The recent advances in pharmacogenomics and pharmacogenetics show promise for the diagnosis and management of chronic pain. Chronic pain affects an estimated 100 million adults in the US and it is believed that at least twenty percent of the populations in industrialized countries live with chronic pain—as populations age it is expected that the prevalence will increase. Chronic pain can have significant impact on quality of life for the patient and their caregivers. In addition, the economic burden to societies exceeds that of heart disease, diabetes, and addictions combined. Pharmacogenetic studies have the ability to greatly reduce risks of side effects for study patients and can improve trials by stratifying group populations by genetic differences. Genotypic heterogeneity contributes to the variable responses to safety, efficacy, and tolerability of drugs. The ability to identify populations that are at risk of increased side effects or greater efficacy from drugs may be enhanced with pharmacogenetics testing.
AN INTRODUCTION TO AND HISTORY OF PHARMACOGENOMICS

Pharmacogenomics (the entire genome) and pharmacogenetics (specific candidate genes) have emerged as important disciplines in the evaluation, safety, and efficacy of treatments used. The use of genomic data, biomarkers and associated technology, and the concept of “personalized” treatment have received increased attention in recent years. This is governed by the growing understanding of the inter-individual differences in DNA sequences as well as the ability to link a particular drug response to variations in the human genome.

More than 60 years ago, very little was known about the genetic factors that contribute to human disease. In 1953, James Watson and Francis Crick described the double helix structure of DNA. Methods to determine the order—or the sequence—of the chemical letters in DNA were developed in the mid-1970s. In 1990 the National Institutes of Health (NIH) and the Department of Energy joined with international partners to start the Human Genome Project (HGP). The goal of HGP was to provide researchers with powerful tools to understand genetic factors in human disease, preparing the ground for new strategies for diagnoses, treatment, and/or prevention. In 1998 the NIH set up a task force to standardize the definition of biomarkers. Biomarkers are defined as being key molecular or cellular events that can link a specific environmental exposure to a health outcome. They can play a key role in understanding relationships between exposure to environmental chemicals, the development of chronic human diseases, and the identification of subgroups that are at increased risk for disease.¹

Biomarkers in relation to a disease should expose critical features and should ideally:

- Have a direct consequence of the disease pathology
- Be a close mediator of one or more components of the clinical syndrome
- Be measurable in both clinical and “real world” settings
- Be detectable in pre-clinical state

In 2003 the HGP was successfully completed.

To date, the identification of genomic factors that influence variability in drug response has been limited to the following encoding genes:

- Enzymes that are drug metabolizing (eg, Cytochrome P450)
- Drug transporters
- Drug targets (eg, receptors)

¹ http://www.niehs.nih.gov/health/topics/science/biomarkers/
Current research in the area of pharmacogenomics has enabled the prediction of adverse drug reactions by analysis of host human leukocyte antigen haplotypes, as well as revealing important variable loci and single-nucleotide polymorphism that influence drug response.

Pharmacogenetic studies could benefit clinical trials in 3 ways:

1. Optimizing pharmacovigilance by identifying the percentage of individuals at risk of adverse drug reactions
2. Recommending therapeutic dosage regimens of specific drugs for specific populations
3. Improving clinical trials by stratifying group populations based on genetic differences in ethnic and cultural identities and their susceptibility for drug activity

In the pre-marketing stage a medicinal product is exposed to a relatively small number of subjects due to the confines of the clinical trial. As such, rare and/or serious adverse drug reactions may only be identified later in the drug development process. Considerations should be made to identify sub-populations who may have increased or decreased sensitivity to medicinal products as a result of genomic factors. Identification of these subpopulations has the potential to greatly reduce the risk of side effects and significantly increase the therapeutic benefit to the subjects.

During preparation and maintenance of risk management plans it is essential to consider the potential risk of genomic variations and identify risk minimization measures.2, 3

THE GENETICS OF PAIN

Scientists are only now beginning to examine the genetic variations that may influence pain processing. If a genetic basis underlies how pain is expressed and perceived, including the varying mechanisms of nociceptive, neuropathic, and visceral pain, then the potential exists for new analgesic targets affecting such gene products. Pain expression can also be linked to environmental factors, such as cultural attitudes, attention, sleep, and stress. Fibromyalgia, tension headaches, and irritable bowel syndrome are just a few examples of functional pain disorders influenced by environmental factors.4

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2 EMA “Guideline on key aspects for the use of pharmacogenomic methodologies in the pharmacovigilance evaluation of medicinal products” (EMA/281371/2013, published January 2014)
3 EMA “Guideline on good pharmacogenomic practice” (published for public consultation April 2016)
4 Webster Lynn R and Belfer Inna, Pharmacogenetics and Personalized Medicine in Pain Management, Clinical Laboratory Medicine 2016
WHY FOCUS ON PAIN?

Globally there is a cultural movement to diminish the use of opioids which has left, in many cases, few options for those on chronic opioid therapy. Currently there are over 12 million Americans who receive some form of chronic opioid therapy. To further diminish the reliance on opioid therapy there is a need for continued investment in research for alternative pain therapies. 5

In the US alone there are estimated to be around 100 million adults suffering with some type of chronic pain. Around 80% of people undergoing surgeries report some degree of post-operative pain. Within that pool, less than 50% feel they received adequate pain relief and between 10-50% developed some type of chronic pain. The estimated annual national economic cost of pain management is around $560-635 million.

There is an observed increase in the rates of people suffering with some degree of chronic pain. The rising rates can be attributed to the following causes:

- Surgery: Inadequate analgesia resulting in acute pain becoming chronic
- Obesity: An increasingly obese population leading to painful chronic conditions and orthopedic problems
- Aging Population: Continued improvements in healthcare and disease treatment, resulting in an increase in life expectation. Approximately 10,000 Americans per day turn 65 and with an aging population an increase in diseases associated with chronic pain are observed or expected
- Progress in Saving Lives: Advances in the treatment of disease (ie, cancer) result in an increase in survival rates, many of which will lead to people with lasting chronic pain. In addition, survival from catastrophic injuries would potentially result in life-long pain
- Awareness and Access: An increased level of awareness about the causes of pain and access to treatment produces a larger dataset of people for analysis

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Increasing age, obesity related pain disorders, chronic pain following trauma and surgery, and pain due to successful cancer therapy continue to increase the number of people with chronic pain.\(^5\)

Furthermore, many people reported that they, or a close friend or family member, needed to make a number of lifestyle adjustments due to their degree of pain. A snapshot of such lifestyle adjustments for subjects suffering from chronic pain is outlined below:

- Moving home: 8-13%
- Needing help performing daily activities: 13-18%
- Changing job or profession: 6-17%
- Taking leave from work: 17-20%

As well as established chronic pain, long-term consequences of unmanaged acute pain exist.

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\(^5\) Lynn R. Webster, M.D. Personalized Medicine: Genetic testing for Predicting Opioid Response, 23-Mar-2016
Pharmacogenetics therapy in pain requires consideration of two different genetic substrates to determine the outcome of pharmacotherapy. The first is the genetic contribution of the variety of different pain types, and the second is the genetic influence of drug effectiveness and safety.

Inter-individual differences in DNA sequences as well as the ability to link a particular drug response to variations in the human genome can help improve the efficacy and safety of treatments used. It is important to consider other factors, separate to the genome, which might further contribute to inter-individual variability in drug response:

- Demographics (ie, age, gender, race, ethnicity)
- Weight
- Concomitant Diseases
- Concomitant Drugs
- Social Factors (ie, cultural/religious beliefs)
- Environmental Factors (ie, diet, clinical/medical history, stress)
- Psychological Factors (ie, mood patterns)
- Physiological Factors (ie, sleep patterns)

Understanding all potential contributing factors is the first step in the development of personalized treatments. That said, it is widely considered that known contributing factors only account for around 5-20% of inter-individual variability to drug response; this suggests that between 80-95% of inter-individual variability to drug response is linked to an individual’s genome.

Recent findings for pain pharmacogenetics have indicated variability in responses from multiple genes and that differences in the efficacy of analgesic drugs are genetically controlled. There are many variations in the definition of polymorphism. In this context, it refers to variations in shape and form that distinguish individuals from one another. A gene is considered to be polymorphic if more than one allele occupies that gene’s locus within a population. Polymorphic genes can determine:

- Extensive, reduced, and poor metabolizers
- Drug toxicity
- Decreased efficacy with increased dosing
- Lack of pro-drug conversion
- Prolonged or adverse drug effects
Laboratory analysis of genomic samples is a growing industry which in turn can provide greater flexibility and cost efficiency to the customer. The DNA sample can be extracted from a simple buccal swab, as opposed to a blood sample, which represents a less invasive experience for the individual. The process of DNA extraction and analysis can be completed within 6-8 hours and an associated pain panel can be used to flag identified pain biomarkers.

Pharmacogenetics can help to identify individuals who are at risk of poorly responding to pain medicine and those who might be more susceptible to adverse drug effects. Genetic testing may help to inform clinical decisions regarding the best therapeutic option and help in predicting outcomes. Collection of large datasets for different populations will enable the collection of meaningful results.

ADOPTING PHARMACOGENOMICS IN THE PRE- AND POST-MARKETING ENVIRONMENT

Analysis of biomarkers gives the potential to play an important role in understanding the relationship between the medicinal product and how it reacts within a patient. Analyzing biomarkers helps identify subgroups that are at increased risk of disease. The use of biomarkers has a potential to increase the safety and efficacy of drugs during therapy. Investigations of biomarkers should be considered during the risk-minimization process in both the pre- and post-marketing phase, exploring the potential to improve understanding of the risk profile of the medicinal product in certain subsets of patients by collecting information during a clinical trial. Such information should be considered within the Risk Management Plan (Section, Part V – Risk Minimization Measures).

HOW RISK MINIMIZATION REDUCES BURDEN TO PATIENTS

This example describes the use of Clopidogrel and how its effectiveness would be influenced according to the genomic type of patient. Clopidogrel is used to prevent myocardial infarction and stroke in patients who are at high risk of these events, including those with a history of myocardial infarction. Clopidogrel requires transformation into an active metabolite by cytochrome P-450 (CYP) enzymes for its therapeutic effect (i.e., prevention of aggregation of platelets). The genes encoding CYP enzymes are polymorphic with common alleles conferring reduced function.
At the time of drug approval, it was not possible to determine the active metabolites. When discussing CYP enzyme function in any particular subject this may be described as one of the following:

- Poor Metabolizer: Little or no function
- Intermediate Metabolizer: Metabolizes drugs at a rate somewhere between poor and extensive metabolizers
- Extensive Metabolizer: Normal function
- Ultrarapid Metabolizer: Multiple copies of the gene are expressed, and therefore a greater than normal function

Studies were conducted which found out that a combined group of either intermediate or poor metabolizer status had a higher rate of cardiovascular events or stent thrombosis compared to extensive metabolizers. Based on meanwhile available data and relevant studies the product information of Clopidogrel was updated in the EU, now including information on increased risk of cardiovascular events in patients with reduced CYP2C19 function.7

**FUTURE INVESTMENTS**

In order to further understand the potential for the use of genomic data there is a need for continued investment in genomic studies, both in the pre- and post-marketing environments.

In the pre-marketing environment there would be a mandatory requirement for a detailed description of the genomic testing outlined within the study protocol. The protocol should clearly outline the genomic testing as part of the screening procedures and eligibility criteria and the Informed Consent Form should be customized to reflect the agreement of the individual to provide a genomic sample. The individual should be fully briefed on the necessity for providing a genomic sample in order to understand the nature of the genomic testing, as well as made aware of how the genomic data will be used and the storage timeframe of these data. Considerations should be made to ensure adequate training of site staff and a support network (ie, genetic counseling) should be in place to handle individual concerns.

Following marketing authorization approval, the applicable reference safety information (ie, the patient information leaflet and summary of product characteristics) should include full details of the benefits of obtaining a genomic sample and the associated genomic testing. Healthcare professionals should be well-informed to ensure that they can cascade the relevant information to patients at the time of

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7 Jessica L. Mega and others, 2009 “Cytochrome P-450 Polymorphisms and Response to Clopidogrel”
consultation and prior to prescription. As with the pre-clinical environment the patient should consent to providing a genomic sample, should be fully supported, and understand the goal of providing the sample.\textsuperscript{8,9}

**IN SUMMARY**

Each individual person carries their own genetic imprint for the risk of severe or chronic pain and their response to pain treatment. Progress in genetic research and pharmacogenomics can help to uncover gene and associated interactions that influence pain perception and treatment pathways among the most painful diseases. Continued advances, investment, and genome associated studies are needed to further complete the genetic puzzle and to identify full genetic signatures for pain and pain treatment in order to help genetic testing become a widespread part of clinical practice.\textsuperscript{10}

**CITATIONS**

- EMA “Guideline on key aspects for the use of pharmacogenomic methodologies in the pharmacovigilance evaluation of medicinal products” (EMA/281371/2013, published January 2014)
- EMA “Guideline on good pharmacogenomic practice” (published for public consultation April 2016)
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\textsuperscript{8} EMA “Guideline on key aspects for the use of pharmacogenomic methodologies in the pharmacovigilance evaluation of medicinal products” (EMA/281371/2013, published January 2014)

\textsuperscript{9} EMA “Guideline on good pharmacogenomic practice” (published for public consultation April 2016)

\textsuperscript{10} Webster Lynn R and Belfer Inna, Pharmacogenetics and Personalized Medicine in Pain Management, Clinical Laboratory Medicine 2016
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