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Progress in the Direct Application of Pharmacogenomics to Patient Care: Sustaining innovation

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Abstract

The application of the knowledge from the Human Genome Project to clinical medicine will be through both industrial drug development and the application of pharmacogenomics (PG) to patient care. The slow uptake of clinical innovations into clinical practice can be frustrating, but understanding the history of acceptance and sustaining medical innovation is critically important to position PG to succeed. This primarily means that PG tests must have legitimacy; they must be thoroughly validated, must be cost-effective, must be widely accepted by medical practitioners, must be supported by public policy, and must have a way of being easily incorporated into current medical practice. They must also lead to actionalble decisions by health care providers for their patients. Innovative PG assays should be tested in the best US laboratories, and reimbursement for testing must be accepted at the federal and state level. The companies providing these PG tests should be capable of supporting the interpretation and use of the test throughout medical practice. Advances such as the addition of PG information to drug labeling and the routine use of validated biomarkers to determine choice of cancer chemotherapy have been made. The PG research community must pay attention to the principles that have been previously described for acceptance and sustaining medical innovations in order for PG to be widely accepted in clinical medical practice.

Introduction

The 21st century should be the century of personalized medicine, but the integration of knowledge gained from the Human Genome Project into clinical practice is a slow process. Even small changes in medical practice have always come slowly, and the full integration of pharmacogenomics (PG) into clinical practice could amount to a complete rebuilding of the drug prescribing and monitoring process. The knowledge that patients who might otherwise benefit from our current knowledge of PG are still either receiving suboptimal care or are suffering adverse drug reactions is frustrating. Calls for a complete restructuring of the pharmaceutical industry to accommodate PG-driven changes are both unrealistic and ignore the usual patterns of inclusions of medical innovations into practice (Evans et al., 2004). However, clear progress is being made in integrating PG into the drug development process and into clinical practice. The objectives of this review are to (1) review the factors that drive and sustain innovation in clinical practice, (2) discuss the implications of these factors for PG, and (3) provide examples of in which progress is being made toward utilizing PG information in clinical practice.

What factors will drive and sustain innovation in clinical practice?

In the social science field, an extensive literature exist regarding medical innovation, and the problems associated with having this innovation adopted and sustained in clinical practice. Table 1 lists the tenets of legitimacy, organizational factors, and intermediary functions which make innovations more or less likely to be adopted (Racine, 2006). The PG implications of each of these tenets are listed in Table 1, and are more extensively discussed with examples below.

Legitimacy:

1. Innovations that are validated are more likely to be adopted and sustained. The validation of a PG test is dependent on a number of factors including the frequency of

the observation, the potential impact that the test has on patient care, and the difficulty in linking the PG test to an established objective surrogate marker or clinical observation (Rolan et al., 2003). Current experience to date provides examples of both PG biomarkers that are well established and validated, and PG tests that should not presently be pursued in clinical practice.

The most obvious examples of PG biomarkers that are clearly validated are those associated with the use of a therapeutic monoclonal antibody or agent directed against the marker. Both the human epidermal growth factor receptor 2 (HER2) marker, where overexpression of HER2 is required for therapy with trastuzumab, and epidermal growth factor receptor (EGFR) expression, which has specified expression patterns as a guide to erlotinib and cetuximab therapy, are examples of validated PG biomarkers. Trastuzumab was approved for use in 2000, and a survey of the use of the HER2 test was reported in 2006. The test is now used in Europe by 84% of the survey respondents, suggesting wide acceptance of the test (Woelderink et al., 2006). The co-development of the test and the drug generally would be expected to lead to a higher uptake rate of the test.

Other well established test procedures include the DNA test for polymorphisms in thiopurine methyltransferase (TPMT). The enzyme TPMT is necessary for the breakdown of myelosuppressive metabolites of 6-mercaptopurine (6-MP) or azathioprine. While the homozygous variant polymorphism is rare (1:300), the implications for therapy can be dramatic. Eleven polymorphisms for TPMT have been found to be associated with lower enzyme activity (Evans, 2004). Children given full doses of 6-MP for acute lymphocytic leukemia who are variant for TPMT have a significantly increased risk of drug toxicity. Organ transplant patients who are heterozygous for variants of TPMT have also been shown to be much more susceptible to myelotoxicity from azathioprine (Kurzawski et al., 2005). In spite of the potential for TPMT PG testing, only 12% of centers surveyed in Europe perform TPMT testing

when TPMT substrates are prescribed (Woelderink et al., 2006). In contrast to HER2/Herceptin, TPMT/6-MP is not well known and 6-MP has been in use for over 50 years. The adverse effects of 6-MP have been accepted as the cost of treating a serious disease. However, that view is changing in the medical community.

The question of whether PG tests have to be validated in prospective trials is under debate, and specifically applies to the testing of VKORC1 and CYP2C9 genotypes in patients given the anticoagulant warfarin. The effect of VKORC1 on warfarin's anticoagulant effect and of CYP2C9 on warfarin metabolism are well documented in numerous retrospective studies (Herman et al., 2005; Rieder et al., 2005; Sconce et al., 2005; Mushiroda et al., 2006). Observational studies, both prospective and retrospective, are an important source of new medical knowledge because they represent real clinical practice settings. Considering the high rate of adverse effects, the fact that up to 7% of patients may have a serious bleed while on warfarin, and the current understanding of the factors that affect warfarin dosing, retrospective studies have provided the basis for relabeling warfarin to include PG information. Pharmacogenetics has explained the significant dosage variations in warfarin dosing between ethnic groups (Veenstra et al., 2005). Even then, skeptics exist as to the positive impact of PG testing when other phenotypic testing, such as the INR, is so commonly performed. What is missed is that INR measurments are reactive and time-delayed whereas PG is intended to predict and prevent events before they happen. Other arguments against PG testing for warfarin include the lack of a common dosing nomogram using VKORC1 and CYP2C9 and the lack of a pharmacoeconomic assessment of this testing. One such nomogram has been suggested, but has not been prospectively tested (Sconce et al., 2005). These arguments may be critical to resolve to be able to have widespread adoption of PG testing for warfarin and for this testing to be sustained in the future.

A real danger exist in promoting PG testing that has not been validated. The

best example of this concept is the promotion of CYP3A5 testing for the dosing of tacrolimus in organ transplant patients (Zheng et al., 2003; Zheng et al., 2004). One author has suggested that double the usual tacrolimus dose be administered to CYP3A5 expressors, but this is a dosing scheme that has not been tested (MacPhee et al., 2004). This tacrolimus dosing scheme is not advisable on the basis of current information (Burckart et al., 2006). Since tacrolimus blood concentrations are routinely monitored after transplantation, a PG test that poorly predicts blood concentrations is not a test that PG advocates should be endorsing. Especially at the beginning of acceptance into clinical practice, PG testing should be based on well validated markers and studies which will sustain the growth of this field in the future.

2. *Cost effective procedures are much likely to be adopted and sustained.* Several pharmacoeconomic studies have been conducted with PG testing. Positive cost savings have been claimed for TPMT in rheumatoid arthritis patients (Marra et al., 2002), for CYP2C19 testing in H. pylori infections (Lehmann et al., 2003), and in CYP2C9 testing for warfarin dosing (You et al., 2004). The end points in these small studies were the prevention of adverse events or the avoidance of a complication, both of which are more difficult to put a specific monetary value on.

One type of PG testing in heart transplant patients is commercially available from XDx (xdx.com), and is called Allomap. This peripheral blood test extracts mRNA from peripheral blood cells and amplifies sequences from 11 genes. Using a scoring system that was validated in comparison to heart transplant biopsies, the Allomap test allows patients with a lower score to avoid undergoing a cardiac catherization and heart biopsy. The heart biopsy procedure cost $3,000 - $4,000, so the company has had no problem in seeking reimbursement of the Allomap test from health insurers.

Pharmacoeconomic studies in patient populations from large health maintenance organizations or pharmacy benefits mangers are still necessary to assure the third party payers that PG testing is cost effective.

3. Innovations that depart from existing procedures are less likely to be adopted. Many health professionals are not trained in the interpretation of PG data, so even a report on one single nucleotide polymorphism (SNP) may be confusing. Therefore the use of PG information in applications to patient care should be well thought out, and use simple but informative formats for reporting and using PG data. The Allomap system cited above is one example of turning a complex result into a score that then has a meaningful interpretation. AIDS resistance testing, and their reporting of results, is another example. With warfarin dosing, dosing nomograms are now being constructed and tested that combine both VKORC1 and CYP2C9 polymorphisms along with clinical information to provide a starting dose for warfarin.

4. Practitioners must accept the legitimacy of the innovation before they will learn, adopt and sustain the procedure. Currently little information is included about PG in university educational programs for physicians and pharmacists. At the University of Southern California, a four-week course in PG was initiated for Pharm.D. students in 2004. Pharmacy schools routinely include some information on PG in their curriculum, but no information is currently available on the inclusion in physician education.

A bigger problem is the training of existing medical personnel currently in practice. The need for education in PG in a variety of settings is of critical importance (Frueh et al., 2005). One Web-based educational program is being developed by the US Food and Drug Administration in collaboration with the American College of Clinical Pharmacology, and should be available for viewing in the Spring of 2007.

For some dosing algorithms, such as the one being developed for warfarin, a Web-based dosing calculation that could be used online or offline may be the best solution for universal availability. Currently, a Web search of warfarin nomograms brings up over 22,000 hits, none of which incorporate PG testing. We are however aware of several nomograms being developed for use over the internet.

5. An innovation is more likely to be sustained if there is a stable public policy supporting it. The adoption of PG into public policy and accepted medical practice is an essential part to the establishment of PG in clinical practice. One approach being pursued by the Office of Clinical Pharmacology, US Food and Drug Administration is to include PG information into drug labeling. Presently about 10% of all approved drug labels contain PG information. Table 2 list the currently approved drugs in the US which have labeling with PG biomarkers (Mummaneni et al., 2006). The relabeling of warfarin to contain information on VKORC1 and CYP2C9 was recommended by the Clinical Pharmacology Advisory Committee in the Fall of 2005, and is negotiating the new label with the sponsor is currently in progress.

A second approach is to pass federal legislation which provides access to PG testing for personalized medicine. In August, 2006, Senator Barack Obama from Illinois introduced a bill entitled the "Genomics and Personalized Medicine Act of 2006" (S.3822), the stated purpose of which is to "improve access to and appropriate utilization of valid, reliable, and accurate molecular genetic tests by all populations, thus helping to secure the promise of personalized medicine for all Americans." This bill would provide for a genomics and Personalized Medicine Interagency Working Group, expansion of genetics and genomics research, training programs for health care providers, and tax credits for the development of new testing methods. While the fate of this bill is uncertain at present, it would have an impact on bringing PG to the forefront of public policy.

6. The more dependent an innovation is on its founder, the less likely that it is to be sustained. At the current time, PG research expertise and clinical research programs are focused in a small number of centers in the US and internationally. The acceptance of PG testing in clinical practice depends upon the wide application of the pivotal studies that have established clear associations with improvements in patient care.

Organizational factors

1. The more prior experience that an organization has with initiating innovations, the more effective that it will be at this process. Some large health maintenance organizations in the US have a history of initiating innovative medical practice. For example, a Medline search of 1996 to 2006 identifies 587 studies conducted by the Kaiser Permanente health maintenance organization. Of those 587 studies, 27 dealt with cost effectiveness, but none of those studies dealt with pharmacogenomics. Kaiser Permanente and similar organizations should be encouraged to undertake PG studies to assess the benefits of PG tests and their cost effectiveness.

2. Innovations that generate symbolic or reputational advantage are more likely to be adopted and sustained. Patient advocacy is a powerful force in the United States. The best example of patient advocacy was the movement to cure AIDS that was initiated in the 1980's in the US and continues today. People are well informed today, and information concerning the potential benefits of the Human Genome Project have been in the news for 10 years now. People, more than ever, want to know what drug is right for them and will this drug or that drug hurt them. A recent editorial in the New England of Medicine even criticized the advertising for genetic testing that was available through the internet (Wolfberg, 2006). Therefore the ability of an institution or organization to perform innovative PG testing must be must be viewed as an advantage by health care providers, and add to their reputational advantage.

3. The more influential the organization, the more likely it is that the innovation will be adopted and sustained by other organizations. The provision of a service by the federal government through one of their health care programs is generally viewed as acceptance by the medical community of the value of that service. While PG has plenty of visibility at the US FDA and National Institutes of Health level, the inclusion in funding for laboratory testing for federal health care beneficiaries is essential for making these services broadly available in medical practice in the US.

Intermediary functions

1. The greater the technical competence of the intermediary, the better it will be to support and maintain the innovation. In order to be accepted into medical practice, PG tests have to readily available and reliable. The coupling of a testing device and a labeling change for a drug by the FDA has been a critical part of making reliable testing available for the medical community. Roche Diagnostics has incorporated Affymetrix technology into the Amplichip for analyzing CYP2D6 and CYP2C19 polymorphisms, and this test is now FDA-approved. While the widespread availability of this test is viewed as being positive, considering that 23% of PG drug labeling is related to CYP2D6, the actual amount of testing that is being performed in the US is minor in comparison with the use of drugs that are CYP2D6 substrates. This fact suggests that CYP2D6 testing has not passed the legitimacy test as presently judged by the medical community, and that a device company as an intermediary has not actively pursued the marketing of this device. Laboratories and laboratory directors, as will as diagnostic companies, should take more inititative in this area coupling test interpretation and education with the provision of a testing service.

2. The greater the contact between the intermediary and the institution, the greater the fidelity in initiating the innovation. This tenet suggest that the companies that market PG tests must be large enough to actively support the wide application of the test to patient care. With many of the currently available tests, the company is small or has limited capacity to directly support the widespread use of the PG test throughout the US. For example, Third Wave Technology is the company that has produced the UGT1A1 test for irinotecan. On its Website, Third Wave Technology presently states that it has 140 customers. While this coverage may be sufficient for major cancer centers in the US, broad availability throughout medical practice for a PG test will require adoption by companies with a much larger customer base and support system.

Conclusion

The incorporation of PG testing into clinical practice is occurring much more slowly than advocates would like, but this is a critical time for establishing the legitimacy of PG testing so that its use is sustained over time. PG cannot be expected to be a revolution in medicine but more of an evolutionary change in practice of medicine. The interest in personalized medicine or individualization of medicine and comprehensive prospective medical treatment of diseases (i.e., "boutique medicine") is increasing in the medical and public sectors. PG has a major role in this. The factors that support the acceptance and sustaining innovations in medical practice, such as PG testing, are well understood, and we should apply these concepts in advancing the clinical science of PG testing. This primarily means that PG tests must be science – based with evidence of clinical utility, thoroughly validated, must be more cost-effective than the alternatves, must be widely accepted by medical practitioners, must be supported by public policy, and must have a way of being easily incorporated into current medical practice. Innovative PG procedures should be tested in the best US and other worldwide institutions, and reimbursement for testing must be accepted at the federal and state level. The companies providing these PG tests should be capable of supporting the use of the test throughout medical practice. Rather than pushing PG testing that may not be sustained in the future, the PG research community must pay attention to the principles that have been previously established for acceptance and sustaining medical innovations.

References

Burckart, G. J. and Liu, X. I. (2006). Pharmacogenetics in transplant patients: can it predict pharmacokinetics and pharmacodynamics? Therapeutic Drug Monitoring **28**(1), 23-30.

Evans, B. J., Flockhart, D. A. and Meslin, E. M. (2004). Creating incentives for genomic research to improve targeting of therapies. Nature Medicine **10**(12), 1289-91.

Evans, W. E. (2004). Pharmacogenetics of thiopurine S-methyltransferase and thiopurine therapy. Therapeutic Drug Monitoring **26**(2), 186-91.

Frueh, F. W., Goodsaid, F., Rudman, A., Huang, S. M. and Lesko, L. J. (2005). The need for education in pharmacogenomics: a regulatory perspective. Pharmacogenomics Journal **5**(4), 218-20.

Herman, D., Locatelli, I., Grabnar, I., Peternel, P., Stegnar, M., Mrhar, A., Breskvar, K. and Dolzan, V. (2005). Influence of CYP2C9 polymorphisms, demographic factors and concomitant drug therapy on warfarin metabolism and maintenance dose. Pharmacogenomics Journal **5**(3), 193-202.

Kurzawski, M., Dziewanowski, K., Gawronska-Szklarz, B., Domanski, L. and Drozdzik, M. (2005). The impact of thiopurine s-methyltransferase polymorphism on azathioprine-induced myelotoxicity in renal transplant recipients. Therapeutic Drug Monitoring **27**(4), 435-41.

Lehmann, D. F., Medicis, J. J. and Franklin, P. D. (2003). Polymorphisms and the pocketbook: the cost-effectiveness of cytochrome P450 2C19 genotyping in the eradication of Helicobacter pylori infection associated with duodenal ulcer. Journal of Clinical Pharmacology **43**(12), 1316-23.

MacPhee, I. A. M., Fredericks, S., Tai, T., Syrris, P., Carter, N. D., Johnston, A., Goldberg, L. and Holt, D. W. (2004). The influence of pharmacogenetics on the time to achieve target tacrolimus concentrations after kidney transplantation.[see comment].

American Journal of Transplantation **4**(6), 914-9.

Marra, C. A., Esdaile, J. M. and Anis, A. H. (2002). Practical pharmacogenetics: the cost effectiveness of screening for thiopurine s-methyltransferase polymorphisms in patients with rheumatological conditions treated with azathioprine. Journal of Rheumatology **29**(12), 2507-12.

Mummaneni, P., Amur, S. G., Goodsaid, F., Rudman, A. and Frueh, F. W. (2006). Genomic biomarkers in FDA-approved drug labels (abst). Journal of Clinical Pharmacology **46**, 1088.

Mushiroda, T., Ohnishi, Y., Saito, S., Takahashi, A., Kikuchi, Y., Saito, S., Shimomura, H., Wanibuchi, Y., Suzuki, T., Kamatani, N. and Nakamura, Y. (2006). Association of VKORC1 and CYP2C9 polymorphisms with warfarin dose requirements in Japanese patients. Journal of Human Genetics **51**(3), 249-53.

Racine, D. P. (2006). Reliable effectiveness: a theory on sustaining and replicating worthwhile innovations. Administration & Policy in Mental Health **33**(3), 356-87.

Rieder, M. J., Reiner, A. P., Gage, B. F., Nickerson, D. A., Eby, C. S., McLeod, H. L., Blough, D. K., Thummel, K. E., Veenstra, D. L. and Rettie, A. E. (2005). Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose. New England Journal of Medicine **352**(22), 2285-93.

Rolan, P., Atkinson, A. J., Jr., Lesko, L. J., Scientific Organizing, C. and Conference Report, C. (2003). Use of biomarkers from drug discovery through clinical practice: report of the Ninth European Federation of Pharmaceutical Sciences Conference on Optimizing Drug Development. Clinical Pharmacology & Therapeutics **73**(4), 284-91.

Sconce, E. A., Khan, T. I., Wynne, H. A., Avery, P., Monkhouse, L., King, B. P., Wood, P., Kesteven, P., Daly, A. K. and Kamali, F. (2005). The impact of CYP2C9 and VKORC1 genetic polymorphism and patient characteristics upon warfarin dose

requirements: proposal for a new dosing regimen. Blood **106**(7), 2329-33.

Veenstra, D. L., You, J. H. S., Rieder, M. J., Farin, F. M., Wilkerson, H.-W., Blough, D. K., Cheng, G. and Rettie, A. E. (2005). Association of Vitamin K epoxide reductase complex 1 (VKORC1) variants with warfarin dose in a Hong Kong Chinese patient population. Pharmacogenetics & Genomics **15**(10), 687-91.

Woelderink, A., Ibarreta, D., Hopkins, M. M. and Rodriguez-Cerezo, E. (2006). The current clinical practice of pharmacogenetic testing in Europe: TPMT and HER2 as case studies. Pharmacogenomics Journal **6**(1), 3-7.

Wolfberg, A. J. (2006). Genes on the Web--direct-to-consumer marketing of genetic testing. New England Journal of Medicine **355**(6), 543-5.

You, J. H. S., Chan, F. W. H., Wong, R. S. M. and Cheng, G. (2004). The potential clinical and economic outcomes of pharmacogenetics-oriented management of warfarin therapy - a decision analysis. Thrombosis & Haemostasis **92**(3), 590-7.

Zheng, H., Webber, S., Zeevi, A., Schuetz, E., Zhang, J., Bowman, P., Boyle, G., Law, Y., Miller, S., Lamba, J. and Burckart, G. J. (2003). Tacrolimus dosing in pediatric heart transplant patients is related to CYP3A5 and MDR1 gene polymorphisms. American Journal of Transplantation **3**(4), 477-83.

Zheng, H., Zeevi, A., Schuetz, E., Lamba, J., McCurry, K., Griffith, B. P., Webber, S., Ristich, J., Dauber, J., Iacono, A., Grgurich, W., Zaldonis, D., McDade, K., Zhang, J. and Burckart, G. J. (2004). Tacrolimus dosing in adult lung transplant patients is related to cytochrome P4503A5 gene polymorphism. Journal of Clinical Pharmacology **44**(2), 135-40.

Table 1. Factors necessary to sustain any new medical innovation in practice[a], and its implications for pharmacogenomics

Factor	Implication for pharmacogenomics
Legitimacy	
1. Innovations that are validated are more likely to be adopted and sustained.	New PG assays should not be pushed into clinical practice until they have been fully validated.
2. Cost effective procedures are much likely to be adopted and sustained.	Cost effectiveness studies are needed as part of the evaluation of new PG assays.
3. Innovations that depart from existing procedures are less likely to be adopted.	The implementation of PG assays and use of assay results must be simplified into procedures that match clinical practice.
4. Practitioners must accept the legitimacy of the innovation before they will learn, adopt and sustain the procedure.	Educational programs in PG should be adopted by universities for clinical trainees, and education for clinical practitioners should be developed and disseminated.
5. An innovation is more likely to be sustained if there is a stable public policy supporting it.	The adoption of PG into public policy (e.g. drug labeling) and accepted medical practice is essential.
6. The more dependent an innovation is on its founder, the less likely that it is to be sustained.	PG studies must be widely reproduced so that their results are widely applicable.

Organizational factors	
1. The more prior experience that an organization has with initiating innovations, the more effective that it will be at this process.	Innovative healthcare organizations should be targeted for implementation of new PG assays and procedures.
2. Innovations that generate symbolic or reputational advantage are more likely to be adopted and sustained.	Patients should be informed of availability of PG innovations so that they will seek out organizations that provide these services.
3. The more influential the organization, the more likely it is that the innovation will be adopted and sustained by other organizations.	The certification and reimbursement for PG analyses should be sought from federal and state healthcare providers.
Intermediary functions	
1. The greater the technical competence of the intermediary, the better it will be to support and maintain the innovation.	Companies supporting PG assays should extensive experience with the assay before widespread distribution.
2. The greater the contact between the intermediary and the institution, the greater the fidelity in initiating the innovation.	The assimilation of PG assays into institutions will work best when the institution has an established relationship with the assay company.

[a] From (Racine, 2006)

Table 2. Pharmacogenomic biomarkers currently in labeling in US approved drugs.[a]

Biomarker	Drug	Label status
EGFR expression	Erlotinib	Required
Her2/neu Over-expression	Trastuzumab	Required
TPMT Low and intermediate Activity	Azathioprine	Recommended
UGT1A1*28 Allele	Irinotecan	Recommended
VKORC1 Variants	Warfarin	Recommended
C-KIT expression	Imatinib mesylate	Information only
CYP2C19 Variants	Voriconazole	Information only
CYP2C9 Variants	Celecoxib	Information only
CYP2D6 Variants	Fluoxetine HCL	Information only
DPD Deficiency	Capecitabine	Information only
G6PD Deficiency	Rasburicase	Information only
NAT Variants	Rifampin, isoniazid, and pyrazinamide	Information only

[a] From (Mummaneni et al., 2006)