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PHARMACOGENOMICS OF THYROIDITIS AND OVARIAN CANCER: AUTOIMMUNITY AND ONCOLOGY OF PRECISION MEDICINE

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Abstract

Background: *The introduction of pharmacogenomics in clinical practice is a paradigm shift towards personalized medicine, which allows the use of individualized therapeutic approaches in accordance with respective genetic profiles. Though a lot of progress has been made in the area of oncology, especially in ovarian cancer, the use of pharmacogenomic principles of autoimmune diseases like thyroiditis has not been fully explored.*

Purpose: *The purpose of the review is to provide a synthesis of existing evidence on pharmacogenomic biomarkers and their clinical use in thyroiditis and ovarian cancer, to explore common mechanism pathways, and to establish the gaps in research that need to be addressed by scholars in the future.*

Findings: *In ovarian cancer, sound pharmacogenomic data and clinical utility on the use of BRCA1/BRCA2 and homologous recombination deficiency (HRD) testing to select a PARP inhibitor has been reported, with further prognostic potential of ADME gene variants (ABCB1, ABCC2, ABCG2, UGT1A cluster) and multi-gene expression signature. Pharmacogenomics enables clinicians to customize the treatment plan, decrease the adverse effects, and improve patient outcomes by determining the genetic factors of drug metabolism, efficacy and toxicity.*

Conclusions: *Although ovarian cancer pharmacogenomics has reached clinical maturity and actionable biomarkers allow selecting the treatment, thyroiditis needs specific genomic and pharmacokinetic investigations to develop evidence-based personalized treatment programs. To achieve the full potential of pharmacogenomics in both conditions, future studies ought to focus on functional classification of variants, multi-omic integration, population-based validation and implementation science.*

INTRODUCTION

1.1 Pharmacogenomics The Promise of Pharmacogenomics in Medicine.

The research of the effect of genetic variation on drug response has come to be known as pharmacogenomics and will become a pillar of precision medicine [1]. Pharmacogenomics enables clinicians to customize the treatment plan, decrease the adverse effects, and improve patient outcomes by determining the genetic factors of drug metabolism, efficacy and toxicity. Over the last 20 years, the field has experienced dramatic progress as it has moved

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out of hypothetical potential to clinical practice in the variety of therapeutic contexts.

The fact that pharmacogenomic-guided therapy is rationale-based and is grounded on well-established principles of pharmacokinetics and pharmacodynamics. Drug exposure to and absorption by the body and effect on tissues and those on drug targets can be significantly affected by genetic polymorphism in drug metabolizing enzymes (especially the cytochrome P450 family), in drug transporters (ATP-binding cassade and solute carrier families), and in drug targets [2]. These genetic determinants have been recognized, and the regulatory guidelines of various agencies such as the Food and Drug Administration (FDA) and the Clinical Pharmacogenetics Implementation Consortium (CPIC) now offer dosing recommendations on many drug-gene interactions.

1.2 Thyroiditis: Clinical Scenario and Therapy Problems

Thyroiditis is a heterogeneous collection of inflammatory thyroid infections, the most regular being autoimmune thyroid infections (comprising of Hashimoto thyroiditis and Graves disease). These involve the destruction or stimulation of thyroid tissue and is mediated by immunological processes which result to hypothyroidism and hyperthyroidism, respectively. Autoimmune thyroid disease is found in the world at a rate of 5-20 percent according to the geography and the criteria used in its diagnosis; however, it is predominant among women [3].

The main forms of standard treatment of hypothyroid thyroiditis include replacement therapy using levothyroxine thyroid hormone, and hyperthyroid disorders could be treated using antithyroid drugs (methimazole, propylthiouracil), radioactive iodine ablation, or thyroidectomy. Although these therapeutic modalities are widely used, there is a great disparity in response to treatment, dosage needs and adverse effects profile among interindividuals. The patients respond to standard dosing schedules with a rapid euthyroid response and some need a long period of dose adjustment and some of the patients develop unremitting symptoms despite a biochemical normalization of thyroid functional tests.

Such clinical heterogeneity implies that drug response is genetically predetermined, and that the genetic determinants of drug response have not been fully characterized. Moreover, autoimmune thyroiditis patients might need they be treated with concomitant immunomodulatory agents or treatment of related autoimmune diseases, which add another pharmacogenomic concern of drug-drug interactions and polypharmacy.

1.3 Ovarian Cancer A Pharmacogenomic Success Story.

Ovarian cancer is the deadliest gynecologic cancer and its total worldwide occurrence is estimated to be more than 300,000 cases in a year and the survival rate after 5 years is about 45 percent [4]. Approximately 70 per cent are of high-grade serous ovarian carcinoma (HGSOC) which is late-onset, diffusively spread through the peritoneum, and is initially sensitive to chemotherapy but ultimately develops platinum resistance in the majority of patients.

The conventional treatment paradigm is consisting of cytoreductive surgery and chemotherapy (typically carboplatin and paclitaxel) based on platinums. There is however a big difference in clinical responses with some patients realizing a lasting complete response and others a fast course of disease despite same treatment regimens. This treatment response heterogeneity has contributed to the rigorous research on predictive biomarkers.

Another breakthrough in cancer pharmacogenomics is the finding that germline and somatic mutations in BRCA1 and BRCA2 genes make them sensitive to platinum chemotherapy and poly(ADP-ribose) polymerase (PARP) inhibitors [5]. The BRCA mutations are present in approximately 15-20% of ovarian cancers, and another group has the phenotype of BRCAnessa, which is homologous recombination deficiency (HRD) caused by the epigenetic silencing of BRCA, mutations in other DNA repair genes or other mechanisms [6]. The success of pharmacogenomic discoveries into clinical intervention achievements are the clinical evidence of BRCA/HRD testing and regulatory approval of multiple PARP inhibitors (olaparib, niraparib, rucaparib).

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1.4 Rationale and Objectives

Although the clinical and pathophysiological distinctions between autoimmune thyroiditis and ovarian cancer seem quite obvious, some conceptual similarities are worth being mentioned. These two conditions have large interindividual differences in response to treatment, they both follow intricate interactions between genetic predisposition and environmental factors, and they both can be addressed through personalized treatment by molecular biomarkers.

Moreover, it is observed that there is some emerging evidence of possible mechanistic links between autoimmunity and cancer. A classic characteristic of autoimmune diseases, chronic inflammation, has already been implicated in carcinogenesis by a series of mechanisms such as oxidative damage to DNA, immune homeostasis, and cellular signaling pathway alteration [7]. On the other hand, immune therapy of cancer has shown that autoimmune phenomena can be induced by perturbation of immune checkpoints, which also points to the interdependence of immune homeostasis and malignancy.

The purpose of this review is to: (1) review the existing evidence on pharmacogenomic biomarkers in thyroiditis and ovarian cancer; (2) address the research questions on common mechanistic pathways and potential research opportunities; (3) outline clinical application and implementation issues; and (4) provide research gaps that need to be filled by future studies. This analysis aims at contributing to the overall objective of precision medicine in different disease settings by connecting knowledge in autoimmunity and oncology.

2. Pharmacogenomics in Thyroiditis: Status and Knowledge needs

2.1. Thyroiditis treatment landscape

Pharmacological therapy of thyroiditis depends on the type of a subdisorder and a clinical manifestation. In hypothyroid disorders caused by Hashimoto thyroiditis or in post-ablative patients, levothyroxine (synthetic T4) is the treatment option. The objectives of treatment are the biochemical euthyroidism (restoration of normal levels of thyroid-stimulating hormone and free thyroxine) and elimination of the clinical manifestation. Even though the practice of thyroid hormone replacement may seem to be quite straightforward, there are still significant issues on clinical practice.

It is a common practice that dose optimization may take several changes during months or even years with significant interindividual differences in dose needed to reach target thyroid function tests. The requirements of levothyroxine depend on such factors as body weight, age, thyroid function remaining, gastrointestinal absorption and comorbid medication. Nevertheless, despite considering these clinical variables, there remains unaccounted variability, which implies the existence of genetic determinants of drug disposition and response.

In the case of hyperthyroidism, antithyroid drugs like methimazole and propylthiouracil are used which prevent the production of thyroid hormone by inhibiting iodination of thyroglobulin through thyroid peroxidase. The effect is variable in these agents, and the remission rates following medical therapy vary between 20 and 60% depending on the severity of the disease, the size of the goiter, and the levels of the antibodies [8]. Other severe side effects, such as agranulocytosis and hepatotoxicity, have a small yet clinically significant proportion of patients, indicating the possibility of genetic variants that can identify patients at risk.

2.2 Lack of Thyroiditis-Specific drug Pharmacogenomic Evidence.

As an overall literature search indicates, there is an alarming lack of pharmacogenomic research specifically in the area of thyroiditis drug response. Thyroiditis is a field that has not been substantially addressed in terms of precision medicine as compared to such areas as oncology, cardiology and psychiatry where substantial evidence has been produced in terms of pharmacogenomic. This gap in knowledge is a serious drawback in the sphere and should be seen as a serious request to conduct specific studies.

There are a number of possible reasons behind this deficit that should be considered. To start with, the apparent ease of thyroid hormone replacement therapy might have deterred the study of genetic determinants, on the premise that dose-setting by use of biochemical surveillance suffices to overcome interindividual disparities. Second, the relatively

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mild disposition of thyroiditis in comparison with other life-threatening diseases like cancer can have been the cause of decreased research priorities. Third, lack of a clear pharmacogenomic success story in the autoimmune diseases that could be compared to BRCA testing in cancer may have held back passion in exploratory studies.

In spite of such evidence gap, there are some general principles of pharmacogenomics that indicate a number of possible candidate genes and pathways that should be examined in thyroiditis. These are drug-metabolizing enzymes, drug transporters, thyroid hormone receptors, and immune related genes which might affect the response to treatment, dose response and susceptibility to adverse effects.

2.3 Candidate Pharmacogenomic Pathways in Thyroiditis .

2.3.1 Genes of Drug Metabolism and Transport.

Even though there is no direct evidence, it is extrapolated based on the general principles of pharmacogenomics that the variability of absorption, distribution, metabolism, and excretion (ADME) genes can determine the response to thyroiditis treatment. The absorption of levothyroxine is most common at the small intestine through passive diffusion and active transport. Thyroid hormones are taken up in the cell by organic anion-transporting polypeptides (OATPs), which are the products of the SLCO gene family and could affect bioavailability [9].

SLCO1B1, the gene encoding OATP1B1, has been investigated in the literature on the pharmacokinetics and toxicity of statins at the level of polymorphisms. As OATP1B1 is also implicated in transport of thyroid hormones, it cannot be ruled that the level of genetic variation in the activity of the transporter could influence the absorption and systemic exposure of levothyroxine. Likewise, the presence of gene variations in efflux transporters including P-glycoprotein (coded by ABCB1) could have an impact on the distribution and excretion of thyroid hormones.

The peripheral conversion of T4 to T3 is done by deiodinase enzymes (DIO1, DIO2, DIO3). In population studies, polymorphisms in deiodinase genes have been linked with the difference in the levels of thyroid hormone and metabolic parameters [10]. The variants of levothyroxine therapy and whether these variants determine the efficacy of the therapy or cause patients to be under the focus of possible combination T4/T3 therapy is an open question that has not been studied prospectively yet.

In case of antithyroid drugs, the enzymes of cytochrome P450 have the potential to influence the metabolism and toxicity of the drug. Methimazole is hepatially metabolized, and hereditary deviations in metabolic ability have the potential to affect both efficacy and the risk of adverse effect. Although Propylthiouracil-induced hepatotoxicity is uncommon, it is a severe complication, which might have a genetic predisposition element, including human leukocyte antigen (HLA) alleles or other genetic elements related to immunity.

Thyroid hormone receptor variants Thyroid hormone Thyroid hormone receptor (T3) and thyroid hormone receptor (T4) are glandular hormones produced by the thyroid gland.<|human|>Thyroid Hormone Receptor Variants Thyroid hormone Thyroid hormone receptor (T3) and thyroid hormone receptor (T4) are thyroid hormones, glandular hormones secreted by the thyroid gland.

The genomic effects of thyroid hormones are mediated by the thyroid hormone receptors (TR -, TR -, coded by THRA and THRB). The syndromes of thyroid hormone resistance are the rare mutations in these genes which result in the heightened levels of thyroid hormone with normal or excessively high TSH. Frank resistance syndromes are also rare; however, variants of receptors that are less obvious may have a hypothetical effect on the dose-response relationship of levothyroxine treatment.

The relationship between metabolic phenotypes, cardiovascular risk, and bone density and polymorphism in thyroid hormone receptor genes has been studied in population studies. Nevertheless, they have not been critically studied in establishing the response to the treatment of thyroiditis patients. This is a rational target of future pharmacogenomic studies based on the central role of these receptors in mediating the action of thyroid hormone.

2.3.3 Genetic Factors which are Immune-Related.

Autoimmune thyroiditis is caused by the loss of immunological tolerance to thyroid antigens, and is

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facilitated by cellular and humoral immunities. HLA alleles (or HLA-DR3), especially, PTPN22 and other genes associated with the immune system have been well-researched as genetic predisposers to autoimmune thyroid disease [11]. Nonetheless, the interaction amid the disease susceptibility genes and the response to treatment has not been studied.

When applying immunomodulatory therapies to thyroiditis, it is likely that genetic variants that affect immune functioning may also have an effect on response to immunomodulatory therapy. As an illustration, glucocorticoids, rituximab or other immunosuppressive medications can be administered in patients with refractory Graves' disease or severe thyroid eye disease. Genetic predictors of immunosuppressive drug response have been established in pharmacogenomic research in rheumatology and transplantation medicine and it could be suggested that this type of research be applied to thyroiditis.

2.4 Thyroiditis Pharmacogenomics Research priorities.

In order to fill the existing knowledge gap, there are a number of research priorities:

Candidate Gene Studies: The first step involves research on candidate genes that have high evidence of the ADME (CYP family members, UGT enzymes, SLCO and ABC transporters) and deiodinase genes with proven genotyping panels in groups of thyroiditis patients with extensive pharmacokinetic and treatment response information.

Genome-Wide Association Studies (GWAS): The approach that is unbiased on a genome-wide basis can serve to reveal new genetic determinants of treatment response, dose requirements or adverse effects that would not be anticipated by existing mechanistic knowledge.

Pharmacokinetic Studies: Mechanism level Pharmacokinetic analyses that compare genetic variations with the levothyroxine absorption, distribution, and elimination values would give enlightenment on the mechanism and be able to distinguish variants with functional implications.

Longitudinal Cohort Studies: Prospective cohorts of standardized treatment plans, systematic outcomes measures and biobanked samples would allow a robust investigation of genetic foretellers of enduring treatment accomplishment, superior living, and impregnable events.

HLA Typing and Adverse Event Risk: Since the involvement of HLA alleles in drug hypersensitivity has been already determined, the exploration of HLA correlations with antithyroid drug toxicity (agranulocytosis, hepatotoxicity) is a high-priority application of safety pharmacogenomics.

The use of the pharmacogenomic testing in the treatment of thyroiditis is not based on evidence but speculative until such studies are carried out. Funding on research and networked efforts on the field would contribute significantly to the creation of the background evidence necessary in the application of precision medicine.

3 Ovarian Cancer Pharmacogenomics: Known Biomarkers and Clinical Uses.

3.1 BRCA1/BRCA2 and Homologous Recombination Deficiency- The Central Role.

One of the most affected pharmacogenomic discoveries in cancer therapy is the finding that the presence of germline BRCA1 and BRCA2 mutations predisposes the presence of ovarian cancer and determines the response to treatment. BRCA1 and BRCA2 encode proteins that are needed in homologous recombination (HR), the high-quality repair pathway of DNA double-strand breaks. HR is compromised in BRCA loss, and the cells are forced to repair with alternative repair pathways that are inaccurate and use poly(ADP-ribose) polymerase (PARP) enzymes to repair single-strand breaks [12].

In general, approximately 15-20% of the ovarian cancers carry the germline BRCA mutations, and another 5-7% have the somatic BRCA mutations. BRCA-mutant tumors have been shown to be more sensitive to platinum-based chemotherapy, which causes the formation of crosslinks in DNA, and the repair of which depends on HR. It has been established in clinical studies that patients with BRCA-mutant ovarian cancer treated with platinum-based regimens have a better progression-free survival and overall survival than do BRCA-wild-type patients [13].

BRCAness is not limited to frank BRCA mutation, but it is a larger phenotype of homologous recombination deficiency (HRD). The mechanisms that have led to HRD include:

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Epigenetic silencing: BRCA1 promoter methylation is found in about 1015% ovarian cancers and phenocopies genetic BRCA1 loss [14].

Other mutations in other HR genes: The mutation of RAD51C, RAD51D, BRIP1, PALB2, and other components of the HR pathway may result in HRD.

Genomic signatures: There are some genomic scars (large-scale changes in state, loss of heterozygosity, telomeric allelic imbalance) that are evidence of genetic impairment of HR, and that can be assessed using commercial technologies.

The validated assays are now a part of clinical practice, and the BRCA mutation status is measured in combination with the genomic instability scores by using HRD testing. Those tests can identify a wider range of patients who are likely to respond to DNA-damaging treatments and PARP inhibitors besides patients with blatant BRCA mutations [15].

3.2 PARP Inhibitors: Synthetic Lethality to Clinical Benefit.

Synthetic lethality, in which a two genetic or pharmacological perturbation is non-lethal by itself, but when the two are combined together the cell dies has been beautifully used to develop PARP inhibitors of BRCA-deficient cancers. PARP enzymes are involved in the repair of single-strand breaks; their inhibition of the process in cells with an HR causes the accumulation of unhealed DNA damage, fork collapse, and apoptosis [16].

Various PARP inhibitors have been approved by the regulators to treat ovarian cancer:

- Olaparib The first-in-class PARP, has been approved as maintenance therapy in platinum-sensitive recurrent ovarian cancer and first-line maintenance in BRCA-mutant or HRD-positive metastatic ovarian cancer.
- **Niraparib**: It is recommended as a maintenance therapy in BRCA-positive or negative malignancies that have the greatest effects on people with HRD.
- **Rucaparib:** Recommended to treat BRCA-mutant recurrent ovarian cancer and platinum sensitive recurrent disease maintenance therapy.

The maintenance therapy using PARP inhibitors has shown a significant progression-free survival in patients with BRCA-mutant and HRD-positive groups, with clinical trials. SOLO-1 study, which assessed the maintenance use of olaparib after the initial platinum-based chemotherapy in BRCA-mutated ovarian cancer, demonstrated a tremendous 70% decrease in risk of disease progression or death (hazard ratio 0.30) [17].

The combination of BRCA/HRD test and application of PARP inhibitor therapy is a paradigm of successful pharmacogenomic application in the field of oncology. It is currently suggested that all epithelial ovarian cancer patients should undergo universal germline and somatic BRCA testing, and those who are BRCA-wild-type undergo HRD testing to inform treatment decisions [18].

3.3 Mechanisms of resistance to PARP Inhibitors and Platinum Therapy

Most ovarian cancers develop resistance to platinum chemotherapy and PARP inhibitors, despite such responses. The knowledge of resistance mechanisms is fundamental to devising strategies to overcome resistance or prevent resistance as well as to determinants of biomarkers that can predict failure of treatment.

Secondary BRCA Reversion Mutations: BRCA genes have the best-characterized resistance mechanism, where secondary mutations in BRCA genes are seen to revert the open reading frame and resume protein expression. The revert mutations may occur in several ways such as deletion of the initial mutation, deletions within intra-genes, or replacement of the bases. Reverse mutations in floating tumor DNA might be detected and used as a biomarker of the next approach to failure in treatment and initiate the idea of alternative medicine [19].

- **Homologous recombination restoration:** In addition to BRCA reversions, homologous recombination can be restored by means of loss of 53BP1 (a protein that facilitates non-homologous end joining and silences HR in BRCA1-deficient cells) or by Homologous recombination upregulation of RAD51. RAD51 foci formation functional assays which determine whether a patient will respond to a PARP inhibitor have been suggested as predictive biomarkers of the response [20].

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- **Drug Efflux and Pharmacokinetic Resistance:** Overexpression of efflux transporters, especially, P-glycoprotein (coded by ABCB1) may decrease the intracellular concentrations of the PARP inhibitors. ABCB1 and other transporter genes have polymorphisms that could be contributing factors to baseline drug exposure and primary or acquired resistance.
- **Replication Fork Stabilization:** PARP inhibitors generate replication stress which replication fork stabilization can be resistant. The loss of PTIP or CHD4 has been associated with the fork stabilization as well as resistance to PARP inhibitors in preclinical models.

The implications of learning about these various mechanisms of resistance include the treatment sequencing, combination strategies and biomarker development. Functional assays, which directly determine HR capacity, could be better than genomic biomarkers in prediction of treatment response and inform therapy choice.

3.4 Variants of ADME Gene and Chemotherapy Responses.

In addition to BRCA/HRD biomarkers, germline mutations in drug-metabolizing enzymes and transporters genes change chemotherapy pharmacokinetics, toxicity, and responses in ovarian cancer. These ADME (absorption, distribution, metabolism, excretion) forms are a complementary pharmacogenomic aspect, which involves drug handling and not tumor biological.

ATP-binding cassette (ABC) Transporter Variants.

Transport of efflux of chemotherapeutic agents between cells is mediated by ABC transporters, as well as affecting tumor sensitivity and normal tissue toxicity. A number of polymorphisms in the genes of ABC transporter have been implicated in the consequences of ovarian cancer:

- **ABCB1 (P-glycoprotein):** There is an overall survival correlation with the presence of the polymorphism of the ABCB1: rs1 045642 in the ovarian cancer patients undergoing platinum-based chemotherapy. This synonymous form influences mRNA folding and protein expression, which can have an effect on the capacity of drugs to exit the body [21].
- **ABCC2 (MRP2):** Nominal association with outcome of higher survival in an electronic medical record-germline genotyping interaction between the Pharmacogenetics Ovarian Cancer Knowledge to Individualize Treatment (POCKIT) study [22] with the rs2273697 variant in ABCC2.
- **ABCG2 (BCRP):** The polymorphism of ABCG2 (rs3219191) was included in a pharmacogenetic prognostic score that has stratified patients into high- and low-risk groups in terms of overall survival (hazard ratio 1.8), progression-free survival (hazard ratio 2.0), and platinum-free interval (hazard ratio 1.9) [23].

Phase II Metabolism, UGT1A Cluster Variants.

Uridine diphosphate glucuronosyltransferase (UGT) enzyme is an enzyme that catalyzes glucuronidation which is a significant phase II metabolic route in the majority of drugs and endogenous substances. Chemotherapy toxicity and outcome in a variety of cancer types have been linked to variants in the UGT1A gene cluster.

In ovarian cancer, UGT1A cluster polymorphs rs10929302 and rs2741045 were also associated with the above pharmacogenetic prognostic score, having independent survival endpoints associations. Such variants can either impact the metabolism of chemotherapeutic drugs or endogenous mechanisms that impact tumor biology and treatment responses [23].

3.4.3 Cytochrome P450 Variants

The platinum agents and taxanes are not mainly metabolized by cytochrome P450 enzymes, however, CYP variants can have an impact on the effects via effects on endogenous metabolism, drug-drug interactions, or effects on supportive care drugs metabolism. The POCKIT study found nominal relationships between CYP2A61801272 and CYP2E118070673 and overall survival but the mechanism behind the associations needs to be uncovered [22].

The variants of the Solute Carrier (SLC) Transporter are described.

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Solute carrier transporters facilitate cellular intake of many substances such as chemotherapeutic drugs. The variant of SLCO2B1 rs2306168 was found to be linked to overall survival in POCKIT study and this may have been as a result of its impact on platinum uptake or other pharmacologically relevant substrates [22].

Multi-gene expression signatures and proteogenomic biomarkers exemplify the second method that has been proposed as an alternative approach to microarray analysis (Asagai et al., 2017).

In addition to the single-gene biomarkers, the multi-gene expression signatures and integrated proteogenomic signatures provide greater predictive capabilities due to their ability to reflect complicated biological phenotypes and pathway functions.

IndividCRS: A Validated Chemotherapy Response Signature: This paper presents the results of a prospective cohort study conducted by the authors on the prediction of chemotherapy response across 10 cancer treatment and chemotherapy groups, involving 302 individuals and 1424 course-years of therapy.

The IndividCRS (Individualized Chemotherapy Response Score) is a 16-gene signature of expression created by a combined evaluation of more than 2,200 samples of ovarian cancer in numerous cohorts. This signature is an indicator of platinum response and is associated with status of HRD, which can be used as supplementary information to genomic HRD testing [24].

The IndividCRS paradigm shows that transcriptomic signatures of cellular condition can reflect functional impacts of varied genetic and epigenetic modifications, that may recognize platinum-sensitive tumors with no typical HRD indicators. Validation of these signatures within clinical trials is a prerequisite to their implementation in routine practice.

COXEN: Co-Expression Extrapolation of Drugs In silico Prediction Co-expression extrapolation (COXEN) is a predictive drug in silico assay system in which a co-expression of two proteins is observed to predict the toxicity of compounds in vivo (Yu et al., 2005).

The COXEN (Co-Expression Extrapolation) methodology utilizes gene expression profiles to predict drug response across diverse tumor types and model systems. COXEN-predicted paclitaxel, cyclophosphamide and topotecan in a retrospective study of recurrent ovarian cancer showed better survival in patients getting drugs that were recommended by the biomarkers [25].

Overall survival was essentially better in patients receiving predicted therapies using COXEN by about 21 months relative to patients receiving non predicted therapies. Although these retrospective results are hypothesis-generating, they end up justifying the possible usefulness of expression-based drug selection and therefore require prospective validation in biomarker-driven clinical trials.

3.5.3 Proteogenomic Integration

Newer data is indicating that theoretically combined analysis of genomic, transcriptomic and proteomic data can find predictive biomarkers that are better than those found by genomic alone. Proteomic research on ovarian cancer has shown that the protein-level changes are not necessarily associated with genomic changes and it has been found that post-transcriptional and post-translational regulation are important [26].

Proteomic signatures have the potential to identify PARP inhibitor responders who genomic testing with BRCA /HRD cannot detect, which could increase the number of individuals who could benefit with targeted therapy. Furthermore, phosphoproteomic could depict activated signaling pathways which serve as vulnerable to therapy or combination therapy.

Biomarker-guided therapy choice and patient-derived models represent the subject of the last two chapters of the book.

The existing models of patients-derived xenografts (PDX) and organoid models allow the evaluation of drug sensitivity in a particular tumor, which represents the basis of a one-to-one selection of the choice of a therapy. An experimental study of a cohort of ovarian cancer PDX models revealed that biomarker-guided matching of tumors to targeted therapy was possible, and almost 90% of PDX models sensitive to at least one biomarker-directed therapy [27].

Although the time frame to establish PDX and drug testing (normally some months) makes them not applicable in the fast-evolving disease, they can guide

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the choice of treatment in the maintenance or recurrent environment. Patient tumor derived organoid models provide more rapid turnaround and can permit real-time functional drug sensitivity analysis to direct treatment choice.

3.7 Genome-Wide Association Studies: NRG3 and BRE Variants.

Germline polymorphisms linked to ovarian cancer survival and treatment outcomes have been determined by genome-wide association studies (GWAS). Two fragments, NRG3 rs1649942 and BRE rs7572644, were first discovered by GWAS and then confirmed in a different cohort [28].

Allele A of NRG3 rs1649942 and allele C of BRE rs7572644 demonstrated associations with survival that were dependent on disease stage, with the observed effects varying according to the stage at diagnosis. Although the functional mechanisms of these associations are not fully understood, these variants can be regarded as prognostic variables and their consideration as multi-variant prognostic variables should be considered.

4 Common Mechanistic Processes and Transversal Opportunities.

4.1 DNA Repair Signaling: Cancer Susceptibility to Autoimmune Immunology.

DNA repair processes are an essential cell process, whose application is not limited to cancer biology. The therapeutic value of repair pathway vulnerabilities is demonstrated by the clinical success of the purposeful repair deficiency approach to BRCA-mutant ovarian cancer using the PARP inhibitor agents.

Recent findings are also indicating that DNA repair pathways might also be involved in autoimmune disease although the relationships are not direct as in cancer. The fault of repairing DNA may result in the concentration of cytosolic DNA, which causes the activation of innate immune sensors, including cGAS-STINGDNA sensing pathways. Chronic activation of these pathways in preclinical models has been shown to induce autoimmune characteristics [29].

Moreover, oxidative stress, which is the characteristic of inflammation in the autoimmune illnesses, causes a damage in DNA which needs effective repair system. The genetic variations in DNA repair capacity could be a source of susceptibility to autoimmune diseases, as well as a response to immunomodulatory therapy, but this assumption must be proved experimentally.

In the context of pharmacogenomics, the general concept of therapeutic advantage by targeting certain molecular vulnerabilities is applicable to all disease models. Similarly to how BRCA deficiency produces artificial lethal interactions between PARP inhibition and cancer, discovering molecular weaknesses in autoimmune diseases would allow the creation of targeted therapies that would be more effective, with fewer adverse effects, than general immunosuppression.

4.2 The immune pathways and pharmacogenomics are quantified

Immune system has leading roles in autoimmunity as well as in cancer immunosurveillance implying possible common principles of pharmacogenomic in immunomodulatory therapy.

4.2.1 HLA Pharmacogenomics

Human leukocyte antigen (HLA) alleles are some of the most diverse genetic factors in the human genome that are essential in antigen presentation and immune recognition. HLA pharmacogenomics has been proven to have clinical utility in prediction of drug hypersensitivity reactions with well validated associations such as HLA-B57:01 and abacavir hypersensitivity, and HLA-B15: 02 and Stevens-Johnson syndrome caused by carbamazepine [30].

HLA alleles have been shown to determine the susceptibility of an individual to autoimmune diseases and, probably, response to treatment. There is an example of HLA-DR3 being closely related with the risk of Graves disease. It has not yet been investigated whether HLA alleles also determine response to antithyroid drugs or immunomodulatory therapies in thyroiditis, but is a logical direction to research.

HLA typing has also attracted interest in immunotherapy as far as ovarian cancer is concerned. The effect of immune checkpoint inhibitors requires the presentation of tumor antigens, which is affected by HLA genotype as well as somatic HLA loss-of-heterozygosity tumor. The

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evolutionary divergence in HLA (degree of sequencing difference between the two HLA alleles at each locus) has been implicated with immunotherapy outcome in a few forms of cancer [31].

4.2.2 Immune Checkpoint Pathways

PD-1, PD-L1 and CTLA-4 are immune checkpoint molecules which control immune activation and tolerance. The use of checkpoint inhibitor immunotherapy has transformed the treatment of cancer although the response rates differ significantly depending on the patients and the type of cancer.

Immune checkpoint gene germline variations have been studied as immune therapy response predictors and immune-related adverse events. As an example, up to now, the outcomes in several cancers receiving checkpoint inhibitors have been linked to polymorphisms in the PD-1 and PD-L1 gene, but findings were mixed across trials [32].

Interestingly, the checkpoint inhibitor therapy has autoinflammatory adverse events on various organ systems, including thyroiditis. It is estimated that between 10 and 15 percent of patients taking checkpoint inhibitors suffer thyroid dysfunction, and this further falls into two categories: transient thyrotoxicosis and long-term hypothyroidism that requires levothyroxine replacement [33]. The existence of genetic variants that may be used to predict the predisposition to checkpoint inhibitor-related thyroiditis is a critical pharmacogenomic question that has oncology and endocrinology implications.

The CTLA4 gene which is the T cell activation inhibitor of activation carries a polymorphism to increase the risk of autoimmune thyroid disease. The CTLA-4 blocking antibody Ipilimumab applied in cancer immunotherapy triggers autoimmune adverse events such as thyroiditis. The reciprocity between autoimmune and immunological self-regulation demonstrates how these processes are mutually dependent.

4.3 Pharmacoepigenomics: A Common Regulatory Stratum.

The epigenetic processes, such as DNA methylation, histone, and non-coding RNA regulation, regulate the gene expression but do not change the DNA sequence. The analysis of the relationship between epigenetic variation and drug response is known as pharmacoepigenomics and has become a new aspect of precision medicine that applies to autoimmunity and cancer.

DNA Methylation and Drug Response: This paper has performed a study on the impact of drugs on DNA methylation in relation to genetic markers.<|human|>4.3.1 DNA Methylation and Drug Response: The paper has conducted a study of the effect of the drugs on the DNA methylation concerning genetic markers.

Promoter methylation of BRCA1 in ovarian cancer forms a BRCAness phenotype which predicts sensitivity to platinum and PARP inhibitors, similar to genetic BRCA mutations. Equally, the promoter methylation of MLH1 exists in a proportion of the ovarian cancer and it affects the response to chemotherapy [34].

Epigenetic silencing of drugs of interest, drug transport systems, or metabolic enzymes can contribute to efficacy of therapy. As an example, the response to alkylating agents in glioblastoma can be predicted by methylation of the MGMT promoter, which is a clinically validated pharmacoepigenomic biomarker.

Aberrant DNA methylation has been found in T cells and B- cells of patients with systemic lupus erythematosus, rheumatoid arthritis and other diseases in autoimmune diseases. It has been under-investigated as to whether these changes in methylation are relevant to response to immunomodulatory therapies, yet this is a possible mechanism of heterogeneity of treatment response.

4.3.2 MicroRNA Regulation

MicroRNAs (miRNAs) are non-coding small RNAs, which mediate post-transcriptional gene regulation. Chemotherapy resistance in ovarian cancer has been suggested to be caused by specific miRNAs, which regulate drug targets, DNA repair pathways, and apoptotic machineries [35].

An example is miR-214 which has been demonstrated to modulate the expression of PTEN which has an effect on PI3K/AKT signaling pathway and sensitivity to cisplatin. Equally, the inflammatory responses and chemoresistance can be regulated with

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the help of miRNAs that act upon the elements of the NF-κB pathway.

Unregulated expression of miRNA has been reported in autoimmune diseases and could play a role in the pathogenesis. The potential effect of miRNA profiles to predict the treatment response to immunosuppressive or immunomodulatory therapy in thyroiditis or other autoimmune diseases is an open research gap.

4.4 ADME Genes: Generic Pharmacogenomic Determinants.

Genes that encode pharmacodynamics and pharmacokinetics pharmacogenomics enzymes and transporters act universally in both thyroiditis and ovarian cancer.

Drug absorption, distribution, metabolism and excretion are determined by the cytochrome P450 (CYP) superfamily, UDP-glucuronosyltransferases (UGTs), ATP-binding cassade (ABC) transporters, and solute carrier (SLC) transporters. These genes have been linked to genetic variations in drug exposure, efficacy, and toxicity in a wide variety of drugs.

As is discussed in the earlier sections, variants of the ABCB1, ABCC2, ABCG2, and UGT1A have been linked to the outcome of ovarian cancer, presumably via their impacts on the pharmacokinetics of chemotherapy (GB 58). The same thing can be said about thyroiditis as transporter variants can have effects on levothyroxine absorption and distribution, but there is no direct evidence.

In certain healthcare systems, the principle of pre-emptive pharmacogenomics has been put into practice, that is, genotyping patients with a series of actionable variants of ADME variants prior to exposure to the drug. This would allow pharmacogenomic dose control in the event of multiple drug exposures in the lifetime of a patient, both in the treatment of an autoimmune disease and in cancer treatment once the disease is diagnosed.

Certainly, inflammation, oxidative stress and carcinogenesis are interconnected and cannot be separated.<|human|>4.5 Inflammation, Oxidative Stress and Carcinogenesis There is no doubt that inflammation, oxidative stress and carcinogenesis are all interconnected and must not be separated.

Chronic inflammation is a mechanistic interaction of autoimmune diseases and cancer risk. The epidemiological research has reported the enhanced risk of cancer in patients with a variety of autoimmune diseases, with the extent and the type of cancer differing according to autoimmune disease [36].

The mechanisms connecting inflammation with carcinogenesis are:

Maladaptive DNA damage: Maladaptive DNA damage may result from reactive oxygen and nitrogen species generated during persistent inflammation, leading to mutations and genomic instability.

Impaired immune surveillance: Extended immune activation can lead to immune dysregulation, enabling malignant cells to evade immune detection.

Signaling Cytokine signaling Pro-inflammatory cytokines (IL-6, TNF- 2, IL-1 2) stimulate signaling pathways (NF- 2, STAT3, PI3K/AKT), resulting in cell proliferation, cell survival, and angiogenesis.

Genetic variants affect both autoimmune disease activity and cancer risk or progression, which can be viewed through a pharmacogenomic perspective, which is based on the genetic variants affecting inflammatory pathways. Indicatively, autoimmune disease susceptibility and severity have been linked to the presence of polymorphisms in the genes of cytokines. It is a poorly studied research question whether whether these same variants modify the risk of cancer in autoimmune disease patients or predictive response to anti-inflammatory therapies.

5 Personalized Medicine and Clinical Implementation Approaches.

5.1. FDA Approved Clinical Uses in Ovarian Cancer.

One of the most successful experiences of using precision oncology is the integration of pharmacogenomic testing into ovarian cancer management. The evidence-based applications in use today are:

5.1.1 Universal BRCA Testing

The National Comprehensive Cancer Network (NCCN), European Society of Gynaecological Oncology (ESGO) and others advise that all women diagnosed with epithelial ovarian cancer should undergo germline BRCA testing despite their family

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history or age at diagnosis [37]. This recommendation is based on the high rate of BRCA mutations (15-20%), the therapeutic consequences of eligibility to Parisp inhibitor, and the cascade genetic implications of genetic testing in family members.

The patients having no germline mutations should undergo somatic BRCA testing on tumor tissue as an extra 5-7 per cent of ovarian cancers contain somatic BRCA changes also associated with a predictive of PARP inhibitor sensitivity. Conjugated germline and somatic tests determine about 20-25 percent of ovarian cancer patients with exploitable BRCA mutations.

5.1.2 Homologous Recombination Deficiency Testing.

Using validated commercial tests (like Myriad myChoice CDx) for HRD testing in BRCA-wild-type cancers can identify additional patients who would benefit from PARP medicines. These assays integrate both BRCA mutation analysis and genomic instability assessments, derived from next-generation sequencing of tumor specimens.

It has been shown in clinical trials that HRD-positive, BRCA-wild-type tumors can be of substantial benefit in the maintenance therapy using PARP inhibitors, although the benefit level is typically lower than in BRCA-mutant tumors. By existing assays, approximately half of high-grade serous ovarian cancers are HRD-positive [38].

5.1.3 Selection and sequencing of PARP Inhibitors.

Multiple poly (ADP-ribose) polymerase (PARP) inhibitors have been formulated, demonstrating subtle distinctions in approved indications, treatment protocols, and adverse effect profiles. Biomarkers in pharmacogenomics can be used to select patients who can be treated with PARP inhibitors:

First-line maintenance: Olaparib and niraparib are indicated for first-line maintenance therapy in advanced ovarian cancer with BRCA mutations or homologous recombination deficiency (HRD) following treatment with platinum-based chemotherapy.

Maintenance therapy Recurrent ovarian cancer All three accepted PARP inhibitors (olaparib, niraparib, rucaparib) are indicated in platinum-sensitive recurrent ovarian cancer, with additional benefit in BRCA-mutant and HRD-positive populations.

Recurrent disease treatment: Olaparib and rucaparib are indicated in the treatment (not just maintenance) of recurrent ovarian cancer in patients with germline/somatic BRCA mutations that have received more than one line of prior treatment.

The decisions made on treatment sequencing like the use of PARP inhibitors in initial maintenance scenario versus use as a second-line treatment have varied based on various factors such as the biomarker status, treatment objectives, and toxicity.

5.1.4 New Applications: Combinations Strategies.

Combination therapy Clinical trials are evaluating the utilization of PARP inhibitors in conjunction with other targeted therapies or immunotherapy to enhance therapeutic effectiveness and mitigate treatment resistance. The strategies of biomarkers on these combinations are developing:

PARP inhibitor + anti-angiogenic therapy: PARP inhibitors have been used as synergies with bevacizumab (VEGF inhibitor), and combinations of olaparib-bevacizumab and niraparib-bevacizumab have been approved by the FDA as first-line maintenance therapy. The combinations are investigated as biomarker approaches.

PARP inhibitor + immune checkpoint inhibitors: This may be used in conjunction with immune checkpoint inhibitors; preclinical evidence indicates that PARP inhibitors can be used to promote tumor immunogenicity with increased tumor mutational burden and neoantigen presentation. Clinical trials are currently evaluating the efficacy of PARP inhibitors in conjunction with PD-1/PD-L1 inhibitors, and biomarker studies are investigating the predictive value of HRD status, tumor mutational burden, and PD-L1 expression.

5.2 Implementation Problems and Resolutions.

Although there is a robust evidence base on the use of pharmacogenomic testing in ovarian cancer, there are a number of challenges to its implementation:

5.2.1 Access and Equity

The access to genetic testing is significantly different in healthcare systems and regions. The BRCA/HRD testing and treatment options of PARP inhibitors

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could be prohibitive in resource-limited environments. The strategies to enhance access are:

Tiered testing techniques: Conducting initial germline BRCA testing, followed by somatic testing and HRD analysis just in germline-negative patients, can enhance cost-efficiency while preserving clinical effectiveness.

Generic PARP inhibitors: With the expiry of patents and the introduction of generic formulations, cost barriers to the treatment of PARP inhibitor could reduce.

International partnerships: The collaboration between high-income and low- and middle-income countries can be used to help in accessing testing and transferring knowledge.

5.2.2 Variant Interpretation

A large fraction of BRCA sequence variants is categorical as variants of uncertain significance (VUS), which generates clinical uncertainty. Treatment choices in VUS patients are normally treated as BRCA-negative but this could lead to missing a potentially effective treatment in case the VUS is pathogenic.

The reclassification of VUS by functional assays is a research priority. CRISPR-based saturation mutagenesis methods have been established to comprehensively determine the functional impact of all potential BRCA variants, which can be used to reclassify evidence-based [39]. With these functional genomics technologies coming of age, the percentage of VUS is likely to reduce, making genetic testing useful in clinical practice.

5.2.3 Heterogeneity and Clonal Evolution in tumors.

The ovarian cancer is very heterogeneous within the tumor, and different genetic alterations can happen in various regions of the same tumor. In addition, during treatment, clonal evolution can result in the formation of resistant subclones with alternative biomarker phenotypes (e.g. BRCA reversion mutations).

The use of circulating tumor DNA (ctDNA) techniques in liquid biopsy could be an effective solution to this problem in that it allows serial evaluation of biomarker status and early detection of resistance mechanisms [40].

5.2.4 Clinical Workflow Integration.

The integration of pharmacogenomic testing into clinical practice requires collaboration among multiple specialties, including gynecologic oncology, medical oncology, genetic counseling, pathology, and molecular diagnostics. Their implementation is achieved through the integration of electronic health records, clinical decision support systems, and multidisciplinary tumor committees.

Pre-emptive pharmacogenomic testing, or the practice of carrying out germline genotyping at the time of diagnosis, not in relation to a particular treatment choice, will help to cut turnaround time and allow a person to be treated sooner. It should be noted though that this method has to be used with great caution in regards to the genes that are to be tested, informed consent, and handling of incidental findings.

5.3. Potential Clinical Applications in Thyroiditis: A Framework to be implemented in the future.

Although there are no evidence-based applications of pharmacogenomics to thyroiditis at the moment, the ovarian cancer experience offers a template on how the same could be created and introduced:

Candidate Clinical Scenarios: This section of the questionnaires presents clinical scenarios to candidates, and they are expected to reply to questions regarding the physician's role in each scenario.

5.3.1 Candidate Clinical Scenarios:

This part of the questionnaires will present the candidates with clinical scenarios and they will then be expected to answer questions about the role of the physician in the scenario.

Dose optimization of levothyroxine Genotype-based dose optimization algorithms that include SLCO, ABCB1 and deiodinase variants have the potential to reduce the time to stable euthyroid levels and reduce the dose changes.

Prediction of antithyroid medicine toxicity: HLA typing to detect patients at high risk of agranulocytosis or hepatotoxicity with either methimazole or propylthiouracil may be effective in guiding the choice of antithyroid medicine and severity of monitoring.

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Selection of T4/T3 combination therapy: The deiodinase variants in relation to disturbed T4-to-T3 conversion could help to select those patients who would likely respond to combination levothyroxine-liothyronine therapy, but currently there is no evidence to establish combination therapy as a routine therapy.

Response to immunomodulatory therapy: Pharmacogenomic biomarkers that have been validated during the treatment of rheumatology may also be applicable in predicting response to glucocorticoid, rituximab, or other therapies in patients who have refractory thyroid disease who are being treated with immunomodulatory therapy.

Generation of evidence required: Within the suggested methodology, the required evidence is generated through a literature review and qualitative data analysis.<|human|>Evidence needed: In the proposed methodology, the evidence needed is the result of a literature review and qualitative data analysis.

Prior to these potential applications being implemented, there are a number of evidentiary steps involved:

1. Associate candidate genetic variants with levothyroxine and antithyroid drug pharmacokinetics in well-characterized follow-up groups of patients.
2. Association studies: depict statistically significant and clinically meaningful relationships between genetic variants and treatment outcomes (dose requirements, time to euthyroid status, adverse events).
3. Prospective validation: Comparative prospective studies of genotype-informed treatment method and normal care, with preset outcome measures.
4. Cost-effectiveness analysis: determine the economic usefulness of pharmacogenomic testing as compared to conventional empiric dose titration methods.
5. Implementation studies: Determine the feasibility, acceptance of pharmacogenomic testing by clinicians, and the patient viewpoint on pharmacogenomic testing in the management of thyroiditis.

Multicomentric integration of various genomic approaches can be used to predict awareness of systems pharmacogenomics. Precision medicine Future integration of various types of data, which are genomics, transcriptomics, proteomics, metabolomics, and clinical phenotypes, promise to produce more complex molecular portraits predictive of treatment response with more accuracy than single-platform methods.

Proteogenomic analyses in ovarian cancer have revealed that protein level assays give an additional dataset to genomic information, and can detect therapy-sensitive patients that were not detected by genomic biomarkers. On the same note, metabolomic profiling can identify metabolic susceptibilities or resistance mechanisms, which are not reflected by genomic analysis.

In the case of thyroiditis, multi-omic would involve the integration of:

Genomics: Germline changes in ADME genes, thyroid hormone receptors, and immune-related genes.

Transcriptomics: Outcomes in diseases and treatment of thyroid disease showing gene expression patterns in the thyroid tissue or peripheral blood.

Proteomics: Dynamics of proteins in terms of their expression and post-translational modification of the tissues of interest.

Metabolomics: Bio-markers of treatment response metabolic signatures, metabolites of thyroid hormone, Biomarkers of oxidative stress.

Immunophenotyping: elaborate explanation on the populations of the immune cells and activation state.

This detailed molecular profiling, though at this stage of research, has the potential to be more accurately used to select treatment and monitor in autoimmune diseases such as thyroiditis, in the future.

6. Future Directions and Research Priorities

6.1 Bridging the Thyroiditis Evidence Gap

The establishment of fundamental pharmacogenomic evidence in thyroiditis is the most pressing research priority emphasized in this study. Recommended studies include

Prospective Cohort Studies: Extensive multi-center cohorts of thyroiditis patients, utilizing standardized treatment protocols, systematic outcome evaluations, and comprehensive biobanking, would facilitate robust pharmacogenomic discoveries. Outcomes should encompass pharmacokinetic parameters, dosage requirements, time to achieve euthyroid status, quality of life assessments, and adverse events.

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Candidate Gene Analyses: Initial investigations should concentrate on well-characterized ADME genes possessing established functional variations. Targeted genotyping panels including CYP enzymes, UGT enzymes, SLCO transporters, ABCB1, and deiodinase genes would provide a cost-effective initial assessment.

Genome-Wide Association Studies: Unbiased GWAS methodologies could identify novel genetic variables determining treatment response that are not anticipated based on existing mechanistic knowledge. Replication in other cohorts and sizable sample sizes (ideally >5,000 patients) are necessary for these kinds of investigations.

Pharmacokinetic Modeling: Population pharmacokinetic analyses integrating genetic, demographic, and clinical covariates would elucidate sources of variability in levothyroxine and antithyroid medication exposure, thereby informing the formulation of dosing algorithms.

HLA and Adverse Event Studies: Considering the well-established association of HLA alleles with drug hypersensitivity, case-control studies comparing HLA types among patients who experience severe adverse reactions (such as agranulocytosis and hepatotoxicity) versus matched controls would facilitate the identification of risk alleles and aid in the development of pre-treatment screening strategies.

6.2 Functional Variant Classification and Saturation Mutagenesis

The existence of variants of uncertain significance (VUS) restricts the clinical applicability of genetic testing across all contexts. About 10–15% of BRCA testing for ovarian cancer detect VUS instead of variations that are obviously harmful or benign, which leads to clinical ambiguity.

Functional genomics methodologies, especially CRISPR-based saturation mutagenesis, facilitate comprehensive evaluation of variant impacts on protein function. For BRCA genes, saturation editing techniques have produced functional data for thousands of variants, which supports evidence-based reclassification. [39].

Similar approaches should be applied to other pharmacogenomically relevant genes, including:

Drug-metabolizing enzymes: Functional valuation of CYP, UGT, and other enzyme variants to quantify effects on catalytic activity

Drug transporters: Functional assays measuring transport activity of variant ABCB1, ABCC2, ABCG2, and SLCO proteins

Drug targets: Functional significance of variants in thyroid hormone receptors, immune checkpoint molecules, and other therapeutic targets

High-throughput functional assays integrated with computational prediction techniques will expedite variant interpretation and enhance the clinical utility of genetic testing.

6.3 Proteogenomic Integration and Multi-Omic Biomarkers

Recent findings indicate that genomic biomarkers, on their own, are inadequate for comprehensively predicting treatment efficacy. Proteogenomic integration, which combines genomic, transcriptomic, and proteomic data, has the potential to identify predictive biomarkers with enhanced performance compared to approaches based on a single platform.

In ovarian cancer, proteogenomic studies have revealed:

Discordance between genomic alterations and protein expression: Not all genetic modifications lead to proportional variations in protein levels, underscoring the significance of post-transcriptional regulation.

Proteomic signatures of drug sensitivity: Protein expression profiles may serve as predictors of response to PARP inhibitors and chemotherapy, independent of genomic HRD status.

Phosphoproteomic pathway activation: Phosphoproteomics reveals activated signaling pathways that serve as potential therapeutic vulnerabilities or prospects for combination therapy.

Future research should integrate proteomics with genomics to establish comprehensive biomarker panels. Proteomic examination of thyroid tissue, peripheral blood, or thyroid hormone-responsive tissues in thyroiditis might reveal biomarkers indicative of therapy response or indicate patients necessitating alternate therapeutic strategies.

6.4 Liquid Biopsy and Dynamic Biomarker Monitoring

Traditional tissue-based biomarker analysis provides a singular temporal picture that may not accurately

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represent tumor evolution or alterations produced by treatment. Liquid biopsy methodologies utilizing circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), or extracellular vesicles provide continuous biomarker surveillance and immediate evaluation of therapeutic efficacy.

In ovarian cancer, ctDNA-based monitoring has demonstrated utility for:

Early detection of resistance mechanisms: BRCA reversion mutations may be identified in ctDNA some months prior to radiographic progression, thus facilitating early treatment adjustments.

Minimal residual disease monitoring: Detection of persistent circulating tumor DNA (ctDNA) following primary therapy is indicative of an elevated risk of recurrence and may facilitate the identification of patients who would benefit from treatment intensification.

Treatment response assessment: Fluctuations in ctDNA levels throughout treatment are associated with therapeutic efficacy and offer more prompt indicators than conventional imaging evaluations.

For thyroiditis, liquid biopsy methods are less directly applicable; however, serial evaluation of thyroid hormones, antibodies, and potentially circulating immune biomarkers may facilitate dynamic assessment of treatment efficacy and inform dosage modifications.

6.5 Artificial Intelligence and Machine Learning Applications

Machine learning methodologies provide the capability to incorporate complex, high-dimensional data and to discern predictive patterns that are not evident via traditional statistical techniques. Applications in pharmacogenomics include:

Predictive Modeling: Machine learning algorithms can integrate genomic, clinical, and demographic data to predict therapeutic response, optimal dose, or adverse event risk with superior accuracy compared to single-variable methods.

Drug Repurposing: Computational methodologies can detect existing pharmaceuticals with prospective effectiveness in novel indications by analyzing molecular profiles, thereby potentially expediting the development of therapies.

Biomarker Discovery: Unbiased machine learning analyses of multi-omic datasets can potentially identify novel biomarker combinations that exhibit superior predictive performance compared to hypothesis-driven biomarker selection.

Treatment Optimization: Reinforcement learning techniques can optimize dose and treatment sequencing according to the unique characteristics of each patient and their past medical history.

Application of these methodologies to the pharmacogenomics of thyroiditis may expedite biomarker identification and facilitate the creation of precision dosing algorithms, even without a comprehensive mechanistic understanding.

6.6 Population Pharmacogenomics and Health Equity

Pharmacogenomic allele frequencies differ significantly among populations, with notable implications for clinical application and health equity. The majority of pharmacogenomic investigations have been undertaken within populations of European descent, thereby constraining the applicability of findings to other demographic groups.

For instance, CYP2C19 deficient metabolizer alleles are more frequently observed in East Asian populations, whereas CYP2D6 ultrarapid metabolizer phenotypes are more common among populations of Middle Eastern and North African descent. These distinctions have direct implications for medication dosages and the potential for adverse effects.

To ensure equitable implementation of pharmacogenomics, research priorities include:

Diverse Cohort Studies: Pharmacogenomic research must encompass numerous populations to find population-specific alleles and validate biomarker efficacy across different ancestry groups.

Global Allele Frequency Databases: Comprehensive databases detailing pharmacogenomic allele frequencies across diverse global populations would facilitate the development of population-specific testing strategies and prescription algorithms.

Implementation Research in Diverse Settings: Research assessing the implementation of pharmacogenomics across varied healthcare contexts, including those with limited resources, is critical for

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identifying and mitigating obstacles to equitable access.

Community Engagement: Engagement with diverse communities is vital for addressing concerns related to genetic research, fostering trust, and ensuring that advancements in pharmacogenomics confer benefits upon all populations.

6.7 Regulatory Science and Evidence Standards

As pharmacogenomic testing is progressively incorporated into clinical practice, regulatory frameworks must adapt to guarantee suitable evidence requirements while promoting innovation. Key considerations include:

Analytical Validity: The assays must demonstrate accurate and reproducible measurement of genetic variants, incorporating appropriate quality control measures and proficiency testing.

Clinical Validity: Evidence must establish that genetic variants are linked to clinically significant outcomes (such as drug response, toxicity, or survival) with effect sizes adequate to guide clinical decision-making.

Clinical Utility: Research must establish that pharmacogenomic testing enhances patient outcomes relative to conventional care, preferably through prospective randomized trials or rigorous observational studies.

Economic Value: Cost-effectiveness analyses should assess whether pharmacogenomic testing offers value compared to alternative strategies, accounting for testing expenses, medication costs, and healthcare resource utilization.

For pharmacogenomics of thyroiditis to attain clinical integration, the accumulation of evidence must encompass all these aspects, not solely establish statistical correlations between genetic variants and treatment results.

6.8 Ethical Considerations and Patient Perspectives

The implementation of pharmacogenomic testing raises several ethical considerations that warrant careful attention:

Informed Consent: Patients must comprehend the objectives, limitations, and potential consequences of genetic testing, including the possibility of uncovering incidental findings unrelated to the primary indication.

Privacy and Discrimination: Genetic information must be safeguarded against illegal access and exploitation. Legal safeguards against genetic discrimination in employment and insurance differ by jurisdiction and may be insufficient in certain contexts.

Return of Results: Policies concerning the return of incidental findings (e.g., detection of pathogenic variants in cancer susceptibility genes during pharmacogenomic testing) must carefully balance patient autonomy, clinical utility, and resource limitations.

Family Implications: Genetic testing outcomes can have ramifications for biological relatives, thereby presenting complex considerations regarding the duty to disclose information to family members and the protection of individual privacy.

Patient Preferences: Empirical studies indicate that patients typically express support for pharmacogenomic testing; however, preferences differ concerning the specific results desired and the preferred method of information dissemination. Patient-centered methodologies should acknowledge individual preferences while concurrently ensuring sufficient comprehension.

7. Conclusions and Perspectives

This extensive review has analyzed the present landscape of pharmacogenomics in thyroiditis and ovarian cancer, highlighting a notable disparity between the well-established evidence in ovarian cancer and the almost complete lack of thyroiditis-specific pharmacogenomic data.

7.1 Key Findings

Ovarian Cancer: A Pharmacogenomic Paradigm

Ovarian cancer illustrates the effective application of pharmacogenomic findings in therapeutic settings. BRCA1/BRCA2 and HRD testing inform PARP inhibitor selection, supported by strong clinical trial evidence indicating significant survival advantages in biomarker-selected cohorts. In addition to BRCA/HRD, mutations in ADME genes (ABCB1, ABCC2, ABCG2, UGT1A cluster) and multi-gene expression profiles offer supplementary prognostic and possibly predictive insights. Innovative methodologies such as proteogenomic integration, liquid biopsy surveillance, and patient-derived model

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systems offer the potential for enhanced personalization of treatment methods.

Pharmacogenomic implementation necessitates the following: (1) a strong biological rationale that links genetic variants to drug response mechanisms; (2) robust clinical evidence from well-designed studies; (3) clinically accessible and validated testing platforms; (4) clear clinical guidelines for the interpretation of results and treatment selection; and (5) healthcare system infrastructure that supports testing access and multidisciplinary care coordination. This is demonstrated by the experience with ovarian cancer.

Thyroiditis: A Critical Evidence Gap

Conversely, the pharmacogenomics of thyroiditis remains largely unexamined. Despite significant diversity among individuals in treatment response, dosage needs, and susceptibility to side events, no research has comprehensively examined the genetic factors influencing these results. This evidence gap signifies both a research deficiency and a lost chance to enhance care for millions of individuals suffering from thyroid illness.

Potential candidate genes for future research encompass ADME genes, notably SLCO transporters and ABCB1, as well as deiodinase enzymes, thyroid hormone receptors, and HLA alleles that may be linked to antithyroid medication toxicity. Nevertheless, in the absence of dedicated investigations, the clinical implementation of pharmacogenomic testing in thyroiditis remains premature and lacks supporting evidence.

Shared Mechanistic Themes

Despite the clinical and pathophysiological distinctions between autoimmune thyroiditis and ovarian cancer, several mechanistic themes appear to be potentially pertinent to both conditions:

ADME genes, Influence drug pharmacokinetics across various therapeutic areas and serve as universal pharmacogenomic determinants relevant to both conditions.

DNA repair pathways, although most extensively examined in cancer, it may also impact the pathogenesis and treatment response of autoimmune diseases through effects on genomic stability and innate immune activation.

Immune pathways, including HLA alleles and immune checkpoint molecules, are fundamental in autoimmunity and cancer immunosurveillance, with reciprocal interactions emphasized by autoimmune adverse events induced by checkpoint inhibitors.

Pharmacoepigenomic mechanisms, Including DNA methylation and microRNA control, these factors influence treatment response in both cancer and potentially autoimmune illnesses.

These shared themes suggest that advances in one field may inform approaches in the other, though direct translational applications require empirical validation.

7.2 Implications for Clinical Practice

Current Recommendations

For ovarian cancer, comprehensive BRCA testing and HRD evaluation in BRCA-wild-type tumors constitute evidence-based standards of care that should be adopted across all healthcare settings managing ovarian cancer patients. PARP inhibitor therapy should be administered to individuals with BRCA-mutant or HRD-positive malignancies in accordance with approved indications and clinical trial data.

Currently, there is no evidence supporting the use of pharmacogenomic testing for thyroiditis. Treatment must adhere to established clinical protocols grounded in biochemical monitoring and symptom evaluation. Clinicians should recognize that genetic factors probably influence diversity in therapy responses; nonetheless, particular genetic testing cannot currently be endorsed for clinical application.

Future Prospects

As pharmacogenomic evidence in thyroiditis is developed, potential clinical applications may encompass genotype-guided levothyroxine dose, HLA-based risk assessment for antithyroid drug toxicity, and the identification of patients who are likely to benefit from alternative treatment modalities. Nonetheless, many applications necessitate stringent validation prior to implementation.

In ovarian cancer, continued research is expected to broaden the demographic that benefits from targeted therapy by enhancing HRD testing, discovering more

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prognostic biomarkers, and formulating combination methods to counteract resistance. Liquid biopsy methods may provide real-time treatment optimization according to changing tumor features.

7.3 Research Priorities

The following research priorities emerge from this review:

1. **Foundational thyroiditis pharmacogenomic studies** examining associations between candidate genetic variants and treatment outcomes
2. **Functional variant classification** using saturation mutagenesis and other high-throughput approaches to resolve variants of uncertain significance
3. **Proteogenomic integration** to develop multi-omic biomarker panels with superior predictive performance
4. **Liquid biopsy** applications for dynamic monitoring of biomarker status and early detection of resistance
5. **Population pharmacogenomics** ensuring diverse representation and addressing health equity
6. **Implementation science** evaluating optimal strategies for integrating pharmacogenomic testing into clinical workflows
7. **Economic evaluation** assessing cost-effectiveness of pharmacogenomic approaches relative to standard care
8. **Artificial intelligence applications** for biomarker discovery, predictive modeling, and treatment optimization

7.4 Broader Implications for Precision Medicine

The differing pharmacogenomic profiles of thyroiditis and ovarian cancer exemplify broader themes pertinent to the advancement of precision medicine across various diseases:

Research Investment Drives Progress: The significant research funding allocated to cancer pharmacogenomics, motivated by high mortality rates, extensive patient populations, and interest from the pharmaceutical industry, has resulted in the development of clinically actionable biomarkers. Relatively overlooked conditions, particularly those impacting substantial populations, remain underdeveloped. Addressing these disparities necessitates intentional prioritization of research efforts and strategic allocation of funding.

Evidence Standards Must Be Maintained: The comprehensive body of evidence that underlies ovarian cancer pharmacogenomics—including mechanistic insights, association research, prospective clinical trials, and analyses of cost-effectiveness—demonstrates adherence to the appropriate standards for clinical application. The premature implementation of pharmacogenomic testing, lacking sufficient data, poses hazards to patient safety, leads to financial wastage, and undermines trust in precision medicine.

Multi-Omic Integration Enhances Prediction: Genomic biomarkers derived from a single platform, although informative, do not comprehensively represent the multifaceted nature of therapeutic response. The integration of genomic, transcriptomic, proteomic, and additional data types offers the potential for enhanced predictive accuracy and may facilitate the identification of responders that are overlooked by genomic markers alone.

Implementation Challenges Require Attention: Even with compelling evidence, the translation of pharmacogenomic discoveries into routine clinical practice encounters significant obstacles, including issues related to access, cost, variant interpretation, integration into clinical workflows, and concerns regarding health equity. Research in implementation science is crucial for tackling these difficulties.

Patient-Centered Approaches Are Essential: Pharmacogenomic testing should be implemented in a manner that respects patient preferences, ensures informed consent, protects patient privacy, and addresses pertinent ethical considerations. Patient involvement in the development and planning of research design improves its relevance and acceptability.

7.5 Concluding Remarks

Pharmacogenomics possesses the transformative potential to individualize medical treatment across a wide range of conditions, enhancing therapeutic effectiveness while reducing adverse effects. The success narrative of BRCA/HRD testing and PARP inhibitors in ovarian cancer illustrates that this potential can be achieved through the integration of rigorous scientific research, clinical validation, and meticulous implementation.

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However, the almost total lack of pharmacogenomic evidence in thyroiditis highlights a sobering reminder that progress in precision medicine varies across different diseases and therapeutic fields. Addressing these disparities necessitates ongoing research efforts, sufficient funding, and acknowledgment that even "standard" remedies for prevalent conditions may benefit from pharmacogenomic enhancement.

With ongoing advancements, the incorporation of multi-omic data, functional genomics, artificial intelligence, and implementation science will facilitate the development of increasingly refined personalized treatment approaches. The overarching objective of administering the appropriate medication, at the correct dosage, to the suitable patient, at the optimal time, persists as an ambitious yet progressively attainable endeavor.

For patients with thyroiditis and ovarian cancer, the potential of pharmacogenomics lies in revolutionizing treatment from empirical, trial-and-error methods to evidence-based, biomarker-driven precision medicine. Achieving this objective requires sustained scientific advancement, the production of robust evidence, judicious clinical application, and an unwavering commitment to improving patient outcomes across diverse populations and disease manifestations.

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