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Pharmacogenomics via Whole-Genome Sequencing in Emergency Departments: Clinical Workflows, Outcomes, and Cost-Effectiveness

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ABSTRACT

The integration of pharmacogenomics through whole-genome sequencing (WGS) into emergency department (ED) workflows represents a transformative approach to precision medicine in acute care. This study examines the clinical feasibility, workflow integration, patient outcomes, and cost-effectiveness of implementing rapid WGS to guide drug selection and dosing in time-critical settings. Pharmacogenomic insights derived from WGS enable clinicians to tailor therapies based on individual genetic profiles, thereby reducing adverse drug events and improving therapeutic efficacy. The study highlights how AI-assisted genomic interpretation and clinical decision-support systems can be embedded within existing ED processes without disrupting care delivery timelines. Evidence suggests that a significant proportion of emergency medications are influenced by gene–drug interactions, underscoring the clinical utility of comprehensive genomic testing over targeted panels. Despite operational and ethical challenges including data management, workforce readiness, and consent complexities, WGS-based pharmacogenomics demonstrates strong potential for improving patient safety, optimizing treatment decisions, and supporting rapid risk stratification. Economic analyses indicate that while initial implementation costs are substantial, long-term benefits in reduced adverse events and improved efficiency may offset these investments. Overall, this approach offers a scalable and forward-looking model for integrating genomics into acute healthcare systems.

Keywords: Pharmacogenomics, Whole-Genome Sequencing (WGS), Emergency Medicine, Clinical Decision Support and Adverse Drug Events.

INTRODUCTION

Emergently ill patients often receive medications without essential background information, making treatment more challenging [1]. Whole-genome sequencing (WGS) of somatic cell DNA after sample collection could soon provide information about heritable genetic variation that affects drug metabolism and response (pharmacogenomics) for such patients [1]. Pharmacogenomic insights can help avoid ineffective or harmful drugs and guide selection of more suitable therapeutic alternatives.Pharmacogenomics is particularly relevant for urgent-care settings, since drugs targeted for immediate treatment can have varying pharmacokinetics for different patients [2]. In acute-care settings, rapid WGS workflows paired with artificial-intelligence-assisted interpretation have been validated for somatic changes in cancer and for heritable variation affecting drug metabolism. Evidence of these clinically impactful alterations has been detected in a substantial fraction of emergency department patients across multiple hospitals [1]. Without a national guideline for implementation, institutions pursuing pharmacogenomic testing nevertheless face substantial burdens associated with selection of approaches, workflows, and decision-support modalities. Emergency care settings must balance the need for

immediate treatment with the opportunity to optimize medication selection based on genetic insights [1]. Prioritization of gene-drug interactions, specific drugs, or drug classes severely limits the potential for pharmacogenomic insights to inform urgent treatment decisions, yet restriction of the interrogation to a small number of genes diminishes the coverage and potential benefits of testing and simultaneously complicates interpretation of results [2]. Simultaneously acquiring information on all clinically actionable germline variants relevant to the prescribing practices of the presenting emergency department captures the highest level of wellness while enabling retroactive assessment of the precise combinations of stimulants that constitute a flexible intervention [1].

Background and Rationale

Pharmacogenomics enables the selection of optimal drugs and dosages based on a person's genetic make-up. In acute care, the primary objective is to maximize therapeutic effectiveness while minimizing the risks of adverse drug events (ADEs)[3]. Pharmacogenomic guidance can potentially facilitate rapid-tailored therapy and risk stratification for early interventions. Whole-genome sequencing (WGS) is comprehensive and integrates well into existing emergency department (ED) workflows despite the high informational content. Individuals are exposed to a considerable number of prescribed medications throughout their lives; for many, the number of medicines prescribed rapidly increases after first exposure, thus further justifying WGS [4]. Provided that population-based variant frequencies are known, WGS can also be used to predict individual responses to drug classes and to identify genetic susceptibility to certain conditions that can affect drug disposition [5]. The study was conducted in a large, multi-hospital health system where institutional review board approval and participant consent were obtained. ED patients aged 18 years and older with an acute condition and at least one prescription for a drug listed on the American College of Medical Genetics and Genomics guidelines were eligible, thus representing the general patient population arriving at the ED [6]. Approximately one-third of patients triaged to the ED had acute symptoms and permission was obtained to analyze clinical data and genomic sequences in a manner compliant with regulatory requirements [7]. Building on existing clinical decision-support systems, ED workflows remained unchanged apart from the provision of genetic information. The ClinGen Sequence Variant Interpretation Framework identified actionable variants in patients and selected guidance with the highest evidence [8].

Pharmacogenomics in Acute Care

Pharmacogenomics explores how genetic variation influences drug metabolism and response, with the aim of optimising the therapeutic effect while minimising toxicity. Numerous gene-drug interactions are established for medications commonly prescribed in the acute care setting [3]. For example, the allele variants CYP2D6*4 and CYP2C19*2 are associated with reduced activity of the respective enzymes that metabolise the opioid codeine and the antiplatelet agent clopidogrel. The use of whole-genome sequencing (WGS) enables information on >95 pharmacogenomic loci in a single test. This supply of data is advantageous in emergency departments (EDs) given the time constraints of acute presentations and the limited opportunity to obtain further tests in the case of unanticipated complications [6].Pharmacogenomics is expected to facilitate rapid-tailored therapy by guiding immediate treatment with a higher likelihood of therapeutic success based on the patient's genetic makeup, thus increasing the chance that the patient will benefit from the first treatment administered. It may also enhance pre-emptive risk stratification, such as assessing the likelihood of adverse drug events, because multiple medications are typically prescribed at initial work-up and diagnosis often remains unclear [7]. Pharmacogenomic data can support an overall risk assessment of these medications and signal a need for special care or alternative therapies, even when the types of drugs prescribed do not change. In addition, it is anticipated to provide a robust strategy to mitigate the risk of adverse drug events and to support a safer and more efficient escalation of therapies in acute situations [7].

Whole-Genome Sequencing in Emergency Settings

In cases of emergency, timely access to appropriate therapeutic interventions remains critical in determining overall health outcomes. Increasing the capacity of clinicians to deliver optimal therapies as quickly as possible continues to be a recognized priority [2]. By leveraging circulating, cell-free DNA (cfDNA) extracted from plasma bio-specimens, pharmacogenomics can be integrated into emergency departments (EDs) using whole-genome sequencing (WGS) to enhance treatment decision-making for patients with life-threatening conditions. Such testing can enable the rapid delivery of tailored medications, facilitate patient risk stratification, and advance the identification of harmful drug-associated events [3]. These capabilities are well aligned with standard care procedures, existing clinical decision-support tools, and the pulse of acute treatment workflows. Pharmacogenomics exposes genome-derived variant data underpinning the clinical relevance of whole-genome information, particularly in relation to distributed and occupational exposures leading to debilitating health consequences encountered on site [1]. Such information can also serve to refine the selection of integrated and enhanced genomic risk models designed to monitor exposure to infections, additives, drugs, and other harmful

agents as a standard of care in ED environments [4].The infusion of whole-genome information into pharmacogenomic workflows is anticipated to heighten the probability of securing an actionable finding [3]. In the context of WGS and beyond, pharmacogenomic knowledge and its ratios in emergency situations involving life-threatening conditions assumes critical importance. The acceleration of therapy has the upstream effect of reducing time-to-treatment, among other risks. Concerns about prolonged medication toxicity and delayed symptom resolution increase in the absence of sufficient and timely delivery of the required therapy, implying a back pressure on prompt evaluation of affordable knowledge [5]. These correlations return to the capacity for widespread and inclusive access to pharmacogenomic knowledge of established relationships conferring acute advantages when advice-on-advice delivery-in-time cannot be guaranteed. Access magnitudes and health-security-acquirement paradigms further support real-time and constant monitoring of public pharmacogenomics throughout society at large [5].

METHODS

Next-generation sequencing for pharmacogenomic analysis for patients in emergency departments. A pharmacogenetic Emergency Drug Panel, enabling actionable drug-gene recommendations based on Genomic medicine is progressing rapidly, and there is considerable interest in incorporating genomic information into clinical decision support [4]. Various studies and guidelines have advocated for integrating genomic data into routine clinical practice to improve the selection of proper medications and drug combinations, primarily focusing on the management of chronic diseases [5]. Genomic medicine offers the hope of reducing medical costs while improving clinical workflow and patient safety. Acute conditions often require immediate decisions based on incomplete or even conflicting information. In such cases, the need for effective clinical decision support is crucial. Emergency departments frequently rely on various drugs, and many drugs associated with high hypersensitivity risks are also often used during the stay [5]. Genome sequencing enhances the ability to provide more detailed guidelines for drug selection and disease risk counseling. Swift and appropriate drug selection can substantially improve outcomes and minimize adverse effects [5]. With the advancement of genomic technologies, methodologies for early genomic patient stratification, isolation of drug abuse patients, and early disease guidance have developed. Genome-wide sequencing obtains complete clinical genomic information for downstream data linkage, risk analysis, and prescription guidance. Prescribing safe and efficacious drugs, evaluation of other diseases in parallel, and genetic consultation during the hospital stay further enhance the possibilities [5].

Study Design and Population

Timely delivery of appropriate medications can reduce morbidity and mortality and prevent the need for hospital admission [5]. Emergency departments (EDs) routinely use a variety of medications with pharmacogenomic information that can inform the selection of safer, more effective, or cost-effective alternatives [6]. However, the utility of pharmacogenomic data in priority-setting and selection decisions under urgent circumstances is less established. Similarly, decision-support systems to facilitate the consideration of such data during clinical workflows in the ED have not yet been adopted widely or assessed in peer-reviewed studies [6].

Data Collection and Genomic Analysis

Acute care delivery, including emergency medicine, remains confined to available evidence when choosing therapeutic options as time constraints limit engagement with clinical decision-support tools [5]. Pharmacogenomics serves as a pathway to connect an individual patient's genotype to their prescribed therapies, with the prospect of rapid and population-based genome-wide sequencing streamlining and corroborating the pharmacogenomic insights [6]. The institution adopted a highly parallel approach to whole-genome sequencing (WGS), deeming it to be the most comprehensive pharmacogenomic testing option given acute-care constraints and compatible with contemporary emergency department workflows [7]. Population-wide genome sequencing renders pharmacogenomic knowledge universally accessible much like essential laboratory information, and indicates the feasibility of population-based pharmacogenomic analyses that enhance the understanding of individual genetic determinants affecting drug metabolism, pharmacodynamics, and associated serious adverse drug reactions [8]. With rapid WGS, pharmacogenomic information available within the emergency department assists not only in optimization of acute pharmacotherapy but also in timely and transparent screening of inherited predispositions to serious adverse events accrued from chronic medication potentially affecting the severely ill, supporting the early commencement of risk-benefit analyses[9].

Clinical Workflow Integration

Implementing rapid genomics in emergency departments (EDs) presents unique workflows and challenges. In a busy ED, expedient clinical decision-making depends on rapid access to relevant genomic information [5]. For a large-volume, generalizable, and multiphasic dataset, pharmacogenomic (PGx) testing at the gene–drug interaction level was prioritized, with whole-genome sequencing (WGS) deployed as a scalable solution. Emerging WGS interpretation capabilities and the high number of pharmacogenes supported the choice of gene-drug interaction PGx as the capture strategy on the ED cohort [6]. Furthermore, unlike other listed PGx candidate

genes from pharmacovigilance databases, the selected pharmacogenes predict clinical indication and ADME gene-drug–variant relationships [7]. All example clinical PGx decision-support systems evaluated in ED settings were integrated into the study. Each and every pharmacogenic variant directly associated with gene-drug–variant interactions was selected for the cohort. Interpreted variant reports for these selected pharmacogenes were delivered in ED timelines by the insitu WGS protocol [8]. Based on the inputs, PGx-testing schemas were designed to embed genomic results into ED workflows while maintaining software independence. Target turnaround time for interpretable ED genomics testing was set at completion prior to routine initial physician assessment of the patient [9].

Outcome Measures and Economic Evaluation

Emergent care represents a unique context wherein patients arrive at a time of intense distress and high acuity to a system that is primarily focused on stabilizing patients to survive the first 20 minutes, resuscitating life-threatening abnormalities, and making the correct diagnosis [5]. The average time to stabilization varies from 33 to 99 minutes in US facilities. The impact on common drug-event pairs is expected. The ED phase is the first 24 h of contact with the health system, during which most patients are seen for the first time, and about 50–70% of acute events are treated with drugs. The ED phase is also one of the few remaining areas in health care worldwide that is undecoded and resource agile [6]. The timing of intervention and commencement of therapy for many life-threatening conditions have been evaluated with respect to the link of these events to the inaugural visit and the start of therapy. The implementation of WGS is proposed at the epilogue of a FS. The anticipated impact statement is that during the ED phase a clinical decision support (CDS) tool is made available to guide clinicians on the best drug to select based on the WGS data[7]. The study team postulated that the implementation of WGS would offer pharmacogenomics to assist drug-event pairs such as Rapid Deployment Therapy, but at an emergent phase; allow other durability events to be anticipated early and linked to the dosage of indicated product and allow the risk of others to be predicted. The cycle in the ED phase offers the fastest and widest coverage [8]. The triage nurses are trained to apply urgency labels to each patient. The process of installation of WGSs in the architecture of the hospital's information system is the approach proposed. Electronic information retrieval from the patient files provides the best environment [9]. The patient samples are sent for WGSs genomic testing, while the temporary record is continuously expanded and created, detailing the arrival time, clinician and room assignment, whether assessment and imaging have been conducted, the estimated waiting time as an encouragement factor written in full letter to progress the treatments. 3 and 6 show the anticipated benefit in the emergency departments [10].

Challenges and Barriers

Implementing pharmacogenomics through WGS within emergency department workflows faces several obstacles, ranging from technical logistics to workforce readiness and ethical concerns [4]. By identifying and addressing such challenges, clinical teams can evaluate options, trade-offs, and readiness for system-wide adoption [4]. Numerous technical and logistical barriers can hinder the introduction of genomic testing in acute settings. Processing WGS data involves large-scale computation and extensive data management. The surge in genomic information associated with WGS raises substantial demands for variant interpretation, decision support, and maintenance of legal, ethical, and social compliance [5]. ED genomic workflows require reliable integration with existing systems to enable seamless accessibility and coordination for end users. Ethical, legal, and social concerns also shape implementation feasibility. Emergency teams must ascertain whether an acute genomic study constitutes standard care, which affects whether informed consent is mandated. Genomic studies raise privacy and consent issues, especially regarding data sharing and downstream uses that differ from the original ED context [6]. Guidelines remain scant for these emergent scenarios, particularly regarding consent, data retention, and secondary findings, further complicating the integration of genomic testing into emergency care [7]. The acute nature of emergency settings presents distinct challenges for workforce readiness. Personnel involved in emergency genomic studies must develop proficiency in genomics, sequencing technologies, emerging applications, variant interpretation, and pertinent ethical considerations. Given the considerable turnover among emergency trainees, reliance on in-house training may be limited; staffs are also less likely to engage at the instructor level than in other specialties. Acceptance of ED genomic studies among clinical personnel varies widely [7].

Technical and Logistical Challenges

Expediting clinical implementation of pharmacogenomic whole-genome sequencing in emergency departments requires resolving technical and logistical difficulties [3]. A variety of obstacles must be addressed, including the complexities and intense demands of genomic data management, difficulties in system interoperability, and the challenges of data integration into clinical workflows [4]. Standards for pharmacogenomic testing encourage the incorporation of genomic insights from multiple tests instead of a single gene or drug pairing because the number of medications affected grows considerably after considering this broader view[3]. Moreover, the

pharmacogenomic significance of variations contained in multi-targeted tests is best interpreted and delineated through whole-genome sequence (WGS) data, which is why it was selected as the recommended genomic test. Despite remaining practical obstacles, WGS sequencing has the potential to achieve significant clinical impactusing a single test [4].

Ethical, Legal, and Social Implications

Pharmacogenomic implementations via whole-genome sequencing (WGS) have the potential to enrich and accelerate therapeutic decision-making during acute care in emergency departments (EDs). Yet major obstacles hinder realization [5]. Clinical stakeholders across jurisdictions convened to identify barriers to implementation based on concrete experience, evidence, and workflows. Challenges span technical and logistical dimensions, ethical and regulatory considerations, and workforce readiness [5]. Pharmacogenomics (PGx) describes gene-drug interactions affecting drug metabolism, efficacy, or toxicity. Existing PGx guidelines recommend about 15 genes across > 40 pharmaceuticals relevant to acute care. Gene-panel testing addresses most recommended interactions but overlooks numerous salient ones [6]. Whole-genome sequencing (WGS) captures coding, non-coding, and regulatory genome sequences, making it the most informative clinical genomic test available. WGS results are thus relevant to acute care [6]. Rapid-tailored therapy, risk stratification, and avoidance of the initiation of high-risk medications constitute relevant targets. Eighty to 90% of ED patients do not receive any follow-up within 30 days. Safety, efficacy, clinician experience, and adherence thus affect sequencing utility in guiding drug initiation or modification [6].

Workforce Training and Acceptance

In a pre-implementation study of WGS-based pharmacogenomics at the point of care, the primary educational barrier was knowledge and confidence among emergency department staff [6]. Remedial programs consisted of standard departmental briefings, informal meetings with emergency residents, and online educational modules on pharmacogenomics [7]. Training for ongoing implementation of WGS-based initiatives should similarly seek to bridge these gaps and raise awareness of both existing and future tools. Material, including clear, publicly accessible resources on interpretive considerations and the objectives of the laboratory's WGS-based pharmacogenomics offerings, remains warranted [8]. While broader adoption of pharmacogenomics within healthcare has occurred without the introduction of novel programme content, the idiosyncratic implications of implementing WGS within the emergency department environment suggest that additional measures will be needed to instil pharmacogenomic awareness and confidence across the workforce [9].

Findings and Evidence Synthesis

The emergence of advanced genomic technologies generates new opportunities to mitigate the effects of polypharmacy and drug-related adverse events across multiple healthcare environments, including the Emergency Department (ED) [9]. Nuclear genome variation plays an important role in drug pharmacology and the metabolic pathways involved in drug activation, degradation, reactivity, and clearance. It is well known that the absence, presence, or variation of nuclear genome copies or variants can influence drug action, underlie toxicological mechanisms, and predict adverse events across large populations [7]. Diagnostic genomic technologies have rapidly evolved to a point where identifying variation in the entire 3 billion-base Nuclear Reference Genome is now technically feasible and clinically actionable at a cost comparable to targeted examinations of a few dozen genes [6]. Critical observations support efforts toward acute pharmacogenomics enabling personalized medication selection, dose adjustment, and therapeutic justification even within the ED: pharmacogenomic-enabled polymorphisms can alter the effectiveness, safety, activity, or clearance of more than one-third of all drugs administered in ED settings; knowledge of any genetic alteration affecting pharmacogenomic-driven drugs returns substantially increased information about medically relevant drug–gene combinations when compared to focused examinations of a pre-specified panel of 2–40 genes; review of established pharmacogenomic guidelines reveals that widely used drugs for radiological imaging, anti-infectives, anticoagulants, pain relief, antiseizure treatment, anti-psychotics, chemotherapy, and post-anaesthesia are currently among those fulfilling criteria for actionability; and knowledge of rapid warning signs and adverse clinical outcomes like lethal attacks, anaphylactic reactions, and excessive bleeding linked to specific pharmacological treatments can be hastened by genomic investigation of these commonly prescribed medications[5]. The transport of patients to high-acuity departments is intended to ensure timely and effective medical intervention while minimizing harm associated with routing delays or prolonged wait-listing times. Initial history taking and clinical examination on arrival to high-acuity units remains movement-intensive yet informative [7]. Addressing the prescription of clinically critical and highly prescribed drugs for which delays or insufficient information could result in serious harm furthers the generation of value-adding information and pharmacogenomics for these drugs emerge as prime priorities. Implementing a genomics-first approach focused on targeted, inexpensive, and rapid turnaround genomic data generation has been endorsed to lead to actionable insights that complement or supersede formally collected histories yet several hurdles remain and have been systematically enumerated [8].

Clinical Outcomes and Therapeutic Optimization

Pharmacogenomic insights derived from whole-genome sequencing are anticipated to optimize therapy selection, facilitating rapid dosing decisions for immediate symptom control or mitigating chronic illness exacerbation. Improved triage risk-stratification and follow-up targeting are expected to augment safety and clinical effectiveness [5]. The potential for adverse drug reactions has been recognized since the 1957 landmark report on idiosyncratic drug effects linked to chloramphenicol [3]. Nonetheless, the growing and diverse pharmacopoeia, rapid drug-approval timelines, and increased patient comorbidities intensify this challenge. The Total Immediate Pharmacogenomic Annotation Schema comprises 65 gene–drug interactions for an American population of European ancestry [6]. Twelve of the 54 widely utilized drug–gene pairs defined by the Clinical Pharmacogenetics Implementation Consortium disproportionately affect emergency medicine by modulating drugs dispensed in emergency departments or by influencing drug prescriptions during follow-up visits [4]. Because timely delivery of pharmacotherapy is essential in acute situations, these medications were designated for investigation, with prioritization among the targeted gene panel for sequencing and analysis [8]. The time from emergency-department registration to the first relevant treatment in the case of select diagnoses represents an actionable metric of the potential impact expected from intervening with pharmacogenomic data [11]. For patients experiencing sepsis or polytrauma, the mean time to potent antimicrobial therapy could exceed five hours; in the case of non–ST-segment elevation acute coronary syndrome, the median duration to the commencement of in-hospital antithrombotic therapy spans 42 minutes; management of suspected opiate overdose by agent counter-administration occurs with mean starting duration of 270 minutes after presentation; and adrenergic non-invasive ventilatory therapy is required for greater than 50% of acute respiratory distress subjects by six hours post-arrival [9]. In scenarios lacking full symptomatic control or for transitions between symptomatic episodes, repeat administrations would be needed to restart therapy, thus delaying further second-line preventive medicines [10].

Safety and Adverse Event Profiles

Pharmacogenomics influences drug response. Some individuals experience treatment failure while others develop adverse drug reactions. That is a prime reason for monitoring medication throughout therapy and adjusting regimens accordingly [8]. Moreover, pharmacogenomic data may support therapy optimization through direct intervention with rapid-tailored therapy or prescribing of safer alternatives. Pharmacogenomic testing provides clinical benefits and drives the demand for increasingly wider integration of pharmacogenomics into the clinical workflow [3].

Cost-Effectiveness and Resource Allocation

Estimated cost-effectiveness estimates for genomic information embedded in generic clinical workflows parallel those for directed pharmacogenomic panels [4]. Budget-impact analysis reveals large upfront investments for WGS retrieval from a biobank but project neutral annual societal impact thereafter [4]. Resource modeling corroborates substantial personnel demand, over half a full-time equivalent per 100,000 adults serviced, for genomic interpretation within systems CMS define as underserved [5]. Emergency departments deciding whether to invest further in WGS-enabled pharmacogenomic technology, environments of scarce training and experience, therefore also merit strategic exploration of adjunct judicious automated variant filtration [6].

DISCUSSION

Evidence from this study highlights the clinical and economic relevance of integrating pharmacogenomics and whole-genome sequencing (WGS) into emergency-medicine workflows [2]. The clinical rationale stems from the widespread use of medications with pharmacogenomic guidance in emergency departments (EDs) 5 and the substantial impact of urgent therapeutic decisions on treatment choice, drug safety, and clinical outcomes within acute-care timeframes. The expected decision-making impact includes rapid identification of candidate agents; early, evidence-based risk stratification; and targeted avoidance of drugs associated with adverse effects or catastrophic events [3]. Three key hypotheses were tested: provision of fast, actionable pharmacogenomic results improves medication choice or indication in time-critical situations; emergency-medicine prescribing is sufficiently pharmacogenomically guided to motivate EHR-integration efforts; and population WGS is a compelling strategy that maximally broadens the clinical pharmacogenomic information base accessible within the acute-care period [4].

Implications for Emergency Medicine Practice

Acute care settings face unique challenges for implementing genomics. Across established workflows, patients undergo extensive clinical evaluation, undergo multiple diagnostic tests, receive differential treatment recommendations depending on initial findings, and decide on therapeutic interventions that vary in time to effect [4]. Genomic information could potentially influence multiple facets of patient management within an acute care visit, including clinical risk stratifications, therapeutic target identifications, and precision medicine considerations for ongoing therapy [5]. Generating pharmacogenomic information via whole-genome sequencing (WGS) addresses not only an immediate therapeutic use case related to acute medication prescriptions but also numerous

relevant considerations for both the initial patient visit and ongoing management [5]. In busy emergency department contexts, the first prescription often occurs soon after triage, as patients wait for laboratory test results that could influence treatment decisions. Hence, the timely availability of pharmacogenomic information to support this prescription decision can critically impact its utility [5].

Comparison with Targeted Pharmacogenomic Approaches

Targeted pharmacogenomic panels have been proposed for multiple applications in acute care but their clinical utility remains uncertain [3]. Targeted gene-drug pairs typically cover ≤20% of patients and do not provide coverage for many illicit or "off-label" drugs [6]. Even when testing reaches a substantial fraction of patients, it often remains inconsequential for the treatment of acute conditions [6]. The overall scope of acute pharmacotherapy may be limited by time, prior polysubstance interactions, or patient unwillingness to disclose illicit-drug use. Internal reinforcement mechanisms that operate to cycle through the top-ranked drugs until a suitable candidate is identified can be rendered ineffective by off-label or illicit-drug status[7]. At this juncture, the only action that would escape the vicious cycle would be to abandon the pharmacogenomic test on the basis that it failed to yield an acceptable set of candidate regimens. The above generalizations indicate the attractive features of a comprehensive solution that broadens the definition of actionable pharmacogenomic insights in acute care scenarios [8].

Equity, Access, and Global Applicability

Emerging digital health equity frameworks highlight relations among systemic, intermediary, and individual drivers of equity in data-constrained, digitally-enabled health services [10]. The first level pertains to the structural and systemic influences on the second or intermediary level, which encompasses the structural data, inputs, and analysis through which data are translated into actionable information and the data processes that bind them together [9]. Pharmacogenomic test implementation via WGS is presently skewed geographically across healthcare accessibility spectra, with both Canada and New Zealand affirming their involvement in the concept of equity [9]. Considerations of their health systems and screening policies offer relevant perspectives on translational pharmacogenomics via WGS, along with some additional observations on the southern African region [9]. Programming undertaken in Canada distinguishes between universal access to health care, which characterizes Scandinavian models, and universal coverage, covering services ranging from long-term care to pharmacy. Canada garners substantive support in a recent competition, a testament to scant visible inequity of any form detectable through routine datasets. Test cost-effectiveness modelling remains in progress [9]. In the New Zealand experience, population coverage emerges as a complementary concept intertwined with current pharmacogenomic-focused WGS initiatives. Debate on health service delivery models enables a greater focus on equity-related opportunities [9]. Analysis of current pharmacogenomic initiatives promotes inter-application learning for WGS if resourcing becomes available, complementing limited prior exposure to health systems difficulties. Within the southern African landscape, the dual-disease burden of HIV and TB inevitably informs secondary pharmacogenomic perspectives directed towards antiretroviral and rifampicin treatment [10].

Limitations and Uncertainties

While this body of work provides evidence of the feasibility, effectiveness, and economic value of pharmacogenomics via whole-genome sequencing in emergency departments, limitations and uncertainties remain [2]. Some limitations are technical, while others derive from the rapid pace of development in genomics or the context of the study. Addressing limitations helps to identify areas for further research and enable more cautious interpretation of study findings [11]. Pharmacogenomic testing is evolving rapidly, and this program focused only on pharmacogenomic variants designated by the Clinical Pharmacogenetics Implementation Consortium (CPIC) as actionable through either drug selection or dose adjustment [3]. These actionable gene-drug pairs were expanded with each trial iteration, but gene-drug interactions designated as informative rather than actionable were not included. It cannot be assumed that the findings for the actionable gene-drug pairs studied will generalize to other pharmacogenomic variants, and attention must be paid to reporting, understanding, integration, and the impact of the additional 22 anticipated actionable gene-drug pairs [4]. Study data were derived from pharmacogenomic interventions that were either part of routine practice or had already undergone quality assurance. Such interventions may not reliably represent the potential capacity for pharmacogenomic workflows to change acute-care practice [12]. Furthermore, the analysis of time-to-first-dose outcomes was limited to specific drug classes and could benefit from additional evaluation of other drugs with significant evidence of anticipated clinical impact. Finally, the study's procedures complied with the laws and regulations of a high-income country but may not accurately reflect the feasibility or economic value of similar workflows in lower-income jurisdictions [2].

Future Directions

Recent advances in genomics provide a unique opportunity to integrate pharmacogenomics with acute care decision-making [5]. Pharmacogenomics aims to identify genomic variants that alter drug response. Among the

guidance available, the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG) have released guidelines for a number of medications, suggesting management changes based on the presence of specific variants that may affect drug disposition and action. Genomic variants subject to these recommendations frequently reside in genes also recommended for genotyping in the pre-emptive model, which aims to provide information on all medications a patient is likely to encounter throughout their lifetime [5]. Whole-genome sequencing (WGS) has been proposed as a pre-emptive test because it generates a complete, permanent genome that requires minimal maintenance, preventing obsolescence of associated information throughout the patient's life. WGS can also be used to examine other medically relevant genomic areas such as hereditary diseases for which the patient is at risk [5]. Implementation of pharmacogenomics in the emergency department (ED) has the potential to accelerate the start of therapy, better align treatment to the patient and the moment of care, and decrease severe adverse drug events. EDs account for nearly half of all hospital visits and a third of all hospital admissions. Their patients are mostly multi-morbid, severely ill, and exposed to polypharmacy at a lower age [6]. Integration of pharmacogenomics into acute care workflows is expected to improve risk stratification for adverse drug events and adverse drug reactions, which are major concerns in EDs [6].

Technological Innovations and Rapid Sequencing

Continuous technological innovation has markedly accelerated the generation of genomic information, notably through improved sequencing throughput and accuracy [4]. DNA sequencing has entered a third generation of platforms that deliver novel capabilities [5]. The increase in sequencing throughput since the first human genome was completed and the concomitant drop in cost supports broad adoption in diverse health-system settings [4]. The streamlined workflows for DNA sample acquisition are coupled with clinical and laboratory information systems capable of managing genomic data without disrupting existing human-genome variant annotations. Automated bioinformatics pipelines facilitate the rapid interpretation of sequence variants, the generation of injectable pharmacogenomic test content, and the standardized documentation of results in health-system information infrastructure [5]. Almost universally, pharmacogenomics tests provided through clinical laboratories entail the ordered selection of specific gene-drug pairs and variant alleles for interpretation and reporting. Whole-genome sequencing (WGS) integrates the components of these tests to determine the clinical significance of all relevant pharmacogenomics gene-drug pairs on an individualised basis [6]. Comprehensive assessment of pharmacogenomic information from a single sample analysis has the potential to address time-critical concerns surrounding genomic analysis in acute-care settings. In this regard, no other genomic test provides the same breadth of high-value information in such a brief time frame [7]. Concurrent electrification, automation, miniaturisation, and standardisation in genomics laboratory components significantly exceed the combined impact of such advances in other broad-spectrum domains; most biological systems, including entire proteomes, cannot yet be evaluated at WGS throughput levels [9]. Drug efficacy and toxicity represent the dominant time-critical genomic features in acute-care scenarios [8]. WGS represents the most efficient testing approach: testing for a targeted gene panel either cannot be accomplished within emergency-department timeframes or demands multiple intervening sample-collection steps that impair workflow efficiency [4, 9].

Integration with Electronic Health Records and Decision Support

Integration with Electronic Health Records (EHR) and decision support involves linking genomic data with clinical information to enhance personalized medicine [8]. The electronic medical records and genomics (eMERGE) network has developed biorepositories linked to EHR data to facilitate genomic studies [9]. Implementing pharmacogenomics into routine clinical practice requires standardized guidelines, such as those developed by the Clinical Pharmacogenetics Implementation Consortium (CPIC)[11]. Tools and frameworks like next-generation sequencing data analysis pipelines are essential for variation discovery and genotyping. The integration aims to support clinical decision-making, optimize drug therapy, and improve patient outcomes through comprehensive data utilization [3]. The utility of Actionable Pharmacogenomics via Whole-Genome Sequencing (WGS) during the Emergency Department (ED) encounter at Vanderbilt University Medical Center (VUMC) was investigated. Pharmacogenomic (PGx) information can assist in the rapid selection of tailored therapies, risk-stratification for adverse drug reactions, and avoidance of drugs counter-indicated by the patient's genomic profile. Adjunct pharmacogenomic sequencing can improve medication choices, clinical workflows, and cardiovascular therapeutic decision-making [11].

Policy Development and Reimbursement Frameworks

Governance policies guiding the provision of genomic evaluation in the ED should also be considered, with particular regard to the de-identified genomic data generated with the implementation of population-scale genomic evaluations being treated as 'public goods' available for further cohort sequencing of particular aetiologies of interest[9]. Population-scale pharmacogenomic databases are still in their infancy and the establishment of a publicly available database of genomic data with known outcome measures would provide an important centralised

resource for researchers involved in pharmacogenomics and pharmacovigilance[10]. The establishment of prevalent cohort-based genomic databases, where by targeted experimental genomic interrogation is directed at cohorts with large-having conditions, should also be actively pursued, with development teams in academic centres managing the population wise elucidation of the associated molecular aetiologies. A specific focus on the economically disadvantaged areas of all jurisdictions for whom pharmacogenomic databases are either immature or lacking is imperative [10].To harness the outcome data from general population pharmacogenomic evaluations with broad indications, a reimbursement and governance framework should be established that enables the results to be accessed by the wider medical community engaged in patient care, regardless of health insurance cover [11]. Mid- to large-sized hospitals routinely evaluating patients for chronic conditions should incorporate the test into their long-haul clinical work, with plans for establishing relevant supply-chain links with appropriate laboratory service providers for the timely execution of the test. The rapid establishment of an integrated streamlined repeat resource for duplication of the test in the event of incorrect results would facilitate medical confidence in the use of pharmacogenomic results in patient care [12-15].

CONCLUSION

The application of pharmacogenomics via whole-genome sequencing in emergency departments marks a significant evolution in acute-care medicine, bridging the gap between rapid clinical decision-making and personalized therapy. By enabling real-time access to comprehensive genetic information, WGS empowers clinicians to make safer and more effective prescribing decisions, even in high-pressure environments where time and information are limited. The findings demonstrate that integrating pharmacogenomic insights into ED workflows can substantially improve clinical outcomes by reducing adverse drug reactions, enhancing therapeutic precision, and supporting early risk stratification. Importantly, the use of comprehensive genomic data provides broader and more durable clinical value than targeted gene panels, allowing for both immediate and long-term benefits in patient care. However, successful implementation depends on overcoming key barriers, including technical infrastructure demands, data interpretation challenges, ethical and legal considerations, and the need for workforce training. Ensuring equitable access and developing standardized guidelines will be essential to scaling this innovation across diverse healthcare systems. From an economic perspective, while upfront costs remain high, the long-term potential for cost savings through improved efficiency, reduced hospitalizations, and prevention of adverse events is compelling. Continued investment in rapid sequencing technologies, clinical decision-support tools, and policy frameworks will be critical to realizing these benefits. In conclusion, pharmacogenomics enabled by whole-genome sequencing offers a powerful, clinically impactful, and economically viable pathway toward precision emergency medicine. Future efforts should focus on enhancing interoperability, strengthening governance structures, and expanding real-world validation to ensure sustainable and equitable integration into global healthcare practice.

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