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Influence of metabolic profiles on the safety of drug therapy in routine care in Germany: protocol of the cohort study EMPAR

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ABSTRACT

Introduction Pre-emptive testing of pharmacogenetically relevant single-nucleotide polymorphisms can be an effective tool in the prevention of adverse drug reactions and therapy resistance. However, most of the tests are not used as standard in routine care in Germany because of lacking evidence for the clinical and economical benefit and their impact on the usage of healthcare services. We address this issue by investigating the influence of pharmacogenetic profiles on the use of healthcare services over an extended period of several years using routine care data from a statutory health insurance company. The goal is to provide clinical evidence whether pre-emptive pharmacogenetic testing of metabolic profiles in routine care in Germany is beneficial and cost-effective.

Methods and analysis The EMPAR (Einfluss metabolischer Profile auf die Arzneimitteltherapiesicherheit in der Routineversorgung) study is a non-interventional cohort study conducted to analyse pharmacogenetic risk factors that are important for drug therapy by means of endpoints relevant for healthcare. The analysis is based on pharmacogenetic profiles and statutory health insurance data. We perform pharmacogenetic, pharmacoepidemiological and pharmacoeconomic analyses using health care utilisation scores and machine learning techniques. Therefore, we aim to include about 10 000 patients (≥18 years) insured by the health insurance provider Techniker Krankenkasse. The study focuses on patients with prescriptions of anticoagulants and prescriptions of cholesterol-lowering drugs. Also, a screening for special pharmacogenetic characteristics will be performed in patients with at least one Y57.9! diagnosis (Complication of medical and surgical care: drug or medicament, unspecified). Outcomes include the utilisation of health insurance services, the incidence of incapacity for work and costs for drugs and treatment.

Ethics and dissemination The protocol was approved by the Ethics Committee of the Medical Faculty, University of Bonn (Lfd. Nr. 339/17). The results of this research project will be published in scientific open access journals and at conferences.

Trial registration number German Clinical Trials Register, DRKS00013909.

Strengths and limitations of this study

- EMPAR is the first study in Germany to analyse pharmacogenetic data matched with statutory health insurance data to evaluate drug safety in routine care.
- The Techniker Krankenkasse routine healthcare database provides reliable information to analyse the influence of pharmacogenetic profiles on the utilisation of healthcare services.
- Possible difficulties in distinguishing between causal diagnoses and adverse drug reactions are addressed by additional information from treatment-related questionnaires provided by study participants.

INTRODUCTION

Adverse drug reactions (ADRs) and therapy resistances increase morbidity and mortality of patients and thus are a clinical problem in routine care. They also complicate drug therapy and exert an economic burden on the healthcare system due to resulting follow-up costs.[1–4] Up to 6.5% of hospitalisations in Germany are assumed to be a consequence of ADRs.[5 6] ADRs and therapy resistances can be induced by extrinsic causes such as drug interactions or medication errors that are avoidable, but also by the individual response to drugs which is influenced by pharmacogenetic variability.[7–12] Patients can be ultra-rapid, extensive, intermediate or poor metabolisers for a certain drug dependent on the involved pharmacogenetic variants. Therefore, due to individual differences in drug metabolism, the same dosage can lead to different drug concentrations, efficacy and safety of therapy.[13–16]

In the last years, data on the influence of pharmacogenetic differences with a high degree of evidence from clinical studies and systematic meta-analyses could be used for therapeutic recommendations and

guidelines on pharmacogenetic tests.[17–22] Such guidelines are provided and constantly updated by the 'Clinical Pharmacogenetics Implementation Consortium' (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG) established by the Royal Dutch Association for the Advancement of Pharmacy. These guidelines and recommendations are based on the pharmacogenetics expertise from research and clinical practice.[23–25]

Correspondingly, pharmacogenetic testing options constantly improve in accuracy and due to discovery of novel variants. They are available for a wide range of genes associated with severe drug–gene interactions and became affordable over time.[26–28] Also, the development of artificial intelligence techniques to support the clinical interpretation of the complex genetic data is progressing. It can be highly useful for a future application of pharmacogenetic testing in daily practice.[29–32]

Although pharmacogenetic testing is a promising und evolving tool in precision medicine, pre-emptive testing, except for mandatory diagnostics for certain prescriptions, is not covered by insurance companies and not adequately used as standard of care in Germany in most cases.[33] Several studies indicate that pharmacogenetics can promote the reduction of healthcare costs by preventing ADRs and can increase patient's safety in therapy with drugs.[34–38] To promote coverage of pharmacogenetic testing by healthcare financiers, more pharmacoepidemiological and pharmacoeconomic studies on the benefit of pharmacogenetic tests are warranted.[39] These studies could encourage the clinical utilisation of pharmacogenetic testing, the expansion of health insurance coverage to this field and the implementation of relevant trainings for a professional application of pharmacogenetics in daily care.[40 41] An expert report commissioned by the German Bundestag outlined the potential of pharmacogenetics in routine care.[42] Therefore, for future directions in this field, the EMPAR (Influence of Metabolic Profiles on the Safety of Drug Therapy in Routine Care) study will analyse whether the use of pharmacogenetic testing could reduce healthcare expenditures and provide benefits for patients, medical practitioners and health insurance providers in Germany.

METHODS AND ANALYSIS

Trial design

The EMPAR study is a non-interventional cohort study, which is conducted to analyse the impact of metabolic profiles based on pharmacogenetic testing on drug safety in routine care. Therefore, pharmacogenetic profiles of participants are investigated. The genetic variant information provided by these profiles is matched with statutory health insurance data. Pharmacoepidemiological and pharmacoeconomic analyses are conducted for endpoints such as usage of healthcare services and healthcare costs.

The study includes three different groups that are defined by the initial prescription of certain drugs and the relevant International Classification of Diseases (ICD)-10 diagnoses. Due to corporate policies, data of insurants can only be provided from 2013 onwards. For each participant group, 1 year without prescription is considered as baseline for analysis. Therefore, the initial prescription is defined as a prescription event of the drug of interest after at least 1 year without a recorded prescription of the drug. Insurants are surveyed via a questionnaire on their initial prescription of the drug of interest to gain additional, supportive information on this issue.

The first group includes patients with initial prescription of anticoagulants such as clopidogrel, clopidogrel plus acetylsalicylic acid, prasugrel, ticagrelor, ticlopidine, phenprocoumon, acenocoumarol, warfarin, dabigatran, apixaban, rivaroxaban and edoxaban in 2014 and 2015 and with or without at least one ADR associated with bleeding or a thromboembolic event after initial prescription. The second group includes patients with initial prescription of cholesterol-lowering drugs such as simvastatin, lovastatin, pravastatin, atorvastatin, fluvastatin, cerivastatin, rosuvastatin and pitavastatin in 2014 and 2015 and with or without at least one ADR associated with muscle pain after initial prescription. In the anticoagulant and cholesterol-lowering drug groups, the pharmacogenetic profiles of patients with ADRs and without ADRs after initial prescription are compared. To identify new single-nucleotide polymorphisms (SNPs) and SNP combinations involved in ADRs, additionally, a screening for special metabolic profiles is performed in a third subgroup that consists of persons with at least one ICD (International Classification of Diseases and Health Related Disorders)-10 Y57.9! diagnosis in 2014–2017. Prior to the selection of this third participant group, an ICD-10 code screening for suitable diagnoses was performed. Also, the Techniker Krankenkasse (TK) database was screened by TK research associates to ensure that a sufficient amount of potential participants can be recruited for this group. The Y57.9! diagnosis includes complications of medical and surgical care due to drugs or medicaments that were not specified. Thereby, the drugs potentially causing adverse effects in therapeutic use were correctly selected and properly administered in therapeutic or prophylactic dosage.

The aim is to recruit about 10 000 insurants of the health insurance provider TK who are at least 18 years of age. In the course of this study, we analyse the patients' relevant metabolic risk profiles concerning side effects or resistance to therapy to identify potential improvement of drug safety and modification of healthcare costs. The long-term goal is to determine the feasibility of the implementation of pre-emptive pharmacogenetic tests in routine care for an optimised drug therapy and treatment.

Study setting

EMPAR is a cooperation project of the Federal Institute for Drugs and Medical Devices (BfArM), the German Centre for Neurodegenerative Diseases (DZNE) and the statutory health insurance provider TK. It is based on data of TK insurants in Germany.

Recruitment procedures

TK insurants who meet the inclusion criteria and do not have any of the specified exclusion criteria receive study information and an informed consent form from their health insurance provider TK. Participants receive buccal swap material from a trust centre after they have provided informed consent. Participants are enrolled in the study in case they send in their buccal swab and successfully provide a high-quality DNA sample for determination of their pharmacogenetic profile.

Participants

Inclusion criteria

1. TK insurant.
2. Aged 18 years or older.
3. Initial prescription of anticoagulants or cholesterol-lowering remedy in 2014–2015 or at least one Y57.9!—diagnosis in 2014–2017.
4. Written informed consent.
5. Successfully provided pharmacogenetic profile.

Exclusion criteria

1. Inapplicable metabolic profile results.
2. Oncological phenotype (All ICD-10 C-diagnoses and D0x, D4x, D37, D38, D39).
3. Severe F-diagnoses (ICD-10: F0x.x, F2x.x, F7x.x, F8x.x, F31.x, F33.x, F38.x, F39.x, F42.x, F43.x, F44.x, F60.x, F61.x, F62.x, F63.x, F69.x, F91.x, F92.x, F93.x, F94.x, F95.x, F98.x, F1x.2, F1x.3, F1x.4, F1x.5, F1x.6, F1x.7, F1x.8, F1x.9, F30.1, F30.2, F30.8, F30.9, F32.2, F32.3, F32.8, F32.9, F34.8, F34.9, F45.2, F45.4, F45.8, F45.9, F48.1, F48.8, F48.9, F50.4, F50.5, F53.1, F53.8, F53.9, F65.2, F65.3, F65.4, F65.6, F65.8, F65.9, F68.1, F68.8, F90.1).
4. Known genetic hematopoietic diseases on initial prescription of anticoagulant (ICD-10 code: D55, D56 D57, D58, D61.0, D64.0, D64.4, D66, D67, D68.0, D68.1, D68.2, D71, D72.0, D74.0, D80.0, D82).
5. Y69! diagnosis (unspecified incident during surgical and medical care) in parallel with Y57.9! diagnosis.
6. Myopathy, myositis or muscle pain before initial prescription of cholesterol-lowering drugs.
7. TK customer management criteria.

Trial outcomes

On the basis of routine care data provided by the health insurance provider TK, the study will examine whether differences in pharmacogenetic profiles have an impact on the incidence of medication problems and therefore, the utilisation of statutory health insurance services. Furthermore, we analyse whether there is a modification of costs for health insurance services based on individual metabolic profiles. Several current studies provide results on cost differences of drug therapy with and without support by pharmacogenetic testing in the therapeutic decision. Thereby, the evaluations on cost reduction vary significantly across drugs and conditions.[37 43 44] With regard to the drug–gene combinations evaluated in our study, supportive evidence of ADR risk reduction and of cost effectiveness is available for clopidogrel–CYP2C19 testing; still information is scarce for other drug–gene combinations and economic evaluations of pharmacogenetics (PGx) panel testing are underrepresented.[37 43] A randomised control study in the USA which evaluated the impact of pharmacogenetic testing service on healthcare costs, suggested a possible annual saving of US$621 per patient in the population analysed.[45] With our study we want to add additional evidence based on lower-cost PGx multigene panel testing and routine healthcare records of a German population.

Primary outcome

The health insurance provider TK provides routine care data. Derived from these data, primary outcomes are incidence of incapacity for work and utilisation of health insurance services for example, hospitalisation due to ADRs, referral to a specialist due to medication problems, change of medication during the observation period. With these outcomes, we assess the impact of metabolic profiles on the incidence of ADRs and resistance to therapy.

Secondary outcomes

Secondary outcomes include the drug costs, treatment and sickness benefit. The aim is to identify a possible modification of costs for health insurance services by preemptive testing in routine care. Thus, we examine the effect of pharmacogenetic profiles on the incidence of ADRs and costs due to health insurance services.

Data collection

Data protection is executed according to the TMF (Technology and methods platform for networked medical research) series ‘Guideline for Data Protection in Medical Research Projects’.[46] The service laboratory represents the biobank module, the TK the clinical module and the BfArM the research module. The trust centre is responsible for identity management and pseudonymisation service.

A pseudonym protects each dataset. The insurant pseudonym is generated by the TK and is linked to healthcare data. A trust centre assigns a genotype pseudonym (G-pseudonym) and a secondary data pseudonym (S-pseudonym) to the insurant pseudonym and creates an assignment table for merging of the different datasets. Participants who provided informed consent receive a questionnaire and a buccal swab test kit by the trust centre that records their address information with the insurant pseudonym provided with the written informed consent. The questionnaire is adjusted for each group and contains questions regarding the initial prescription of the drugs of interest and associated ADRs (online supplementary file). Also, questions on the general perception of drugs on the basis of the Beliefs about Medicine Questionnaire by Horne *et al*[47] are included, supplemented by one question on pharmacogenetics and three questions on

herbal medicines for an evaluation of medical beliefs.[47] Participants send the completed questionnaire and the buccal swab samples marked only with the G-pseudonym to a specialised service laboratory for DNA-extraction and sample registration (DKMS Life Science Lab). Samples are prepared according to genotyping requirements and send to Agena Bioscience for genotype determination. The list of genotypes is forwarded for quality control and derivation of the metabolic profiles to researchers at the BfArM. A list of G-pseudonyms linked to quality controlled and usable metabolic profiles is forwarded to the trust centre where it is translated into an S-pseudonym/insurant pseudonym list. The health insurance provider TK receives this S-pseudonym/insurant pseudonym list, identifies participants by the insurant pseudonym, and anonymises and forwards the respective healthcare data only with the associated S-pseudonym to the BfArM. This way, the TK never has access to the genotype-associated pseudonym, while BfArM researches do not receive the participant data-associated pseudonym. BfArM researchers merge the anonymised datasets via the S-pseudonym and G-pseudonym assignment table that is provided by the trust centre. The merged data are analysed by researchers of the DZNE, BfArM and the TK (figure 1). Before anonymisation of data, the remaining DNA samples are stored by the service laboratory that performed the DNA-extraction. After anonymisation, the samples are stored in a biobank of the BfArM in Germany. They will be discarded after 15 years.

Patient and public involvement statement

The EMPAR study involved no patient and public contribution beyond the study participation described in this article.

Data management

Anonymised datasets will be stored in a secure electronic database at the BfArM, where also the data management and quality assessment of the study database will be hosted. Dataset extractions will be generated for pharmacogenetic, pharmacoepidemiological and pharmacoeconomic

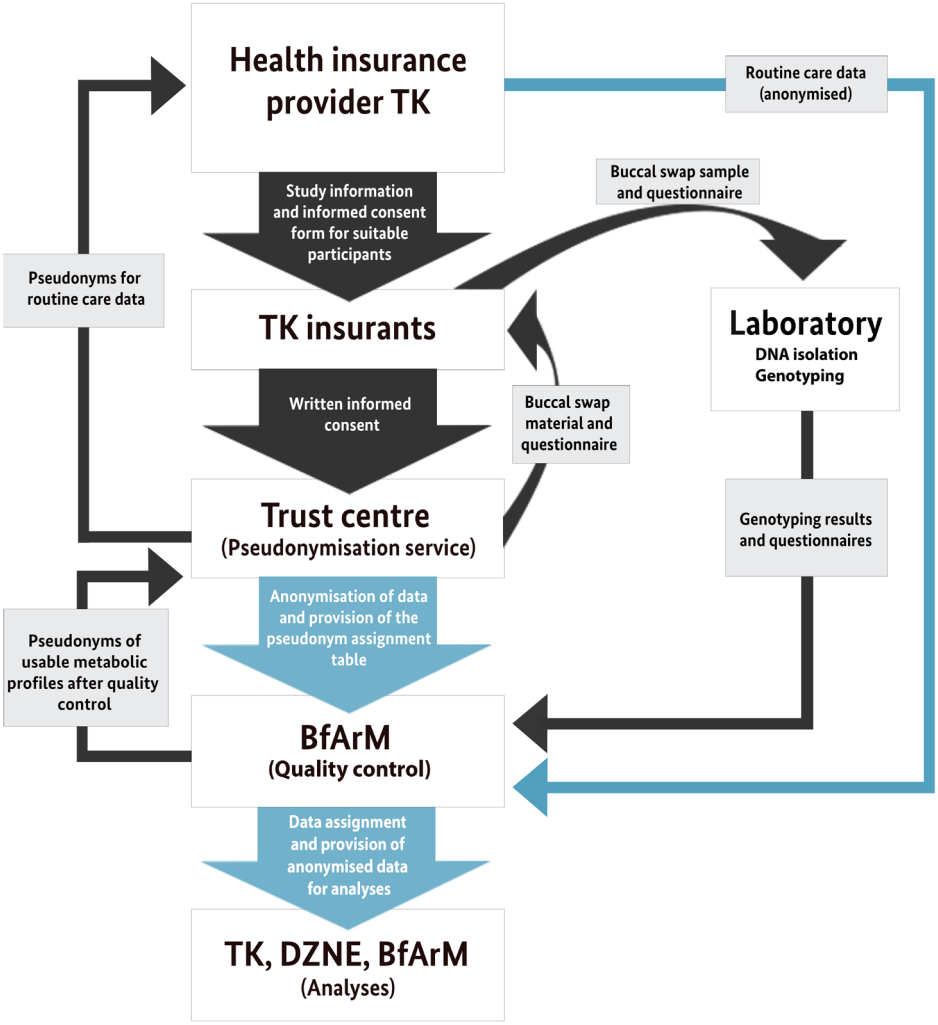

Figure 1 Data management. BfArM, Federal Institute for Drugs and Medical Devices; DZNE, German Centre for Neurodegenerative Diseases, TK, Techniker Krankenkasse.

analyses and analysed in common by researches of the BfArM, the DZNE and the TK.

Statistical analysis

We examine the effect of metabolic profiles on drug safety in routine care. Therefore, we compare participant groups with initial prescription of the drugs of interest in 2014 and 2015 and at least one of the investigated ADRs after initial prescription with a control group. The control group comprises participants with initial prescription of the drugs of interest in 2014 and 2015 without the investigated ADR after initial prescription. Investigated ADRs in the anticoagulant group are ICD-10 diagnoses associated with thromboembolic or bleeding events. Those in the cholesterol-lowering drug group encompass diagnoses associated with muscle pain and myopathy. Additionally, a screening for special metabolic profiles of insured persons with at least one Y57.9! diagnosis (ICD-10) is performed during the observation period. For this screening, no additional control group is recruited. For statistical analysis, data on the pharmacogenetic profile will be matched with routine care records and the questionnaire results via the according pseudonyms.

Statistical design and analysis are performed by researchers of BfArM, DZNE and TK

Pharmacogenetic analysis

For pharmacogenetic analysis, quality of genetic primary data will be stringently controlled. Possible genotyping mistakes will be identified on gene level by classical indicators such as marker and person call rates, Hardy-Weinberg equilibrium, allelic frequencies and haplotype frequencies. Data will be compared with present databases such as the Single Nucleotide Polymorphism Database (dbSNP), the Database of Genomic Structural Variation (dbVar) and the Clinically Relevant Sequence Variations (ClinVar) archive . Haplotype-IDs (haplotype identifiers according to star-allele nomenclature) of the super alleles will be determined by the allele status of single markers of the pharmacogenes of interest with help of the CPIC haplotype set translation tables. On the basis of the CPIC guidelines and the Human Cytochrome P450 Allele Nomenclature Database, the individual haplotypes, repectively star-alleles, can be used to derive the metabolic phenotype of a participant for the relevant pharmacogenes.

Pharmacoepidemiological analysis

For pharmacoepidemiological analysis, we use matched primary data (genetic data) and secondary data (healthcare data), provided by TK. We examine parameters that correlate with drug exposure, therapy resistance and ADRs. Those parameters include for example individual dosing of drugs, utilisation of health insurance services, burden of disease and prescription of medication. Further parameters are economic outcomes such as costs for drugs, treatment and sickness benefit. For statistical evaluation, multivariate regression analysis is used taking into account also propensity and genetic sum scores. Thus, we investigate whether genetic polymorphisms that determine the metabolic profile in drug therapy impact the above-mentioned patient-relevant endpoints. Established comorbidity and healthcare utilisation scores such as Charlson, Elixhauser, ICD-10 structural model classification, Rx Risk and Chronic Disease Score are integrated into the statistical model to address potential confounders such as multimorbidity and polypharmacy. We further plan to include potentially relevant drug–drug interactions for suitable subgroups (eg, based on metabolic profile) into our analysis.

Pharmacoeconomic analysis

Parameters for pharmacoeconomic analyses are costs for drugs and treatments taking into account the costs for pharmacogenetic testing. For estimation of disease-specific total costs, costs for outpatient care and inpatient treatment are calculated and the total costs of the test and the control group are compared in a matched pairs analysis. Multivariate regression analysis, propensity score methods and artificial neuronal network approaches are applied.

DISCUSSION

Between 1995 and 2014, the summary of product characteristics of about 15% of all centrally approved drugs contained pharmacogenetic information. Also, the beneficial potential of pharmacogenetics in preventive healthcare was confirmed in previous and current studies.[19 35 48 49] However, despite of the growing evidence and importance of pharmacogenetic assessment,[27 37 50–53] the implementation of pharmacogenetic testing in standard routine care is not achieved in Germany yet. Already in 2005, an expert report on behalf of the German Bundestag regarding the status and perspectives of pharmacogenetics was published. The report provided a series of tasks for Health Technology Assessment (HTA) which focused on the utility of pharmacogenetic tests in clinical practice and, thus, already considered pharmacogenetics on the future agenda. On the basis of European studies, the report pointed out that HTA can contribute to evaluating the benefits of pharmacogenetic testing for patients, to presenting its possible consequences for the health system, and to identifying options for action.[42 54 55]

However, studies on the effects of pharmacogenetic profiles on the utilisation of healthcare services in cross-sector care are lacking in Germany. Therefore, the EMPAR study uses routine data of a German statutory health insurance provider and patient-derived pharmacogenetic profiles to close this gap. It investigates the potential of pharmacogenetic testing to be implemented as pre-emptive testing in drug therapy in routine care. Thereby, it addresses the important clinical need to identify approaches that meet the current and future developments and use contemporary possibilities for a beneficial and cost-effective advancement in healthcare. This study

is the first study in Germany to analyse the pharmacogenetic data matched with statutory health insurance data for an evaluation of drug safety in routine care. The results of this study on the effect of pharmacogenetic profiles on drug safety will provide insights into the clinical utility of pharmacogenetic testing in clinical practice in Germany. EMPAR represents a milestone in HTA for future directions in the field of pharmacogenetics in German routine care.

Ethics and dissemination

The protocol was approved by the Ethics Committee of the Medical Faculty, University of Bonn (Lfd. Nr. 339/17). The study started in January 2018. Recruitment was initiated in July 2018 and is expected to be finalised by the end of the year 2019. Written informed consent is obtained from all study participants. The results of this research project will be published in scientific open access journals and at conferences.

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Contributors MS, RL, BH and JS jointly conceived the study, developed the study design and received funding for the study. TH was the study coordinator. JF contributed to ID and database management. DL, MG and FF coordinated the selection of insurants and managed the mailing of cover letters from the Techniker Krankenkasse. MS, CR and WG designed the statistical analyses. TH wrote the first draft of the manuscript. All authors critically revised the manuscript and approved the final version. Due to equal contribution TH and MS share the first authorship and BH and JS share the last authorship.

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