Genomed Connect
ISSN: 3006-9033
2025, Article ID. x, Cite as: https://www.doi.org/10.69709/xxx

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OPEN ACCESS

Editorial

Current Insights into Pharmacogenomics of Noncoding RNAs for Cancer Therapy

Running Title: ***Genomics of Noncoding RNAs in Cancer***

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ISSN: 3006-9033
2025, Article ID. x, Cite as: https://www.doi.org/10.69709/xxx

Keywords: pharmacogenomics; noncoding RNA; cancer therapy; personalized medicine; pharmacometrics

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], estimated new cancer cases in the US will be over 2 million in 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 seeks to identify genetic variations among individuals (pharmacogenomic variants) in order to predict drug efficacy and the likelihood of adverse drug reactions, thereby optimizing and personalizing treatment outcomes while minimizing side effects to the patient [4]. In the last decade, increasing attention has 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 the individual differences in treatment response due to genetic germline variations in a select few genes, for instance CYP2D6 [5]. Advances in next-generation sequencing and computational bioinformatics have enabled detecting thousands of other rare variants, however their phenotypical

functions are still unknown [6]. Using claims data in the Swiss population [7], drug switching amongst users of the antidepressant escitalopram was more likely in the younger population (less than 20 years old) and women. A Japanese study [8] employed pharmacogenomic data on CYP450 enzymes and predicted human pharmacokinetic changes due to genetic variants for drugs used in Asian populations. A pharmacogenomic study in Chinese patients studied polymorphisms in DNA-thioguanine nucleotide metabolism to inform precision dosing for thiopurine therapy [9]. In recent times, we have recently reported the whole genome transcriptome profiling of *Withania somnifera* with 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 are untranslated but nonetheless 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* show extensive involvement of noncoding RNAs including miRNAs, lncRNAs and circRNAs in mediating the health-beneficial effects of *Withania* (data not published) and explain, in part, pharmacokinetic profile differences between males and females [12].

The expression levels of ncRNAs 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 leading to 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 in various solid tumor malignancies such as multiple myeloma [26], malignant mesothelioma [27] and prostate cancer [28, 29].

The association between rs7958904 polymorphism in the lncRNA HOTAIR with 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 in this study enabled the identification of core therapeutic targets for therapy 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 be used as non-invasive biomarkers in diagnostic techniques such as liquid biopsies besides conventional markers such as cell-free DNA (cfDNA) or circulating tumor-derived 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 within and with their microenvironment [38], and also crosstalk with lncRNAs [39]. Their sensitivity and specificity compared to traditional markers has been demonstrated in certain cancers, e.g. prostate cancer [40]. ncRNAs also have potential in therapeutic use, mainly in two contexts; they can either compensate for the functions of downregulated RNAs (known as 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]. There are numerous options for delivering ncRNAs to their targets – using viral or plasmid vectors, liposomes, natural or manufactured nanoparticles, or cell-derived exosomes.

4. Challenges in precision oncology implementation

Substantial leaps are made in the domain of noncoding RNA research each year, unearthing new functions and 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 issue of specificity is arguably the most challenging one; as ncRNAs can be sequentially homologous to endogenous RNAs, non-specific binding of therapeutics can lead to silencing of unintended targets. Further, even if the molecule 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, being a class of RNA, have a relatively short half-life [44, 45] owing to being intrinsically temperature sensitive and more vulnerable to nucleases and hydrolysis, both *in vitro* and *in vivo*. ncRNAs 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 complicates 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; these pleiotropic and contextual actions of ncRNAs complicate traditional pharmacokinetic and pharmacodynamic workflows and the development of signature biomarker panels for cancer diagnosis and screening. Since ncRNA research and application is an emerging field, it cannot be held to 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' to the patient, however, to be efficient in precision oncology, it must use models developed from existing patient data [33]. In addition, as we have discussed previously elsewhere [47], it is important to appreciate the sociocultural context especially when applying pharmacogenomic models to autochthonous and vulnerable patient populations.

5. Conclusion and Future Perspectives

There is, indeed, a pressing need to integrate pharmacogenomics and pharmacogenetics as part of the pharmacometric healthcare paradigm globally [33]. In this context, the very successful implementation in clinical practice in Spain of

pharmacogenetics and personalized medicine 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 similar programs to be implemented worldwide to benefit the patient. 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 **H**uman **m**icroRNA **D**isease **D**atabase (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 approaches and further enabling its integration into a clinically actionable framework of personalized drug prescription akin to the MedeA approach will prove beneficial to the patient community at large and 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.

Genomed Connect
ISSN: 3006-9033
2025, Article ID. x, Cite as: https://www.doi.org/10.69709/xxx

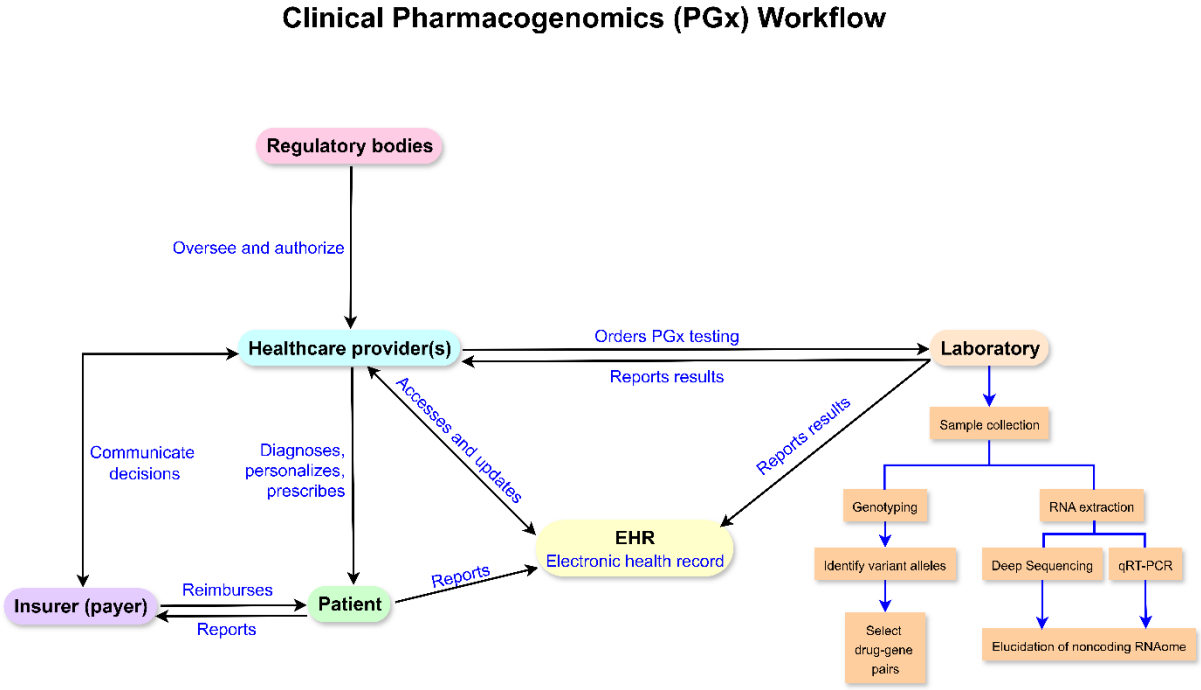

Figure 1. Workflow for clinical pharmacogenomics. Adapted from [63] and [64].

List of Abbreviations

- **SEER** – Surveillance, Epidemiology and End Results
- **ACS** – American Cancer Society
- **ncRNAs** – Noncoding RNAs
- **miRNAs** – MicroRNAs
- **lncRNAs** – Long Noncoding RNAs
- **lincRNAs** – Long Intergenic Noncoding RNAs
- **circRNAs** – Circular RNAs
- **snoRNAs** – Small Nucleolar RNAs
- **piRNAs** – Piwi-Interacting RNAs
- **vRNAs / vtRNAs** – Vault RNAs
- **tsRNAs** – tRNA-derived Small RNAs
- **mRNA** – Messenger RNA
- **cfDNA** – Cell-free DNA

- **ctDNA** – Circulating Tumor-derived DNA
- **MIDD** – Model-Informed Drug Development
- **MedeA** – Medicina Personalizada Aplicada (Applied Personalised Medicine)
- **HMDD** – Human microRNA Disease Database

Author contributions

Writing – original draft, Investigation, Writing – review and editing, Visualization: AB; Writing – review and editing: YZ; Conceptualization, Resources, Writing – review and editing, Supervision, Project administration: SN.

Ethics statement

The authors declare that this work does not involve any original research with human or animal participants. All data and studies discussed have been previously published and are publicly available.

Funding

The authors declare that no financial support was received for the authorship of this article.

Conflicts of interest

The authors declare no conflicts of interest regarding this manuscript.

Acknowledgment

The authors would like to acknowledge JGraph Ltd. and draw.io AG for the draw.io/app.diagrams.net visualization application, Source: https://github.com/jgraph/drawio

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