Pharmacogenetics - opportunities and challenges
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Pharmacogenetics - Opportunities and Challenges

Description of a generic evaluation model to assess the clinical usefulness of pharmacogenetic testing

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Abstract

Pharmacogenetic research tries to explore genetic variability between patients to explain observed differences in effectiveness of a drug therapy or adverse event profile. Pharmacogenetic testing could therefore provide information to better foresee and prevent treatment failure and adverse drug reaction in patients and thus, raises the hope for an individualized pharmacotherapy.

Large-scale efforts in pre-clinical research have led to the development of an increasing number of genetic tests. In contrast, the clinical evidence of their usefulness for clinical practice is limited. The findings of different clinical studies on the same study question rarely allow solid conclusions to be drawn. Evidence-based approaches, however, are required to determine the usefulness of a genetic test in clinical practice. Otherwise we risk that new genetic tests will creep into routine clinical practice as results of technological drive rather than as results of clinical evidence. Thus, if we are not preparing a method to evaluate genetic testing, we risk applying genetic tests of high-cost and uncertain value.

The overall objective was to generate a framework for the field of clinical pharmacogenetics, which describes the level and kind of evidence required to make decisions about the application of new genetic tests in clinical practice. This framework presents a sequential process addressing methodological, clinical, and economic aspects of pharmacogenetic studies. More specifically, with respect to the methodology, the aim was to outline standards applicable to pharmacogenetic research. Concerning clinical aspects, the goal is to describe a meta-epidemiological approach to allow the combination of results on drug effectiveness. And finally, regarding economics, I aimed at proposing a cost-effectiveness model to assess the utility of genetic testing. The feasibility of this complete evaluation model was empirically illustrated using data from the literature of one of the most-researched genetic mutations, the ACE insertion/deletion polymorphism.

In a first step, I evaluated different methodological aspects to determine the most-appropriate study design for pharmacogenetic studies. Advantages and disadvantages of different study designs have been addressed in Chapter 3. Concerning principles of epidemiology, the extent of such differences in
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treatment effects between genetically determined subgroups, defined as effect modification, can only be
determined in randomized controlled trials. In contrast to other non-experimental and experimental study
designs, randomized controlled trials also represent the most appropriate study design to control for
confounding. To further improve the validity of the results, additional relevant methodological criteria
unique to pharmacogenetic studies, such as restriction to a single ethnicity, use of reliable genotype
determination techniques, and sample size calculations, have been presented.

Focusing on the example of the ACE I/D polymorphism, the application of the discussed
methodological standards of pharmacogenetic studies has been explored. I observed a large variability in
study designs used to evaluate the influence of the ACE I/D polymorphism on effects of ACE inhibitors.
Only one-third of these pharmacogenetic studies used an appropriate study design allowing the
quantification of the effect modification by the I/D polymorphism. This illustrates the urgent need to apply
agreed-on methodological recommendations for pharmacogenetic primary studies in order to increase the
number of high quality methodological studies.

In the following chapter, I discuss how the data of different pharmacogenetic primary studies
addressing the same study question could be summarized. The systematic identification and
summarization of evidence-based data have become a central element of research to inform decision-
making in medicine. Historically, evidence-based medicine has focused on the summarization of the
evidence of therapeutic studies. I showed that this methodology can also be applied in an adapted version
to summarize the evidence of pharmacogenetic studies. Compared to literature retrieval of therapeutic
trials, the identification of pharmacogenetic studies is recognized to be more difficult. This argument was
raised due to the inconsistent indexing of these studies in biomedical databases and due to the aggravated
problem of publication bias. Additional problems limiting the summarization of pharmacogenetic data are
mainly attributed to poor reporting of genetic results.
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Chapter 4b represents the first systematic review of pharmacogenetic studies. It shows how the effect modification of the I/D polymorphism in patients treated with ACE inhibitors can be quantified and summarized. However, the lack of sufficient genetic data from reviewed randomized controlled studies precluded drawing any convincing conclusions. Nevertheless, I found a trend towards better response in DD Caucasian to ACE inhibitor therapy compared to II carriers, who seemed not to benefit. Better reporting of genetic data is therefore needed to confirm our preliminary observations concerning better response to ACE inhibitors among Caucasian DD carriers as compared to II carriers.

To finally translate the genetic science into a clinically useful genetic test, not only the effectiveness but also the costs need to be considered. The purpose of such a cost-effectiveness analysis is to structure evidence on clinical and economic outcomes in a way that helps allow for decisions concerning clinical practices. Chapter 5 proposes such a cost-effectiveness evaluation model to allow for justification of pharmacogenetic testing in clinical practice. I used a combination of Decision-analytic and Markov modeling techniques to evaluate the long-term incremental clinical and economic effect of pharmacogenetic testing. Using the data of our systematic review on the I/D polymorphism, I showed that screening patients with nephropathies for this polymorphism before starting ACE inhibitor therapy might likely be beneficial not only from a clinical perspective, but also from a cost saving point of view.

I conclude that this thesis provides a generic evaluation model for pharmacogenetic studies. This model describes the nature of evidence required to inform clinicians about the rational use of pharmacogenetic testing. To my knowledge, this is the first complete description of methods to assess drug effectiveness using a meta-epidemiologic approach and cost-effectiveness evaluations in pharmacogenetic research. The feasibility of this model has been empirically illustrated using data from the literature of the I/D polymorphism. Since all ingredients of the model are in principle available, the model appears to be applicable to the field of pharmacogenetic research at large.
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The application of this methodological framework would ensure not only the conduction of high quality studies, but also adequate analysis and reporting of the results. Improvements of the reliability of pharmacogenetic primary studies would further lead to a better performance of systematic review and subsequent cost-effectiveness analysis. Thus, the presented evaluation model has not only important implications for researchers, who seek to generate evidence relating to pharmacogenetic testing, but also for clinicians, who will need to apply the evidence of pharmacogenetic tests.
Kurzfassung


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Kurzfassung

beruht auf der inkonsistenten Indexierung dieser Studien in medizinischen Datenbanken und aufgrund nicht veröffentlichter Studiendaten (Publication Bias).


Kurzfassung

auch bestätigt werden. Da alle nötigen Teilspekte des Evaluationsmodells prinzipiell vorhanden sind, ist dieses Modell auf das gesamte Forschungsgebiet der klinischen Pharmakogenetik übertragbar.