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Integration of Pharmacogenomics into Clinical Practice: Opportunities and Challenges

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ABSTRACT

This potential of precision veterinary medicine to be implemented through the use of pharmacogenomics (PGx) by animal-based clinical practice is immense. This review brings out the species and breed specific genomic differences which affect drug clearance, and effectiveness and toxicity in animals. It also looks into the importance of principal active enzymes, including cytochrome P450s, UGTs and ABC transporters and the employment of genetically altered animal models, including CYP knockout mice and Beagles, in comprehending gene drug relationship. Methodologies used in veterinary PGx research, regulatory and ethical considerations and the utility of animal pharmacogenomics in drug discovery in animal preclinical studies are also discussed in the review. In spite of substantial advantages of the field, which are associated with better therapeutic results, fewer side effects, and a higher level of ethical animal tests, it has specific restrictions connected with unfinished genomic databases and the absence of guidelines on clinical implementation. In the current paper, the authors point at the necessity of joint efforts to develop genomic data, standardize veterinary testing procedures, and develop a framework that will promote incorporating PGx into standard veterinary practice and support the One Health approach.

Key Words:

Pharmacogenomics, Veterinary Medicine, Drug Metabolism, Animal Models, Precision Therapy

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1. INTRODUCTION

Pharmacogenomics or at the crossover of pharmacology and genomics provides the hope of personalizing drug treatment to the genetic makeup of an organism. This discipline is quick to find its relevance in veterinary medicine and animal research studies, and this is because researchers are learning how the species and breed genetic differences affect the drug metabolism and effectiveness, and their safety[1]. Contrary to human medicine where individualized medicine has taken substantial progress, the veterinary practice continues to struggle with the individualized approach to the pharmacotherapy of a population. This may result in development of adverse drug reactions, inappropriate dosing or therapeutic failures in

animals with special genetic profile[2]. Further, animal models also provide essential tools in preclinical studies which provides a standardized platform to study drug response to the genetic polymorphisms of the drug-it can finally provide more effective and safer treatment which is applicable to both animal and human population.

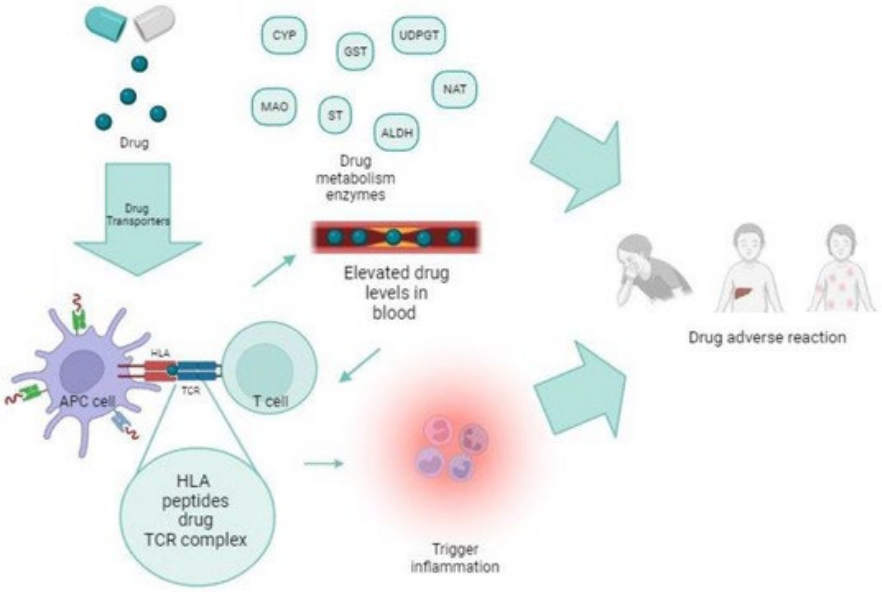

Figure 1: Pharmacogenomics in Clinical Practice[3]

Along with all of the potential benefits comes significant difficulty in implementing pharmacogenomics in a clinical veterinary setting. These are low supply of genomic data on different species of animals, the absence of standardized genotyping methods, incomplete regulatory measures, and the disease about awareness on the veterinary professionals. Moreover, the inter-species variability in drug-metabolism enzymes like cytochrome P450 (CYP) isoforms and UDP-glucuronosyltransferases (UGTs) makes it hard to interpret animal model findings. The aim of this review is to review what is currently known in animal pharmacogenomics, evaluate what the applicability of different animal models is, as well as outline the potential opportunity as well as obstacles of utilizing pharmacogenomic knowledge in clinical practice[4].

1.1 Background Information and Context

The first pharmacogenomic studies in animals involved compounding the necessity to comprehend variable drug reaction in preclinical research and Experimental animals kept with the householders[5]. Research in dogs, cat, rodents, and equines has identified vital polymorphisms of the drug absorption, distribution, metabolism, and excretion genes. As a demonstration, a mutation of MDR1 gene in herding dog breeds causes supersensitivity to any type of antiparasitic drug, whereas cat lacks vital UGT enzymes therefore ineffective glucuronidation. Meanwhile, mice and rats were a genetically engineered laboratory animal in order to model human metabolic pathways, allowing high-fidelity drug tests and toxicology tests. These trends validate the importance of pharmacogenomics in enhancing the level of patient care of veterinary patients as well as in enhancing the quality of animal models utilized in the process of human drugs development[6].

1.2 Objectives of the Review

The primary objective of this review is to explore how pharmacogenomic principles can be effectively integrated into veterinary clinical practice and preclinical animal research. Specifically, it aims to:

- To explore breed- and species-specific drug response variations.
- To review genomic and functional tools in animal pharmacogenomics.
- To analyze animal models used in gene-drug interaction studies.
- To identify regulatory and ethical challenges in veterinary PGx.
- To suggest future directions for personalized veterinary care.

1.3 Importance of the Topic

Since veterinary medicine can be characterized as a field that welcomes the principles of precision, the role of pharmacogenomics becomes more and more crucial[7]. By identifying the genetic variability of the animals used, not only could we improve the therapeutic process, reduce the adverse effects of a treatment but also be able to develop a decent animal model that could help in bridging the gap between the preclinical data and clinical trials carried out in humans. The implications of the implementation of pharmacogenomics in animal healthcare are intercontinental to the aspect of One Health in regard to drugs development, animal welfare and public health. The opportunities and the challenges involved in the interaction are therefore essential in driving further the veterinary practice and the development of the biomedical research[8].

2. PHARMACOGENOMIC VARIABILITY IN VETERINARY SPECIES: RESEARCH ADVANCES, METHODOLOGIES, AND CHALLENGES

Veterinary and preclinical studies of pharmacogenomics demonstrated the species and breed differences which impact drug efficacy and safety. The major genes, CYP2D15, MDR1, CYP3A and UGTs exhibit functional polymorphism in dogs, horses and cats with respect to metabolism and antidrug targets[9]. The current advanced methodology that includes whole-genome sequencing and functional enzyme assays, in addition to knockout models using the CRISPR-Cas9 technology can be used to map and validate pharmacogenes. Although such tools can improve translational knowledge and patient-specific veterinary treatments, they are faced with issues because of gaps in the genomic data and interspecies metabolic divergence, environmental factors, and how to translate pharmacogenomics to veterinary medicine at the regulatory level.

2.1 Summary of Key Research Studies

It has been demonstrated by many studies that pharmacogenomic similarities and differences are species- and breed-specific in companion animals, agricultural species, and preclinical models. As an example, the CYP2D15 gene in dogs, which plays an identical role to the corresponding human CYP2D6 gene, has substantial polymorphism that greatly influences the way that antidepressants and opioids (e.g., fluoxetine, tramadol and codeine) are metabolized,

leading to treatment failures or toxicity. The much more widespread mutation in the MDR1 (ABCB1) gene especially in Collies, Australian Shepherds and other herding breeds, involves an enzyme defect resulting in impaired P-glycoprotein transport, as a consequence exposing them to neurotoxicity in the form of ivermectin, loperamide, or other chemotherapeutics.

CYP3A isoform(s) and polymorphisms (P-glycoprotein, multidrug resistance-associated protein 1, ABC transporter) affect these drugs (NSAIDs-phenylbutazone, flunixin; anthelmintics-ivermectin, moxidectin) in equine species. As an illustration, the Thoroughbreds have a different rate in the breakdown of these drugs than ponies, which implies breed-specific dosing approaches. The same is true of cats, where impaired UGT enzymes (UGT1A6 and UGT1A9) weaken glucuronidation and so they are extremely sensitive to acetaminophen and some nonsteroidal anti-inflammatory medicines[10].

Genetically engineered rodents (CYP2D6, CYP3A4, UGT1A knock out mice) have enabled the researcher to sort out the metabolic pathways in the light of opioid pharmacokinetics and toxicity. These models attempt to simulate human drug metabolism and support the testing of the hypothesis of different pharmacogenomic applications prior to their clinical interpretation.

2.2 Methodologies and Findings

Veterinary and preclinical pharmacogenomic research employs a combination of genomic, proteomic, and metabolomic approaches to identify and validate drug-gene interactions:

- **Genomic Tools:**

Exome-Sequencing and Whole-Genome Sequencing (WGS) have dominated to map pharmacogenes in different classes of dogs and the reference genomes such as CanFam3.1 have been used to classify the breed-specific genetic variations. These methods yield an in depth perspective of drug metabolism coding and regulatory regions. To supplement this, SNP genotyping arrays can be utilized to interrogate specific genes of interest to pharmacogenetics such as cytochrome P450 enzymes (CYPs), UDP glucuronosyltransferases (UGTs) drug transporters such as members of the ATP binding cassette (ABC) and Solute carrier (SLC) families, and nuclear receptors such as Pregnane X Receptor (PXR) and Constitutive Androstane Receptor (CAR), all of which are instrumental in absorption, distribution[11].

- **Functional Assays:**

In vitro metabolic capacity is determined by enzyme activity assays in which liver microsomes are incubated with an appropriate substrate to enable researchers to measure the functional activity of the drug-metabolizing enzymes e.g. CYPs and UGTs. Along with these in vitro procedures in vivo phenotyping methodology involve exposing animals to the administration of probe drugs; including dextromethorphan to determine the activity of CYP2D15 and midazolam to illustrate the functioning of CYP3A, after the exposure parent drug-to-metabolite ratios in urine or plasma are analyzed. All these methods give us an idea of pharmacokinetics of action and enzymatic activity of various species and breeds[12].

- **Gene Editing and Knockout Models:**

Modifications of animals A variety of genetically modified animal models have been created via advanced gene-editing approaches, including CYP3A-null mice, UGT-null mice, and P-

glycoprotein (P-gp)-deficient mice. In these models it is possible to dissect the metabolic functions of individual enzymes and transporters by inhibiting them and then recording changes in pharmacokinetics and pharmacodynamics. These models are useful in drug metabolism, toxicity and disposal to give useful insights on the gene-specific functions in drug processing and also make beneficial applications in the veterinary and human translational pharmacogenomics.

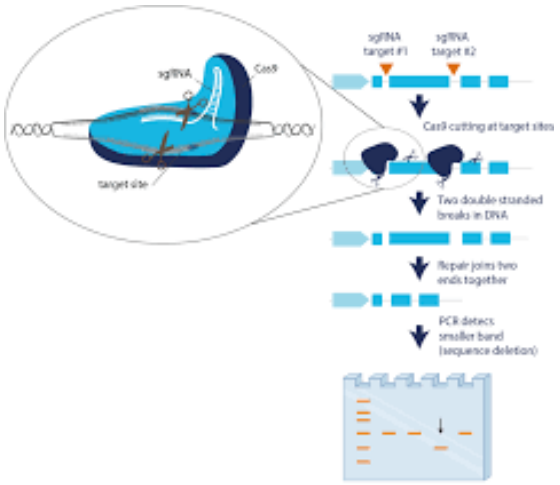

Figure 2: CRISPR-Cas9 Gene Knockout Models[13]

2.3 Critical Evaluation

Strengths:

- A limited setting in the laboratory reduces the variability in the environment and hence the reproducible and standard pharmacogenomic studies can be conducted.
- Knockout and humanized models are used to advance our knowledge into gene specific functions in drug metabolism, especially first-pass metabolism and CNS bioavailability.
- There are clinical implications to breed-specific observations in veterinary populations (e.g., dogs, horses, cats), informing safe and effective treatment approaches in food, companion animal and livestock practice[14].
- Animal models play crucial roles in the translational backdrop between in vitro pharmacology and clinical translation and particularly in case of newer drug entities.

Weaknesses:

- Many veterinary species genomic data is incomplete and the identification of new polymorphisms and gene-drug relations in less-studied species of animals such as goats, camels or birds may not be possible.
- Use of animal data in humans is frequently limited by interspecies variation in enzyme orthologs, tissue pattern of expression, and metabolic pathways (e.g. divergence in enterohepatic recirculation or renal transporter).

- The expression of genes and drug action may be affected by phenotypic plasticity and exposure to the environment (diet, microbiota, medications). This fact complicates the drug interpretation based on the pharmacogenomics.

- The existing regulatory systems (e.g., EMA, FDA-CVM) give little assistance to the integration of pharmacogenomics in the development of veterinary drugs, introducing an uncertainty with respect to labeling, the need to make dose modifications and the prediction of adverse events[15].

3. VETERINARY PHARMACOGENOMICS: SPECIES DIFFERENCES, MODELS, AND TOOLS

Veterinary Pharmacogenomic studies have shown large breed specific and species specific differences in drug metabolism as a result of polymorphisms in major enzymes and transporters, including mutations in the MDR1 gene in herding breed dogs or UGT deficiencies in cats. Extensive preclinical experiments in CYP and UGT knockout mice, Beagles, pigs and non-human primates assist in investigating gene-drug interactions and making prediction of the response in humans. Laboratory methodologies include genomic tools, such as GWAS, NGS and qPCR, bioinformatics tools, including Ensembl and the Dog Genome Project, functional assays, including microsomal incubations, liver slice models, probe drug phenotyping, and transporter activity assays, combined with a complete framework, to advance precision medicine in veterinary and translational pharmacology[16].

3.1 Pharmacogenomic Variability in Veterinary Species

The pharmacogenomic variability plays a very important role in the drug response, safety, and efficacy across breeds and species since the genes responsible in the metabolism of the drugs and transporters in veterinary species vary:

- **Dogs**:

The so-called herding dogs which include Collies, Australian Shepherds, and Shetland Sheepdogs are commonly affected by the mutation(s) in the MDR1 (ABCB1) gene that encodes P-glycoprotein, a key efflux transporter at the blood-brain barrier. The nonfunctional P-gp has been found to lead to greater penetration of drugs into CNS which results in neurotoxicity upon encountering drugs such as ivermectin, loperamide, vincristine and acepromazine etc.

As well, CYP2B11 polymorphisms influence barbiturate metabolism, and CYP2D15 variation influences the biotransformation of antidepressants, opiates, and other drugs acting upon the central nervous system, especially in Beagles and Greyhounds. Because of these breed specific variations, careful dose calibration and drug choice is also needed[17].

- **Horses**:

Polymorphisms that have been identified to have an impact on oral bioavailability and the clearance of drugs in equine pharmacogenomics include CYP3A subfamily of genes, transporters (e.g., ABCB1, SLCO1B3) of drugs that include NSAIDs, corticosteroids, macrolide antibiotics, and anthelmintics. There is faster metabolism of certain drugs in

thoroughbreds and the Standardbreds than the ponies or draft horses and this requires breed-specific treatments.

- **Cats**:

Feline impairment in the glucuronidation pathways predisposes feline to drug toxicity. They lack or have low activity of UGT1A6, UGT1A9, and UGT2B7 that are essential enzymes in Phase II processes. Because of this, medications such as acetaminophen, aspirin, benzodiazepines and morphine are simply incapable of being processed in a satisfactory manner, making them result in adverse effects (severe or even death) at therapeutic levels[18].

- **Other species**:

Less information is available in cattle, sheep and goats where early results indicate interspecies differences in the expression and functional element of CYP isoforms. By way of an example, sheep have slower clearance of some antiparasitics compared to cattle, perhaps related to differences in hepatic enzymes. There is a marked advancement in the study of food residue and withdrawal issues in pharmacokinetics modeling and residue depletion modeling in pigs and chickens.

3.2 Animal Models in Preclinical Research

Animal models remain essential in pharmacogenomics to dissect gene-drug interactions and predict human pharmacological outcomes:

Figure 3: Animal Models in Preclinical Research[19]

- **Rodent Models**:
    - **CYP Knockout Mice:** Deletion of CYP genes such as CYP3A, CYP2D6 or CYP1A2 in mice allowed the scientists to emulate drug metabolism in humans, study metabolic bottlenecks and forecast the occurrence of drug-drug interaction. Even more of a reflection upon human pharmacokinetics are humanized models, i.e. mice expressing human CYPs[20].
    - **UGT Knockout Mice:** It is useful to investigate drugs that are subject to glucuronidation (e.g. morphine, acetaminophen, mycophenolic acid). Compensatory metabolic pathways are observed in knockout models and

responses to hepatotoxicity or nephrotoxicity are observed in the absence of glucuronidation.

They even use dual or multiple knockout models to focus the effects of polygenes over drug disposition.

- **Dog Models:** Canine models are the gold standards in veterinary drug development because they are well characterized genetically, they are relatively sized and their pharmacokinetic outcomes can be predicted accurately. They find regular usage in the process of evaluating oral bioavailability, cardiovascular safety, CNS activity, and long term toxicity. Translational information is accessible on polymorphism in CYP1A2, CYP2B11, UGT1A and P-gp in Beagles[21].
- **Large Animal Models:** Pigs (and minipigs in particular) are becoming popular in preclinical testing owing to the fact that they share a certain physiological similarity to human beings, especially concerning the skin, the GI system, and liver metabolism. They are beneficial in xenobiotic, cardiovascular and dermal metabolism research.
- **Non-Human Primates:** These are relied upon cases where proximate genetic similarity, or metabolic similarity with humans is required, particularly in drug research based on the immunologic or neurologic response. The unacceptability and expenses infringe on mass consumption.

3.3 Methodological Tools

Veterinary pharmacogenomic studies employ a multi-tiered methodological framework that integrates genomics, bioinformatics, and functional validation:

Genomic Tools

The genome-wide association studies (GWAS) play a crucial role in defining the correlation of particular single nucleotide polymorphisms (SNPs) and the phenotypic trait like the selection of drugs, adverse reactions, or the rate of metabolism in veterinary subjects. GWAS can be utilized to identify breed-specific pharmacogenomic variants by assessing variation among different populations of animals or animal breeds, which promote personalized veterinary medicine. Such studies are particularly useful in organisms with specified genetic lineages such as in dog species and horses whereby the known phenotypic variety is well established[22].

High-throughput analysis of known and novel genetic variants in pharmacogenes across species can be performed with Next-Generation Sequing (NGS) technologies such as whole-genome and whole-exome sequencing. Such platforms network accurately summarize non-coding and coding areas of drug metabolism and transport. In complement of these techniques, quantitative PCR (qPCR) and digital PCR are applied in accurate quantifying gene expression, copy number variations and validation of specific SNPs in drug-metabolizing genes such as CYPs, UGTs, ABCB1, and nuclear receptors like PXR and CAR, serving as helpful sources of information about inter-individual and inter-breed pharmacogenomic variations[23].

Bioinformatics Platforms

In veterinary pharmacogenomics, bioinformatics tools like the Ensembl Genome Browser, the NCBI and the UCSC Genome Browser are invaluable, with links to annotated genomes, variant databases and gene ontology in several species. These resources give the researchers a scavenge through the structures of genes, variations in transcripts and known polymorphisms in essential pharmacogenes to help discover species- and breed-specific pathways by which drugs are metabolized. This Dog Genome Project is very useful in the canine research and this gives detailed genomic information pertaining to the breed-specific characteristics, heritable diseases and genes affecting drug responses so as to use the pharmacogenomic information in a much more specific way in treatment of the veterinary medicine[24].

Also, available tools of comparative genomics allow alignment of genes across species and, therefore, researchers can determine the conservation of evolution, orthologs and domains of functional significance to pharmacogenes. These comparisons are then critical in the translation of findings of model organisms (e.g. rodents) into the target species such as dogs, cats, or horses. In silico prediction of genetic variants is applied to provide an idea about the functional importance of genetic variations using tools like SIFT, PolyPhen-2 and PROVEAN. These algorithms analyze the amino acid replacements and in order to predict their impact on protein structure and functioning, these applications aid in prioritising potentially harmful mutations to be further experimentally evaluated.

- **Functional Assays**

Functional assays are highly important in veterinary medical pharmacogenomics, in vitro functional assays are used to measure drug metabolism and enzyme activity. By incubating the animals liver microsomes (or intestinal microsomes) of animals, which have been put in a test tube with or without drug material, researchers can estimate drug biotransformation and enzyme repression or induction, and determine major metabolic paths of drugs. These assays prove especially applicable in the study of cytochrome P450 enzymes and UDP-glucuronosyltransferases. The precision-cut liver slice assays represent a more physiologically relevant model because the tissue architecture and the cell variety of the liver are preserved and the phase I and phase II liver metabolism can be evaluated alongside cytotoxicity, all at a controlled ex vivo environment[25].

Other in vivo probe drug phenotyping methods supplement these methods by involving the administration of marker substrates (e.g., midazolam to test CYP3A; dextromethorphan to test CYP2D) to animals and examination of urine or plasma drug-to-metabolite ratios as evidence of drug metabolism individuality. The method is useful in categorising individuals or breeds as poor, intermediate or rapid metabolisers. Also, transporter activity assays are performed where cell models such as MDCK-MDR1 or Caco-2 cells would be used to determine the presence of efflux transporters and uptake transporters such as P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) in the permeability and tissue distribution of drugs. Such tests help to develop inter-species differences in drug absorption and penetration of the central nervous system[26].

4. REGULATORY AND ETHICAL CONSIDERATIONS IN VETERINARY PHARMACOGENOMICS

Veterinary pharmacogenomics is a new area that holds the opportunity of better therapeutic efficacy, safety of animals, but it is underrepresented in the official regulatory channels. In contrast to human pharmacogenomics, in which regulatory agencies (FDA and EMA) have developed guidelines on how to incorporate genetic information in drug registration, no harmonized global standards exist on the regulation of veterinary drugs. Such regulatory agencies as the FDA Center for Veterinary Medicine (FDA-CVM) and the European Medicines Agency Committee for Medicinal Products for Veterinary Use (EMA-CVMP) are usually concerned with the safety, efficacy and residue analyses of drugs, disregarding species-specific pharmacogenomic variability. The use of pharmacogenomic data in the context of the veterinary drugs is not legally required upon their submission, though certain data, such as breed-specific profiles of adverse drug reactions (ADR) can be voluntarily provided. This knowledge gap hinders the pace of personalized veterinary medicine and restrictions in accessing genetically individualized dosing recommendations[27].

Ethics are also of paramount concern due to the ever growing access to genetic tests in companion species. Genotyping breeds like MDR1 mutation in herding dogs is now a clinical reality that enables veterinarians to prevent an asymptomatic but life-threatening drug toxicity exerted by such drugs as ivermectin. The emerging market in commercial genetic testing, however, contributes to the fear of the misuse, such as overdiagnosis, overuse of exclusion to treatment procedures, or genetic stigmatization. Moreover, general reproducibility and clinical importance of pharmacogenomic results are discounted because there are not any uniform testing commissions beyond species and breeds. There is still no consensus on the validation, interpretation, and reporting of tests, so there is a big possibility of discrepancy in results in distinct laboratories.

Data governance-wise, dilemma and increased necessity are arising to develop an ethical standard in genomic data collection, storage, and sharing in the veterinary sphere. Animal genetic material biobanks and repositories, e.g. canine and feline genome projects, are still developing and are commonly fragmented in terms of organization, e.g. in both academic and privately held institutions. A policy that guarantees de-identified sharing of secure data can be facilitated to establish collaborative research by preserving ownership rights and the sensitive natures of breeders or owners. The implication of veterinary pharmacogenomics are also spilled over into the One Health framework and, in particular, the One Health contexts like antimicrobial stewardship[28]. By learning about the область pharmacogenomic effects on antibiotic metabolism in animals, one may be able to create a prevention of these subtherapeutic dosage and could perhaps even reduce the potential of antimicrobial resistance and decrease the threat of zoonotic transmission, as well. Within this wider framework, the utility and potential application of pharmacogenomics on veterinary practice should not only extend to animal welfare, but also to health concerns of the population and the environment which further pays a major role in the development of global health policies in their totality.

Table 1: Overview of Selected Studies on Pharmacogenomics and Nutrigenomics[29]

Author(s)	Study	Focus Area	Methodology	Key Findings
Roosan et al. (2023)[30]	Opportunities to integrate nutrigenomics into clinical practice and patient counseling	Nutrigenomics integration in clinical care	Qualitative review and analysis	Highlighted potential of genomics-based dietary personalization; emphasized need for clinician training.
Sukri et al. (2022)[31]	Systematic review on the cost-effectiveness of pharmacogenomics in developing countries	Pharmacogenomics cost-effectiveness	Systematic review	Identified challenges such as poor infrastructure; noted potential for long-term cost savings.
Ta, Cayabyab & Coloso (2019)[32]	Precision medicine: A call for increased pharmacogenomic education	Pharmacogenomic education in healthcare	Opinion-based educational review	Stressed lack of training as barrier; urged integration of pharmacogenomics in medical curricula.
Tafazoli et al. (2021)[33]	Applying next-generation sequencing platforms for pharmacogenomic testing in clinical practice	Clinical application of NGS in PGx	Review of current applications and technologies	NGS found effective and scalable; challenges include interpretation and data integration.
Turner et al. (2020)[34]	Pharmacogenomics in the UK NHS: Opportunities and challenges	Implementation of PGx in healthcare system	Case study and policy analysis	Recognized PGx potential; implementation limited by systemic constraints; called for national strategy.

5. DISCUSSION

It is highlighted that pharmacogenomics plays a crucial role in the improvement of veterinary therapeutics and preclinical research to help in the understanding of how genetic

polymorphisms in drug-metabolizing enzymes and transporters affect responses to drugs interspecies. It highlights the advantages of personalized dosing to enhance the treatment response and decrease adverse effects and in companion animals, also, the safe development of drugs and antimicrobial stewardship within the One Health approach[35]. There remain, however, issues of concern, such as a limited amount of genomic information on most species, the absence of uniform testing methods, inadequate regulatory incorporation, and the ethical aspect of using genetic information. These gaps should be filled by future studies: by increasing genomic databases, creating cost-effective diagnostic tools, proving genotypephenotype relationships, and improving ethical, regulatory, and interdisciplinary framework to guide mass clinical implementation..

5.1 Interpretation and Analysis of the Findings

This review demonstrates the body of evidence growing in favor of pharmacogenomics as a crucial element in the enhancement of veterinary medicine as well as preclinical studies. The genetic polymorphisms in drug, metabolizing enzymes (e.g., CYP2D15, CYP3A, UGTs) and transporters (e.g., MDR1/ABCB1, SLCO1B1), and their impact on drug absorption and metabolism, as well as drug efficacy and toxicity, have highlighted that the conventional one-size-fits-all philosophy cannot address the needs of all species evenly[36]. The examples of breed-specific differences in dogs and horses, the differences in the metabolic ability of cats, illustrate that unidentified pharmacogenetic variability may lead to adverse drug reaction or treatment failure. The use of genetically modified rodent models, e.g. CYP or UGT knockout mice, can yield important mechanistic data on drug metabolism applicable both to animal and human pharmacogenomics. Finally, advanced genomic methodologies, such as genome wide association studies (GWAS) and next generation sequencing (NGS) have effective applications in determining the gene-drug interaction and metabolic phenotypes, which further support its implementation in furthering precision veterinary medicine.

5.2 Implications and Significance

The implementation of pharmacogenomics in the veterinary clinical practice can become a revolutionary step to increase levels of therapeutic precision, reduce adverse drug effects, and advance the animal welfare. With drug dosing being breed- or species-specific, depending on the genotype, treatment results can be much better, especially in cases of companion animals in which frequent therapeutic-monitoring might not be a routine[37]. The pharmacogenomic data attained in animal study in preclinical drug development has assisted in decreasing the translational gap between laboratory results and human usage, thus creating drug development safer and more productive. Moreover, pharmacogenomics helps to achieve the objectives of public health within the One Health ancillary since it allows prescribing anti microbial medication to necessary individuals in the correct dosage, which can prevent the emergence of antimicrobial resistance. Ethical use of genetic testing also provides the veterinarians with evidence-based approaches, which enhances the faith of pet owners, clinicians, and pharmaceutical developers.

5.3 Gaps in Knowledge and Future Research Directions

Although much has been achieved, there are some gaps experienced in the extensive application of pharmacogenomics to veterinary medicine:

- **Poor Genomic Coverage:** Genomic databases of the majority of veterinary species, particularly livestock and exotic species are still incomplete hampering identification of novel polymorphisms and clinically useful variants[38].
- **Standardization Deficits:** The results are inconsistent, as there are no standardized guidelines between veterinary laboratory pharmacogenomic testing.
- **Regulatory Gaps:** The regulatory regimes of the FDA-CVM and EMA-CVMP currently lack requirements and systematic integration of pharmacogenomic data into the process of approving veterinary drugs. Clinical use and pharmaceutical investment are restricted by this inactivity.
- **Ethical Supervision:** Genetic examination rapidly reaches commercialization so there are concerns of utilizing information erroneously, inadequate validation, and deficiencies of owner-data on genetic results[39].

Further improvement must now be made in the bank of pharmacogenomic data in underrepresented species, cost effective genotyping platforms to be done to serve routine clinical practice, and in verification of the genotype-phenotype correlations through large scale breed-diverse clinical trials. It is also necessary to develop interdisciplinary collaboration to develop standardized frameworks of testing, enhance regulatory channels, and set ethical principles of gathering, sharing, and interpreting veterinary genetic data[40].

6. CONCLUSION

The inclusion of pharmacogenomic in veterinary care is a major step towards precision animal care. Pharmacogenomics can help identify species- and breed-specific genetic differences that affect drug metabolism, absorption and efficacy and thus help in designing more precise and patient-tailored treatment plans that improve therapy outcomes and minimizes adverse drug reactions by revealing the species-specific and breed specific genetic differences that affect drug metabolism, absorption and efficacy. The approach has the advantage of helping clinical veterinary practice and also enhancing the translational value of pre-clinical research, and help to achieve global health, including fighting antimicrobial resistance using the One Health approach. Nevertheless, to reach all its potential, the following crucial obstacles should be overcome and overcome, such as the insufficiency of genomic data presented on a variety of species or unstandardized testing practices, regulatory environments, and the ethical objections to the use of genetic information. Priority in the future should be put on continued construction of rigorous veterinary pharmacogenomic databases, validation of clinical use in large-scale studies, and development of more cost-effective testing technologies, as well as building multidisciplinary relationships to guarantee safe and effective ethical conduct. The emergence of such innovations makes pharmacogenomics a potentially revolutionary way to make veterinary medicine turn out to be more evidence-based, personalized, and open to global problems.

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