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Return of research results from pharmacogenomic versus disease susceptibility studies: what's drugs got to do with it?

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Abstract

One of the most controversial ethical issues in genomics research is the return of individual research results to research subjects. As new technologies, including whole-genome sequencing, provide an increased opportunity for researchers to find clinically relevant research results, the questions related to if, when and how individual research results should be returned become more central to the ethical conduct of genomic research. In the absence of federal guidance on this issue, many groups and individuals have developed recommendations and suggestions to address these questions. Most of these recommendations have focused on the return of individual results from disease susceptibility studies. However, in addition to predicting the development of disease, genomic research also includes predicting an individual's response to drugs, especially the risk of developing adverse events. This article evaluates and compares the return of individual research results from disease susceptibility studies versus pharmacogenomic studies.

Keywords

clinical utility; clinical validity; disclosure of results; disease susceptibility; pharmacogenomics; research ethics; return of results

Setting the stage

One of the most challenging ethical issues in genomic research is the return of individual research results (ROR) to research subjects. The NIH data-sharing policy for genome-wide association studies, suggests that "contributing institutions and institutional review boards (IRBs) may want to establish policies to determine when it is appropriate to return individual findings from research studies" [101]; however, the content of such policies is left

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to the individual institution. In the absence of national guidance, recommendations from individuals and groups have flourished to address if, when, under what conditions and how individual genomic research results should be shared with research participants [1–6,102]. Most of these efforts have focused on the return of research results that have implications for the susceptibility of developing a future disease. However, genomic researchers study not only the prediction of disease, but also individual responses to treatment. The goal of pharmacogenomics (PGx) research is to evaluate genetic variations in an individual's genome to predict how a patient may respond to a particular therapy or dose, including predicting toxicity and effectiveness [7]. PGx research is the most promising area of genomic research that has a direct application in clinical practice today, which lends urgency to addressing the ROR issues it raises [7]. Furthermore, cancer genomic researchers have indicated that one of the most frequent types of clinically relevant research results being found is related to PGx [8].

Consider the following scenario: you are conducting a genome-wide association study in women with breast cancer, analyzing peripheral neuropathy following treatment with doxorubicin. Your population is young (<45 years old), newly diagnosed patients undergoing their initial treatment. You discover that three patients demonstrate multiple variations that, in previous retrospective studies, were each associated with severe, often permanent neuropathy. What is your responsibility to communicate this finding to some oversight or advisory committee? What are the risks and benefits of returning the finding to the patient and/or their treating physician? In the same study, you also discover that three different women show a gene variation that, in previous retrospective studies, was associated with development of non-small-cell lung cancer. Although this is an incidental finding, unrelated to your study aims, what is your responsibility to communicate this finding to some oversight or advisory committee? What are the risks and benefits associated with communicating this finding to the research subject?

The issue of return of individual research results is challenging because providing individuals with clinically significant personal information crosses the boundaries that are supposed to distinguish research from clinical practice [2,9,10]. A central concern of many IRBs and genomic researchers is that by returning research results and having individuals (and/or their physicians) act on the result, medical care, rather than research, is being practiced [2]. As genomic technologies allow for more detailed analysis of the human genome, clinically relevant research findings will be discovered, both related and unrelated to the scope of the original study. In this paper, we address whether and how the return of research results from PGx studies may be different from results from disease susceptibility studies (DSS).

The goals of this paper are to: analyze the ethical implications (risk of harm and anticipated benefits) of returning individual research results to research subjects from PGx studies compared with DSS; identify factors that need to be considered when making decisions about return of individual PGx compared with DSS genomic research results; and present an argument supporting the return of PGx research results that predict serious adverse events.

Arguments for & against return of individual research results

Most investigators in the USA would probably not have a problem sharing the findings of the scenarios described above with another colleague; the author has observed this type of data sharing for more than 20 years. Yet there are considerable differences of opinion about sharing this information with the research participant and/or their treating physician [2,3,11,12]. Proposed recommendations addressing the issue of return of results frequently involve the researcher as part of the process to determine whether or not a research result should be returned [2]. Since the researcher is the first observer of the finding, he/she would need to take the first step to bring the observation to the attention of an oversight body (i.e., IRB, advisory group and so on). However, most recommendations, including the National Bioethics Commission [102], indicate that if a research result is to be returned, it should be communicated by a trained medical professional (e.g., medical geneticist or genetic counselor), not by the genomic researcher [1,3,13]. Although in the international setting there is an emerging ethic for research results with clinical or health relevance to be returned to research participants [14], traditionally in the USA, the research community has followed a ‘nondisclosure’ policy [1]. To begin the ROR discussion, it is important to review the arguments both for and against return of individual research results [1].

Arguments for the return of individual research results often cite the ethical principle of respecting the autonomy of the research subject; those individuals who want to know research information learned about them should be able to obtain those results [1,2]. Some argue that returning results is a form of reciprocity for the individual’s participation in the study [1,2]. Those in favor of return indicate that the result may be of value to the research subject – it may have personal meaning (e.g., empowerment – knowledge is power), help make lifestyle decisions (e.g., change diet or take out long-term care insurance) and/or be clinically important (e.g., predicting immediate or long-term health risk) [1,2]. The ethical principle of non-maleficence is also cited to support return of research results, especially when the result could help prevent or ameliorate a medical condition. However, many supporters also recognize that research results may need to be withheld in certain circumstances, especially when disclosure would predictably compromise the safety of a participant or third party or would compromise the scientific validity of the study [1]. In addition, even among supporters, most agree that only validated results should be returned. What constitutes a validated result, however, is still unclear [1,2].

Arguments against return of individual research results also cite the ethical principles of respect for autonomy and non-maleficence but have different perspectives on how and why these principles apply [1]. Some indicate that by not returning research results, a researcher is respecting the autonomy of a research subject who initially agreed to participate in the study under conditions of nondisclosure [1]. The National Bioethics Advisory Commission recommended that a clear statement be included in the consent document indicating whether or not results would be disclosed, and if yes, what the risks associated with that disclosure might be [1,102]. Until recently, however, most consent documents have indicated that results of research would not be returned to research participants. The most common arguments for not returning research results include the following: unconfirmed (or unvalidated) results may do more harm than good (e.g., an inaccurate finding may lead to

unnecessary psychosocial distress and potential for discrimination); by law, in the USA, only Clinical Laboratory Improvement Amendment (CLIA)-approved laboratories can provide results for treatment decisions [103] (until recently, it was rare to have a researcher's laboratory be CLIA-approved and therefore return of results was considered by some as a nonissue); and returning research results was contrary to the intent of research, which is to provide generalizable results for the public's benefit, not for individual benefit [1].

However, as investigators utilize new genomic technology, (e.g., whole-genome sequencing) and discover more health-related information, and as social scientists conduct studies of the consequences of returning genomic results to research subjects, the concept of what is considered 'research' is likely to evolve as will the arguments on either side of the issue of return of research results.

Questions, assumptions & guides

In the context of return of individual research results, the main questions addressed in this paper are the following: are results from PGx studies, especially those predicting an adverse event (PGx_{AE}), different than results from DSS?; and how do the ethical implications and consequences (potential for harm and anticipated benefits) of returning a research result from these two types of studies compare? This comparative assessment is limited to studies of inherited (germline) DNA variations or mutations in adults. For a PGx_{AE} result, this would include a polymorphism(s) or variation(s) in one or more genes associated with an adverse response or toxicity to drug X. For a disease susceptibility result, this would include a variation(s) or mutation(s) in one or more genes associated with development of disease A (Box 1).

Box 1

Context of risk–benefit assessment

- The context of the risk–benefit assessment is focused on research results from pharmacogenomics studies predicting toxicity or adverse events (PGx_{AE}) and disease susceptibility studies predicting future development of disease. Our assessment will be limited to inherited (germline) DNA variations or mutations. For a PGx_{AE} result this would include polymorphism(s) or variation(s) in one or more genes associated with an adverse response to drug X. For a disease susceptibility result this would include variation(s) or mutation(s) in one or more genes associated with development of disease A.

Assumptions

The assessment begins with the following assumptions: research subjects have the right to control whether they learn research results about themselves or not [2]; genomic researchers agree that it is their responsibility to consider the clinical relevance of a finding and act on those that pose imminent risks of severe, preventable harm to the subject, by reporting this to the Principal Investigator and/or the IRB or an oversight body [11]; preliminary,

unvalidated results should not be returned to research subjects [1–3]; and if results are returned, medical professionals expert in communicating genetic/genomic findings to individuals (e.g., a medical geneticist or genetic counselor), should return the results, not the research investigator (Box 2) [1,2].

Box 2

Assumptions of risk–benefit assessment

- Research subjects have a right to know and a right not to know research results.
- Genomic researchers agree that it is their responsibility to consider the clinical relevance of a finding and act on it (i.e., report to Principal Investigator or responsible oversight body).
- Preliminary unvalidated results should not be returned.
- Results should only be returned by medical professionals expert in communicating these findings, not the research investigator.

Guides & definitions

As a guide for this assessment, conditions for return of individual research results recommended by the National Heart, Lung and Blood Institute (NHLBI) [3], integrated with recommendations from the Incidental Findings Working Group (IFWG) [5] were used. Traditional variables used in information disclosure were also incorporated. These included analytic validity, clinical validity, predictive value and clinical utility (as defined by/ available through the CDC [15,104–106]).

NHLBI conditions for return of research results

Two NHLBI recommendations address the criteria necessary to determine when genetic results ‘should’ or ‘could’ be returned to study participants [3]. Both of these recommendations are built on the premise that informed consent has been obtained and that the study participant’s identity and contact information is available. Return of individual results does not apply to anonymous studies or secondary analysis where there is no means to re-identify or recontact participants. NHLBI recommends that the investigator, along with the IRB, and ideally through a central advisory board including other experts, make the determination regarding when results should or could be offered to the research participant.

NHLBI recommendation for when results should be offered—According to NHLBI, “Individual genetic results should be offered to study participants if they meet all of the following criteria: a. the genetic finding has important health implications for the participant, and the associated risks are established and substantial; b. the genetic finding is actionable, that is, there are established therapeutic or preventive interventions or other available actions that have the potential to change the course of the disease; c. the test is analytically valid, and the disclosure plan complies with all applicable rules; and d. during the informed consent process or subsequently, the study participant has opted to receive his or her individual genetic results” [3].

NHLBI recommendation for when results could be offered—NHLBI also offered recommendations for when a result could be offered: "Investigators may choose to return individual genetic results to study participants if the criteria for an obligation to return (i.e., should return) are not satisfied, but all of the following apply: a. the investigator has concluded that the potential benefits of disclosure outweigh the risks from the participant's perspective; b. the investigator's IRB has approved the disclosure plan; c. the test is analytically valid and the disclosure plan complies with all applicable laws; and d. during the informed consent process, or subsequently, the study participant has opted to receive his/her individual genetic results." Part A of this recommendation relies on the investigator's judgement to assess the risks and benefits from the research subject's perspective and include individual results associated with reproductive risks, and those that have personal meaning or utility or health risks in select circumstances [3].

IFWG

The recommendations from IFWG focused on the return of 'incidental' findings. They were based on the net benefit of returning the finding to the research participant [5]: results of strong net benefit should be disclosed; those with possible net benefits could be disclosed and those with unlikely net benefits should not be disclosed (unless the participant elected to know). In general, recommendations were influenced by whether the result revealed a life threatening or serious condition for the individual or their offspring that could be avoided or ameliorated (should disclose); revealed a condition that could not be avoided or ameliorated but was still grave or serious yet non-fatal (may disclose); or that the results were not likely to be of serious health or reproductive importance or whose importance cannot be ascertained (do not disclose). Except for the focus on reproductive decision-making, many of the IFWG conditions for 'return' or 'may return' were subsumed in the NHLBI recommendations.

CDC model for genetic testing

The definitions provided by the CDC Analytical Validity, Clinical Validity, Clinical Utility and Ethics (ACCE) Model for Genetic Testing [103] (and incorporated by Evaluation of Genomic Applications in Practice and Prevention [EGAPP™] [104]), were also used to guide our assessment. These definitions (Analytical Validity, Clinical Validity and Clinical Utility) along with other terms used in this paper are summarized in Box 3. In brief, analytic validity refers to how accurately and reliably the test (or result) measures the genotype of interest; clinical validity refers to how well the result detects or predicts the associated disorder (disease) or condition (response to therapy); and clinical utility refers to how effective the result is at avoiding or minimizing adverse clinical consequences (prevent/reduce severity of disease or prevent/reduce severity of adverse drug response).

Box 3

Definitions used to guide the risk–benefit assessment

Related results

- Research results with potential health or clinical relevance that are related to the aims or scope of the study [1].

Incidental results

- Research results with potential health or reproductive importance; discovered in the course of conducting research, but are beyond the aims of the study [5].

Analytic validity

- Accurately and reliably measures the genotype of interest; includes analytic sensitivity and specificity, laboratory quality control and assay robustness [104].

Clinical validity

- Detects or predicts the associated disorder or condition; includes clinical specificity, positive predictive value, negative predictive value and prevalence of specific disorder [104].

Predictive value

- The ability to predict disease or treatment response. Positive predictive value is the absolute risk of developing the disease or response in carriers of the mutation or variation. Negative predictive value is the probability that noncarriers will not develop the disease or response [15].

Clinical utility

- Availability and effectiveness of intervention to avoid/minimize adverse clinical consequences [104].

Similarities & differences between PGx & DSS results

Research results from PGx and DSS share many features. Both types of results are predictive and probabilistic in nature. PGx_{AE} predicts the risk of developing an adverse response to a drug; DSS predicts the risk of developing future disease. Both types of results have varying degrees of uncertainty regarding whether the risk estimate is correct. Research results both related and incidental to the original aims or scope of the research may be obtained in either type of study. Results from both PGx_{AE} studies and DSS may have important health implications for the research participants and because of this, for both types of studies, research participants may want to know the research result. When conducting either type of research, it is important to clearly communicate to the research subject the tenuous nature of research and how associations between variations and outcome may change as time goes on and more is understood about the disease or drug therapy.

PGx, DSS & the continuum of health & disease

Although PGx and DSS results share many similarities, important differences also exist. To highlight some of these differences, we will first briefly examine the temporal relationships of these results along the dynamic continuum of health and disease. From the schematic in Figure 1, an individual can move through a continuum of being in a healthy state to being in a state of disease. Once the individual is diagnosed or develops a disease or condition,

treatment, if available, is usually sought. If the individual is aware of the potential to develop disease and there is an intervention available, it may be possible to prevent the disease from occurring or at least minimize the severity of disease. This is also true if the individual is aware of the potential to develop an adverse response to a drug. In this continuum, disease development (T_x) and treatment response (T_y) are considered as two separate events. Recognizing that many different contexts are possible, in general, when disease susceptibility is predicted in an otherwise healthy individual, there is often a long timeframe (e.g., decades, years) until the event (T_x). By contrast, when an adverse drug response is predicted (PGx_{AE}), especially in a patient with a disease diagnosis, there is often a short timeframe (e.g., weeks, days or hours) to the event (T_y). Even when an individual is otherwise healthy, the prediction of an adverse drug reaction (e.g., an incidental finding predicting an adverse response to codeine) may be equally time sensitive and have a short time to the event. When the predicted PGx event relates to drug effectiveness (PGx_{EFF}), however, the time to the event (T_z) can often take months or years (e.g., measuring effectiveness of chemotherapy as time to tumor recurrence or death [16]).

It is also recognized that the implications of returning a research result to an otherwise healthy individual will be different compared with an individual already diagnosed with disease. DSS predictions often involve healthy individuals, while PGx predictions related to adverse events (PGx_{AE}) are often associated with individuals already diagnosed with disease. Even when DSS are conducted with diseased individuals, the stigma of disease, if it exists, is already present, and the prediction of developing another condition is still in the future. It is also important to recognize the difference between a DSS and a PGx_{AE} event in relation to clinical care. The PGx_{AE} research result is often obtained when an individual is either considering or undergoing treatment (prospective study) or has already received treatment (retrospective study) – that is, the research participant is already involved in the clinical care setting. By contrast, the DSS result, especially for healthy individuals, is frequently obtained when the research participant is not involved in clinical care. Unless there is a medical intervention available to prevent the disease, a PGx_{AE} prediction is more closely associated with clinical care compared with DSS.

When should results from PGx & DSS be returned? Applying NHLBI criteria

Applying the NHLBI criteria for when research results should be returned [3], it was assumed, for both the PGx_{AE} and DSS research result, that the following NHLBI conditions were met: the result was analytically validated and may have important health implications for the individual research participant; during the informed consent process or subsequently, the research participant opted to receive her/his genomic results; and the disclosure plan complies with all applicable laws [3]. With these conditions fulfilled, the remaining NHLBI criteria were applied to each type of result and included the following: first, the associated risks are established; second, the associated risks are substantial; and third, the result is medically actionable (intervention or prevention available) [3]. In developing the NHLBI criteria for when results should be returned, the working group did not designate a firm threshold of risk, because they considered that the importance of genetic information to a study participant would depend on the magnitude of the risk as well as its consequences. For

the current assessment, an additional criterion, from the IFWG, was also incorporated: fourth, the result would be useful in reproductive decision-making [5].

Using these four conditions, we compared how well PGx_{AE} versus DSS results met the criteria for when a result should be returned (see Table 1). For both the PGx_{AE} and DSS result, applying the first two criterion, the associated risks may (+) or may not (−) be established and the risks could be substantial (++). The DSS result might be useful in reproductive decision-making (++) [17,18]; however, a PGx result indicating lethal- or high-grade toxicity to a drug would probably not be relevant to decisions about reproduction (+/−), unless it predicted harm to a fetus, pregnant woman or side effects altering fertility. Turning to the third criterion, the medical actionability of a PGx result is likely to be high (+++), because in theory all PGx results predicting an adverse event have an intervention or could be prevented. This is because of the choices that PGx data make possible: whether to forego the drug or drug dose; whether to give an alternative drug; or whether to increase monitoring and add supportive therapy if no alternate drug is available [7]. By contrast, the medical actionability of DSS results, as defined by NHLBI, depend entirely on whether or not there exists an established intervention or prevention or other action to alter the course of the condition and lead to improved outcome [3]. Medical intervention for DSS results are much less likely compared with PGx_{AE} results. Following the NHLBI criteria, medical actionability is the main difference between the two types of results when deciding to return results.

The overall benefit of returning a PGx_{AE} result compared with a DSS result was also assessed, including the prospect for personal meaning, clinical benefit, clinical utility, and time to clinical benefit (Table 2). For both types of research results, the research subject may benefit personally from the knowledge or meaning he/she associates with the research result. However, compared with DSS, PGx_{AE} results have a higher prospect for clinical benefit because there is likely to be clinical utility and medical actionability. It is also likely that the research subject may have clinical benefit sooner with the receipt of PGx_{AE} versus DSS results, especially if he/she is continuing to receive treatment for their condition and the PGx_{AE} result can prevent a severe or life-threatening toxicity from a subsequent drug.

Leveling the playing field

To allow the results from PGx_{AE} and DSS to be more similar, let's now assume that the research results from both studies are medically actionable – that is, have clinical utility (Box 4). This removes the main difference between the two kinds of results observed in the assessment above. When clinical utility is similar, the focus of the assessment shifts to clinical validity – the association of the research result with a clinical condition or treatment response. Analyzing clinical validity includes evaluating the risks and benefits of returning a false-positive result as well as the ethical implications of not returning (i.e., withholding) a true-positive result, especially results with high positive-predictive value.

Box 4

Leveling the playing field

- To allow the results from a pharmacogenomics study predicting drug adverse events (PGx_{AE}) and disease susceptibility studies to be more similar, we then assumed that the research results from both studies were medically actionable thus removing the largest difference we had observed in the initial assessment. When clinical utility is similar, the focus of the assessment shifts to clinical validity, including the risks and benefits of returning a false-positive result and the risks and benefits of not returning a true-positive result, especially results with high positive-predictive value.

Harm in returning a false-positive result

Table 3 summarizes the potential harms (clinical, psychosocial, reproductive and economic) of returning a false-positive PGx_{AE} versus DSS result to the research subject. In general, for PGx_{AE}, the clinical or health harm in returning a false-positive research result might include the following: the individual would not be given a potentially effective drug (because the research result predicted an adverse event); the individual might be given an alternate drug not as effective as the original drug; and/or the alternate drug could cause an adverse event (especially if no test existed to predict response to that drug). In addition, if no alternative drug was available and the drug was administered, the individual may be anxious about the predicted adverse effect and be needlessly monitored or given supportive therapy to offset the falsely predicted toxicity.

By contrast, the consequences of returning a false prediction that an individual would develop a disease for which there exists a medical intervention might subject the individual to receive unnecessary treatment to prevent the disease. The treatment may lead to other clinical or health-related harms (e.g., pain, hair loss, harm to organ systems [liver, kidney, heart and so on]). The potential for psychosocial harm, including emotional consequences (e.g., anxiety, worry and depression), stigmatization, family discord and change in career path would be more likely to develop from returning a false-positive DSS compared with PGx_{AE} results. Studies in the literature document the concern for these negative implications, consequences and stigma associated with an individual research participant learning about the potential to develop certain diseases (e.g., cancer, mental illness and Alzheimer's disease) [2,19,20]. Although fears of blood draws, mistrust of researchers and the healthcare system and confidentiality concerns about genetic testing have been raised for both PGx_{AE} and DSS [21], the public may perceive a PGx_{AE} result to be associated with less harm for stigmatization and discrimination, and possibly more good (because they could do something about it) compared with learning about the risk of disease development. This reasoning stems from the likelihood that more people are familiar with and have had the experience of suffering a side effect from taking a drug, compared with the experience of being diagnosed with or having the susceptibility to develop a chronic or life-threatening disease.

The return of false-positive results from both PGx_{AE} and DSS research may also have harmful economic consequences. Returning the PGx result may cause the individual to pay a higher price for the alternate drug and/or the potential that the insurance company may not cover that costly drug; the DSS result may cause the individual to suffer a drop in income due to a change in career path and additional costs if he/she decides to purchase long-term or additional life insurance.

Consider the situation where a DSS result falsely predicts development of a neuro-muscular disorder in midlife compared with a PGx_{AE} result which falsely predicts transient neuropathy in response to taking a drug for treating the disorder. Here, the return of the DSS result is likely to have a significant effect on reproduction, including the decision to have children, the decision for existing children or other blood relatives to receive testing or if no testing was available, the consequence that other family members may receive unnecessary treatments hoping to prevent the disease.

In general, compared with PGx_{AE}, we considered the risks of returning a false-positive DSS result to have the potential to lead to more harm and less benefit for the research participant.

Harm in not returning a correct result

Table 4 summarizes the harm of withholding a correct result, especially a result with a high positive-predictive value. We considered that withholding this kind of PGx_{AE} result is likely to have the potential for significant clinical harm. The research participant may develop a lethal side effect and die from taking the drug or drug dose. If not lethal, the individual may develop a serious adverse event and may need to be hospitalized. Harmful clinical consequences of not returning a correct DSS result are that the individual may develop a disease that could have been prevented or may not have taken steps to ameliorate or otherwise prepare for the disease or its consequences. With a genetic disease that lacks a preventive intervention, but is associated with a highly penetrant mutation, the individual may still develop the disease and receive clinical treatment, if available, at that future time. In contrast to DSS, we often cannot wait for a PGx_{AE} event to occur to intervene or ameliorate its effect, especially if it predicts a lethal event.

Significant psychosocial consequences could occur when the result, either PGx_{AE} or DSS, predicts a preventable condition [1]. However, since most genomic diseases lack a preventive intervention, it is likely that withholding a correct DSS result will result in less harm compared to withholding a correct PGx_{AE} result (which, in theory, is always associated with a medical intervention). If a correct DSS result is withheld for a non-preventable disease, the individual and/or their family will not have benefited from the potential personal utility (i.e., personal meaning, empowerment and life choices) of anticipating the development of the disease. The individual may feel a wide variety of emotions (e.g., anguish, anger, despair and frustration) upon developing the disease, which may or may not have been mollified by having had previous knowledge of the impending condition. Other individuals, who do not derive any personal meaning or empowerment from learning their disease susceptibility, may actually benefit psychologically from not knowing the result's prediction.

Reproductive consequences are more likely to be significant for DSS compared with PGx_{AE} results, especially if the individual might have used the DSS result to decide not to have children or additional children. Economic consequences could be significant for withholding both DSS and PGx results.

Overall, in this assessment, not returning a correct PGx_{AE} result is considered more harmful than not returning a correct DSS result (unless an intervention exists to prevent the predicted disease or there are serious reproductive consequences) (Box 5).

Box 5

Returning a false-positive result

- In general, compared to a pharmacogenomic result predicting an adverse event, PGx_{AE}, result, we considered the harms of returning a false-positive disease susceptibility study result to lead to more harm for the research participant, especially related to psychosocial and reproductive implications, as well as the potential for more long-term economic harm.

Summary

Thus far in this comparison, several differences have been identified that distinguish PGx_{AE} from DSS research results (Box 6). Compared with DSS, PGx_{AE} results are medically actionable, may offer benefit immediately and may be more closely related to the clinical care setting. In general, compared with DSS results, PGx_{AE} results are associated with less psychosocial and life choice consequences: the return of an incorrect PGx_{AE} result is likely to result in less harmful consequences for the research subject; and result is likely to withholding a correct PGx_{AE} result in more harmful consequences. Overall, the ethical implications (i.e., potential for risk of harm versus anticipated benefit) favors the return of analytically and clinically validated PGx_{AE} results compared with DSS results. However, the decision to return or withhold research results, whether PGx_{AE} or DSS, should be made on a case-by-case basis, and will be influenced by the contextual nature of the research result and the research participant's desire to know the result [1,2,102].

Box 6

Summary: returning PGx_{AE} results versus disease susceptibility study results

- Our assessment has identified several differences between research results from pharmacogenomics studies predicting adverse drug events (PGx_{AE}) and disease susceptibility studies: PGx_{AE} results are medically actionable; PGx_{AE} results may offer benefit immediately; in general, PGx_{AE} results are associated with less psychosocial and life choice consequences; in general there is less harm if an incorrect PGx_{AE} result is returned and more harm if a correct PGx result is not returned. Overall, our risk–benefit assessment favors the return of analytically and clinically validated PGx_{AE} results compared with disease susceptibility study results. The actual decision to return or withhold research

results should be made on a case-by-case basis and will be influenced by the contextual nature of the finding and the research participant's desire for the result.

When could results be offered? Applying NHLBI recommendations

NHLBI criteria also address when research results could be returned to the research participant. These criteria are based on the investigator's (and the IRB's) judgement of the net benefit of returning results from the perspective of the research participant [3]. The recommendation is largely subjective and will be heavily influenced not only by the context of the result but also the point of view of the investigator (and IRB) in making this assessment. Return of PGx_{AE} results continues to demonstrate a higher net benefit for the research participant compared with DSS results because in theory, all are medically actionable, and, for some results, the time to benefit may be quite soon. Therefore even though there is some uncertainty associated with the risk of developing the adverse response or the magnitude of the adverse response, it is likely that a research participant would want to learn of a result that has some chance of preventing physical harm. Furthermore, as discussed in the assessment above, psychosocial and reproductive issues are likely to be more significant for DSS compared with $PGx_{AE.}$ So, results from PGx_{AE} studies are more likely to be considered by investigators and IRBs to have a higher net benefit compared with results from DSS studies.

Therefore to address when results should or could be shared with the research participant, one must consider the types of PGx_{AE} results that have a higher net benefit than others. In the following section, we integrate parameters derived from the assessment presented in this paper (including recommendations by NHLBI and IFWG) with an adaptation of a proposed system for returning incidental findings from whole-genome sequencing results [4].

Return of pharmacogenomic results that predict an adverse event: adapting the 'bin' approach

Returning or withholding research results is very context dependent and is influenced by whether the individual research subject wants to know the results [1–3]. Many individuals and groups have recommended that only analytically validated results, with a known medical intervention, should be returned [1,3,4,102]. In this paper, it is also argued that the ethical decision to return PGx_{AE} results turns on both the risk of harm in withholding an accurate research result and the risk of harm in returning a false-positive research result (where harm includes clinical, psychosocial, reproductive and economic harm). A critical question in this paper regarding the decision to return a PGx_{AE} research result that is 'related' to the study aims, is whether one should wait until the finding is considered a clinical result – that is, an established test that is used in clinical care – or return the result at some point in time before the process of clinical translation has occurred.

Although the 'bin' approach, described by Berg *et al*. is intended for making decisions regarding return of incidental (not related) results in the clinical (not the research) setting, it can be adapted to guide the return of PGx_{AE} research results [4]. In the bin approach, similar

to the approach in this paper, guidance for return of results from whole-genome sequencing assays is determined by the results' clinical relevance: bin 1 results demonstrate clinical utility and are medically actionable; bin 2 results demonstrate clinical validity; and bin 3 results have unknown clinical implications. Similar to the approach we have taken in this paper, bin 2 results, are further categorized based on the level of risk or harm that would be expected if the result was to be returned to the individual [4]. In addition, for a genomic variant to be reportable (in the clinical context), the bin approach considers whether the variant will have a 'known' or 'presumed' deleterious effect (in which case the result, if medically actionable, is reportable) or whether the variant is presumed or known to be benign or is a variant of uncertain clinical significance (in which case the result, even if medically actionable, is not reportable) [4].

Proposed guidelines for the return of PGx_{AE} results

In this article we have argued that PGx_{AE} research results are, in theory, medically actionable, and that often these results, if returned, will likely have low to medium risk of harm to the individual. Applying the bin conditions (i.e., prediction of a deleterious, benign or unknown clinical effect) and combining them with toxicity grades [107,108], we present a framework for the return of PGx_{AE} results. This framework can be utilized to guide decisions, whether the PGx_{AE} results are related or incidental to the study aims.

We propose the following guidelines (also see Table 5).

Should be returned—Results that are known or presumed to be deleterious (based on previous literature or retrospective studies) and are medically actionable should be returned to the research subject and do not require a prospective clinical validation study to warrant return. Examples of these types of research results include: PGx_{AE} research results that predict a lethal response to a drug or drug dose (e.g., anaphylaxis or Stevens–Johnson syndrome). This position is based on the understanding that the prediction of a lethal result always has an intervention-do not give the drug. If the result is withheld but is correct, the individual may die; even if the result, in subsequent prospective validation studies, turns out to have a low–medium predictive value, the risk of return is still reasonable compared with the potential harm. PGx_{AE} results that predict serious responses, including those that predict a response likely to require hospitalization (e.g., cardiac toxicity), likely to be disabling and/or permanent (e.g., permanent peripheral neuropathy; blindness) and/or those that would seriously limit daily adult function (e.g., severe vomiting or migraines) should also be returned even in the absence of a prospective clinical validation study because the net benefit to the research subject is likely to be high. If the result is withheld but is correct, the individual may suffer physical, psychosocial and economic harm, not being able to work and/or requiring additional at home care for themselves or their family. If the result is returned and, in subsequent prospective validation studies turns out to have a low–medium predictive value, the risk of altering medications or providing additional monitoring and therapeutic support based on the result is still reasonable compared with the potential harm.

Should not be returned unless confirmed in a prospective study—Results that are known or presumed to predict serious, but not life-threatening responses, that are

unlikely to require hospitalization, but may result in temporary (reversible upon drug discontinuation) toxicity (e.g., temporary peripheral neuropathy or moderate neutropenia) should not be returned unless confirmed in a prospective clinical validation study (clinical trial or alternative study design) and a medical intervention exists.

Should not be returned—Results that are uncertain or predict presumed or known benign responses should not be returned. Examples of these types of research results include the following: PGx results that predict mild, temporary drug responses (e.g., nausea, diarrhea, mild skin rash) that will either resolve in a reasonable time or are treatable by over the counter or prescription medication and that do not impose an economic burden on the family or individual, should not be returned. Overall, there is little or no net benefit, clinically or economically, in returning the result. The drug will still be utilized and the response to the drug can be managed reasonably. PGx variants of uncertain clinical relevance might be useful in the future and, depending on the nature of the variant and resources, the researcher may consider maintaining a registry of these results, and/or monitoring the clinical relevance over time and/or invite research subjects to participate in future research.

Other considerations

Comparing results of PGx studies evaluating treatment effectiveness versus DSS

Although this paper has focused on PGx_{AE} results, many pharmacogenomic studies also evaluate the effectiveness, rather than the adverse effects, of a drug or drug regimen to treat a disease (PGx_{EFF}). In the author's experience, especially conducting cancer genomic and genetic research, in contrast to PGx_{AE}, but similar to DSS, PGx_{EFF} studies generally predict a future rather than a more immediate event. Similar to DSS, PGx_{EFF} may require several years to observe an outcome (e.g., risk of disease recurrence or risk of disease development). By contrast, PGx_{AE} results may only take a few days, weeks or months to observe the toxic event (e.g., development of peripheral neuropathy). Both DSS and PGx_{EFF} results could have significant clinical, psychosocial and economic consequences for the individual. In contrast to PGx_{AE}, returning a false-positive result or withholding a result with high positive-predictive value from either DSS or PGx_{EFF} studies, may have similar clinical consequences. The factors that influence decision-making regarding return or withholding results from DSS and PGx_{EFF} may be more similar than different. In other words, the factors that distinguish PGx_{AE} from DSS – the potential for a more rapid time to benefit, less harm if an incorrect result is returned, more harm if a correct result is withheld, and less potential for psychosocial harm – may not apply when comparing the return of PGx_{EFF} versus DSS results. It follows therefore that, overall, the return of results from PGx_{EFF} and DSS may be more similar than different.

Pleiotropy, DSS, PGx & return of results

Although this paper has discussed return of individual results in the context of genomic variations predicting a single response or disease, polymorphisms or mutations may have more than one effect [22]. This situation, known as pleiotropy, adds another layer of complexity in deciding whether to return or withhold research results. For example,

variations in the *APOE4* gene are associated with cardiovascular disease, risk of Alzheimer's disease and progression to HIV+/AIDs-predicting susceptibility to three different conditions [23]. Variations in the *CYP2D6* gene are associated with response to the drug tamoxifen [24–26], but are also associated with response to many other drugs that are metabolized by or influenced by the CYP2D6 enzyme, including codeine and selective serotonin re-uptake inhibitors, respectively [26]. Mutations in the *BRCA1* gene may predict susceptibility to developing breast and ovarian cancer (DSS) and may also be useful in predicting effectiveness (PGx_{EFF}) to cancer agents [27]. As we learn more about pleiotropic associations ($disease_a$–$disease_b$, $response_a$–$response_b$, and $disease_a$–$response_{b)}$, we will need to consider their effect on the ethical implications and decision to return individual research results. In time, the distinction between a PGx_{AE} result and DSS result may be less important than the overall ethical implications of finding results that are pleiotropic compared with those that are not.

Conclusion

The return of any individual result requires a careful assessment of the potential risks and anticipated benefits and the ethical implications of such return to the individual and/or their family. This includes the clinical/health, psychosocial, reproductive and economic impact of receiving and acting on the result. Because each situation is context dependent, the decision to return an individual research result should be made on a case-by-case basis. However, these decisions can be guided by the following conditions and observations. The return of any individual research result requires analytical validity. Compared with disease susceptibility results, pharmacogenomic results from studies predicting adverse response to drugs (PGx_{AE}) are medically actionable, may offer benefit immediately, and are likely to be associated with less psychosocial and life-choice consequences. Compared with a DSS result, it is likely that less harm will be associated with returning a false-positive PGx_{AE} result and more harm will be associated by withholding a correct PGx result. Therefore, the return of PGx_{AE} results must be guided by the expected toxicity and the clinical and ethical implications of that response if the individual were to receive the drug or drug dose. In addition to analytic validity, most results should also be clinically validated in a prospective study. However, PGx_{AE} results predicting a lethal toxicity and those predicting serious or life-threatening drug responses should be returned even in the absence of a prospective clinical validation study if they meet our guidelines. Uncertain results (i.e., analytical validity not established) or those with little or no clinical or personal benefit to the research participant should not be returned since the risk of harm is high and there is no net benefit.

Future perspective

The challenges and controversies surrounding the return of individual research results are likely to be minimized as empirical studies analyze the process of how these decisions are made, how results are communicated to research subjects, what kind of results research subjects want and the actual consequences of returning (or not returning) individual research results. Whether from PGx or DSS or other 'omic'-based studies, it is likely that in the near future federal guidance and best practices, informed by these empirical studies will be forthcoming. This guidance will likely include general conditions for deciding when

research results should be returned and how this process should proceed, including what steps a researcher should take if he/she discovers a health-related result, and who should be responsible for making the decision. Guidance should also be forthcoming not only on who should communicate this information, but how it should be communicated and to whom. In addition, guidance should be forthcoming on how to address the responsibility of recontact if new data influences interpretation of results that may or may not have been initially returned. In the future, it is also likely that there will be more efficient translation of genomic research findings into the clinical setting, especially for PGx_{AE} results. Electronic medical records will be including genomic profiling results that can be useful for clinical management, especially with advances in health information technology to integrate this information [28]. We will be developing rapid learning systems [29], point-of-care applications and other educational approaches for clinicians to be able to evaluate this information and stay up-to-date with emerging discoveries. We will be developing patient portal systems to capture patient reported outcomes and provide more individualized education according to patient needs. But for many of these advances to take place, the key players will need to agree on some standards of reference for determining analytical and clinical validation of a research result. We will need to determine how much risk or uncertainty is reasonable to warrant return of the results and seriously consider the costs to patients, the healthcare system and the public to develop (or not) an infrastructure required to support this. For those who are interested and can afford it, personal genomic sequencing, of varying degrees of quality, will be available from the private sector, outside the research or clinical setting, and will provide an option for some interested in receiving results about their genome.

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Executive summary

Background

- As genomic technologies allow for more detailed genomic analysis, clinically relevant findings, both related and unrelated to the scope of the original study, will be discovered. In the context of the controversial issue of return of individual research results, how does returning results from pharmacogenomic (PGx) studies compare with disease susceptibility studies (DSS)?

Arguments for & against return of individual results

- The main argument in support of returning research results is respect for research participant's autonomy as a research participant; the main argument against return is that it may do more harm than good, especially if the finding is preliminary or not validated. One of the main challenges in deciding whether or not to return research results is that doing so crosses the boundary between research and clinical practice.

Conditions guiding the comparative assessment of returning individual research results from PGx studies versus DSS

- Guided by the recent National Heart, Lung and Blood Institute criteria for return of individual research results, the potential risks and anticipated benefits were compared for returning results from PGx studies, especially research results predicting an adverse event (PGx_{AE}), with results from DSS.

Similarities between PGx & DSS research results

- Both types of results are predictive and probabilistic, are associated with results both related and incidental to the study aims and may have important health implications for the research participant.

Differences between PGx & DSS research results

- Medical actionability and time to benefit are the two most striking differences between the two types of results: in theory, all PGx_{AE} results are medically actionable (do not give drug or drug dose) and, compared with DSS results, PGx_{AE} results are more likely to have an earlier/immediate benefit to the research participant.

Harm in returning a false-positive result

- Even when both types of results are medically actionable, there is likely more harm (especially psychosocial, reproductive and economic consequences) in returning a false-positive DSS compared with PGx_{AE} result.

Harm in not returning a correct result

- In the situation where a research result has a high positive-predictive value, the research participant is likely to suffer more harm from withholding a PGx_{AE}

compared with a DSS result (unless an intervention exists to prevent development of the predicted disease).

Conclusion

- Overall, compared with DSS results, PGx_{AE} results are medically actionable, may offer benefit immediately, have less harmful consequences if an incorrect result is returned, and more harm if a correct finding is withheld. We conclude that PGx_{AE} results are different than DSS results. Our risk–benefit assessment supports the return of analytically validated PGx_{AE} results that predict lethal or high-grade adverse events. Owing to the highly contextual nature of genomic research, a case-by-case risk–benefit assessment is required.

Future perspective

- Although some federal guidance will be forthcoming, the eventual integration of certain genomic results into medical records will occur, requiring a careful curation, analysis, and evaluation of which PGx findings are medically significant and could be acted upon, even before they have become ‘standard-of-care’ tests.

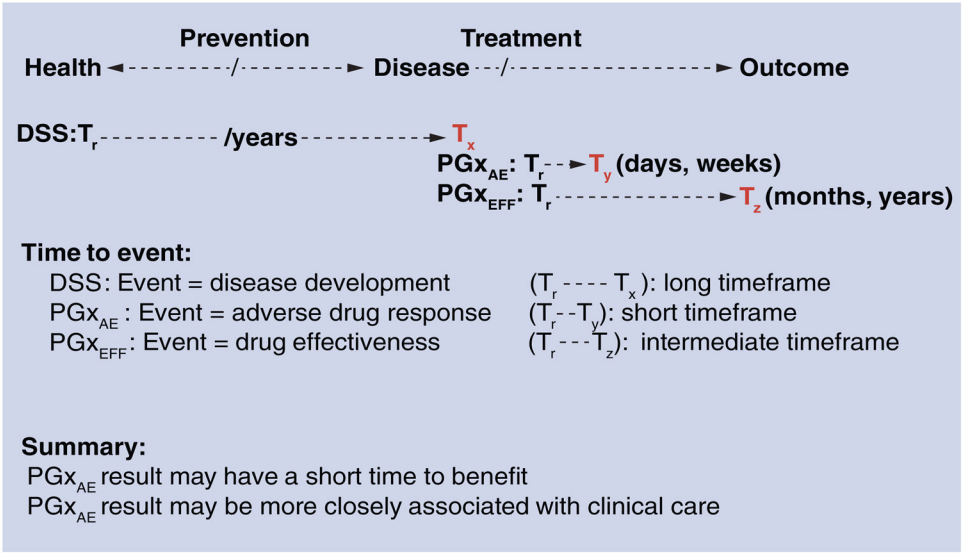

Figure 1. Health–disease–outcome continuum

As an individual moves along this continuum, he/she moves from being in a healthy state to being in a diseased state, with some type of outcome. When a DSS result is obtained (T_r) it can often result is obtained take years before the event occurs (T_x). By contrast, when a PGx_{AE} (T_r) it may only be days or weeks before the event occurs (T_y).

DSS: Disease susceptibility study; PGx_{AE}: Pharmacogenomics study predicting drug adverse events; PGx_{EFF}: Pharmacogenomics study predicting drug effectiveness; T_r: Time of initial research result; T_x: Time to event predicted by the DSS research result; T_y: Time of event predicted by the PGx_{AE} results; T_z: Time to event predicted by the PGx_{EFF} result.

Table 1

Meeting criteria for when results should be returned: pharmacogenomic versus disease susceptibility study results.

Criteria	PGx_{AE}	DSS
Associated risks are established†	+/−	+/−
Associated risks are substantial†	++	++
Medically actionable†	+++	+
Useful in reproductive decision-making‡	+/−	++

Where (+) is associated with likelihood of meeting the criterion and where (−) indicates the result is not likely to meet the criterion.

† National Heart, Lung and Blood Institute 2010 criteria [3].

‡ Incidental Findings Working Group 2008 criteria [5].

DSS: Disease susceptibility study; PGx_{AE}: Pharmacogenomic adverse event study.

Table 2

Anticipated benefit of returning pharmacogenomic versus disease susceptibility study result.

Characteristic	PGx_{AE} result	DSS result
Prospect of personal benefit (potential for personal meaning)	High, especially if subject associates knowledge of result with personal meaning	High, especially if subject associates knowledge of result with personal meaning
Prospect of clinical benefit	High	Low, unless medical intervention
Clinical utility	Medically actionable	Possible medical intervention
Time to benefit	Immediate, early or future	Mainly future

DSS: Disease susceptibility study; PGx_{AE}: Pharmacogenomic adverse event study.

Table 3

Potential harm in returning a false-positive result.

Type of harm	PGx_{AE} result	DSS result
Clinical/health	Not given potentially effective drug Individual given alternate drug not as effective Alternate drug may cause other adverse event	Given unnecessary treatment to prevent disease Treatment may be harmful
Psychosocial	Less trust in medical and research enterprise Less likely to participate in research/clinical testing	Emotional consequences (e.g., anxiety, worry and depression); stigma; family discord Change in career path, in response to anticipating onset of disease
Reproductive	Unlikely to affect reproductive decision-making Other family members may avoid the drug	May affect decision to have children or additional children Family members may receive unnecessary treatment
Economic	Alternate drug may cost more Insurance may not reimburse	May purchase more insurance Change career or work, resulting in reduced income

DSS: Disease susceptibility study; PGx_{AE}: Pharmacogenomic adverse event study.

Table 4

Potential harm in not returning a correct result.

Type of harm	PGx_{AE} result	DSS result
Clinical/health	May develop serious or lethal side effect May be hospitalized Cannot ameliorate once lethal event occurs	May develop disease Will not benefit from prevention available
Psychosocial	Less trust in medical and research enterprise Noncompliant with drug therapy owing to distrust	If disease develops: emotional (e.g., anguish, despair, anger, distrust and depression); stigma; change in career path
Reproductive	Unlikely to affect reproductive decisions Other family members with variation may be harmed if take drug	May have affected children Family or children will not receive preventive treatment, if available
Economic	Hospitalization, insurance, loss of income	Medical bills, need additional insurance, less income

DSS: Disease susceptibility study; PGx_{AE}: Pharmacogenomic adverse event study.

Table 5

Guidance for returning a pharmacogenomics result that predicts adverse events[†].

Decision	Requirements	Examples
Should return		
Results that predict lethal response	Analytical validity Retrospective clinical validity	Anaphylaxis Stevens–Johnson syndrome
Results that predict serious or life-threatening responses, including those likely to: require hospitalization, be disabling or permanent or seriously limit daily adult function	Analytical validity Retrospective clinical validity	Cardiac toxicity Permanent peripheral neuropathy Debilitating migraines
Could return		
Results that predict serious, but not life-threatening responses, that are unlikely to require hospitalization, but may result in temporary toxicity (i.e., not permanent or disabling)	Analytical validity Prospective clinical validity	Temporary peripheral neuropathy Mild–moderate neutropenia
Do not return		
Results that are uncertain or predict mild, temporary responses that will resolve in a reasonable time or are treatable by medication that neither impose an economic burden nor have serious psychological consequences for the individual or family	Do not return	SNPs that are not analytically or clinically validated Prediction of mild diarrhea or nausea

[†]Guiding principles: first, in general, results should be returned only to research subjects who want to know the findings, unless withholding the results will reasonably cause death or irreversible harm to the individual. Second, return of results should be made on a case-by-case basis and must consider the clinical, psychosocial, reproductive and economic implications of return of the result to the individual and/or their family. Third, only analytically validated results, with a known medical intervention, should be returned. Fourth, the decision to return a pharmacogenomic result that predicts adverse events turns on balancing both the risk of harm in withholding an accurate result and the risk of harm in returning a finding of low predictive value with the anticipated benefit.