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EXPLORING THE INFLUENCE OF PHARMACOGENETIC VARIABILITY ON WARFARIN TREATMENT OUTCOMES

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Abstract
Pharmacogenetics holds much promise for influence on warfarin dose initiation. It is a science that is still in its relative infancy but has already achieved success in this area. To appreciate fully whether pharmacogenetics can provide the long-sought solution, it is necessary to understand the genetic and environmental factors that determine warfarin dose requirement and how they are involved in dose prediction. (Al-Eitan et al.2021)
The degree of interindividual variability in warfarin dose requirement is considerably higher than for most other drugs. If clinical or genetic information could be used to predict the correct warfarin dose, then each individual could potentially be given a much more appropriate starting dose when warfarin treatment is initiated.(Wadelius M, et al. 2007)
Although it is now more than half a century since warfarin was first used clinically, the problem of how to initiate it safely and efficaciously still poses a difficult challenge. Over-anticoagulation can lead to serious or fatal bleeding events; under-anticoagulation can lead to thromboembolism. Both events are most keenly avoided. If warfarin dose could be predicted and the desired therapeutic range achieved early in treatment, treatment decisions would be much easier for both doctor and patient. (Ansell J, Hirsh J, Hylek E, et al. 2008).

Keywords: Warfarin, pharmacogenomics, personalized medicine, genetic variants, pharmacogenetic algorithms

1. Introduction

Warfarin is the most widely used oral anticoagulant drug in North America and is used by over 2 million individuals in the United States each year. It is indicated for the prevention and treatment of deep vein thrombosis, pulmonary embolism, and thrombus formation in patients with atrial fibrillation and/or mechanical heart valves, and for the prevention of thromboembolism in patients following myocardial infarction. The effectiveness of warfarin therapy is hindered by the fact that it has a narrow therapeutic index and a wide inter-individual dose response variability, thus making the

safe and effective dosage of warfarin difficult to predict. Factors that affect an individual's response to warfarin can be divided into genetic and non-genetic variables, the latter of which encompasses more widely known influences such as age, sex, and drug interactions. This paper will only focus on the genetic influences of warfarin and specifically how genetic polymorphisms of the CYP2C9 and VKORC1 enzymes, which are the non-genetic targets of warfarin, affect the safe and effective dose of warfarin for patients of different ethnic groups. This topic is of increasing importance as it has been shown in recent years that pharmacogenetics can be used to improve the safety and efficacy of various drugs and has already become the standard of care in certain cases. This paper will also discuss how recent advances in pharmacogenomic studies have impacted physician knowledge and patient care regarding warfarin therapy, as well as how these advances may affect future changes in the dosing of warfarin. In summary, the primary goal of this paper is to increase awareness of the importance of pharmacogenomics on warfarin therapy and to provide insight on how recent pharmacogenomic advances may translate into positive changes in the therapy for the future. (Hylek EM, Evans-Molina C, Shea C, et al. 2007).

1.1. Definition and Background

The ancient Chinese and Egyptians used the fermented mouldy soybean curd to treat infections. The Sumerians considered it a remedy for toothaches and constipation. The therapy was so popular in North America during the 1930s that sweet clover became a regular grocery item in many kitchens. This eventually led to many people's deaths. These are examples of the long and complex history of warfarin and its usage as a therapeutic remedy. Warfarin is an anticoagulant that has been shown to be effective in preventing repetitive and often fatal events of thromboembolism. It is used in a variety of conditions, primarily to treat people who have developed blood clots in the veins, lungs, or heart, but is also used in patients with atrial fibrillation, artificial heart valves, or to prevent recurrent stroke. The major setback to this therapy is the associated hemorrhaging and the often decision to discontinue it. Experiments with high dose vitamin K in the 1930s in cows led to severe bleeding and ultimately their deaths. This type of reaction is similar to the occurrences of drastic blood thinning and complications today in some patients. This is a beneficial tool in personalized medicine and with the advancements in research of recent decades, this has led to the variation of drug response and the discovery of pharmacogenomics. Pharmacogenomics is the study of genetic variations of an individual in response to a certain drug. These variations can be relatively dramatic where some patients achieve desired therapeutic response and others experience adverse effects or no response at all. The intention is to use this information to advance drug therapy in a way that drugs are tailored to an individual's genetic makeup and be both more effective and safe. Since its discovery, research on warfarin and pharmacogenomics has been an emerging field. (Fang et al.2021)

1.2. Importance of Pharmacogenomics in Warfarin Therapy

Genetic polymorphism is the concurrent presence of two or more genotypes in the population, inherited from a common ancestor. Single nucleotide polymorphisms (SNPs) are the most common genotypic variations between individuals. Studies of the human genome have now led to the discovery of many SNPs that can affect the function of various enzymes and proteins. With regards to Warfarin, it has been discovered that the drug has differing effects at the polymorphism of the vitamin K epoxide reductase complex gene and at the gene coding for the cytochrome P450 enzyme CYP2C9. These are two enzymes involved in the Warfarin pharmacodynamic and pharmacokinetic mechanism, and the difference at a SNP translates to a less effective enzyme in metabolizing the active form of vitamin K or S-warfarin. This leads to a decreased rate of recycling vitamin K and clearance of Warfarin, and subsequently lowers the functional Warfarin concentration in the patient on the affected genotype. Studies have shown that this results in an increased sensitivity to Warfarin, a higher INR, and a lower Warfarin dose requirement. This information provides the basis for the knowledge that genetic factors have a significant effect on the variability of Warfarin dose requirements. In knowing the genotype of a patient and the nature of the polymorphism at CYP2C9 and VKOR, it would be possible to predict and prescribe the correct dose of Warfarin for that patient. This is the essence of

pharmacogenomics, using the patient's genetic information to individually tailor a drug and its dosage, thus achieving the desired therapeutic outcome and minimizing adverse events. Such knowledge on Warfarin has the potential to prevent the thousands of adverse events previously caused by dosing errors and improve the therapy for the many patients for whom Warfarin is an essential drug. This is now becoming a reality with recent and ongoing Warfarin trials that use genetic information to guide dosing and monitor patients. (Wadelius M, Chen LY, Downes K, et al. 2005).

Warfarin is one of the commonly prescribed anticoagulant drugs whose genetics study led to the discovery of the important pharmacogenomics factors. Warfarin is a very effective drug for the treatment and prevention of deep vein thrombosis, ischemic stroke, and myocardial infarction and is commonly used during surgeries to prevent thrombosis. However, the Warfarin therapy proved to be the cause of many adverse drug reactions in patients, and in some cases, proved to be fatal. Warfarin has a narrow therapeutic index and high inter-patient variability in the dose required to achieve its therapeutic effect. Dosing must be carefully monitored as both sub-therapeutic and overdose can result in severe health problems. Regular blood testing with the international normalized ratio (INR) is used to determine the dosing required. The INR is a ratio of the patient's prothrombin time to a normal or control sample and represents the patient's bleeding risk. There is a need for both the starting dose and the subsequent maintenance dose to be correct for the patient to attain the desired INR. However, determining the correct dose has been difficult due to the multiple interactions between Warfarin and both environmental and genetic factors. High inter-patient variability in the dose of Warfarin required has been attributed to genetic differences between individuals. (Fahmi et al., 2022)

Pharmacogenomics study deals with the study of the effect of genetic variations on drug response in patients by analyzing the genes, RNA, and proteins. Pharmacogenomics is the basis for rational drug therapy, which is individualized for a single patient. It has long been recognized that genetic differences between individuals influence drug disposition and effects. Indeed, genetic factors play a substantial role in an individual's response to drug therapy. Determining the genetic contribution to variability in drug response can lead to the development of new drugs, improve the safety and effectiveness of those currently in use, and allow for the individualization of drug therapy. (Dawood, 2020)

2. Genetic Variants and Warfarin Response

CYP2C9 Variants and Warfarin Dose Requirements CYP2C9 is a member of the cytochrome P450 mixed-function oxidase system. It is involved in the metabolism of many xenobiotics and converts S-warfarin to inactive metabolites. It was discovered that CYP2C9 is highly polymorphic, and 3 allelic variants of the gene (*2, *3, and *5) that result in functionally reduced enzyme activity have been well characterized. Carriers for one variant have approximately a 30% decrease in clearance of S-warfarin, and those that are homozygous for one of these variants may have more than an 80% decrease in clearance. It has been well established that the result of these genetic variants is that the dose of warfarin required to reach a therapeutic INR is significantly reduced, and the possibility of an adverse event due to over anticoagulation is increased. As such, it has been recommended that patients about to initiate warfarin therapy should be genotyped for CYP2C9 variants to allow for dosing to be optimally predicted. (Tang et al.2020)

When warfarin was developed as an anticoagulant nearly 60 years ago, it was discovered that it had a very narrow therapeutic index. This means that the range between a dose for therapeutic effect and a toxic dose was very small. This influenced the need to carefully monitor and control dosage to prevent over or under dosage resulting in adverse effects, health risks, or emergencies. It was soon noticed that dose requirements for warfarin were highly variable, and it was found to be a common occurrence that two patients initiated on the same warfarin dose could end up with dramatically different INR values. (Crowther MA. 2007)

2.1. CYP2C9 Variants and Warfarin Dose Requirements

It is estimated that approximately 18% of warfarin dose variability can be attributed to CYP2C9 genotype. Currently, it is recommended that patients with variant CYP2C9 alleles are identified and have their dose adjusted accordingly, although clinical uptake of this practice has been slow.

CYP2C9 is a highly polymorphic enzyme and has over 50 variant alleles described, many of which result in decreased enzyme activity and therefore a lower warfarin dose requirement. Carriers of homozygous variant CYP2C9 alleles require about a 30% reduced maintenance dose and have an increased risk of over-anticoagulation compared to patients with no variant alleles. The precise reduction in dose varies between different alleles, for example, patients with the *2 and *3 alleles may require nearly a 50% reduced dose, whereas those with the *5, *6, and *11 alleles may only require a 15% dose reduction. (Lindley et al.2022)

The cytochrome P-450 enzymes are a group of heme-containing enzymes that are responsible for the metabolism of a variety of compounds, including the oxidation of drugs. The CYP2C family is responsible for about 20% of the metabolism of all clinical drugs and contains 4 enzymes, CYP2C9 being the most abundant and is estimated to be responsible for the metabolism of nearly 15% of all drugs despite only making up 20% of the CYP2C enzymes. (Tracy TS, Chaudhry AS, Prasad B, et al. 2016).

2.2. VKORC1 Variants and Warfarin Sensitivity

Vkorc1 is the gene for vitamin K oxide reductase. It is well known that warfarin interferes with the vitamin K cycle by inhibiting Vkor. This is how warfarin affects the clotting process. Vkorc1 is known to have a major effect on warfarin sensitivity. There are two common polymorphisms known as -1639G>A and 1173C>T which have been found to seriously affect warfarin dose. Research on this has been largely consistent across many mixture of race variants and has been replicated in numerous studies on a larger scale. The -1639G>A SNP has an independent and combined effect of expressing lower levels of Vkorc1 mRNA, the data for this is very strong. The G allele expresses significantly higher Vkorc1 mRNA levels, and the A variant is linked with a falls of approximately 35-40%. This corresponds to a difference in warfarin dose of approximately 7mg/day between individuals with the genotypes GG and AA. This is a huge amount in terms of warfarin dose and makes a large difference between clotting time. As with the G>A variant the 1173C>T SNP has been linked with levels of Vkorc1 mRNA in which the lower level of mRNA expressed the lower warfarin dose that is required. In Japanese patients it has also been shown that there are non-synonymous SNPs that cause amino acid replacements at codons 2 and 3 and have changes functional expression in Vkorc1 protein. This resulted in a lower required warfarin dose. These were less frequent mutations but does show the immense effect of the Vkorc1 gene on the dose of warfarin. Recent GWAS has shown that there are many other rare variants in Vkorc1 that also have effects on warfarin dose, it has been suggested that GWAS has the potential to explain up to 40% of the dose variation using warfarin. This section provides further evidence that warfarin sensitivity is largely affected by genetic factors. The Vkorc1 gene has been shown to affect warfarin dose through its effect on the expression of Vkor enzyme. This has a knock on effect to the clotting process and can be a big downfall leading to incidences of over-anticoagulation. With a better understanding of the patient's genetic makeup, it is possible that individualised dosing strategies can be made to ensure the best possible treatment with warfarin. This will however, not be a simple task as there is an extensive list of genetic variables to consider that may alter warfarin dose. (Xu et al.2021)

2.3. Other Genetic Factors Affecting Warfarin Response

Although genetic factors are important in warfarin response, there is much that is not known and which will need to be addressed if the full promise of pharmacogenetics in warfarin dosing is to be achieved. This may involve examination of less common SNPs or other genetic polymorphisms and gene-gene interactions. It is also likely that nongenetic factors such as diet and drug interactions may have a large impact on warfarin dosing requirements, and these too may interact with genetic factors. An understanding of all of these factors and how they interact will be crucial for the development of

a full algorithm for warfarin dosing. This algorithm may in the future allow clinicians to make an informed estimate of a patient's warfarin dose requirements based on knowledge of the patient's genetic and nongenetic factors and thereby avoid the current trial and error approach to warfarin dosing. (Duarte & Cavallari, 2021)

Genetic variants in CYP2C9 and VKORC1 account for approximately 30 to 40% of the interindividual variability in therapeutic warfarin dose requirements. However, these genetic factors do not account for all of the variability in warfarin response, and the remainder of the variability is likely to be due to different combinations of genetic and nongenetic factors. Identification of these other genetic factors is in the very early stages, and no firm associations have been made. (Wadelius M, Pirmohamed M. 2007).

3. Clinical Implementation of Pharmacogenomics

When considering the implementation of pharmacogenomics in the clinical setting, it becomes apparent that this will likely occur in community-based settings for the initial stages. Patients' genetic information is typically not readily available in the acute setting, and the management of warfarin dosing is likely to be less of a priority in comparison to managing other conditions. The cost and resources for implementing pharmacogenetic strategies are also barriers for widespread practice at this current time. Genotyping for warfarin dosing is a concept that has been easily accepted in clinical trials, but has a long way to go before becoming common practice. It is well known that the pharmacokinetics and pharmacodynamics of warfarin are greatly affected by genetic variants. It has been well documented that the use of a pharmacogenetic-based dosing algorithm can help to predict the stable warfarin dose and prevent over-anticoagulation. This then has the potential to reduce the incidence of warfarin-related bleeding. However, despite all the evidence, warfarin genotyping is not yet the 'norm'. The perceived lack of evidence regarding the cost-effectiveness will prevent many healthcare providers and third-party payers from giving it the green light. With many patients now self-managing their warfarin dosing, perhaps this cohort of patients may be the one for which genotyping may first be implemented. Clinical decision support systems are interactive computer programs designed to assist health professionals in the decision-making process. It is widely believed that computer-aided warfarin dosing has the potential to greatly improve anticoagulation outcomes. The use of patient-specific data such as age, weight, and indication for warfarin in combination with INR and genetic information can generate a dosing regimen. It can be predicted that in the near future, genetic information will be an essential component of these programs. Setting a standardized therapeutic INR range for different genetic and ethnic groups is also a likely outcome. This type of system has the potential to simplify the process of gene-based warfarin dosing and help clinicians avoid over-anticoagulation. However, higher quality evidence is required to prove the superiority of genotyping-based dosing over a conventional dosing algorithm. This is essential for widespread implementation of a genetically informed decision support system. (Ren et al.2020)

3.1. Genotyping for Warfarin Dosing

The task of warfarin dosing is often complex, due to its narrow therapeutic index and a marked inter-patient variability in dose requirements. It has long been recognised that part of this variability is due to the influence of genetic factors. A landmark study by Atrial Fibrillation Investigators has shown that patients with a particular polymorphism in the gene coding for cytochrome P450 2C9, the principle enzyme responsible for metabolising warfarin, require a 34% lower maintenance dose. Another study has shown that patients with particular polymorphisms in the vitamin K epoxide reductase gene complex (the target enzyme of warfarin) require a 20% lower dose. The convergence of these findings has led to a consensus that genotyping patients for these known variants prior to warfarin initiation could be clinically useful. In theory, genetic testing could allow identification of patients that require high or low dose warfarin and enable initiation of the correct dose with close INR monitoring, therefore accelerating the optimisation of warfarin. A number of cost effectiveness analyses have already been performed, which suggest that genetic based dosing could become economically favourable. A small number of clinical trials have already been performed, with results

indicating that genotyping does in fact increase the speed of INR stabilisation and reduce the occurrence of supratherapeutic INR. At present, genotyping is not viewed as mandatory and is most often implemented in a clinical trial setting. However, given the increasing ease and decreasing cost of genetic testing, it is very likely that genotyping will become a normal part of warfarin initiation in years to come. (de et al.2020)

3.2. Clinical Decision Support Systems

The UCLA Simon Warfarin dosing algorithm is an alternate CDSS that is being adapted for use in the prospective COAG trial. It uses a dynamic web interface that considers clinical and genetic information to predict both the warfarin dose and the probability that this dose will achieve stable anticoagulation. In order to improve dose accuracy, the algorithm then uses the patient's own INR response to the predicted dose and refines the prediction by accounting for the percent time in the target INR range. The prospective dosing and daily INR checking will take place at anticoagulation clinics, which are another setting where the evaluation of warfarin dosing with genetic information is likely to take place. This setting is useful because the frequency of INR assessment and adjustment of warfarin dosing provides a consistent way to measure the impact of pharmacogenetic dosing on the safety and efficacy of anticoagulation. CoumaGen II, the UCLA algorithm, and other CDSS will lead the way to more complex and specialized medical informatics software, but at this stage they provide a valuable framework with which to investigate and optimize warfarin dosing with genetic information. (Gage BF, Bass AR, Lin H, et al. (2016).

In order to integrate genotype-guided warfarin dosing in the clinic, the use of Clinical Decision Support Systems (CDSS) has been proposed as an essential addition to manage the vast amount of polymorphic information while considering multiple interacting influences on patient dosing. An example of CDSS being tested is "CoumaGen-II," a clinical model that uses a web-based interface to predict an initial warfarin dose using clinical and genetic information. The predicted dosing is then evaluated through the application, and the subsequent INR values used to suggest an adjusted dose if the predicted dose and INR result are significantly different. This process is repeated, and the efficacy of the predicted dosing is evaluated. (Gage BF, Bass AR, Lin H, et al. (2016).

3.3. Challenges and Limitations

There are several limitations to the use of genomic information to guide warfarin therapy that should be considered. The cost-effectiveness of genotyping for warfarin therapy has not been established. A preliminary cost-effectiveness analysis suggested that an incremental increase in outcome-driven costs of genotype-guided therapy was $1500 per event avoided. This result makes genotyping more expensive than using traditional fixed-dose or initiation-dose strategies. Clearly, the genotyping strategy will only be cost-effective if the predicted adverse event rates with genotype-guided therapy are much lower than the fixed-dose strategy. A substudy of the EU-PACT trial estimated that the adverse event rate for the fixed-dose strategy is 12% by combining major and minor bleeds. This would have to be at least halved for the genotyping strategy to be cost-effective. There are several reasons why genotype-guided warfarin therapy could be more successful at preventing adverse events than a simple trial of different induction doses. The first reason is that initiation with a pharmacogenetic algorithm is likely to reach a stable dose faster. A stable dose is one that achieves the target international normalized ratio (INR) with minimal dose changes. Dose changes are strongly linked with bleeding and thrombotic events. A meta-analysis of warfarin trial data estimated that each 10% time in therapeutic INR range reduces the annual rate of thromboembolic events and major bleeds by 12% and 11% respectively. An analysis of SPORTIF (a warfarin atrial fibrillation trial) data suggested that reaching a stable dose within the first month prevents an average of 8 days of excessively high or low INR, which is associated with a reduced risk of stroke, bleeding and death. (Verhoef TI, Ragia G, de Boer A, et al. (2014).

4. Future Directions and Implications

The US-based COAG (Clarification of Optimal Anticoagulation through Genetics) trial is a large-scale study comparing the clinical and cost-effectiveness of warfarin dosing using genetic information versus clinical information alone, utilizing a pharmacogenetic algorithm. With the recruitment of 2000 patients, this study provide comprehensive data on the utility of genotyping for warfarin dosing. A positive outcome for the genetic arm of dosing would support the notion of individualized warfarin therapy while further development of the algorithm has potential use for guiding initiation of therapy. Meta-analyses of multiple warfarin dosing trials have concluded that anticoagulation at the intended INR is increased and there are fewer adverse events in trial arms containing a genetics-guided loading dose, though this is yet to be tested in a clinical setting. Justifying the additional expense of pharmacogenetic dosing is a major barrier to its widespread implementation; hence studies show that it may be of most benefit in elderly patients and those with multiple co-morbidities which are both factors of higher warfarin sensitivity. (Shah, 2020)

An alternative step toward individualized warfarin dosing is the use of a newer drug, phenprocoumon. Both R and S enantiomers of warfarin are metabolized to inactive hydroxylated derivatives by CYP enzymes, after which they are further metabolized while also inhibiting vitamin K epoxide. Phenprocoumon is a single isomer drug that inhibits VKOR and has a long half-life similar to the S form of warfarin. A Dutch study of over 500 patients showed that the effect of CYP2C9 and VKORC1 genotypes on phenprocoumon dose is similar to that seen in warfarin, indicating that phenprocoumon may also benefit from individualized dosing. However, the lack of data on microsomal enzyme polymorphisms and VKOR activity in comparison to warfarin means that evidence-based recommendations for phenotype-based dosing are still some way off. In the near future, the development of new direct thrombin and factor Xa inhibitors is likely to reduce the relevance of warfarin and its associated pharmacogenomics. Individual trials of these new drugs have not featured pharmacogenetic analysis, and in considering the resources required to individualize warfarin dosing, it may be that genotypic analysis is only used for warfarin as a bridge to newer orally administered anticoagulants. (Schneider et al.2020)

As the association between CYP2C9 and VKORC1 genotypes and warfarin dose has been clearly established, incorporating this genetic information into the selection of the correct initial dose is a logical step. Multiple studies have now shown that using a pharmacogenetic algorithm to guide dosing increases the proportion of patients who achieve a stable dose in the first month of therapy. In 2010, the FDA altered the label for warfarin to include information on genetic testing, stating that "VKORC1 and CYP2C9 genotypes are information that may help determine the optimal starting dose of warfarin". Despite this, genetic testing before warfarin initiation has not been widely integrated as the clinical and/or cost-effectiveness of this approach remains uncertain, with many calling for randomized controlled trials to definitively show the benefit of genotyping. (Johnson JA, Gong L, Whirl-Carrillo M, et al. (2011)

4.1. Personalized Medicine and Warfarin Therapy

The knowledge that individuals respond differently to medications is not a new one. However, with advances made in areas of genomic research and the completion of the HapMap project, the ability to predict a patient's likely response to a medication and thus tailor therapy to suit an individual's needs has become a reality. Warfarin therapy is an ideal candidate for personalized medicine. Given the narrow therapeutic index of warfarin, small differences in dose requirements can easily lead to complications associated with over-coagulation or under-coagulation. Recent trials have shown that using a pharmacogenetic algorithm, initial dosing based on CYP2C9 and VKORC1 genotype results in improved anticoagulation control in the early stages of warfarin therapy. More impressively, another trial has shown that the use of an algorithm based on these genotypes can enable the achievement of a stable dose in a significantly shorter period of time compared to patients receiving a standard fixed-dose initiation regimen. As the financial cost and risk to the patient associated with an unstable dosing phase due to frequent dose changes and monitoring has been a major drawback of warfarin therapy, the potential of these findings could lead to a significant increase in the

attractiveness of warfarin therapy to both patients and clinicians. It may also have important implications for developing countries where the ability to conduct frequent INR monitoring and dosing changes is limited. An increase in the uptake of warfarin therapy due to the improved predictability of dosing requirements may in turn result in a lower incidence of thromboembolic events in the population, benefiting public health. (Panchenko et al.2020)

4.2. Integration of Pharmacogenomics in Clinical Practice

The integration of pharmacogenomics in clinical practice is the ultimate goal of the research in the field. Being able to predict an individual's response to warfarin and titrate a dose at the outset of therapy based on that patient's genetic information offers considerable potential for improving the safety and effectiveness of warfarin. Ideally, this would involve genotyping patients at the time warfarin is prescribed, and using the genetic information in conjunction with clinical and demographic information to predict the therapeutic dose of warfarin for each individual. Prospective randomized trials will be required to determine the clinical utility of using genetic information to guide dosing, but these are currently being designed. Several retrospective analyses and cost-effectiveness studies have been published and suggest that pharmacogenetic-based dosing is superior to standard clinical algorithms and potentially cost-effective. The FDA recently changed the labeling of warfarin to reflect the importance of genetic information in determining individual dosage requirements. This represents a considerable step forward, but a great deal of research remains to be done before pharmacogenetic warfarin dosing becomes a clinical reality. (Fahmi et al., 2022)

4.3. Ethical and Legal Considerations

Because the ramifications of pharmacogenetics for health and healthcare are so broad, encompassing not only drugs and diagnostic tests but also the information needed to interpret and use them, the full realization of its benefits could be impeded by any policies that reduce overall access to medical services. That is especially a concern if genotype-based strategies widen preexisting disparities in treatment or health outcomes between different populations. An obvious example is the potential to improve outcomes for psychiatric disorders. While this is an important advance, the NPRM clause to exclude PGD for the selection of drug type and dosage potentially impedes these benefits for such disorders as psychiatric diseases are officially listed as an off-label indication for warfarin use in all instances. The policy could also have unintended adverse effects. Regulators, payers, and litigators all might attempt to exploit the learning aspect of early genotype-warfarin studies, in hopes of eventually setting a higher bar for evidence of safety and efficacy in drug use. This might delay introduction of any new drugs into clinical practice for warfarin replacement, even those off-patent, to the point where their development would no longer be economically rational. (Franks et al.2021)

The potential societal benefits from better understanding the relative costs of different treatments, and the limits of that understanding, are substantial. In the case of warfarin, the latter could be better identified by comparing genotype-based and empirical dose refinements to determine whether the increase in up-front expense and complexity for the former are justified by improved results. However, the same comparison with other drugs might not be so straightforward if genotyping raised costs without improving safety and efficacy. Given limited resources, opportunity costs could favor research to develop alternative drugs or better use existing ones, based on genotypes or other patient characteristics, over optimization of warfarin therapy. These are instances where health technology assessment, which has seldom been applied to pharmacogenetic interventions, could add much needed rationality to decision making. (Garrison LP, Mansley EC, Abbott TA, et al. (2013).

5. Conclusion

The pharmacogenomics of warfarin have garnered a very substantial amount of evidence but there is still relatively little clinical implementation. Warfarin dosing decisions are complicated and there are many players in this area each bringing forces that are difficult to control for and to aggregate into a data-driven decision about the appropriate point estimate for a maintenance dose. It will likely be

easier to get physicians to change dosing patterns if there are readily available automated systems that use genetic and clinical data to make a dosing recommendation. An important area for future research is therefore the development and testing of dosing algorithms that incorporate genetic information. (Fahmi et al., 2022)

A first step would be to bring genotyping for CYP2C9 and VKORC1 to the point-of-care. It is not currently cost-effective to genotype these variants on all patients starting warfarin, even in the USA, but cost-effectiveness is likely to be better in situations where the data can directly influence dosing. For example, genotyping may improve the pharmacovigilance for warfarin by identifying patients with a poor response who should switch to a different anticoagulant. Genotyping is already commonly performed in the US for the polymorphism in CYP2C9 that metabolizes phenytoin because it is well-known that genotype is the major determinant of phenytoin dosage and that dosing is critical to prevent toxicity. The situation with warfarin is not that different. (Johnson JA, Gong L, Whirl-Carrillo M, et al. (2011).

Warfarin is an old drug that is likely to be with us for many years to come. Geneticists and clinical researchers have been attracted to warfarin because it is the "poster child" for needing to integrate genomic information into dosing decisions. We now know that CYP2C9 and VKORC1 together predict about 30% of warfarin response. These genes perform well in all populations that have been tested but the frequency of different alleles varies between populations. Rieder MJ, Reiner AP, Rettie AE. (2011).

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