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Perioperative genetic screening: entering a new era

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Malignant hyperthermia (MH) and butyrylcholinesterase (BCHE, pseudocholinesterase) deficiency are historically among the first reported pharmacogenetic diseases, defined as inherited conditions that are characterised by an absence of phenotypic changes as long as the triggering agent is absent.[1,2] Only personal or familial history of adverse reactions and molecular genetic investigations are able to preemptively identify such susceptibility. Although traditional molecular genetic analysis is slow and laborious, more advanced, chip-based methods have been developed in order to sequence the loci of BCHE and MH.[3] This editorial accompanies the paper in the *British Journal of Anaesthesia* by Douville and colleagues[4] presenting a novel approach that consists in combining available high-throughput genotyping data for BCHE deficiency, MH susceptibility, and Factor V Leiden thrombophilia with information from an electronic healthcare record (EHR) system. The study used various genotyping platforms to achieve full coverage of the genetic loci under investigation. Three of the known BCHE variants with the largest effect on enzyme activity and the Factor V Leiden mutation were covered using a customised dense genotyping chip, or genome wide association (GWA) data. Screening for pathogenic MH variants was performed with sequence analysis of the *RYR1* and *CACNA1S* genes using whole exome sequencing (WES) and single molecule molecular inversion probes.[4]

The study used the Michigan Genomics Initiative (MGI)[5] biorepository that collects blood samples for genetic analysis from tens of thousands of perioperative patients. Genomic

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DNA isolated from blood samples is genotyped and the results are integrated with EHRs, thus creating a powerful resource for multiple and diverse research studies aimed to identify and validate genetic risk factors for a wide range of medical conditions, including susceptibility to adverse drug responses.

The authors demonstrated the feasibility of identifying patients with an increased risk of developing perioperative complications because of the three above-mentioned conditions, taking advantage of the availability of the genotyping data linked to the EHR-derived phenotypes for a cohort of 40 769 perioperative patients. They developed and validated a computer application for variant annotation designed for clinicians that allowed them to identify, based on patients' *F5* and *BCHE* genotype information, 36 patients with a high risk of drug-related perioperative complications who had no EHR-documented history of such complications. Genetic screening for a subpopulation of 1224 patients led to identification of two patients with *RYR1* variants diagnostic for MH susceptibility.[6] Neither of the two patients had a self or family history of MH, although each had one uneventful exposure to anaesthesia, a finding that can be explained by incomplete penetrance of MH susceptibility trait.[7–9] Indeed, their findings show that this approach can be applied to genetic disorders with incomplete penetrance and variable expressivity, such as MH susceptibility, and that it is advantageous to have genotype information before perioperative drug administration in order to avoid adverse and potentially life-threatening drug-related complications.

The development of a large biorepository with tens of thousands of patients' biospecimens that is reliably linked to patient EHR records is an essential prerequisite for pharmacogenetics/pharmacogenomics studies to advance understanding of gene-drug and gene-disease associations and to enable truly *personalised* medical care once a patient's genetic information is documented in the EHR. Such biorepositories as the Michigan Genomics Initiative,[5] the Health Outreach Program for the Elderly (HOPE),[10] and UK Biobank[11] are the best examples of biorepositories with close links to EHRs that are created as a long-term resource for multiple ongoing research studies. However, there are several challenges to a universal practical application of biorepositories linked to EHRs and to clinical implementation of preemptive genotyping for personalised medicine.

The first challenge is to ensure the quality of biospecimen collection, processing, and storage. For this purpose, hundreds of standard operating procedures in the field of human biospecimen science have been collected from international medical institutions and made available within the National Institutes of Health Biospecimen Research Database.[12]

The second challenge is the lack of accepted mechanisms to connect clinical data to specimens collected from each patient. This includes obtaining informed consent, which is associated with issues of patient privacy and confidentiality that need to be addressed through the use of coded private information and encrypted specimen identification, and issues of ethical, legal, social, and economic implications of pharmacogenetics testing. The challenges of developing and operating a biorepository have already been addressed in more than 2000 scientific publications, and are covered in depth in a recent research white paper on biorepositories.[13]

The third major challenge is a complexity of assessment of drug/gene associations emerging from pharmacogenomics studies, in establishing phenotypic properties to molecular genetic findings[14] and then translation of the validated connections into clinical recommendations for clinicians.[15,16] Advances in genotyping technologies during the last 20 yr generated a wide range of high-throughput genotyping platforms (e.g. genome wide association marker genotyping, next generation sequencing gene panels, and whole exome sequencing), which makes genotyping more affordable, especially when a large number of samples are being genotyped. As exome and genome sequencing become less expensive and as more clinically-relevant drug-response variants are validated, a genotype-based approach in perioperative medication prescription is expected to become more common.

However, clinicians who receive patient clinical genetic test results will need clear clinical guidelines to be able to identify patients at risk for medication-related perioperative adverse events (i.e. to be able to translate the patient genotype information into clinical decisions).[15] This leads to the difficulties of interpretation of variants of unknown significance (VUS) (i.e. genetic variants with unknown pathogenic effect). Dealing with comprehensive results from exome or genome sequencing may require support from clinical geneticists and genetic counsellors to delineate the likelihood of pathogenicity of each variant, which involves a large amount of work and is not always straightforward. And it must be recognised that although population screening may reveal susceptibility for adverse effects, this approach is unable to exclude such susceptibility in view of our incomplete knowledge of all the genetic factors involved.

Development of clinical decision support tools within EHRs that would apply the integrated pharmacogenetics guidelines to patient genotype information is crucial to clinical implementation of pharmacogenetics.[15,16] Freely available peer-reviewed, updatable online resources, such as The Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines,[17] have been created to guide clinicians in drug prescribing decisions based on genetic results and represent an essential step toward this goal. The updated list of CPIC gene/drug response pairs, based on the Pharmacogenomics Knowledge Base (PharmGKB) Clinical Annotation Levels of Evidence, includes all four analysed genes, *F5*, *BCHE*, *RYR1*, and *CACNA1S*; however, prescription action recommendations exist for only two of these genes (*RYR1* and *CACNA1S*).[18] The guideline focuses on cases where genetic testing has identified one of the 50 MH diagnostic variants, and states that the potent volatile anaesthetic agents and succinylcholine are contraindicated in such cases. The guideline cautions that neither a negative genetic result nor detection of a VUS in one of the MH genes confers a definite MH status. Until pathogenicity of a VUS is established, a person carrying a VUS and a person with a negative genetic result should be considered as having uncertain MH susceptibility status. The clinician should interpret negative or inconclusive genetic results on the basis of clinical findings, family history, and *in vitro* contracture testing.[18] In concurrence with this guideline, the European Molecular Genetics Quality Network (EMQN) guidelines[19] state that only pathogenic and likely pathogenic variants have diagnostic value and have to be reported, while reporting of unclassified variants is not regulated. Reporting of VUSs has not been made obligatory because a VUS does not improve diagnosis and its uncertain clinical significance can cause unnecessary anxiety in a patient. At the same time, reporting a VUS is a way for collecting evidence to eventually classify it as pathogenic or benign, either by analysing, where possible, its segregation with the disease trait, by submitting a report of a VUS together with the de-identified patient's

clinical information to public genetic variation databases such as ClinVar[20] or Leiden Open Variation Database,[21] or both.

Another important challenge hampering implementation of routine preoperative genotyping is an absence of definitive data regarding cost-effectiveness.[15] To overcome this challenge, a number of international multisite collaborative studies, such as IGNITE[22] and eMERGE[23] in the USA, and the PREPARE study[24] within the Ubiquitous Pharmacogenomics Consortium program[24] in Europe, have been initiated with the aim to determine feasibility of implementation of preemptive genomic testing into routine clinical care. The first results of these studies have revealed potential cost-saving benefits of targeted pharmacogenomics gene panel sequencing in patient populations that are at an increased risk of exposure to a drug with known genotype-sensitive effects. The approach of preemptive gene panel genotyping has already been implemented in the Canadian healthcare system where next generation sequencing-based MH gene panel testing is being routinely offered for individuals at increased risk of MH.

Identification of further pharmacogenetic genes and validation of novel genetic markers predisposing to drug-related perioperative complications on the one hand, and the development of tools facilitating translation of clinically actionable variants into personalised drug therapy on the other hand, have the potential to improve cost-effectiveness of preoperative genotyping, making its implementation feasible for averting perioperative adverse events in wider population cohorts. A noticeable benefit of using a larger panel of pharmacogenomic genes for preemptive genotyping is that the patient's genetic information, obtained once in a lifetime, can be used for optimal drug prescription at present and also for therapy re-adjustment in the future whenever novel clinically validated variants are identified.

The study of Douville and colleagues,[4] by validating strong associations between *F5* and *BCHE* genotypes and corresponding drug-response phenotypes in a large cohort of perioperative patients, reinforces evidence for these two gene/drug pairs and thus aids development of corresponding CPIC prescribing recommendations. Furthermore, by showing how to use a preoperative genetic biorepository in the actual diagnosis of certain conditions with potential perioperative complications, such as MH, and by creating an open source computer programming script designed for clinical use of pharmacogenomics data, they have made a substantial contribution to the development of precision medicine-based clinical decision support tools.

Authors' contributions

Literature analysis and interpretation, writing, and revising the draft: NK, TG and SR
Approved the final manuscript: all authors

Declarations of interest

The authors declare that they have no conflicts of interest.

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