Pharmacogenetics: Routine genetic testing for the general population at birth and periodically afterwards can decrease healthcare cost and improve patient care. A systematic review

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ABSTRACT

Context: Increasing evidence suggest that routine pharmacogenetic testing for the general population at birth and routinely afterwards can decrease healthcare cost and improve patient care. Objective: To systematically review and evaluate the possible economic impact of universal pharmacogenetic testing on the general population and its effects on quality of patient care measured by Adverse drug events. Data Sources and Extraction: Data was extracted using predefined categories of desired information. Using keywords, Boolean operators and Pubmed search engine, Medline and the National Library of Medicine was searched for indexed systematic reviews, meta-analysis, case reports and observational studies with information of interest. Results: Nineteen articles met inclusion criteria. 2 articles reported economic benefits of pharmacogenetic testing, 8 articles reported positive relationship between pharmacogenetic testing and adverse drug reactions and the remaining articles had general and support information pertaining to the objective. I found evidence supporting cost effectiveness of pharmacogenetic testing and its possible impact on patient compliance as well as adverse drug events. Limitation: This review was unable to provide evidence for acceptable time interval between pharmacogenetic testing to account for epigenetic changes to gene expression overtime. It was also unable to adequately account for how genetic profiles will be appropriately kept and who will have access to them to avoid discrimination from insurance companies. Conclusion and Discussion: Pharmacogenetic testing has made great strides in the past few decades and continues to do so as research in this field intensifies and the medical community strives to discover its usefulness and implication in medicine to the wellbeing of patients. However, the current standard way of prescribing most medications still remains the trial and error approach. It has been estimated that more than 770,000 people are injured or die each year in hospitals from adverse drug events (ADEs), costing over 4 billion dollars in healthcare costs each year [1]. Studies have shown that pharmacogenetic testing does not only decrease ADEs and the cost involved but also increases medication compliance in patients [2]. Some institutions such as Mayo Clinic, St. Jude Children's Hospital and the NIH have already instituted a more generalized routine pharmacogenetic testing for sections of their patient population and are reaping the benefits of it [3]. Considering the cost and risk involved in the trial-and-error approach and the benefits associated with genetic testing, routine genetic testing for the general population at birth will not only save healthcare dollars but also optimize patient care. However, since epigenetics has the ability to turn genes on or off overtime, periodic updates will be needed to determine what medication is well suited for a specific patient and whether or not a patient is still responding the same way to a medication.

Keywords: Pharmacogenetics, pharmacogenomics, personalized medicine, adverse drug events, cost-effectiveness

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INTRODUCTION

The history of pharmacogenetics can be traced as far back as 510 B.C. when Pythagoras noted that ingestion of fava beans resulted in fatal reaction in some, but not all, individuals [4-18]. Since then there has been numerous landmarks that have shaped this field of research, and have led to the current wave of interest. Although there are a number of different types of polymorphic markers, most attention recently has focused on single nucleotide polymorphisms and the potential for using these to determine the individual drug response profile [19].

THE TRIAL-AND-ERROR APPROACH

Since time immemorial, the standard way of prescribing medications to patients with various ailments has been the "trial-and-error" approach. Physicians and other healthcare providers experiment various medications and dosages on patients until
success is achieved. Common medications that are often prescribed using this approach include codeine, warfarin, statins, plavix, SSRIs to mention a few. While this might sound innocuous, this approach can lead to extra cost and exposure of patients to risks such as drug toxicities, worsening of medical condition and even death. A case report published in 2006 talks about a 2-year-old boy who died from ultra-rapid metabolism of codeine resulting in toxic accumulation of morphine in his tissues. Postmortem examination including Cytochrome P-450 2D6 (CYP2D6) genotyping revealed functional duplication of the CYP2D6 allele [17]. Several reports have been published on codeine intoxication and/or death following codeine use in children and adults with ultra-rapid CYP2D6 activity. It is estimated that 90–99% of women take some type of pain medication in the first week postpartum and as many as three to four drugs during breast-feeding and oral analgesics have been reported to be the second most commonly used drug after vitamins during the postpartum period [1]. Another example is plavix. Unlike codeine, plavix is metabolized by CYP2C19 and is estimated that approximately 1–7% of Caucasians and African-Americans, and 13–23% of Asians are poor CYP2C19 metabolizers [1]. Combined, drugs that are currently approved and recommended by the FDA for pharmacogenetic testing prior to initiation are used by a considerable number of patients. Hence the trial-and-error approach of medication prescription seems to be affecting majority of the patient population.

In 2005, the FDA approved its first pharmacogenetic test- The AmpliChip™ CYP450 Test- based on Affymetrix microarray technology. It was approved for genotyping 27 alleles in CYP2D6 and three alleles in CYP2C19 genes that code for different metabolizing enzymes. The test is recommended for assessing the metabolism rate for drugs that are substrates for CYP isoenzymes 2D6 and 2C19[18]. Since its inception, pharmacogenetic testing has mostly been used as a last resort on targeted patient populations most often after a patient has failed a trial-and-error approach. In recent years the FDA has instituted recommendations and advice to clinicians to perform genetic testing prior to initiation of some medication such as abacavir, trastuzumab, mercaptopurine and irinotecan.

THE CONCEPT OF EPIGENETICS AND ITS PLACE IN PHARMACOGENETICS:

Epigenetics is defined as any process that alters gene activity without changing the DNA sequence, and leads to modifications that can be transmitted to daughter cells. Overtime, a gene can be turned on/off depending on environmental factors a person is exposed to. Known or suspected drivers behind epigenetic processes include many agents, including heavy metals, pesticides, diesel exhaust, tobacco smoke, polycyclic aromatic hydrocarbons, hormones, radioactivity, viruses, bacteria, and basic nutrients. If the gene affected is responsible for coding a drug metabolizing enzyme, a patient can respond differently at different times to the same medication [9]. Hence due to epigenetics, periodic update of changes in gene expression will be warranted to determine if a patient is responding the same way or differently to the same medication.

METHOD

Using PRISMA guidelines, I conducted a systematic literature review of manuscripts indexed by MEDLINE and the National Library of Medicine. My search strings were: (pharmacogenetic testing OR personalized medicine), (Epigenetics*) and (Pharmacogenetics AND Healthcare cost) where the asterisk means that any ending may follow the beginning of the specified term. I used these search strings at the beginning of a 4-phase process (identification, screening, eligibility, and inclusion) that determined manuscripts to be included in this review. The bibliographies of included manuscripts were also reviewed for additional studies of interest. I was interested in identifying systematic reviews, meta-analysis, case reports and observational studies that reported the associations among pharmacogenetics, healthcare cost and adverse drug events, which were published in English. When multiple studies were published based on the same study population, I included the study that used a prospective design, was published most recently or was most closely related to my information of interest if all studies were cross sectional. I performed the
literature search, reviewed search results, and extracted data from identified manuscripts based on prespecified categories of information.

RESULTS
Flowchart describing the algorithm used to select studies for this review (Figure 1). I initially identified 2,071 records using the search criteria described above (Identification phase). These articles were screened based on title, abstract and relevance to desired information, at which point 1932 articles were excluded either because they were not written in English or did not evaluate the association of interest (Screening Phase). This left me with 139 full-text articles to evaluate for eligibility of which 15 were determined to be eligible for inclusion (Eligibility Phase) [1-15]. Six additional studies were identified based on review of the bibliographies from these manuscripts and information obtained from FDA website was also included [16-21]; thus, in total, 20 studies were included in my review (Inclusion Phase).

Figure 1: Algorithm showing the process involved in selecting articles for review.

Conclusion and Discussion
Although research into pharmacogenetic and pharmacogenomic testing is still in its preliminary stages of evaluation to determine its potential value in medicine, current evidence obtained so far from various studies all point to the fact that its benefits far outweigh potential harm if any. There have been discussions about potential challenges that generalized pharmacogenetic testing might encounter if instituted. As part of the issues that have been raised is the question as to what the appropriate timing should be for universal pharmacogenetic tests to be performed on the general population. Personally I believe these genetic tests should be added to the newborn screening panel of every state and performed at birth with periodic updates performed to account for epigenetic changes in gene expression. Also, there have been questions about who will be responsible for the cost of these genetic tests. Just like newborn screening where cost is borne by insurance companies, State Children’s Health Insurance Programs or Medicaid, initial cost of these genetic tests can be borne by these same.
entities and subsequent costs from periodic updates borne by insurance companies.

Considering the number of patients that depend on medications that are currently approved by FDA for genetic testing and the unnecessary cost and risk involved in the trial-and-error approach, routine genetic testing for the general population will not only save healthcare dollars but also improve medication compliance and optimize patient care.

REFERENCES