

Mini Review

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The integration and interpretation of pharmacogenomics – a comparative study between the United States of America and Europe: towards better health care

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Abstract: The study of pharmacogenomics has, by harnessing sequence information from human genomes, the potential to lead to novel approaches in drug discovery, an individualized application of drug therapy, and new insights into disease prevention. For this potential to be realized results need to be interpreted to the prescriber into a format which dictates an action. This mini review briefly describes the history, the regulatory environment, opinions towards, and implementation, integration and interpretation of pharmacogenomics in the United States of America and Europe. The article discusses also how interpretation of pharmacogenomics could move forward to better implementation in health care.

Keywords: implementation; pharmacogenetics; pharmacogenomics; regulatory bodies.

Introduction

Pharmacogenomics

Pharmacogenetics is defined by the International Conference of Harmonisation (ICH) as ‘The study of variations in DNA sequence as related to drug response’ [1]. The terms pharmacogenetics and pharmacogenomics are often used interchangeably in the literature [2]. Pharmacogenomics

refers to the whole-genome application of pharmacogenetics, which has traditionally been considered to be concerned with single-gene effects [3].

History

In the mid 20th century Vogel coined the term pharmacogenetics amidst growing evidence of difference in reactions to pharmaceutical drugs [4]. An example is the observed adverse reactions to the anti-malarial drug primaquine in individuals with a glucose-6-phosphate dehydrogenase deficiency [5]. Studies in the late 1960s furthered the field by showing that genetically identical individuals, monozygotic twins, had a more similar drug metabolite profile than di-zygotic twins [6]. For a time more detailed studies were limited by technology. The advent of DNA cloning identified in 1988 that variations in cytochrome P450 2D6 (*CYP2D6*) were responsible for differences in the metabolism of debrisoquine [7]. Subsequently, several *CYP2D6* polymorphisms have been characterized [8], and the protein has been shown to be involved in the metabolism of ~25% of all prescribed drugs [9]. *CYP2D6* is now thought to have over 100 variations, 11 of which have clinical relevance [10]. Towards the end of the 20th century more associations of genes encoded in disease pathways, drug metabolism, or drug target were discovered [11] leading to the current knowledge base we now have.

Current knowledge

In the post-genome era more candidate genes for drug response have been identified through micro-arrays and genome-wide association studies [12]. Due to the volume of information accrued, detailed databases have

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been created to present the data in a comprehensive and searchable fashion [10, 13]. One database, the Pharmacogenetic Knowledge Base (PharmGKB), has published peer-reviewed guidance on 46 genes that have pharmacogenomic relevance and are otherwise known as pharmacogenes.

Academic, regulatory and industry of pharmacogenomics in healthcare

United States of America

The US is showing the lead in the translation of pharmacogenomic knowledge into the clinical setting. It is home to global pharmacogenomic networks and produces the majority of novel research in the field. The Pharmacogenetic Global Research Network (PGRN), funded by the National Institute of Health in 2000 also initiated the PharmGKB database. The Clinical Pharmacogenetics Implementation Consortium was set up in 2009 to provide peer-reviewed, updated, evidence-based, freely accessible guidelines for gene/drug pairs [14]. PharmGKB's data are available open source to research institutions who subscribe; however, for commercial use it is exclusively licensed to an interpretation company based in the US [15].

From a regulatory standpoint the Food and Drug Administration has issued their highest recommendation, a boxed warning, to three drug/gene pairs (Abacavir – *HLA-B 57:01*, Carbamazepine – *HLA-B 15:02* and Clopidogrel – *CYP2C19*) to advise testing before prescribing. This is clearly laid out in a table of over 100 drug/biomarker pairs (pharmacogenomic, proteomic, etc.) and their various levels of warning [16]. It is estimated that 7% of all approved medications in the US have actionable pharmacogenomics data incorporated in the drug label, and many more include relevant information [17].

Also, select insurance companies offer reimbursement for such testing to make it accessible to physicians and the public [18]. A number of private companies such as YouScript [19] have also started offering pharmacogenomic testing to the medical community and to provide interpretation.

United Kingdom and Europe

The UK and Europe has a rich history in genetic research with many key discoveries taking place there.

Pharmacogenomic networks are emerging but are less established than the PGRN. In 2001 the Committee for Medicinal Products for Human Use established a multi-disciplinary expert group to look at pharmacogenomics called the Pharmacogenetic Working Party, which was formalized in 2005 and renamed in 2008 to Pharmacogenomics Working Party (PGWP) [20]. Also in 2005, the Dutch Pharmacogenetic Working Group was established [21], which has become influential in the area providing research to PharmGKB. In 2012 the UK set up the UK Pharmacogenetics and Stratified Medicines Network, that acts as a portal to novel research [22]. The European Society of Pharmacogenetics and Therapeutics, now known as The European Society of Pharmacogenomics and Personalised Therapies, was formed after the fifth meeting of The Santorini Conference on prospective biology, genomics and pharmacogenomics in 2010 [23].

In Europe, regulatory recommendations about pharmacogenomics vary from country to country. Of the 517 medications approved by the European Medical Agency (EMA), which was set up in 1995 with the aim to harmonize member country regulatory efforts, 15% have pharmacogenomic recommendations in drug labels [24] these include Abacavir, Carbamazepine and Clopidogrel as in the US (see Section “United States of America”). In 2011, Prasad and Breckenridge predicted that the EU regulatory bodies will gain momentum in the field [25], and subsequently more guidelines have been released [26]. An example of this are the guidelines which came into effect in August 2012 [27]. These state that any pharmaceutical company that wishes to market a medication in Europe is required to carry out pharmacogenomic studies on the pharmacokinetics of novel small molecules. It is also highly recommended that databanks of such data should be collected during the drug testing phases. The PGWP is tasked to advise companies with such initiatives [28].

Currently, in Europe and the UK, demand for tests is low. Four out of 12 genetic laboratories versus 14 out of 15 histocompatibility and immunogenetics laboratories offer pharmacogenomic testing in the UK [29], which is in line with Germany where ~36% of laboratories offer testing [30]. Only one germline genetic test, the *HLA-B*5012*, to predict Abacavir response is used regularly in the UK [29].

Opinions on pharmacogenomics

Public support has been shown to be essential to translate a new technology [31], as are physician's opinions, which are of particular importance as they have been shown to

be a vital part of the process for integrating an innovation into a healthcare setting [32].

Few studies have been conducted globally into the opinions of various different focus groups. Understanding opinions towards novel technologies can focus research efforts into those areas that need more development to reassure adopters and end-users.

Lay persons

In lay-opinion studies in the UK, the public are not at first aware of the concept but, when described the technology of pharmacogenomics, they are generally optimistic. Members of the public are also not too worried about who gives them the information as long as it is communicated clearly and confidently [33]. In an open dialogue study carried out by the Royal Society opinions were again optimistic. Concerns that reoccur are privacy of data and interpretation of results [34]. In a US study, the public, on the whole, were strongly supportive of pharmacogenomic testing. Although interest was influenced by a combination of factors, most notably if an individual had experienced a previous side effect as a consequence of drug treatment [35].

Physicians

Stanek et al. carried out a study of the medical profession to determine what distinguished early adopters of pharmacogenomic tests in the US [36]. About 12.9% of respondents had ordered a test in the 6 months prior to the study, 26.4% predicted using a pharmacogenomic test in the next 6 months, and the rest would not order such a test. The groups were known as early adopters, future adopters and non-adopters, respectively. Early adopters of pharmacogenomics testing were more likely to be those practicing in urban settings, at an intermediate stage in their careers (15–29 years since leaving medical school), and practicing oncology or a surgical specialty.

In a qualitative study of 184 healthcare professionals carried out by Dodson and van Riper [37], five themes were identified as reoccurring when pharmacogenomics is considered. These are negative concerns for the application of pharmacogenomics, lack of successful integration into standards of care, accessibility of pharmacogenomic testing, potential harm and optimism. Versions of these themes are also apparent in most opinion-based studies globally.

In the UK, to date three studies have been conducted to assess physician's opinions [33, 38, 39]. The Fargher et al. study incorporated 17 views of healthcare professionals with the lay opinions mentioned above [33]. Hedgecoe solely conducted a qualitative study on two physicians [38]. Fargher concluded that the opinions of healthcare professionals differ from those of the lay persons who are more concerned about patient exclusion than information delivery. Hedgecoe identified that physicians from different specialties highlight different needs from pharmacogenomic data. Bartlett et al. [39] collected responses from 701 participants and showed that the more education about pharmacogenomics an individual had, the more likely they were to have a positive opinion about testing.

There is a reported lack of pharmacogenomic knowledge in the professional clinical population globally. Calls to amend the medical school syllabus to prepare trainee doctors for the emergence of personalized medicine have appeared in the literature since 2003 [40]. Little has changed, with the average syllabus containing no, to little, pharmacogenomic information. There has also been a call for more Continual Professional Development courses for qualified physicians [39]. This is very important, as it will create a sympathetic environment for the uptake of the technology in line with regulatory guidance.

With new discoveries, alongside better education, demand for genetic testing has been predicted to rise significantly [41]. In the US especially, there is a rise in direct to consumer (DTC) genetic testing companies. However, it has been shown that doctors in general are not comfortable and on the whole still dubious about the clinical utility of such tests [42]. The rise in demand for DTC genetic testing shows that people are more and more becoming engaged with their own genome. Europe is very varied in its legislation regarding DTC testing [43] with German law stating genetic tests can only be reported back to a patient by a doctor, while other member states allow a more liberal use of such tests.

Implementation, integration and interpretation

Various models for implementation of pharmacogenomic testing have been proposed in the US [44–46], and reviews into how pharmacogenomic information should be integrated into an electronic medical record (EMR) are available [47]. The RAPID GENE trial is the first study to show efficacy of a point-of-care pharmacogenomic test to determine antiplatelet treatment [48]. The test was an example

of how pharmacogenomic information can integrate into a physician's workflow to improve clinical outcomes.

The PREDICT (Pharmacogenomic Resource for Enhanced Decisions in Care and Treatment) study at Vanderbilt, Tennessee [49] is collecting a participant's 184 common polymorphisms across 34 pharmacogenes to store in their EMRs and be used in clinical decision support (CDS) when needed. As of November 2013 more than 10,000 patients have been enrolled, and a preliminary look at the first 9589 participants showed that 91% of the population had at least one clinically actionable genotype for five of the tested pharmacogenes [50].

Most pharmacogenomic implementation projects are being carried out at multiple sites across the US [51]. In Europe, the Dutch Pharmacogenetic Working Group has implemented guidance on 53 drug/gene pairs [52] in pharmacies across Holland; however, this is not a formal study. The first European-wide implementation project called Ubiquitous Pharmacogenomics (U-PGx) has recently received Horizon 2020 EU grant funding due to start early 2016 [53].

Interpretation is defined as 'the action of explaining the meaning of something,' and as the power and validity of pharmacogenomic studies increases, geneticists need to understand how best we can do this for healthcare professionals. In the US, a systematic review has shown that from 1990 to 2011, 38 primary studies were conducted to assess how all genetic results, not just pharmacogenomics, were interpreted by CDS systems [54]. Six of these studies looked at pharmacogenomic interpretation, four of which were conducted in the US and two in Europe. These initial studies provide evidence for applications of pharmacogenomics from genetic-guided therapy in HIV treatments to novel pharmacogenomics guidelines and proof of concept for integration of PharmGKB into clinical decision support.

Integration of pharmacogenomic data into digital health solutions has been a major focus for all implementation projects as it is an efficient way to present relevant data in a timely fashion to prescribers [55]. Drug-drug interaction clinical decision support in electronic prescribing (UK nomenclature) or Computerized Physician Order Entry systems (US nomenclature) can act as a model to understand how to best present drug-gene interactions. The positive impact on costs and patient outcomes of drug-interaction checkers has been proven in a trial environment [56]. However, electronic prescribing needs improving as in the clinical environment, 52.6% of alerts are overridden due to alert-fatigue [57]. In half of overrides it is thought that ignoring alerts could cause significant harm. Although there is optimism around these digital solutions from users, adoption can be slow [58].

Discussion

In summary, there seem to be large cultural differences surrounding the adoption of pharmacogenomics between the US and Europe. Europe presents a more conservative attitude to translational research than does the US.

Initiatives like Genomics England [59], which is the UK's 100,000 whole genome sequencing project launched in 2013, will no doubt push genomic research and translation forward. However, with a specific focus on rare disease and cancer genomics, the nuances of pharmacogenomics data interpretation will not be studied. On the other hand U-PGx will look at pharmacogenomics interpretation and integration; however, results will not be published until 2020 which seems like a long time to realize the expected patient benefits of the technology.

The US has been leading the adoption of pharmacogenomics globally and has a more established infrastructure to support this. The networks across Europe are younger; however, support for the industry is growing and the relatively connected state health-care systems can provide a strong platform for integration. The US also has strong leadership from regulators in the field with clear guidelines about the efficacy of pharmacogenomic testing. These guidelines have been shown to be a good source of education for physicians and provoke adoption of technologies [60]. Clearer guidance from the EMA might encourage the adoption of pharmacogenomics into European clinics.

In both geographical areas, more work is needed to understand how to present pharmacogenomic information in an actionable format to healthcare professionals. Trials have shown that integration of pharmacogenomics is effective in creating better outcomes for patients. However, optimism must be controlled, as with drug-drug interaction CDS, the real challenge will be how to ensure that warnings are implemented. The advent of digital technologies to inform the medical profession, combined with improved education in pharmacogenomics, holds much promise for assessing the best treatment for an individual based on their genetic make-up.

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