Pharmacogenomics in Pain Management
Personalized Pain Therapy

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EXECUTIVE SUMMARY

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. It is believed that at least 20% of people in industrialized countries live with chronic pain, and as populations age, it is expected that the prevalence will increase. Chronic pain can significantly affect quality of life for patients and their caregivers, and the economic burden exceeds that of heart disease, diabetes, and addictions combined. Pharmacogenetic studies can greatly reduce the risks of side effects for patients and can improve clinical trials by stratifying group populations by genetic differences. Genotypic heterogeneity contributes to the variable responses to safety, efficacy, and tolerability of drugs. Pharmacogenetics testing may improve the identification of populations at risk of increased side effects or greater efficacy from drugs.
AN INTRODUCTION TO PHARMACOGENOMICS

Pharmacogenomics (the entire genome) and pharmacogenetics (specific candidate genes) have become important disciplines in the evaluation, safety, and efficacy of treatments used. The use of genomic data, biomarkers, the associated technology, and the concept of personalized medicine have expanded in recent years. This growth has been driven by our deeper understanding of the differences in the DNA sequence between individuals and the ability to link a particular drug response to variations in the human genome.

For years, 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 of determining the order—or the sequence—of the chemical letters in DNA (deoxyribonucleic acid) were developed in the mid-1970s. In 1990, the US National Institutes of Health (NIH) and the Department of Energy (DOE) joined with international partners to initiate the Human Genome Project (HGP). The goal of HGP was to provide researchers with tools to understand genetic factors of human disease, and it established the foundations for new strategies for diagnosis, treatment, and prevention. In 1998, the NIH established a task force to standardize the definition of biomarkers. Biomarkers are defined as key molecular or cellular events that can link a specific environmental exposure to a health outcome. They play an important role in understanding the relationship between exposure to, for example, certain chemical compounds and the development of human disease, and in identifying subgroups that are at increased risk of developing disease.¹

The HGP was successfully completed in 2003. To date, the identification of genomic factors that influence variability in drug response has included these encoding genes:

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

Biomarkers examined in the context of a given disease should expose critical features and 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 clinical and real world settings
- Be detectable in pre-clinical state

Current research in pharmacogenomics has enabled the prediction of adverse drug reactions by analyzing host human leukocyte antigen haplotypes and revealing important variable loci and single-nucleotide polymorphism that influence drug response.

Pharmacogenetic studies can benefit clinical trials by:

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

In the pre-marketing stage, a medicinal product is exposed to a relatively small number of patients due to the confines of the clinical trial. As such, rare and/or serious adverse drug reactions may only be identified later in the development process. Pharmacogenetic studies allow researchers 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.

It is essential to consider the potential risk of genomic variations and identify risk minimization measures.² ³

THE GENETICS OF PAIN

Scientists are beginning to examine the genetic variations that influence pain processing. If the expression and perception of pain (including the mechanisms of nociceptive, neuropathic, and visceral pain) have a genetic basis, the potential exists for new analgesic targets affecting such gene products. Pain expression can also be linked to environmental factors, such as cultural attitudes, sleep status, 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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WHY FOCUS ON PAIN?

There is a cultural movement to minimize the use of opioids, which for many leaves few options for those on chronic opioid therapy. More than 12 million Americans currently receive some form of opioid therapy. To decrease the reliance on opioids, there is a need for continued investment in research for alternatives.6

In the US, an estimated 100 million adults suffer with chronic pain. Approximately 80% of those undergoing surgery reported some degree of post-operative pain; less than 50% felt they received adequate pain relief and between 10%-50% developed chronic pain. The estimated annual national cost of pain management is $560–635 million.

Figure 1: The Percentages of Pain

We have observed more and more 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: Improvements in healthcare and disease treatment have increased life expectancy. Approximately 10,000 Americans turn 65 every day and we can expect to observe even more cases of chronic pain as the population continues to age.
• Progress in Saving Lives: Advances in the treatment of a variety of diseases (eg, cancer) result in higher survival rates, but also to many more instances of chronic pain. Catastrophic injuries that were until recently fatal are now treatable, but the survivors are likely to live with permanent pain syndromes.

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• Awareness and Access: Greater awareness of the causes of pain and access to treatment produce a larger dataset of people for analysis.

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.\(^6\)

Figure 2: Causes of Rising Rates of Chronic Pain

Another consideration in assessing chronic pain is its significant impact on the patterns of daily life. Many people reported that they—or a close friend or family member—were forced to make adjustments to accommodate their chronic pain, which included these:

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

In addition to the effects of established chronic pain, we also observe many long-term consequences of unmanaged acute pain, including those in Figure 3.

Figure 3: Progression of Acute Pain to Chronic Pain

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Given the number of factors and societal impacts of chronic pain discussed above, chronic pain is a very promising area of focus for pharmacogenomic research. We begin with considerations of 2 genetic substrates to determine the possible outcomes of pharmacotherapy. The first is the genetic contribution of the variety of different pain types, and the second is the genetic influence on drug effectiveness and safety.

Inter-individual differences in DNA sequences and the ability to link a particular drug response to variations in the human genome can help improve efficacy and safety. It is important to consider factors other than the genome that may also 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 these potential contributors is the first step in developing personalized treatments. However, it is widely considered that known contributing factors account for only 5%-20% of variability to drug response; this suggests that between 80%-95% of variability to drug response is linked to the individual genome.

Recent findings for pain pharmacogenetics have demonstrated variability in responses from multiple genes; furthermore, 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. A gene is considered to be polymorphic if more than one allele occupies that gene’s locus within a population. Polymorphic genes can determine:

- Metabolizer level (ie, extensive, reduced, or poor)
- 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 that 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), a less invasive option for the individual. The process of DNA extraction and analysis can be completed within 6-8 hours and an associated pain panel used to flag identified pain biomarkers.

Pharmacogenetics can help to identify individuals who are at risk of a poor response to pain medicine and those who may 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- & POST-MARKETING ENVIRONMENT

Analysis of biomarkers provides the potential to play an important role in understanding the relationship between the medicinal product and how it reacts within a patient. It may also help identify subgroups 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.

HOW RISK MINIMIZATION REDUCES BURDEN TO PATIENTS

This example describes the use of Clopidogrel and how the patient’s genomic type influences the drug’s effectiveness. 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 (ie, preventing the 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. CYP enzyme function may be classified 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, triggering higher than normal function

Studies found that a combined group of either intermediate or poor metabolizer status had a higher rate of cardiovascular events or stent thrombosis than did extensive metabolizers. Based on available data and relevant studies, the product information for Clopidogrel was updated in the European Union to include information on increased risk of cardiovascular events in patients with reduced CYP2C19 function.\(^7\)

**FUTURE INVESTMENTS**

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

In the pre-marketing environment, study protocols would mandate genomic testing as part of screening and eligibility assessment; the informed consent form (ICF) would reflect participants’ agreement to provide samples. The individual should be fully briefed on the necessity for providing a genomic sample to understand the nature of the genomic testing, and 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 address 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 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.\(^8,9\)

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IN SUMMARY

Each individual 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 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 identify full genetic signatures for pain and pain treatment to help genetic testing become a universal part of clinical practice.\textsuperscript{10}

CONTACT INFORMATION

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