Disclosure of individual pharmacogenomic results in research projects: when and what kind of information to return to research participants

In the growing field of genomics, the utility of returning certain research results to participants has become a highly debated issue. Existing guidelines are not explicit as to the kind of genomic information that should be returned to research participants. Moreover, very few current recommendations and articles in the literature address the return of pharmacogenomic results. Although genetics and pharmacogenomics have many similarities, the circumstances in which disclosure could have a benefit for the participants are different. This review aims to describe the conditions in which disclosure of pharmacogenomic results is appropriate.

KEYWORDS: clinical relevance, clinical utility, disclosure, pharmacogenomics, research participants

In recent years, an important debate has emerged regarding the disclosure of individual results to participants of research studies [1–8]. More particularly, this question has been raised in the newly expanding field of genomics and pharmacogenomics [9–23]. As the clinical utility of certain genetic tests is being acknowledged, the necessity of returning research results to participants in certain situations is being increasingly advocated [6,9–22]. However, much uncertainty and controversy surrounds such points as the kind of information that should be returned, as well as how and in which circumstances [13,21,26].

As highlighted by others [27], guidance related to the disclosure of pharmacogenomic results is even more limited. In the literature and in the existing guidelines, the debate revolves around the disclosure of genetic research results related to disease susceptibility [9–22,25]. Pharmacogenomics studies the association between genetic variants and interindividual variations in the response to a given medication, specifically, the drug’s efficacy, adverse events and dosing requirements. Although this science is not yet widely used in clinical practice, the growing amount of research being conducted is leading the way towards a future where drug and dose selection become personalized [28,29]. Pharmacogenomic results can be generated from various studies, such as genetic, genomic, pharmacogenetic and pharmacogenomic research. Many attributes are shared by genomic and pharmacogenomic data [27] (Box 1). Yet, the relevance and actionability of pharmacogenomic information differs from genomic data, as it will be later described in this article, for it is tightly related to the prescription of a given drug. The actionability of a result can be defined as being ‘capable of being acted on’ [30].

The objective of this article is to address specifically the return of individual pharmacogenomic results to research participants, generated from either genomic or pharmacogenomic projects and to suggest conditions that would be necessary for the disclosure of individual pharmacogenomic results to research participants.

Materials & methods
We conducted a review of the scientific literature and guidelines from professional organizations. This literature search was conducted on PubMed and Google Scholar. Articles written up until June 2012 were reviewed with different combinations of the following keywords: ‘disclosure’, ‘informing’, ‘return’, ‘communication’, ‘pharmacogenomic research’, ‘genetic research’, ‘research participants’ and ‘incidental findings.’ Focus was placed essentially on articles discussing disclosure of genetic and pharmacogenomic results in a research context. Articles about genetic predispositions to specific pathologies were excluded from our search in order to focus on pharmacogenomic information. Additionally, the HumGen database was used in order to identify international and national laws, policies, guidelines or recommendations that explicitly address disclosure of pharmacogenomic results to research participants [101]. The following keywords were selected for this search: ‘pharmacogenomics’ and ‘research’.

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Box 1. Differences and similarities between pharmacogenomic and genomic results.

Differences between genomic & pharmacogenomic results
- Genomic result (disease predispositions):
  - May be relevant at any point in life
  - Prevention of a disease, decrease of its severity or change in lifestyle
- Pharmacogenomic result:
  - Relevance is sensitive to the prescription of a given drug
  - Prescription of the specific drug must be considered for the patient’s treatment

Similarities between genomic & pharmacogenomic results
- Most laboratories: not CLIA-certified [13,22,31,36]
- Probabilistic [10,13,21,22,27]
- Vast quantity of information [17,26,45,46]
- Pleiotropy [8,60] and incidental findings [8,23,24,62]
- Issues of privacy, confidentiality [13,41] and discrimination [10,13,37,63–65]
- Potential adverse psychological and social consequences [8–10,26,27]
- Feasibility of returning results to research participants [37]: increase in resources [10,18] and costs [14,43,69]

Guidelines
We found only three sets of recommendations pertaining to disclosure of pharmacogenomic results to research participants [31,102,103]. Moreover, they were elaborated a decade ago, at a time when pharmacogenetic research was limited to a very small number of genetic variants. From the academic literature, we found only one article that specifically focused on returning pharmacogenomic results to research participants [27]. Thus, we also included into our evaluation key national and international guidelines identified in previous systematic reviews [3,13,19,22].

Pharmacogenomic guidelines
Although we identified three sets of recommendations focusing on the disclosure of pharmacogenomic research results, none of these documents provide a clear distinction between the return of pharmacogenomic results and genomic results to research participants. The first set of recommendations came from the Report of the Consortium on Pharmacogenomics ‘Ethical and Regulatory Issues in Research and Clinical Practice’ (2002). In terms of disclosure, they state that researchers have the obligation to offer to the participant the option of disclosure, under the condition that their reliability has been established and disclosure is of potential benefit to the participant [102]. The second source was the Nuffield Council on Bioethics ‘Pharmacogenetics: Ethical Issues.’ In their report, they recommend disclosure in cases in which results have been validated: ‘In the atypical cases in which a clinical trial is likely to produce validated and clinically useful data regarding individual participants, we recommend that all participants should be offered the opportunity to receive individual feedback of such data as part of the process of obtaining consent.’ They define the ‘immediate clinical relevance’ of a result with both genomic and pharmacogenomic data as ‘presence of or significantly increased susceptibility to a disease, or which might affect the current treatment of a participant’ and stress the difficulty of evaluating this element in terms of future implications. On the subject of reliability, they mention that ‘passing on individual results of research whose findings have not been replicated is irresponsible, since participants are unlikely to be informed subsequently if later research comes to a different conclusion’ [103]. Additionally, an article written by Anderson et al. in 2002 presents the perspectives of the Pharmacogenetics Working Group: ‘Elements of informed consent for pharmacogenetic research; perspective of the Pharmacogenetics Working Group.’ The members of this group come exclusively from pharmaceutical companies. Although they discuss results from pharmacogenetic studies, they do not clearly distinguish between genetic and pharmacogenetic results that are generated from these studies. They mention that the decision to return results could depend on several factors: ‘Many factors may influence decisions to share results of pharmacogenetic studies with study subjects, including the standard operating procedures of the research sponsor, the robustness and clinical usefulness of the pharmacogenetic results, the ability of the researchers/sponsors to provide the appropriate counseling, and regional regulations and policy statements from bioethics bodies.’ Also, they state that the results should not be returned if they are ‘preliminary in nature, are of no direct medical relevance to the subject, or cannot be used to guide clinical management.’ They consider pharmacogenomic information to be generally exploratory [31]. However, since 2002, advances have been made in this field and we elaborate on this progress later on in our article.

Relevant considerations from genomic guidelines
Given the limited number of guidelines focusing on precise and explicit criteria for the return of pharmacogenomic results, we evaluated whether the same principles governing the disclosure of genetic results may apply to the communication of pharmacogenomic results. Previous reviews
have commented extensively on these guidelines. In particular, the reader is referred to the excellent reviews of Knoppers et al. [19], Van Ness [22], Lévesque et al. [3] and Renegar et al. [13]. As highlighted by these and other authors [4,17,19,26], many of these guidelines limit their recommendations to a simple recognition that individual research results should be returned to participants [32,33]. Other groups have developed criteria that the information should meet in order to be considered important enough for disclosure [34]. Many authors [4,6,9,14,27] have underlined the fact that the existing criteria do not necessarily give a sufficient amount of guidance for researchers to make a decision. From these reviews, existing guidelines can be summarized in a few points. First, the participant must have consented to the disclosure of genetic results [39,34,35]. Second, the test should be analytically valid [39]. Furthermore, the information should have important health implications and can be actionable through therapy or prevention [35]. Finally, disclosure should have a clear clinical benefit, while preventing or minimizing significant harm [34]. These characteristics are also important for the evaluation of pharmacogenomic information. In our view, the harm, benefit and actionability of a pharmacogenomic result are dependent on the prescription of a given drug, as developed below.

In the US, an additional obligation is the Clinical Laboratory Improvement Amendments (CLIA), which requires laboratories to be CLIA certified in order to report results to patients [104]. The National Heart Lung and Blood Institute Working Group (NHLBI) suggests that researchers planning to report results to study participants should use a CLIA-certified laboratory or re-test samples in a CLIA-certified laboratory [35]. Organizations such as the National Academy of Clinical Biochemistry recommend that laboratories comply with CLIA or local rules in order to return pharmacogenomic results in clinical practice [105]. However, as most research laboratories are not CLIA certified, they do not meet the standards for disclosure [13,22,31,36]. Finally, it is worth stressing that the qualifications of a laboratory to provide research results to participants are less explicit in many other countries, including Canada.

**Ethical principles**

Scientists’ considerations for returning individual results stem from particular ethical principles. Both sides of the debate use these principles in their argumentation. The first two ethical concepts are human dignity and respect [8,37–39]. These two principles imply that research subjects, being human, cannot merely be used as a means to an end [2,3,6,37]. This view is shared by both sides of the debate. The principle of autonomy is also critical in this issue [14,15,39,40]. Supporters of disclosure argue that the participants should decide themselves if they wish to run the risk of knowing certain negative information [9]. However, others argue that nondisclosure does not violate autonomy because people who choose to participate are fully informed of the nondisclosure policy [6,9]. In the case where a participant is given the choice of receiving results, their consent is obtained through the consent form. For both genomic and pharmacogenomic results, it is difficult for the participant to imagine all of the many possible results and to foretell what impact that information would have on their life [41]. Consequently, writing the consent form can be a challenge for the research team. Regarding genetic information, it can be difficult for the participant to make a choice about a possible prediction of developing a disease in the future. For instance, there would have to be many different categories of choice, such as life-threatening and treatable diseases, life-threatening and non-treatable diseases, non-life-threatening but serious diseases, and results associated with lifestyle and reproductive choices. Many of these categories could also be relevant to pharmacogenomic results. In addition to the prevention of disease-related events, pharmacogenomic results could also provide information on potential adverse reactions and dosing adjustments. Unless the patient is being prescribed the drug of interest, autonomy can be difficult to exercise in these scenarios because the participant has to take into account the unpredictable relevance of the test, that is, whether they will ever be prescribed that specific drug. Finally, the concepts of nonmaleficence [9,10,42] and beneficence [3] are frequently mentioned. Beneficence stemming from genomic tests may entail an improvement in a person’s health or quality of life, a prevention of a disease to the point of potentially being life-saving, or a more informed approach about reproductive and lifestyle decisions [10,21]. In fact, certain authors refer to a ‘duty to rescue’ [10,16] when disclosure may have an obvious benefit. However, caution is required with some of this terminology because authors mention that legal liability to rescue carries legal penalties [43,44]. When discussing nonmaleficence and beneficence, one significant challenge is the fact that it is difficult to define the extent to which a person’s health or quality of life may improve after disclosure.
Characteristics of pharmacogenomic results

A fundamental distinction exists between genomic and pharmacogenomic result characteristics. A genomic result predicting the development of a disease can be potentially relevant to an individual at any point in their life. Returning this kind of information can lead to prevention, decrease in severity or a change in lifestyle that may or may not be relevant to the prevention of a disease. For example, an individual at a high risk of developing a disease may change their retirement plans or reproductive decisions. Although certain factors, such as age, could affect the utility of returning the result, the research participant could gain directly from the disclosure of these genetic research results, if they are clinically useful. On the other hand, a pharmacogenomic result will generally only indicate whether and how an individual would respond to a given medication or class of medications aiming to treat one or some specific diseases. Thus, knowing a pharmacogenomic result becomes useful for an individual only in certain circumstances, particularly when the prescription of a drug for which such a result is relevant is considered, as it will be developed below (in the ‘Relevance’ section).

Pharmacogenomic information also shares some common characteristics with genomic results. An important obstacle in disclosure is that both types of research results are probabilistic [10,13,21,22,27]. The probabilistic nature of the result means that an association will predict with only a particular degree of certainty the response that an individual will have to a specific medication. A low probability entails an important degree of uncertainty. As such, pharmacogenomic results require a certain amount of interpretation. Therefore, in their selection of the results that may be returned to the participants, the researchers are faced with an important dilemma: what level of validity and what predictive value should a result have in order to be disclosed to the participants in their study? The answer to this question is rather subjective and depends on the decision-makers’ expertise in this field. Consequently, we believe that the researcher should not be the only party making this decision.

Another important factor to consider for both genomic and pharmacogenomic results is the excessively large amount of information [48] that may be transferred to study participants [17,26,46]. For pharmacogenomic results, some authors have limited their discussion to the transmission of adverse drug reactions [27]. This kind of result could indeed provide extremely important information when the prescription of this drug to the participant is being considered and could represent a manageable amount of information. Nevertheless, its relevance in the absence of intent to prescribe the given medication is questionable and represents only a fraction of the results that may be clinically relevant enough to be transmitted to participants. Indeed, an increasing amount of evidence points to the clinical utility of common markers associated with genes influencing drug pharmacokinetics and dosing requirements (e.g., CYP3A5 [47,48], CYP2C9 [47,49–53], CYP2CI9 [51,54–57], CYP2D6 [47,49] and SLC01BI [58]). These markers could represent an overwhelming and unmanageable amount of data for patients, researchers and healthcare professionals without access to the proper infrastructure. Moreover, as we are entering an era of gene sequencing related to the absorption, distribution, metabolism and elimination of drugs [47,57,59], information on hundreds or even thousands of SNPs could be generated as part of these experiments, even if limited to carefully selected absorption, distribution, metabolism and elimination genes. Undoubtedly, disclosure of such information directly from the researcher or a collaborating health professional to the participant would be impossible. The necessity of dealing with such large amounts of genomic and pharmacogenomic information in a clinical setting highlights the pressing need to develop tools that are able to provide this information in a usable format.

Since high-throughput commercial assays may be used in genomic and pharmacogenomic studies, such as genome-wide scans or whole exon sequencing [8], an enormous amount of genetic variations unrelated to the drug or disease that is being studied may be generated [46]. Also, a single gene can contain information about several phenotypes due to the phenomenon of pleiotropy [60], where one gene is responsible for several phenotypes [8]. A frequently mentioned example is the APOE4 allele [21,40] that contains both pharmacogenomic and genomic information. This allele may modulate the effects of statins [40,61] but is also associated with a risk of Alzheimer’s disease and heart disease [8]. Thus, for a study participant, the information generated as part of a pharmacogenomic study may have implications that are beyond the specific aims of the study, also referred to as incidental findings [8,23,24,62]. They are not related to the study’s objectives or hypothesis and consist of risks factors for different diseases [3,8]. The
Return of pharmacogenomic information

Potential consequences of disclosure

One of the main concerns regarding the return of genomic and pharmacogenomic information is the difficulty of respecting privacy and confidentiality in the disclosure process [13,41]. Authors state that in certain kinds of research, re-identifying samples does not respect this moral obligation of keeping results private [30]. Also, the lack of confidentiality of genetic information can lead to discrimination from insurance companies [10,13,37,63] or even potential employers [13,63]. Although Affleck mentions that there are existing antidiscrimination laws related to insurance and employment in certain countries [14], they do not necessarily fully protect the participant. For instance, they do not protect individuals against potential discrimination in life insurance, disability insurance, long-term care insurance [64,65] or incidentally gained information by employers [64]. Erwin goes so far as to state that for an insurance company, monetary sanctions for discrimination are less expensive than providing insurance for an at-risk individual [64]. Aspinwall points out that some of these laws still allow the company to set the rate of insurance [65]. Since pharmacogenomic information is also related to an individual’s future health, we cannot exclude the possibility that discrimination could also apply to pharmacogenomic results, even though this information could influence the use of a medication for a disease that the participant has not and may never develop. The impact that this information would have on the decisions that insurance companies or employers would make is unknown. Indeed, the Consortium on Pharmacogenetics gives the example of an individual who would not have any suitable medication in the event that they are diagnosed with a serious condition due to a lack of efficacy or severe adverse reactions. They explain that in such cases, an insurance company or an employer could classify the individual as ‘having an untreatable serious illness’ [102]. Therefore, it cannot be ruled out that disclosure of pharmacogenomic information could constitute an important risk for the research participant. The Report of the Secretary’s Advisory Committee on Genetics, Health and Society, issued in 2008 by the US Department of Health and Human Services: ‘Realizing the Potential of Pharmacogenomics: Opportunities and Challenges’ emphasizes the importance of balancing between the protection of the results and the access to the information that could lead to beneficial outcomes [106].

Second, one could question whether the adverse psychological and social consequences frequently mentioned by authors for general genomic results [8–10,26,37] may also originate from pharmacogenomic results. As the participant may not possess a sufficient amount of knowledge to correctly understand the information [6,10], they may have an excessive level of distress even if they do not require treatment with the specific medication. Although a pharmacogenomic result does not indicate an increased probability of developing the disease that is related to the test, the participant may still be worried about developing this disease because there would be no suitable medication for them in the event that they are diagnosed with the condition. Moreover, the Nuffield Council on Bioethics states that pharmacogenomic information is not necessarily ‘less ethically problematic’ as ‘it may also be an indication of a patient’s prognosis, either because it reveals that there is no effective treatment, or that the patient has a particular subtype of a disease, with a distinct prognosis’ [103]. A similar interpretation is given by the Consortium on Pharmacogenetics [102].

In fact, studies on patients’ and physicians’ views on pharmacogenomics in the clinic, such
as the survey conducted by Rogausch et al., demonstrate that 72% of patients are worried about the ‘lack of a suitable drug’ following a pharmacogenomic test. More specifically, 35.2% were very worried and 36.7% were slightly worried [66]. Similarly, in a study by Kumar and Gantley consisting of grounded theory interviews that addressed the issue of implementing genetic tests into clinical practice, results indicated that general practitioners are concerned with the possibility of having a ‘therapeutic gap’ in possession of genetic information but with no treating option [67]. In a survey that was recently conducted on pharmacists’ expectations of pharmacogenomics, results revealed that 41.6% of pharmacists were very worried or moderately worried about not having a suitable drug after getting the test result [68]. The possibility of such a therapeutic gap is certainly relevant to address the potential risks raised by pharmacogenomic information. In addition, the potential consequences of pharmacogenomic results on family relationships are uncertain. The psychosocial consequences may depend on the nature of the disease that is related to the pharmacogenomic result, the probability of developing this disease, and the availability of other drugs.

In addition to the risks that disclosure presents to an individual participant, it may also pose a risk for research as an institution. Disclosure of individual results would require a more complicated structure and more financial resources. As human, technical, and financial resources are limited, these increased financial demands may limit other research initiatives [9,69]. These issues are developed in the ‘Practical perspective’ section.

Despite these risks, disclosure of pharmacogenomic results may have enormous benefits for the participant, because the individual would know prior to treatment how they would respond to a specific medication. As a result, if the participant is diagnosed with the disease later on in life, health professionals would immediately have access to the results of the pharmacogenomic test that was conducted in a research study. They would then not need to perform the test, and the information would guide them in their choice of pharmacological treatment [70,71]. Nevertheless, one cannot know if the individual’s treatment would consist of that particular medication. The possibility of using pharmacogenomic data generated in a research context as clinical preemptive genotyping for future clinical use will be discussed in later sections.

### Which pharmacogenomic results should be disclosed to participants?

We consider that two fundamental criteria should be met in order to disclose the result of a pharmacogenomic test to patients: the clinical utility of the test is recognized, making it a standard of practice; the test results are currently relevant in the management of the patient. These concepts will be described in the following sections.

#### Clinical utility

In the process of selecting the appropriate information, we favor the scientific and medical value of the data. Scientific robustness is based on analytical validity, clinical validity and clinical utility. These concepts are also discussed by many other authors [8,9,16,18,21]. Their importance is also mentioned in the Report of the Secretary’s Advisory Committee on Genetics, Health and Society [106]. Indeed, although the current controversy takes place in a research context, choosing to disclose information is part of a medical decision and should therefore be based on whether clinical utility is established. Hence, the researcher’s priority during disclosure is to reduce an undesirable clinical outcome related to hospitalization, morbidity, mortality, and quality of life [72]. It is precisely the evidence-based approach used by professional societies that can determine the most accurate way the extent to which a pharmacogenomic result could prevent certain devastating consequences.

As with genomic results, pharmacogenomic information should be evaluated according to the scientific principles of analytical validity, clinical validity and clinical utility. Analytical validity, considered as the technical performance of the test [72], is defined as a result that is accurate and reliable [21]. Thus, an analytically valid test identifies a genetic mutation that is truly present in an individual’s genome and does not generate false-positive or false-negative results [18]. This component is essential because inadequate decisions based on analytical error could translate into a decrease in efficacy, an increase in adverse events [27] or errors in dose adjustment. Clinical validity means that the association between the genotype and the phenotype is strong enough to be predictive of clinical outcome [21]. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group defines it as the ability of the test to diagnose a disorder, assess the susceptibility of the risk, or provide information on prognosis in drug response [72]. Clinical utility refers
to the usefulness in a person’s life of knowing a genetic result. This last quality determines the ability of the test to change patient management decisions and improve net health outcomes [72].

EGAPP presents very accurately these tools as a chain of evidence, where strong analytical validity can potentially lead to significant clinical validity, which, if the benefits can overcome the risks, can result in clinical utility [72]. An important element arising from these concepts is that of actionability. The NHLBI qualify a result as being actionable when there is possible therapy, prevention or other actions that could modify the course of the disease [35]. For genetic results, the possible actions after disclosure may include treatment, prevention, lifestyle changes and reproductive decisions [10] that can change the clinical course of a disease [30]. For pharmacogenomic results, actionability involves choosing to treat or not to treat the individual with the related medication or adjusting the dose [73].

Although such organizations as the NHLBI have outlined a few conditions for returning results, they have not established a threshold of utility [35]. Other authors also mention this problem [27]. The Report of the Secretary’s Advisory Committee on Genetics, Health and Society briefly describes the qualifications that the associations should have in order to be implemented into the clinical setting: the information must “be appropriate; alleviate a problem involving a patient’s health, functioning or well-being; be in accordance with accepted medical practice; and not be investigational, experimental or educational” [106].

We believe that just as medical decisions made by the treating health professional in a clinic are based on a scientific consensus of professional societies, so should researchers follow these same recommendations in the selection and disclosure of pharmacogenomic or genomic information to the participants in their studies. As such, disclosure should be considered only once the clinical use of this information has been formally recommended by professional societies. Depending on the phenotype that is associated with the genetic information under examination, the consensus could come from such professional associations as the American Heart Association (AHA), or the American Society of Clinical Oncology (ASCO). Researchers could also follow the recommendations of the EGAPP Working Group or the guidelines of the Clinical Pharmacogenetics Implementation Consortium (CPIC). Consequently, only results that have been validated and recognized as being clinically useful by the experts in a certain disease would be disclosed to participants. This kind of rigorous assessment minimizes the subjectivity of the selection process. It also insures that participants obtain valid medical information that has been demonstrated to be important enough to be recommended as a standard of care.

Relevance

Beyond establishing the clinical validity and utility of a test, an additional element must be considered, that of clinical relevance [13,27,73,105]. Indeed, although the clinical utility of a test may be established in a given patient population, it may not necessarily be relevant for an individual person at a given time in their life. This fact has been highlighted by the Consortium on Pharmacogenetics: “what counts as sufficient accuracy will vary contextually; sound judgement will be required to determine how accurate the information must be before the researcher is obliged to disclose it to the subject” [102]. We must note that here, once again, there is no consensus on the situations in which a result could be relevant. The difficulty of defining clinical relevance has been mentioned by the Nuffield Council on Bioethics [103]. Dressler argues that pharmacogenomic results about potential adverse events may always be actionable, in part because they will usually be obtained from participants who are already diagnosed with a disease: “The pharmacogenomic adverse event 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” [27]. Depending on the different types of studies, this is not always the case. A participant can be a healthy individual or a patient for whom the pharmacogenomic information is not immediately useful. In addition, a study using a broad-based approach can produce many pharmacogenomic findings that, once again, will not necessarily be relevant for the participant. We believe that pharmacogenomic information about a specific medication is relevant only when the use of this drug is being considered. Even for the treatment of those patients who do have the disease that is connected with the pharmacogenomic result, the use of that specific drug may not always be considered. For example, the patient may present a contraindication to the drug. Therefore, the information may still be irrelevant and the return of these results would only expose the patient to unnecessary risks, such as those described previously in the section ‘Potential consequences of
disclosure.’ As such, we conclude that, in general, only pharmacogenomic information that is relevant to the participant’s current or foreseen therapy should be disclosed in a research environment. Conversely, the considerably vast amount of pharmacogenomic data which is only ‘theoretically actionable’ and of no immediate benefit to the patient should not be returned to them.

To illustrate this point, we will consider the example of a participant in a cancer pharmacogenomic study and the results of a genetic test that screens for the HLA-B*5701 allele. The variant predicts a hypersensitivity reaction to abacavir, an antiretroviral medication used to treat patients with HIV. The clinical utility of this test has been demonstrated in a randomized clinical trial [75,76]. Specifically, the test has 100% sensitivity and 100% negative predictive value. Hence, healthcare professionals can safely treat individuals who do not present this variant with abacavir, with minimal risk of developing the hypersensitivity reaction [75,76]. Accordingly, in the drug’s monograph, screening for the HLA-B*5701 allele is recommended before starting treatment [107]. Furthermore, its use is recommended in clinical guidelines [77] and is widely used for the treatment of HIV in clinical practice. Since the association is fully validated, testing the allele and disclosing it to the patient becomes part of the treating physician’s responsibility in the clinical setting, because conducting this test is part of routine clinical practice. In other words, it is the treating physician who has the professional and ethical obligation to conduct the test. The Consortium on Pharmacogenetics precises that it is the physician’s duty when the test is mandatory according to the drug label [102]. In such an environment, the test can be prescribed when it is necessary and the results can be conveyed by qualified personnel, thereby maximizing the clinical utility of the information. By contrast, this allele has not been established as a risk factor for any other adverse drug reaction, for drugs that are available in North America. Therefore, making a patient participating in a cancer pharmacogenomic study aware that they are a carrier (or not) of this allele serves no purpose if they do not have HIV.

Thus, since pharmacogenomic results are relevant only at the time at which the medication is being prescribed, we consider that pharmacogenomic information should only be revealed in the context of a research project if it is relevant to the patient’s current or foreseen treatment.

One could argue that revealing a pharmacogenomic result would have a benefit if the individual has an existing disease or is at risk of developing that specific condition. For instance, knowing that a given individual is a carrier of CYP2C19*2 may be relevant for someone who is at risk of heart disease. Indeed, this polymorphism has been associated with a decrease in the transformation of the antiplatelet drug clopidogrel to its active metabolite. When treating a patient for an acute coronary syndrome, the existence of this allele leads to an increased risk of cardiovascular events following a percutaneous coronary intervention [70,78]. However, even in such cases, the predictive value of risk scores that are used to predict the occurrence of cardiovascular diseases are so limited [79-81], and the treatment options so diverse [82], that it would be virtually impossible to identify all of the individuals for whom the information would actually be useful, once again, exposing many individuals to unnecessary risks.

Considering the impact that pharmacogenomic variations can have on drug response, we cannot ignore the fact that certain polymorphisms present a high likelihood of affecting a participant at some point in their life, as some genes encode for isoenzymes responsible for the metabolism of multiple drugs. For example, it has been estimated that CYP2D6 is responsible for the metabolism of 25% of drugs, including commonly used drugs such as codeine, metoprolol and tamoxifen [83,84]. Thus, there is a high likelihood that during their lifetime, a participant would be prescribed a drug that is metabolized by this isoenzyme. Once the clinical utility of genotyping for CYP2D6 is established, disclosing information on the genotype of CYP2D6 may be beneficial for the participant. In such cases, disclosure of results would be used, at a later time, as a guide for treatment with one of these drugs. However, as discussed in the following section, simply informing the participant of their genotype would not meet clinical standards and the transmission of such results should be performed with educational resources regarding the significance of these results, as well as a clinical interpretation [12,21,109]. These interventions must be relevant to the participant’s situation; they must take into account drug–drug interactions, contraindications and other clinically relevant information. It is not possible to satisfy these requirements by simply performing pre-emptive disclosure of pharmacogenomic information. An exception to these requirements would be a genetic variant that puts the patient at a high risk of a severe adverse reaction. In such a case, the clinical interpretation is unlikely to change over time and the risks of using the associated drug would probably always outweigh its benefits.
One could argue that pharmacogenomic research results could be used as a method for pre-emptive genotyping [85,86], which has been proposed for clinical practice. This method would consist of prospectively genotyping individuals on many pharmacogenomic variants and entering this data into the patient’s electronic health records (EHR). Thus, in the event that the prescription of a certain drug is being considered, the health practitioner could consult specifically the information that is related to the personalized response to the desired medication [86]. Unlike pre-emptive disclosure, pre-emptive genotyping would have the advantage of minimizing the amount of information that one would need to transmit to the patients because a result concerning a specific variant would be returned to the participant only once it becomes relevant. Pulley et al. discuss the potential implementation of prospective genotyping programs in the clinical setting where communication between different health professionals is organized and systematic [88]. This necessity of collaboration between clinical laboratories and drug-dispensing departments is also mentioned by the National Academy of Clinical Biochemistry [109]. EHR will undoubtedly be crucial in the implementation of these services, as they allow storing mass amounts of (genetic) information. They could also be useful in the incorporation of decision support tools [106]. Given the fact that pharmacogenomic information does not change during the course of a lifetime, such an approach is likely to be widely adopted in clinical practice as part of the process of implementing personalized medicine into clinical care. However, such programs are being designed for long-term use of pharmacogenomic information in a clinical environment rather than the research setting. In the latter, as funding is generally provided for a limited amount of time, it is unlikely that the implementation of pre-emptive genotyping in the context of a research project could be useful for long-term care, unless such information can be readily transferred to a clinical laboratory. Coordination between healthcare providers, product developers and researchers will be paramount in the development of the EHR or other infrastructures [106]. This level of standardization could lead to the clinical use of pharmacogenomic data generated from research projects, particularly if this information is to circulate between a central laboratory and multiple clinical centers.

Similarly, disclosure might be contemplated if a relevant pharmacogenomic test would not be available to the patient in a clinic. It would have to be reasonably expected that it could become clinically useful to them in the future [31,87]. The availability of the test could depend on a country’s level of development and healthcare system, as well as the individual’s insurance and financial situation. Disclosure in a research project could then offer information to the participant that they would not be able to access at a later time when it could become relevant, if they develop the disease. Yet, once again, in practice, it is virtually impossible to anticipate these kinds of different scenarios.

Practical perspective
The necessity of establishing a valid purpose for revealing a result is important not only from a medical standpoint but also from a practical perspective. Many of the difficulties that authors discuss in genomic research are just as relevant in pharmacogenomic studies.

First of all, disclosure of pharmacogenomic results would have to be part of the consent process [102,103], which would have to be conducted wisely. The Consortium on Pharmacogenetics states that the consent form should provide information on who would be responsible for determining the reliability and the benefit of the result. We would follow the recommendations of Renegat et al. as well as Kollek and Peterson’s recommendation of using a two-step consent process. At the beginning of the study, the subjects would consent to having the results returned to them. Once the results become available, the participants would consent again before they are revealed to them [12,13]. The decision may become even more difficult for the participants when the result is not immediately relevant to them, which may often be the case for pharmacogenomic results, particularly for studies conducted on healthy individuals. We must then wonder whether it is necessary to ask participants to make such complex decisions about information that is not currently relevant to their health.

Authors often discuss the question of feasibility [88] because disclosure requires more resources [10,18] and may, therefore, significantly increase the costs of a study [17,43,69]. This increase is due to many influencing factors. First of all, the investment of time [9,14,37], not only for disclosure, but also for follow-up and genetic counseling [10,37], can be costly. Moreover, if research results are returned to participants or treating health professionals, the manner of feedback should satisfy clinical requirements. The Nuffield Council on Bioethics points out that in the process of disclosure: ‘the nature and implications of the information to be
obtained should be explained to participants’ [103]. The National Academy of Clinical Biochemistry recommends laboratories that return results to provide ‘educational resources to recipients’, more particularly, consultation [105]. They also mention an additional element of complexity in the interpretation of results when they refer to patient-specific drug–gene interactions. Indeed, it is important to know the patient’s current treatments in order to anticipate whether another drug from the patient’s regimen would modify the phenotype that is associated with a specific genotype [105]. For instance, the antiarrhythmic drug amiodarone is an inhibitor of CYP2C9. When used in combination with the anticoagulant drug warfarin, it inhibits the CYP2C9 metabolism of S-warfarin to S-7-hydroxywarfarin [89]. Thus, although a ‘normal metabolizer’ would be expected to benefit from higher doses of warfarin than a carrier of a variant associated with decreased metabolism, a clinical interpretation is necessary when suggesting a dose. Existing data clearly show that such a comprehensive approach is superior to predict warfarin dosage than simply using an individual genotype [90]. Second, the change in logistics also has a financial impact [37]. Another problem is the fact that many research laboratories do not use the required methodology and do not have the qualifications that clinical facilities must have in order to disclose their test results [103], such as CLIA certification [13]. Consequently, re-testing in CLIA-certified laboratories (or laboratories with equivalent local qualifications) may be necessary. This requirement may constitute a significant financial burden in pharmacogenomic or genomic research. As such, it may also be a significant limitation to returning research results to participants [9, 21, 26]. Even more importantly, disclosure can be practical only if the research results can be readily transferred back to the individual [37]. This task becomes particularly difficult when there is a great quantity of pharmacogenomic data that could be interpreted, or a complicated coding system.

While some of these obstacles appear feasible for single center studies, they present a significantly greater problem in large multicenter studies. The NHLBI recommends that investigators make their decisions with the help of institutional review boards (IRBs) and a central advisory board consisting of certain experts [35]. Although it may be possible to follow this recommendation in large or academic centers, small participating centers will not always have the means to use this kind of sophisticated structure. In addition, these centers will not necessarily have the qualified personnel to interpret the results and perform the duty of disclosure to participants. Likewise, they may not possess the tools to maintain confidentiality.

Although databases could be designed to return data to local investigators when results are generated in a central laboratory, the increase in costs related to the development of such database software and logistics [37] could be exorbitant. Moreover, in this novel structure, it would be more difficult to assure complete confidentiality and more measures would then have to be put in place in order to guarantee it [37]. A contact would have to be kept between the research team and the participant in order to be able to re-contact [38] the person. This association would be difficult to keep for a long period of time [37]. As such, one must observe that a considerable amount of resources and money would have to be invested into disclosure instead of research [14, 38, 69]. Many authors have suggested that researchers integrate the costs of disclosure into their research budget and grant application [1, 8, 9, 16, 21, 26]. Yet, such growth in cost may prevent these and other potential researchers from carrying out their research due to the limited resources of funding agencies.

**Conclusion & future perspective**

Based on the previous arguments, we have developed conditions that should be met before disclosing pharmacogenomic information to a study participant. We also explain, in light of distinct characteristics, how the differences between pharmacogenomic and other genomic or genetic information change the way that the results respect these conditions. In accordance with other authors’ views, our ultimate goal is to maximize benefit for participants while minimizing the risk of exposing them to the negative consequences of useless and potentially harmful information [10, 13, 38, 63], such as described in the ‘Potential consequences of disclosure’ section. The decision-making process must be as pragmatic as possible.

First, the participant must have consented to receive the pharmacogenomic information. While the obtainment of such consent may be challenging, proposals have been made to help researchers and IRBs in the elaboration of appropriate consent forms [12, 13]. It would require a two-step consent process where the participant would consent to the return of the results at the beginning of the study, and would then reaffirm this decision at the end of the study when the results become available. Second, the clinical utility of the pharmacogenomic marker must be recognized by a professional society, since the consensus would imply that the test meets clinical standards.
Third, the test must be clinically relevant for the participant at the time at which the result is obtained. The third condition distinguishes the disclosure of pharmacogenomic results from that of genomic results. While genomic results associated with disease susceptibility may be useful throughout an individual’s life to prevent the onset of a given disease or decrease its severity, the utility of pharmacogenomic results is linked to the use of a drug. Therefore, pharmacogenomic results respect the third condition if they identify a genetic variant that may interact with a drug that is currently prescribed or will likely be prescribed to the participant at some point in their life. Fourth, the genetic analysis must be performed, or validated, in a CLIA-certified laboratory or a certified laboratory based on local regulations, using a validated clinical approach, such as that described by the National Academy of Clinical Biochemistry [105]. Fifth, all measures should be taken for the information to be transferred to the participant and kept in a confidential manner. Sixth, disclosure should be provided by a qualified health professional with appropriate education and clinical recommendations based on the patient’s current status.

We must emphasize the fact that, ideally, pharmacogenomic information that would meet the first four conditions should be disclosed to participants. However, the fifth and sixth conditions may impede the feasibility of disclosing the results. Indeed, fulfilling these last requirements may not be a problem for small single-center studies involving a few genetic variants. On the other hand, respecting these conditions may be a significant challenge and a financial burden in multicenter studies that include a large number of participants or a large amount

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### Executive summary

**Background**

- As the clinical utility of genomic tests in research is being recognized, returning these results to study participants is becoming part of a growing debate.
- Few guidelines and articles in the literature address the return of individual pharmacogenomic research results. Instead, most documents focus on disclosure of genetic research results.

**Current guidelines**

- Guidelines developed by organizations focusing on the disclosure of pharmacogenomic research results do not present a clear distinction between the return of genomic and pharmacogenomic information.
- Most guidelines pertaining to the return of individual genetic results require the participant’s consent and consider the option of disclosure when the result is actionable through therapy or prevention. The aim is to maximize benefit and minimize harm.
- A CLIA-certified laboratory is mandatory in the USA for quality control.

**Characteristics of pharmacogenomic results**

- In contrast with a genomic result that can be useful throughout a person’s life, the relevance of a pharmacogenomic result depends on the use of the drug of interest.
- Both genomic and pharmacogenomic results are probabilistic and generate a large amount of data. In both cases, the data may contain incidental findings that would be difficult to interpret and communicate for the researchers and clinicians.

**Potential consequences of disclosure**

- The return of pharmacogenomic results may raise risks that are similar to those that are found in the return of genomic results, such as stigmatization and loss of privacy and confidentiality.
- Disclosing pharmacogenomic results can benefit the participant by improving the management of their condition.

**Which pharmacogenomic results should be disclosed**

- Pharmacogenomic results must meet the standards of clinical utility.
- Disclosing a pharmacogenomic result is relevant only in the case in which the participant is being prescribed or is likely to be prescribed the drug of interest.

**Practical perspective**

- Proper informed consent must be obtained.
- The clinically relevant test must be performed in a certified laboratory.
- Disclosure must be performed in a confidential manner by qualified personnel.

**Conclusion & future perspective**

- Disclosure requires: consent from the participant, recognition of the test by a professional society, clinical relevance at the time at which the result is available, a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory or an equivalent, protection of privacy and communication by qualified personnel. In the coming years, these considerations should be incorporated into research guidelines.
of genetic information that has to be transferred. As previously mentioned, the responsibility to develop the standardized infrastructures to share and interpret these results should not fall exclusively on the researchers, but it must be shared by research and healthcare institutions, product developers and funding agencies.

Once these conditions have been met, disclosure ‘packages’, a term used by some authors [10], should be developed. They would describe which pharmacogenomic information would be returned and in what manner. An important step would then be to submit these packages to the research team’s IRB. Only after the approval of the packages by the IRBs could disclosure happen. In our opinion, IRBs could also determine who would be involved in the disclosure process.

In conclusion, after conducting a review of the scientific literature, we have outlined the circumstances in which pharmacogenomic results should be returned to research participants. In upcoming years, as more pharmacogenomic tests become clinically useful and formally recognized by professional societies, specific recommendations for the disclosure of such information should be incorporated into existing guidelines and regulations.

Financial & competing interests disclosure
S de Denus is a Scholar of the Fonds de recherche du Québec – Santé and holds the Université de Montréal Beaulieu-Saucier Chair in Pharmacogenomics. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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** of considerable interest

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