JPPT

Editorial

Ethical Issues in Pediatric Pharmacogenomics

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INDEX TERMS ethics, pediatrics, pharmacogenomics

J Pediatr Pharmacol Ther 2013;18(3):192–198

INTRODUCTION

Over the last several years, the field of pharmacogenomics has moved into an ethically complicated, if temporary, situation. Evidence is accumulating that certain applications of

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pharmacogenomics are "ready for prime time." Five years ago there were already 10 drugs for which the Food and Drug Administration recommended or required the use of a pharmacogenetic test,[1] and recent data indicate that prescribers are increasingly ordering such tests.[2–5] Pharmacogenomic applications are also finding their way into pediatric practice. In this edition of the Journal, Lala et al.[6] reports findings that will help improve the dosing of warfarin in children through the use of a pharmacogenomic test. As a result of this and work on other drug-gene pairs, a number of sites have recently implemented programs to provide prospective, multiplex genetic testing for use in pediatric pharmacogenomic applications.[7,8]

Despite this progress in the realm of pharmacogenomics, it remains unclear how best to manage the nonpharmacogenomic results that may be generated through pharmacogenomic testing. Consider, for example, the remarkable controversy that has arisen in the wake of the recent recommendations from the American College of Medical Genetics (ACMG).[9-11] According to these recommendations, variants in 56 genes are considered pathogenic and should therefore be reported to patients when discovered incidentally through genomic testing. This recommendation is intended by its authors to apply regardless of a patient's age or preferences about learning incidental findings.[10]

To be sure, the risk of incidentally producing one of these 56 findings through focused pharmacogenomic testing is low. Consider, for example, that none of the 56 genes on the ACMG "minimum list" are also listed among the 301 genes on the extended list of pharmacogenomic-relevant genes produced by the PharmaADME group.[12] However, it is clear that genetic testing focused on pharmacogenomic applications can still produce a significant number of ancillary findings.[13] And it is also clear that the use of technologies such as whole genome and whole exome sequencing for pharmacogenomic applications could produce a great number of ancillary results.

Controversy over the recent ACMG recommendations demonstrate that there is still no consensus on how pharmacogenomic testing programs should manage incidental, nonpharmacogenomic results. This observation is strengthened by the fact that even the most experienced sites are still searching for the best way to return nonpharmacogenomic results in a way that is efficient, effective, and compatible with other important health interventions.

At present, the ethical challenges surrounding pharmacogenomic testing in both research and clinical settings are dominated by issues related to incidental, nonpharmacogenomic results. This tension is unfortunate, because this unresolved debate weighs heavily on the other ethical issues that need to be addressed in efforts to deliver pharmacogenomic testing in clinical and research settings. First, the debate on how best to manage

incidental findings seems at times to dominate the discourse to the point that other ethical issues do not receive much attention. Second, and more importantly, the solutions we might select for many ethical challenges in pharmacogenomics depend on plans related to the management of nonpharmacogenomic results.

At this point, then, it is important to the effective implementation of pharmacogenomics to identify the downstream ethical issues that arise in pharmacogenomics, with a focus on clarifying how the relevant solutions will look different in situations where nonpharmacogenomic results will be returned compared with situations where only pharmacogenomic results will be returned. In this editorial, I will raise a number of ethical issues that can and do arise when pharmacogenomic testing is performed, with a focus on those issues unique to pediatric settings. Given this format, I cannot be comprehensive. But perhaps it will be helpful to the development of effective pediatric pharmacogenomic projects simply to draw attention to the diverse set of issues that still face us, especially since the dominant ethical challenge in the implementation of pediatric pharmacogenomic testing remains unresolved.

INFORMED CONSENT

Nonemergent clinical interventions, including pharmacogenomic testing, can only be performed when proper consent has been obtained. However, the approach to consent that is appropriate in different situations can vary widely. When surgical interventions are planned, the informed consent process that is undertaken addresses risks and benefits both verbally and in writing. The patient is then able to ask questions and document her consent in writing. More routine forms of medical care utilize verbal or implicit approaches to informed consent. When providers order laboratory tests or radiographic studies, they usually explain to the patient why this is being recommended. The patient then signifies her consent verbally. Sometimes, the patient's consent remains implicit. In such situations, the patient will signify her consent by participating in the procedures performed in the radiology suite or phlebotomy lab.

Depending on the situation, the approach to consent appropriate for pharmacogenomic testing could vary from implicit or verbal consent to more formal written consent. At least 3 factors will influence this decision. The first is related to the regulatory requirements for consent that apply uniquely to research settings. When pharmacogenomic testing is performed under the rubric of human subjects research, regulations in the United States and elsewhere usually require a written consent process. There are a number of resources available that provide guidance on how to carry out written consent for a research study involving genomic testing.[14]

When pharmacogenomic testing is being performed outside the research setting, however, there is no reason to expect that patients and providers should treat it differently from other routine blood tests. This is especially the case when the effectiveness of the testing being performed is supported by clinical trials or other empirical evidence. Ideally, patients and providers will discuss the indications for such testing and how the results will be handled. Verbal consent by the patient should be adequate.

Despite this analysis, laws in a few states currently preclude the use of verbal consent for pharmacogenomic testing. These statutes require written informed consent prior to genetic testing for any purpose.[15] However, as genetic testing becomes more routine across a range of settings, these statutes and the genetic exceptionalism they embody are likely to seem both unjustified and unworkable to state legislatures. It is likely that many of these laws will undergo revision in the coming years.

This distinction between clinical and research settings creates a unique situation for consent to translational research. Studies looking at the integration of pharmacogenomic testing into routine clinical care might need to simulate the verbal consent often used in clinical settings in order to generate findings relevant to real-world situations. However, the usual requirement is that research should utilize written consent procedures. Fortunately, local institutional review boards have the authority to waive the requirement for written consent in cases where a research study could not practicably be carried out without a modified consent process.[16] Translational research of the T3 or T4 variety, in which real-world situations need to be simulated, might meet this requirement in certain situations.

The second factor that will influence the design

of an informed consent process for pharmacogenomic testing is the approach planned for managing nonpharmacogenomic findings. In cases where pharmacogenomic programs are interested in returning nonpharmacogenomic results, written consent is arguably still required. This is because there is still a great deal we do not know about the risks and benefits of incidental findings. Until those factors are better understood, and until they are more readily apparent to patients themselves, institutions seeking to return nonpharmacogenomic results will need to provide patients with a detailed consent process.

The third factor that influences the type of consent process appropriate for pharmacogenomic testing relates to the developmental stage of the patient undergoing testing. In settings where a child is to undergo pharmacogenomic testing, and the factors mentioned above create the need for a written informed consent process, the child's parent or guardian will need to provide the written consent required. This is true regardless of the child's age, except in very limited situations.[17]

Even though the parent's written permission is required, the child should also be provided with developmentally appropriate information about the testing. For young children—perhaps those younger than 7 year of age—the proper information is probably limited to an explanation of how the sample will be collected. This information should be provided in terms the child can understand. Since children at this developmental stage cannot understand the risks and benefits of pharmacogenomic testing, it would be developmentally inappropriate to ask them for their permission to perform this test.[18] Nonetheless, their refusal to allow a sample to be collected could be definitive if their resistance makes it impossible to collect a sample safely.

Children who are old enough to understand the risks and benefits of testing should be asked for their assent to perform pharmacogenomic testing. Many offer the opportunity to provide assent starting at age 7, but it is probably best for providers or researchers to use their judgment, combined with the insights of the parent, to decide when a child is ready to engage in an assent process. When children are ready developmentally, involving them in the decision-making process not only demonstrates respect for their developing autonomy, it also can help them develop the knowledge and skills necessary to one day make decisions on their own. For some older children in this group, the appropriate information is likely to be exactly the same as that provided to the parent, since some adolescents are ready to receive information intended for adults. Younger children will need an explanation tailored to their developmental level.

When the parent is asked to provide written informed consent, either because the testing is taking place in a research setting or incidental findings will be returned, children should be asked to provide assent in writing. If the child is old enough to understand a verbal explanation but is not yet able to read an assent document, verbal assent is more appropriate. When parents are asked simply to provide verbal consent to pharmacogenomic testing, then the verbal assent of the child is also acceptable.

Unfortunately, it is beyond the scope of this overview to consider the complex situations that can arise when either a child or a parent agrees to an intervention while the other refuses.[19] However, it is worth noting that even as pharmacogenomic testing increasingly becomes a part of the standard of care, it will still be rare for circumstances to arise that would require testing to be performed over the objections of either a parent or an older child. Such measures are generally appropriate only when omission of testing threatens to cause imminent harm to the child.[20]

IMPLICATIONS FOR FAMILY MEMBERS

As with any genetic test, pharmacogenomic testing raises the possibility that results will carry implications for family members. For example, a pharmacogenomic test of a patient may lead to the discovery of a variant indicating a significant risk for the development of a preventable condition, including an adverse effect from a medication. The discovery of this result in one person often indicates that her biological relatives are also at risk for carrying this variant. Some have argued that the opportunity that this situation creates to provide benefit to family members can in certain circumstances create a duty for the physician to inform the family members of the risk.[21]

Although it is true that health professionals are obligated to protect third parties from harm in a number of circumstances, it is not at all clear that this obligation would apply in the vast majority

of cases having to do with genetic risk. First, any duty to protect a third party including a family member would need to be balanced with the confidentiality of the patient.[22] This concern is particularly important in genetics, where certain findings are likely to be considered stigmatizing by patients. Patient confidentiality is protected under the law, including by the Health Insurance Portability and Accountability Act (HIPAA). The Privacy Rule component of HIPAA probably prohibits the release of genetic results to family members without the express permission of the patient.[23]

A second factor limiting any duty to warn a family member involves the practical limitations of the health care provider or researcher. Providers do not always have enough information about a patient's family in order to be able to recognize who might be at risk. This factor explains, along with concerns about confidentiality, why the Florida Supreme Court hearing the case *Pate vs. Threlkel* concluded in 1995 that any duty providers might have to warn about genetic risk to family members would be satisfied by informing the patient.[24] To require a provider to identify and warn all potentially affected family members would create an unreasonable burden on the provider. This challenge only increases as pharmacogenomic testing begins to be utilized for medications that are used by a great number of patients. As this new situation develops, it is likely to be unworkable for providers to inform the family members of every patient who has a variant conferring increased risk. This limitation is not only legally relevant, it is also ethically relevant.

A third factor that limits the scope of a duty to warn family members is the foreseeability of adverse medical events. Just because a patient has a high-risk genetic variant does not mean that her family member will experience an adverse event. The net risk to the family member is a function of the likelihood that the family member carries the relevant variant (which is determined by the heritability pattern of the variant) and the penetrance of the trait. For many incidental findings generated by pharmacogenomic testing, the risk resulting from this combination of factors is likely to be quite low. Most of the related legal cases, such as the well-known Tarasoff case, involved adverse events that were far more foreseeable by the involved providers.[24]

From a practical perspective, then, the implications of this proposed duty can be difficult for providers and patients to navigate. They are left to balance any benefit that might be provided to family members with the confidentiality of the proband and the effort required to provide results to family members.[25] The analysis of this tension is influenced by factors similar to those analyzed earlier in our discussion on approaches to consent. The distinction between pharmacogenomic results and incidental, nonpharmacogenomic results is relevant here, as are the special circumstances that arise in pediatric settings.

First, the challenges posed by results that are relevant only to pharmacogenomic applications are likely to be less complex than those posed by nonpharmacogenomic results. In the short term, pharmacogenomic testing remains limited to research settings and clinical pilot projects, and is not likely to be available to family members who are not involved in such programs. During these early stages of translation if a heritable, highly-penetrant pharmacogenomic variant is identified, then the provider and the patient could have an ethical duty to inform family members of this. However, the case for such a duty would only be compelling in cases where there is reason to believe a family member is taking or will take a relevant medication. When it is anticipated that such a circumstance could arise, this possibility should be discussed with patients and their parents prior to testing. Fortunately, most patients are likely to respond favorably to this possibility, since few will consider pharmacogenomic results to be highly sensitive or stigmatizing. However, one could imagine scenarios when such information could be considered sensitive by a patient, such as when the discovery of a genetic variant indicates that a much more expensive medication would be needed.

In the long term, however, the obligation to inform family members of pharmacogenomic results will decrease. As such testing becomes part of the standard of care, patients and providers will be increasingly justified in assuming that any relatives taking medications will have undergone the proper testing. In this situation, the duty to notify relatives is significantly mitigated.

Much more extensive concerns are raised by the implications nonpharmacogenomic findings could hold for family members. There are a number of such results that patients could

reasonably consider sensitive, including variants demonstrating an elevated risk for developing serious illnesses and misattributed paternity. This observation highlights the importance of confidentiality for the patient undergoing testing. As noted above, the foreseeability of adverse events is also relevant. Very few genetic variants currently known are both highly penetrant *and* reveal risk that is preventable, and even fewer are urgent in this regard. For this reason, it will be uncommon for a genetic variant revealed incidentally through pharmacogenomic testing to meet the standard required to create a duty to notify family members.

However, as pharmacogenomic testing increasingly utilizes whole exome or whole genome technologies, this challenge is going to arise occasionally. This is 1 reason that a careful informed consent process is recommended when plans for pharmacogenomic testing also involves plans to return incidental findings. Patients need to be informed of the possibility that information relevant to family members could be produced. They also need to be provided with information about the approach that will be taken should such information be discovered.

In the setting of pediatric pharmacogenomic testing, these challenges could be simplified in certain ways. The discovery of a high-risk genetic variant in a proband is most relevant to his or her first degree relatives. In many pediatric cases, then, all of the family members most affected by a child's genetic test results will live in the same household. Since the parents are often the proper adults to receive these results, they will have the opportunity to consider the implications of this information for themselves and for their other children.

Of course, there are still a number situations in which potentially affected first degree relatives of a child do not live in the same household. These situations include children who have adult-age siblings who live on their own, children with parents who are separated, children in foster care, and children who have been adopted. In these situations, the confidentiality of the child significantly restricts the obligation to inform family members. Parents or guardians may still decide to inform biological family members of results that could be relevant to them. But this action should only be taken with careful consideration for the best interests of the child.

PEDIATRIC ETHICS AND THE FUTURE OF PEDIATRIC PHARMACOGENOMICS

Recent work has shown that pharmacogenomic testing has the potential to both mitigate health disparities based on race and ethnicity[26] and also exacerbate them.[27] The same will arguably be true for the impact of pharmacogenomics on disparities between adult medical care and pediatric medical care. Pediatric drug development has posed a range of challenges over the years, with the net effect being that children are often treated with medications that have been inadequately tested in the pediatric population.[28] If the trend toward performing drug studies primarily in adults continues in the pharmacogenomic era, then these disparities could worsen. On the other hand, pharmacogenomics provides one promising opportunity to improve the suitability of medications for children.[29,30] It will be important, then, to not only balance research in adult and pediatric populations, but to actively pursue research efforts that are specially adapted to the issues relevant to pediatric populations.

Unfortunately, ethical concerns like those explored above have in the past been identified as a barrier to performing clinical trials in children.[31] While the significance of this concern can be doubted, we can at least agree that the complexity of pediatric ethics can be daunting for investigators. It is important, then, that ethicists and investigators in pediatric therapeutics work together to anticipate and clarify the ethical challenges that will arise in pediatric pharmacogenomics. If we are able to develop responses that are both workable and ethically appropriate, we should be able to make pediatric drug treatments safer and more effective, even as some ethical challenges remain unresolved.

DISCLOSURE The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

ACKNOWLEDGMENTS I would like to acknowledge the contribution of Mark Rothstein (University of Louisville) who provided helpful comments on a draft of this manuscript. This work was funded in part by the project "Genomic Diagnosis in Children with Developmental Delay," NIH/NHGRI grant 1UM1HG0007301-01.

ABBREVIATIONS ACMG, American College of Medical Genetics; HIPAA, Health Insurance Portability and Accountability Act

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