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ADVANCEMENTS IN PHARMACOGENOMICS AND TAILORED MEDICATION THERAPIES

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Abstract
Since genetic variation in pharmacokinetic and pharmacodynamics processes intimately affects drug response and toxicity, interest in integrating pharmacogenomics with the field of nanomedicine has steadily increased. Indeed, the genetic code of an individual may in the future become a standard diagnostic to tailor the use of new medication therapies. This review combines the most recent knowledge regarding pharmaco- and toxicogenomics for a variety of drugs and drug targets with perspectives on emerging technological platforms in nanomedicine. The aim is to create improved guidance complementing drug development and clinical application of nanotherapeutical approaches on an individual basis (M. Lauschke et al., 2019).
Therapeutic regimens feature a variety of unequal outcomes—both between individuals and in the same individual at different times. The concept of providing treatment regarding the individual genetic history of diseases and drug response has seen a massive shift forward with the accomplishment of the draft sequence of the human genome and the construction of high-throughput methodologies to analyze the human genetic code. Pharmacogenomics is focused on the understanding of specific sequence changes of the genome that can discriminate between patients that respond optimally to treatment and those who could be at risk of severe adverse effects. These genetic variant biomarkers are testimony to an optimized therapeutic approach. The impressive increase in information regarding genetic variability has led to vast improvements in the predictive potential of pharmacogenomic tests. This information can help in the determination of pharmacological-drug treatment at initiation of therapy or following therapy in the form of companion diagnostics. Pharmacogenomics concerns the occurrence of base-pair changes in single nucleotides assuring the sequence diversity of the human genome.
The genome sequence is the same in all cells but a single nucleotide polymorphism (SNP) refers to a chromosomal position where different sequences can be present in diverse individuals but not in a pair of homologous chromosomes. SNPs are the most numerous form of genetic variability and it is anticipated that three million SNPs are occurring in the human genome. However, not all SNPs are randomly spread and the majority may have no functional consequence on the proteome. For given bases, only four diverse nucleotides are possible in a nucleotide chain; and that the coding sequences, giving rise to the protein repertoire, display only three please-. Hence, it is common for SNPs having no consequence on the protein product. If a SNP is positioned in a transcription factor binding site it could affect gene regulation. The diversity and complexity of the genetic code has ramifications for the comprehension of polymorphisms of drug-metabolizing

enzymes since a largely heterologous network of auxiliary proteins makes the metabolism of every drug unique.

Keywords

Personalized pharmacogenomics medicine is a way to optimize drug therapy, developing tailored medication therapies. The medications prescribed for the treatment of various disorders may need to be personalized for the precise condition, genetics and circumstances of the individual. The developments in analyzing genetic makeup can accurately identify drug-metabolizing enzymes. Modern individual genetic verification can furnish the necessary knowledge to formulate tailored medication schedules.

Review reveals the relevant discoveries on tailored medication therapies for post-surgery and cardiovascular disorders: tailored medication schedule for individuals is significantly necessary. They must be presented with the suitable form of anesthetics and analgesics in order to achieve an enhanced restorative effect after the operations that provide these benefits. The implementation of medications with sufficient care post-surgery enhances patient security and speeds up the recovery. In a similar connection, it is undoubtedly true that conventional surgical procedures and medication therapy will not achieve the anticipated treatment outcome satisfying individuals. Tailored medication treatment schedules can be formed through the use of personalized medicines, reliant on each individual's exact genetic status. Study designed to pinpoint an individual's genetic profile in post-surgery has showed that tailored medication schedules should be practiced. This approach can be brought in as clinical practice to derive personalized medication therapy. On the other hand, with the readying time for tailored medication therapies, an individual's various factors need to be evaluated, including gender, age, genetic status, and BMI. All the medical factors such as BP, heart rate, cholesterol levels, and glucose levels should be taken into consideration. Medications must be carefully administered in post-surgery.

Current drug therapy for varied cardiovascular disorders may be not productive in showing the precise restorative outcome in individuals. This is since the drugs and dosage forms chosen for the treatment of cardiovascular problems will not be personalized. Formulation of improper drug therapies can set off the hospital readmission of individuals. Pharmacogenomic discovery is occurred in the uptake of synthetic formulations. Frequently occurring adverse events regarding the hospital admission are accountable for the benefits of prescription medication by design, on the foundation of a particular genetic status. Privacy consideral data continuity has developed usage of biometric equipment which keeps each individual's body status and DNA profile.

1. Introduction to Pharmacogenomics

Pharmacogenomics aims to personalize medication therapies using genetic variants that guide drug absorption, distribution, metabolism, or excretion (ADME) or influence response or adverse reactions. Several sequencing platforms for pharmacogenomic testing are available, but it is not straightforward how to analyze the large number of data generated, nor is it easy for clinical care to interpret and apply the results. We present a computational framework that includes bioinformatics processing, functional analysis, and application of outcomes. By connecting the genomic data to the pharmacological characteristics of the administered drugs, this integrated

method is designed to predict drug response to and potential adverse reactions or drug inefficacies of medications. It is suitable as an open-source framework for the implementation in both clinical and research settings. With a vast number of drugs administered to a highly complex patient population, drug treatment regimens would ideally be individualized to maximize therapeutic effects and simultaneously manage side effects. Such a therapy, referred to as precision or personalized medication, aims to tailor interventions to a specific patient. The development of customized treatments, however, is critically reliant on differential efficacy and toxicity factors that, if unaccounted for, can lead to poor therapeutic outcomes. It is in this context that the field of pharmacogenomics has gained significant interest in the past decade. Made possible by an extensive cataloging of genetic loci, pharmacogenomics studies the response to treatments that are drug-dependent and aids in personalizing medication therapies. However, the application and broad efficacy of pharmacogenomics solutions in routine medical practice have been limited. This can be attributed to a limited ability to carry out costly and complex sequencing, data analysis, interpretation of results, and difficulties incorporating and applying the resulting recommendations to patient care. On the one side, the technology to conduct high-throughput sequencing has allowed for the elucidation of many genetic alterations in an individual. On the other hand, established techniques for testing drug-drug interactions for a panel of well-described single nucleotide polymorphisms can compare the patient's DNA to the genetic database.

Pharmacogenomics has the potential to significantly improve the efficacy and safety of drug treatment. The genotyping of individuals for polymorphic genes related to the drug's pharmacokinetics or pharmacodynamics before drug prescription or in the early phase of treatment may help identify poor responders or individuals at risk for drug adverse effects. However, the implementation of these useful tests into clinical practice is far from being realized due to a range of medical, economic, ethical, legal, and social issues. Some of these barriers are related to misconceptions by health care providers. Therefore, the purpose of this work is to provide an educational tool, a myth buster, by highlighting the most common misconceptions with the supporting evidence on the importance of pharmacogenomic testing.

2. Historical Background

Pharmacogenomics is the most promising arm of genomic medicine anticipated to revolutionize drug discovery, drug delivery, and drug efficacy analysis with the ultimate goal of personalized medicine. The basic promise of this approach was based on the idea that pharmacogenomics (PGx) science will be able to predict an individual's clinical response to a drug. This could lead to defining personalized medicine starting with drug selection; choosing the right drug or dosage for the right patient to attain a better effect. This would allow for the reduction of possible adverse events or a loss of the gravedigger effect, as currently prescribed with the trial-and-error method. The first steps to thoroughly validate potential markers for patient-tailored drug therapy have been made (Avery et al., 2009).

However, there are ethical, social, economic, legislative, and research protocol issues causing stumbling blocks that need to be sorted before the promising personalized medicine approach becomes a customary approach in clinical practice. In this context, principles and arguments are

put forward that underlie the need for a universal call to data openness in pharmacogenomic research and development and in the development of pharmacogenomic-based diagnostic tests. Moreover, public skepticism about PGx and the way it is commercialized causes public doubt since the announcement of major achievements is characterized by "hype" or exaggerated advertising. A lot remains to be done in education for both the public and health care professionals before overall acceptance of the personalized medicine approach will occur. Recent advances have rapidly been pushing this approach closer to clinical practice even in the management of complex diseases, like the common variable asthma where genomic discoveries have led to novel therapeutic applications. Pharmacogenomic investigations in the field of inheritance of the response to therapy in this cohort of patients are growing. An expansion of T2D-genetics studies now involves significant advancements in the field of molecular evolution mechanisms and new methods of analysis. Moreover, identify genetic unlinked from the main clinical and metabolic parameters of the disease. Explorations of pharmacogenomic genes in T2D have found as a new system, genomic loci of changes with translational effects that modify disease susceptibility risk, clinical course and change of traditional therapy. Observations of gene polymorphisms in drug transporters, effector proteins, targets, and metabolizing enzymes increased the understanding of a potential polygenic nature of drug response to diseases that were additionally identified by gene autopsy findings that increase the risk of the onset of illness when utilizing special drug forms for other threats to health.

3. Key Concepts in Pharmacogenomics

3.1. Genetic Variability

3.2. Drug Response Mechanisms

4. Technological Innovations

4.1. Next-Generation Sequencing

4.2. Bioinformatics Tools

5. Clinical Applications

Pharmacogenomics is a growing field within healthcare that tailors an individual's medication therapy using genetic testing to improve patient care by increasing medication efficacy, decreasing the risk of an adverse drug event, and reducing patient healthcare costs. The application of pharmacogenomic principles is based on literature guidelines when adjustments in medication therapy are necessary due to identified genetic variations within a patient. Interaction between drug and patient's DNA can interfere with the drug's physiologic response, including how well the medication works, unwanted side effects, or the potential to cause harm. Offsetting these risks, genetic variations might reduce the likelihood of benefit from the medication therapy or impact its safety and tolerability. There are also notable studies that demonstrate improvements in the patients administered with the genotype-guided dosing protocol, where the medication is administered, and the dosing criteria are adjusted based on the specific genetic test result. Main benefit endpoints achieved among patients receiving PGx testing are significant reductions in the symptomatology scores compared with the Care as Usual standard treatment. Furthermore, this particular therapy demonstrates statistically significant benefits associated with the cost-

effectiveness of genotype-guided dosing protocols with the overall cost of patient care compared with the Care as Usual medication therapy (W. Guy et al., 2020). Although studies point to the potential clinical usefulness of adjusting radiotherapy based on genetic biomarkers, others suggest some susceptibility genes are yet not proven as reliable predictors. As more precision medicine tailored to a patient's genetic makeup becomes available, new questions arise about how widespread use of such drugs might affect populations. Some studies investigate the future implications for healthcare systems, particularly the potential demand on healthcare services, ethical considerations, pregnant women, and how both adverse events and successful uptake are managed.

5.1. Oncology

Cancer is a common disease that claimed the lives of about 7–10 million people annually. Because of the complexity of cancer therapy pharmacogenomics, there are many studies that investigate the associations between genetics polymorphisms and cancer chemotherapy efficacy and toxicity. Some interesting progresses may become new breakthroughs to empower pharmacogenomics of cancer therapy. For example, in the chemo-drug uptake or efflux process of cells, some key trans-factors including encoding genes have very important effects on the individual pharmacokinetics of chemo-drugs. Recent studies show that some genetics polymorphisms of transcription or bioprotein genes have significant associations with some cancer chemotherapy adverse reactions. Meta-analyses also present similar conclusions. So, in the future, deeper research in the ways of transcription or bioprotein genes will be needed in cancer therapy pharmacogenomics, and it indeed will provide many new insights to pharmacogenomics of cancer therapy. Moreover, cancer therapy pharmacogenomics is no longer limited to the studies in the biotechnology field. It is also necessary to integrate interdisciplinary studies with other technological and empirical medical disciplines, for the structure and function relation of genomics and proteomics has been developed. Will the information from metabolomics provide more implications for drug discovery and cancer therapy pharmacogenomics? In the future, it is promising to explore the pharmacological mechanisms of cancer chemotherapy by integrating genomics, proteomics, and most hopefully, metabolomics technologies. Thus, some new breakthroughs may be empowered to get from beyond twenty-one.

5.2. Cardiology

The success of pharmacologic therapy in a particular patient depends upon the bioavailability of the drug at the target tissue, and the sufficient duration of contact for the expected therapeutic effects to occur without causing significant adverse reactions. The nutritional condition of a patient can significantly affect the metabolism and disposition of drugs. Dosed medications also contain chemicals other than the therapeutic agent and the patient may have a hypersensitivity to any number of these additional chemicals. Variation of the drug metabolism can cause a sudden increase in blood levels, harming the patient. Methadone is extensively used for maintenance therapy in heroin addicts; it is mainly metabolized by cytochromes, and an induction in their activity can make the therapy ineffective. Both codeine and tramadol are prodrugs and need to be metabolized to exert analgesia. The major metabolite of codeine is morphine, while in the case of

tramadol the two main metabolites are O-desmethyltramadol and N-desmethyltramadol. The activity of Cytochrome P450 2D6 is essential for the analgesic properties of codeine. The 2D6 genetic polymorphism can result in a decreased codeine analgesic effect. The metabolism of tramadol also depends on CYP3A4, CYP2B6 and CYP2D6, and their pharmacogenetically relevant genetic polymorphisms change tramadol hydroxylation, negatively affecting tramadol effects. In addition, the polymorphism of P-glycoprotein, a membrane efflux pump participating in the blood-brain barrier and in the placental barrier, can further add variability in the pharmacological effect of tramadol.

5.3. Psychiatry

Psychiatry is a medical specialty with particular attention to the mind and mental states, behavioral changes. Its primary goal is to achieve a thorough understanding of the biological basis of mental illness in order to better understand patients and to determine the optimal treatment for each individual. This involves the ability to diagnose mental illness, determine factors that may have contributed to the illness, and knowledge of biological, psychological and social treatments. Psychiatry aims to reduce the prevalence and suffering of mental disorders and improve the overall quality of life (van Westrhenen et al., 2020).

Psychiatry faces a number of complex challenges in terms of diagnostic and therapeutic strategies. Diagnosis of mental illness is based on the assumption that mental states are influenced by the brain. However, terminology such as “depression”, “anxiety”, “schizophrenia”, “bipolar disorder” are conditioned by particular mental phenotypes, i.e. common thoughts, emotions, behaviors. Biologically, mental states correspond to the activity of different parts of the brain, as brain structures seem to be responsible for different behaviors. Classical psychiatric treatment relies on the use of drugs that have effects on mood or reality perception based on the monoaminergic balance of the brain. Antidepressants work mainly by increasing monoaminergic neurotransmission by blocking the reuptake of them. Suicides are mentioned in the label as one of the side effects (increased risk). Antipsychotics are drugs that reduce mesolimbic dopaminergic neurotransmission by blocking, among others, dopamine D2 and 5-HT2A receptors. Besides their lack of efficacy, there are hundreds of thousands of people worldwide suffering irreparable movement disorders due to the use of a dopamine blocking drug, antipsychotic-induced Parkinsonism.

6. Pharmacogenomic Testing

6.1. Types of Tests

6.2. Interpreting Results

7. Regulatory Framework

7.1. FDA Guidelines

7.2. Ethical Considerations

8. Challenges in Implementation

The rapid growth of pharmacology in the last twenty years has brought to patient care a wealth of new medications and new ways of treatment. At the same time, increasing attention is focused on adequate medication therapy. Tailored medication therapies are aimed at ensuring that individual

patients are treated with exactly the right medication and dosage. Pharmacogenomics is a new branch of genomic medicine that studies the influence of common genetic variations on drug response. As a part of the larger initiative in pharmacogenomics, clinical pharmacogenetics implementation program provides recommendations on how to change drug prescribing based on genotypes and other patient parameters. Tailored medication therapy can be provided by incorporating the results from those biobank cohort genotyping projects with other relevant factors, such as patient characteristics, into the previously mentioned recommendations. A specific challenge that arises in implementing these types of recommendations in practice is the difficulty of efficiently synthesizing patient information and conveying the results to clinicians.

Pharmacogenomics is defined as the parallel study of a patient's genome and that patient's response to medication. Pharmacogenomics uses this information to help doctors choose medications that are more likely to work well for a patient and less likely to cause adverse effects (J. Caraballo et al., 2017). It is a new and rapidly developing field in which it is not always easy to differentiate between hope and hype. There are many medications that are proven to be influenced by genes. Using pharmacogenomics, use of these medications can be tailored for each patient, potentially resulting in better patient outcomes and/or less adverse effects. Different doctors consider the same drug not suitable for one patient or consider the same drug suitable for another patient. For example, if only the clopidogrel response is mentioned, a doctor may switch this medication to another patient's equally appropriate option, but another doctor may still choose clopidogrel for another patient. Current drugs have been developed to the extent that they can cure the patient. However, none of these medications are effective in every patient. Components in the body are responsible for the medications to degrade or become active. Often, the levels of metabolites found in a person are more or less compared to other people. This situation causes the drugs to be metabolized more or less quickly and thus changes the working hours in the body. So while a drug shows a permanent effect, it may not work at all or cause toxic effects. This situation is in question in many drugs. Metabolizing processes show a genetic-based natural difference for each person. This difference is inherited from parents.

8.1. Cost and Accessibility

Current and Future Pharmacogenomic Services as Seen by Prescriber Stakeholder Surveys

8.1. Cost and Accessibility Consistent with the literature on the high cost of medications, communications between patients and providers could be improved. In the case of pharmacogenomics for oncology, recent literature also suggests that challenges to accessible tests could increase disparities in genomic service uptake (Chen Wu et al., 2017). How "experiences and perceptions of stakeholders on the services of pharmacogenomics testing will inform the understanding of the current situation and development needs of future service platforms is discussed" (Breaux et al., 2020). Pharmacists tested 180 patients with a simplified chemistry drug-interaction test. Four participating pharmacists discussed the service and 120 patient evaluations were carried to identify operations, challenges, and acceptance. Quantitative analysis was performed on 84 filled paper evaluations collected as described above. A survey of stakeholders was conducted to examine the interest and potential influence of satellite cancer services,

understanding the perception of the feasibility of the tests of pharmacogenomics and next-generation sequencing in relation to development barriers. Overwhelmingly the feasibility of delivery over a broad range appears to be perceived well. Suggestions provided by respondents on infrastructure limitations closely aligned with the strategies mapped out in terms of future national development plans. Ideas included national mark schemes of quality, the deployment of semi-regional positions of pharmacists or scientists specialize in genomics, organized managed service networks shared between different primes care and hospital departments, and other collaborations. Multiple suggestors from the South West Peninsula brought up the possible provision advantages of cancer nursing specialists monitoring satellite stations.

8.2. Provider Education

As the prevalence of pharmacogenomic testing and the offerings for such testing increase, healthcare providers will need a better understanding of the clinical relevance of potential test results and their implications for patient care. Studies have shown that pharmacists would benefit from additional information resources and educational opportunities to support their work with genetic and pharmacogenomics information. Some sources of pharmacogenomics education for healthcare professionals include the pipeline of new medications analyzed for genetic relevance and information on how genetic changes affect certain processes and how medications work. Another source of education is billboards in North Carolina to raise awareness of a program providing free or reduced cost access to genotyping for various diseases and drug responses, verbal and written informed consent formats for pharmacogenetic testing that can clearly communicate the benefits, risks, and alternatives available, and a paper-based decision aid to educate African American female breast cancer patients concerning genetic testing.

A recognized need for methods to better educate all providers who order or interpret pharmacogenetic test results, which will be important in effectively deploying the Clinical Pharmacogenetics Implementation Consortium guidelines, highlights the importance of this research. The medical and pharmaceutical schools at the local university have recently expanded education on pharmacogenomics. A survey tool and semi-structured discussion guide have been developed with feedback from a focus group of practising pharmacists to better understand their needs for pharmacogenomics education. The results of the study are discussed, along with the publication of additional learning resources and presentation of the findings at a meeting of pharmacy professionals.

9. Future Directions

A ‘serious’ challenge – adoption of pharmacogenomics

The recent development of massive biobanks of genotypic and phenotypic data assembled into databases and combined with computerized predictive models now offer the means for estimating, on individual basis, risk of various diseases as well as response to many drug treatments. These advances in precision medicine nevertheless present a serious, and so far, largely undiscussed, ethical challenge for preserving the privacy and autonomy of the individuals concerned. The challenge is to find a balance between the needs of clinical care and research using the data contained within the biobanks, and the individual’s right to know what information is held on them

and from detailed knowledge of how this information is being applied. Although the technical hurdles have largely been overcome, the wider potential use of these biobanks is limited by the lack of a funded and co-ordinated approach, and ethical guidelines to protect the individual privacy. It is important to stimulate a dialogue involving a wide range of stakeholding groups, including representatives of the public, and to work closely with other initiatives in this area. The latter includes the creation of Accredited Third Parties, a proposed European BioBank written with the advice of an Ethics Board and legislative agendas covering data protection. Public health implementation agreements have been signed with Member States to improve the effective and safe use of genetically-developed diagnosis and therapeutics. As an example, PhIII is a pharmacogenomics database project that has been created to retrieve and store pharmacogenomics data, as well as related data, such as diseases, drugs and links to medical literature. This technology is used as a platform to build tools able to interpret personal human genetic data and generate in real-time predictions concerning personal response to drugs and risks for each drug toxicity (M. Lauschke et al., 2019).

Advances in laboratory medicine continue to increase with the development of a range of tests that by 2020 will allow for 'personalized treatments'. However, innovative approaches are already in place with 'personalized medicine' approaches for over 20% of breast cancer patients in Scotland. Importantly, ongoing efforts describe future scenarios and suggest that the costs of genetic tests will decrease sufficiently to motivate 'on demand' as well as routine testing. Given the rising number of drugs that carry a 'black box warning' by the US FDA, the proposed use of computational barriers within EMR is of particular interest for its real-time identification of patients with an increased likelihood of an outlier response. It is further suggested that additional tools will flag such patients during data processing in the clinical laboratory to allow physicians to adjust follow-up schedules and prepare for drug level monitoring and dose titration (Godman et al., 2013). It is anticipated that a number of challenges inherent to the clinical implementation of pharmacogenomics (PGx) will be addressed and metabolites of prodrugs defined. Personalization of treatment is an emerging field that defines the most effective remedies for individual patients.

9.1. Integration into Clinical Practice

Patient care is progressing toward achieving the utmost tailored, safe, and effective treatment options through advancements in pharmacotherapy. Healthcare professionals, as well as individual consumers, are now using knowledge about an individual's genetic makeup as the basis for directing pharmacological therapy. Although there are multiple factors influencing dose requirements, there is evidence that a significant fraction of inter-individual variability in drug response is due to variability in individual genetic make-up. With the support of pharmacogenomics, there are available guidelines describing drug metabolizing enzyme and transport protein polymorphisms associating with altered medications' efficacy and/or toxicity. Put this information into clinical practice, a deeper understanding and knowledge is needed in pharmacogenomics (PGx) and drug-gene interactions, including interpretation and implications of testing.

Pharmacists, as medication therapy experts, are a good profession to bring this genotype information to benefit patients. Using a proactive approach, along with clinicians, and informing them of relevant genotype information could result in better medication selection, optimization and dose selection. Therefore, it is important for pharmacists to be knowledgeable of the current evidence in the literature regarding PGx (W. Guy et al., 2020). Subsequently, based on the PGx evidence, target particular medications where actionable PGx testing is relevant but underutilized, and provide recommendations of best practices for pharmacists.

9.2. Personalized Medicine Initiatives

There is considerable variety in how patients respond to treatments driven by differences in their geno- and/or phenotypes which has led to a more tailored approach (Godman et al., 2013). This is already happening for many common diseases and will accelerate with developments in personalized medicine initiatives. However, its promise has not always translated into improvements in patient care due to the complexities involved. This is a concern as healthcare systems need to ensure patients derive maximum benefit from new health innovation, particularly in the future when life expectancy is expected to continue to increase in developed countries, particularly among females. Consequently, there is a need for payers to integrate current knowledge from a payer's perspective in order to provide future guidance on the main implications for healthcare systems such as the need to introduce protocols for use in hospitals. This will assume more importance given increasing patient power with the support of politicians to governs of over the coming decade in order to secure the most appropriate treatment.

Personalized medicine is defined as a more tailored approach to patient care which uses information about patients' geno- and phenotype to select compounds likely to be successful in preclinical and clinical testing. These may be pre-existing molecules or developed as a result of the knowledge obtained from the genomic sequencing of patients or their disease. In this way, drugs are targeted at subgroups of patients likely to respond to treatment and/or avoid adverse drug reactions. Personalized medicine has the potential to revolutionize care, particularly as the considerable variability that exists in how individual patients respond to pharmacological treatments is well recognized.

10. Case Studies

Pharmacogenomic Theatre is a multi-disciplinary event which is aimed at promoting the dissemination of research findings on pharmacogenomics, pharmacovigilance, and patient-focused pharmacotherapy. This event is supported by various academic and research institutions.

Case consultation opportunities will be presented where participants will be able to interact with a diverse panel of pharmacogenomics researchers, clinical investigators and medical practitioners. The pharmacogenomics cases that will be discussed are: pharmacogenomic re-implementation of thiopurine pharmacotherapy post-adverse drug reaction and therapeutic drug monitoring, pharmacogenomic management of long-term methadone treatment & sleep apnea medication, development of a pharmacogenomic rubric as an educational tool, and recommendations on the accurate representation of pharmacogenomics research in student dissertations and early career professional submissions.

The judging panel is invited to take notes on each of the pharmacogenomic consultations presented, ask questions where needed, and use the diagnostics developed by the panel members to shape the format for an impending scientific symposium.

10.1. Successful Implementations

Between 2012 and mid 2018, about 40 successful pharmacogenomic implementation projects were completed by a certified geneticist in a variety of care models (P. Jarvis et al., 2022). Some offered products geared toward specific patient groups and others were built around combinations of CPT codes stacked together to deliver cascaded care. Over this period, like in other areas of genomics, the clinical landscape became considerably more complicated concerning pharmacogenomics due to advances in testing equipment and the volume of primary literature. Over the past several years, laboratory technology for genotyping reached a critical mass and achieved a level of maturity broadly considered fully established and scalable. Several genotyping chemistries were approved by the FDA for PGx testing and achieved industrial levels of efficiency. High-throughput array technology was developed first, followed by several PCR-based approaches systems. These tests were already in use or in experimental stages in laboratory when most people graduated nursing school in 2016. API interfaces were developed by the lab in 2018 and prior discussions about the operational use of these tests no longer apply due to the fact that group is Team Vivian Jarvis and they have a Hoxworth in-house pharmacist for this. However, some questions anticipated from fellows will be answered. A notable development occurred recently: following escalation in consumer advertising in early 2013, the FDA took action in November 2013 and sent warnings to the company, as well as several others, about providing medical advice without premarket regulatory participation. Initially, the company fought back, however within a month agreement was reached and the company received FDA approval to provide limited results to customers through a password-protected portal. Other companies took a completely different approach and developed a reporting mechanism contingent on traditional laboratory services for test ordering companies. 'Results would be available to you through the laboratory portal,' a local representative explains. 'But that result is a full-service clinical interpretation of the pharmacogenomic panel, which includes variants and medications that they might have some (adverse) effect on. And then we upload that report into your medical record.' This was distinct from the DTC approach, where results are reported back directly to the patient and are good for use by a prescribing clinician if accompanied by an interpretation. Furthermore, results of the DTC tests are not widely accepted by the FDA, AMA, or major medical societies. In contrast, the test mentioned by the representative is done by a lab under CLIA and are reported with links to actionable pharmacogenomic guidelines. This provides a reasonable degree of legalese protection. It is also beneficial in other respects - for example, when medications have different severity ratings across sources, the more conservative will be respected.

10.2. Lessons Learned

In the 1950s, Ovsell and Schulsinger published a riveting piece that reported on the variability in clinical response to standard therapeutic dosage of the tuberculostatic drug Iproniazid. It would take another 27 years before Daly et al. identified that this variability was associated with a genetic

polymorphism in N-acetylation. This association is now known as the 4th corner stone of pharmacogenetics relating monogenic polymorphisms to variations in drug metabolism, transport or target. There are two basic premises underlying the concept of pharmacogenomic-guided drug therapy. The first premise is the observation that interindividual variability in response to a drug is genetically determined. This variability can result in either treatment failure or an adverse drug event (ADE). The second premise is that once the genetic determinants of this variability are known, it is technically feasible to identify the patients susceptible to treatment failure or ADEs. In the wake of the human genome project, pharmacogenomics is set to revolutionize the concept of drug therapy. The term pharmacogenomics has been coined to designate the application of genomics to drug discovery, design and development. In the broadest sense, this term refers to the use of genomic technologies to predict a patient's susceptibility to a certain disorder and the extent to which they will respond to a certain drug. However, this should not be confused with pharmacogenetics, which has the more limited focus of studying the influence of genetic variation on drug response (W. Francis Lam, 2013). Scientists have made considerable progress in identifying the major components of the genome that influence drug response. On the basis of these discoveries, the FDA has begun to approve drugs or recommend changes in the product information to make the determination of certain genetic markers of drug response a condition of therapy. However, the road to personalized drug therapy and tailoring medical care to an individual's genetic profile is still years away. To achieve the goal of personalized medicine, a sound ethical and legal framework needs to be developed swiftly. Personal health information includes sensitive data. Thus the utilization of this type of information in health care must be in compliance with certain rules that guarantee patient's rights and prevent abuses. Implementing pharmacogenomic tests into routine prescribing practices is nonetheless complicated. Like any other new technology, the development and implementation of pharmacogenomic tests are complex processes. They require time and significant investment in both capital and expertise. These challenges are particularly pronounced considering the complexity of the tasks to be addressed and the involvement of a great diversity of stakeholders. Processes and strategies for the development and deployment of pharmacogenomic tests in evidence-based prescribing contexts will be described. From what has been learned so far in the pharmacogenomics community, it has become apparent which medical, scientific, financial, and organizational efforts need to be taken so that a new approach to drug therapy is efficiently introduced and reaps the expected benefits promptly. Launched in 1991, the Pharmcolgenetics for Every Nation Initiative was an effort to stimulate research into the pharmacogenetics of affordable drugs in the developing world. Aware that pharmacogenomics could also increase drug costs, safety, ethical and infrastructure issues were considered. Despite major scientific advances and expectance in cost-reduction of pharmacogenomic tests, 15 years later, the implementation of PGTs remains scant (F. Carr et al., 2014). The development and implementation pathways for pharmacogenomic tests are described. Broadly, these consist of several stages. Before understanding the methodology and main procedures for this evaluation, it is important to acknowledge the simplified view of pharmacogenomic drug interaction presented here. For example, a statistical result may be

considered a biomarker in the clinical setting, while the scientific and theoretical circumstances governing the actual pharmacokinetic-drug interaction have not been fully established. Moreover, while it is certainly necessary that pharmacogenomic drug interaction is detailed and reviewed, other pharmacogenomic applications in drug therapy may hold more immediate dopamine.

11. Patient Perspectives

11.1. Awareness and Acceptance

11.2. Impact on Treatment Outcomes

12. Global Perspectives

The passing of the final ruling on Clinical Laboratory Improvement Amendments (CLIA) waiver criteria for laboratory-developed tests in October 2017 marked a move toward broader adoption of pharmacogenomics (PGx) testing. More recently, pharmacogenomic approaches have made it possible to devise tailored strategies aimed at mitigating or overcoming resistance. In the past two decades, many academic–clinical institutions have invested in dedicated facilities, including genome transcriptome and epigenome platforms, handling a large patient population. The possibility to analyze a plethora of genetic, transcriptomic, and proteomic parameters on patient samples, providing a comprehensive portrait of a disease with unprecedented detail. Translating laboratory findings into clinical practice represents the obvious and most crucial bottleneck in the diagnostic process. Many technical and regulatory aspects still need to be meticulously addressed in pre-analytical, analytical, and post-analytical areas of the in-house assay, in order to guarantee a robust and reliable test on a routine basis. To maximize flexibility and capacity, high-throughput platforms are preferable. However, selectivity may be more effectively accomplished by multiple low-multiplex applications. Furthermore, miniaturized devices would make it possible to perform the test in outpatient daily clinics, providing information on the optimal treatment variation in just 2–3 days.

12.1. International Collaborations

Several years after the completions, there are increasing achievements in advancing of pharmacogenomics. Thanks to international collaborations, several ongoing and completed pioneer's lectures of pharmacogenomics were delivered. Subsequently a Nordic pharmacogenetic information newsletter was initiated. Videoconferences on a North European Pharmacogenetics Network were organized, as well as ongoing bilateral Scandinavian meetings of pharmacogenetic interest. Economic agreement among the affiliates was not accomplished. Desire to delve deeper in the pharmacogenomic field led to new acquaintances with great people and fascinating places. Historically, both international collaboration and success in research benefit from studying abroad. The aim of this letter is not only to report personal experiences, albeit almost comically disheartening at first glance, but also to encourage continuing efforts to make new acquaintances and establish collaborations throughout the world. This is highly relevant in the field of pharmacogenomics, and motivating adequate success stories from the rest of the world would be beneficial for all.

12.2. Variations in Practice

The potential impact of pharmacogenomics is immeasurable, but there are many hurdles that it currently faces: economic, legislative, educational, social, research protocol, and more. Since the Human Genome Project was completed on April 13, 2003, prospects for personalized medicine have leapt from the pages of science fiction to the threshold of clinical reality. As a result, it is now possible to take a new approach to tailoring medical interventions to suit a person's unique genetic make-up. This new approach, termed pharmacogenomics, could provide an enormously powerful tool for maximizing the benefit of pharmacotherapy whilst minimizing its associated risks, thereby ushering in a new era of truly individualized medicine. Such a development would be a long-awaited apex to a long history of medical and scientific endeavour (Avery et al., 2009). Yet exciting though these possibilities are, pharmacogenomics is still an embryonic science with a number of difficult issues that need to be resolved if its promise of personalized medicine is to be realized.

Pharmacogenomics can be expected to revolutionize the management of both acute and chronic medical conditions. A significant portion of the cost-effectiveness gap can be bridged by recognizing that some drugs are more conducive to pharmacogenomic strategies than others and by considering pharmacogenomics early in the life cycle of drugs. Pharmaceutical companies would be well advised to expand research and development in this area to help realize the potential of drug therapy more fully, which will likely lead to new and innovative strategies in the acquisition and management of intellectual property. The rapidly-advancing field of pharmacogenomics promises to substantially improve the efficacy of drug therapy. It is broadly anticipated that pharmacogenomic strategies will both improve patient outcomes and reduce costs associated with the adverse drug events that are complications of most drug therapies (Barone et al., 2009). It has been suggested, however, that pharmacogenomic strategies may not achieve cost savings and may even increase costs.

13. Economic Implications

13.1. Cost-Effectiveness Analysis

13.2. Insurance Coverage Issues

14. Ethical and Social Considerations

14.1. Privacy Concerns

14.2. Equity in Healthcare

15. Conclusion

Pharmacogenomics and personalized medicines have emerged as new directions of medical treatment in the last few years. Since the decoding of the human genome, the identification and the interpretation of the genetic variations in the human genome have become a challenging, but extremely important procedure. The pharmacogenomics employments of the microarray technologies are spreading quickly for the analysis of the differences between the patients of the DNA, RNA and protein profiles. These microarray technologies enable the investigation of tens of thousands of DNA SNPs and gene expressions their own in a single experiment. By using these advanced technologies some treatment predicting approaches are getting feasible. Nowadays, biopsy materials are necessary for the estimation of the most efficient treatment type for the cancer

patients. However, the treatment selection based on the personal genetic characteristics of a given patient will be possible in the near future for other, non-cancer diseases too (Avery et al., 2009). Cancer comes out as one of the diseases in which the pharmacogenomics investigations are having the most promising outcomes. The therapy is often adjusted regarding the genetic characteristics of the tumor. Virtually, a parallel treatment is possible for the case of only a few malignancies.

In order to improve the predictability of how the patients responds to drugs, substantial efforts and various platforms have been developed in the area of pharmacoproteomics and pharmacogenomics. Despite personal genotyping platforms have now installed in some large hospitals in some of the developed Western countries, thanks to their funds potential, the routine clinical applications personal genetics/genomics testing are far from satisfactory (F. Carr et al., 2014). There have been remarkable advances in biological and medical research in the last decades, providing detailed insights, for example, into the human genome or the pathogenesis of individual diseases and making promising innovative therapies feasible. Similarly, in conventional cultures, good manufacturing practice and good laboratory practice of regulatory agencies have been implemented in the biotechnology and pharmaceutical industries. Auxiliaries such as the biohybrid approach of a single dose of drug and multiple detections and controlled releases of drug have also boosted the fastest development of drug formulations.

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