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Ocak 2008'de yürürlüğe giren "Gözlemsel Çalışmalar Kılavuzu", çeşitli geribildirimler ve uygulamada karşılaşılan sorunlar doğrultusunda, Sağlık Bakanlığı İlaç ve Eczacılık Genel Müdürlüğü tarafından güncellendi. Güncellenen kılavuza KFÇG web sayfasından ulaşabilirsiniz.

Konunun güncelliği nedeniyle biz de önümüzdeki sayılarda e-bültenimizde farmakoepidemiyoloji konulu bir seri yazı yayınlamayı planladık ve konunun uzmanlarından bize destek vermelerini rica ettik. Ayrıca, üyelerimiz arasından da bu konuda e-bültene katkıda bulunmak isteyenlerin yazılarını bekliyoruz.

Elbette e-bültenimize katkınız bu konuda yazı yazmakla sınırlı olmamalı. Klinik farmakolojiyi ilgilendiren her türlü konuda yazı, haber, yayınlanan yazılar hakkında geribildirimler, tartışma, vb ile katkılarınızı da beklediğimizi bir kez daha hatırlatmak istiyorum.

E-bültenimiz, aktif katılımınız olmadan yaşamını sürdüremez. Lütfen ebulten@tfd.org.tr adresine e-bültenle ilgili görüş ve önerilerinizi yazın.

Hepinize güzel bir yaz dilerim.

Prof. Dr. Şule Oktay

A Call for Scientific and Ethical Standards on Clinical Pharmacogenomics Association Studies in Personalized Medicine

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Özet: Farmakogenetik kisiye özel ilaç tedavisi açısından güncel ve önemli bir araştırma konusu olmaya devam ediyor. Klinik Farmakoloji Elektronik Bülteninin son üç sayısında farmakogenetik bilimsel gelişmeler detaylı olarak tartışılmıştı. Bu yazımızda kişiye özel tedavinin gerçekleşmesi açısından çok önemli bir role sahip olan 'genetic association study design' üzerinde bilimsel ve etiksel standartların geliştirilmesinin önemini vurguluyoruz.

1. Introduction

Pharmacogenomics is an undeniable reality in biomedical research and increasingly, in clinical practice (Lesko, 2008). In the last three issues of the Turkish Pharmacology Society Association (TFD) Clinical Pharmacology Study Group E-Bulletin, pharmacogenomics science and its promise were described elegantly by Nacak (2008), Babaoğlu (2008) and Şardaş (2008). The aim of the present socio-ethical analysis is to complement the molecular pharmacogenomics research in understanding the key factors that can limit and/or facilitate the progress in pharmacogenomics science from the laboratory to the community. While this concise article cannot provide all the necessary nuances, we will direct the readers, when possible, to recent and significant articles in the field of personalized medicine. Specifically, we will evaluate the clinical pharmacogenomics association studies from a socio-ethical angle.

With these overarching aims in mind, this brief paper will first outline the rationale for personalized medicine, the very application context in which pharmacogenomics is presently situated. Second, drawing upon the historical origins of pharmacogenomics in 1950s, we will discuss why the development of scientific and ethical standards for

pharmacogenomics association studies is timely, and does matter.

2. The rationale for personalized medicine

Since the tragedy of thalidomide in 1960s, adverse drug reactions (ADRs) have become a central focus of scientific debate and public health research (Ji et al. 2008). Despite this sustained attention, ADRs remain implicated in 106,000 deaths annually, making them the fourth to sixth leading cause of mortality in the United States (Lazarou et al. 1998a). Reports from different global regions collectively support the notion that ADRs are a formidable drug related public health problem (Lazarou et al. 1998b; Van der Hooft et al. 2006; Zed et al. 2008). Based on an estimate of ADRs as being responsible for 3% to 8% of hospital admissions in internal medicine (Hallas et al. 1992; Einarson 1993), the economic burden of drug-related morbidity and mortality sums up to $130 billion annually (Johnson and Bootman 1995; Ernst and Grizzle 2001). Predictors of ADRs are urgently needed for targeted or "personalized" prescription of medicines to minimize the risk for drug toxicity.

In addition to these concerns over ADRs, a second driver of targeted or personalized medicines is the limited efficacy of medicines. To this end, there is no denying that medicines can be life saving for certain patients but a deeper analysis of drug response across therapeutic areas reveals a different picture. For the majority of drug classes prescribed for common human diseases, only about 50% to 60% of patients appear to respond to therapy (Spear et al. 2001). For example, while 80% of patients respond to pain medications such as Cox-2 inhibitors, response rates drop to 30% for treatments directed at Alzheimer's disease and 25% for cancer chemotherapies (Spear et al. 2001). Marked interindividual variability in drug response and safety is problematic because it introduces substantial uncertainty in choice of the drug type and dose by health professionals. For life threatening diseases such as sepsis and cancer, the uncertainty in drug therapy and attendant delays in finding the optimal therapeutic regimen may result in disease progression and potential mortality.

3. Pharmacogenomics: Transformation from fringe intellectual curiosity to a centerpiece of personalized medicine research

Pharmacogenomics is the study of variability in the human genome in relation to individual and population differences in drug response and toxicity (Maitland-van der Zee et al. 2007). Studies with monozygotic twins in late 1960s and 1970s have firmly established that genetics markedly influences variability in drug concentrations and pharmacokinetics (Nebert et al. 2008; Kalow et al. 1999; Vesell and Page 1968). Pharmacoepidemiology data further suggest that genetics is also important for pharmacodynamics, i.e., the effects of drugs on the human body. For example, a detailed analysis of 27 drugs frequently cited in ADR studies found that 59% are metabolized by one or more enzyme with a genetic variant allele associated with deficient metabolism (Phillips et al. 2001). By contrast, only 7% to 22% of drugs selected at random were influenced by a genetically polymorphic metabolic pathway.

Insofar as the drug industry and pharmaceutical development are concerned, the promise of pharmacogenomics is, in part, envisioned to be an increased precision in the rational and early selection of drug candidates through considerations of patients' genetic make up and molecular heterogeneity in drug targets (Sadee 1998). Although pharmacogenomics may speed up regulatory approval of drugs by stratified clinical trials in subpopulations of patients who are estimated to be "good responders", this assumption still remains as a hypothesis which needs empirical support. Nevertheless, pharmacogenomics has become a key component of the '"decision-making tool box" for risk assessment concerning pharmacokinetic and pharmacodynamic outcomes in biomedical research and clinical medicine (Gunes and Dahl 2008; Bertilsson 2007; Babaoğlu et al. 2004; Nacak et al. 2004).

The idea of genetic contribution to individual variability in response to exogenous substances (e.g., drugs, food, toxins) dates back to the observations made by the English physiologist Garrod (1923) in his analysis of the 'inborn errors of metabolism' in the early part of the 20th century. This idea was further advanced in 1950s and 1960s by the seminal works of Arno Motulsky, Friedrich Vogel and Werner Kalow. In fact, the term pharmacogenetics was coined by Friedrich Vogel of Heidelberg, Germany in 1959 (i.e., long before 'pharmacogenomics' became a popular research topic). Subsequently, the debrisoquine/sparteine (CYP2D6) polymorphism was identified in 1970s by Smith in England, and Eichelbaum in Germany (Mahgoub et al. 1977; Eichelbaum et al. 1979). Collectively, these breakthroughs established a foundation for in-depth investigations towards personalized medicine using genetic approaches.

4. Pharmacogenomics and the road less traveled: The rules of prognostication

Despite the long history of, and the present enthusiasm for pharmacogenomics research, there is a need for a healthy pause and socio-ethical reflection. While the promise of pharmacogenomics cannot be denied, it is important to take the road less traveled and consider the following questions:

- Can we be confident that the future pharmacogenomics tests will be developed (and accessible) in an equitable manner (Haga and Burke 2008)?
- How will the pharmacogenomics tests be implemented in different countries including the developing world? To this end, what does a pharmacogenomics test and personalized medicine mean to individuals in a context where some members of the society may not have access to essential medicines or other basic human needs for sustenance (e.g., clean water and shelter) (Pang 2003)?
- Are regulatory frameworks and policy measures in place to evaluate and support these innovations?
- What does the future hold for pharmacogenomics science in Turkey, the Eastern Mediterranean region, the Middle East, and in countries beyond North America and Europe, where personalized medicine research is ostensibly playing a marked role in translational pharmacogenomics and establishment of biobanks (Tamaoki et al. 2004)?
- What are the socio-ethical consequences and risks associated with the increasingly prevalent direct-to-consumer advertising (DTCA) of genetic tests, especially in the face of inadequate consumer knowledge on the 'added value' of pharmacogenomics tests?
- How will pharmacogenomics tests be implemented, and public expectations balanced (and by whom) in resource-limited countries (McBride et al. 2008)?

- What are the areas of synergy, challenges and missed opportunities in facilitating pharmacogenomics innovations among different stakeholders and user groups (Smart and Martin 2006)?
- What should be the key ingredients of an earnest, transparent and socially responsible partnership between academics, pharmaceutical industry, biotechnology companies, governments and the public in development of pharmacogenomics-guided personalized medicines?
- Should race and ethnicity play a role (if at all) as a stratification axis in the practice of pharmacogenomics science (Lee et al. 2008; Ozdemir et al. 2008)?
- Could pharmacogenomics tests result in 'geneticization' of therapeutic outcomes in the clinic thereby overlooking important social and environmental determinants of health (Arnason and Hjörleifsson 2007)?
- Should professional societies [such as the Turkish Pharmacology Society Association or its Clinical Pharmacology Study Group] play a leadership role to ensure commensurate and parallel progress in pharmacogenomics science and associated social, ethical, economic, regulatory and policy dimensions (Caelleigh 2003)?

The wisdom of the popular quote by the Danish physicist Niels Bohr (1885 - 1962) "Prediction is difficult, especially about the future!" would caution that attempts to seek precise answers to such complex questions would be a naive mistake. On the other hand, it would be yet a worse mistake to overlook the principles of prognostication by Robert X. Cringely (1998). Among these prognostication rules, the following two are particularly noteworthy:

- "Past performance is a predictor of future results but not a good one".
- "We tend to underestimate the amount of change that will take place in the long term".

Bearing these rules of prognostication in mind, it becomes clear that the future of pharmacogenomics, and personalized medicine more generally, is still undecided. The reliance on past accomplishments does not necessarily guarantee success in the 'pharmacogenomics future' in a manner that is firmly grounded in both bioscience and socio-ethical dimensions noted above. This calls for a careful reexamination of the key components of and standards on pharmacogenomics science. Hence, we shall turn our attention in the next section on clinical pharmacogenomics association studies, a crucial driver of pharmacogenomics innovations and knowledge from the laboratory bench to the clinic, the marketplace and the community. By examining the pharmacogenomics association studies, we suggest that a more realistic prediction of the future trajectory of pharmacogenomics can be constructed.

5. What is a pharmacogenomics association study? And why do we need standards?

Pharmacogenomics association studies decisively influence the innovation path from gene discovery on the bench-side to the commercially available genetic test in the clinic. Pharmacogenomics association studies have thus a dual impact on prioritizing basic genomics discoveries (e.g., focusing bench research on certain candidate genes) as well as translational medicine. There are three essential components of a pharmacogenomics association study. These include:

(1) the molecular genetic analysis of person-to-person differences in the human genome,
(2) the ascertainment of pharmacological phenotypes (e.g., measurement of drug response and side effects) and,
(3) the bioinformatics analysis to evaluate the relationship between (1) and (2); i.e., genome-phenotype statistical association analysis.

The pharmacogenomics association studies are rapidly proliferating in the bioscience literature. With the decreasing costs of genotyping, it is anticipated that this trend will accelerate further in the coming years. The exponential increase in representation of pharmacogenomics associations is not limited to the scientific literature; we often encounter in the popular media and newspapers the discovery of genes that predict response or toxicity to a pharmaceutical agent (Edelson 2008).

An objective and balanced interpretation of pharmacogenomics associations is important - not only because of their proliferating numbers - but also because they determine future public and private investments in the field of personalized medicine and importantly, which 'genetic locus' may become a 'genetic test' in the clinic. An incorrect evaluation of the association findings may thus adversely impact translational pharmacogenomics research and the development of downstream innovations and appropriate policy on genetic tests. Meta-analyses that rely on biased or substandard pharmacogenomics association studies may carry forward these inaccuracies to the realm of policy and commercialization of genetic tests. Substandard association data could mislead other researchers by diversion of their valuable time, research funds and focus on spurious genetic associations reported in the literature. While our article is not intended to address the required standards per se, we wish to highlight some of the contentious (and hitherto relatively silent) issues that have pertinence for both scientific and ethical standards on pharmacogenomics association studies.

Of great concern about the media representations of pharmacogenomics associations is the lack of a quantitative focus. These reports often indicate that an association has been discovered without mention of the attendant statistical metrics such as odds ratios. Moreover, reporting of the precise percentage of the risk attributable to a certain genetic allele can be problematic. Consider a researcher claiming in the newspaper that 50% of the individual variability in risk for a debilitating drug side effect can be explained by a genetic locus in his/her study sample. In these representations of pharmacogenomics associations in the media (and in scientific journals), the standard error associated with such metrics should also be considered. Returning to the example above, it would be informative to mention not only the percentage of risk explained (50%) by a given allele in the study sample, but also the uncertainty (e.g., standard error or confidence intervals) associated with pharmacogenomics associations.

In parallel to the need for standardization of the reports on pharmacogenomics associations, a 'one-size-fits-all standard' is unrealistic and in fact, may be detrimental to progress in personalized medicine. Different quality standards are necessary for (1) candidate-gene and (2) whole-genome association studies (Freimer and Sabatti 2005). Moreover, the standards can be shaped by unique nuances of different disciplines. For example, the disciplines of human disease genetics and clinical pharmacology/pharmacogenomics contain significant differences in their scientific practices. Clinical pharmacology is, by-and-large, an experimental science whereas human disease genetics is primarily observational in nature. This results in a significant asymmetry in scientific method that can

differentially impact the investigators' ability to control for gene-environment interactions and, by extension, the study sample size requirements. This is a significant point because the sample size in an association finding is often deemed to be an important criterion of the study quality and the extent to which the associations can be generalized. Failure to recognize discipline-specific nuances (i.e., the greater ability to control for environmental factors in clinical pharmacogenomics than disease genetics) may lead to inappropriate dismissal or silencing of meritorious pharmacogenomic investigations with a small sample, even though they may have adequate statistical power (see Ozdemir et al. 2007).

With the decreasing cost of genotyping, and the greater availability of statistical tools for analysis of genotype-phenotype associations, the rate limiting step (i.e., the bottleneck) in pharmacogenomics association studies is now the ascertainment of pharmacological phenotypes in large samples of patients; the latter is also needed to statistically compensate for the increased scope of genomics analysis. This is not simply an administrative issue but one with potential socio-ethical relevance for scientific governance and accountability. The traditional role of scientists as persons who design and interpret studies is transforming to an additional role for subject recruitment for association studies. In some sense, this is not a new role for investigators in clinical pharmacology. On the other hand, the scale of this responsibility has now increased enormously in order to recruit very large samples of patients necessary to establish robust genotype-phenotype associations that stand the test of time and replication. As we analyze a greater number of genes in each association study, this means that those who can recruit subjects may become influential and powerful stakeholders in pharmacogenomics research governance. In effect, in the absence of comprehensive standards on pharmacogenomics association studies, conflict of interests and ethical dilemmas may emerge (e.g., in authorship decisions between researchers and those engaged in recruitment of patients; in collection and archiving of DNA samples between academic and pharmaceutical industry laboratories). The experience from the case of clinical trials literature attests that this is an issue that warrants further socio-ethical reflection (Ozdemir et al. 2007).

Race and ethnicity has a long (and contested) history as variables frequently used in biomedical research. A recent paper thoughtfully outlines the risks associated with the use of "race-as-biology' in genomics medicine. We recommend the readers of the Clinical Pharmacology Study Group E-Bulletin make a note of this timely article (Lee et al. 2008). Because race and ethnicity (social constructs that are often conflated in the literature with biology as well as nationality) are used in pharmacogenomics studies, the future standards on reporting of pharmacogenomics associations should incorporate guidelines on use of race and ethnicity in publications.

In conclusion, development of standards on pharmacogenomics association studies is an arduous and complex but timely task. The associated responsibility is shared by many stakeholders including editors, researchers, sponsors, readers of biomedical journals and the public. The present article is an attempt to highlight the need for standards in this intersection of pharmacology and genomics medicine. As for prognostication rules concerning personalized medicines, we could add that scientific standards on genetic associations would render the innovation path from the pharmacogenomics laboratory to the community more predictable, and reduce misrepresentations of pharmacogenomics associations in the media and scientific literature.

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References:

- Arnason V, Hjörleifsson S. Geneticization and bioethics: advancing debate and research. Med Health Care Philos 2007;10:417-431.
- Babaoglu MÖ. Kanser tedavisinde farmakogenetik bilginin kullanılması. TFD Clinical Pharmacology Study Group E-Bulletin. June 2008 Issue. Available at: http://www.tfd-kfcg.org/. Accessed on August 18, 2008.
- Babaoglu MÖ, Yaşar U, Sandberg M, Eliasson E, Dahl ML, Kayaalp SO, Bozkurt A. CYP2C9 genetic variants and losartan oxidation in a Turkish population. Eur J Clin Pharmacol 2004;60:337-342.
- Bertilsson L. Metabolism of antidepressant and neuroleptic drugs by cytochrome p450s: clinical and interethnic aspects. Clin Pharmacol Ther 2007;82:606-609.
- Caelleigh AS. Roles for scientific societies in promoting integrity in publication ethics. Sci Eng Ethics 2003;9:221-241.
- Cringely RX. The five rules of prognostication. Forbes ASAP (November 30, 1998).
- Edelson E. Genetic test predicts response to warfarin. U.S. News and World Report. August 14, 2008.
- Eichelbaum M, Spannbrucker N, Steincke B, Dengler HJ. Defective N-oxidation of sparteine in man: a new pharmacogenetic defect. Eur J Clin Pharmacol 1979;16:183-187.
- Einarson TR. Drug-related hospital admissions. Ann Pharmacother 1993;27:832 - 840.
- Ernst FR, Grizzle AJ. Drug-related morbidity and mortality: updating the cost-of-illness model. J Am Pharm Assoc (Wash) 2001;41:192-199.
- Freimer NB, Sabatti C. Guidelines for association studies in human molecular genetics. Hum Mol Genet 2005;14:2481-2483.
- Garrod AE. Inborn Errors of Metabolism. 2nd ed. (Henry Frowde and Hodder, Stoughton, London, 1923).
- Guneş A, Dahl ML. Variation in CYP1A2 activity and its clinical implications: influence of environmental factors and genetic polymorphisms. Pharmacogenomics 2008;9(5):625-637.
- Haga SB, Burke W. Pharmacogenetic testing: not as simple as it seems. Genet Med 2008;10:391-395.
- Hallas J, Gram LF, Grodum E, et al. Drug related admissions to medical wards: a population based survey. Br J Clin Pharmacol 1992;33:61-68.
- Ji Y, Ying H, Farber MS, Yen J, Dews P, Miller RE, Massanari MR. Identifying unknown adverse drug reaction signal pairs in postmarketing surveillance using an active multi-agent system approach. IEEE 8th International Conference on Computer and Information Technology Workshop. CIT Workshops 2008; July 8-11 2008, pp. 444-449.
- Johnson JA, Bootman JL. Drug-related morbidity and mortality. A cost-of-illness model. Archives of Internal Medicine 1995;155:1949-1956.
- Kalow W, Ozdemir V, Tang BK, Tothfalusi L, Endrenyi L. The science of pharmacological variability: an essay. Clin Pharmacol Ther 1999;66:445-447.
- Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA 1998a; 279:1200-1205.
- Lazarou J, Pomeranz BH, Corey PN. Reply-Adverse drug reactions in hospitalized patients. JAMA 1998b; 280:1743.
- Lee SS, Mountain J, Koenig B, Altman R, Brown M, Camarillo A, Cavalli-Sforza L, Cho M, Eberhardt J, Feldman M, Ford R, Greely H, King R, Markus H, Satz D, Snipp M, Steele C, Underhill P. The ethics of characterizing difference: guiding principles

on using racial categories in human genetics. Genome Biol 2008;9(7):404.
- Lesko LJ. The critical path of warfarin dosing: finding an optimal dosing strategy using pharmacogenetics. Clin Pharmacol Ther 2008;84:301-303. Mahgoub A, Idle JR, Dring LG, Lancaster R, Smith RL. Polymorphic hydroxylation of debrisoquine in man. Lancet 1977;2:584-586.
- Maitland-van der Zee AH, Aitchison K, Kirchheiner J; European Pharmacogenetics/Genomics Sciences Community. Workshop outcomes report: initiatives to establish a European Network of pharmacogenetics/genomics and progress. Eur J Pharm Sci 2007;31(3-4):151-155.
- McBride CM, Alford SH, Reid RJ, Larson EB, Baxevanis AD, Brody LC. Putting science over supposition in the arena of personalized genomics. Nat Genet 2008;40:939-942.
- Nacak M. Farmakogenetik ve psikotropik ilaçlar. TFD Clinical Pharmacology Study Group E-Bulletin, July 2008 Issue. Available at: http://www.tfd-kfcg.org/. Accessed on August 18, 2008.
- Nacak M, Davutoğlu V, Soydinç S, Dinçkal H, Türkmen S, Erbağci B, Akçay M, Aynacioğlu S. Association between angiotensin converting enzyme gene polymorphism and coronary artery disease in individuals of the South-Eastern Anatolian population. Anadolu Kardiyol Derg 2004;4(1):45-51.
- Nebert DW, Zhang G, Vesell ES. From human genetics and genomics to pharmacogenetics and pharmacogenomics: past lessons, future directions. Drug Metab Rev 2008;40(2):187-224
- Ozdemir V, Graham JE, Godard B. Race as a variable in pharmacogenomics science: From empirical ethics to publication standards. Pharmacogenet Genomics 2008 October. Advance e-pub DOI: 10.1097/FPC.0b013e32830a48f3.
- Ozdemir V, Williams-Jones B, Graham JE, et al. Asymmetry in scientific method and limits to cross-disciplinary dialogue: toward a shared language and science policy in pharmacogenomics and human disease genetics. J Investig Med 2007;55:130-141.
- Pang T. Impact of pharmacogenomics on neglected diseases of the developing world. Am J Pharmacogenomics 2003;3:393-398.
- Phillips KA, Veenstra DL, Oren E, Lee JK, Sadee W. Potential role of pharmacogenomics in reducing adverse drug reactions: a systematic review. JAMA 2001;286:2270-2279.
- Sadee W. Finding the right drug for the right patient. Pharm Res 1998;15:959-963.
- Şardaş S. Farmakogenetik bilgiyi uygulamakta gecikiyoruz. TFD Clinical Pharmacology Study Group E-Bulletin, May 2008 Issue. Available at: http://www.tfd-kfcg.org/. Accessed on August 18, 2008.
- Smart A, Martin P. The promise of pharmacogenetics: assessing the prospects for disease and patient stratification. Stud Hist Philos Biol Biomed Sci 2006;37:583-601.
- Spear BB, Heath-Chiozzi M, Huff J. Clinical application of pharmacogenetics. Trends Mol Med 2001;7:201-204.
- Tamaoki M, Gushima H, Tsutani K. Pharmacogenomics in Asia. Pharmacogenomics 2004; 5(8):1023-1027.
- Van Der Hooft CS, Sturkenboom MCJM, Van Grootheest K, Kingma HJ, Stricker BHC. Adverse drug reaction-related hospitalizations: A nationwide study in the Netherlands. Drug Safety 2006;29(2):161-168.
- Vesell ES, Page JG. Genetic control of drug levels in man: antipyrine. Science 1968;161:72-73.
- Vogel F. Moderne problem der humangenetik. Ergeb Inn Med U Kinderheilk. 1959;12:52-125.
- Zed PJ, Abu-Laban Balen RM, Loewen PS, Hohl CM, Brubacher JR, Wilbur K, Wiens MO, Samoy LJ, Lacaria K, Purssell RA. Incidence, severity and preventability of medication-related visits to the emergency department: a prospective study. CMAJ 2008;178(12):1563-1569.

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