



# feature

## Development of predictive genetic tests for improving the safety of new medicines: the utilization of routinely collected electronic health records

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Serious adverse drug reactions are an important cause of hospitalization and can result in the withdrawal of licensed drugs. Genetic variation has been shown to influence adverse drug reaction susceptibility, and predictive genetic tests have been developed for a limited number of adverse drug reactions. The identification of patients with adverse drug reactions, obtaining samples for genetic analysis and rigorous evaluation of clinical test effectiveness represent significant challenges to predictive genetic test development. Using the example of serious drug-induced liver injury, we illustrate how a database of routinely collected electronic health records (EHRs) could be used to overcome these barriers by facilitating rapid recruitment to genome-wide association studies and supporting efficient randomized controlled trials of predictive genetic test effectiveness.

Adverse drug reactions are estimated to be responsible for over 5% of hospital admissions [1,2]. Approximately 150 drugs have been withdrawn from the market since 1960 owing to safety issues [3], in some cases many years after initial approval [4]. Evidence is increasing for a genetic predisposition to several serious adverse drug events [5]. For a limited number of drugs, observational genetic studies of association and subsequent randomized controlled trials (RCTs) of effectiveness of genotype-guided treatment have enabled predictive genetic tests to be developed that have allowed valuable medicines to remain on the market with greatly improved risk:benefit profiles [6].

Serious drug-induced liver injury is a leading cause of drug withdrawals [3]. Associations

between specific genes and susceptibility to drug-induced liver injury caused by several drug therapies have been identified, although predictive genetic test development has been minimal and many genes conferring susceptibility are yet to be identified [7,8]. A major challenge is the time and cost associated with finding patients who have had a reaction of interest, and recruiting sufficient numbers for initial genome-wide association studies (GWAS) and subsequent replication studies [9]. Following predictive genetic test development, an RCT to evaluate effectiveness of the genotype-guided treatment versus standard care might be required [10], introducing further logistical challenges. The possibility of using databases of routinely collected EHRs to support

pharmacogenomics has been discussed elsewhere (Yasmina *et al.* unpublished; [11–13]). In this article, we provide further detail by illustrating how an EHR database could be used to: (i) identify patients who have had serious adverse reactions linked to a newly licensed drug to invite them to provide genetic samples for GWAS; and (ii) test the efficacy of any developed genetic test in a cluster RCT. We illustrate these ideas using drug-induced liver injury as an example of an adverse drug reaction.

### Identification of drug-induced liver injury within routinely collected EHRs

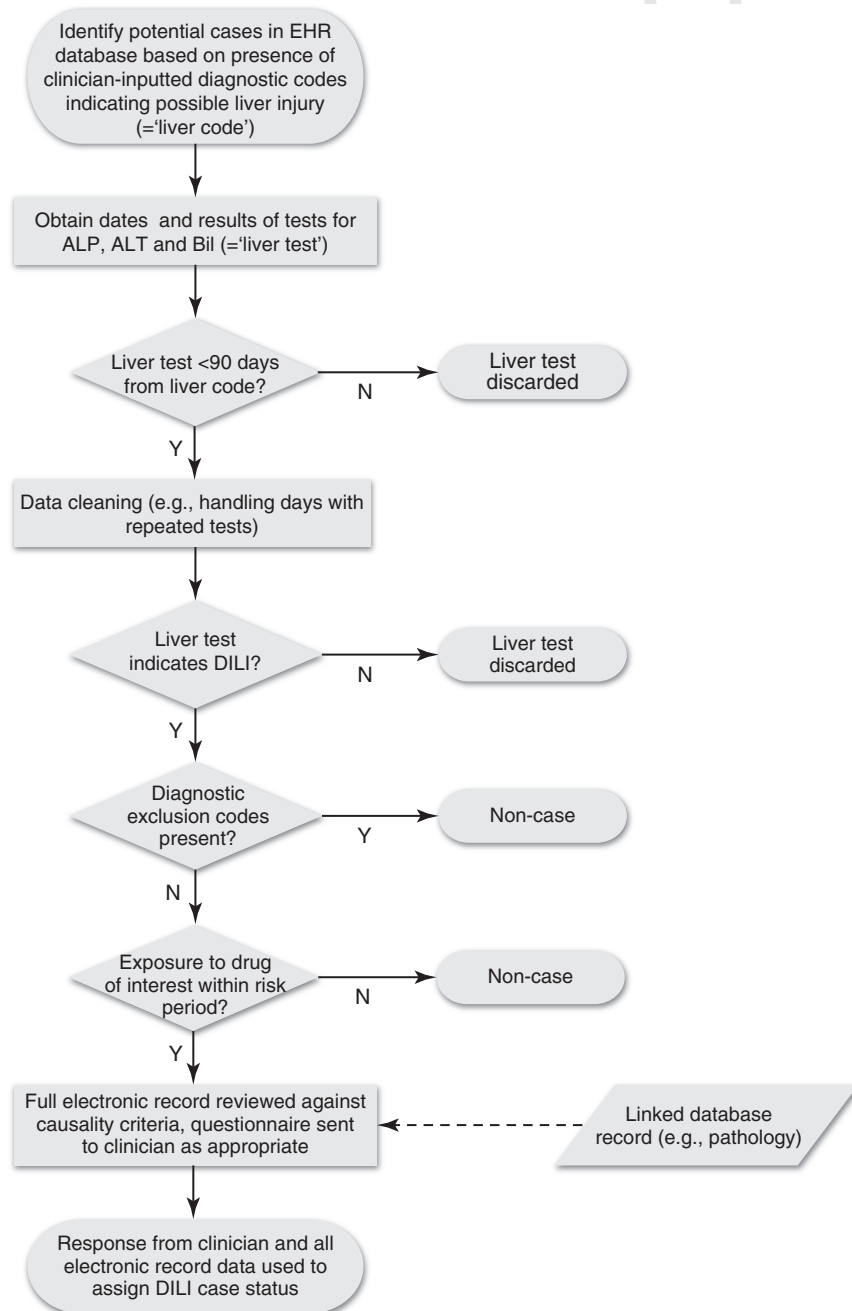
Routinely collected EHRs provide the potential for low-cost, efficient epidemiological cohort

identification and analysis [14]. Although database specific, an EHR for an individual patient typically includes a unique patient id, clinical diagnoses (as standardized diagnostic codes), drug prescriptions, laboratory test results and, in some cases, lifestyle information, such as smoking, drinking and body mass index. Coverage of the underlying population is likely to be broad, and new linkages between databases are enhancing the ability to ascertain disease status.

For example, the UK Clinical Practice Research Datalink (CPRD) primary care database contains anonymized health information for approximately 8% of the total UK population and can be linked to the UK Hospital Episode Statistics database [15].

Effective case identification algorithms can be developed that utilize EHR databases to identify cases of drug-induced liver injury. Work has been performed demonstrating the portability of such

algorithms across different institutions [16] and work is ongoing to facilitate standardized implementation across databases in different countries (Ruigomez and Brauer for the IMI-PROTECT group [17]). An example algorithm is provided in Fig. 1. Potential drug-induced liver injury cases are identified based upon specific diagnostic codes (routinely inputted by clinicians). The database is searched for liver test results within a specific time period from the



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FIGURE 1

Example algorithm for identifying cases of drug-induced liver injury using a database of electronic health records. Drug-induced liver injuries (DILI) are injuries defined as  $ALT.5 \times ULN$ ,  $ALP.2 \times ULN$ , or  $ALT.3 \times ULN$  with  $Bil.2 \times ULN$  [13]. Causality criteria are as determined by international consensus [17]. Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; Bil, bilirubin; HER, electronic health record.

diagnostic code indicating possible liver injury. Patient records with no liver test results or results not indicative of drug-induced liver injury are removed, and the remaining patients are considered to be characteristic of drug-induced liver injury. The type of liver injury can be determined as required [13], before a set of exclusion codes is applied to remove individuals with other underlying (non-drug) causes of their liver symptoms. Verification of the cohort of potential cases can be performed by analyzing the association between being an algorithm-selected case and having recently been advised to take drugs that are well-known causes of drug-induced liver injury (such as flucloxacillin or amoxicillin-clavulanate [8]).

For potential cases with a prescription for the drug of interest within a specified risk period, a history of prescriptions and diagnoses (within a defined period) can be extracted from the database, enabling information on other potential causes of the liver injury to be obtained. Additional data on whether the patient was referred to hospital, and from linked databases could also be considered at this point (such as pathology databases or general hospital statistics databases). Brief questionnaires can then be sent to the responsible clinician as appropriate, to obtain any referral letters from liver specialists, and to ascertain whether the responsible clinician considers the events to represent drug-induced liver injury as a result of the drug in question. The totality of the health data obtained for each patient can then be reviewed by medically trained professionals and considered against international causality criteria [18], to identify probable cases.

### Active monitoring of EHRs for recruitment to genetic association studies

Drug-induced liver injury algorithms as described above have typically been applied to database study populations at a single time point following drug registration, to identify retrospectively cases for inclusion in epidemiological studies [19,20]. For recruitment to genetic association studies, we propose an alternative ‘active monitoring’ model. Genetic sampling kits would be sent directly to the clinician of individuals identified as cases by continuous database surveillance, and the clinician would obtain consent and take a blood sample to be sent to the study coordinator.

Two possible information-processing approaches could support this model. The first approach would utilize the regular (e.g. monthly) download of EHRs from contributing health centers to the central database. The drug-induced liver injury algorithm could be run against the

database following each download, and the clinicians of selected potential cases could then be invited to complete the short questionnaire described above, before a genetic sampling kit is sent to them if appropriate (Fig. 1). The second approach would be to utilize technology comparable to that installed on clinician desktops for performing pragmatic randomized trials within the UK CPRD database [21]: patients advised to take the drug of interest would be identified at the EHR database center and added to lists of eligible patients. The algorithm would be run locally on the clinician's desktop when an eligible patient had their health record updated and, if potential drug-induced liver injury was suggested, the patient would be flagged as an eligible potential case. The clinician would make the final decision on case status, and obtain and provide genetic samples using pre-provided genetic sampling kits (Figs 2 and 3).

### EHR-based RCTs of predictive genetic test effectiveness

Following development of a potential predictive test, an RCT would provide rigorous evidence

that genotype-guided treatment improves health outcomes [10,22]. Existing EHR database infrastructure could enable a cluster RCT to be set up in which contributing health centers are randomly assigned to implement use of the predictive test or not, an approach that is already being applied for other disease areas [23]. In the intervention arm, patients with an indication for the drug of interest would be tested for the gene of susceptibility and the results could be used to inform subsequent treatment and monitoring; in non-intervention-arm health centers, treatment would be based on information available according to standard care only. Follow-up of the participating health centers could then be performed by using the algorithm to monitor EHR data on a monthly basis, to assess whether the rate of adverse drug reaction for the drug of interest differed between health centers randomized to use of the predictive test and those randomized to give standard care. An evaluation of subsequent changes in treatment approach based upon predictive test result could also be performed in this way.

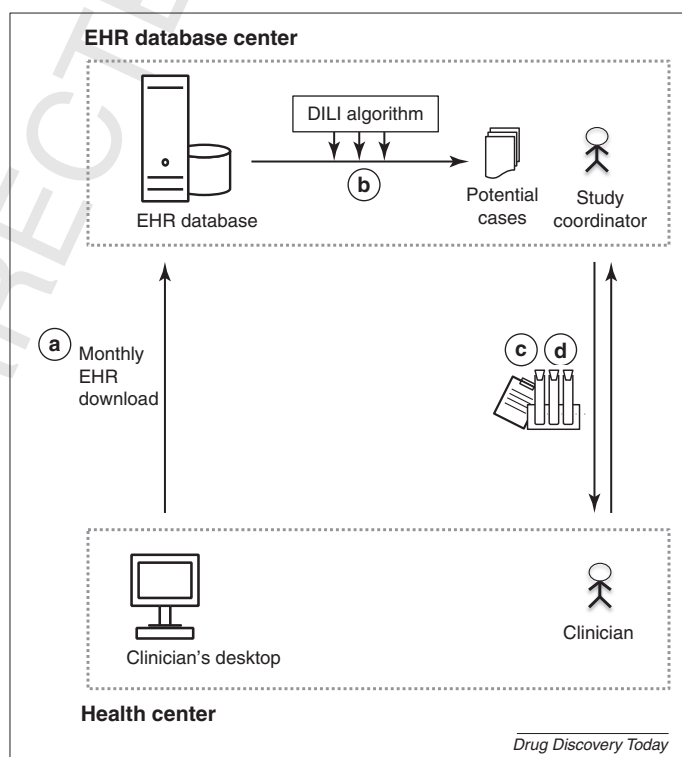


FIGURE 2

Actively monitoring an electronic health record (EHR) database to recruit to drug-induced liver injury (DILI) genetic association studies: approach one. (a) Updated EHRs are uploaded from the clinician's desktop to the EHR database according to the usual protocol (e.g. monthly); (b) the drug-induced liver injury algorithm is applied to the database of EHRs, to identify potential cases; (c) the study coordinator sends a short questionnaire to the responsible clinician of all the potential cases, and the coordinator uses this response and all the electronic record information to identify probable cases; (d) the study coordinator sends a genetic sampling kit to the clinician, who obtains consent from the probable case before taking genetic samples and sending back to the study coordinator.

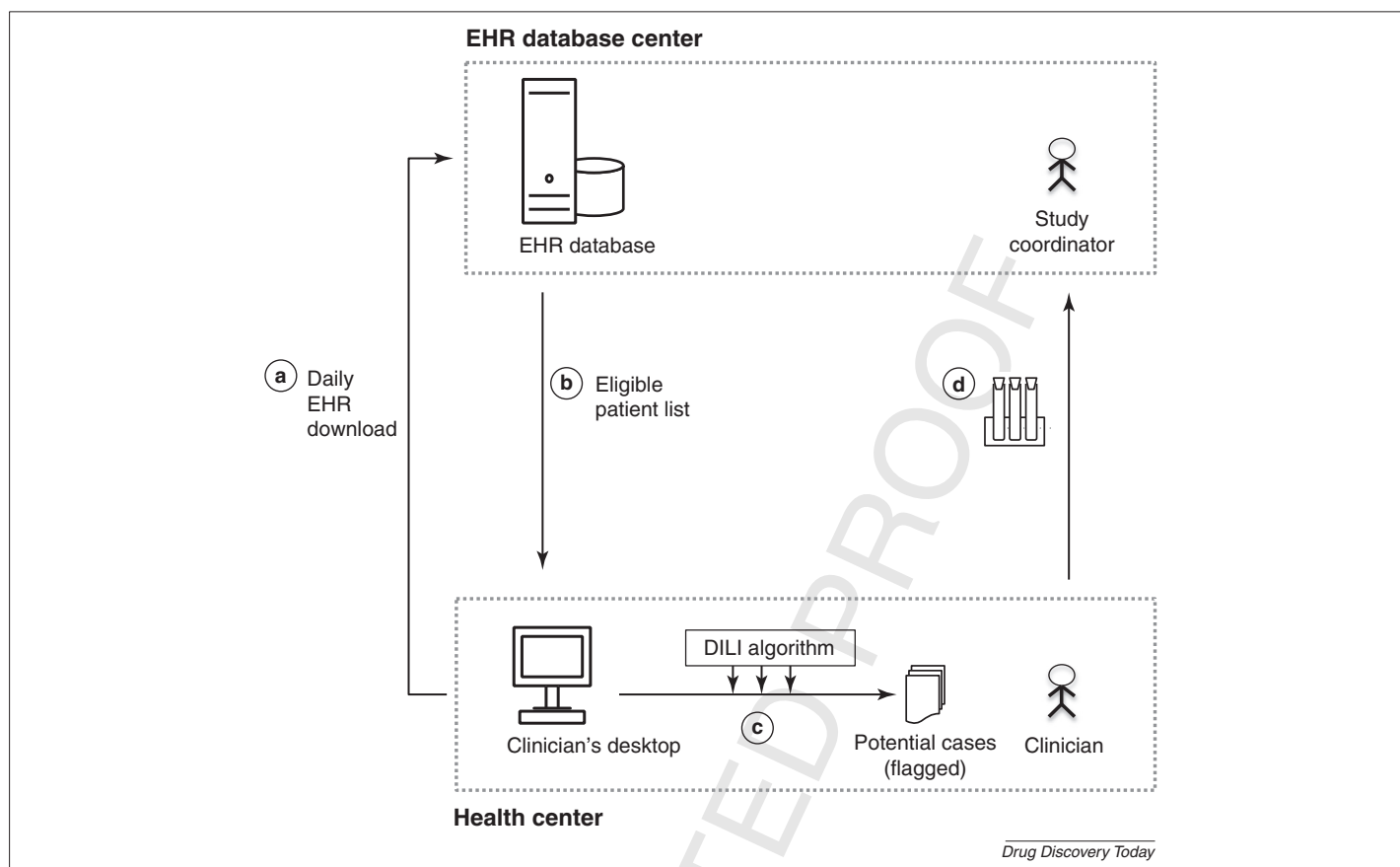


FIGURE 3

Actively monitoring an electronic health record (EHR) database to recruit to drug-induced liver injury (DILI) genetic association studies: approach two. (a) Daily downloads of information on drug prescriptions are transferred between the clinician's desktop and the EHR database. (b) This updates an eligible patient list within the EHR database, which is sent to the clinician's desktop each time it is updated. (c) The algorithm is run on the clinician's desktop for eligible patients. (d) Potential cases are flagged to the clinician, who makes a decision on case status. (e) Genetic samples from probable cases are provided by the clinician to the study coordinator.

## Discussion

In an ideal world, one might investigate genetic determinants of drug-induced liver injury owing to a newly licensed drug by setting up a multicenter prospective observational study at hospital liver clinics, in which genetic samples are taken rapidly after a patient with a drug reaction is identified. However, such studies require a dedicated infrastructure and are costly to perform. Biobanks represent an alternative source of genetic information. Typically, these are repositories of prospectively stored genetic information for large numbers of patients [24] that provide valuable resources for studying (relatively common) complex gene–disease genetic associations. Unfortunately, the typically low

frequency of SAEs means that recruiting sufficient patients from biobanks to carry out an adequately powered GWAS study within a short timeframe following drug registration would be difficult [25]. Further disadvantages include the high financial and environmental cost of each

repository, and the possibility that a lack of inter-biobank standardization could result in measurement error within studies across biobanks [26]. One possible approach for addressing these challenges is the formation of collaborative groups, such as the International Serious Adverse Event Consortium (iSAEC), a large-scale private–public biomedical consortium [27,28]. Genetic samples obtained from large prospective studies and biobanks are shared between stakeholders, with an indication of the resource applied to this effort provided by the fact that six of the collaborators are top ten-ranked pharmaceutical companies [29]. This level of collaboration has contributed significantly to recent progress in the identification of adverse drug reaction–gene associations [30].

Our proposed model provides an alternative to an iSAEC-type approach, could be implemented at relatively low cost, and would enable active monitoring and recruitment for newly

licensed drugs. By continuous retrospective selection of recent drug-induced liver injury from a population-based database of routinely collected EHRs, the beneficial characteristics of a large prospective multicenter prospective study are conferred, but with the most costly components already in place (i.e. multiple study centers, on-site study staff and individual patient records). Furthermore, the same infrastructure could be utilized for multiple drugs, the population being screened for the reaction is inherently large, detection does not rely on a hospital referral, and a source of population-based controls for case–control studies of genetic association is provided. Data are also routinely collected that would enable analysis of some coexisting clinical and environmental determinants of susceptibility to adverse drug reactions (another factor that might have contributed to a lack of progress in this area [9]). A comparable approach has enabled recruitment of over 700 patients from the UK CPRD for a statin-induced

myopathy genetic association study, demonstrating the feasibility of this approach [31]. The ongoing work within the IMI-PROTECT consortium to standardize definitions across databases opens up the possibility of rapid recruitment for a single gene association study across multiple databases (such as the UK CPRD, Dutch Mondrian and Spanish BIFAP databases) [17]. As EHR databases start to become linked to biobanks [11], genetic samples collected in this way could be stored for use in future studies of specific adverse drug reactions.

We also propose a role for EHRs in performing RCTs of genetic test effectiveness [21]. The costs of a conventional multicenter RCT are likely to represent a serious obstacle to progress, and results might have limited generalizability [21]. Adoption of a recently proposed model for cluster RCTs performed within an EHR database [23] could address both of these challenges: whole health centers could be randomized to the use of a newly developed predictive genetic test, with minimum set-up costs, maximum reusability and a focus on test effectiveness in real-world settings.

Although this article focuses on the development of predictive genetic tests, we feel that the active monitoring approach described compares favorably with the current passive yellow card system for pharmacovigilance, and would also support adaptive licensing [32]. Spontaneous reporting systems suffer from reporting bias, missing denominator information and vague or incomplete case definitions, problems that would be minimized by applying real-time detection to one or multiple EHR databases. Targeted detection of adverse drug reactions observed during drug development could begin immediately following product launch (from day 1), and could be included as part of iterative data gathering within an adaptive licensing framework.

### Concluding remarks

It is important to try and ensure that innovative products are not removed from the market because of risks associated with detectable genetic variation in the population, as has occurred previously [33]. In a climate where urgently needed new drugs (such as antibiotics) could have a worldwide impact on public health, unnecessary withdrawals could have severe consequences. Databases of EHRs can facilitate the development of rapid and low-cost predictive genetic tests, which could in turn prevent avoidable withdrawals, and reduce the number of patients unnecessarily exposed to serious adverse drug reactions.

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Q4



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