A Review on:-Pharmacogenomics

Author –Mayuri Fulsoundar
Guide - Bhavna P. Hon
Principal – Megha T. Salve
Shivajirao pawar college of pharmacy

ABSTRACT–
Pharmacogenomics is the study of genes and the effects of drugs on an individual's response. Pharmacogenomics is a new, emerging field that combines both pharmacology (the science of drug discovery) and genomics (the science of genetic research) to develop effective doses and safe medicines tailored to individual needs. The individual genetic composition of the patient. Pharmacogenomics is the application of genome-wide pharmacogenetics that studies the interactions of individual genes with drugs.(1)
Numerous resources have been presented to narrow the gap between researchers, clinicians, and patients in understanding the utility and benefits of pharmacogenetics. Some of the most common clinical examples of genetic variants are discussed and how pharmacogenetics can be used to determine treatment options for patients with these variants. Pharmacogenomics in clinical practice is intended to facilitate drug selection and dosing and has the potential to improve treatment outcomes, reduce the risk of drug-related morbidity and mortality, and be cost-effective.(2)
Keywords –pharmacogenomics, implementation, bioinformatics, breast cancer(3

I.   INTRODUCTION -

Pharmacogenomics is the study of how genetic variation influences drug response. The terms "pharmacogenetics" and "pharmacogenomics" are often used interchangeably, but there are minor differences. As early as the 1930s, scientists discovered a connection between innate enzymatic variability and drug response. In 1959, the German Friedrich Vogel coined the term "pharmacogenetics" to describe the influence of a single gene on the effect of a drug.(4)

Pharmacogenomics, the application of genomic techniques to study the pharmacological functions, distribution and effects of drugs, will lead to a better understanding of drug response at the individual level. This is the most important foundation for the transition to more individualized medicine, commonly referred to as personalized medicine. To better describe the concept of using pharmacogenomics to identify subgroups (rather than individuals), a recent article introduced the term "stratified medicine."(5)

The increase in technological capabilities and the reduction in costs associated with such analysis have led to the effective implementation of exome sequencing as a research tool, especially for the identification of new genes responsible for rare diseases. Various treatments are currently used, such as cancer chemotherapy and oral anticoagulants. Use the patient's pharmacogenetic status to minimize toxicity and failure of drug treatment 2, 3. Currently, the traditional method of drug and dosage form selection is being replaced by the pharmacogenomic method.(6)

Genetic variants have been identified that affect the pharmacokinetics (I.e. absorption, distribution, metabolism, elimination) or pharmacodynamics (I.e, pharmacologic effects) of specific drugs. A patient who has a variant allele of one of these genes may experience severe and even life-threatening adverse events when exposed to certain drugs. Such events are a leading cause of morbidity and death in the United States and are costly to manage, and nearly half are estimated to be preventable.1,2
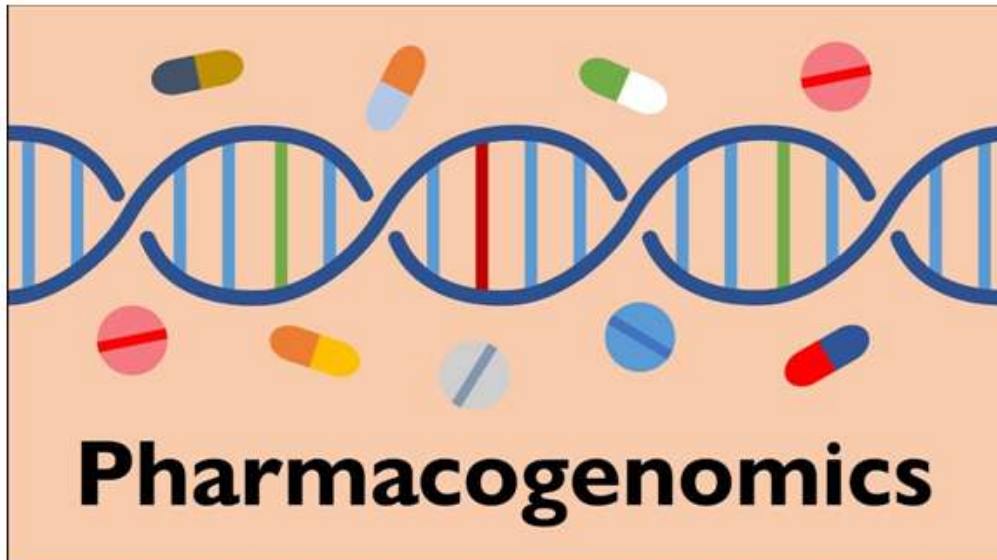
History –

Genomics was established by Fred Sanger when he first sequenced the complete genomes of a virus and a mitochondrion. His group established techniques of sequencing, genome mapping, data storage, and bioinformatic analyses in the 1970-1980s. The actual term genomics is thought to have been coined by Dr. Tom Roderick, a geneticist at the Jackson Laboratory (Bar Harbor, ME) over beer at a meeting held in Maryland on the mapping of the human genome in 1986.(7)
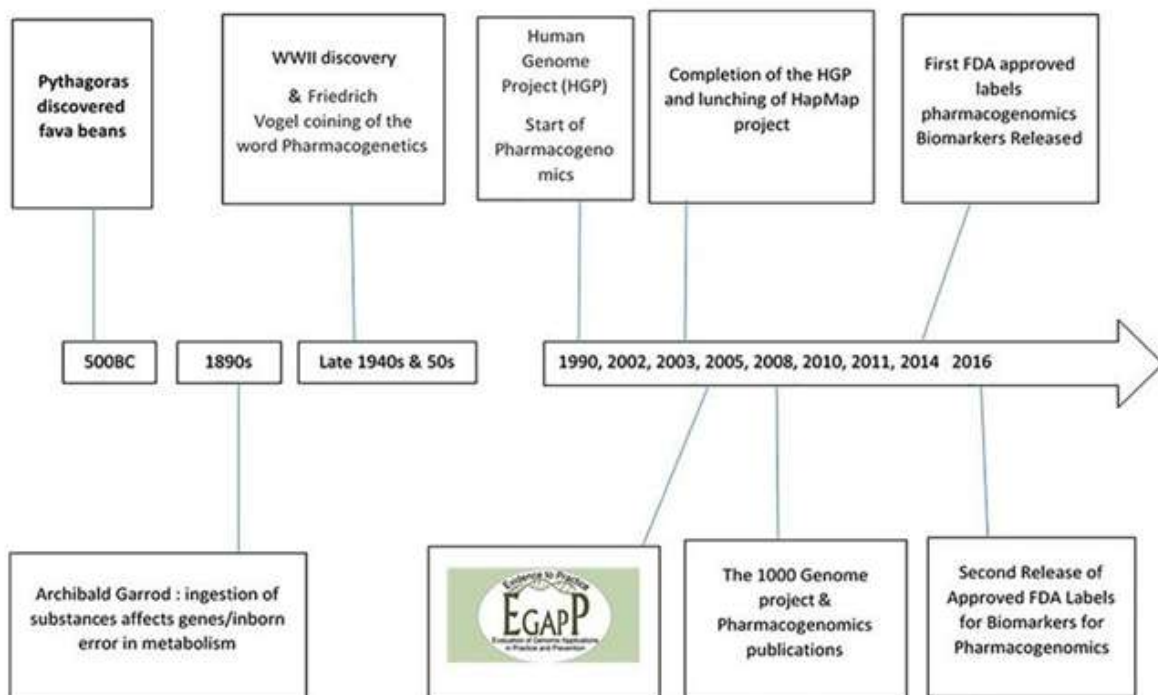
Pharmacogenomics could ultimately lead to an overall reduction in healthcare costs by reducing: the number of adverse drug reactions; number of failed drug trials; the time it takes for a drug to be approved; how long patients take medication; the number of medications a patient must take to find effective treatment; the impact of the disease on the body (thanks to early diagnosis).(8)

Importance of Pharmacogenomics –

The goal of pharmacogenomics is to use genetics to optimize drug therapies, maximize the effectiveness of drugs and minimize their side effects. For this reason, many pharmacogenetic tests have been developed that are valuable for diagnosis and therapy. Pharmacogenomic tests are DNA-based tests Detect genetic changes associated with risk of side effects or drug reactions. Several important pharmacogenetic tests have been available in Clinical Laboratory Amendments (CLIA)-approved laboratories for many years, but their use is limited. The FDA identifies alleles that influence drug efficacy and toxicity as pharmacogenetic biomarkers.

This system enables the development of drugs that the average patient responds to. However, as the statistics above show, there is no one-size-fits-all solution, which sometimes has devastating consequences. It is important to find a way to treat the side effects before they occur. However, the solution is visible and is called pharmacogenomics.(9)

Importance of Pharmacogenomics –

The purpose of pharmacogenomics is to use genetics to optimize drug therapies, maximize drug efficacy, and minimize adverse drug reactions . For this reason, many pharmacogenetic tests have been developed and are valuable in diagnostic and therapeutic . Pharmacogenomics testing is a DNA-based test thatdetects genetic changes associated with the risk of side effects or drug reactions. Several important pharmacogenetic tests have been available in Clinical Laboratory Amendments (CLIA)-approved laboratories for many years, but their use is limited. The FDA identifies alleles that influence drug efficacy and toxicity as pharmacogenetic biomarkers.

This system enables the development of drugs that the average patient responds to. However, as the statistics above show, there is no one-size-fits-all solution, which sometimes has devastating consequences.It is important to find a way to treat the side effects before they occur. However, the solution is visible and is called pharmacogenomics(10)

Pharmacogenomics and Drug development –

Originally, the discovery of drugs in psychiatry was based on chance. After the identification of lithium in 1949 and chlorpromazine in the 1950s, the laxative mechanism of action was clarified after the drug's effectiveness was demonstrated. New paradigms for drug discovery depend on the synthesis and identification of a new compound through combinatorial chemistry and biological screening of biological activity against known receptors or other biological targets with established endogenous ligands or substances.

The experimental paradigms used in pharmacogenomics are borrowed from the field of population genetics and the methodology used in previous genetic studies of common complex diseases. According to the Human Genome Project, all available human genes serve as potential drug targets. A major challenge in drug development therefore lies in the functional and therapeutic use of these genes and the product they express. Pharmacogenomics brought experimental paradigms from the field of population genetics and from the methodology used in previous genetic studies of common diseases. The microarray is a powerful and emerging technological advance that enables the study of global gene expression patterns and sequence variation at the level of 62 genomes.

The DNA microarray is an advanced form of the Southern screw method in which stretching of various cDNAs or oligonucleotides is performed on a hard surface such as silicate or a glass plate. In the DNA chip, each DNA species represents a specific gene or expressed sequence tag, which is used to identify different SNPs or transcripts through hybridization and fluorescence detection.(11)
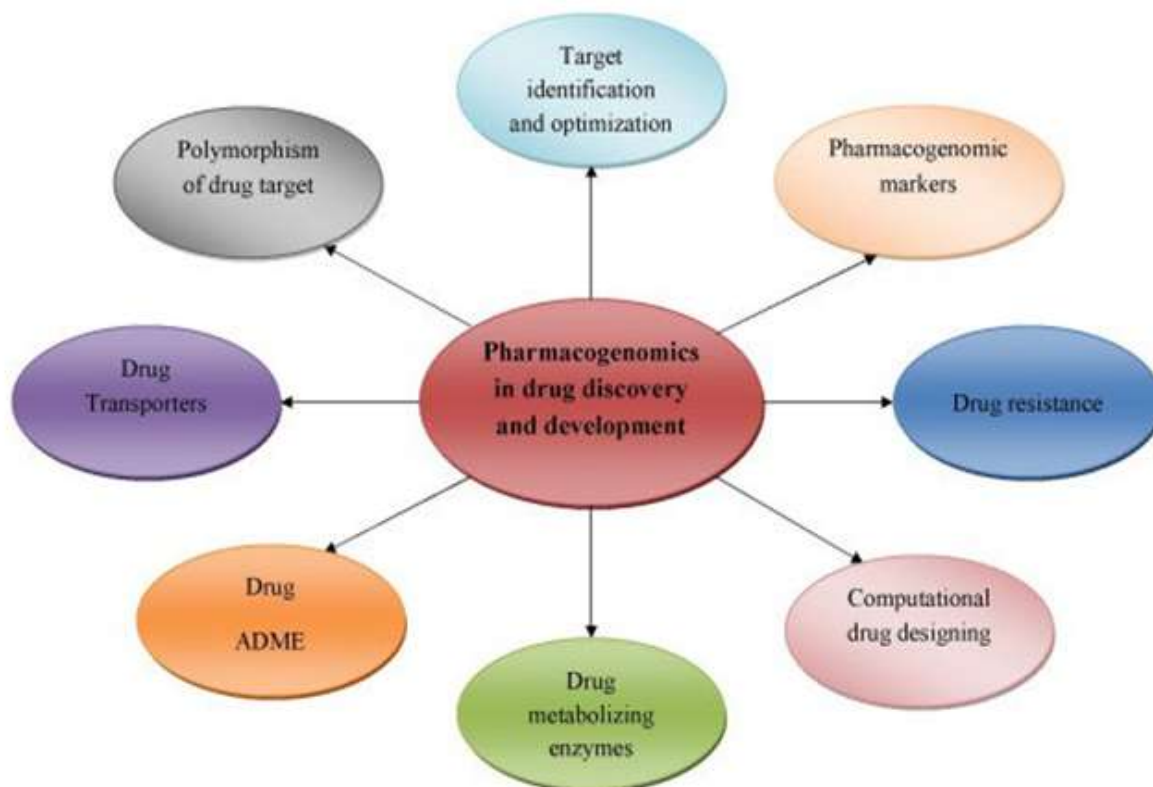
Pharmacogenomics today-

The cytochrome P450 (CYP) family of liver enzymes is responsible for the breakdown of over 30 different classes of drugs. Differences in the DNA of the genes that encode these enzymes may affect their ability to metabolize certain drugs. Less active or inactive forms of CYP enzymes that cannot effectively break down and remove drugs from the body can cause drug overdoses in patients. Clinical trial researchers are currently using genetic testing to detect changes in the cytochrome P450 genes to select and monitor patients. Additionally, many pharmaceutical companies test their chemicals to see how well they are broken down by various forms of CYP enzymes(12)

Future pharmacogenomics –

New developments in this field will impact on drug design at three main levels: the interaction of the drug with its receptor binding site; the absorption and distribution of the drug; the elimination of the drug from the body.

Pharmacogenomics in the era of next generation sequencing from byte to bedside(13)
Hematological Disorder –

Overall survival in hematologic malignancies is improving in children and adults. This development can be partly attributed to the advancement of sequencing technology and the discovery of new somatic mutation targets. Imatinib was the first drug in a long list of small molecule tyrosine kinase inhibitors (TKIs) that target the oncogenic chimeric tyrosine kinase BCR-ABL. BCR-ABL is the result of a chromosomal translocation known as the Philadelphia chromosome. Despite the promise of imatinib for leukemia patients, drug resistance has emerged in nearly a third of high-risk patients with chronic myelogenous leukemia.The mechanisms of resistance are heterogeneous and include altered drug distribution in tumor cells resulting from reduced OCT1-mediated drug uptake or increased drug efflux due to increased MDR1 activity, overexpression of BCR-ABL, and acquisition of escape mutations affecting the fusion kinase itself make resistant imatinibThomas. Resistance mechanisms are innate or acquired after treatment. Overall survival in hematologic malignancies is improving in children and adults. This development can be partly attributed to the advancement of sequencing technology and the discovery of new somatic mutation targets. Imatinib was the first

drug in a long list of small molecule tyrosine kinase inhibitors (TKIs) that target the oncogenic chimeric tyrosine kinase BCR-ABL. BCR-ABL is the result of a chromosomal translocation known as the Philadelphia chromosome. Despite the promise of imatinib for leukemia patients, drug resistance has emerged in nearly a third of high-risk patients with chronic myelogenous leukemia.The mechanisms of resistance are heterogeneous and include altered drug distribution in tumor cells resulting from reduced OCT1-mediated drug uptake or increased drug efflux due to increased MDR1 activity, overexpression of BCR-ABL, and acquisition of escape mutations affecting the fusion kinase itself make resistant imatinibThomas. Resistance mechanisms are innate or acquired after treatment.(14)

Breast Cancer –
Breast cancer is generally divided into four intrinsic subtypes: (i) luminal A, (ii) luminal B, (iii) HER2 positive, and (iv) triple negative. Luminal A and B tumors are generally positive for estrogen and/or progesterone, whereas HER2-positive tumors are generally negative for hormone receptors and tend to have a worse prognosis. Triple-negative breast cancer is hormone receptor and HER2 negative and is usually associated with BRCA1 mutations.

Triple-negative breast cancer is the most aggressive subtype and has an overall poor prognosis. Chemotherapy has been the main treatment modality, but the addition of targeted therapy for BRCA1/2 mutations with poly(ADP-ribose) polymerase (PARP) inhibitors (olaparib and talazoparib) in combination with cisplatin or carboplatin improved outcomes. therapeutic results.In addition, treatment with the checkpoint inhibitor atezolizumab in combination with paclitaxel is beneficial in lethal ligand 1-positive (PD-L1+) programmed triple-negative breast cancer. Studies on the safety and effectiveness of other immune checkpoint inhibitors are ongoing and further FDA approvals are expected in the near future.(15)12

Genome,Exomes and the variation with in-
The human genome is the totality of an individual's genetic information, including coding and non-coding regions of DNA and RNA, while the human exome includes the coding regions of genes - exons - which make up about 1-2% of the entire haploid genome. Genome sequence. Since the creation of the reference genome and the

subsequent sequencing of several individual genomes, observations have been made about the significant differences in the genome within and between different ethnic groups. This variation can be roughly divided into simple nucleotide changes on the one hand and structural changes on the other. The first includes single nucleotide polymorphisms (SNPs) and small insertions/deletions (indels) that have been studied in large groups of people, leading, for example, to dbSNP, a database of over 10 million variants common among ethnic groups. However, more information about the architecture of the genome has been revealed; The spectrum of variation was much broader than these nucleotide changes, called structural variation.These include not only inversions and copy number changes (CNVs, i.e. deletions and duplications), but also, for example, the presence of megabase stretches of DNA that are unique to a single personal genome. It is now clear that the structural diversity of the genome is surprisingly large and much more complex than previously thought. In pharmacogenomics, single nucleotide variants and structural changes such as CNVs were shown to contribute to drug response in subject .The pleiotropy that produces this variation has implications for the identification of functional drug response variants as well as the analysis and interpretation of genomic screening tests.(16)

Education and infrastructure Needed-
Challenges in integrating pharmacogenomics into clinical medicine include the lack of infrastructure to store and report test results and limited physician confidence in interpreting, applying, and communicating results to patients.6 A survey of 47 primary care physicians and 375 specialists Also revealed a lack of pharmacogenomic testing guidelines and a lack of medical knowledge of pharmacogenomics represent major barriers to adoption.44 As with other clinical guidelines, the ICPC guidelines are regularly updated to reflect the growing body of evidence. However, combining recommendations can be cumbersome, especially for patients who are prescribed multiple medications.

To overcome these challenges, it is necessary to form interdisciplinary teams that draw on the knowledge of many medical professionals. Informaticians can develop the infrastructure necessary to incorporate pharmacogenomic test results into medical records in a clinically meaningful manner. They could also work with

pharmacists and physicians to develop clinical decision support principles to alert end users to important drug-gene interactions when prescribing the drug and to provide alternative recommendations. Pharmacists and genetic counselors can guide physicians in the use of pharmacogenomics Train tests. and communicate the meaning of the test results directly to patients. Implementation efforts often need to be tailored to each facility as recommendations may vary depending on the medications available in the formulary and the characteristics of the patient population.(8)

Benefits of pharmacogenomics –
Pharmacogenomics combines traditional pharmaceutical sciences such as biochemistry with annotated knowledge of genes, proteins, and single nucleotide polymorphisms. Following are the benefits.

Barriers of pharmacogenomics -
1.Drug label –
Over the past five years, the number of drug labels containing detailed information about PGx has increased significantly. Of course, this information is useful for predicting dosage and clinical effects (e.g. side effects) within the usual dosage range before prescribing. However, the best way to use this genetic information for drug prescribing (e.g. drug selection and dose adjustment decisions) is not yet clear.

2.concise and reproducible evidence –
The lack of robust and reproducible evidence of the benefits of PGx compared to current medical practice is one of the reasons for the low use of PGx in clinical settings. Most clinical evidence comes from small studies that have led to very complex findings between genotypic and phenotypic relationships.

3.Clinical trial –
Lack of controlled dinical trials is often pointed out as a reason for the limitation. To date,

in order to evaluate the dinical utility of PGx information, a few randomized con- trolled clinical trials have been done by comparing genotype-based treatment to the standard one such as warfarin (bleed- ing or thromboembolism), abacavir (hypersensitivity), and tacrolimus (target serum levels) .

4.Education –
Doctors decide whether to prescribe the drug or not. The above study on the utility of PGx suggests that acquiring knowledge of PGx testing and its clinical significance during undergraduate and postgraduate studies will enable clinicians to better utilize PGx in clinical practice. Lack of education and training of health workers appears to be a significant problem in the implementation of PGx. In most cases in Japan, PGx training can be introduced into the postgraduate program; However, it is necessary to start it at a higher level of university study (e.g., Bachelor's degree).

Impact of pharmacy profession-
Presently doctors diagnose and prescribe a drug on the trial and error basis and pharmacist

advices about side effects and drug-drug interaction. But a day will come when you will take a gene report instead of blood reports .Thus after the diagnosis, pharmacist would interpret the panels of genetic results and advice you which drug would be best for your particular gene so that you have fast recovery.

Advanced screening for disease
Knowing one's genetic code will allow a person to make adequate lifestyle and environmental changes at an early age so as to avoid or lessen the severity of a genetic disease. Likewise, advance knowledge of particular disease susceptibility will allow careful monitoring, and treatments can be introduced at the most appropriate stage to maximize their therapy.

Application of pharmacogenomics –
Today, there are many common diseases with high morbidity and mortality that have well-

established genetic components. Sibling analysis predicts the extent to which genetics plays a role in diseases such as obesity and diabetes. Likewise, some rare genetic mutations can shed light on more complex biological processes. For example, if a patient has extreme levels of HDL in the blood, the effect of CETP (cholesterol ester transfer protein) on the patient's HDL level can be easily demonstrated. In another case, a person with inactivating mutations caused by the Janus 3 kinase gene (JAK 3) suffers from severe combined immunodeficiency syndrome, as inhibition of JAK3 is sometimes predicted to impact immunosuppression in humans has.This then led to further research into drugs that show inhibition of CETP and JAK3. With the advent of pharmacogenomics, the relationship between disease states and human genes is now clarified, leading to the appropriate selection of therapeutic agents.
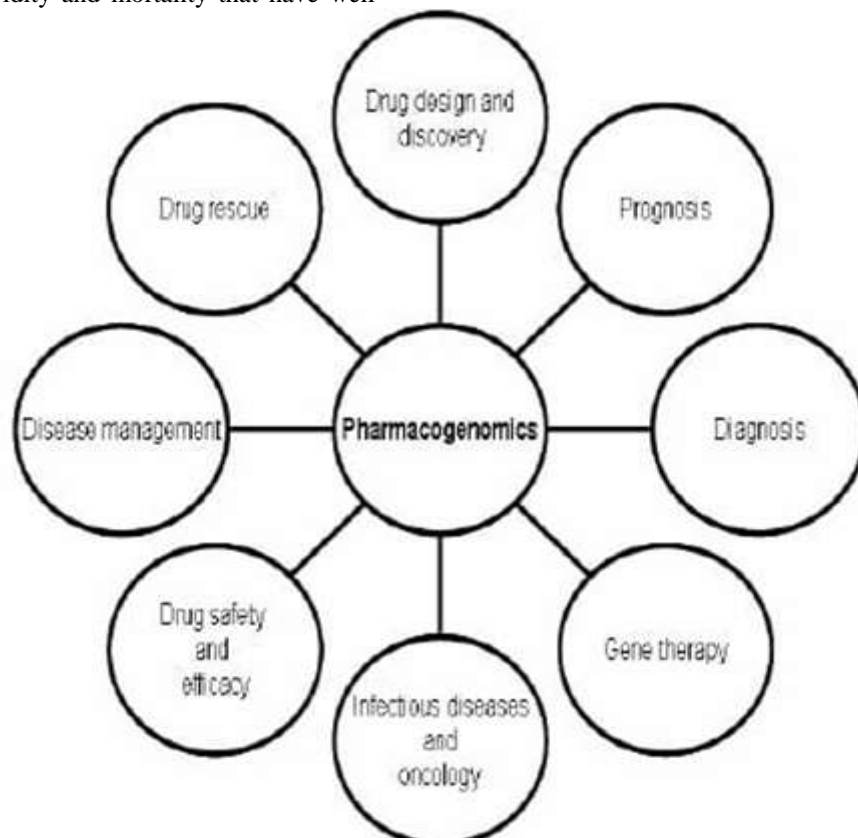
II. CONCLUSION –
Pharmacogenomics in the pharmaceutical industry is a potential tool waiting to be exploited to achieve maximum benefit. This represents a radical advance in the history of medicine. Its main

objectives are: personalized therapy, improved effectiveness and reduction of drug side effects, correlation of genotype with clinical genotype, identification of new drug targets and pharmacogenetic profiling of patients to determine

disease susceptibility and the Predict response to medication. In the past, most drugs were designed to work at a population level rather than a specific patient. By reversing this trend, pharmacogenomics is helping to refine the focus of treatment and make drugs more effective and less toxic.Instead of relying on external symptoms of the disease, doctors test and treat by genotype, which they call phenotypic pharmacogenomic medicine. The gradual integration of pharmacogenomic testing into the drug discovery and development process will lead to a significant reduction in drug development costs.

REFERENCE –

1) Shukla, R., 2020. Pharmacogenomics: overview, applications, and recent developments. Drug Design-Novel Adv Omics Field Appl.

2) Oates, J.T. and Lopez, D., 2018. Pharmacogenetics: an important part of drug development with a focus on its application. International journal of biomedical investigation, 1(2).

3) Hockings, J. K. et al. (2020) "Pharmacogenomics: An evolving clinical tool for precision medicine," Cleveland Clinic journal of medicine, 87(2), pp. 91-99. doi: 10.3949/ccjm. 87a.19073.

4) A review on the role of Pharmacogenomics in drug discovery and development (2016) INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH | IJPSR. INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH. Available at: https://ijpsr.com /bft-article/a-review-on-the-role -of-pharmacogenomics-in-drug -discovery-and-development/ (Accessed: October 19, 2023).

5) Vanakker, O.M. and De Paepe, A., 2013. Pharmacogenomics in children: advantages and challenges of next generation sequencing applications. International Journal of Pediatrics, 2013.

6) Hockings, J. K. et al. (2020) "Pharmacogenomics: An evolving clinical tool for precision medicine," Cleveland Clinic journal of medicine, 87(2), pp. 91-99. doi: 10.3949/ccjm. 87a.19073.

7) Pirmohamed, M. (2023) "Pharmacogenomics: current status and future perspectives," Nature reviews. Genetics, 24(6), pp. 350-362. doi: 10.1038/ s41576-022-00572-8.

8) Aneesh, T.P., Sekhar, S., Jose, A., Chandran, L. and Zachariah, S.M., 2009. Pharmacogenomics: the right drug to the right person. Journal of clinical medicine research, 1(4), p. 191.

9) What is pharmacogenomics? (no date) Medlineplus.gov. Available at: https://medlineplus.gov/genetics /understanding/genomicresearch /pharmacogenomics/ (Accessed: October 19, 2023).

10) Roden, D. M. et al. (2019) "Pharmacogenomics," Lancet (London, England), 394(10197), p. 521. doi: 10.1016/ S0140-6736(19)31276-0.

11) Shukla, R., 2020. Pharmacogenomics: overview, applications, and recent developments. Drug Design-Novel Adv Omics Field Appl.

12) Russell, L.E., Zhou, Y., Almousa, A.A., Sodhi, J.K., Nwabufo, C.K. and Lauschke, V.M., 2021. Pharmacogenomics in the era of next generation sequencing-from byte to bedside. Drug Metabolism Reviews, 53(2), pp.253-278.

13) Magdum C S, VelingkarV S, Gupta Meenu K. Pharmacogenomics: The search for the Individualized Therapy. Indian Journal of Pharmaceutical Education & Research. 2006;40(2 (April-June)): 84-91. [Google Scholar]

14) Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA. 1998;279(15):1200-1205.[PubMed] [Google Scholar]

15) A review on the role of Pharmacogenomics in drug discovery and development (2016) INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH | IJPSR. INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH.

16) Available at: https://ijpsr.com /bft-article/a-review-on-the-role -of-pharmacogenomics-in-drug -discovery-and-development/(Accessed: October 19, 2023).