Just how feasible is pharmacogenetic testing in the primary healthcare setting?

“In an attempt to tackle the perceived lack of knowledge of pharmacogenetic tests, several groups have initiated the development of algorithms to aid physicians in their interpretation and use of pharmacogenetic data.”

KEYWORDS: implementation • pharmacogenetic testing • pharmacogenetics • primary care

Over 10 years ago, back in 2001, Francis Collins envisioned in The Journal of the American Medical Association that within a decade “… many primary care clinicians will become practitioners of genomic medicine…” [1]. In the following years, pharmacogenetics was consistently named as one of the first clinical applications arising from the new genetic knowledge. Indeed, pharmacogenetic information is accumulating rapidly and is beginning to show consistent, reproducible results for an increasing number of genetic markers for drug response. The US FDA have approved a number of genetic tests and pharmacogenetic markers have been included in multiple drug labels [101]. We are beginning to see the application of pharmacogenetics in secondary and tertiary care settings. However, application in primary care is not as common as was once anticipated. This leads to questions regarding the feasibility of pharmacogenetic testing in the primary care setting.

The first questions which need to be asked are how relevant pharmacogenetic testing is to primary healthcare, and which benefits can we anticipate from adopting a pharmacogenetic strategy? To date, pharmacogenetics has mainly been advocated to improve drug therapy with ‘high-risk’ medications (e.g., within the field of oncology). While this appears a sound idea, pharmacogenetics might also prove beneficial for drug therapies with lower risks [2]. Although commonly used drugs in primary care are, generally speaking, less toxic than drugs in other clinical fields (e.g., oncology), they are still a major cause of adverse drug events [3]. Approximately 60% of the drugs most commonly associated with adverse events are metabolized by a polymorphic enzyme [4]. While these data already indicate a clear potential for pharmacogenetics to improve drug therapy in primary care by reducing toxicity, even more benefit may be gained by increasing efficacy. Current response rates to major therapeutic classes of drugs are ranging from 25 to 60% [6]. While the current benefits for individual patients may appear relatively small (e.g., a 5–10% increase in chance of efficacy), the impact from a population perspective may be enormous given the large number of patients treated in primary care.

An issue closely related to these anticipated benefits is the required evidence base for preemptive genotyping. Some healthcare practitioners argue that a pharmacogenetic test should only be implemented after it complies with the standards of evidence-based medicine [7]. While we agree in general to these standards, the relatively small benefits from pharmacogenetics that can be anticipated in primary care may never fully justify expensive tools such as a randomized clinical trial. A randomized clinical trial for each individual gene–drug combination seems particularly unlikely for enzymes that are involved in the metabolism of multiple drugs such as the genetically polymorphic CYP450 enzymes. For example, CYP2D6 is involved in the metabolism of 25% of all drugs on the market. If a randomized clinical trial were to demonstrate that pre-emptive genotyping for CYP2D6 could improve the outcome from a population perspective may be enormous given the large number of patients treated in primary care.

Following these randomized clinical trials, a
strong biological rationale combined with observational data may be sufficient to justify clinical implementation of prospective pharmacogenetic testing for individual gene–drug interactions. Currently, multiple projects aimed at evaluating pre-emptive genotyping are in progress [9].

“Our current benefits for individual patients may appear relatively small (e.g., a 5–10% increase in chance of efficacy), the impact from a population perspective may be enormous given the large number of patients treated in primary care.”

Although integrating pharmacogenetic testing in primary care could potentially benefit many patients, clinical adoption remains limited. This gives rise to a second set of questions of a more practical nature. For example, is ordering a pharmacogenetic test in primary care technically possible? Do laboratories aimed at primary care offer pharmacogenetic tests? It was reported in 2005 that only ten out of 507 surveyed Australian laboratories offer genotyping tests for drug-metabolizing enzymes [10]. However, in recent years this number may have increased significantly. We recently investigated the technical feasibility of pharmacy initiated pharmacogenetic testing in a small study in a population of elderly polypharmacy patients. One of the key findings was that a majority of patients are willing to participate in a pharmacy-initiated pharmacogenetic screening study with 58.1% of the patients agreeing to participate. Considering that the invited population had no actual medication-related problems, willingness to participate may be even higher in a population with medication-related problems. This study also showed that pharmacogenetic screening was feasible with regard to obtaining good quality DNA samples. An important problem that was not investigated in our recent study was the time lag between the time of ordering the test and the availability of the actual test result. In many situations, postponing a prescription while waiting for a pharmacogenetic test results might not be acceptable because it obstructs regular workflow. Therefore, upfront availability of genotypic information may prove essential to increase pharmacogenetic test adoption. However, the time-lag problem appears to be temporary. Given the rapid and continuing significant price drop of pharmacogenetic tests, in addition to the increasing availability of companies directly offering pharmacogenetic testing to consumers, the number of patients with available pharmacogenetic information may rapidly increase.

Of major importance in the adoption of any innovation is how it is experienced by its intended target audience. Several reports have assessed the views of healthcare professionals on pharmacogenetic testing and some have even looked specifically at physicians and pharmacists working in primary care. In general, most studies conclude that the concept that variation in patients’ drug response is associated with genetic variation is widely accepted by both physicians and pharmacists. Furthermore, both groups agree that pharmacogenetics can offer great potential benefits to patient care. A recent survey among 10,303 US physicians showed that the percentage of early adopters of pharmacogenetic testing was much lower among family physicians compared with oncologists (11.7 and 68.8%, respectively) [11]. The primary reason for not ordering a pharmacogenetic test was a lack of information regarding testing and genomic markers. Only 10.3% of the responding physicians reported that they had adequate knowledge to use pharmacogenetic testing when prescribing drugs. Other perceived reasons for not using a pharmacogenetic test were the use of drugs for which no pharmacogenetic test was available or recommended, lack of insurance coverage for testing and low or uncertain value of test results. Another reason for the large difference between family physicians and oncologists might be that most pharmacogenetic tests available in oncology are related to a single drug and a single genetic variation (e.g., with irinotecan) [12]. This is a much less complex situation than in primary care, where available pharmacogenetic tests are often related to multiple drugs, and drugs are related to multiple different polymorphic enzymes.

“Another reason for the large difference between family physicians and oncologists might be that most pharmacogenetic tests available in oncology are related to a single drug and a single genetic variation (e.g., with irinotecan).”

In an attempt to tackle the perceived lack of knowledge of pharmacogenetic tests, several groups have initiated the development of algorithms to aid physicians in their interpretation and use of pharmacogenetic data. The Royal Dutch Pharmacists Association have established a working group that has published guidelines concerning 53 drugs and 11 genes [13]. To increase clinical utility, these recommendations are incorporated into systems for...
computerized drug prescription and automated medication-surveillance systems in The Netherlands, thereby directly linking them to the decision-making process. In 2009, the Clinical Pharmacogenetics Implementation Consortium was launched [102]. This international initiative to create pharmacogenetic guidelines recently published its fourth guideline that is publicly available [14]. The Dutch working group and the Clinical Pharmacogenetics Implementation Consortium are currently exploring ways to collaborate to better address the perceived lack of knowledge among clinicians even further. In addition, several medical and pharmacy schools have now included pharmacogenetic courses in their curriculum to prepare future generations of clinicians and make them much more comfortable with ordering and interpreting a pharmacogenetic test.

So how feasible is pharmacogenetics testing in primary care? Maybe not as feasible as once anticipated in the peak of the ‘genomics revolution’ at the turn of the century. Yet, several large US pharmacy chains have moved into pharmacogenetic testing [15]. In addition, a recent survey showed that despite the fact that only 12.9% of the physicians ordered a pharmacogenetic test in the preceding 6 months, 24.6% intended to do so in the next 6 months indicating that the adoption, acceptance and application of pharmacogenetics is increasing. Thus, successfully bridging the gap from research to clinical practice seems within reach in the field of pharmacogenetics. Challenges remain, but we should expect routine pharmacogenetic tests to enter the process of drug prescribing and dispensing in primary care soon.

Financial & competing interests disclosure
The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

Websites
101. US FDA. www.fda.gov/Drugs/ScienceResearch/ ResearchAreas/Pharmacogenetics/ ucm083378.htm