software that analyzes only sections of the genome needed for the study, but most research settings have apparatuses that analyze the entire genome (Dal-Ré, Katsanis, Katsanis, Parker, & Ayuso, 2014). There is a general consensus in the informed consent, that investigators have a responsibility to make clear to their participants whether or not incidental findings will be offered to participants (Parens et al., 2013). Do participants have the right to know about potential health problems happening in their bodies?

**Option of Right to Know and Right to Not Know**

Autonomy is one of the most crucial principles concerning research enrollment and incidental findings (Presidential Commission for the Study of Bioethical Issues, 2013). In order to demonstrate respect for persons, the researchers must disclose the fundamental aspects of the research to their participants. This way the participant can make an autonomous decision about whether they would like to enroll. How should researchers discuss incidental findings in the informed consent? Researchers’ duty to inform participants about whether or not they will disclose incidental findings should flow from the ethical responsibility to respect the participant’s autonomy and interests. Researchers should communicate in advance about whether or not to disclose incidental findings in their informed consent to show respect for the individual’s autonomy (Presidential Commission for the Study of Bioethical Issues, 2013).

There have been many ethical discussions about participants’ right to know, but one neglected area of discussion is participants’ right not to know. Respecting autonomy
includes respecting the individual’s interests and opinions. If a participant does not wish to know of incidental findings from a research study and the investigator respects their decision, then they are respecting that participant’s autonomy (Vayena & Tasioulas, 2013). What if the investigator detects an incidental finding in genetic research that could signify potential harm for others, such as extended biological family members, but the participant does not want to know about it? A biological family member such as a cousin could carry the gene or the participant may carry a gene that could ultimately result them harming their own family such as wife or child. Do the family members have a right to know the results? In such situations, the core ethical principles of respect for autonomy (toward the participant) and beneficence (toward the family members) come into conflict (Vayena & Tasioulas, 2013). Should autonomy trump beneficence, or should beneficence trump autonomy? In this case, the investigator could respect the participant’s autonomy and accept that he or she may potentially harm others or himself, or that an incidental finding could signify potential harm to family members (Brief & Illes, 2012). On the other hand, the investigator could follow a dimension of beneficence called the rescue principle, in which preventing anything bad from happening cannot be considered wrong (Brief & Illes, 2012). In whichever decision the researcher makes, there will be some violation of one of these principles. Some sources suggest that the researcher should ultimately respect the participant’s autonomy when such a case occurs (Brief & Illes, 2012; Vayena & Tasioulas, 2013). However, depending on the nature of the genomic and genetic research, the results may not be as certain or have as much verifiable significance (Solberg & Steinsbekk, 2012).
What Do We “Owe” Them?

It is suggested to the researchers that the work is depended on the generosity of participants and their willingness to be in the research study, and that researchers have a duty to reciprocate. Kohana, professor of pediatrics and Health Sciences and Technology at Harvard Medical School argued that allowing participants to gain access to their discovery makes them “partners in the research,” and that many participants may, as a result, mistake research for clinical treatment and care (Kohana, et al., 2007). But what if participants believe they should gain treatment or care from participating in a clinical research study? Let’s consider a large-scale genomic biobanking research conducted by the American Red Cross as an example (Solberg & Steinsbekk, 2012). Does the American Red Cross owe any moral duty to their participants for donating money to their activities? How should the American Red Cross show respect to their donors? From a donor’s point of view, the only moral duty the American Red Cross holds is to use their donation for the maximum intended good. In order to respect the donor, the American Red Cross should maximized the research as much as possible- in action which they publicize to their participants by giving newsletters, magazines, and creating 5K marathon events. But population genomic biobanking research is far from being a clinical setting, and thus the duties and rights from a clinical setting are not valid for this research setting. If a participant has engaged in the American Red Cross research study only to gain therapeutic aid and therefore expected to be informed of any incidental finding, than they have came for the wrong reason (Solberg & Steinsbekk, 2012). Although Solber and Steinsbekk explore the specific example of research by the American Red Cross in their study, their reasoning is applicable on a more general level to incidental findings in
clinical research.

**General Beneficence in Professional Relationship**

The level of care researchers must give to their participants is not the same level of care physicians must give to their patients, but the researchers do owe more to the participants than what is within the scope of the research protocol (Miller, Mello, & Joffe, 2008). Even though researchers are not doctors they do have a professional relationship with their subject participants. A professional relationship is one that involves a person who has specialized knowledge, practices the knowledge frequently, and is obliged to exercise that knowledge by an ethical code of conduct (Miller et al., 2008). The key factor in a professional relationship between a researcher and participant is reciprocal trust concerning access to private information.

Let us consider a scenario in which the professional relationship between a researcher and participant is implicated by incidental findings. A man walks into a research setting seeking to be part of a genetic Alzheimer’s research study. The investigator, someone who is knowledgeable in the field and practices his expertise frequently, discusses the informed consent, including willingness to allow access to private information. The man trusts him and allows the researcher to obtain his personal confidential information. During the research study, the investigator incidentally finds that the participant inherited a genetic mutation linked to retinitis pigmentosa, an eye disease that could cause blindness in the future (Beltran et al., 2011). The situation is not life threatening, but may drastically lower the participant’s quality of life. Is the researcher obligated to inform the participant?

Many would argue that this incidental finding is outside the scope of the research
and should not be disclosed to the participant (Solberg & Steinsbekk, 2012). Those who oppose disclosing the finding may believe that the only obligation the researchers owe in this area is to maximize the research output from their donation. But researchers do owe their participants a professional duty aside from their research. In the scenario, the participant trusts the researcher with private information, and is giving it voluntarily for the purpose of the research. The professional relationship between the researcher and the participant is based on the consent form and the standard ethical code of conduct (Milstein, 2008). Subjects trust their investigators not only with their private information, but trust their investigator to avoid exposing them to any risk and harm (Miller et al, 2008). The participant trusts that their samples are being used for beneficent and not maleficent purposes. Professional relationship is essential in maintaining an ethical interconnection between the researcher and the volunteers, a relationship that is different in significant ways from the physician-patient relationship in standard clinical practice (Wolf et al, 2008).

**Principle of Justice and Fairness**

The principle of justice and fairness means that equal benefits and burdens are distributed in the research (Presidential Commission for the Study of Bioethical Issues, 2013). The decision to disclose incidental findings, including allocating time and effort to interpret the findings, necessarily concerns the distribution of the benefits and burden in the research. Depending on the nature of the incidental findings, the researcher that discloses the findings may benefit the participant or cause burden to the participant (Presidential Commission for the Study of Bioethical Issues, 2013). Disclosing incidental findings could also have a negative effect on the research institution or industry if the
results were inaccurate (Solberg & Steinsbekk, 2012). For instance, if an incidental finding is uncovered during a clinical research study in its infancy, the patient may have a very rare small chance of getting the disease, and the results may not be accurate; therefore, in such cases, the findings may not be worth disclosing to the participant (Solberg & Steinsbekk, 2012).

The principle of justice and fairness in incidental findings can make a positive impact for those with serious, urgent, and unmet needs. In particular, those who lack sufficient access to health care may be more likely to have undetected health complications leading to a higher likelihood of incidental findings. In genetic and genomics research, incidental findings can make health disparities more visible. Yet regardless of health disparities all participants should be treated equally and fairly. For example, if a researcher were to encounter a sign of early detection breast cancer in both a wealthy individual and a low-income individual, the researcher would uphold justice by informing both participants about the incidental finding, as it would implicate the same level of private information for both participants. However, to take the scenario further, if both individuals needed to have their left breast removed, but the insurance did not cover this procedure for the low-income individual, it would not be the duty of the researcher to pay for the treatment. Unlike physicians in a clinical setting, researchers do not have the duty to treat. The researcher is not responsible for giving equal treatment, but is responsible for giving equal information.

**Conclusion**

As genetics and genomics research technology advances further, incidental findings will only be a growing problem. Data that may contain incidental findings will
be archived increasingly, due to federal data-sharing regulation and policies (Presidential Commission for the Study of Bioethical Issues, 2013). But this does not preclude the standard that incidental findings should be handled ethically and with professional integrity.

Detailed guidelines must be established to determine how incidental findings should be handled in informed consent. The researcher must allocate time to discuss and explain the disclosure of incidental findings during the enrollment process. Incidental findings in informed consent should have clarity about the difference between a research setting and clinical care. Researchers need to clarify the types of incidental findings generated, statistical prevalence of the incidental finding, cost of evaluating, and potential positive and negative impact on the research participants. The autonomous decision of the participant regarding his or her right to know, or right to not know, should be respected. Participants should also have the option of changing their mind regarding their desire to be informed of incidental findings at any point during the research. If this is to occur, the researcher must create a new informed consent for the participant to sign.

As a general rule, it is ethically required to disclose incidental findings if the results are interpretable, accurate, and medically related to the participant’s health. Incidental findings are a significant matter that can potentially save the participant’s life, lead to new positive research, and alter the standards of clinical care; therefore, incidental findings should be handled at high ethical standards that find the best fit between the participant’s concerns and the goals of the research study.
References


