

Ethics of disclosing results of genetic testing of donor-derived leukemia to recipient in a
hereditary cancer biology research setting

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Abstract

Disclosing appropriately to patients of incidental findings found in a research setting has been long debated. There are recommendations and guidelines but no strict regulation to disclosing results at the federal level. This paper discusses different scenarios of how to disclose to a sister, who received a bone marrow transplant from her brother. Researchers found that she carries a germline mutation that increase the risk of leukemia from which she received from her brother through the bone marrow transplant. Different scenarios of how much information were demonstrated. Scenarios of when the researcher discloses all results and not disclosing any results did more harmful outcome to both parties. A series of questions could be asked to determine how much information the patient would like to be disclosed that is not overbearing and at a level the research is comfortable at in disclosing. Ethical dilemmas could be avoided if the researcher asked these questions. The issues of these outcomes are similar to other areas of research such as neuroimaging, biotechnology, and pharmacology where researchers are likely to be put in an ethical dilemma of disclosing their results. Once these questions are tried and perfected over time, it can eventually become a federal guideline. These questions will expand good communication and relationship between the researcher and participant, which enhance and improves the public's perception of hereditary genetic research.

Keywords: disclose, informed consent, patient, researcher

Introduction

The responsibility of the researcher in disclosing research results to their participants is a controversy that exists in the field of hereditary cancer biology research. Disclosure should be addressed in the informed consent and discussed in detail to the participant before enrolling. Disclosing results of incidental finds is more controversial. Incidental findings are results that have potential importance to the research participant's health and well-being, which are unintentionally discovered while conducting research but are beyond the aim of the study. The debate on who, how and when incidental findings should be appropriately disclosed to the participant is ongoing. Incidental findings in a research setting are not valid and confident enough to be used for diagnosis, treatment or any clinical care. Research laboratories are not Clinical Laboratory Improvement Amendments (CLIA) approved labs. CLIA is a set of federal regulations that requires and ensures clinical laboratories to handle their sample with special care and protocol in order for results to be confident and valid for use in a clinical setting.¹ The main aim of a CLIA approved lab is to produce results from patient samples for diagnosis, treatment, and care for the patient.¹ Sample handling in a CLIA approved lab are different than that of a research lab. Research labs may have a higher chance of contamination in samples, because they maybe working with difference species samples and other factors.

There are recommendations and guidelines but no strict regulation to disclosing results at the federal level.² There are several highly respected groups in the United States such as Office of Protection from Research Risks, National Bioethics Advisory Commission, and the National Heart, Lung, and Blood Institute that have attempted to

create policies to disclosing research results to study participants.² The institutional review board is a committee that reviews and monitors the ethics of human subject research, but still there is no definite law that is directly addressed to disclosing results.³ Disclosing research results should be handled with great care and caution; otherwise it could harm the participant causing unnecessary medical interventions. These participants are not only subjects of the research but also patients as well.⁴ This paper focuses on one particular case, but the issues of these outcomes are similar to other areas of research such as neuroimaging, biotechnology, and pharmacology where researchers are likely to be put in a ethical dilemma of disclosing their results.

Case of donor-derived mutation in found in recipient

An acute myeloid leukemia (AML) patient received a bone marrow transplant from her brother (Fig. 1). After the transplant, the researcher consented the recipient and donor to his hereditary cancer biology research study. It was found through research, that the brother carried a germline mutation that increases the risk of leukemia. Lets call this mutation A. Mutation A is still being studied, and has been found through research that it increases the risk of leukemia, and can be passed from parent to offspring.

Mutation A has not been studied well enough to be used for a clinical setting, or tested in a CLIA approved lab, meaning the patient cannot receive clinical care based on this incidental finding. If the patient consented that he or she wanted to know the results, don't they have a right to know what is happening to their own body? Shouldn't the researcher respect the patient's autonomous decision? My primary thesis is: It is unethical to not disclose medically relevant information to the patient. Ongoing communication between the researcher and the participant is important in order to recognizably respect

the participant's voluntary decision to continue or to opt out of the research as well as recognizing the importance of their altruistic contribution to the progress of the genetic research. (<http://www.nature.com/ejhg/journal/v14/n11/pdf/5201690a.pdf>)

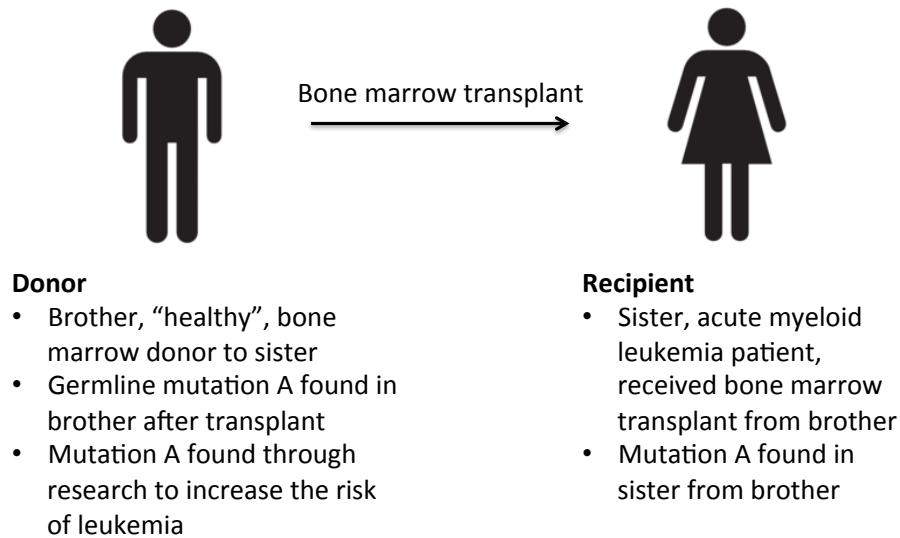


Figure 1. Donor-derived leukemia cells in recipient: Diagram of mutation A found in brother after transplanting to his sister, who has acute myeloid leukemia

Say for the exact same scenario but instead the mutation was **CLINICALLY** proven to increase the risk of leukemia, meaning physicians can give a proper diagnosis, treatment, and early preventatives for the patient. Lets call this mutation B. An easy solution to this would be to test mutation B in a CLIA approved lab; therefore, the results are confident and valid enough to give to the patient. For clinically proven cancer mutations, should every donor have genetic testing before donating to the recipient? Some biopsy takes weeks to finally have results such as the testing of skin. What if the patient's case is in an emergency and needs a transplant immediately? At this point the physician should determine whether the life expectancy of the recipient would be lower if donor gave their mutated cells versus the wait of finding another donor to match. This information is crucial since it is medically relevant to her health and since mutation B is

CLIA approved, these findings should be disclosed to the patient. What about in the case for mutation A? Mutation A has not been clinically proven and has not confidently been proven to be medically relevant in a clinical setting. This paper will discuss scenarios of how much results the research discloses to the patient and determine the outcomes for each one.

Scenario #1: Disclosing all medically relevant information

Since mutation A is not studied well enough, some researchers would not want to disclose any results to their patients. In this scenario, the researcher decides to disclose all results. This scenario was the actual option that was selected. What if the patient has depression and a family history of mental health problems is it beneficial to disclose to the patient even though the mutation is not studied well enough? Researchers may take into account the psychiatric history of this patient. In this case, the patient was on parole and emotionally unstable. If told that the cells from her brother were mutated and maybe the cause of her transplant failing, this would devastate her enough to trigger an extreme emotional state that would cause her to break her parole. Breaking her parole could lead her to go back to prison making her more in a depressed state then before. It maybe better to not disclosed the information to her at all to prevent this possible scenario. She does not carry a germline mutation; therefore it cannot be passed on to her biological offspring. There would be no need to disclose to them, even if the offspring could handle the disclosure of this situation, since the patient herself do not know the results, it would be a HIPPA violation to disclose these results to the offspring.

What about the donor that carries the germline mutation, should results be disclosed to him? Researchers may argue that since he does carry the germline mutation,

there is a concern for his health and his offspring; therefore, disclosure is necessary.

Even though, he carries the germline mutation, researchers have reasons to believe that disclosing results may turn him into an unstable emotional state given his family mental illness history and his personal mental history. Does the benefit of not disclosing to the donor because of his psychiatric background outweigh his health in the future and genetic testing for his next of kin? There is a possibility that the donor may handle the situation extremely well and would be proactive about his health and follow recommendations for preventatives. Telling him could potentially make him believe he has a moral obligation to inform his offspring and family members and help other family members like his. Scientist could argue that since mental issues run in the family, the donor's children, and all biological family members would be at risk of mental problems. How could researchers determine who within the family would be able to handle disclosure results without developing a depression or any mental issues?

If a patient commits suicide from knowing that they carry a mutation that could potentially give them a high risk of cancer then the researcher may feel at fault. Not only is the care of the recipient, donor, and family members taken into account, but also the researcher. Researchers have a professional relationship with their participants. "Professional," means a person who exercises their special expertise in a moral ethical manner; therefore general beneficence should be practiced in a research setting.⁵ The participants entrust the researcher with their own private information and will use it to their best judgment. Researchers should balance the magnitude of responsibility for disclosing to their participants and what is best for their research. Even though researchers have an obligation to maintain a professional relationship, this does not mean

researchers have an obligation to actively seek incidental findings in their research study protocol or to provide clinical care to their patients. The obligations of professional relationship in a research setting are different than that of a clinical setting, which should not be confused. Researchers are researching to seek knowledge that could potentially lead to treatment trials or help the greater good of society, but not to provide clinical care to their participants. This duty is for clinical physicians.

Lets say in the same scenario, the researcher choice to disclose the findings and later found out it is not significant enough to be medically relevant. A recipient and donor are consented to the research study. The recipient is in the middle of a transplant preparation. In preparation of a transplant, the recipient is given massive amount of chemotherapy to strip out their entire immune system. This is so the recipient would be given a “new” immune system from the donor through transplant. The recipient and donor would then be in an isolation room for the start of the transplant. This isolation room is intended to be extremely clean so there will be no germs or disease spread to the recipient with no immune system. If the researcher recently found out that the donor carried a mutation while the recipient is in the middle of a transplant preparation and decided to disclose to the recipient and transplant physicians, then the transplant would be stopped depending on the significance of the finding. If the transplant were stopped, the issue would be the well-being of the recipient. The recipient would be in the isolation room with no immune system. Even a very small cough or sneeze could infect the recipient ultimately killing him or her since they have no immune system. The recipient is forced to stay in the isolation room while waiting for another potential donor. Depending on the donor match and preparation, the recipient could be lying in the

isolation room from weeks to months. In this case, the researcher must be careful in deciding whether or not the end result of disclosing outweighs the end result of not disclosing to the recipient.

Scenario #2: Not disclosing any relevant medical information

What if the researcher believes the incidental findings are not significant enough to disclose and chooses not to disclose the results to the recipient and the researcher later found out that this is indeed crucial information for the recipient's well being? The mutation cells from the donor maybe the ones that could have caused the leukemia to grow faster or trigger a different type of cancer in the recipient. This could be a liability on the researcher for not disclosing to the recipient in the first place.⁶ Complaints and lawsuits could be filed against the researcher, which could potentially shut down the entire research study by the IRB.⁶ On the other hand what if the researcher chooses to disclose and then later found out that it is NOT significant enough to be crucial information, lawsuits could be filed against the researcher as well.

Scenario #3: Disclosing partial medically relevant information

The researcher has no upper hand in either scenario. In both scenarios, the researchers entire study could be shut down and suffer more consequences. Not only does the researcher have to pay a fine, but potentially be let go, lose their credibility, be imprisoned, and their entire laboratory could be shut down. Since there is no favor in the researcher in any of these scenarios, it is still the researchers duty to do what is best for the research. It is the researchers professional duty to only disclose results to the patient that will make a significant impact on the patient's well being. It is unethical to not

disclose medically relevant information to the patient unless the information is overbearing.

The physician should disclose only partial amount of medically relevant information to the recipient that is enough for the patient to be aware of what is going on in her body and not too much information to overwhelm her. Good communication between the researcher and patient on details of disclosing should be addressed before the informed consent and addressed again during if any incident was to occur.

All possible scenarios

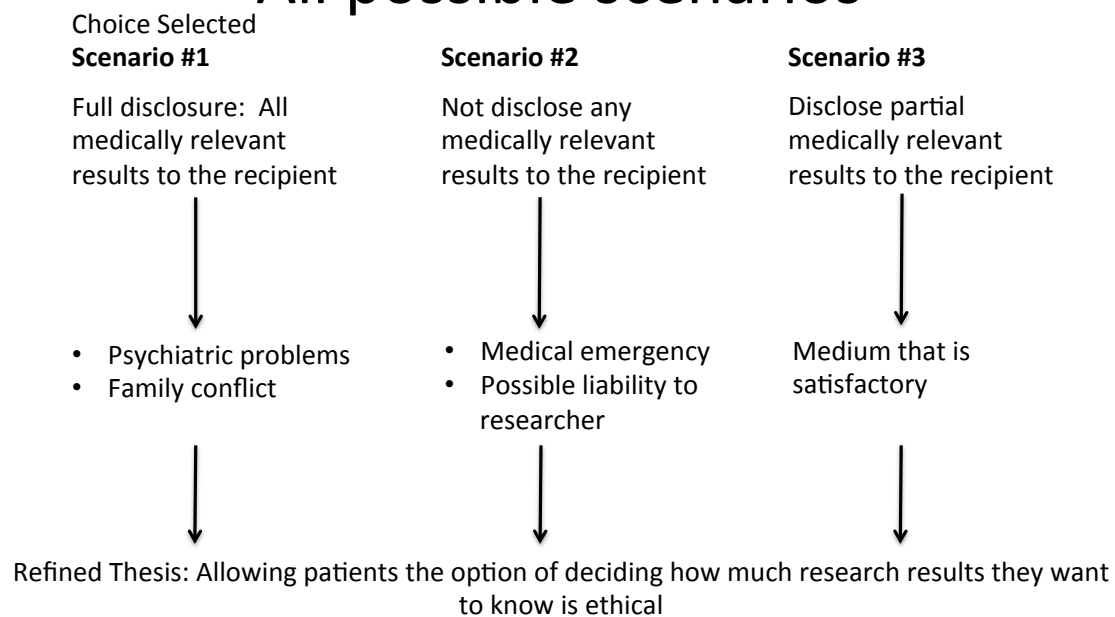


Figure 2. Flow chart of possible scenarios: Scenario of disclosing all information, not disclosing relevant information, and disclosing partial information are put together in a diagram: The patient should be allowed the option of how much information to be disclosed to them that is not overbearing

Improving Scenario #3: Options on how much information should be discussed

Scenarios of giving all information, not giving any information, and giving partial information was demonstrated. It would be more helpful if the researcher were to give the participant's a flow chart or options of what results they would like to know.⁷ Physicians

and genetic counselors should counsel the patient so they are fully informed about each option before they make a decisive decision. The importance of informing these options can help physicians and patients themselves determine whether or not the patient can handle the option they decide that is not overbearing. Whether it is disclosing all information, not disclosing any information, or disclosing partial information all should lead to an “ideal” amount that is disclosed that satisfies the patient and researcher (fig. 2) leading to my refined thesis.

How to determine how much to disclose?

Since there is no federal policy to disclosing results to the patient, a way to help initiate towards that goal would be to create a series of questions of how much results to be disclosed (fig.3). First, the researcher needs to educate the patient about hereditary cancer through genetic counseling. If the patient agrees to participate, the researcher should then ask if the patient would like to be disclosed if found that the patient carries a genetic mutation that has treatment and prevention available. If the patient says no, then the researcher should respect the patients wishes and do not disclose any results unless if it is a medical emergency ask the next question. If the patient says yes, then the researcher should ask the next question: does the patient want to know any mutation that has no clinical utility. No clinical utility means there are no treatment available, no preventative, and no cure. If the patient says no, then the researcher should only disclose mutations that have clinical utility (treatment options and prevention availability) and ask the next question. If the patient says yes then this should be discussed in more detail between parties to determine a comfortable amount to be disclosed. It is possible a patient

would only like to know mutations that have no clinical utilities and not know those that have clinical utilities.

Determining amount of information to be discussed

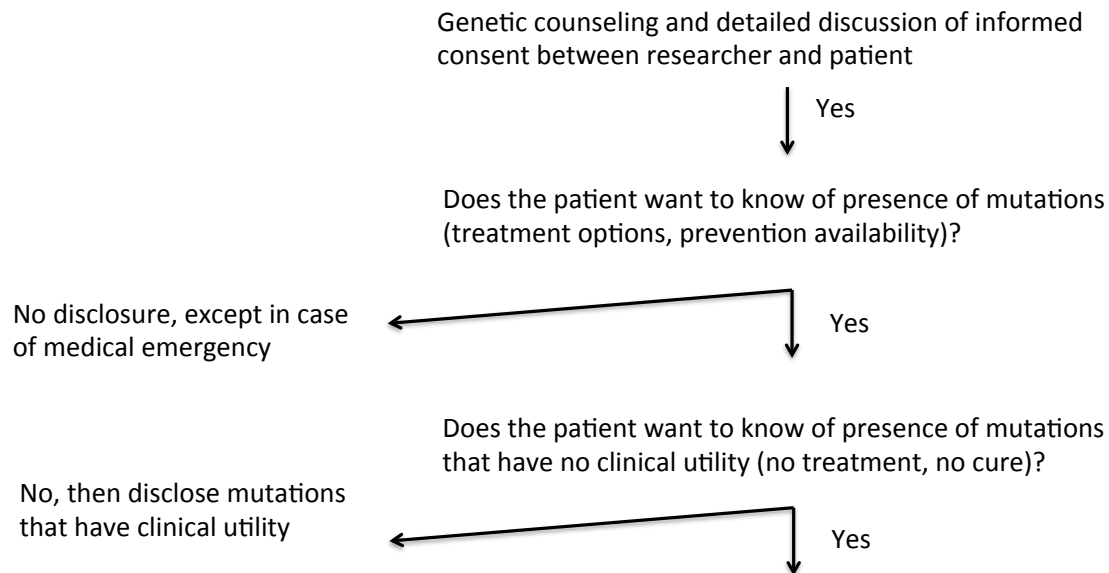


Figure 3. Options of how much information to disclose: Researchers ask a series of questions to understand how much information the patient would like to be disclosed

Determining the amount of how much information the patient would like to disclose could eliminate potential ethical dilemmas. The harmful outcome of the case study could have been avoided if series of detailed questions in fig.3 would have been asked. If the participant believes the option they choose will not harm them psychologically, but the physician has strong reasons to believe it does, then the physician's choice overrides because of they know the validity and confidence of their own research, potential liability, and the patient is thinking in best interest of their curiosity rather than best interest of their mental health. It is the patient's responsibility to balance and know their priority in choosing curiosity verses their mental state of mind.

Conclusion

Generally, in the field of hereditary cancer genetic research, information and results are new, unknown, and uncertain. This is the reason why special care and attentive decision-making must be carefully thought through to prevent any inadequate release of immature data and uncertain results. The researcher must take into account the benefits, burden, and risk of the after disclosure of the results. Results that may cause harm to the participant more by disclosing to the participant causes such as anxiety or any unnecessary health interventions should not be disclosed. Series of questions can determine how much should be disclosed at a level comfortable for both parties. Once these questions are tried and perfected over time, it can eventually become a federal guideline. All these factors put together will expand good communication and relationship between the researcher and participant, which enhance and improves the public's perception of hereditary genetic research.

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