

THE COMMUNICATION OF PHARMACOGENETIC RESEARCH RESULTS: PARTICIPANTS WEIGH IN ON THEIR INFORMATIONAL NEEDS IN A PILOT STUDY

Parvaz Madadi^{1,2}, Yann Joly³, Denise Avard³, David C Chitayat⁴, M Anne Smith^{5,6}, Colin JD Ross^{6,7}, Bruce C Carleton^{5,6,8}, Michael R Hayden^{6,7}, Gideon Koren^{1,2}

¹Division of Clinical Pharmacology and Toxicology, ²Motherisk Program, Hospital for Sick Children, Toronto, Canada; ³Centre of Genomics and Policy, Department of Human Genetics, McGill University, Montréal, Canada; ⁴Prenatal Diagnosis and Screening Program, Mount Sinai Hospital, Toronto, Canada; ⁵Pharmaceutical Outcomes Programme, British Columbia Children's Hospital; ⁶Child and Family Research Institute, Children's and Women's Health Centre of British Columbia, Vancouver, Canada; ⁷Department of Medical Genetics, Centre for Molecular Medicine and Therapeutics, University of British Columbia, Vancouver, Canada; ⁸Dept. of Pediatrics, Faculty of Medicine, University of British Columbia

ABSTRACT

In this brief investigation, the informational needs of research participants [n = 62; mothers who had breastfed, taken codeine, and participated in a pharmacogenetic study] were probed during a counselling session in which they received their *CYP2D6* pharmacogenetic research results and overall study results. In addition to the standard information, developed by a multidisciplinary team and provided to the participants, 38% of individuals had further questions related to potential adverse effects in babies, future codeine or medication use, heredity, and consequences for policies and programmes. The diversity and complexity of the questions raised support the need to communicate the results in the context of personalized genetic counselling information sessions.

Key Words: *Pharmacogenetics; research results; communication; codeine; CYP2D6*

There has been a recent school of thought in favour of disclosing individual research results to participants.¹ This position has been questioned by some researchers who feel that the existing policies, as well as the nature of the ethical debate, do not warrant the adoption of a definite stance at this point in time.² However, those involved in this debate have paid little attention to the participant's opinion and views on this topic.

The issue of communicating research results is particularly applicable to translational research in pharmacogenetics. It is debatable whether the results of pharmacogenetic analysis, pertaining to the effect of genotype on drug disposition, are empirically different than genetic results associated with disease risk.³ For one, the consequence of a positive or negative pharmacogenetic result is usually related to treatment modality and not disease predisposition, although the consequence of administering an

inappropriate medication to a genetically susceptible individual may be life-threatening. Thus pharmacogenetic testing can be viewed as a preventative clinical measure provided the analysis is performed prior to drug administration. Furthermore, the dissemination of disease-related genetic results can be accompanied by significant anxiety⁴⁻⁵, albeit temporarily. The psychosocial impact of disseminating pharmacogenetic research test results has not been sufficiently addressed. Finally, the utility for the patient to receive drug-related genotype information in terms of impact and consequence to future medical decisions has not been evaluated.

Recently, following the completion of a pharmacogenetic study in breastfeeding mothers who had taken codeine⁶, we evaluated participants' perceptions regarding the communication of pharmacogenetic research results, psychosocial implications of receiving this information, and the perceived benefits.⁷ In this

complimentary investigation, we assessed the informational needs of participants in regards to the communication of research results from a pharmacogenetic study.

METHODS

Detailed methods have been described elsewhere.⁷ Briefly, 62 breastfeeding mothers who had taken codeine and participated in a pharmacogenetic study were contacted by telephone at the completion of the study and given the option of receiving the overall study results and their individual genetic results, if desired. A pharmacogenetic counselling session was tailored to suit the needs of different groups of participants in our study: 1) individuals with genotype results associated with increased risk and who reported central nervous system [CNS] depression in their infants, 2) individuals with genotype results not associated with increased risk and who did not

report CNS depression in their infants, and 3) individuals with genotype results not associated with increased risk and who did report CNS depression in their infants.

The sessions all included a discussion of genetic and non-genetic factors that were found to be associated with neonatal sedation, including maternal codeine dose, duration of codeine use while breastfeeding, co-linearity of maternal CNS depression with neonatal CNS depression, and the limitations of the study design. In addition, the metabolism of codeine was explained including the relationship of *CYP2D6* with the production of the active morphine metabolite. A semi-structured interview was conducted before and after the pharmacogenetic counselling session, as previously described.⁷ For this report, participants were asked 1) whether they had any questions or needed further information, and 2) whether they had any suggestions based on their experiences with the study.

TABLE 1 Informational needs of participants who received their *CYP2D6* pharmacogenetic results

	n (%)
<i>Do you have any questions or need further information?</i>	
Yes	23 (37.7)
No	38 (62.3)
<i>Do you have any suggestions based on your experience with this study?</i>	
Yes	25 (41.7)
No	36 (58.3)

RESULTS AND DISCUSSION

After receiving both individual and overall group results, most individuals (62%) reported that the information provided was sufficient for their needs (see Table 1). 38% had questions related to future codeine use, potential adverse effects in babies, heredity, and public policy.

Questions regarding future codeine use

Of the participants who had questions, most were surrounding future codeine use in different scenarios [i.e. with a subsequent child, during pregnancy, when not breastfeeding; *“should I be worried about taking codeine when I am not breastfeeding?”* *“In the future, can I take codeine while I am breastfeeding?”* *“Is this the same when you are pregnant?”* *“Is my new baby going to react the same as the previous one?”*] Tying in the non-genetic characteristics of maternal dose and duration with genotype implications, one participant commented *“if I were to take one Tylenol 3 every 4 hours as the package says, now that I know I won’t make more morphine than expected, would that be safe for me?”* Clearly, participants’ questions stemmed around the implications of the knowledge they derived from this study as they considered future scenarios in which the medication would be required.

Questions regarding genetics/heredity

The societal and familial implications of the pharmacogenetic results were of interest to some of the participants, as well as a need for clarification of heritability. For example, one mother who had two daughters inquired whether *“there was any study to show that it gets passed on?”* Participants wondered about the frequency of the *CYP2D6* gene duplication and in which ethnicities duplication was more prevalent. Grasping the relationship between *CYP2D6*, analgesic effect, and morphine biotransformation, one participant who received very little pain relief from codeine enquired *“can it go the other way? I think it doesn’t work for me.”*

Questions regarding policies and programmes

The participants of this study had all contacted the Motherisk Program, a counselling information service for pregnant or lactating patients and their

healthcare providers regarding risks associated with drug, chemical, infection, disease, and radiation exposure during pregnancy. Some individuals wondered how and to what impact the information derived from the study they had participated in would be translated to clinical practice [*“is the Motherisk Program going to change the information they give out on codeine?”* *“If someone did have an extra copy of the gene, would you tell them not to take codeine?”* *“What are you doing now when mothers receive codeine?”* *“What do nurses at the hospital do?”* *“Can a pregnant woman who is concerned about this ask her doctor to request a test to look at this gene?”*] One participant also inquired about the safety of oxycodone as a replacement for codeine in the postpartum period [*“I had a Caesarean section and needed pain relief but the doctors did not give me codeine because of my past experiences. They gave my oxycodone instead; is it safe?”*] Her question has formed the basis of a follow-up investigation in breastfeeding mothers who have received oxycodone, and analgesic also metabolized by *CYP2D6*, for post-partum relief during breastfeeding.

Suggestions from participants to improve the study experience

Forty-two percent of participants offered suggestions based on their experiences with the study (Table 1). The most common suggestion was a shorter time interval between sampling and receiving test results [*“it would be beneficial to the mother to know the results within one week, immediately;”* *“the time between the test and the results should be shorter; if a woman is pregnant and she wants to make a decision, it can’t be three or four years”*]. This was followed by the suggestion to offer the pharmacogenetic test to a mother before she was prescribed codeine [*“it’s a good idea to be part of regular screening; prenatal screening”*, *“do the genetic screening beforehand during pregnancy”*, *“make it part of standard testing with the OB”*]. Some participants stated a need for a follow-up consultation in-between the lab receiving the sample and the participant’s receiving the results [*“contact [between researcher and participant] in between, it was a long time to wait for”*, *“a quick follow-up every 6 to 8 months would be good”*].

There were also suggestions on how to disseminate study information beyond the participants to the public at large [*“Is there somewhere you can post [this information] on a web-site, for prenatal classes? A lot of people read up and are technologically savvy; post this information on prenatal class websites, magazines, pamphlets, brochures pregnant women receive. There are those free kits in doctor’s offices, preparing for pregnancy and birth that you could put this in. It must be a conscious decision for people before they receive codeine; the free pamphlet would reach the most people.”*]

Research participants were informed of global findings and individual genetic results after the study had been accepted in a peer-reviewed journal. This is in agreement to the response by parents of children with cancer who wished to receive their child’s individual genetic results after the study was peer-reviewed but before it was published in the medical literature.¹¹ For participants in our study, the overall process took up to 3 years since the time of consent. Some individuals reported that they would have been able to utilize the information gained from their genotype if it had been conveyed sooner (for example when a mother had a subsequent pregnancy). Thus, there is value in estimating when the results of the research will be disseminated, and this should be included at the beginning of the study, if possible.

CONCLUSION

Few studies have asked participants what they expect regarding the return of research results. The questions and suggestions raised, in conjunction with participants’ perceptions towards receiving overall and individual pharmacogenetic research results⁷, highlight the breadth of issues that need to be taken into account when the research and clinical team communicate pharmacogenetic research information to study subjects. It is also an indicator that returning results, when the circumstances justify it, is perceived as a valuable benefit that is taken very seriously by research participants.

Acknowledgements / Funding

This work was supported by the Canadian Pharmacogenomics Network for Drug Safety

(CPNDS) and the Canadian Institutes of Health Research (CIHR). The authors would like to thank the participants for making this study possible.

Corresponding Author: gkoren@sickkids.ca

CPNDS Symposium available online:
Vol 18(1):e76-e175

REFERENCES

1. Fernandez CV, Kodish E, Weijer C. Informing study participants of research results: an ethical imperative. *I.R.B.* 2003;25:12-19.
2. Miller FA, Christensen R, Giacomini M, Robert JS. Duty to disclose what? Querying the putative obligation to return research results to participants. *J Med Ethics* 2008;34:210-213 (2008).
3. Joly Y, Knoppers BM, Nguyen MT. Stored tissue samples: through the confidentiality maze. *Pharmacogenomics J* 2005;5(1):2-5.
4. Di Prospero LS, et al. Psychosocial issues following a positive result of genetic testing for BRCA1 and BRCA2 mutations: findings from a focus group and a needs-assessment survey. *CMAJ* 2001;64:1005-9.
5. Hayden MR, Bombard Y. Psychosocial effects of predictive testing for Huntington’s disease. *Adv Neurol* 2005;96:226-39.
6. Madadi P, Ross CJ, Hayden MR, Carleton BC, Gaedigk A, Leeder JS, Koren G. Pharmacogenetics of neonatal opioid toxicity following maternal use of codeine during breastfeeding: a case-control study. *Clin Pharmacol Ther* 2009 Jan;85(1):31-5.
7. Madadi P, Joly Y, Avard D, Chitayat DC, Smith MA, Ross CJ, Carleton BC, Hayden MR, Koren G. Communicating pharmacogenetic research results to breastfeeding mothers taking codeine: a pilot study of perceptions and benefits. *Clin Pharmacol Ther* 2010 Dec;88(6):792-5.
8. Priest L. MDs want codeine banned at hospital. *The Globe and Mail*. August 22, 2008 Page 1. [newspaper article]
9. Priest L. Codeine can prove toxic for breastfed babies. *The Globe and Mail* August 21, 2008 Page 1. [newspaper article]
10. Priest L. Codeine can turn toxic in nursing mothers. *The Globe and Mail* May 10, 2006; Page 1. [newspaper article]
11. Fernandez CV, et al. The return of research results to participants: pilot questionnaire of adolescents and parents of children with cancer. *Pediatr. Blood Cancer* 2007;48, 441-446.