Importance of Pharmacovigilance in Health and Clinical Research

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KEYWORDS

Pharmacogenomics, oncology,alleles, implementation

ABSTRACT

The field of pharmacogenomics has grown to be quite promising for the medical industry. Therefore, it is critical to assess the attitudes and knowledge of healthcare professionals. The study of interindividual differences in DNA sequence linked to pharmacological response is known as pharmacogenomics, or PGx. There have been several attempts to incorporate this area of research into standard therapeutic procedures. Before initiating clinical PGx in a hospital setting, we provide a brief overview of PGx and its function in enhancing treatment outcomes. Prioritization should involve assessing the PGx evidence that is now available, reviewing the medications that are most relevant, and figuring out which variant alleles and drug-gene combinations are the most actionable. Pharmacogenomics, or PGx, is one of the fields of precision medicine with the greatest potential to swiftly transform standard healthcare.Due to the quick advances in PGx knowledge obtained from extensive basic and clinical research as well as the falling costs of laboratory testing, there is presently increased interest in PGx and anticipation of an imminent clinical translation with major therapeutic impact. However, integrating PGx into clinical workflows is not an easy task; multidisciplinary cooperation and thorough procedures are needed. A greater knowledge of unresolved difficulties has resulted from the pioneering models for clinical PGx implementation developed by a number of national and international institutes.

1. Introduction

The pharmacological science associated with the identification, evaluation, comprehension, and avoidance of adverse effects, particularly long- and short-term adverse effects of medicines" is the definition of pharmacovigilance. In India, pharmacovigilance is still a relatively new field with little body of knowledge. Pharmacovigilance has not advanced significantly in India, despite significant strides in Western nations. It is essential to comprehend the significance of pharmacovigilance and how it impacts a product's life cycle [14]. This will make it possible to incorporate best practices in pharmacovigilance into the processes and procedures, improving post-marketing surveillance and clinical trial safety while also ensuring regulatory compliance. [1]

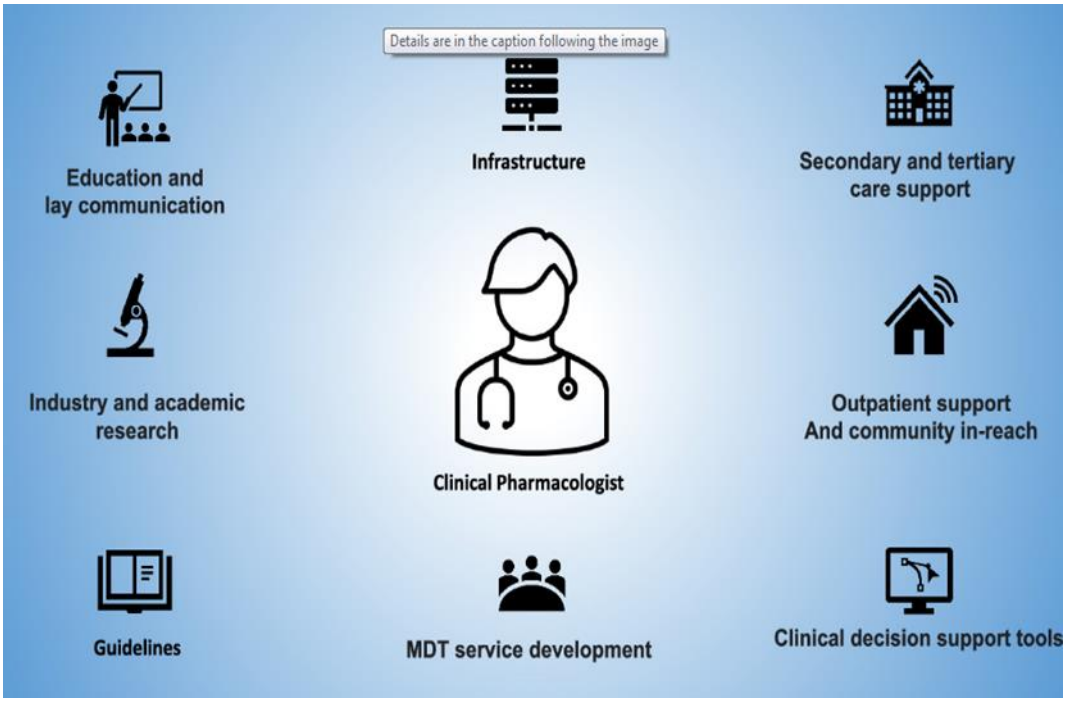

Figure 1. Opportunities for clinical pharmacologists to contribute to pharmacogenomics.

Clinical use of pharmacogenomics (PGx) is not keeping up with its rapid advancement. One of the main goals of the Indiana Institute of Personalized Medicine (IIPM) is to incorporate PGx research into clinical practice. We will outline the conditions that must be satisfied for a PGx installation in a sizable

healthcare system to be effective and long-lasting. [9].

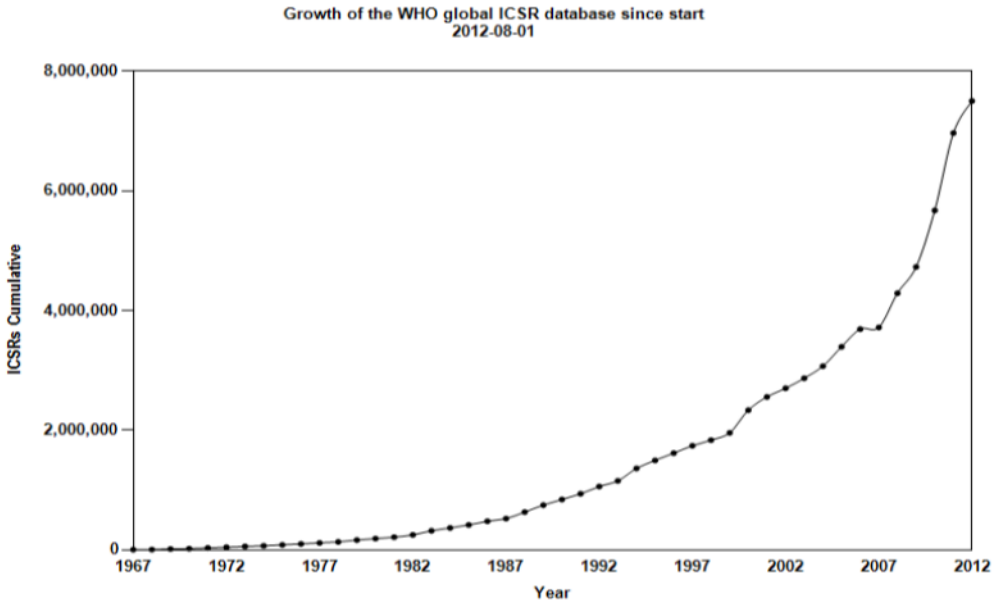

Figure 2. Drug Safety Report Worldwide

The cost of conducting PGx testing has significantly decreased over the last five years; yet, new technological advancements have made it easier to move PGx from research benches to CLIA-approved laboratories. Francis Collins predicted in 2001 that by 2020, PGx will be the accepted method for determining if a medication is appropriate for treating a variety of conditions and prescription medications [4]. A survey of PGx studies that have been published shows that clinical research has been growing quickly. However, as observed by AR Shuldiner et al., "there are a number of substantial barriers to the adoption of pharmacogenetic tests into clinical practice." The paucity of robust and thorough clinical evidence to support the routine and prospective use of genetic testing, as well as the lack of health economic data tying genetic testing to lower healthcare costs, are the two key barriers to the widespread use of PGx testing [10]. The first guideline was published in 2011 and the Clinical Pharmacogenetics Implementation Consortium (CPIC) was established in 2009. Since then, 12 distinct guidelines and 4 revisions have been published, covering over 26 medicines. Despite significant and ongoing efforts, a sizable number of drugs continue to have FDA-issued "Black Box" warnings and no dosage guidelines. It's also critical to understand that it takes time to adopt any changes to clinical standards of care [6]. It might take up to three years for a novel therapeutic technique to become the standard for therapy, according to the National Institute for Health and Therapeutic Excellence. It often takes more than 10 years between ten and twenty-five years for clinical translation, or the process of moving from research to clinical use. [3]

2. Literature Review

There are several methods to define this subject, but the author of this paper thinks that the de Leon et al. categorization is the most thorough since it takes into account the difficulties in applying pharmacogenetic testing in both general practice and psychiatric care. [5]. As a result, the author has employed the same classification while doing a thorough search for more research on each topic. According to Ehrmann et al. (2014)[7] and Mehta et al. (2020), the regulatory agencies in the US and Europe, the FDA and EMA, are in responsibility of regulating the addition of PGx information and determining the degree of PGx labeling, whether it is needed, indicated, actionable, or instructive [2]. HCPs can get all relevant prescribing information and guidance by visiting the PharmGKB website, which offers recommendations. The FDA and EMA recently released recommendations about the use of PGx data in drug development and labeling [8]. The sponsor may choose to include PGx data—which do not currently qualify as a valid biomarker—with an investigational or marketing application,

according to the FDA (United States Food and Drug Administration, 2005) [11]. This could be done for a variety of purposes, such as using genetic data to confirm specific toxicities or providing guidance for the design of clinical trials [12]. The application should include any PGx data that are known to impact the efficacy, safety, or welfare of people or animals. Regarding labeling, the PGx data could be presented in an informative or useful way. The guidelines that are established with consideration for key scientific principles that must be followed to ensure that high laboratory standards are met and optimal reliability of the PGx assay are directed towards the European Medicines Agency (EMA, 2010) and the co-development of PGx biomarkers or assays. [15].

3. Methodology

Clinical Research

Large sample sizes and patients from a range of ethnic backgrounds are needed for replication of the findings in later clinical studies that follow the identification of a potentially important gene variant. Historically, a targeted genotyping strategy has been utilized since sequencing is expensive. Numerous historical research concentrated on Caucasian (of European heritage) populations that were very small and had little representation from ethnic minorities. Thus, in the design of later research, common variations that might significantly affect treatment response or toxicity in different populations were excluded. Studies examining the connection between genetic variation and medication response may therefore yield contradictory findings, especially when their patients come from diverse ethnic origins. Rare variations have not received much attention in research, even in groups with a great deal of study. However, with sequencing costs declining, more research with larger sample numbers is now possible, leading to the identification of frequent variants in non-Caucasian populations and rare variants in all populations. [13]

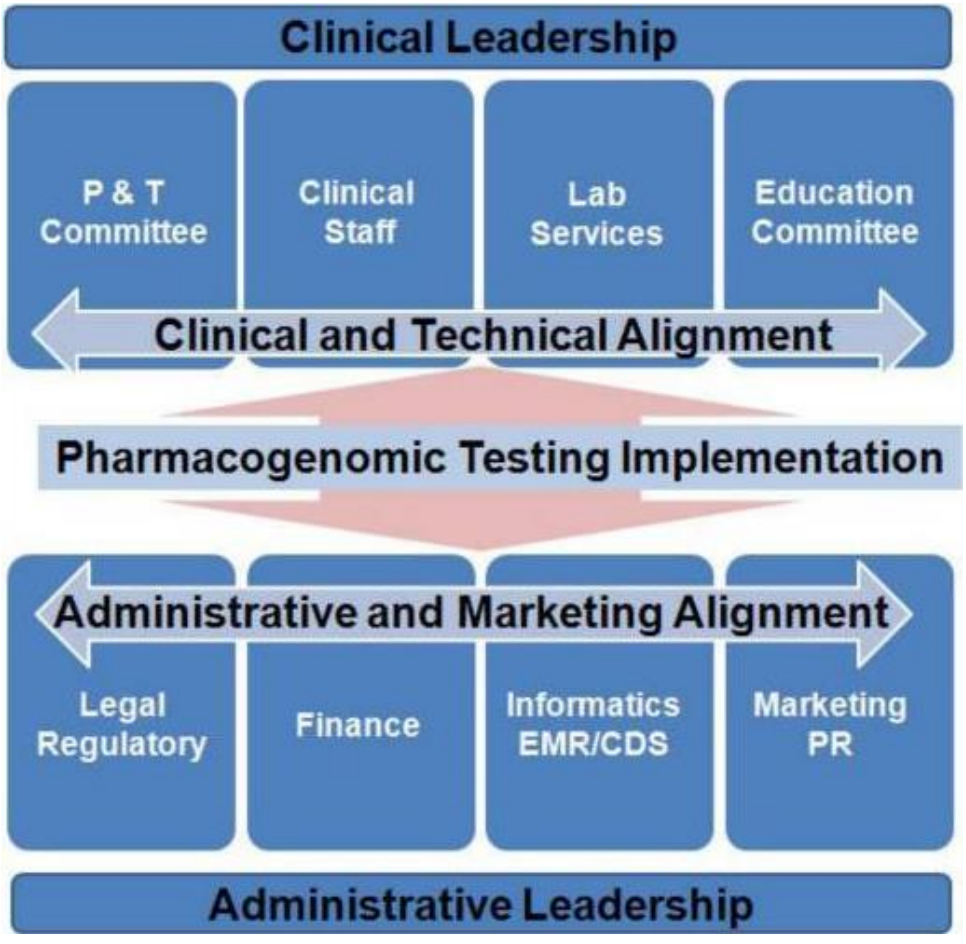

Figure 3. Alignment required within Clinical and Administrative groups in order to facilitate PGx Implementation that is effective and enduring

Adverse Drug Reactions which affects the health

ADRs, which would include those that are severe or frequent and that may potentially affect how the product balances its risks and benefits. If accessible, this material should contain proof of a causative association as well as details like severity, seriousness, frequency, reversibility, and at-risk categories. It is important to talk about risk variables and possible mechanisms. As part of the Pharmacovigilance Plan, these adverse events/deficits should typically prompt additional assessment (e.g., frequency in normal conditions of use, severity, outcome, at-risk populations, etc.). In this section, significant potential dangers ought to be discussed. It is necessary to provide the data that supported the determination that there was a possible risk. It is expected that additional analysis will be necessary to fully describe the link for any significant potential danger.

4. Results and discussion

In order to develop the area of PGx and produce the evidence required for its wider clinical use, ongoing research is crucial. Research involving a larger range of drug combinations and variations will require more financing. Sequencing-based methods can identify both common and uncommon mutations that may contribute to PGx symptoms; however, targeted genotyping methods are usually less costly. Including a variety of populations will also make it easier to spot notable differences in non-Caucasian populations. Further studies on these mutations can identify and clarify differences in the way that various groups respond to medications. The advancement of PGx research will depend on the development of increasingly complex artificial intelligence methods and computing infrastructure. These tools might enable more intricate in silico variant evaluation, thereby doing away with the need for costly and time-consuming functional genomic investigations of each variant. Furthermore, they might make it possible to study variation combinations in several genes within the same pathway simultaneously.

Case Study: To correlate serum methotrexate level and side effects of High Dose Methotrexate infusion in Paediatric patients with Acute Lymphoblastic Leukaemia (ALL)

drawing blood and testing for methotrexate 48 hours after the HDMTX infusion began, 3 mL of blood samples were taken and allowed to coagulate in a plain tube. The serum was separated from the coagulated blood and centrifuged for 15 minutes at 3000 rpm prior to analysis. The Abbott ARCHITECT Methotrexate test was used to assess the medication levels of methotrexate in serum. Clinical research labs employ the ARCHITECT Methotrexate Assay, which uses Chemiluminescent Microparticle Immuno Assay (CMIA) technology to quantify the amount of methotrexate in human serum or plasma. The Abbott ARCHITECT Methotrexate assay kit has a measurement range of 0.040 µmol/L to 1.500 µmol/L. Specimens containing more than 1.500 µmol/L of MTX ought to be manually diluted using the method advised by the manufacturer. Serum MTX concentrations beyond safety thresholds, which were set at 1.0 micromol/L 48 hours after HDMTX infusion started, indicated heightened susceptibility to unfavorable outcomes following high-dose methotrexate treatment with folinic acid rescues. SPSS version 18 and Excel Analyze IT XP were used to analyze the data. 48 hours following the start of HDMTX infusion, patients were categorized based on their serum MTX level, and the differences in toxicity incidence and severity between the groups were assessed using the Chi-square test. To determine whether there was a relationship between the amount of methotrexate and the existence of toxicity, we used logistic regression analysis. The statistical significance of the P-value of 0.05 was established. For 62 ALL patients, a total of 244 HDMTX infusions were given. Of the 62 patients, 45 (72.6%) were male and 48.4% were between the ages of 1 and 6 years. The average age of the group was found to be 7.89±4.64 years. 56 cases (90.3%) out of all the cases with an ALL diagnosis had PreB ALL predominant. Forty (65.6%) of the patients received 2 g/m2 as per their treatment plans. Out of 244 cycles, 97 cycles (36.7%) had toxicities found. Thirty-one (88.6%) of the 244 cycles included toxicity notes, and 35 cycles had blood methotrexate levels ≥ 1.0 micromol/L 48 hours after

HDMTX infusion started. The MTX level was found to be less than 1.0 micromol/L in 209 cycles, with 66 cycles having documented toxicity. (31.6%) (Figure No 4). 48 hours after the HDMTX infusion began, the mean blood methotrexate level in 35 cycles was determined to be 2.01 micromol/L. When the patient's serum MTX level was reviewed 72 hours later, it was found to be 0.18 micromol/L.

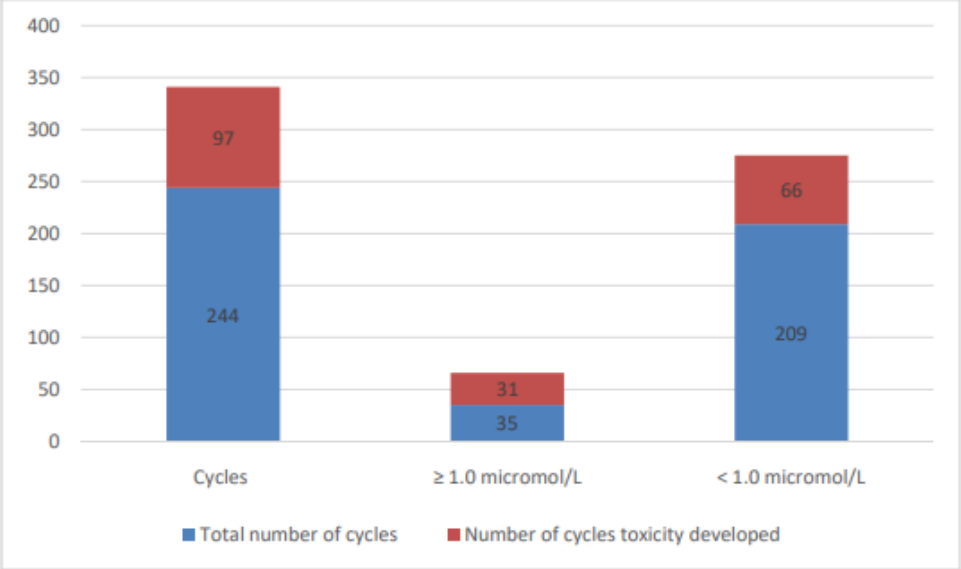

Figure 4. Distribution of ALL patient's serum methotrexate level (micromol/L) and toxicities in different cycles

5. Conclusion and future scope

A crucial and essential component of clinical research is pharmacovigilance. Throughout the product lifecycle, post-marketing pharmacovigilance and clinical trial safety are both essential.This work has speculated about a future in which genotype information may be easily accessible, at minimal cost, for every patient as part of their electronic health records, given the declining prices of genetic testing and its growing availability. To incorporate pharmacogenetics into family medicine and psychiatric treatment, however, cooperation between pharmacologists, pharmacoepidemiologists, general practitioners, psychiatrists, clinical psychologists, pharmacogenetic scientists, and regulatory scientists is required. Pharmacovigilance evaluates a drug's safety profile by examining all relevant data. The benefit of the medication should also be considered in pharmacovigilance. To systematically identify and correlate medications with side effects and take corrective action, pharmacovigilance is necessary.

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