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Pharmacogenetics and ethical considerations: why care?

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Introduction

Pharmacogenetics is an area of research encompassing a variety of different goals and applications (for an overview see Nuffield Council on Bioethics[1]). Basic research interests include for example drug metabolism pathways. Clinical applications like the enhancement of drug safety and efficacy through more precise prescriptions and the more precise treatments of molecular disease subgroups are prominent goals in the (still not widespread) public perception of the field. Yet very important aims lie also in the realm of drug development, for example the development of pharmacogenetically optimized or 'neutral' drugs, the improvement of clinical studies through patient selection, and the discovery of new targets.

As some of these goals are more realistic to achieve than others and since different applications could be associated with differing societal consequences, it is hardly possible to summarize the ethical aspects for all of these applications without losing specificity. Also, due to the uncertainties of future developments in the field, thoughts on the ethical aspects are somewhat preliminary at this point. However, some aspects of pharmacogenetics are likely to have a potentially profound impact on medical practice, research and on society as a whole. Therefore, much thought has been invested in the anticipation of ethical, legal and social aspects of pharmacogenetics, resulting in the publication of several comprehensive studies[1–3] and an impressive number of research and review papers on these issues.[4–8] The more general issues needing to be addressed have been identified and there is a widespread notion that more focused discussions of particular aspects are needed, which is also reflected in the number of original research papers featuring different aspects.[9–11]

However, it is striking that the debate on ethical and regulatory issues of pharmacogenetics is still mostly a scientific one and a public debate is still missing.[2] The number of industry stakeholders involved in the ethical debate is also noteworthy. There seems to be a large interest to address the ethical issues in advance, which can be seen as a paradigmatic case of successful integration of societal concerns in the development process. Yet there is a possibility that this could draw attention to certain ethical issues and not to others. The issues most written about may not be the issues of greatest importance to the public.

In spite of the many publications, the ethics of pharmacogenetics is still a rather new field needing further investigations as pharmacogenetics moves towards clinical utility.

Ethics and pharmacogenetics

Of the many different ethical aspects that are being discussed in the context of pharmacogenetics, most are neither new nor specific to pharmacogenetics, but also of relevance to other fields. It is not the severity, but the large number of ethical issues pharmacogenetics touches upon that makes it a subject of concern (Table 1). (This review summarizes issues raised by several authors from a variety of different ethics approaches. Conclusions and statements not cited are based on my analysis of ethical aspects of pharmacogenetics[12] using the Principles of Biomedical Ethics approach of Beauchamp and Childress.[13]).

General considerations

Goals

The different goals of pharmacogenetics are usually regarded as desirable, unproblematic and worthy, but some of them are criticized for being partly unrealistic.[8,14]

Genetic information

Many ethical examinations focus on issues of confidentiality, privacy and the use and storage of genetic information. In this context, different options of informed consent and data protection measures are being discussed as well as potential third party interests (insurers, employers, relatives). These questions are of particular concern, because some pharmacogenetic tests carry the possibility of revealing sensitive additional information for example on disease progress or disease predispositions.[6] They are also relevant to the establishment and use of biobanks for research purposes. In this context, the notion of informational self-determination is frequently mentioned and the status of pharmacogenetic information is discussed in the context of genetic exceptionalism, the idea that genetic information is significantly distinct from any other medical information.

Other issues

Other areas of concern are potential changes in the doctor–patient relationship as well as regulatory issues

Table 1 Ethical considerations in pharmacogenetics

Goals
Genetic information
Additional information revealed by a pharmacogenetic test
Confidentiality, privacy and the use and storage of genetic information
Genetic exceptionalism, geneticization of society
Changes in professional-patient relationships
Handling complexity
Education and training
Pharmacogenetics at home
Regulatory issues
Service provision, quality control, off-label use and liability
Discrimination and stigmatization of groups and individuals
Stratification of patients and study participants according to genotype
Use of racial and ethnic categories
Availability and access to pharmacogenetic services
Orphan drug policies
Research on the vulnerable

Table modified from the reference Schubert[8].

like specifications on how pharmacogenetic services should be provided and who should provide them, on necessary quality control measures, on the prevention of nonindicated (off-label) use and on liability. Also, the stratification of patients and study participants according to genotype is the subject of debate, and the possibility of stigmatization and discrimination of groups and individuals as well as the availability of and access to drugs are being discussed.[7–9,11].

It is striking that some of the most important issues, like the difficulty to protect data collected in biobanks or the unequal global distribution of medical resources, cannot be adequately addressed in the context of pharmacogenetics alone. It is uncertain to what extend these issues should play a role in ethical considerations of the field. Can one ignore them because they are not specific to this context, or are they particularly pressing because they are so prevalent in many areas?

Considerations for clinical practice

Handling complexity

Among the most important issues that need to be addressed in clinical practice is a likely increase in the complexities of the doctor–patient encounter. In order to harvest the benefits of pharmacogenetic tests, it may be necessary to integrate vast amounts of data into therapeutic concepts. To this end, doctors may need to rely on computerized data interpretations.[14,15] However, although databases might aid automated prescriptions in the future, the information provided still needs to be integrated into a therapeutic scheme considering patient history and the specifics of each case, and cannot replace counselling.[2] As result of this it is also advisable that pharmacogenetic tests should be performed by doctors and not marketed online or over the counter.[1]

Education and training

As genetics services expand there will be an increasing need for genetic knowledge on all levels of medical services. Potential harms to patients that need to be avoided are stressing the need to address educational issues. Doctors need to be well educated if they are to decide when a test is obligatory and/or the result has to be followed and when it is open to their own judgement if the result may be ignored, which relates to the question of non-indicated, off-label use. Therefore, it is critical to develop ways to integrate pharmacogenetics into educational curricular of health care providers.[3,16–18] Both education and implementation could be different for specialists and generalists, as costs and benefits of pharmacogenetic may vary significantly between clinical situations.

In addition to special training for physicians of different fields, it may also be necessary to establish specialists for pharmacogenetic services and advices.[19] Criteria for the use of pharmacogenetic information are needed, yet it seems unlikely that they can be thought up without a close interaction with the practical experiences gained as pharmacogenetics moves into clinical practice. If the development of pharmacogenetics is more 'a logical, consequent step in the history of medicine-evolution, rather than revolution',[20] then this should also be true of the guidelines regulating the field.

Pharmacogenetics at home

While the future development of the physician–patient relationship has received some attention, further research is needed on implications for other health professionals. Additionally, it seems necessary to address the question of how pharmacogenetics could affect the often-neglected part of medicine that consists in services performed by family members of patients at home.

Data sensitivity

Since not all pharmacogenetic tests are of the same problem potential, they should not all be treated equally. It is likely that some pharmacogenetic tests will be used without special informed consent as a routine diagnosis, while others will require protective measures. Rationale for such measures cannot be the fact that the tests are genetic (indeed many pharmacogenetic tests are not or at least not only), but that they are connected to certain risks of discrimination or have implications for relatives.[21] The necessity of informed consent is posed not by the pharmacogenetic data itself, but by

the possibility that a pharmacogenetic test may reveal additional information.[6] However, as the scope of this problem is still unclear, it is too early to decide which tests are of a negligible problem potential. In the long run, criteria will be needed to know when to obtain an informed consent and when to use the test as a routine measure. Such criteria should include medical necessity, positive and negative predictive values of the tests, the possibility of additional information revealed, potential implications for relatives, if the results are valid for the entire life of the individual or only for a particular moment in time, the impact the information could have on the patients life, potential third party interests, the potential of stigmatisation and the difficulty to interpret the tests.

Research on the vulnerable

Another issue deserving attention in the context of informed consent is that of research on the vulnerable, another common issue in bioethics. In order to benefit from pharmacogenetics, vulnerable persons such as those with mental disorders, but also children would need to be included in trials, in the long run. Issues of pharmacogenetics research in children have been discussed for example by,[22] where the need to make the benefits available for children in clinical settings are stressed and it is proposed to base the ethics of research on children on an assessment of risks and harms rather than on the presence or absence of a disease, a notion that needs a critical analysis and specification. Pharmacogenetics in the psychiatric setting has been reviewed and discussed for example by Morley and Hall,[19] including some recommendations for the regulation and distribution of pharmacogenetic testing services and drugs.

Consideration of secondary arguments

As no single argument forbids pharmacogenetic research, secondary arguments are of particular importance in the context of pharmacogenetics. A type of argument of particular relevance is a special form of a slippery slope argument termed escalator argument.[8] Slippery slope arguments are arguments from consequences that claim that a particular action should be rejected (or accepted) because it might be the first step onto a slippery slope leading to undesirable (or desirable) consequences. In contrast, escalator arguments do not assume that there is an automatic slide down the slope, but a more controlled, energy and effort-dependent movement up (positive escalator argument) or down (negative escalator argument) a slope.

Positive escalator arguments in the context of pharmacogenetics claim that investments in pharmacogenetics will lead to a variety of benefits. They are used to motivate the development of the field. Negative escalator arguments claim that a number of negative side effects may accompany the new developments, unless precautions are being taken to prevent for example a geneticization of society, the abuse of data and the discrimination and geneticization of groups.

In the pharmacogenetic realm geneticization of society could consist in a growing importance of genetics to the way we define our lives in genetic terms, due to a more widespread use of pharmacogenetic tests and less restrictive legislature. Discrimination of traditionally defined groups is being discussed in the context of racism in research and clinical practice. The potential to abuse data is particularly relevant to the context of research and the establishment and use of biobanks. At a time when long held liberties are easily cut back in the name of the war against terror in many countries, the problem of data protection is virulent and governmental abuse of data in the name of security interests seems possible.

Conclusion

This paper is focused on ethics in pharmacogenetics and addresses the question why both scientists and the public should care about both pharmacogenetics and ethical aspects of the field. The visions to achieve the worthy goals of pharmacogenetics motivate the development of the field. It is desirable that pharmacogenetic research progresses and that further studies on how it can best be translated into practice are being performed. However, the chances and new developments in the field are leading to an increased need for practitioners to gain knowledge of pharmacogenetics and to integrate this knowledge in education schemes. Also, it is vital to the development of the field to avoid hyping.

Additionally, some ethical considerations point towards the necessity to avoid negative side effects and to regulate certain developments within the field. A special form of slippery slope argument termed escalator argument points towards the issues of data abuse, the use of race and ethnicity in research, and a potential geneticization of society. These issues need to be examined in more detail in further studies. As the future developments of the field are still unclear, ethical considerations are preliminary and pharmacogenetics is still in need of ethical investigations as it progresses. Also, a public debate on certain ethical issues would be desirable, for example to discuss financial aspects and the distribution of services. There is not only a need to educate medical professionals, researchers and the public about pharmacogenetics, but also on ethical issues connected to the field.

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Duality of Interest

None declared

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References

1 Nuffield Council on Bioethics. *Pharmacogenetics: Ethical Issues*. Nuffield Council on Bioethics: London, 2003.
2 Rippe KP, Bachmann A, Faisst K, Oggier W, Pauli-Magnus C, Probst-Hensch N *et al.* (TA SWISS): *Pharmakogenetik und Pharmakogenomik*. TA 48/2004. Bern 2004.
3 European Commission. *Ethical, Legal and Social Aspects of Genetic Testing: Research, Development and Clinical Applications*. Report of the STRATA Expert Group: Brussels, 2004.
4 Mahlknecht U, Voelter-Mahlknecht S. Pharmacogenomics: questions and concerns. *Curr Med Res Opin* 2005; **21**: 1041–1047.
5 van Delden J, Bolt I, Kalis A, Derijks J, Leufkens H. Tialor-made pharmacotherapy: future developments and ethical challenges in the field of pharmacogenomics. *Bioethics* 2004; **18**: 303–321.
6 Netzer C, Biller-Andorno N. Pharmacogenetic testing, informed consent and the problem of secondary information. *Bioethics* 2004; **18**: 344–360.
7 Smart A, Martin P, Parker M. Tailored medicine: whom will it fit? The ethics of patient and disease stratification. *Bioethics* 2004; **18**: 322–343.
8 Schubert L. Ethical implications of pharmacogenetics – do slippery slope arguments matter? *Bioethics* 2004; **18**: 361–378.
9 Lee S. Racializing drug design: implications of pharmacogenomics for health disparities. *Am J Public Health* 2005; **95**: 2133–2138.
10 Mackenzie R. Reprogenetics and pharmacogenetics: in whose best interests? *Med Law* 2005; **24**: 343–354.
11 La Caze A. Does pharmacogenomics provode and ethical challenge to the utilisation of cost-effectiveness analysis by public health systems? *Pharmacoeconomics* 2005; **23**: 445–447.
12 Marx-Stoelting L. *Pharmakogenetik*. LIT: Muenster, 2006 accepted.
13 Beauchamp TL, Childress JF. *Principles of Biomedical Ethics, 5th edn*. Oxford University Press: Oxford, 2001.
14 Schmedders M, Aken Jv, Feuerstein G, Kollek R. Individualized pharmacogenetic therapy: a critical analysis. *Community Genet* 2003; **6**: 114–119.
15 Kollek R, Feuerstein G, Schmedders M, van Aken J. *Pharmakogenetik: Implikationen für Patienten und Gesundheitswesen: Anspruch und Wirklichkeit der 'individualisierten Medizin'*. Nomos: Baden-Baden, 2004.
16 Gurwitz D, Lunshoff JE, Dedoussis G, Flordellis CS, Fuhr U, Kirchheiner J *et al.* Pharmacogenomics education: international society of pharmacogenomics recommendations for medical, pharmaceutical, and health schools deans of education. *Pharmacogenom J* 2005; **5**: 221–225.
17 Frueh FW, Goodsaid F, Rudman A, Huang SM, Lesko LJ. The need for education in pharmacogenomics: a regulatory perspective. *Pharmacogenom J* 2005; **5**: 218–220.
18 Melzer D, Raven A, Detmer DE, Ling T, Zimmern RL. *My Very Own Medicine: What Must I Know? Information Policy for Pharmacogenetics* 2003.
19 Morley KI, Hall WD. Using pharmacogenetics and pharmacogenomics in the treatment of pychiatric disorders: some ethical and economical considerations. *J Mol Med* 2004; **82**: 21–30.
20 Lindpaintner K. Pharmacogenetics and the future of medical practice: conceptual considerations. *Pharmacogenomics* 2001; **1**: 23–26.
21 Green MJ, Botkin JR. 'Genetic Exceptionalism' in medicine: clarifying the differences between genetic and nongenetic tests. *Ann Internal Med* 2003; **138**: 571–576.
22 Freund CL, Clayton EW. Pharmacogenomics and children: meeting the ethical challenges. *Am J Pharmacogenom* 2003; **3**: 309–404.