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Pharmacogenomics through Proteogenomics in Primary Care: Clinical Workflows, Outcomes, and Cost-Effectiveness

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ABSTRACT

Pharmacogenomics has emerged as a cornerstone of precision medicine, enabling safer and more effective prescribing through the identification of genetic determinants of drug response. Proteogenomics extends this approach by incorporating protein expression, modification, and functional data, offering a more comprehensive understanding of interindividual variability in therapeutic outcomes. This review examines the integration of pharmacogenomics through proteogenomics in primary care, focusing on clinical workflows, patient-centered outcomes, and cost-effectiveness. Evidence indicates that both pre-emptive and reactive testing models can support medication optimization, reduce adverse drug reactions, and improve adherence and clinical outcomes across multiple therapeutic areas, particularly psychiatric, respiratory, and cardiovascular conditions. Integration with electronic health records and clinical decision-support systems enhances real-time prescribing guidance and longitudinal patient management. Economic analyses suggest that pharmacogenomic-guided medication management can be cost-effective and may reduce healthcare utilization, although the high cost of proteomic assays and limited reimbursement remain barriers. Implementation challenges include a lack of workflow standardization, insufficient clinician training, limited population diversity in reference datasets, and translational gaps between research and routine practice. Strengthening implementation science, expanding diverse cohort studies, and developing standardized reporting frameworks will be essential to realizing the full clinical and economic potential of proteogenomics-enabled pharmacogenomics in primary care.

Keywords: Pharmacogenomics**,** Proteogenomics**,** Primary Care**,** Clinical Decision Support, **and** Cost-Effectiveness.

INTRODUCTION

Pharmacogenomics, variations in drug response explained by genetic profile, promises safer, more effective prescribing and wider clinical adoption [1]. Proteogenomics, joining pharmacogenomics and proteomics, expands patient empowerment and therapeutic scope. Nevertheless, clinical workflows lack standardization, many studies conflate pharmacogenomics with proteogenomics, and firm economic analyses remain scarce [2]. Furthermore, 85% of tests originate from non-U.S. sources; genotype–drug pairing criteria mostly pertain to antidepressants; large populations and diverse settings remain underexplored; and progress from evidence generation to real-world adoption is limited [3, 4]. Clinical workflows employing next-generation sequencing to generate whole-exome or whole-genome information span two prototype paradigms, one pre-emptive, the other ordered reactively [5, 6]. Pre-emptive sequencing occurs at universal newborn screening or any subsequent life moment, independently of presented symptoms [7]. Ordered reactively follows prescription initiation, concurrent with therapeutic monitoring and drawing on archived specimen collections. The information is acquired only for pharmacogenes and proteogenes relevant to the specified drug. The former denotes genomic loci influencing drug response; the latter, inheritable protein-coding alterations [8].

Background and Rationale

The overall objective of pharmacogenomics is to improve therapeutic responses by revealing interindividual variation in drug metabolism and action [2]. The precise statements of the nature and extent of these variations sound very similar to those of proteins [9]. Proteogenomics focuses on the protein-coding aspect of the human genome sequence and is therefore playing a fundamental role in constructing an inclusive atlas of biological and pathological systems, which encompasses human health and disease, metabolites, and environmental influences [10]. Collectively, pharmacogenomics and proteogenomics would constitute a system of system bioinformatics that is extremely useful for patient wellness, education, and safety [11]. Pharmacogenomics and proteogenomics are relevant to health prevention and primary care practice because drugs account for the second leading cause of death in the United States, and early intervention would avoid unnecessary suffering and loss, thus enhancing the quality of life and minimizing associated costs [4].

Pharmacogenomics and Proteogenomics: Concepts and Definitions

Two complementary fields that have the potential to transform medical practice both individually and collectively are pharmacogenomics and proteogenomics [12]. Pharmacogenomics is the study of the role of genetics in drug response. The FDA has identified more than 200 drugs for which response may vary based on genetic factors and has established a pharmacogenomics knowledge base to support clinical translation of scientific knowledge about drug-gene interactions 5. Genetic variation can influence each of the four major determinants of pharmacokinetics: absorption, distribution, metabolism, and excretion [6]. It can also affect drug targets, modifying drug efficacy by altering receptor structure or abundance [1]. Pharmacogenomic information is therefore highly relevant to drug selection, dosage optimization, and the identification of alternative therapeutic options [8]. Proteogenomics builds on the findings and principles of genomics. The latter is not without its limitations; for example, complete variant transcription or translation does not always occur following the expression of an mRNA sequence. Proteogenomics deals with these limitations by focusing on proteins instead of genes, thus addressing mismatches between the sets of expressed proteins that are encoded and the actual proteins that are produced within a physiological environment [16]. It generates information on the presence, absence, expression levels, and mutations in proteins [2]. This is important because understanding protein behaviour but not protein identity severely constrains insight into other cellular processes and regulatory pathways, limiting the possibility of predicting inundations in cell-cell communication, for instance. Proteogenomic data can therefore ease the understanding of pharmacogenomic mechanisms [1].

Relevance to Primary Care Practice

Pharmacogenomic guidance has the potential to benefit patients across all health care settings, making it a relevant service for primary care practice. Several factors contribute to the appeal of pharmacogenomic services implemented in primary care [8]. First, primary care physicians provide management for a broad range of conditions and prescriptions, including treatment of chronic diseases in pediatric patients and adults that commonly require multiple medications, such as asthma or hypertension [18]. Second, pharmacogenomic testing is recommended by several specialty professional organizations for numerous commonly prescribed medications that fall within the primary care therapeutic area [11]. Third, the demand for pharmacist services to assist with medication management is expanding, as shown by pharmacist curricular content changes initiated by the Accreditation Council for Pharmacy Education 1 and state-level policies allowing pharmacists to independently prescribe medications [5]. Establishing pharmacogenomic clinics is not the only approach to delivering pharmacogenomic services in primary care settings [2]. Since pharmacogenomic interpretation guidance is available via both point-of-care tools and telehealth consultations, online chat and web-based forums represent potential options for pharmacogenomic services that generate patient and provider activity outside traditional clinic visits [7]. These options can accommodate jurisdictions where patient-provider contact is prohibited before pharmacogenomic testing, keeping services accessible yet compliant with rules in place prior to scheduling initial appointments [13].

Current Clinical Workflows

The pharmacogenomic clinical workflow includes pharmacogenetic and proteogenomic testing to inform prescribing for a wide range of therapeutic areas [8]. Models have emerged that extend the pharmacogenomic clinical workflow framework to incorporate simplified biomarker-driven proteogenomic testing, identifying protein-level markers that complete the patient-centered pharmacogenomic testing process[11]. Simplified proteogenomic testing identifies clinically important markers not captured during broader pharmacogenomic sequencing and helps ensure patient safety across a range of medications and therapeutic areas. A pharmacogenomic consultation and explanation of complementary simplified biomarker-driven proteogenomic tests among broader sequencing-tested patients can flag these actionable needs, support prescribing confidence, personalize medication selection, and address complex case scenarios typically outside routine prescribing applications[15]. These approaches have been adopted in multiple patient-centered pharmacogenomic testing

initiatives supported by the microbiome and clinical DNA sequencing, including distinctions for infectious indications and integrated treatment improvement initiatives spanning varied therapeutic areas [2]. The results of these integrated biomarker-driven proteogenomic workflows have been clinically tested across diverse patient populations to assess their safety, effectiveness, and toxicity across general and specific indicator declarations and safety-dedicated reports for medication selection across multiple therapeutic areas[12]. Detailed specifications for patient-centered pharmacogenomic reports and supplementary options accompanying broad sequencing have been established, and work is ongoing to harmonize complementary biomarker-centred proteogenomic clinical testing and wider proteogenomic standardization efforts with broader pharmacogenomic initiatives [6].

Workflow Models in Primary Care Settings

Pharmacogenomics and proteogenomics are precision medicine approaches that consider individual genomic and protein information, respectively, to personalize drug therapy [4]. These approaches are frequently considered together because they share a similar rationale [4]. Proteogenomics can support pharmacogenomic decision-making by identifying genomic regulatory-related and non-genomic alterations that, although not directly linked to drug metabolism, can influence drug response [15]. Depending on the pharmacogenomic markers considered, such as variants detected in drug-metabolizing enzymes, transcription factors, or drug targets, proteogenomics can reveal patient-specific gene-expression, protein-abundance, and post-translational-modification profiles of genes that impact drug response to enable the selection of the most appropriate drugs [2]. In primary care, medication errors are estimated to occur in 15% of prescriptions and to be the top cause of avoidable morbidity and mortality [4]. Only rarely are patients tested for pharmacogenomic markers or treatment decisions tailored accordingly. Evaluation of current clinical-healthcare workflows for pharmacogenomics and proteogenomics in primary care reveals two distinct models of execution [13]. First, the patient provides an oral therapeutic-history summary at the first appointment [5]. Based on this, a panel of drugs prescribed and the corresponding pharmacogenomic markers are suggested [14]. Patients with ongoing therapy are invited to obtain pharmacogenomic analysis by digital procedures and are alerted to treatment-associated pharmacogenomic markers [7]. The choice of the second model is based on the drug-associated pharmacogenomic markers annotated in the patient's EHR. Routine clinical genomic analysis would thus provide continuous reanalysis and would enable the generation of an updated pharmacogenomic report when new drug-therapy information becomes available [17].

Integration with Electronic Health Records and Decision Support

Pharmacogenomic testing is gaining traction as an avenue to identify genotypes or biomarkers that correlate with drug efficacy or toxicity [9]. In most cases, these tests measure germline single-nucleotide polymorphisms from a sample of saliva or blood. Proteogenomic testing builds upon the germline foundation. It assesses variants from the exome and transcriptome to inform the medical decision-making process. It provides additional relevant information by capturing the somatic alterations from the somatic genome and transcripts. Although the genotypes are important, the protein expression and function may ultimately determine how the drug will act in the organ [11]. Proteogenomic tests are critical for the treatment of cancers, infectious agents, and psychiatric disorders. Very few evolve into routine tests/assays in a primary care context. To date, pharmacoproteomic testing performs a suite of tests on drugs such as statins, antidepressants, antipsychotics, anticoagulants, and some others. Given that both pharmacogenomics and pharmacoproteomics are in common use in primary care, both have been systematically integrated into a clinical workflow to guide the treatment of chronic diseases [10]. The need to improve the safety and effectiveness of medication therapy in patients with multiple chronic conditions prompted the development of a pharmacogenomic-enriched comprehensive medication management (PGx-CMM) program [13]. The clinical and economic impact of PGx-CMM with proteogenomic support integrated with electronic health records across diverse settings in a large integrated delivery system demonstrates the value of this initiative. The PGx-CMM program enabled clinical pharmacists to conduct face-to-face and telephone encounters for medication therapy management [8]. Pharmacists used interoperable clinical information to evaluate medication safety and effectiveness, enhance medication adherence, assess substance use disorders, and provide weight management guidance. The testing results are provided free of charge to the end-user through the EHR. The report summary is displayed during the clinical encounter [7]. The test report is colour-coded to offer a quick overview of the observed variant patient reception. The complete report is appended following the summary. Longitudinally updating the EHR further eliminates the need for cumbersome manual documentation [7].

Stakeholder Roles and Training Requirements

Implementation of pharmacogenomics and proteogenomics requires formal roles and responsibilities among stakeholders [1]. In primary care settings, active engagement by general practitioners, family physicians, nurse practitioners, pharmacists, and other health professionals is essential [1]. Different professional groups assume the specific roles of lead clinician, support clinician, scientist, educator, technician, and administrator. A novel role

of a specialised practitioner can also be established in certain settings [2]. Medical doctors and prescribers, including general practitioners, family physicians, physician assistants, and nurse practitioners, lead the process and determine indications for proteogenomic testing [8]. They request the test, validate the results, integrate them into the routine prescribing practice, and monitor subsequent health outcomes. Pharmacists assume a support role, advising on test selection and, in some cases, on the interpretation and clinical consequences of the results. Health service regulation, privacy law, and professional ethics, however, prohibit other medical personnel from reopening or co-signing the prescription [19]. Professionals involved in proteomic and extended pharmacogenetic laboratories provide specialized scientific and technical input on generating additional evidence [12]. Educational institutions, trainers, and pharmaceutical companies fulfil the educator task by teaching health professionals about the technology and its application. In some cases, a technician, combined with a passing educator role, deals with laboratory preparation, file transfer, document delivery, and other technical aspects of the workflow [13]. The administrative task includes conducting or coordinating operational aspects such as order generation and reporting feedback to customers. Pharmacy education offers insufficient training in pharmacogenomics and related digital health technologies, and undergraduate programmes should reinforce these aspects [14]. Nevertheless, the acquired knowledge base varies, with postgraduate education or short courses recommended to further individualise training. Continuing education courses demonstrate a positive impact on pharmacogenomics-related knowledge among pharmacists, but high scores are not sustainable without repeated exposure [15]. Further enhancement of pharmacogenomics education promotes knowledge transfer to broader healthcare teams and underpins more effective clinical practice. Interprofessional education is therefore advocated to ensure all healthcare providers gain awareness, understanding, and competency [16].

Evidence on Clinical Outcomes

Evidence supporting the clinical utility and value of pharmacogenomics and proteogenomics testing comes from several related lines of investigation: the emergence of pharmacogenomics and proteogenomics as components of diverse medication-management programs; a body of studies examining comprehensive pharmacogenomic panel testing in medication management; and a complement of analyses demonstrating the effects of pharmacogenomics-supported medication adjustments on patient-centered outcomes[6]. Medication-management programs informed by pharmacogenomics have demonstrated clinically meaningful, statistically significant improvements in patient-centered outcomes across diverse populations; these programs have addressed a variety of medication-related challenges, including polypharmacy, chronic condition management, medication adherence, medication-use optimization, and medication misuse and opioid safety[4]. Although the exact nature of pharmacogenomic testing employed in these programs has varied widely, the medications targeted for review have frequently included psychotropics, conventionally used across the broad settings served by the programs [8]. Workflows have encompassed combinations of PGx testing and review or adjustment of medications in mental health, chronic pain, bipolar disorder, and learning- and developmental-disorder contexts [1]. Proteogenomic testing has entered certain comprehensive medication-management programs, with evidence supporting the approach [7]. Demonstrating the theory of change linking pharmacogenomics to improved clinical outcomes, substantial evidence shows that adjustments prompted by pharmacogenomic data often remediate potential medication-related problems and mitigate adverse events [8]. Pharmacogenomic variables become the most frequently addressed medication targets in these programs, with more than three-quarters of patients receiving attention on the basis of pharmacogenomic data alone. Available evidence also suggests that proteogenomic data follow a similar pattern.

The face validity of pharmacogenomics as a pathway for translating biological information to clinical decisions and outcomes complements these results [11]. Pathways linking increased adherence to improved clinical outcomes further strengthen ties to desired patient-centered objectives. Several studies have also investigated pre-emptive pharmacogenomic testing prior to the initiation of therapy across diverse medication classes [9]. These approaches encompass psychotropic, cardiovascular, and pain-management medications, with pharmacy-led interventions integrating pharmacogenomic data into ongoing medication management to address a range of adherence-challenge scenarios [10].

Patient-Centered Outcomes

Pharmacogenomics, bridging the gap between genetics and drug therapy, has gained momentum in recent years, warranting seamless translation to primary care practice [4]. Proteogenomics serves as the next frontier by coupling exome sequencing with mass spectrometry proteomics, supporting clinical interventions across drug classes and therapeutic areas, yet still awaiting widespread implementation [7]. Incremental but substantial evidence establishes patient-centered outcomes, safety, efficacy, adverse event profiles, and comparative effectiveness as distinct yet overlapping benefit pillars supporting broader adoption and reimbursement across diverse settings and regions [3]. Proteogenomics in particular offers primary care practitioners a robust platform to engage in clinical and economic evaluations, guiding clinical-decision support tools and educational initiatives [8, 7].

Safety, Efficacy, and Adverse Event Profiles

Adverse drug reactions (ADRs) lead to over 100,000 deaths per year in the USA, making them a major public health concern [10]. Pharmacogenomics (PGx) offers a strategy to mitigate these risks by using genetic variants related to drug processing, response, and toxicity to predict individuals' responses to medications [12]. A systematic review and meta-analysis of the effects of germline PGx on chemotherapy toxicity, including severe toxicity, hospital admissions, and symptomatic burden, found that treatment guidance based on the presence of germline PGx variants significantly reduced the risk of severe adverse medicine-related events [11]. This included a reduction in chemotherapy-related mortality. A subsequent analysis indicated that the effects of PGx guidance on severe toxicity were larger for multigene assays than for single-gene tests, suggesting that urgent clinical trials of comprehensive multi-gene PGx panels are warranted to support simultaneous evaluation of drug-gene interactions across therapeutic contexts [13]. Many of the PGx variants most frequently linked to severe adverse reactions are not currently referenced in established guidelines but show strong evidence of hazard associations [11].

Comparative Effectiveness across Therapeutic Areas

The literature review evidence indicates that a greater relative improvement in pharmacogenomic-enriched medication management was achieved for 80% of clinical and economic outcomes for patients receiving medications in two therapeutic areas (respiratory and psychiatric) compared to those in other therapeutic areas, including cardiovascular, diabetes, infectious, pain, and neurology [8]. All three studies meeting the pragmatic effectiveness criteria, assessing the real-world impact of pharmacogenomics, were conducted in patients with a high prevalence of respiratory and/or psychiatric conditions[7]. The health authority decision-analytic modelling of pre-emptive population-wide pharmacogenomic testing in Canadian urban primary care patients demonstrated that 1 in 5 medications prescribed are associated, through genetically mediated drug–drug interactions, with an increase in the likelihood of experiencing a serious adverse drug event [9]. While the model predicted a decrease in adverse drug events due to on-label antimicrobials, the greatest absolute increase was projected in a second therapeutic area: 51% of these patients had a concomitant psychiatric medication, and half of these were guided to better-tolerated alternatives [4].

Cost-Effectiveness and Economic Considerations

Despite the widely recognized clinical value of pharmacogenomic testing, questions remain regarding economic viability, influencing its acceptance as routine care [7]. Widespread reimbursement has not materialized; careful evaluation of price/value relationships is essential. Cost-effectiveness analysis systematically studies interventions to inform optimized spending, helping prioritize where resources yield maximal health gains [19]. Testing's potential affordability hinges on labor and assay nature. Genomic diagnostics often show minimal upfront costs; proteomic testing relies on expensive single-cell protein analyses [18]. Investments increase for curated drug-gene-pair selections, complex cellular-tissue enrichment, and translation to clinical report formats [7]. The prevailing pharmacogenomic-testing paradigm evaluates orally administered drugs associated with genotype-based dosing predisposition [9]. The most fully articulated and modeled testing approach exists for clopidogrel and the CYP2C19 genotype. When validated in the managed-care system, pharmacogenomic testing's incremental cost-effectiveness ratio approximates USD 45 600 per quality-adjusted life year regained [5]. High confidence supports testing's favorable cost-effectiveness when evaluating upstream clinical-waterfall interventions [8]. Analysis across diverse therapeutic areas consistently confirms that even pharmacogenomic-guidance testing conducted at scale can attain commercially sustainable resource-allocation profiles [7].

Analytic Approaches to Economic Evaluation

Economic evaluation supports the appropriate allocation of healthcare resources. Decision-analytic models can analyze the cost-effectiveness of intervention and control strategies over predefined time horizons [9]. Pharmacogenomic interventions often reduce costs while improving health outcomes, indicating widespread economic benefits [2]. The "modelling" approach to economic evaluation employs a simplified disease progression model with parameters specified from the literature for cost-effectiveness estimates. Cost-effectiveness analysis enables serving diverse stakeholders, such as healthcare providers and patients, by examining prevention, treatment (whether pharmacological therapy or lifestyle changes), and testing strategies across many target health conditions [1]. The "economics" approach evaluates the total cost of genetic tests (both for targeted conditions and other incidentally-uncovered conditions), incorporating resource-use details gathered during the prospective clinical study. Cost-effectiveness data should provide per-year estimates of public health consequences (e.g., cases treated, onset-times postponed, adverse events avoided) for chronic yet low-mortality conditions [2]. Such figures are pivotal for gauging potential impacts for actionable diseases [9].

Budget Impact and Resource Allocation

In an analysis of the budget impact of pharmacogenomics-driven Comprehensive Medication Management (PGx-CMM) among older adults in community pharmacies in Michigan, [8] found that the approach not only

improved clinical outcomes, but also led to a reduction in healthcare utilization and overall cost savings for third-party payers. A pharmacogenomics (PGx)-enriched medication management program deployed in older adults was associated with a 9% reduction in outpatient, emergency, and inpatient events, consistent with the prevailing trend of shifting resource utilization toward a primary-care focus [6]. The resulting projected savings were approximately $826 per person in the first 12 months [2]. The program, conducted in over 170 pharmacies, employed a PGx-guided decision-support tool integrated within the pharmacy electronic health record (EHR) to direct evaluation and management of 25 common high-risk medications [4]. By protocol, qualified patients received education regarding the PGx evaluation and its potential impact on medication therapy, as well as reinforcement of the ongoing pharmacist-directed CMM service [3].

Barriers to Implementation and Reimbursement Implications

A multitude of factors, particularly those related to reimbursement, affect the effective implementation of pharmacogenomics in clinical practice. Attitudinal barriers, such as perceived lack of utility in the absence of formal clinical guidelines and misperceptions of the value proposition of pharmacogenomics, hinder integration into workflows [12]. The implementation of pharmacogenomics has been delayed by the need for further educational outreach, the enhancement of clinician perception of utility, and the provisional nature of commercial test results [13]. Pharmacogenomics implementation in Quebec witnessed some success, although budget impact predictably affected uptake. Similarly, across the remainder of Canada, a three-level adoption metric has been adopted: [8] scholarship and dissemination, [5] adaptation of service provider structures possessive of genomics competencies, and [10] the clinical introduction of shallow, standard, or deep–core pharmacogenomic databases. Pharmacogenomics implementation under a prevalence–based monetized assessment might favour a diverse range of stakeholders, with an indicative annual valuation of $C99 million [7].

Gaps in Current Evidence

Most clinical studies supporting the integration of pharmacogenomics and proteogenomics into primary care are limited in either design or generalizability [1]. A few studies observe laboratory measures as a surrogate for clinical outcomes, relying on improved adherence to evidence-based guidelines, underspecified biomarkers, or post hoc analyses [2]. A substantially larger literature proposes overall clinical utility rather than direct patient or system outcomes, depending, for example, on abstract definitions of doctor-patient interactions or simulated population models, many of which misallocate fundamental expenditure or apply overly coarse classification schemes and ignore the nuances vital for deriving expectation probability [3]. Beyond conventional pharmacogenomics, proteogenomics, a comprehensive strategy monitoring the entirety of drug metabolism, offers a clearer connection to both clinical and economic impact, yet investigation remains scant. Implementation challenges persist as well, underlining both the need for rigorous studies in diverse settings and the broader issue of translational failure in the pharmaceutical domain [6]. In a chronic disease setting, studies of biomarkers can take decades to assess clinical or budgetary consequences, while the further removal from initial discovery marks an even steeper cost in primary care [7].

Methodological Limitations in Existing Studies

Current literature on pharmacogenomic testing in the UK and Germany lacks robust evidence on clinical and economic benefits [1]. Existing studies typically involve small cohorts, focus on selected drug-gene pairs, evaluate screenings restricted to a few therapeutic areas, or omit health and resource use data needed for economic modelling [3]. Moreover, most analyses examine single-gene tests, failing to capture the value of multi-gene approaches that encompass treatments for diverse chronic conditions prevalent across the adult population and would likely yield greater clinical and economic value [7].

Population Diversity and Equity Considerations

Implementing clinically relevant pharmacogenomic (PGx) and proteogenomic (PGxG) testing in primary care practice is paramount if genomics is to realize its potential to improve health equity and reduce healthcare disparities [13]. For the majority of existing PGx and PGxG tests, if the ancestry of the reference population and the study population differ, these tools are usually of little or no utility [14]. Recent studies have shown that the development of PGxG reference data may be limited by the lack of genome sequencing information from racially diverse samples in the pharmacogenomics literature, especially in European ancestry populations. If advancements in PGxG are made, for instance, the identification of PGxG biomarkers for at least ten drugs, including warfarin, tacrolimus, and tamoxifen, that have been demonstrated to differ across populations, these biomarkers will be of no use in populations for which PGxG information is lacking unless the requisite reference data are obtained [10].

Health disparities will also multiply in the absence of affordable examinations such as those offered by commercial PGx-based gene panels [11]. One barrier to widespread PGx implementation is the availability of investigational drug alternatives, which are lacking in underserved and rural areas. Commercial PGx gene panels typically have restricted on-label options, making them less relevant and impactful in such communities. Fortifying gene-drug recommendations for investigational medications is one approach to facilitate the development of PGx-based

precision medicine in these locales [15]. Environmental and social determinants also play a crucial role in health equity, and routinely acquiring socioeconomic data is vital for holistic clinical decision-making. Features such as homeownership, education level, and proximity to public transport or grocery stores affect individual and population well-being and need to be integrated into the existing systems to optimize healthcare delivery [16].

Translational Gaps from Research to Routine Care

The translational gap between pharmacogenomic research and clinical workflow implementation further hinders the uptake and use of proteogenomic medication response testing. A study of the implementation of pharmacogenomics into UK general practice found that, while knowledge of pharmacogenomics was generally low, health professionals recognized its potential value [5]. Barriers to implementation included concerns regarding cost-effectiveness, insufficient resources, lack of professional and public understanding, and ethical, legal, and social implications. Additional issues included evidence-based quality, bioinformatics complexity, and use of pre-symptomatic disease testing [3]. Proteogenomic testing, as an extension of pharmacogenomics, faces the same implementation hurdles yet offers benefits such as the ability to provide medication response information earlier in treatment and the additional possibility of routine monitoring through proteomic follow-up tests [2]. Addressing translational gaps between established functional testing and workflow implementation in primary care remains critical for advancing proteogenomics [1].

Future Directions and Research Priorities

Implementations of pharmacogenomics that employ next-generation sequencing technologies for germline variant detection are being investigated. Next-generation sequencing can enhance the understanding of polygenic variability and how it relates to drug response [1]. Novel applications such as the simultaneous sequencing of multiple pathogens and the tracking of drug-resistant mutations are emerging [9]. Full-sample sequencing will soon make it feasible to review and annotate all previously overlooked variants. Some centres are exploring the development of functional assays to evaluate variants in PK and PD genes, enabling patients to make decisions about selective DMTs [2]. Consensus still needs to be developed on the optimal configurations of proteogenomic workflows, how proteogenomic data should be reported to end users, and the training needed to support adoption. Essential features include the uncompromised delivery of all relevant information in the initial report. Working groups have been convened to define a set of desirable specifications complementary to the structure proposed by the Clinical Genomics Working Group [6]. Work is also underway to develop methods for the sensitive quantification of proteosomic outliers and aberrantly processed products [16]. Clinical best practices for the delivery and utilization of proteogenomic information also require further development [12]. Coverage of the whole genome along with DNA methylation, RNA splicing, integration of 5'-UTR and 3'-UTR data, and virio-genomic assessment across the target gene panel remains important when variant annotations are available in the accompanying report. Actions to broaden the confidence baseline for proteogenomic services are essential, together with a clearer indication of their target populations [11]. Tackling these challenges by undertaking experimental work to strengthen the limitations of transcriptome-independent processing could play a critical role in improving the integration of proteogenomic data. The deployment of widely adopted proteogenomic applications is anticipated within the next decade [1].

Innovations in Proteogenomic Testing

Innovations in proteogenomic testing aim to improve drug response and reduce adverse drug reactions, which cause over 200,000 hospital admissions and up to 20,000 deaths annually in British Columbia, costing around $49 million per year [7]. Despite the potential benefits, implementation faces challenges such as low acceptance of pharmacist recommendations, mixed patient receptivity, limited reimbursement, and lack of resources[9]. The high cost of pharmacogenomic testing, ranging from $200 to $500, often leads to consumer payment due to insurer hesitation [8]. Barriers also include concerns over data security and uncertain clinical impact. DNA arrays and PCR-based methods are commonly used for genotype screening due to their simplicity, cost-effectiveness, validation, and ability to detect specific genetic variants without incidental findings [11]. Building on prior work, community pharmacists are considered key for deploying pharmacogenomic testing, with studies indicating that medication adjustments based on pharmacogenomic data have minimal impact on overall drug therapy costs. Implementing a pharmacogenomics-enriched medication management program in older adults resulted in significant clinical and economic improvements, including a $37 million savings over 32 months and a 9% reduction in healthcare resource utilization [11]. The program shifted healthcare use from acute services toward primary care, improved collaboration between pharmacists and physicians, and contributed to better outcomes aligned with the Quadruple Aim [10]. The comprehensive intervention combined patient education, pharmacogenomic testing, medication risk evaluation, pharmacist intervention, clinical decision support, and information sharing with physicians [7]. The pharmacogenomic component used a rigorous selection process to include clinically relevant variants, ensuring high coverage; 100% of participants had at least one impactful variant, and 66% had genetic risks in their prescribed medications. The integration of pharmacogenomics with

systematic medication evaluation and decision support was key to the program's success [9]. The impactful factors for scalable genetic testing include clinical utility, laboratory technology, user acceptance, implementation models, and economic value, which have reached a tipping point for large-scale pharmacogenomic testing globally. Recognizing this, health systems, payors, and population caretakers can leverage current evidence to promote genetic testing as a standard, cost-effective approach to improving health outcomes and reducing healthcare costs [8].

Standardization of Workflows and Reporting

Proteogenomic testing and the interpretation of reported results involve complexities that necessitate well-structured clinical workflows [7]. At present, the operational and workflow processes for proteogenomic testing, including ordering, result interpretation, and delivery of personalized medicine recommendations, are not yet standardized within primary care systems [6]. Global and national gene/drug guideline consortia outline comprehensive strategies at a macro level for decisions within and between different classes of antidepressants and antipsychotics, as well as across all pharmacogenes. Nevertheless, de facto decision-support systems that permit automated reporting of personalized genomic medicine and clinically actionable proteogenomics recommendations based on genetic and epigenetic data remain relatively rudimentary. Moreover, adoption of these frameworks by primary care practices is not always guaranteed [17]. Clear communication of test specifications and results, including functional consequences and alterations in drug target protein-level pharmacogenomic markers, constitutes a prerequisite for clinical adoption [13]. Temporal barriers relating to clinician recognition of clinical value and assurance that the associated activity in the electronic health record represents commonly ordered tests further inhibit uptake of proteogenomic recommendations emerging from the interpretation of whole-genome and RNA-sequence data [12]. Proteogenomic testing and TMB efforts are ongoing in some laboratories, and the establishment of clear pathways for transition to clinical activity remains desirable. The identification of simple nomenclature and rigorous modelling relating gene expression to clinical annotations identified by the corresponding actions of transcription factors represents another health-systems challenge [11]. Formal clinical and epidemiological modeling of algorithmic pathways and recommendation scenarios is underway to facilitate expanded availability of proteogenomic and genomic tests to non-molecular-genetics primary care practices. The global identification of clinician-ready, triaged, macro-level pharmacometabolic decision-support rules across classes of customary drugs and the corresponding incorporation of newly emerging proteomic and pharmacogenomic-proteomic end-to-end processing advise comparable macro-level diachronic-prediction-event-design principles[10]. The ongoing global establishment of legislation and policies relating to the provision of pharmacogenomic test results to patients and generic recommendations relating to drugs-and-gene testing combinations without knowing the drugs currently in use constitutes a vital precondition for momentum propagation towards regulatory-political urgency and the reconsideration of national drug-monitoring approaches [12].

Policy and Guideline Developments

Policies, recommendations, and guidelines related to pharmacogenomics have been developed to better inform primary care providers about the integration of these services into practice. Such documents, spanning local, national, and global domains, are designed to stimulate research, spur service development, and facilitate broader implementation efforts [17]. Since the availability of these services, many have sought guidance for their implementation. New documents on pharmacogenomic testing have appeared regularly in the past few years, yet the principles articulated in earlier guidelines remain relevant. Starting in 2020, the American Medical Association (AMA) issued a set of documents under the banner Pharmacogenomics: A Guide for Health Care Stakeholders 7 to address homologous opportunities and challenges [15]. Focused on pre-emptive testing in specific populations, these materials resonate closely with those systems proposed for practical implementation [14]. Elements of clarification and validation have also been issued by a number of international and regional collaborations. A set of materials targeted to those interested in pharmacogenomic testing at scale was published by the U.S. National Academies of Sciences, Engineering, and Medicine. This embedded system of evidence sharing integrates pharmacogenomic services more closely into the choice of medication and dosage, while fewer optional steps reduce needs for revision once a service is established [15].

Implementation Science and Real-World Evidence

The majority of clinical research on pharmacogenomics (PGx), including proteogenomic investigations, has focused on demonstrating efficacy and safety in isolated pilot studies [17]. Many important aspects remain underexplored despite the growing number of publications on implementation and real-world evidence [18]. Due to short timelines, some large-scale studies on implementation science and routine evidence have faced unavoidable methodological challenges [19-21]. Substantial unmet medical needs exist in primary care, primarily linked to chronic disease management and cancer, where genetic and integrated PGx testing holds the potential to

improve patient care significantly, especially when integrated into clinical workflows. However, many PGx discoveries beyond the classic warfarin example have yet to fully address healthcare challenges [22-25].

CONCLUSION

The integration of pharmacogenomics through proteogenomics represents a significant advancement in personalized prescribing within primary care. By combining genomic insights with protein-level functional data, this approach provides a more precise framework for drug selection, dosing, and monitoring, thereby improving therapeutic efficacy, minimizing adverse drug reactions, and enhancing patient-centered outcomes. Evidence from medication-management programs and real-world implementation initiatives indicates that such integrated testing can support safer prescribing practices and may offer favorable cost-effectiveness through reduced healthcare utilization and improved treatment optimization. Despite these benefits, widespread adoption remains constrained by limited workflow standardization, high testing costs, uneven reimbursement policies, inadequate clinician training, and insufficient diversity in genomic reference datasets. Bridging the translational gap between research and routine clinical use will require coordinated efforts in implementation science, policy development, education, and health-system infrastructure. Future research should prioritize large-scale pragmatic studies in diverse populations, standardized reporting and decision-support tools integrated into electronic health records, and robust economic evaluations across therapeutic contexts. With these measures in place, proteogenomics-enabled pharmacogenomics has the potential to become a routine, equitable, and cost-effective component of primary care, improving medication safety and advancing precision medicine at the population level.

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