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Implementing Pharmacogenomic Clinical Decision Support into German Hospitals

Marc HINDERER[a, 1], Melanie BOERRIES[b], Martin BOEKER[b], Michael NEUMAIER[c], Frank-Peter LOUBAL[d], Till ACKER[d], Manfred BRUNNER[e], Hans-Ulrich PROKOSCH[a] and Jan CHRISTOPH[a]
[a]*Friedrich-Alexander-Universität Erlangen-Nürnberg, Germany*
[b]*Albert-Ludwigs-University Freiburg, Germany*
[c]*Ruprecht-Karls-University Heidelberg, Germany*
[d]*University Hospital Giessen and Marburg, Germany*
[e]*University Hospital Erlangen, Germany*

Abstract. *Background*: Pharmacogenomic Clinical Decision Support Systems (CDSS) are considered to be the most feasible tool for adopting pharmacogenomic testing into clinical routine. *Objective*: To discuss important factors for implementing pharmacogenomic CDSS into German hospitals. *Methods*: We analyzed two relevant studies. Furthermore, we interviewed data privacy officers of three German university hospitals and examined relevant legal regulations in literature. *Results*: There are three major barriers for implementing pharmacogenomic CDSS into German hospitals: (i) the legal uncertainty; (ii) the lack of machine-readable data; (iii) the remaining knowledge gap of both genetics and pharmacogenomics among physicians. *Conclusion*: The implementation of passive clinical decision support (CDS) for somatic mutations in the form of structured pharmacogenomic reports might be the most feasible CDS feature for clinicians in German hospitals.

Keywords. Personalized medicine, clinical decision-making, pharmacogenetics

1. Introduction

The implementation of pharmacogenomic testing into routine practice has been slow in most clinical settings and could not keep pace with the rapid growth of the scientific knowledge base [1]. Some hospitals have started to implement pharmacogenomic clinical decision support systems (CDSS) into their electronic health records (EHR) to overcome this problem and incorporate pharmacogenomics into clinical practice [2–4].

Pharmacogenomic CDSS combine genetic test results with biomedical knowledge in order to support clinicians in making molecular-guided decisions [5]. According to Hicks et al. a CDSS can either be classified as passive or active clinical decision support (CDS). Passive CDSS simply represents relevant genetic results and its interpretation to the treating clinician in form of a pharmacogenomic report, for instance. As opposed to that, active CDS comprises rules and algorithms which need to be triggered by a predefined event. If one of these rules is triggered, the active CDSS delivers an alert to

[1]Corresponding Author: Marc Hinderer, Chair of Medical Informatics, Friedrich-Alexander-Universität Erlangen-Nürnberg, Wetterkreuz 13, 91058 Erlangen, Germany. E-Mail: marc.hinderer@fau.de

the physician. In most cases, these alerts are delivered through the local electronic health records (EHR) [6].

The objective of this study was to discuss important factors for the implementation of pharmacogenomic CDSS into German hospitals.

2. Methods

During a nine month period, we approached the topic of pharmacogenomic clinical decision support from several different perspectives. First, we analyzed two of our three previously conducted studies for relevant parts that might indicate important factors for the implementation of pharmacogenomic CDSS into German hospitals which has not yet been discussed in the two respective papers [7,8].

Second, data privacy officers of three German university hospitals were asked about their data privacy concerns regarding the incorporation of genetic results into their local EHR. Third, we analyzed legal regulations regarding data privacy and data protection with a special focus on the German Genetic Diagnostics Act (GenDG).

Furthermore, all results were discussed with a member of the German Commission on Genetic Testing (established in 2009 by the German Federal Ministry of Health).

3. Results

3.1. Legal regulations

Genetic examination and genetic analysis which aim at the detection of germline mutations in human genetics has to be in accordance with the GenDG (GenDG section 3(4): "human genetic information inherited upon fertilization or otherwise gained before birth."). A pharmacogenomic test is applied to a patient in a therapeutic situation rather than to a healthy individual. Therefore it is considered a diagnostic test rather than a predictive test.

As opposed to that, the GenDG does not apply to genetic examinations if it is solely intended to detect somatic mutations [9]. This includes any kind of molecular defects which occur during tumor development and progression. If it remains uncertain whether a detected gene mutation is a somatic or germline mutation [10] a post-hoc germline examination has to be carried out in accordance with the GenDG.

The legal responsibility of a genetic examination remains with the ordering physician throughout the entire process from the initial order of the genetic examination up to the storage of the genetic results. Therefore, it is up to the ordering physician to obtain the informed consent and to select an appropriate test. Moreover, the ordering physician is the only person authorized to be informed about the test results. Furthermore only she/he is entitled to communicate any information to the patient. The ordering physician has to obtain the written consent from the corresponding patient if she/he wants to inform other persons about the test results. However, the GenDG is not applicable to the field of research [9].

Regardless of the GenDG, each genetic examination has to be compliant to the medical confidentiality, the German Federal Data Protection Act and to the particular laws of data protection of the German States [10]. According to these regulations, the

physician needs an informed consent from the patient prior to the genetic examination to handle the genetic data and genetic samples gained thereby for medical purposes.

3.2. Structural and organizational barriers

The physician's knowledge of both pharmacogenomics and pharmacogenomic testing still remained low in 2016. Physicians in German hospitals require additional education of both genetics and pharmacogenomics [8].

In our most recent study [7], we observed heterogeneity in both the organization of genetic testing and the management of the Molecular Tumor Boards among the five hospitals. Furthermore, they used free-text documents in most of their support procedures rather than machine-readable documents. No hospital had a dedicated tool to support the interpretation of the annotated gene variants and mutations. Therefore, we proposed a standardized workflow in our previous study of the Molecular Tumor Boards in German hospitals. This standardized workflow comprised automated variant calling and annotation to support the interpretation of the annotated gene variants and mutations. However, all five hospitals used the same file formats BAM, FASTQ, VCF, annotated VCF and Excel spreadsheets for organizing their genetic results and annotated somatic gene variants and mutations. While these files were finally stored in a file system within the diagnostic departments, the reports for the Molecular Tumor Board were stored in the EHR.

4. Discussion

4.1. Legal uncertainty

The data privacy officers were uncertain about the storage and the distribution of genetic data within an EHR. According to the GenDG, only the ordering physician is authorized to be informed about the genetic results if the results report contains germline mutations [9]. This is different from other diagnostic tests such as leukograms, for instance, which might be shared with other physicians.

Overall, it remains uncertain whether the genetic results of germline mutations may be delivered via an electronic report or not. Moreover, it remains uncertain whether an informed consent of the patient might legitimate the delivery of germline mutations via an electronic CDSS. As opposed to that, storing and distributing somatic mutations in an EHR seems to be legally feasible including both raw genetic results as well as the associated phenotypes.

4.2. Lack of machine-readable findings

Active CDS in the form of alerts, for instance, require rule engines and machine-readable data. All files which contained data from sequenced raw data up to the annotated variants were only stored in a file system within the diagnostic department rather than within the EHR. Only the signed medical reports were stored in the EHR. However, these medical reports were generated as free-text documents which are difficult to be interpreted within a pharmacogenomic CDSS.

As a result, German hospitals lack of machine-readable findings within the EHR although appropriate machine-readable data were generally available in filesystems of the diagnostic departments. Moreover, these machine-readable data were stored in the same file formats what might facilitate standardized workflows.

It seems to be crucial to incorporate a documentation process to generate machine-readable findings. Therefore, the files of sequenced raw data up to the files of annotated variants need to be stored in the EHR.

Nevertheless, the technical feasibility of an active pharmacogenomic CDSS has to be evaluated within the clinical environment prior to its development and establishment. Passive CDS, in contrast, presents relevant genetic results and the pharmacogenomics interpretation to the physician. This is usually in the form of a pharmacogenomic report, which is technical more feasible than features of active CDS.

4.3. Knowledge gap and unfamiliarity with pharmacogenomics

The participants in our previously conducted survey preferred active CDS in general. Nevertheless, we believe that the implementation of a passive CDS tool in form of pharmacogenomic reports might be more appropriate. It seems to be the most feasible CDS feature in the first instance.

This opinion is based on our survey among the clinicians of the eight hospitals. Participants in this survey revealed a deficit in their knowledge of genetics, pharmacogenomics and pharmacogenomic CDSS. It means that physicians in German hospitals are still unfamiliar with this topic. Therefore, a pharmacogenomic CDSS has to be implemented carefully to receive the physicians' attention and acceptance for such CDSS.

In contrast, clinicians in German hospitals are already used to be provided with genetic reports by the physicians of diagnostic departments. Furthermore, clinical members of the Molecular Tumor Board are used to structured free-text presentations in their Molecular Tumor Boards.

5. Conclusion

The implementation of passive CDS in the form of structured pharmacogenomic reports might be the most feasible CDS feature for clinicians in German hospitals. However, we only included approximately one-fourth of all German university hospitals (eight out of 33) in this paper. Therefore, further research covering a larger number of German university hospitals is required to verify these assumptions.

The legal situation in Germany regarding germline mutations remains uncertain and needs to be resolved. Until then, pharmacogenomic reports should only include somatic mutations and exclude germline mutations. That legal uncertainty might also give some time to resolve technical issues that currently make passive CDSS more feasible.

6. Conflict of Interest

The authors state that they have no conflict of interests.

Contributions

MH analyzed the included studies. MH, FPL, MaBo and MaBr analyzed relevant legal regulations. MH and JC conducted the interviews and contributed to the data analysis and interpretation of data. MH has written the first draft of the article and has edited the final version. All authors have contributed to the article by revising the first draft and providing various comments. All authors read and approved the final manuscript.

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