

Telemonitoring Alerts and Blood Pressure Control in Rural Hypertension Patients

Johanne T. Møller*

Department of Clinical Medicine, Faculty of Medicine, Aalborg University, Aalborg, 9000, Denmark

Corresponding author: johanne.tmler@gmail.com

Abstract

Hypertension remains a leading cause of cardiovascular morbidity and mortality globally, with rural populations facing disproportionate risks due to geographic and socioeconomic barriers to healthcare access. Telemonitoring has emerged as a promising strategy to bridge this gap, yet the mechanisms by which remote data collection translates into tangible clinical outcomes remain insufficiently understood. This implementation study investigates the direct link between telemonitoring alerts and blood pressure control among rural hypertension patients. Over a twelve-month period, we evaluated a digital health intervention deployed in resource-constrained settings, focusing on how automated clinical alerts generated by home blood pressure readings influence provider response times, patient engagement, and ultimate hemodynamic control. The findings indicate that the clinical responsiveness to actionable alerts is a critical determinant of treatment success, significantly outperforming passive data collection models. Furthermore, the integration of telemonitoring systems into rural primary care workflows faces unique infrastructural and behavioral challenges, including alert fatigue and connectivity issues. By elucidating the operational pathways that maximize the efficacy of digital health alerts, this study provides actionable evidence for optimizing telehealth programs. The insights derived from this research are vital for policymakers and healthcare administrators seeking to scale rural telecardiology initiatives and improve chronic disease management in underserved communities.

Keywords: Telemonitoring; Hypertension; Rural Health; Clinical Alerts; Digital Health Integration

1. Introduction

1.1 The Global and Rural Burden of Hypertension

Hypertension is universally recognized as a primary modifiable risk factor for cardiovascular disease, stroke, and chronic kidney disease, contributing to a substantial proportion of global mortality [1]. Despite the availability of effective pharmacological interventions and lifestyle modification guidelines, achieving optimal blood pressure control remains a persistent clinical challenge [2]. The burden of uncontrolled hypertension is particularly pronounced in rural and remote communities, where healthcare disparities are exacerbated by systemic inequities [3]. Patients residing in these areas frequently encounter significant barriers to accessing continuous primary care, including extended travel distances to medical facilities, a scarcity of specialized healthcare providers, and limited health literacy [4]. Consequently, rural populations often present with higher baseline blood pressure levels, experience delayed diagnoses, and suffer from elevated rates of end-organ damage compared to their urban counterparts [5]. Addressing this rural-urban health divide necessitates innovative models of care delivery that transcend geographical limitations and facilitate proactive

chronic disease management. Traditional episodic care models, which rely on infrequent clinic visits for blood pressure measurement and medication adjustment, are fundamentally inadequate for the dynamic nature of hypertension, particularly in settings where physical access to clinics is constrained [6].

1.2 The Evolution of Telemonitoring Solutions

In response to the limitations of conventional care, telemonitoring has garnered considerable attention as a transformative approach to chronic disease management [7]. By enabling patients to measure their physiological parameters in the home environment and transmit this data electronically to healthcare providers, telemonitoring facilitates a continuous stream of clinical information [8]. This continuous data collection paradigm has the potential to overcome the phenomenon of white-coat hypertension, improve diagnostic accuracy, and empower patients to take an active role in their health management [9]. Early iterations of telehealth primarily focused on passive data collection, wherein patients submitted readings that were periodically reviewed during scheduled appointments. However, contemporary telemonitoring systems have evolved to incorporate sophisticated algorithmic processing, capable of identifying anomalous trends and generating real-time clinical alerts [10]. These alert mechanisms are designed to flag acute hypertensive episodes or persistent suboptimal control, thereby prompting timely clinical interventions [11]. The transition from passive monitoring to active, alert-driven management represents a critical evolution in digital health, theorized to be the primary driver of improved clinical outcomes in remote care models [12].

1.3 Identifying the Implementation Gap

Despite the theoretical advantages and technological advancements of alert-driven telemonitoring, the empirical evidence regarding its efficacy in rural settings remains highly variable. A significant gap exists in the literature concerning the translational pathway between the generation of a digital alert and the realization of improved blood pressure control [13]. Many pilot programs demonstrate high rates of patient compliance and data transmission but fail to demonstrate corresponding improvements in clinical endpoints. This discrepancy often stems from implementation failures, such as poor integration of alert systems into existing clinical workflows, provider alert fatigue, and insufficient resources to manage the increased volume of actionable data [14]. Furthermore, the unique infrastructural challenges of rural environments, including inconsistent broadband connectivity and limited clinical support staff, introduce additional complexities that are frequently overlooked in studies conducted within well-resourced academic medical centers [15]. Understanding how telemonitoring alerts are received, processed, and acted upon by rural healthcare teams is essential for optimizing system design and maximizing therapeutic impact.

1.4 Study Objectives and Significance

This implementation study aims to bridge the aforementioned knowledge gap by comprehensively evaluating the relationship between telemonitoring alerts and blood pressure control in a rural cohort of hypertensive patients. The primary objective is to quantify the clinical response times to automated alerts and assess their direct correlation with longitudinal blood pressure reduction. Secondary objectives include analyzing the types of alerts generated, identifying patient and provider-level factors that influence response efficacy, and characterizing the operational bottlenecks encountered during system deployment in a resource-constrained primary care network. By focusing on the implementation mechanics rather than merely the technological capability, this research provides a nuanced understanding of digital health interventions in real-world settings. The findings of this study are intended to inform the development of evidence-based protocols for telemonitoring integration, guide resource allocation for rural health initiatives, and ultimately contribute to the reduction of cardiovascular disparities in underserved populations.

2. Literature Review and Background

2.1 Historical Context of Rural Telemedicine

The application of telecommunications technology to healthcare delivery in rural areas has a rich history, evolving in tandem with advancements in communication infrastructure. Initial efforts in the late twentieth century primarily utilized telephone-based consultations to connect isolated patients with regional medical centers [16]. While these early modalities improved access to medical advice, they lacked the capacity for objective physiological monitoring, rendering them insufficient for the precise management of complex chronic conditions like hypertension. The advent of internet-based platforms and the subsequent proliferation of mobile health technologies catalyzed a paradigm shift, enabling the remote transmission of digital health data. However, the adoption of these technologies in rural regions has historically lagged behind urban centers due to the digital divide, characterized by disparities in internet access, digital literacy, and the availability of compatible cellular networks [17]. Overcoming these infrastructural barriers has been a primary focus of rural telehealth research, with numerous initiatives demonstrating the feasibility of deploying store-and-forward technologies and cellular-enabled diagnostic devices in remote communities [18].

2.2 Mechanisms of Alert-Driven Clinical Intervention

The efficacy of modern telemonitoring systems is largely predicated on their ability to filter extensive datasets and generate actionable alerts for healthcare providers. The theoretical framework supporting alert-driven intervention suggests that timely identification of physiological deviations allows for preemptive clinical action, thereby preventing adverse events and accelerating the optimization of therapeutic regimens. In the context of hypertension management, alerts are typically triggered by specific algorithmic criteria, such as a single severely elevated reading indicative of a hypertensive crisis, or a sustained pattern of moderately elevated readings suggesting medication inadequacy [19]. Upon receiving an alert, the clinical response pathway ideally involves a structured triage process, patient contact for symptom assessment, and subsequent intervention, which may include medication titration, lifestyle counseling, or a request for an in-person evaluation. The efficiency and appropriateness of this response pathway are critical; delays in processing alerts or a failure to initiate meaningful clinical changes negate the benefits of continuous monitoring. Consequently, understanding the human-computer interaction between the telemonitoring platform and the clinical care team is paramount.

2.3 Challenges of Alert Fatigue and Workflow Integration

One of the most significant barriers to the successful implementation of alert-driven telemonitoring is the phenomenon of alert fatigue. As remote monitoring systems generate large volumes of data, healthcare providers are frequently overwhelmed by a high frequency of notifications, many of which may be clinically insignificant or false positives resulting from user error or technical artifacts. This sensory overload can lead to desensitization, causing providers to ignore or delay responses to genuinely critical alerts, thereby compromising patient safety and undermining the utility of the monitoring system [20]. In rural primary care settings, where providers often manage disproportionately large patient panels with limited administrative support, the burden of managing telemonitoring alerts is particularly acute. Integrating alert management into existing clinical workflows requires deliberate redesign of care processes, including the establishment of dedicated telehealth nursing roles, the implementation of standardized triage protocols, and the configuration of alert thresholds to maximize specificity without sacrificing sensitivity. Research indicates that systems lacking these supportive structures frequently result in provider burnout and early abandonment of the technology.

2.4 Patient Engagement and Behavioral Dynamics

Beyond the clinical response, the success of telemonitoring is intrinsically linked to patient engagement and adherence to measurement protocols. The act of self-monitoring has been shown to enhance patient awareness of their condition, fostering a greater sense of self-efficacy and promoting positive behavioral modifications [21]. However, sustaining long-term engagement in telemonitoring programs is challenging, particularly among older rural populations who may harbor skepticism toward digital technology or experience cognitive and physical limitations that impede the use of monitoring devices. The occurrence of automated alerts can serve as a dual-edged sword in this context; while prompt clinical follow-up to an alert can reinforce the value of monitoring and strengthen the patient-provider relationship, excessive alerts or punitive responses to elevated readings may induce anxiety and lead to monitoring avoidance [22]. Therefore, patient-facing interfaces and communication strategies must be carefully designed to provide constructive feedback, normalize fluctuations in blood pressure, and encourage consistent participation without inducing unnecessary distress.

3. Methodology and Implementation

3.1 Study Design and Setting Selection

This research was structured as a prospective, observational implementation study conducted over a twelve-month period within a network of rural primary care clinics. The selected region is characterized by low population density, an aging demographic profile, and historical challenges in recruiting and retaining specialized medical personnel. Primary care services in this area are predominantly delivered by a combination of general practitioners, nurse practitioners, and community health workers. The study was designed to evaluate the real-world deployment of a novel telemonitoring program, specifically observing the spontaneous interactions between the technological platform, the clinical staff, and the patient cohort. By eschewing the tightly controlled environment of a randomized clinical trial, this implementation approach allowed for the identification of systemic frictions and workflow adaptations that naturally occur during the adoption of digital health innovations in resource-constrained settings. The observational period included distinct phases of baseline data collection, system deployment, active monitoring, and post-intervention assessment.

3.2 Participant Recruitment and Stratification

Participants were recruited from the active patient panels of the participating rural clinics. Inclusion criteria required individuals to be adults over the age of eighteen, carry a documented diagnosis of essential hypertension, and demonstrate a history of suboptimal blood pressure control, defined by consecutive clinical readings exceeding standard therapeutic targets over the preceding six months. Exclusion criteria encompassed secondary causes of hypertension, severe cognitive impairment precluding the independent use of monitoring equipment, and terminal illnesses with a life expectancy of less than one year. Eligible patients were approached by their primary care providers during routine visits and provided with comprehensive information regarding the telemonitoring program. A purposive sampling strategy was employed to ensure diverse representation across age groups, socioeconomic statuses, and varying distances from the primary care facilities. Upon enrollment, participants underwent a standardized baseline assessment to record demographic variables, current pharmacological regimens, and baseline hemodynamic parameters.

Table 1: Baseline Demographic and Clinical Characteristics of the Study Cohort

Variable Category	Parameter	Measurement Value
Demographic	Total Number of Participants	Four Hundred Fifty
Demographic	Mean Age in Years	Sixty-Two point Five

Variable Category	Parameter	Measurement Value
Demographic	Proportion of Female Participants	Fifty-Four Percent
Geographic	Average Distance to Primary Clinic	Thirty-Five Kilometers
Clinical	Baseline Systolic Blood Pressure	One Hundred Fifty-Eight
Clinical	Baseline Diastolic Blood Pressure	Ninety-Four
Clinical	Average Number of Antihypertensive Drugs	Two point Three
Technological	Prior Experience with Digital Health Apps	Twelve Percent

3.3 Telemonitoring System Architecture and Deployment

The technological infrastructure deployed for this study comprised cellular-enabled, automated sphygmomanometers distributed to each participant, coupled with a secure, cloud-based data aggregation platform accessible to the clinical care teams. The monitoring devices were specifically selected for their simplicity; they required no localized wireless network configuration, automatically transmitting encrypted measurement data via available cellular networks immediately upon completion of a reading. This design choice was critical for accommodating the varying levels of internet connectivity prevalent in the rural target area. The central data platform was integrated into the existing electronic health record systems of the participating clinics. Participants were instructed to perform standardized blood pressure measurements twice daily, once in the morning and once in the evening, following a brief period of seated rest. Clinical staff received specialized training on the operation of the platform, the interpretation of remote data trends, and the standardized protocols for responding to system-generated alerts.

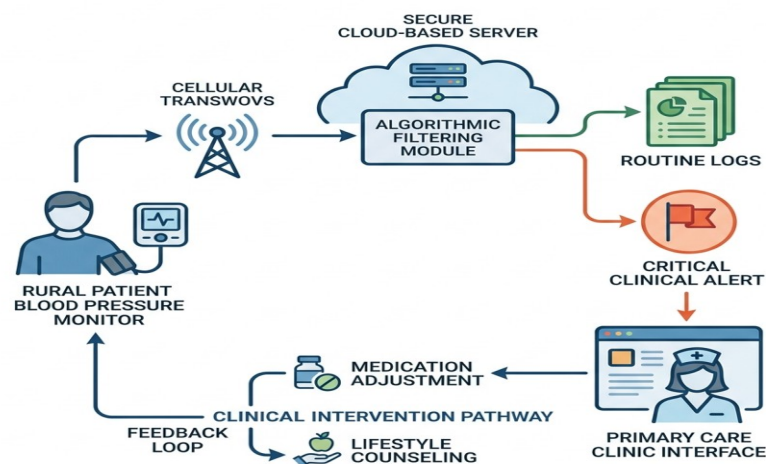


Figure 1: Comprehensive Schematic of Telemonitoring Alert Data Flow and Clinical Intervention Pathway

3.4 Alert Generation Algorithms and Triage Protocols

The core component of the implementation study was the alert generation mechanism, which was calibrated to balance clinical safety with the mitigation of provider alert fatigue. The algorithmic criteria for triggering an alert were established through a consensus process involving rural health practitioners and cardiovascular specialists [23]. Alerts were categorized into three distinct tiers based on clinical urgency. Tier one alerts, representing potential hypertensive emergencies, were triggered by singular systolic readings exceeding exceptionally high thresholds or diastolic readings indicating immediate risk. Tier two alerts, indicative of persistent uncontrolled hypertension, were

generated when a predefined percentage of a patient's readings over a consecutive seven-day period remained above their individualized target range. Tier three alerts were administrative in nature, flagging patients who failed to transmit data for several consecutive days, suggesting technical malfunctions or non-adherence. A centralized triage protocol was implemented, delegating the initial assessment of all alerts to designated telehealth nurses. These nurses were responsible for contacting patients to verify the readings, assess for acute symptoms, and subsequently escalate actionable cases to the prescribing physician for medication adjustment.

3.5 Data Collection and Analytical Framework

Continuous data streams were collected throughout the twelve-month study period, encompassing both physiological measurements and system utilization metrics. The primary independent variables analyzed were the frequency of alerts generated per patient and the median clinical response time, defined as the duration between the generation of a system alert and the documentation of a corresponding clinical intervention in the electronic health record. The primary dependent variable was the change in mean ambulatory blood pressure from baseline to the conclusion of the study period. Secondary data points included the proportion of alerts resulting in pharmacological modifications, the incidence of emergency department visits for cardiovascular events, and patient retention rates. Analytical procedures involved rigorous stratification of the cohort based on alert responsiveness. Descriptive statistics were utilized to characterize the distribution of alert types and response times, while comparative analyses evaluated the differential impacts of rapid versus delayed clinical interventions on long-term hemodynamic control, adjusting for baseline demographic and clinical covariates.

4. Results and Analysis

4.1 Volume and Distribution of System Alerts

Over the duration of the twelve-month implementation study, the telemonitoring platform processed hundreds of thousands of individual blood pressure readings transmitted by the rural cohort. From this extensive dataset, the algorithmic filtering system generated a substantial volume of clinical and administrative alerts. The distribution of these alerts revealed significant patterns in patient physiology and adherence behaviors [24]. Tier two alerts, representing sustained periods of suboptimal blood pressure control rather than acute crises, constituted the vast majority of the clinically actionable notifications. This high prevalence underscores the chronic nature of the management challenges faced by this population and highlights the system's utility in identifying persistent therapeutic inadequacies that would otherwise remain undetected between conventional clinic visits. Tier one alerts, while infrequent, consistently correlated with critical clinical situations requiring immediate triage and intervention. Administrative tier three alerts regarding non-transmission were most frequent during the initial two months of the program, subsequently declining as patients acclimatized to the daily monitoring routine and technical troubleshooting protocols were refined by the support staff.

4.2 Clinical Responsiveness and Workflow Impact

The analysis of clinical response times exposed substantial variability across the participating rural clinics, largely driven by differences in staffing models and workflow integration strategies. Clinics that successfully implemented dedicated telehealth nursing roles demonstrated significantly shorter median response times to all tiers of alerts compared to clinics that attempted to absorb alert management into the routine duties of existing primary care providers. In the highly integrated settings, tier one alerts were routinely addressed within a matter of hours, and tier two alerts were typically processed within two business days. Conversely, in clinics lacking dedicated personnel,

response times were frequently delayed, with tier two alerts sometimes remaining unaddressed for over a week [25]. These delays were primarily attributed to the competing demands of in-person acute care and the administrative burden of navigating parallel documentation systems. The study also documented instances of alert fatigue, particularly when minor technical artifacts triggered false positive alerts, emphasizing the necessity of continuous algorithmic refinement to maintain provider confidence and engagement in the platform.

Table 2: Categorization of Telemonitoring Alerts and Subsequent Clinical Actions

Alert Classification	Proportion of Total Alerts	Most Frequent Clinical Action Taken
Tier One (Acute Elevation)	Four Percent	Immediate Telephone Triage and Referral
Tier Two (Sustained Suboptimal)	Sixty-Eight Percent	Pharmacological Regimen Adjustment
Tier Three (Data Non-Transmission)	Twenty-Eight Percent	Technical Support and Adherence Counseling
False Positives (Artifacts)	Twelve Percent of All Tiers	Device Recalibration and Education

4.3 Correlation Between Alert Response and Blood Pressure Reduction

The central finding of this implementation study is the robust correlation between the promptness of clinical interventions triggered by alerts and the magnitude of longitudinal blood pressure reduction achieved by the patients. The cohort was stratified into subgroups based on the average clinical response time they experienced throughout the monitoring period. The subgroup receiving the most rapid interventions demonstrated the most profound and sustained reductions in both mean systolic and diastolic parameters compared to their baseline measurements. In contrast, patients whose alerts were frequently met with delayed responses exhibited negligible improvements in overall hemodynamic control, despite maintaining high rates of adherence to the home monitoring protocol. This divergence starkly illustrates that passive data collection, in the absence of timely clinical action, is insufficient to alter the disease trajectory. The mechanisms driving improvement in the rapid response group primarily involved more frequent and precise up-titrations of antihypertensive medications, coupled with timely lifestyle counseling delivered via telehealth consultations immediately following periods of instability.

4.4 Demographic and Geographic Influences on Outcomes

Further analysis explored the interplay between patient demographics, geographic location, and the efficacy of the alert-driven intervention. Interestingly, the distance a patient resided from their primary care clinic did not inversely correlate with their degree of blood pressure improvement, provided they were managed by a clinic with efficient alert response protocols [26]. This suggests that effectively implemented telemonitoring can completely neutralize the geographic barriers that traditionally hinder rural chronic disease management. However, distinct disparities were observed concerning digital literacy and age. Older participants, particularly those with no prior experience using digital health applications, required significantly more administrative support and generated a higher volume of non-transmission alerts during the onboarding phase. Nevertheless, once the initial learning curve was overcome, adherence rates in the older demographic were exceptionally high. Additionally, patients who experienced rapid and tangible clinical responses to their initial alerts reported higher levels of trust in the system and sustained longer-term engagement, indicating a positive feedback loop between clinical responsiveness and patient adherence behaviors.

5. Discussion and Conclusion

5.1 Interpreting the Efficacy of Alert-Driven Management

The findings of this implementation study provide compelling evidence that the value of telemonitoring in rural hypertension management is inextricably linked to the efficiency of the clinical response mechanism. The data definitively show that generating alerts is only the first step in a complex intervention pathway; the timely translation of these alerts into pharmacological adjustments or targeted counseling is the actual driver of improved clinical outcomes [27]. This underscores a critical paradigm shift for digital health initiatives: technology must be viewed not merely as a data collection tool, but as a catalyst for dynamic clinical workflows. The significant improvements observed in patients managed by clinics with dedicated telehealth staff highlight the necessity of structural reorganization within primary care practices. Attempting to overlay high-frequency data streams onto traditional, episodic care models invariably leads to workflow bottlenecks, provider burnout, and suboptimal patient care. Therefore, the successful scaling of telemonitoring programs requires concomitant investments in personnel and the redesign of triage protocols to handle the influx of actionable health data.

5.2 Addressing Systemic Limitations and Barriers

Despite the positive outcomes associated with rapid alert responses, this study also illuminates substantial barriers that must be addressed to optimize rural telemonitoring. The prevalence of alert fatigue, even with stratified algorithmic thresholds, remains a formidable challenge. The occurrence of false positives not only strains limited clinical resources but also diminishes provider trust in the technology. Future iterations of telemonitoring platforms must incorporate more sophisticated, adaptive algorithms that utilize machine learning techniques to personalize alert thresholds based on individual patient baselines and historical variability, thereby enhancing specificity [28]. Furthermore, the initial high volume of non-transmission alerts underscores the persistent impact of the digital divide and the absolute necessity of robust, localized technical support for rural patients. Providing cellular-enabled devices circumvents the need for residential broadband, but it does not eliminate the need for comprehensive patient education and ongoing troubleshooting assistance to ensure consistent data flow.

5.3 Future Directions for Rural Digital Health

The implications of this research extend beyond the immediate management of hypertension, offering a blueprint for the application of alert-driven telemonitoring to a broader spectrum of chronic diseases prevalent in rural populations, such as heart failure and diabetes. Future studies should focus on the economic evaluation of these integrated systems, assessing whether the upfront costs of technology and dedicated telehealth personnel are offset by downstream savings from reduced emergency department utilization and hospital readmissions [29]. Additionally, there is a pressing need to explore the integration of patient-reported outcome measures and behavioral data into the alert algorithms, creating a more holistic picture of patient well-being that guides clinical intervention. The development of interoperable systems that seamlessly transmit alert data across different electronic health record platforms will also be crucial for facilitating coordinated care in fragmented rural health networks.

5.4 Conclusion

This comprehensive implementation study confirms that linking telemonitoring alerts to rapid clinical interventions is a highly effective strategy for improving blood pressure control among rural hypertension patients. By analyzing the entire continuum of care from remote data generation to clinical action, the research highlights that the therapeutic benefit of digital health lies in its ability to facilitate timely, proactive management rather than passive surveillance. Overcoming the geographic barriers inherent to rural healthcare requires more than just distributing technology; it demands a fundamental restructuring of clinical workflows to ensure that every actionable alert is met with a

meaningful response. As healthcare systems increasingly transition towards decentralized care models, the insights generated from this study provide essential guidance for designing and deploying resilient, alert-driven telemonitoring programs that can genuinely reduce cardiovascular disparities and enhance the quality of life for underserved populations.

References

1. Tan, M.L.; Zhao, P.; Zhang, L.; Ho, Y.F.; Varma, M.V.S.; Neuhoﬀ, S.; Nolin, T.D.; Galetin, A.; Huang, S.M. Use of Physiologically Based Pharmacokinetic Modeling to Evaluate the Eﬀect of Chronic Kidney Disease on the Disposition of Hepatic CYP2C8 and OATP1B Drug Substrates. *Clin. Pharmacol. Ther.* 2019, 105, 719–729.
2. Martischang, R.; Nikolaou, A.; Daali, Y.; Samer, C.F.; Terrier, J. Guidance on Selecting Optimal Steady-State Tacrolimus Concentrations for Continuous IV Perfusion: Insights from Physiologically Based Pharmacokinetic Modeling. *Pharmaceuticals* 2024, 17, 1047.
3. Singh, D.K.; Ahire, D.; Davydov, D.R.; Prasad, B. Differential Tissue Abundance of Membrane-Bound Drug Metabolizing Enzymes and Transporter Proteins by Global Proteomics. *Drug Metab. Dispos.* 2024, 52, 1152–1160.
4. Emoto, C.; Hahn, D.; Euteneuer, J.C.; Mizuno, T.; Vinks, A.A.; Fukuda, T. Next Challenge From the Variance in Individual Physiologically-Based Pharmacokinetic Model-Predicted to Observed Morphine Concentration in Critically Ill Neonates. *Clin. Pharmacol. Ther.* 2020, 107, 319–320.
5. Polasek, T.M. Virtual twin for healthcare management. *Front. Digit. Health* 2023, 5, 1246659.
6. Brown, B.H.; Barber, D.C.; Seagar, A.D. Applied potential tomography: Possible clinical applications. *Clin. Phys. Physiol. Meas.* 1985, 6, 109–121.
7. Costa, E.L.V.; Chaves, C.N.; Gomes, S.; Beraldo, M.A.; Volpe, M.S.; Tucci, M.R.; Schettino, I.A.; Bohm, S.H.; Carvalho, C.R.; Tanaka, H.; et al. Real-time detection of pneumothorax using electrical impedance tomography. *Crit. Care Med.* 2008, 36, 1230–1238.
8. Ke, X.-Y.; Hou, W.; Huang, Q.; Hou, X.; Bao, X.Y.; Kong, W.X.; Li, C.X.; Qiu, Y.Q.; Hu, S.Y.; Dong, L.H. Advances in electrical impedance tomography-based brain imaging. *Mil. Med. Res.* 2022, 9, 13.
9. Zhang, Y.; Ye, J.; Jiao, Y.; Zhang, W.; Zhang, T.; Tian, X.; Shi, X.; Fu, F.; Wang, L.; Xu, C. A pilot study of contrast-enhanced electrical impedance tomography for real-time imaging of cerebral perfusion. *Front. Neurosci.* 2022, 16, 1027948. [Central]
10. Iwashita, Y.; Takeda, S.; Kawashima, S.; Koshi, T.; Nomura, K.I.; Sato, S.; Sato, R.; Yamada, N.; Nebuya, S. A Clinical Case of Three-Dimensional Electrical Impedance Tomography (3D-EIT) Measurements. *Cureus* 2024, 16, e73291. [Central]
11. Jiang, Y.D.; Soleimani, M. Capacitively Coupled Electrical Impedance Tomography for Brain Imaging. *IEEE Trans. Med. Imaging* 2019, 38, 2104–2113.
12. Rostami-Hodjegan, A.; Tucker, G.T. Simulation and prediction of in vivo drug metabolism in human populations from in vitro data. *Nat. Rev. Drug Discov.* 2007, 6, 140–148.
13. Drummond, D.; Gonsard, A. Definitions and Characteristics of Patient Digital Twins Being Developed for Clinical Use: Scoping Review. *J. Med. Internet Res.* 2024, 26, e58504.
14. Dunson, D.B. Commentary: Practical Advantages of Bayesian Analysis of Epidemiologic Data. *Am. J. Epidemiol.* 2001, 153, 1222–1226.
15. Silva, J.Q.D.; Moraes, N.V.; Estrela, R.; Coelho, D., Jr.; Feriani, D.; Migotto, K.; Caruso, P.; Silva, I.; Oliveira, D.A.; Telles, J.P.; et al. Amikacin Dosing Adjustment in Critically Ill Oncologic Patients: A Study with Real-World Patients, PBPK Analysis, and Digital Twins. *Pharmaceutics* 2025, 17, 297.
16. Lau, J.; Schmid, C.H.; Chalmers, T.C. Cumulative meta-analysis of clinical trials builds evidence for exemplary medical care. *J. Clin. Epidemiol.* 1995, 48, 45–57; discussion 59–60.
17. Roy, N.; Downes, M.H.; Ibelli, T.; Amakiri, U.O.; Li, T.; Tebha, S.S.; Balija, T.M.; Schnur, J.B.; Montgomery, G.H.; Henderson, P.W. The Psychological Impacts of Post-Mastectomy Breast Reconstruction: A Systematic Review. *Ann. Breast Surg. Open Access J. Bridge Breast Surg. World* 2024, 8, 19.
18. Mostafa, S.; Polasek, T.M.; Bousman, C.; Rostami-Hodjegan, A.; Sheffield, L.J.; Overall, I.; Pantelis, C.; Kirkpatrick, C.M.J. Delineating gene-environment effects using virtual twins of patients treated with clozapine. *CPT Pharmacomet. Syst.*

Pharmacol. 2023, 12, 168–179.

19. Lee, J.J.; Chu, C.T. Bayesian clinical trials in action. *Stat. Med.* 2012, 31, 2955–2972.

20. Krauss, M.; Tappe, K.; Schuppert, A.; Kuepfer, L.; Goerlitz, L. Bayesian Population Physiologically-Based Pharmacokinetic (PBPK) Approach for a Physiologically Realistic Characterization of Interindividual Variability in Clinically Relevant Populations. *PLoS ONE* 2015, 10, e0139423.

21. Pourian, M.; Mostafazadeh, D.B.; Soltani, A. Does this patient have pheochromocytoma? A systematic review of clinical signs and symptoms. *J. Diabetes Metab. Disord.* 2016, 15, 11.

22. Dzobo, K.; Wilgus, T.A.; Mora, V.Z.; Zoncsich, A.; de Mezerville, R.; Khumalo, N.; Bayat, A. Biomimetic Optimization of Silicone Breast Implant Integration: Insights into Wound Healing and the Foreign Body Response. *Front. Bioeng. Biotechnol.* 2025, 13, 1668930.

23. Delpierre, C.; Lefèvre, T. Precision and personalized medicine: What their current definition says and silences about the model of health they promote. Implication for the development of personalized health. *Front. Sociol.* 2023, 8, 1112159.

24. Mansoor, A.; Mahabadi, N. Volume of Distribution. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2025.

25. Upton, R.N.; Foster, D.J.R.; Abuhelwa, A.Y. An introduction to physiologically-based pharmacokinetic models. *Pediatr. Anesth.* 2016, 26, 1036–1046.

26. Electrospun Poly(ϵ -Caprolactone) Fiber Scaffolds Functionalized by the Covalent Grafting of a Bioactive Polymer: Surface Characterization and Influence on in Vitro Biological Response | *ACS Omega*. Available online: <https://pubs.acs.org/doi/10.1021/acsomega.9b01647> (accessed on 7 March 2026).

27. Polasek, T.M.; Rostami-Hodjegan, A. Virtual Twins: Understanding the Data Required for Model-Informed Precision Dosing. *Clin. Pharmacol. Ther.* 2020, 107, 742–745.

28. Darwich, A.S.; Ogungbenro, K.; Vinks, A.A.; Powell, J.R.; Reny, J.L.; Marsousi, N.; Daali, Y.; Fairman, D.; Cook, J.; Lesko, L.J.; et al. Why has model-informed precision dosing not yet become common clinical reality? lessons from the past and a roadmap for the future. *Clin. Pharmacol. Ther.* 2017, 101, 646–656.

29. Necchi, S.; Molina, D.; Turri, S.; Rossetto, F.; Rietjens, M.; Pennati, G. Failure of Silicone Gel Breast Implants: Is the Mechanical Weakening Due to Shell Swelling a Significant Cause of Prostheses Rupture? *J. Mech. Behav. Biomed. Mater.* 2011, 4, 2002–2008.