

Personalized medicine in psychiatry: ethical challenges and opportunities

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Pharmacogenomic developments hold promise for personalized medicine in psychiatry with adjusted therapeutic doses, predictable responses, reduced adverse drug reactions, early diagnosis, and personal health planning. The prospects are exciting, but at the same time, these new techniques stand faced with important scientific, ethical, legal, and social challenges that need to be met in order for the scientific advances to be responsibly applied. This review discusses the ethical balance between challenge and opportunity of personalized medicine in psychiatry under the aspects of adequacy, cost:benefit ratio, and therapeutic equity. It is argued that the promising nature of these therapeutic possibilities makes it all the more important to avoid exaggerating the expectations, and that a sophisticated social infrastructure needs to be developed in order to ensure the realistic and responsible application of personalized medicine in psychiatry.

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Pharmacological developments in the 20th century have produced a wide range of drugs that have greatly improved the treatment of many serious diseases. In psychopharmacology, the discoveries of antipsychotic, tranquillizing, or antidepressant agents, such as selective serotonin reuptake inhibitors (SSRIs), were milestones in the treatment of mental illness. However, compared with the general pharmacological progress, the psychopharmacological development, whilst noteworthy, has been somewhat less spectacular. Despite heavy investments in mental health-related research,¹ there have been few important discoveries since the 1950s, when a number of psychopharmacological agents were discovered that are still in use. For example, clozapine was synthesized over 50 years ago but continues to be described as the “most effective antipsychotic drug” for the treatment of schizophrenia,² and is recommended in the UK National Institute of Health and Clinical Excellence (NICE) 2009 update to its schizophrenia guidance.³

Traditionally, the drugs developed have been “one size fits all,” ie, standardized drugs targeting symptoms or syndromes that can be shared by various diseases, rather than being disease-specific, let alone patient-specific. Even though health care is by definition personalized in the sense that the patient’s needs broadly determine the nature of recommended treatment, eg, type and dosage of medication, traditional medication leaves little room for individual variations in responses to treatment, notably through the randomized double-blind procedure used in clinical trials that is incompatible with individu-

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alized assessment. This can be regarded both as a strength, because the structure of the trials ensures that known or unknown confounding factors are evenly distributed between the treatment groups, thus yielding accurate results; or as a weakness because individuality is not taken into account. For better or for worse, drugs are not individually developed; they do not target the individual biological system.

However, human individuals are, biologically as well as socially, highly varied, and a common medical problem is that people with similar symptoms, or the same illness, may react quite differently to a prescribed drug. Even if available data justify the prescription of a given drug, the effects of this drug can vary extensively between distinct individuals. Whereas one individual may be greatly helped by the drug, another may be more or less non-responsive to it; and whilst one patient will suffer severe side effects, another will not. From the point of view of the patient, it is clearly of interest to know if one belongs to the group (normally, the majority) that is helped by the drug, or to the minority that is not, whether one will suffer side effects, and, if so, of what type and degree. For society, adverse drug responses (ADRs) are a major medical and economic problem. ADRs cause thousands of deaths and serious injuries yearly, and have even been suggested to constitute between the fourth and the sixth leading cause of death in the US, which would rank ADRs ahead of pneumonia and diabetes.⁴ Thus the concern felt by many people regarding what side effects they are likely to experience is very valid: even a brief glance at the most common or important side effects may be rather alarming. The side effects of psychopharmacological drugs can be very serious, including loss of muscular coordination, slowing of reactions, addiction, and psychiatric conditions other than the one targeted by the drug (eg, depression or anxiety).

The prescription of drugs that may have serious side effects is not a satisfactory area for a trial-and-error strategy, by which one might prescribe or take a drug with reasonable hope for good results but without knowing in advance what will happen. Even if side-effect profiles are admittedly dynamic, the risk:benefit ratio positive, serious side effects statistically uncommon, and prescription of the drug in agreement with the gold standard of psychiatric treatment in a given context, a physician or a patient might *still* hesitate to prescribe or take it, and wish to know if her/his individual biological struc-

ture is compatible with the drug or not. Will the drug help? If so, at what price? What can be done to optimize its therapeutic effects?

Until recently, there were no options available other than a probability calculus based on data collected from previous and ongoing experience. There were scant possibilities to determine in advance how the patient as an individual would react to the drug. Unsatisfactory, perhaps, but unavoidable: he or she had to take it to find out, a fact that we have “generally accepted with a certain fatalism.”⁵

The door to making such informed individual predictions was opened when, in the mid 1950s, the link between genetic makeup and drug metabolism was identified⁶; ie, when it was discovered that the causes for individual variation in drug response could be genetic.⁷ More precisely, when the *extent* to which the causes of diverse drug response could be genetic was realized, for the genetic determination of the capacity of an organism to respond to its environment has long been accepted in biology,⁸ including the implication of enzymes in the detoxification of foreign substances.⁹ In addition to nongenetic and environmental causes and lifestyle factors, eg, age, gender, family support, good diet, care in following prescriptions, etc, variations in DNA sequence among individuals (genetic polymorphisms) were also found to be involved in the response to drug therapies.¹⁰ Accordingly, knowledge of the individual genome became strongly relevant to drug prescription.¹¹

Increasing knowledge of the human genome has given rise to the development of genomic medicine, genetic testing, and also helped in diagnosing some unusual disorders; still, the impact of genetics in medicine during the 20th century was relatively modest.¹² The recent development of new technologies for genetic testing has promoted new studies in how drugs and genes interact with potentials for much larger impact.¹³ Pharmacogenetics (a term coined in the 1950s¹⁴) is the study of individual variations in drug response due to heredity. It can be distinguished from pharmacogenomics, a broader term denoting all genes in the genome that may influence drug response, but the terms are often used interchangeably.¹⁵ There is considerable hope that new and more effective treatments for numerous mental disorders can result if drugs are developed that specifically target the responsible genes, eg, schizophrenia susceptibility genes.¹⁶

If drug prescription can be personalized, ie, tailored to suit the individual's genetic makeup,¹⁷ this holds promise

of enormous benefits in terms of, notably, personalized medication with adjusted therapeutic doses, predictable drug responses, reduced ADRs, and personal health planning.¹⁸ It should be noted that personalization and individualization, depending on how the concepts are interpreted, need not mean the same thing, and that they are in this context a matter of degree. Here, “personalized medication” can logically, but not realistically, be interpreted as medication developed to suit the singular individual. The realistic interpretation is that personalized medication is “relatively individualized” in the sense of drugs having a more limited group specificity than the earlier “one size fits all” drugs.

Other suggested benefits are considerable time and cost reductions in the pharmaceutical development,¹⁹ and the possibility of pharmacogenomics to simplify the clinical trial process.²⁰ The prospects are exciting, but at the same time, these new techniques stand faced with important ethical, legal, and social challenges that need to be met in order for the scientific advances to be responsibly applied. Below, the ethical balance between challenges and opportunities of personalized medicine in psychiatry from the points of view of adequacy, cost, and therapeutic equity, are reviewed.

Sound promotion versus hype

The sequencing of the human genome and the tentative identification of genes' underlying susceptibility to mental disorders suggest the possibility of developing novel and more effective treatments for these disorders. Increased knowledge of the pathways for the pathophysiology of major mental illnesses can, it is hoped, lead to major therapeutic breakthroughs, the assumption being that understanding of the pathophysiological basis of these illnesses will enable the development of targeted drugs and new curative therapies.²¹

On the basis of genetic knowledge about patients' drug metabolic status, several studies recommend adjustment of therapeutic doses of antidepressants²² or antipsychotics²³ in relation to CYP2D6, CYP2C9, and CYP2C19 phenotypes. The implementation of these techniques in clinical practice—which is the ultimate goal of pharmacogenomics research in this field—can significantly improve psychiatric treatment in terms of adequate dosing, reduced side effects, averted toxic events, and improved treatment adherence and efficacy.²⁴ On the other hand, looking at the development in pharmaco-

nomics from the perspective of earlier hopes for gene transfer-based therapies, there is a non-negligible risk that scientists and their funding agencies, as well as the pharmaceutical industry, play up or hype the possibilities.²⁵

The primary concern is with scientific adequacy. Are the scientific underpinnings of the pharmacogenomic promises sound? Do the players sufficiently acknowledge the scientific uncertainties that are connected to pharmacogenomics research; for example, the complex interactions between genes/brain/environment that underlie the development of mental disorders? In order to appreciate the significance of genetic explanations of complex and heterogeneous disorders, such as schizophrenia, eg, in terms of the genetic susceptibility for its development, it is necessary also to understand the role of epigenetic factors (heritable genomic functions that are not contained in the DNA sequence code) and factors related to the psychosocial environment.²⁶ Likewise, in order to properly assess genotype-specific psychopharmacological products, complex epigenetic interactions must be taken into account. The human brain is fundamentally a biosocial structure, and mental health throughout life depends on social as well as biological conditions.²⁷ The brain develops within a “genetic envelope,” but the evolution of its architecture is subject to important social impact, notably, through the gigantic weight of the cultural imprints epigenetically stored in our brains.²⁸ The formation of synapses is both prenatal and postnatal; it is far from complete at birth. The postnatal development of the human brain lasts considerably longer than in any other animal. The most intense development occurs during the first 2 years, but it continues to puberty and after, and the highest executive functions that are determined by the frontal lobe are not fully mature until the age of around 20.²⁹ The environment is important for this process to be efficient. If neural networks are not active, they vanish³⁰: “Use it or lose it!” as the mantra goes. In the absence of adequate stimulation, the cerebral network suffers irreversible injury,³¹ and serious mental disorders might develop.

Genetic, epigenetic, neurophysiologic, and psychosocial explanations of mental illness are complementary; they do not stand opposed in modern psychiatry. However, a correct understanding of the interactions between these distinct perspectives in the complex causal structures underlying mental disorders and their curative therapies is hard to achieve. This is not a new challenge, specific to

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pharmacogenomics, but a classical one that is reactualized in this new context. More effective treatments for mental disorders can indeed result if drugs are developed that specifically target the genes responsible. Yet the role of genes in causing mental disorders is extremely complex, as is the connection between genotype and phenotype in drug metabolism.³² It is, for example, not possible to base high-probability predictions of drug responses on single genetic variations.³³ Whilst the possible contributions of molecular biology to psychopharmacological drug discovery are important,³⁴ they must not be overemphasized or oversimplified.³⁵

It is important and legitimate for science, health care, and the pharmaceutical industry to try to promote new ideas and new types of drugs; however, if the expectations are exaggerated this may undermine public trust³⁶ and reduce financial support in the longer perspective. This is what happened to gene therapy: “When legitimate promotion became hype, followed by very public failures of clinical trials, venture capital and government sponsors withdrew from the field. The result was that scientific research suffered, and the public and other stakeholders were left holding an empty bag of promises.”³⁷

It has been claimed that enthusiasts within the academic and business fields of pharmacogenomics are guilty of too much speculation and unsubstantiated claims.³⁸ Skeptics point not only to the scientific uncertainty concerning the promises held out, but also to exaggerations in the promised reductions in ADRs,³⁹ and to the cost:benefit ratio suggested. There are signs of hype being created, when, in 2006, the pharmaceutical industry predicted that by 2010, “the discovery and development process will take half as long as it does now, and costs per drug will fall to a quarter of the current average.”⁴⁰ It is not impossible that their prediction will come true in due course, but we are not there yet, and at the time of writing that prediction seems, at least timewise, overly optimistic.

The sociological analyses of these expectations have focused on how key actors communicate visions about future prospects of the new technology.⁴¹ These key actors represent different interests, eg, industry, government, health care providers, or patient groups. Their visions are seen as coconstructions where each actor is actively helping to shape the trajectory of an emerging promising technology.⁴² Even bioethics is suggested as a helpmate, actively recruited by pharmaceutical companies and the biotech scientific community in order to

serve as a “political brooker.”⁴³ A basic message in these sociological analyses is that industry, the medical profession, and patient groups are coresponsible for producing hype, and they call for a more social-science based analysis of the science behind pharmacogenomics to obtain a more realistic view of what can actually be achieved, to unravel the interests pressing for early implementation, and to deconstruct the hype.⁴⁴ In that context, it must not be ignored that social scientists, eg, ethicists, themselves may feed on the hype and be guilty of producing it. In other words, the methods of social science should be used without, however, excluding social science as an object for scrutiny.

Cost versus benefit

The first-generation antipsychotic drug clozapine is still recommended in the UK National Institute of Health and Clinical Excellence (NICE) 2009 update to its schizophrenia guidance, but in a 2002 Press Release, NICE “recommends newer antipsychotic drugs as one of the first-line options for schizophrenia.”⁴⁵ The choice between newer and first-generation drugs depends in part on the relative benefits of the drugs and their side effects, and in part on the health care budget.

An important reason to recommend newer rather than first-generation psychopharmacological drugs is that the latter tend to have more severe side effects (eg, heart disorders such as myocarditis and cardiomyopathy, the blood disorder agranulocytosis, or tardive dyskinesia, a movement disorder that is potentially irreversible). On the other hand, the newer drugs tend to be more expensive, sometimes considerably so. Often the incremental efficacy is not very spectacular, but the tolerance is improved at a cost that is unbearable for the health care system. Hence, there is a clear health care budget issue involved in the selection of drugs.

Developing new drugs is an increasingly costly procedure.⁴⁶ The development phase can take many years and is very expensive. The testing phase needed to determine, eg, if the drug is effective, safe, and by what method and dosage it is best delivered to the organ system, can also take many years and is likewise very expensive. More and more requirements are raised by the regulatory agencies, and, of potential new medicines, few will ever reach the stage of marketing and selling—a phase that can cost even more than the preceding two combined. These factors jointly make pharmaceutical

development extremely costly, and consequently, pharmaceutical companies do what they can to recoup their outlays.

In recent years, the balance of power has shifted, and the market has become more difficult for the pharmaceutical companies, due to, for example, expiring patents, attrition in the pipelines, and the fact that governments, insurance companies, and patients increasingly dictate what kind of drugs they want, and how much they are willing to pay for them. This means that it is not just the drug makers who define the threshold of innovation, but also the health care demanders. In this situation, where the pharmaceutical industry has seen its value dwindle compared with the glory days of the 1990s, the contributions of molecular biology to drug discovery hold promise of increased profit for the pharmaceutical companies.

Concerning the cost:benefit ratio of pharmacogenomic drug development, there are profoundly different visions of the future. According to the optimistic vision, a better understanding of how different diseases function both at a molecular level and as part of a biological system might enable the industry to define diseases far more precisely, and to develop drugs that are targeted towards specific disease types, rather than making one-size-fits-all drugs focusing on symptoms shared by a range of different diseases.⁴⁷ Many new drugs will then be based on biology rather than chemistry because biologic entities are typically more predictable and less toxic than chemical entities. In the aim to “get the right drug into the right patient,”⁴⁸ human research subjects will be genotyped in clinical trials to find out likely drug responses, a development also predicted importantly to reduce the time and cost of making new drugs.

If that prediction is correct, then the cost of drug development might pose less of a problem in the case of targeted medication than in the case of one-size-fits-all drugs. Pharmacogenomic developments could thus lead to better health care without increasing the customer prices, and perhaps even reducing them. This can then be a win-win situation, where patients receive better health care whilst industry boosts its revenues.

Skeptics (amongst whom we also find some sectors of the pharmaceutical industry)⁴⁹ recommend a more cautious view, arguing that the niche products that pharmacogenomics would produce risk segmenting the market, increasing the development costs, and reducing profits. The research, argue the skeptics, will take longer than

predicted to produce clinical applications, and that the alleged cost-saving will therefore not be provided.⁵⁰

Of course, the cost:benefit ratio of new therapeutic cures may be difficult to determine in advance; yet the argument of pharmacogenomic cost-efficiency can be questioned on a general basis. The market for a genotype-specific drug is perforce smaller than that of the one type fits all variety. Even if the development process becomes more efficient, the development of highly specialized drugs that target small rather than large populations can also lead to very expensive drugs. The need for pharmaceutical companies to recoup their investments is an economic reality that can clash with the interests of health care, and it is not self-evident that the latter's concerns will outweigh the former.

Therapeutic winners versus losers

The screening of participants in clinical trials by genotype raises several ethical problems. Such stratification might lead to the unfair representation of specific groups in these trials, as well as a reduction in the number of subjects included, which could affect the study's external validity and clinical applicability.⁵¹ Even with more cost- and time-efficient clinical trials, if researchers can recruit only people with a certain genotype for the testing of a specific drug,⁵² there is a risk connected to the fact that the prospective drug is tested only on a small and genetically homogenous group. Side effects might go undetected in the case of people who do not have this genotype, which means that a drug could be marketed with less premarketing exposure and less information about adverse effects. This may not be a problem if only patients with the tested genotype use it, but if (eg, through prescription error, or nonprescribed uses) someone with a different genotype takes it, the knowledge of possible additional side effects for these people is wanting. This is different from drug errors with the randomized tested traditional drugs. In the case of the latter, if a person unjustifiably takes a nonprescribed drug, or if a psychiatrist erroneously prescribes a drug, eg, an antidepressant, the possible risks and side effects are reasonably well foreseeable, and can probably be treated if the person seeks medical assistance. If the same person erroneously takes a genotype-specific drug, there is no tested knowledge about what might happen.

This is not an argument against the development of genotype-specific drugs, but an argument for the development

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of a social infrastructure to handle their distribution. The problem highlights many challenges involved in integrating pharmacogenomic drugs into psychiatric care, eg, the need for simple and accessible pharmacogenetic tests with clinical guidelines that allow psychiatrists and health care personnel to use these tests adequately, and to prescribe or recommend pharmacogenetic drugs,⁵³ as well as the need for effective measures to prevent nonprescribed use. The genetic information obtained must also be legally safeguarded to protect privacy and confidentiality,⁵⁴ and calls for caution have been made to “regulate the use of genetic tests.”⁵⁵

A further problem remains, from the point of view of the patient, that is connected to the costs involved in targeted drug development. This concerns the fact that some people may belong to less profitable patient groups.

In order to regain the investment in a drug that is targeted towards a small population, the price must be higher than if the drug were able to be distributed to a large population. This economic principle poses a problem for so-called “orphan diseases,” ie, medical conditions that are either too rare, or that touch populations too poor for drug development in that area to be profitable. Less profitable patient groups stand a smaller chance of having remedies developed than profitable patient groups with diseases that are also prevalent in developed countries. To remedy the situation, public policies in many countries fund or facilitate research aiming to produce “orphan drugs” specifically targeted to treat these rare conditions, or these diseases that primarily haunt poor populations. Now pharmacogenomics introduces a new way of belonging to a less profitable patient group. To the traditional criteria of having a rare disease, or being burdened by poverty, we may now add having a rare genotype.

When new pharmacogenomic drugs are developed they need to be tested in specific patient groups targeted by specific drugs. However, it might be difficult to find a sufficient number of patients for a trial of rare variants of individual biomarker profiles.⁵⁶ It can also be expensive to develop a new drug for such small groups. Patients with less profitable genotypes are therefore at risk of becoming “therapeutic orphans,” and governments may need to extend their orphan drug policies to remedy this additional form of inequity.⁵⁷

If pharmacogenomic drug development enables precision in the inclusion of patients that can be helped by a

drug, it ipso facto entails the equally targeted exclusion of those that cannot. The limit between pharmacological inclusions versus exclusions can in some cases be a question of race, or ethnicity. For example, drugs to treat high blood pressure, or hypertension, have different effects on black versus Caucasian populations, as the high number of clinical trials investigating this listed on the US National Institute of Health’s Web site on clinical trials illustrates.⁵⁸ The concept “race” is scientifically controversial; some claim that “race is biologically meaningless,”⁵⁹ whereas others argue that this depends on how the concept is defined.⁶⁰ In pharmacology, it seems well established that different ethnic groups, at least, respond in different manners to drugs, which is one reason why the International Conference on Harmonization (ICH) was created to harmonize the technical requirements for registration of pharmaceuticals for human use in the three main regions: Europe, the US, and Asia. Japan has insisted that due to their ethnic pharmacological specificity, phase 1 studies must always also be done in Asian populations.⁶¹

If therapeutic (in)equity can be connected to race, or ethnicity, this is something that the social assessment of pharmacogenomic drug development needs to take into account. As the problem of orphan drugs and diseases illustrates, pharmaceutical companies have no obligation to develop drugs in an equitable manner, eg, with racial or ethnic nonbias. If a racial or ethnic group is very small, for example, the cost:benefit ratio for developing drugs to treat that group may not be economically rewarding. This is a further form of possible discrimination that governments may need to deal with in their health care and health research policies in order to ensure the protection of genetic or ethnic minorities.

Conclusion

Personalized medicine in psychiatry, eg, in the form of tailored antidepressant or antipsychotic treatment, has already made important progress, notably in terms of adjusted therapeutic doses, and predictable drug responses or drug-induced side effects. Although promising, these opportunities also give rise to numerous scientific, ethical, legal, and social challenges. An adequate assessment of personalized medicine in psychiatry must within all these perspectives be based both on analyses of the science behind pharmacogenomics research to get a realistic view of what can actually be achieved, and on

analyses of the relevant sociopolitical structures surrounding this research. Justified hopes must not be inflated to become hypes of exaggerated promises that would serve no legitimate purpose. Signs of hype, for instance in the form of pressures for rash implementation, should be forestalled and a realistic view presented. Realistic cost:benefit analyses are needed to produce reasonable health care budgets; pharmacogenetic tests must be developed together with guidelines for their use, so that the new techniques can be responsibly implemented in clinical practice; public policies on orphan diseases and drugs may need to be extended to avoid creating a new group of “genetic orphans”; whilst legal

regulations are needed to ensure that the genetic information obtained is safely protected from misuse, and that genetic or ethnic minorities are protected from discrimination.

The ethical considerations that have here been considered in terms of adequacy, cost, and therapeutic equity raise no objections to the development of personalized medicine per se in this domain. Rather, they point to the necessity of developing a social infrastructure with adequate guidelines to ensure the responsible implementation of these promising new techniques. □

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REFERENCES

- National Institutes of Mental Health: www.nimh.nih.gov/about/budget. Accessed May 15, 2009.
- McEvoy JP, Lieberman JA, Stroup TS, et al. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. *Am J Psychiatry*. 2006;163:600-610.
- UK National Institute of Health and Clinical Excellence. Core interventions in the treatment and management of schizophrenia in adults in primary and secondary care. 2009 update. www.nice.org.uk/Guidance/CG82. Accessed May 15, 2009.
- Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA*. 1998;279:1200-1205.
- Weinstein JN. Pharmacogenomics – teaching old drugs new tricks. *N Engl J Med*. 2000;343:1408-1409.
- Bullock PL. Pharmacogenetics and its impact on drug development. *Drug Benefit Trends*. 1999;11:53-54.
- Linder MW, Prough RA, Valdes R Jr. Pharmacogenetics: a laboratory tool for optimizing therapeutic efficiency. *Clin Chem*. 1997;43:254-266.
- Mancinelli L, Cronin M, Sadée W. Pharmacogenomics: the promise of personalized medicine. *AAPS PharmSci*. 2000;2:Article 4.
- Garrod AE. The incidence of alcaptonuria: a study in chemical individuality. *Lancet*. 1902;ii:1616-1620.
- Grahame-Smith, DG. How will knowledge of the human genome affect drug therapy? *Br J Clin Pharmacol*. 1999;47:7-10.
- Evans WE, Johnson JA. Pharmacogenomics: the inherited basis for interindividual differences in drug response. *Annu Rev Genomics Hum Genet*. 2001;2:9-39.
- Emery J, Hayflick S. The challenge of integrating genetic medicine into primary care. *BMJ*. 2001;322:1027-1030.
- Snedden R. The challenge of pharmacogenetics and pharmacogenomics. *New Genet Soc*. 2000;19:145-164.
- Weber WW. *Pharmacogenetics*. New York, NY: Oxford University Press; 1997.
- Elliot ESV Vesell. Advances in pharmacogenetics and pharmacogenomics. *J Clinical Pharmacol*. 2000;40:930-938.
- Harrison PJ, Weinberger DR. Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. *Mol Psychiatry*. 2005;10:40-68.
- Science. New research horizons. *Science*. 1997;277:393-395.
- Fierz W. Challenge of personalized health care: to what extent is medicine already individualized and what are the future trends? *Med Sci Monit*. 2004;10:RA111-123.
- IBM Business Consulting Service. Personalized Health Care 2010. Are you ready for information-based medicine? IBM Institute for Business Value Study. 2003. <http://www-935.ibm.com/services/us/index.wss/ibvstudy/imc/a1001624?cntxt=a1000056>. Accessed May 15, 2009.
- McCarthy A. Pharmacogenetics: implications for drug development, patients and society. *New Genet Soc*. 2000;19:135-164.
- Insel TR, Scolnick EM. Cure therapeutics and strategic prevention: raising the bar for mental health research. *Mol Psychiatry*. 2006;11:11-17.
- Kirchheiner J, Brosen K, Dahl ML, et al. CYP2D6 and CYP2D19 genotype-based dose recommendations for antidepressants: a first step towards subpopulation-specific dosages. *Acta Psychiatr Scand*. 2001;104:173-192.
- Kirchheiner J, Nickchen K, Bauer M, et al. Pharmacogenetics of antidepressants and antipsychotics: the contribution of allelic variations to the phenotype of drug response. *Mol Psychiatry*. 2004; 9: 442-473.
- Kirchheiner J, Fuhr U, Brockmoller J. Pharmacogenetics-based therapeutic recommendations – ready for clinical practice? *Nat Rev Drug Discov*. 2005;4:639-647.
- Martin PA. Genes as drugs: the social shaping of gene therapy and the reconstruction of genetic disease. *Sociology Health Illness*. 1999;21:517-538.
- Petronis A. The origin of schizophrenia: genetic thesis, epigenetic antithesis, and resolving synthesis. *Biol Psych*. 2004;55:965-970.
- Evers K. *Neuroéthique. Quand la matière s'éveille*. Paris, France: Éditions Odile Jacob; 2009.
- Changeux JP. *The Physiology of Truth. Neuroscience and Human Knowledge*. Cambridge, Mass: Belknap, Harvard University Press; 2004.
- Lagercrantz H. *I barnets hjärna*. Stockholm, Sweden: Bonnier Fakta; 2005.
- Wiesel TN, Hubel, D. Effects of visual deprivation on morphology and physiology of cells in the cat's lateral geniculate body. *J Neurophysiol*. 1963;26:978-993.
- Katz LC, Shatz CJ. Synaptic activity and the construction of cortical circuits. *Science*. 1996;274:1133-138.
- Arranz MJ, de Leon J. Pharmacogenetics and pharmacogenomics of schizophrenia: a review of last decade of research. *Mol Psychiatry*. 2007;12:707-747.
- Meltzer D, Raven A, Detmer DE, et al. *My very own medicine: what must I know? Information policy for pharmacogenetics*. London, UK: Wellcome Trust; 2003.
- Roth BL. Contributions of molecular biology to antipsychotic drug discovery: promises fulfilled or unfulfilled? *Dial Clin Neurosc*. 2006;8:303-309.
- Vesell ES. Therapeutic lessons from pharmacogenetics. *Ann Intern Med*. 1997;126:653-655.
- Evers, K. Science and Trust in Conditions of Uncertainty. 2003. Paper presented at: the 2nd Dialogue on Science: Pervasive Computing, Science and Public Trust; Academia Engelberg, October 15-17; 2003, Engelberg, Switzerland.
- McDonald M, Williams-Jones B. Governance and stem cell research: towards the clinic. *Health Law Review*. 2008;16:27-40:33.
- Richards, T. Three views of genetics: the enthusiasts, the visionary and the sceptic. *BMJ*. 2001;322:1016-1017.
- Corrigan OP. Pharmacogenetics, ethical issues: review of the Nuffield Council on Bioethics Report. *J Med Ethics*. 2005;31:144-148.

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La medicina personalizada en psiquiatría: oportunidades y desafíos éticos

Los progresos farmacogenómicos generan esperanzas para la medicina personalizada dentro de la psiquiatría en cuanto a ajuste de dosis terapéuticas, respuestas predecibles, reducción de las reacciones adversas a los fármacos, diagnóstico precoz y programas personales de salud. Las posibilidades son apasionantes, pero al mismo tiempo estas nuevas técnicas se enfrentan con importantes desafíos científicos, éticos, legales y sociales, los que requieren estar de acuerdo con los avances científicos para que ellas se puedan aplicar responsablemente. Esta revisión discute el balance ético entre los desafíos y oportunidades de la medicina personalizada en psiquiatría en relación con aspectos de adecuación, relación costo beneficio y equidad terapéutica. Se argumenta que el carácter prometedor de estas alternativas terapéuticas hace aun más importante evitar la exageración de las expectativas y que se necesita desarrollar una sofisticada infraestructura social para asegurar la aplicación realista y responsable de la medicina personalizada en psiquiatría.

Médecine personnalisée en psychiatrie : opportunités et défis éthiques

Les développements de la pharmacogénomique ont tenu leurs promesses pour la médecine personnalisée en psychiatrie en permettant d'ajuster les doses thérapeutiques, de prévoir les réponses, de diminuer les effets indésirables, d'établir des diagnostics précoces et des calendriers personnels de santé. Les perspectives sont prometteuses mais en même temps, ces nouvelles techniques doivent faire face à des défis scientifiques, éthiques, légaux et sociaux importants afin de permettre aux avancées scientifiques de s'appliquer de manière responsable. L'équilibre éthique entre défi et opportunité de la médecine personnalisée en psychiatrie fait l'objet ici d'une discussion au sujet de sa pertinence, de son rapport coût/bénéfice, et de son équité thérapeutique. La nature prometteuse de ces possibilités thérapeutiques prend le pas sur le risque d'attentes exagérées ; la mise en application réaliste et responsable de la médecine personnalisée en psychiatrie demande de développer une infrastructure sociale sophistiquée.

40. IBM Business Consulting Service. Pharma 2010: The Threshold of Innovation. IBM Institute for Business Value Study. Last updated 09 Feb 2006. <http://www-935.ibm.com/services/us/index.wss/ibvstudy/limc/a1001099>. Accessed May 15, 2009.

41. Hedgecoe A, Martin PA. The drugs don't work: expectations and the shaping of pharmacogenomics. *Soc Stud Science*. 2003;33:327-364.

42. Brown N, Rappert B, Webster, A, eds. *Contested Futures: a Sociology of Prospective Techno-Science*. Aldershot, UK: Ashgate Press; 2000.

43. Salter, B, Jones, M, Human genetic technologies, European governance and the politics of bioethics. *Nat Rev Gen*. 2002;3:808-814.

44. Williams-Jones B, Corrigan OP. Rhetoric and hype. Where's the ethics in pharmacogenomics? *Am J Pharmacogenomics*. 2003;3:375-383.

45. UK National Institute of Health and Clinical Excellence. 2002/030 Press Release. http://www.nice.org.uk/newsevents/pressreleases/pressreleasearchive/pressreleases2002/2002_030_nice_recommends_newer_antipsychotic_drugs_as_one_of_the_first_line_options_for_schizophrenia.jsp. Accessed May 15, 2009.

46. DiMasi JA, Hanses RW, Grabowski HG. The price of innovation: new estimates of drug development costs. *J Health Econ*. 2003;22:151-185.

47. Ginsburg GS, McCarthy JJ. Personalized medicine: revolutionizing drug discovery and patient care. *Trends Biotechnology*. 2001;19:491-496.

48. Marshall A. Getting the right drug into the right patient. *Nat Biotechnol*. 1997;15:1249-1252.

49. Moldrup C. When pharmacogenomics goes public. *New Genet Soc*. 2002;21:29-37.

50. Coats AJS. Pharmacogenomics: hope or hype [editorial]? *Int J Cardiol*. 2000;76:1-3.

51. Issa AM. Ethical considerations in clinical pharmacogenomics research. *Trends Pharmacol Sci*. 2000;21:247-249.

52. Roses AD. Genome-based pharmacogenetics and the pharmaceutical industry. *Nat Rev Drug Discov*. 2002;1:541-549.

53. DeLeon J, Armstrong SC, Cozza KL. Clinical guidelines for psychiatrists for the use of pharmacogenomic testing for CYP450 2D6 and CYP450 2C19. *Psychosomatics*. 2006;47:75-85.

54. Anderlik MR, Rothstein MA. Privacy and confidentiality of genetic information: what rules for the new science? *Annu Rev Genomics Hum Genet*. 2001;2:401-433.

55. Holtzman N. Are genetic tests adequately regulated? *Science*. 1999;286:4539.

56. Palmer LJ, Silverman ES, Drazen JM, Weiss ST. Pharmacogenomics of asthma treatment. In: Licinio J, Wong ML, eds. *Pharmacogenomics: The Search for Individualized Therapies*. Weinheim, Germany: Wiley-VGH, 2002:215-234.

57. Rothstein MA, Epps PG. Ethical and legal implications of pharmacogenomics. *Nat Rev Genet*. 2001;2:228-231.

58. <http://www.clinicaltrials.gov/>. Accessed May 15, 2009.

59. Schwartz RS. Racial profiling in medical research. *N Engl J Med*. 2001;344:1392-1393.

60. Risch N, Burchard E, Ziv E, Tang H. Categorization of humans in biomedical research: genes, race and disease. *Genome Biol*. 2002;3:2007.1-2007.12.

61. <http://www.fda.gov/cber/ich/ichguid.htm>. Accessed May 15, 2009.