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# Pharmacogenomics for Infectious Diseases

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**Abstract**:
Pharmacogenomics is the application of genetic and other omics data to specific medication selection and application for avoiding adverse drug reactions (ADR) and increasing drug potency. Pharmacists are playing an increasingly important role in optimizing medicine usage based on genetic testing results. Effect elucidation, genotype-guided medication and modification, medication asset, adverse reaction monitoring, and patient education are all tasks performed by pharmacists. Microbial invasion leads to infectious diseases, which have afflicted mankind from the early era, and is still impacting the health and one of the major causes of morbidity as well as mortality in the society. The response to therapy and the prognosis of an illness are also influenced by an individual's genetic makeup. The data retrieved by genome sequencing of pathogen and humans is one further step forward in examining host-parasite interactions. Consideration of microbial pathogenicity factors, host genetic makeup, and the genetic mechanism involved in disease pathogenesis has paved the way for novel molecular approaches for medications, disease markers, and vaccinations to be discovered. The regulatory approval of amplification tests that are comparable or patronizing to existing gold standard procedures is now assisting the advancement of molecular diagnostics for infectious diseases. Progress in genetics and computation is altering the scale at which biological systems are depicted, and researchers may now expect a precision-focused variety in how they prepare for and respond to infectious diseases. This review will look at the origins and evolution of pharmacogenomics, as well as some of the controversies surrounding its therapeutic applications.

## INTRODUCTION

Pharmacogenomics is the study of how genomics and other "omics" play a crucial role to individual differences in therapeutic outcomes characteristics (1-3). The investigation of genetic characteristics that impact a person's pharmacological reaction is known as pharmacogenetics. Pharmacogenomics is the use of genetic data to guide medicine and dosage selection based on a person's genetic composition.

Through a wide range of data, precision and personalized medicine aims to provide a platform for effective health and disease management. Retrospective studies of healthy subject for better understanding of transformation from healthy functional to disease states identify the individuals who are at risk for the disease, as well as suggesting precise treatment based on dynamic and growing data from the sets of both individual trials and population-based studies are all triggering inputs for driving precision medicine (4).

Rapid advancements in biotechnological and informatics techniques, particularly in the domains of genetics, genomics, and proteomics, have surfaced the path for detecting, eliminating the cause, and enhancing human health over the last several decades. Treatment for a patient can only be effective if the condition is diagnosed quickly and the causative agent is identified, which is especially critical in the case of infectious disorders. The discovery of fresh insights into the genome and structural features of pathogen macromolecules has given rise to new hope for the

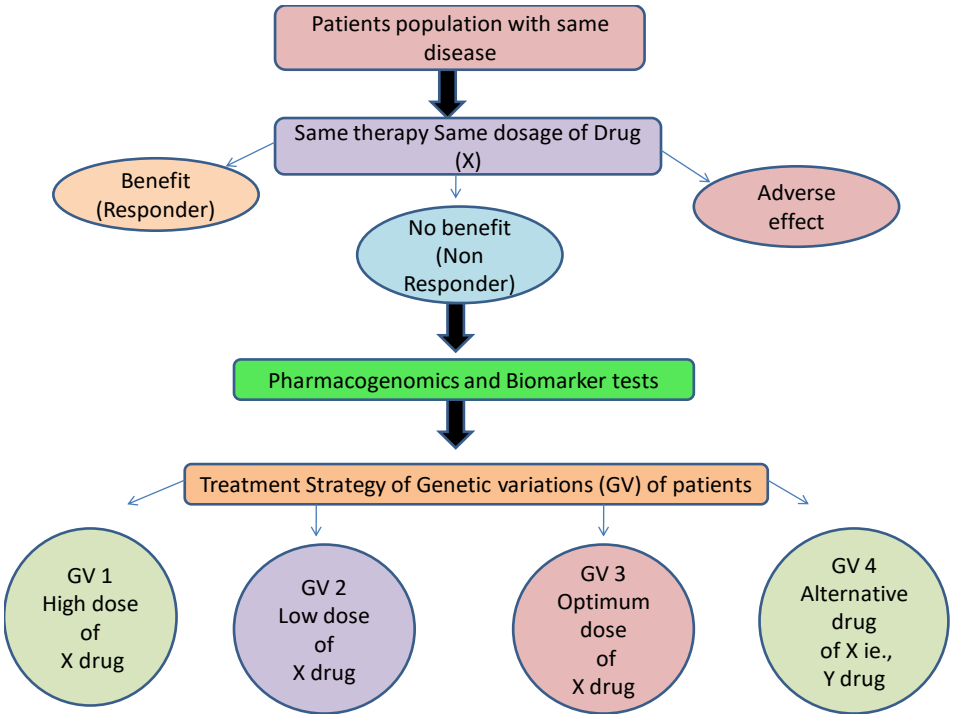


**Figure1:** Treatment Strategy by Pharmacogenomics

treatment of debilitating illnesses. System biology understanding of microbial diseases is still evolving, and the data provided largely belong to few human diseases. The fast growth of NGS technology has resulted in the creation of a contemporary information system, and with further improvement of such edge cutting techniques in the future era, there is optimism that all illnesses will be eradicated. We will soon have entire sequences of whole transcriptomes, much as we did a decade ago with genome sequences, and proteomic methods shall have the specificity, precision, and sensitivity of microarrays. There are also other techniques in the context of infectious diseases, such as metabolomics, glycomics, lipidomics, and phosphoproteomics, which are still at various phases of development, but we are moving in the correct way (5).

*Interactions between the host and the pathogen*

Transcriptomics and functional genomics are revolutionizing the concept of illness caused by microorganisms and aiding our research into the causes of infection vulnerability in humans.

*Transcriptomics*

Scientists have created and applied transcriptomics to improve our understanding of infectious diseases. One of them is cDNA microarray technique widely utilized to investigate the host-parasite interaction. The study focused on the effect of infection on the gene expression of the host cell. The response of the host cell was measured using wild type strain and isogeneic mutant. The key findings of these investigations revealed how pathogen virulence factors alter the expression of host cell components (6).

*Functional Genomics*

By modifying biological pathways, functional genomics has evolved the technique to understand the pathogenesis of disease. Over the recent decade, RNA interference (RNAi) technology has advanced dramatically, allowing for extensive reverse genetic screening in vivo and model species (7).

RNA interference (RNAi) is a technique that employs to target mRNA sequence using dsRNA with complementary sequence which downregulate the target gene expression. Long sequence of dsRNA may form interferons and other nonspecific reactions in host cells which can be overcome using tiny

interfering RNA or shRNA (small hairpin RNA). RNA interference (RNAi) screening with RNA probes, which causes host genes to lose function, contributed to the discovery of Host Resistance Factors (HRFs ). It is made possible when these inhibitory factors are muted, resulting in increased infecting pathogen multiplication. It may also detect Host Susceptibility Factors (HSFs ) and permissive factors, which, when muted, reduce pathogen replication. Because of the off-target siRNA impact, RNAi screens still have significant limitations (8). The data must be integrated which is generated from omics technologies to make system biological techniques such as RNAi well efficient in uncovering processes in the host-parasite interaction and hence deciphers cures for infectious diseases. In addition, utilizing transformed pathogens, cellular RNAi knockdowns, or humanized animal models using mice or primate infection models, numerous rounds of biological experiments are necessary. The inferences drawn from the verified data would aid in the development of prediction models, which might lead to a better understanding of the host-parasite interaction.

*Infection Susceptibility*

A common aspect of many human infections is that only a small percentage of those who are exposed develop clinical illness. For a long time, heritable variables were thought to have a prominent role in explaining inter-individual variations in susceptibility: for example, the early discovery that TB cases concentrated within households led to the belief that tuberculosis was an inherited illness. However, the later identification of bacteria such as Mycobacterium tuberculosis as agents of infectious illness, as well as the experimental proof of the communicable characteristic of diseases, shifted attention to the pathogen (9), potentially overlooking the role of host factors.

It is clear from the history of infectious diseases in humans that not everyone in a particular community gets infected. Both the pathogen's virulence and the host's susceptibility are required for an infective organism to induce an infection. Scientists are working to identify genetic variables that influence the host's innate as well as adaptive immunity and so decide pathogen protection. The genetic determinants and biochemical mechanisms of disease susceptibility have been discovered using animal models of infectious diseases, particularly mouse models (10).

As automated biotechnology and innovative calculation tools evolve, finding genetic signs of natural selection is becoming progressively viable (11,12). The capacity to conduct Genome Wide Association (GWAS ) studies and large-scale genetic-diversity valuations has resulted in an exponential rise of publically available genetic data (13), as well as insights into genomic correlation both within and between populations (14-16).

Precision medicine has already revealed critical information about disease causes, biological targets that might stop disease development, and biomarkers that indicate therapeutic response. In response to this common understanding, significant progress has been made in improving patient treatment outcomes (17–19). Personalized medicine will navigate current drug-selection programs such as pharmacogenomics and patient-derived primary cultures (20–26) with current sources of information and consolidation of data.

It is well-known that understanding the pathogen's mode of action and identifying susceptibility genes are critical for disease management in the terms of public health efforts for prophylaxis, diagnosis, detection, and targeting of susceptibility groups in case of an infectious disease.

*Pharmacogenomics in the management of infectious diseases*

Pharmacogenomics applicability to infectious disorders is still in its early stages. In June 2000, the human genome was fully mapped (27-29). At least 88 bacterial entire genomes have also been sequenced, the majority of which are serious human diseases (30). Researchers can find novel therapeutic targets thanks to the availability of genetic data. As automated biotechnology and innovative calculative tools evolve, discovering genetic signs of natural selection is becoming progressively viable (31-32). The capacity to conduct GWAS studies and large-scale genetic-variation probes has resulted in an algorithmic growth in publically available genetic data (33), as well as

an escalation in genomic correlation both inside and between populations (34–36). These findings highlight the therapeutic importance of discovering natural selection genetic consequences, such as vulnerability loci for infective illnesses that plague mankind (37) and responses when exposed to xenobiotics (38). These breakthroughs have paved the way for precision medicine, which considers a person's genetic statistics when designing clinical care (39,40) and is critical in the quest for individualized or precision medicine. In this respect, genomics offers the ability to advise doctors and accord to precision medicine on various fronts, including illness prognosis, treatment response, and the prophylaxis of adverse drug reactions (ADRs) (41).

Using Genomic Data to Identify Infectious Pathogens

The introduction of large -scale lateral pyrosequencing in 2005 signaled the initiation of the next-generation sequencing era, the first major advancement in sequencing technology after the advent of Sanger sequencing in the 1970s (42,43). The competency of next-generation sequencing increased dramatically in the early years, with yearly sequencing costs diminishing by as much as 80% (44). In public health, these developments were both exciting and intimidating due to the barriers — executing next-generation sequencing may require expenditure in sequencing tools along with cutting edge computing armature to move, store, and analyze large volumes of sequence data (45). Integrating bioinformatics, a relatively new subject in public health, was also critical. Nearly all infectious disease initiatives at the CDC now include pathogen genetics (46).

*Antimicrobial Resistance is Determined by Pathogen Genomic Information*

Fleming anticipated the possibility of bacteria developing resistance to penicillin shortly after its discovery, and now we know that drug resistance (AMR) has evolved to almost every licensed antibacterial agent introduced. The beneficial function of antibiotics in treating bacterial illness was taken for granted during the golden era of antibacterial discovery, when numerous new groups were found and development of identified groups was quick. Antibiotics help lessen the bacterial infection load. Beta-lactam antibacterials (including penicillin, cephalosporin, and carbapenem), amino glycosides (including tobramycin), tetracycline, macrolides (including erythromycin), glycopeptides (including vancomycin), polymyxins (including colistin), and fluoroquinolones, all was expanded and launched between the 1940s and 1980s (including ciprofloxacin). Pleuromutilins, lipoglycopeptides, and oxazolidinones are three new antibiotic classes that have been introduced since 1990, though several variants of earlier classes have also been introduced. It took around two years to develop drug resistance against the Beta-lactam classes between 1940 and 1990, and nine to 16 years to develop against the other classes. Resistance to the oxazolidinone linezolid has emerged since its introduction in 1990(47).

Using omics technology, the mechanisms of acquiring resistance have been explained. Here are a couple such instances. Fluoroquinolones are antibiotics that inhibit bacterial DNA replication of bacteria by binding to DNA gyrase and topoisomerase, two enzymes involved in bacterial DNA replication. The alteration in the quinolone-binding location in the enzymes indicated overhead causes quinolone resistance in bacteria. A modification in the amino acid at the location of fluoroquinolone attachment to enzymes occurs as a result of the mutation. When both bacterial enzymes are altered, the quinolone antibiotic develops high-level resistance, impacting the prognosis of infection, as opposed to the case when just one of the enzymes is changed (48). Antimicrobial resistance in invading organisms may now be detected via a genetic test. The information is crucial since it will support infection treatment and management. After 24 hours of culture in the presence of oxacillin, the MRSA (methicillin-resistant Staphylococcus aureus) phenotype is observed. Prior to the advent of omics technology, the only way to discover resistance was through a time-consuming culture test. Changes in the penicillin-binding protein PBP2a govern MRSA. PBP2a production is regulated by the gene mecA. In reference laboratories, a polymerase chain reaction assay is utilized to identify the existence of mecA, but a commercially created kit can do so using a fluorescein-labeled mecA probe. When employed for analysis,

both DNA probe and PCR technique may identify the mecA-resistant gene presence within 3 hours. Antimicrobial resistance in infections may be detected quickly, allowing patients to receive appropriate therapy (49).

*Infectious Disease Treatment Response is determined by Genomic Factors*

The analysis of the host genomics becomes critical in order to properly comprehend pharmacological effects and, as a result, create more effective treatment strategies. The ultimate objective is to understand the system biological effect, but the trend of single gene effects is equally crucial.

The gene producing interleukin-10 (IL-10), a Th2 cytokine, is one of many polymorphic cytokine genes. The development of significant numbers of antibodies is linked to Th2 responses. Th1-stimulating cytokines suppress Th2 responses, and vice versa. Interferon alfa is a drug that stimulates cell-mediated immune responses and antiviral activity to treat chronic hepatitis C. Although interferon alfa is the most common treatment for chronic hepatitis C, reaction proportions are only approximately 50%, especially when combined with other antiviral drugs (50).

The cytokine environment of an infected person can indicate a strong cell-mediated immune response. Patients suffering from chronic hepatitis C who had the IL-10 genetic polymorphism, which results in reduced IL 10 expression, were five times more likely to have a good response to interferon alfa than those who did not have this polymorphism (51). Individuals with a genotype linked to high IL-10 production, on the other hand, were substantially less likely to respond to interferon alfa therapy (odds ratio, 0.22). The IL-10 genotype might be used to predict interferon alfa response. Indeed, an alternative therapy should be developed for those with chronic hepatitis C who have the IL-10 polymorphism, which is linked to increased cytokine production.

Immunologic memory is used in vaccines to create immune response, which protect us against disease in later exposures. To develop protective immunity, the immunological response to the vaccine should ideally mimic the one caused by the natural illness (52-56). Some people who appear to be healthy do not produce an immunological response to a vaccination. A good example is the reaction to the measles vaccination.

A study of healthy school children's antibody responses to the measles vaccination was done (56). Seronegative people were grouped in families, accounting for 10% of the population. This data strongly suggests a genetic influence. The researcher looked for a genetic influence and used HLA genes as a potential gene. Measles vaccination reactions were linked to both HLA class I and class II alleles. HLA-B7, HLA-B51, HLA-DRB1*13, and HLA DQA1*01, all was unified to a positive rejoin for the vaccination against (56-59). Homozygosity for HLA-B, HLA-DR, and HLA-DQA1 was linked to a lack of response to the measles vaccination (56,58).

It is possible that a lack of variety in antigen presentation is to blame for the low vaccination response. Use of vaccines as immune system probes is an innovative way to finding disease susceptibility genes. Vaccines are given to large groups of people. To track down the in general population by using the procedures presented, those who are not able to develop a protective immune response can be compared to those who do.

*Infection Treatment: Host Genomics Determines Drug Treatment Response*

Drugs used to treat any pathogenic infection can only be effective if we understand how the infection affects the host and pathogen at the genetic level and can explain host efficacy as well as toxicity. We examine a few key infectious diseases where pharmacogenomics research has resulted in a paradigm shift in disease therapy.

*Pharmacogenomics in Treatment of Tuberculosis*

Several DNA fingerprinting methods have been effective for subtyping Mycobacterial TB since the 1990s (60). Detecting groups of instances that might be linked to current transmission cases that require more intensive examination and possibly intervention is made feasible by identifying closely related strains (61). Whole-genome sequencing allows for considerably better subtyping than was

previously achievable, resulting in greater confidence in the inferred links between instances. Investigators in US TB control programs have now scaled up whole-genome sequencing to sequence isolates from all culture-positive cases countrywide, after utilizing it selectively for several years. Whole-genome sequencing has allowed public health officials in California to rule out more than half of probable outbreaks discovered by traditional genotyping, saving time and resources (Shaw T, California Department of Public Health: personal communication). Primary understanding in tuberculosis programs in the United Kingdom (62), Canada (63,64), and the Netherlands (65) has also confirmed that whole-genome sequencing aids more accurate investigations by extra precisely defining outbreaks (62,63,65), providing insights into transmission undercurrents (39,66), and occasionally indicating the presence of previously unidentified cases or possible "super-spreaders" that should be highlighted for exclusion and cure (62,63). Whole-genome sequencing can also reveal if recurring instances are due to relapse, which offers valuable insights into determining the efficacy of a program (67). Countries which have high disease burden of TB and are also under developed countries, might be in high incidence which bear the brunt amount of the world's TB burden, the ability to prioritize case investigations could be beneficial (68). In these countries, though, a new request of NGS of M. tuberculosis directly from sputum — could play an even more remarkable role (69). Straight sequencing of M. tuberculosis from smear-positive sputum samples is now possible in research laboratory (71-72), but it is expensive and time-consuming for normal healthcare settings usage. If the method can be made applicable in term of its cost effectiveness and practicality, it will allow for quick drug susceptibility inference, which is presently very accurate for most first-line medications and will improve as more data becomes available (70-73). In addition to aiding timely therapy with appropriate drugs, next-generation sequencing will reduce the need for routine phenotypic testing, which is complex, tedious, and difficult to sustain in resource-limited laboratory settings. Meanwhile, in high-income nations, an intermediate technique is already in use: whole-genome sequencing straight from early positive cells, a procedure that reveals drug susceptibility information weeks before standard test results are available (71). State Department of Health New York and Public Health Department, England (70) have received regulatory approval to forego traditional drug susceptibility testing of isolates predicted to be susceptible to all four first-line drugs (roughly 70 to 80% of all isolates) based on whole-genome sequencing (70).

Amplicon sequencing, which includes targeted polymerase-chain-reaction (PCR) amplification of specific mycobacterial genes or marker sequences, followed by sequencing of the amplicons, is another promising option (74). Any sequence-centered strategy for figuring susceptibility should be dependent on the constant updating of databanks containing linked genotypic and phenotypic data to remain relevant over time (72).

*Pharmacogenomics in Treatment of Malaria*

In 2010 and 2015, malaria occurrence and fatality rates raised by 21% and 29%, respectively (75). Deep sequencing is being used to uncover the genetic background of P. falciparum, the parasite that causes malaria. Polymorphisms, physical and counterfeit number changes, all of which are important for parasite development, are being identified (76). MalariaGEN and other sequencing consortiums help us better understand the genetics of both the Anopheles vector and the plasmodium species. Polymorphism incidences may be utilized as indicators of high recombination rates, which is a key provider to immune evasion and treatment confrontation, according to a current study on genotyping accuracy utilizing in-depth sequencing of Plasmodium parental generations and their offspring (77). A research found 18 deletions in areas encoding multigene families that are linked to immune evasion using whole genome profound sequencing and microarray analysis (78). The investigators discovered chromosomal crossings in six of the deletions and were able to calculate P. falciparum mutation rates (78).

Human genomics has remained under use to find new malaria resistance loci that give 33% protection against severe malaria (79). Transcriptomics and proteomics are increasingly being used to investigate Plasmodium

pathogenesis. The genome-wide translational dynamics of P. falciparum were studied using bioinformatics and statistical models, revealing that parasite transcription and translation are firmly connected, resulting in a wide range of parasite gene expression patterns with great resolution (80). Polysome profiling has been done using ChIP-Seq and RNA sequencing to better understand the control of Plasmodium gene expression in humans. Bunnik et al. 2013 (81) found a delay in peak polysomal transcript profusion for multiple genes relative to the mRNA fraction, which they attributed to non-coding transcript substitute polysomal mRNA splicing processes.

P. falciparum expression patterns have also been described using RNA sequencing, which has discovered unique gene transcripts, substitute splicing processes, and anticipated untranslated sections of certain genes, offering more data on parasite biology (82).

Yamagishi et al. (83) employed RNA sequencing to compare the transcriptomes of the human host and parasite. They found that some human and parasite genetic factors, such as TLR2 (Toll Like Receptors-2) and TIR domain-containing adapter molecule 2 (TICAM2), were linked to clinical manifestations. The transcriptome of P. vivax was also studied using RNA sequencing, which indicated a hotspot of vir genes on chromosome 2, novel gene transcripts, and the existence of species-particular genes (84).

*Pharmacogenomics in Treatment of Filaria*

Filariasis, along with onchocerciasis and lymphatic filariasis (LF), is a neglected chronic disease initiated by tissue-dwelling nematodes (filariae) which causes considerable health concerns, with a disease burden approaching 86 million people worldwide (85). Onchocerciasis is triggered by Onchocerca volvulus, whereas LF is caused by three parasites Wuchereria bancrofti, Brugia malayi, and Brugia timori (86). Filariasis elimination is difficult in resource-constrained nations due to a lack of sensitive diagnostic instruments, effective therapies, and adequate control measures.

The genomes of W. bancrofti and O. volvulus have been sequenced, allowing for additional genomic research (87,88). Bioinformatics showed the existence of genes coding for host immune system controllers such as human-like autoantigens and serine and cysteine protease inhibitors (91-89).

The filariasis as disease and human as its host, both shall be remained linked together, according to molecular research and computational analysis. Preliminary studies have indicated that LF infections cluster in some families (90,91). These findings suggest that genetic variables play a role in LF infection control, affecting both the presence and severity of microfilariae. However, as with a tropical lymphedema (Podoconiosis) of non-filarial origin, a GWAS would be more thorough in demonstrating this genetic predisposition to Lymphatic Filariasis (92). Note that lymphedema, also known as elephantiasis, is one of the most common symptoms of LF and is caused by a clogged lymphatic system (93). Podoconiosis, unlike LF, is a non-communicable illness caused by soil elements such as aluminium and silica, which are prevalent in volcanic regions (94, 95). A comparative genomics-based investigation of Lymphatic Filariasis might aid in gaining a better understanding of the clinical symptoms.

## CONCLUSION

Experience has demonstrated that infectious diseases will arise with greater vigor and ferocity. If diseases are not managed, they will have a significant impact on human wellbeing in terms of mortality and morbidity. Regardless of area, ethnicity, lifestyle, financial class, or ethnic origin, a developing microbial disease-causing infection would affect people's l ives. A s a result, the threat of infectious diseases is very serious, and its prediction as well as management is extremely difficult. In the future decades, major developments in genetics, genomics, and proteomics may be able to meet the challenge. These tools clearly have the prospective to transform the fields of diagnostics, therapy, as well as drug and vaccine research. The time has come to boost public health initiatives at the national and international levels, as well as omics research, in order to fully exploit the promise of systematic innovations that will lead to the era of personalized medicine based on pharmacogenomics.

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