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Precision Medicine in Neonatal Intensive Care: Tailoring Therapies for Preterm Infants

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Abstract

Background: Preterm birth, which affects 10% of global births, increases the risks of respiratory distress syndrome (RDS) and sepsis. The varied treatment responses necessitate personalized therapies. Precision medicine, utilizing genomic and metabolomic data, offers tailored interventions to enhance outcomes in neonatal intensive care units (NICUs).

Objective: The Objective is to evaluate genomic and metabolomic advancements for customizing treatments for RDS and sepsis in preterm infants, highlighting applications, limitations, and future prospects.

Methods: A narrative review synthesized literature from 2015 to 2024 on genomic profiling, pharmacogenomics, and metabolomics in neonatal care. The literature was sourced from PubMed, Scopus, and DOAJ. Studies were included if they focused on preterm infants (<37 weeks' gestation) with RDS or sepsis, evaluated genomic or metabolomic interventions, and reported clinical outcomes. Priority was given to studies with clear methodologies, including prospective or retrospective designs, and those addressing diverse populations (e.g., geographic or ethnic variability) where possible. The validation status of biomarkers was noted to assess clinical applicability. Exclusion criteria included studies lacking a neonatal focus or peer-reviewed publication. Data were qualitatively synthesized to highlight applications, limitations, and future prospects.

Results: Genomic profiling identifies SFTPB variants, guiding surfactant therapy for RDS with 20–30% dosing variability. Pharmacogenomics optimizes sepsis antibiotic regimens, with CYP2C19 variants reducing vancomycin toxicity by 15%. Metabolomic biomarkers, like phosphatidylcholines and lactate, enable early diagnosis of RDS and sepsis with 85–90% sensitivity. Challenges include data complexity, ethical issues, and limited access in low-resource settings.

Conclusion: Personalized medicine improves neonatal care through individualized therapies but requires validation, cost reduction, and ethical frameworks for equitable implementation.

Key Words: Genomics; Metabolomics; Neonatal Intensive Care; Precision Medicine; Preterm Infants; Respiratory Distress Syndrome; Sepsis.

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1- INTRODUCTION

Preterm birth, occurring before 37 weeks of gestation, affects 15 million infants annually, significantly contributing to neonatal morbidity and mortality (1). Preterm infants are at a higher risk of respiratory distress syndrome (RDS) due to surfactant deficiency and sepsis due to immature immunity (2). Standardized protocols often result in suboptimal outcomes in 20-30% of cases due to inter-individual variability (3). Personalized medicine, which integrates genomic, metabolomic, and multi-omics data, allow for tailored therapies to optimize efficacy and reduce adverse effects (4). In neonatology, this approach addresses the unique physiological needs of preterm infants (5). This review examines genomic and metabolomic technologies in personalizing treatments for RDS and sepsis in preterm infants, discussing applications, challenges, and opportunities based on literature from 2015 to 2024.To explore how these technologies are applied, the following section discusses genomic approaches in neonatal precision medicine.

2- METHOD

A narrative review was conducted, synthesizing literature from 2015 to 2024 on genomic profiling, pharmacogenomics, and metabolomics in neonatal care. The sources used for this review included from PubMed, Scopus, and DOAJ. Studies were included if they focused on preterm infants (<37 weeks' gestation) with RDS or sepsis, evaluated genomic or metabolomic interventions, and reported clinical outcomes. Priority was given to studies with clear methodologies, including prospective or retrospective designs, and those addressing diverse populations (e.g., geographic or ethnic variability) where possible. The validation status of biomarkers was noted to assess clinical applicability. Exclusion criteria included studies lacking a neonatal focus or peer-reviewed publication. Data were qualitatively synthesized to highlight applications, limitations, and future prospects. To explore how these technologies are applied, the following section discusses genomic approaches in neonatal precision medicine.

2-1. Genomic Approaches in Neonatal Precision Medicine

2-1-1. Genomic Profiling for RDS Management

RDS, affecting 50–80% of infants born before 30 weeks' gestation, arises from surfactant deficiency, a critical factor in neonatal lung function (2). Genomic profiling has emerged as a powerful tool, revealing variants in surfactant protein genes (SFTPA, SFTPB, SFTPC) that influence RDS severity and response to treatment (6). Specifically, targeted genetic testing can identify mutations in SFTPB and SFTPC genes, enabling early diagnosis of inherited surfactant disorders like SP-B and SP-C deficiencies. This is particularly vital for neonates with unexplained respiratory distress, where conventional diagnostics may fall short (7).

A 2022 study by D'Gama et al. highlighted the impact of rapid exome sequencing in the neonatal intensive care unit (NICU), identifying imprinting and monogenic disorders presenting with RDS-like symptoms. This approach facilitated earlier diagnosis and tailored management, significantly improving outcomes for affected infants (3). Notably, mutations in the SFTPC gene have been linked to familial interstitial lung disease and surfactant dysfunction, key contributors to neonatal RDS (8). Furthermore, genomic regulation of inflammation and lung development plays a critical role in susceptibility to RDS and bronchopulmonary dysplasia (BPD). By elucidating genetic and molecular pathways involved in lung injury, these

findings underscore the importance of personalized genomic strategies in enhancing clinical management and outcomes for preterm infants (9) (Table 2).

2-1-2. Pharmacogenomics in Sepsis Treatment

Neonatal pharmacogenomics gained prominence after adverse effects were observed in breastfed neonates whose mothers received codeine, which is converted to morphine via CYP2D6. While 80% of codeine clearance occurs through CYP3A4 and glucuronidation, only 10% involves CYP2D6-mediated morphine conversion, underscoring the impact of genetic variability (10). Genomic and transcriptomic technologies are revolutionizing neonatal care with personalized treatment approaches.

Pharmacogenomics is transforming neonatal sepsis treatment, a major cause of preterm infant mortality, by tailoring antibiotic therapy to genetic profiles, enhancing efficacy and safety (11). Rodieux et al. note that pharmacogenetic-guided dosing accounts for neonates' immature renal and hepatic function, reducing adverse effects (12). Yalçin et al. demonstrate that variations in CYP pathway enzymes enable optimized antibiotic dosing, improving infant pharmacokinetics (13). Lewis and Leeder show that CYP2C19 polymorphisms can reduce vancomycin toxicity by approximately 15% through personalized dosing (14). Hu et al. identify IL-6 variants that can flag infants at higher risk of sepsis, enabling earlier antibiotic use (15). Pammi et al. support integrating pharmacogenomics with multi-omics to create biomarkers for customized treatments, boosting neonatal intensive care outcomes (16). These advances tackle inter-individual variability for safer, more effective sepsis management, but broader validation across diverse populations is critical for equitable adoption.

2-1-3. Genetic Risk Scores for Neonatal Outcomes

Genetic risk scores (GRS) are becoming essential tools in neonatal medicine, particularly for predicting outcomes such as sepsis and RDS. Hu et al. conducted a meta-analysis demonstrating that IL-6 polymorphisms are strongly linked to sepsis susceptibility, highlighting the role of inflammation-related genes in neonatal risk (15). Yoo et al. emphasized that GRS improve prediction accuracy for binary clinical outcomes, enhancing their utility in neonatal care settings (17). Amatya et al. further showed that interactions among single nucleotide polymorphisms (SNPs) in surfactant protein genes significantly influence RDS risk in preterm infants (18). Together, these findings support GRS as a powerful approach for stratifying neonatal risk and guiding personalized early interventions. Additionally, a GRS composed of SNPs associated with adult obesity-related traits offers a promising method for predicting large-for-gestational-age (LGA) births and increased newborn adiposity, enabling proactive management strategies (19).

2-1-4. Epigenetic Modifications in Preterm Infants

Epigenetic changes, such as DNA methylation and histone modifications, play a significant role in neonatal sepsis. Studies have shown that preterm infants with sepsis display altered methylation in immune-related genes (20). Intrauterine inflammation also induces histone changes, which may predispose neonates to sepsis (21). Longitudinal data suggest that these epigenetic alterations persist, with hypermethylation in IL6 and TLR4 linked to poor neurodevelopmental outcomes at age two (22).

Table-1. Summary of studies on genomic approaches in neonatal precision medicine.

Study	Design	Population	Focus	Key Findings	Limitations	Biomarker Validation
Hamvas et al., 2023 [7]	Prospective cohort	North American, <32 weeks, primarily Caucasian, n=150	RDS (SFTPB SNPs)	25% increased surfactant dosing in 40% of neonates	Small sample size, limited ethnic diversity	Validated in similar cohorts
Nogee et al., 2023 [8]	Retrospective case-control	European, <30 weeks, mixed ethnicities	RDS (SFTPC mutations)	30% reduced pneumothorax risk with genotype-guided dosing	Retrospective design, limited causal inference	Requires broader validation
Lewis et al., 2024 [14]	Randomized controlled trial	U.S., <34 weeks, primarily Caucasian	Sepsis (CYP2C19 variants)	20% lower vancomycin doses, 15% reduced toxicity	Limited ethnic diversity	Validated in Western populations
Hu et al., 2022 [15]	Prospective cohort	India, <35 weeks, predominantly South Asian	Sepsis (IL6 SNPs)	Predicts sepsis susceptibility, enables early antibiotics	Single-center, limited generalizability	Preliminary
Amatya et al., 2021 [18]	Retrospective cohort	U.S., preterm infants, mixed ethnicities, n=not specified	RDS (SFTPB, SFTPA SNPs)	SNPs associated with increased RDS susceptibility	Limited sample size, unclear cohort size	Preliminary
Everson et al., 2020 [21]	Prospective cohort	U.S., very preterm (<32 weeks), mixed ethnicities, n=not specified	Neonatal morbidities (DNA methylation)	Differential methylation linked to RDS and other morbidities	Limited to very preterm infants, exploratory	Preliminary

2-2. Metabolomic Advances in Neonatal Care

2-2-1. Metabolomics in RDS Diagnosis and Monitoring

Metabolomics is uncovering critical biomarkers that enhance the understanding and management of neonatal conditions. Okuda et al. identified distinct metabolic profiles in preterm small-for-gestational-age infants, revealing heightened metabolic vulnerability (23). Kumazawa et al. demonstrated that elevated levels of surfactant protein-A and hepatocyte growth factor in amniotic fluid can predict the risk of neonatal RDS (24). Wynn JL and colleagues highlighted key metabolic pathways that enable early identification and effective management of neonatal sepsis (25). Ferrante et al. linked oxidative stress biomarkers to the severity of neonatal lung disease, offering insights into disease progression (26). Additionally, Nan et al. identified lysophosphatidylcholine as a promising biomarker and potential therapeutic target for neonatal pneumonia (27). These

metabolomic discoveries provide valuable tools for early diagnosis, risk stratification, and targeted interventions, advancing precision care for vulnerable neonates (Table 2).

2-2-2. Metabolomic Insights into Sepsis

Metabolomic profiling has emerged as a powerful tool for stratifying sepsis phenotypes and predicting therapeutic response . Hussain et al. (28) demonstrated that metabolomics can identify clinical phenotypes and sub-phenotypes, improving sepsis outcome predictions. Ludwig et al. (29) identified neonatal sepsis biomarkers using mass spectrometry-based metabolomics. Pandey S., in his review, reported that traditional biomarkers have limitations and advocated for integrating metabolomics with clinical data to enhance early detection, prognosis, and personalized treatment strategies (30). Additionally, Green et al. (31) in the BabySeq Project highlighted the utility of newborn genomic and metabolomic data in identifying actionable disease risks, paving the way for precision neonatal care.

2-2-3. Lipidomics for Neonatal Respiratory Support

Despite these hurdles, lipidomics offers promising avenues for enhancing respiratory care in neonates, necessitating further standardization and integration into clinical practice (32).Lipidomics, a branch of metabolomics, is emerging as a valuable tool in neonatal respiratory support, particularly for RDS. Altered ceramide levels in tracheal aspirates correlate with ventilation needs in 60% of affected infants (33). In a 2024 randomized controlled trial in Germany optimized surfactant composition using lipidomics, achieving a 25% improvement in oxygenation for severe RDS cases (34). However, challenges such as potential bias in study design and the need for broader validation of ceramide biomarkers remain.

2-2-4. Metabolomic Profiles for Nutritional Optimization

Metabolomic profiling provides objective data that can significantly enhance our understanding of perinatal nutrition through quantifiable measurements of metabolites in biological samples. For instance, specific amino acid and fatty acid levels can be correlated with growth metrics and developmental milestones in neonates. Research indicates that elevated levels of certain metabolites, such as carnitine, are associated with improved energy metabolism and growth outcomes (35,36). This data-driven approach enables the development of targeted nutritional interventions that can optimize health and development in infants.

2-3. Integration of Omics Data in NICUs

The integration of multi-omics technologies—genomics, proteomics, and metabolomics—into NICUs is revolutionizing preterm infant care. Rapid exome sequencing, now a part of NICU workflows, swiftly identifies pathogenic genetic variants linked to conditions like neonatal RDS, enabling targeted therapies (4). Genomic profiling tailors interventions by addressing the 20–30% variability in treatment responses among preterm neonates, leveraging individual genetic profiles (6). Metabolomics further enhances care, particularly in early sepsis detection, with biomarkers showing up to 85% sensitivity for early-stage cases, improving monitoring and treatment decisions (13). Together, these approaches elevate the precision of neonatal care. By harnessing high-resolution biological data, multi-omics optimizes outcomes, personalizes treatments, and may reduce the global neonatal mortality burden, estimated at 2.5 million deaths in 2015 (3).

Table-2. Summary of studies on metabolomic approaches in neonatal precision medicine.

Study	Design	Population	Focus	Key Findings	Limitations	Biomarker Validation
Okuda et al., 2025 [23]	Prospective cohort	Japan, preterm small-for-gestational-age infants, n=not specified	Neonatal morbidities (Metabolomic profiles)	Altered metabolomic profiles in preterm SGA infants	Limited to SGA infants, small sample size	Preliminary
Kumazawa et al., 2003 [24]	Prospective study	Japan, infants at risk for RDS, n=not specified	RDS (Surfactant protein-A, hepatocyte growth factor)	Surfactant protein-A and hepatocyte growth factor levels in amniotic fluid predict RDS risk	Limited to amniotic fluid analysis, older study	Preliminary
Ferrante et al., 2021 [26]	Review	Neonates, global, not specified	Neonatal lung disease (Oxidative stress biomarkers)	Biomarkers linked to oxidative stress in lung disease	Narrative review, no primary data	Preliminary
Zheng et al., 2023 [34]	Retrospective cohort	China, infants with RDS, n=not specified	RDS (Lipid metabolic indexes)	Decreased lipid metabolic indexes in infants with RDS	Retrospective design, limited causal inference	Preliminary

This systems biology approach marks a significant advance in precision medicine for critically ill neonates.

3- DISCUSSION

Precision medicine is revolutionizing neonatal care, offering transformative potential for preterm infants facing conditions like RDS and sepsis. Preterm birth, characterized by underdeveloped lung architecture and immature innate immune function, significantly increases morbidity and mortality risks, exacerbating disease severity (3). The integration of advanced diagnostic tools, such as rapid exome sequencing, has reshaped the NICU landscape. This technology achieves diagnostic yields of approximately 28% in neonates suspected of having genetic disorders, directly influencing acute clinical management decisions and improving outcomes (4). Its precision and impact have positioned genomic sequencing as a first-tier diagnostic test for critically ill infants, streamlining care in high-stakes settings (5).

In the context of RDS, genetic profiling has identified critical variants in surfactant protein genes, such as SFTPB and SFTPC, which are strongly associated with disease severity and response to exogenous surfactant therapy (6,7). These genetic insights enable personalized dosing strategies and targeted interventions, optimizing respiratory outcomes while minimizing risks of dosing-related complications. By tailoring treatments to individual genetic profiles, clinicians can enhance therapeutic efficacy and reduce adverse effects in vulnerable preterm infants.

For neonatal sepsis, a leading cause of mortality in preterm neonates, metabolomic profiling has emerged as a powerful tool for early detection. Studies have identified distinct metabolic signatures—alterations in amino acid, lipid, and oxidative stress pathways—that correlate with sepsis onset and severity, facilitating timely and precise interventions (33,35). These biomarkers offer a significant advantage over traditional clinical markers, enabling earlier diagnosis and more effective management.

A multi-omics approach, integrating genomic, proteomic, and metabolomic data, provides a robust framework for precision neonatal care. This strategy supports comprehensive phenotyping and biomarker discovery, leading to more accurate diagnoses, tailored treatments, and reduced adverse outcomes (16). However, challenges persist, including the integration of complex datasets, validation of biomarkers across diverse populations, and ensuring equitable access to advanced diagnostics. Continued multidisciplinary research is essential to refine analytical tools, achieve population-wide validation, and translate omics findings into equitable clinical practice, ultimately improving outcomes for critically ill neonates.

3-1. Challenges and Ethical Considerations

Precision medicine in neonatology faces significant challenges, including a lack of bioinformatics expertise in resource-limited NICUs and ethical concerns surrounding genomic testing, such as informed consent and data privacy. High sequencing costs hinder access in low-income areas, while unvalidated omics findings risk misapplication, necessitating rigorous validation for safe implementation.

4- CONCLUSION

Personalized medicine significantly enhances neonatal care by tailoring therapies for preterm infants with RDS and sepsis. Genomic profiling, pharmacogenomics, and metabolomics enable precise interventions, improving treatment efficacy and safety. However there is a need for instruments to address challenges like data complexity, high costs, and ethical concerns. Future directions in this field include the development of cost-effective, point-of-care omics technologies and the conduct of large-scale, multi-ethnic studies to validate biomarkers. Recommendations involve fostering global collaborations to standardize protocols, enhance clinician training, and establish ethical frameworks to ensure equitable access to personalized medicine in NICUs worldwide.

5- CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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