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Editorial

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Current Insights into Pharmacogenomics of Noncoding RNAs for Cancer Therapy

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1. Introduction

Cancer remains a significant global health challenge, with varying incidence and mortality rates across the globe. According to the Surveillance, Epidemiology, and End Results (SEER) registry [1] and the American Cancer Society (ACS) [2], more than 2 million new cancer cases are expected in the US by 2025. Understanding the burden of disease and advancements in tailored treatments, also known as precision or personalized medicine, is crucial for improving patient outcomes. Pharmacogenomics is the study of how an individual's genetic makeup influences their response to treatment [3]. This field aims to identify genetic variations among individuals (pharmacogenomic variants) to predict drug efficacy and the risk of adverse drug reactions, thereby optimizing and personalizing treatment while minimizing side effects for patients [4]. In the last decade, attention has increasingly shifted beyond the traditional coding genome to noncoding RNAs (ncRNAs), which serve as key regulators of gene expression and biomarkers in cancer, adding complexity to tumor signaling networks.

2. Pharmacogenomics and Noncoding RNAs

Population pharmacogenomics explains individual differences in treatment response due to genetic germline variations in specific genes, such as CYP2D6 [5]. Advances in next-generation sequencing and computational bioinformatics have enabled the detection of thousands of rare variants; however, their phenotypic functions remain unknown [6]. In claims data from the Swiss population [7], drug switching among escitalopram users was found to be more common in younger patients (under 20 years of age) and in women. A Japanese study [8] used pharmacogenomic data on CYP450 enzymes to predict pharmacokinetic changes caused by genetic variants in drugs commonly used among Asian populations. A pharmacogenomic study in Chinese patients examined polymorphisms in DNA-thioguanine nucleotide metabolism to inform precision dosing for thiopurine therapy [9]. We have recently reported the whole-genome transcriptome profiling of *Withania somnifera*, highlighting its potential benefits for neurodegenerative diseases [10]. Although this study primarily highlighted modulation of significant genes involved in neurodegeneration by *Withania*, an additional regulatory layer arises from noncoding RNAs, functional molecules that, though untranslated, influence translation, genome defense, and gene expression at both transcriptional and post-transcriptional levels [11]. These include microRNAs (miRNAs), long noncoding RNAs (lncRNAs), long intergenic noncoding RNAs (lincRNAs), circular RNAs (circRNAs), small nucleolar RNAs (snoRNAs), piwi-interacting RNAs (piRNAs), vault RNAs (vRNAs or vtRNAs), tRNA-derived small RNAs (tsRNAs), etc. Our studies on *Withania* indicate extensive involvement of noncoding RNAs, including miRNAs, lncRNAs,

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and circRNAs, in mediating its health-beneficial effects (data not published), and they explain, in part, the pharmacokinetic profile differences observed between males and females [12].

ncRNA expression levels are known to be dysregulated in various cancers. Some examples include the well-studied lncRNA MALAT1, in lung, colorectal, prostate, breast, liver cancers, and glioma [13]; lncRNAs HOTAIR and GAS5 in breast cancer; the miRNAs miR-221/222 in stomach and prostate cancers; miRNA miR-106a in colorectal, pancreatic and prostate cancers [14]; circRNAs circ-FOXO3 in lung cancer [15] and circRNA-MYLK in bladder cancer [16].

ncRNAs alter mRNA expression by post-transcriptional modifications. For instance, Tabnak et al. [17] have elucidated the involvement of ncRNAs in the modification of N6-methyladenosine (m^6A), which in turn dysregulates the Wnt pathway and promotes tumorigenesis and cancer progression. piwiRNAs have also been implicated in epigenetic histone and DNA modifications, tumor growth, cancer metastasis, chemoresistance, and modulation of other noncoding RNAs [18]. To date, four human vault RNAs (vtRNA1-1, 1-2, 1-3, and 2-1), part of a ribonucleoprotein 'vault complex', have been discovered and investigated in the context of cancer [19]; Ferro et al. [20] studied the roles of vtRNA1-1 in apoptosis resistance, tumorigenesis, cell proliferation, and chemoresistance. Hu et al. found that tsRNA-5001a promotes cell proliferation in lung adenocarcinoma and is also implicated in its recurrence [21]. We have also previously reported the pharmacogenomics of miRNAs in osteosarcoma [22], miRNAs in cancer chemoprevention and chemoresistance [23,24], lncRNA-miRNA interactions [25] and noncoding RNAs in various solid tumor malignancies, such as multiple myeloma [26], malignant mesothelioma [27] and prostate cancer [28,29].

An association between the rs7958904 polymorphism in the lncRNA HOTAIR and cervical cancer has been established in Bangladeshi women [30]. The Manolopoulos group in Greece has reported that the *MIR27A* rs895819 CC genotype results in reduced miR-27a-3p expression, thus serving as a marker of fluoropyrimidine response in cancer therapy [31]. Interestingly, Su et al. [32] established noncoding RNA regulatory networks and studied drug-target interactions. The integrative approach employed in this study facilitated the identification of key therapeutic targets for the treatment of various cancers. Moving forward, an integrative pharmacometrics approach that combines knowledge of pharmacokinetics, pharmacogenomics, noncoding RNAs, receptor pharmacology, preclinical data, and human clinical trials will be necessary to develop a holistic model that will be useful in drug discovery, biomarker discovery, and precision dosing in cancer, as we have discussed in detail earlier [33,34].

3. Noncoding RNAs in Cancer Diagnosis and Therapy

ncRNAs can serve as non-invasive biomarkers in diagnostic techniques such as liquid biopsies, alongside conventional markers like cell-free DNA (cfDNA) and circulating tumor DNA (ctDNA) [35,36]. They can also be detected in body fluids such as blood and urine; Yuan et al. identified a circulating 4-lncRNA panel from blood samples with value in diagnosing non-small cell lung cancer [37]. miRNAs mediate signaling pathways that facilitate communication between tumor cells and their microenvironment [38], and also crosstalk with lncRNAs [39]. Their sensitivity and specificity compared to traditional markers have been demonstrated in certain cancers, e.g., prostate cancer [40]. ncRNAs also have therapeutic potential in two main contexts: they can either compensate for the loss of function of downregulated RNAs (replacement therapy) or suppress overexpressed RNAs. An example is miRNA-based therapy, where mimics that emulate and restore the functions of endogenous miRNAs, or miRNA antagonists that downregulate miRNA expression, are both being explored [41]. Several strategies are available for delivering ncRNAs to their targets, including viral or plasmid vectors, liposomes, natural or synthetic nanoparticles, and cell-derived exosomes.

4. Challenges in Precision Oncology Implementation

Significant advances are made each year in noncoding RNA research, uncovering new functions and regulatory networks. Multiple ncRNAs may regulate a single gene or target several mRNAs each, while interacting with other ncRNAs. We have also previously described such intricacies [28,29] and their implications in translational medicine [25]. Moreover, an ncRNA might target oncogenes in a certain cancer while itself functioning as an oncogenic molecule in another, such as the miRNA miR-10 [42].

Winkle et al. broadly classify the major hurdles of therapeutic implementations into those of immunogenicity, specificity, and delivery, and describe innovative solutions to each [43]. The mechanistic challenge of specificity is arguably the most critical, as ncRNAs can share sequence homology with endogenous RNAs, and non-specific binding of therapeutics may lead to the silencing of unintended targets. Further, even if the molecule

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binds to the intended target and executes its function, it is challenging to accurately modulate every upstream or downstream consequential effect linked to the respective regulatory network(s). Additionally, ncRNAs, as a class of RNA, have a relatively short half-life [44,45] due to their intrinsic temperature sensitivity and susceptibility to nucleases and hydrolysis, both *in vitro* and *in vivo*. They are also rapidly cleared from the system [46], threatening their structural stability, complicating delivery, and reducing their circulating time. Moreover, their negative charge and hydrophilic nature complicate cellular uptake. Local administration of therapeutics and optimizing carriers has been suggested to protect ncRNAs from degradation and ease entry into the cellular membrane.

The importance of a pharmacometrics perspective cannot be overstated, as the pleiotropic and context-dependent actions of ncRNAs complicate traditional pharmacokinetic and pharmacodynamic workflows, as well as the development of biomarker panels for cancer diagnosis and screening. As ncRNA research and its applications are still emerging, they cannot yet be evaluated against existing standards of molecular and bioinformatics techniques. Many ncRNAs, not being protein-coding, are also not well-conserved between species, making it difficult to interpret their functions and extrapolate pre-clinical findings from animal models in model-informed drug development (MIDD). Therefore, existing regulatory models must adapt their frameworks accordingly. MIDD can reduce 'financial toxicity' for patients; however, to be effective in precision oncology, it must rely on models developed from existing patient data [33]. In addition, as we have discussed previously [47], it is important to consider the sociocultural context, particularly when applying pharmacogenomic models to autochthonous and vulnerable patient populations.

5. Conclusion and Future Perspectives

There is a pressing need to integrate pharmacogenomics and pharmacogenetics into the pharmacometric healthcare paradigm at a global level. [33]. In this context, the highly successful implementation of pharmacogenetics and personalized medicine in clinical practice in Spain, based on electronic health records, by Llerena et al. [48], popularly known as the MedeA (*Medicina Personalizada Aplicada*, Applied Personalised Medicine) initiative, is laudable. This can serve as a benchmark and roadmap for implementing similar programs worldwide to improve patient care. The data on genomics of noncoding RNAs in various diseases, including but not limited to cancer [49,50], is scattered in the scientific literature, such as the widely-studied role(s), as biomarkers, and otherwise [51], of the noncoding RNA interactome—mainly miRNAs, lncRNAs, and circRNAs [52,53]—in cardiovascular diseases [54], neurodegenerative diseases [55,56], inflammatory diseases [57, 58], diabetes [59,60], sepsis, pulmonary diseases, and several more. Also released recently are two valuable databases, both maintained by the Cui laboratory at Peking University, visualizing noncoding RNAs and their links to diseases: the Human microRNA Disease Database (HMDD), which holds over 53,000 manually compiled miRNA-disease associations [61], and the LncRNADisease v3.0 database that has collected over 13,000 lncRNA associations and 12,000 circRNA associations with disease [62]. Harnessing this resource through machine learning and data analysis and integrating it into a clinically actionable framework for personalized drug prescribing, similar to the MedeA approach, could prove highly beneficial for the patient community at large and for clinicians in particular. Figure 1 exemplifies a sample workflow for clinical pharmacogenomics. Future precision medicine approaches in cancer may likely incorporate the role(s) of noncoding RNAs as drivers of diseases, companion diagnostics, and biomarkers for therapeutic intervention.

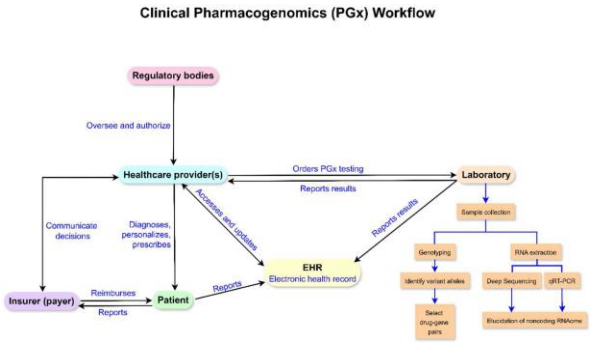

Figure 1: Workflow for clinical pharmacogenomics. Adapted from [63,64].

List of Abbreviations

ACS	American Cancer Society
cfDNA	Cell-free DNA
circRNAs	Circular RNAs
ctDNA	Circulating Tumor-derived DNA
HMDD	Human microRNA Disease Database
lincRNAs	Long Intergenic Noncoding RNAs
lncRNAs	Long Noncoding RNAs
MedeA	*Medicina Personalizada Aplicada* (Applied Personalised Medicine)
MIDD	Model-Informed Drug Development
miRNAs	MicroRNAs

mRNA	Messenger RNA
ncRNAs	Noncoding RNAs
piRNAs	Piwi-interacting RNAs
SEER	Surveillance, Epidemiology and End Results
snoRNAs	Small Nucleolar RNAs
tsRNAs	tRNA-derived Small RNAs
vRNAs/vtRNAs	Vault RNAs

Author Contributions

Writing—original draft, Investigation, Writing—review and editing, Visualization: A.B.; Writing—review and editing: Y.Z.; Conceptualization, Resources, Writing—review and editing, Supervision, Project administration: S.N.

Conflicts of Interest

The authors declare no conflicts of interest.

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