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Review

Precision medicine in neonatology

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Abstract

Neonatal medicine has shown major advances in the past 50 years and this progress has allowed the increased survival, with less morbidity, of extremely preterm and critically ill neonates. Despite some conditions being unique to the neonatal population, neonatologists often have the need to adapt currently approved therapies from other populations. Certain diseases have such a wide variability in phenotype and response to drug therapy that it has become urgent to understand the underlying sources of variability, including genetics.

Precision medicine concerns the application of patient-specific profiles, through the determination and incorporation of genetic data, clinical and environmental factors, to determine individual risks and thus provide the most accurate point-of-care in disease management and prevention.

In this review, we discuss the current available knowledge concerning the applicability of precision medicine in different neonatology fields, such as newborn screening, neonatal nutrition, renal injury, hemodynamic assessment, lung pathology, epilepsy and neonatal pharmacology. To this end, the authors conducted a literature search of the PubMed® repositories, mainly using the terms "neonatology", "individualized medicine", "precision medicine", "personalized medicine", "genomics" and "metabolomics".

This article provides a summarized review of the research that is being conducted in numerous neonatal domains. But how can this new research be integrated in clinical practice?

Although some areas are already being used in neonatologists' daily activity, others, like genomics and metabolomics, seem to be limited to the investigational field. Even though the groundwork in such fields seems promising, its clinical utility and availability are still unknown. Further studies are needed, and the creation of a worldwide database, with the purpose of sharing patient data and outcomes, could be an important step for this evolving science.

Keywords

Precision medicine, personalized medicine, individualized medicine, metabolomics, genomics, neonatology.

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Introduction

Neonatal medicine has shown major advances in the past 50 years [1], with paramount progress in nutrition, ventilation strategies, surgical techniques and infection control practices. These advances have allowed the increased survival, with less morbidity, of extremely preterm and critically ill neonates [1]. Despite some conditions being unique to the neonatal population, neonatologists often have the need to adapt currently approved therapies from other populations.

Certain diseases have such a wide variability in phenotype and response to drug therapy that it has become urgent to understand the underlying sources of variability, including genetics [1].

Precision medicine (also termed "personalized medicine", "personalized genomics", or "genomic medicine") refers to the application of patient-specific profiles, beyond signs and symptoms that were previously observable [2], through the incorporation of genetic and genomic data, as well as clinical and environmental factors, to determine individual risk and guide prevention and disease-management strategies.

With this review, the authors aim to provide an assessment of the current available knowledge and applicability of precision medicine in different neonatology fields, such as newborn screening (NBS), neonatal nutrition, renal injury, hemodynamic assessment, lung pathology, epilepsy and neonatal pharmacology. To this end, the authors conducted a literature search of the PubMed® repositories, mainly using the terms "neonatology", "precision medicine", "personalized medicine", "genomics" and "metabolomics".

Precision medicine and the brain

Seizures are common in the neonatal period and they can be the result of a brain insult, such as hypoxic-ischemic encephalopathy, infection or hemorrhage. In some cases, seizures have a genetic basis. Recently, the development of genome sequencing has led to the discovery of a large number of genes involved in epilepsy. These data may be helpful for family genetic counseling, treatment guidance and prognosis prediction. With increasing molecular diagnosis, precision medicine may be an option to improve treatment choices [3].

However, despite the recent progress in genetic technology, molecular diagnosis for neonatal-onset epilepsy can be difficult due to genetic and phenotypic heterogeneities. Pathogenic variants in the same gene may lead to different epileptic phenotypes in different individuals. The opposite is also true: the same clinical syndrome may be caused by defects in different genes. Yet, some genotypes are known to be associated with specific clinical manifestations and electroencephalogram (EEG) activity [3]. For example, *KCNQ2*-related disorders are associated with both self-limited benign familial neonatal epilepsy and neonatal-onset epileptic encephalopathy.

Functional studies made at different levels (cellular, neuronal, network, and animal models) could lead to the discovery of potential targets and treatments that could correct the biological effect of a specific variant and improve prognosis [4]. In a recent study, data from research on animal models presented three examples of targeted therapy, concerning *KCNQ2* variants, *ARX* and *CDKL5* variants [4]. For instance, retigabine, which acts as an activator of neuron-expressed *KCNQ*-channels, could be a targeted therapy for the rapid control of seizures in patients with some *KCNQ2*-mediated epileptic encephalopathy, particularly those with variants that alter channel properties in terms of current intensity [4].

ARX is a transcription factor selectively expressed in neuronal precursors and *ARX*-related epilepsy is often severe and of early onset. In this study, the administration of estradiol during early postnatal age restored the pool of GABAergic interneurons, preventing spasms in infancy and seizures in adulthood [4].

Seizures caused by metabolic abnormalities, such as citrullinemia, fructose-1,6-bisphosphatase deficiency, biotinidase deficiency and methyl-malonic aciduria, can be treated according to the

molecular diagnosis. These specific treatments are directly provided by molecular findings [5].

If hole exome or exome sequencing analysis is not possible as first-tier, the most frequently implicated epilepsy genes and those with treatment options should be considered as part of the essential panel for early epilepsy diagnosis.

Early genetic diagnosis can be helpful in providing optimal management and improving outcomes, as pharmacogenetics allows for more advanced and tailored treatment choices [3]. Genetic results are beginning to improve therapy via anti-epileptic medication selection and precision medicine approaches [5].

Despite advances in neonatal care to prevent neonatal brain injury and neurodevelopmental impairment, predicting long-term outcomes in neonates at risk remains difficult. Hypoxic-ischemic encephalopathy, perinatal stroke, intraventricular hemorrhage, periventricular hemorrhagic infarction and post-hemorrhagic ventricular dilatation are common scenarios in the Neonatal Intensive Care Unit (NICU). The machine learning approach will provide more detailed information using artificial intelligence for brain imaging tools, EEG, near-infrared spectroscopy (NIRS) and assessment of general movements and Hammersmith infant neurological examination. An algorithm combining all these techniques may give the best decision support tool for defining risk factors for brain injury or impaired brain development. At the moment, assessment of general movements combined with Hammersmith infant neurological examination is the best predictive tool for the early detection of cerebral palsy [6]. In a recent study, epigenetic changes measured in blood leucocytes and analyzed using machine learning appeared to predict cerebral palsy [7]. On the other hand, the urinary metabolic profiles of extremely preterm infants early after birth were associated with moderately to severely abnormal cortical grey matter and white matter abnormalities at magnetic resonance imaging [8].

Instrumental diagnostics

Electromyography

The diaphragm is the main respiratory muscle in preterm infants, and its activity can be measured by electromyography (dEMG). This technique provides objective information on the patients' breathing effort. There are currently two methods to detect the electrical signal of the diaphragm – transcutaneous, in which sensors are placed on the skin, and invasive transesophageal method, in which sensors are mounted on a catheter positioned in the esophagus. Recent studies have shown that both techniques are feasible in preterm infants [9, 10] and are able to detect changes in diaphragmatic activity [11]. However, transesophageal dEMG is relatively invasive, expensive and only available on one specific ventilator. The transcutaneous method is less invasive, cheap, and uses stand-alone equipment allowing its use during all modes of respiratory support, regardless of the ventilator. Observational studies in preterm infants have shown that transcutaneous dEMG is able to detect changes in diaphragmatic activity in response to the weaning of the respiratory support, from nasal continuous positive airway pressure (nCPAP) to low flow nasal cannula [11]. Furthermore, the diaphragmatic activity was significantly higher in those that failed this transition, compared to those in whom weaning was successful [11]. So, dEMG can potentially be used to titrate and trigger the mode and level of respiratory support, but further studies are needed to explore the potential indications in preterm infants.

Electrical impedance tomography

Electrical impedance tomography (EIT) is used to visualize regional lung volume and ventilation changes at the bedside and individualize pulmonary treatment. This technique uses differences in tissue conductance in response to an electrical current to visualize changes in lung aeration [12]. It is a non-invasive technique in which a belt containing non-sticky electrodes is placed around the chest at the level of the nipple. It is possible to read continuous information on relative changes in regional ventilation distribution and end-expiratory lung volume, which has a high correlation to actual intra-thoracic changes in air content [13]. Studies have shown that EIT is able to detect and monitor changes in (regional) aeration caused by pneumothoraces, postural changes, atelectasis, incorrect endotracheal tube placement, surfactant administration, changes in nCPAP levels and lung recruitment procedures during conventional and high-frequency ventilation in preterm infants. EIT has the potential to allow the individualization of respiratory care in preterm infants at high risk for developing bronchopulmonary dysplasia (BPD), as it helps to optimize ventilatory support at an

individual level, and thereby to achieve the goal of homogeneous non-injurious ventilation [12].

Metabolomics for neonatology

The "omics" technologies represent analytical approaches that have a holistic view on molecules, such as genes, transcripts, proteins and metabolites present in cells, tissues or organs [2]. Metabolomics is an innovative approach based on the systematic study of the full complement of molecules of low molecular weight (including sugars, lipids, small peptides, vitamins and amino acids) in a biological sample [2] that has been successfully used in multiple fields. The presence of a metabolic pattern was firstly reported by Roger Williams in 1951 [14], being revisited through the years, until the definition of "metabolomics" was established, in 2002, by Fiehn [14].

Metabolomics research in neonatology is constantly evolving, with a growing number of publications [15].

More recent studies have evaluated how physiological or pathological conditions can affect metabolomic profiles of different biofluids in pediatric populations. The metabolomics workflow consists of sample preparation and analysis, data processing and data analysis [14]. Samples can be collected from mothers (amniotic fluid, placenta, blood, urine, breast milk [BM], erythrocytes, hair, vaginal secretions) or from the neonate (urine, blood, saliva, bronchoalveolar fluid, exhaled air condensate, stool, umbilical cord) [16]. In clinical practice, only a limited number of metabolites are routinely measured in the newborn's biofluids by conventional analytical methods. For example, urine is a particularly suitable biofluid for the metabolomic approach, as it is easy to collect and can provide meaningful diagnostic information [17]. After obtaining the samples, analysis can be performed through several techniques, namely, nuclear magnetic resonance spectrometry (^{1}H-NMR), gas chromatography mass spectrometry (GC-MS) and liquid chromatography mass spectrometry (LC-MS) [16, 17]. Afterward, advanced statistical and bioinformatic tools are used to generate a metabolic fingerprint (reflection of the whole metabolome in a sample) [16]. These fingerprints can be rapidly obtained, being highly reproducible and detecting the smallest concentration changes of several metabolites at the same time. However, changes related to pathological stimuli may be difficult to distinguish from physiological variations [16].

The roles of metabolomics in different neonatology fields have been described by several authors [1, 2, 16, 17].

If more information on perinatal/neonatal maturational processes and their metabolic background were available, the management of sick or preterm newborns could be improved [2]. Together with genomics and proteomics, metabolomics appears to be a promising tool in neonatology for the monitoring of postnatal metabolic maturation, the identification of biomarkers as early outcome predictors, the diagnosis and monitoring of various diseases and the individualized management of neonatal disorders [1].

Hemodynamic assessment

A comprehensive hemodynamic assessment is crucial to timely diagnose cardiovascular failure, elucidate underlying pathophysiology, guide hemodynamic therapy, monitor the effects of interventions and adjust treatment. This enables an individualized hemodynamic management that is optimized for the patient's specific pathophysiology and clinical situation, in order to improve outcomes. Not all newborn infants with hemodynamic instability should be treated in a similar manner, because the presumed underlying pathophysiological mechanisms are different and therapeutic interventions should be adapted accordingly to that. Accurate and precise monitoring of neonatal hemodynamics, using for example neonatologist-performed echocardiography (NPE), non-invasive cardiac output assessment and NIRS can be challenging [18].

Patent ductus arteriosus

Hemodynamic management of preterm infants with a patent ductus arteriosus (PDA) can be adapted according to the specific cardiovascular physiology and clinical context of the individual patient. NPE is used to estimate the degree of transductal shunt volume and determine the hemodynamic significance of the PDA [19, 20], in order to help decide if a persistent PDA should be treated [21-23]. NPE can be used to evaluate the vasoconstrictive action of cyclooxygenase-inhibitors on the ductus arteriosus allowing to optimize dosing schemes of indomethacin or ibuprofen: a subsequent dose should only be prescribed when ductal constriction is considered

insufficient after evaluation of the change in transductal diameter [24, 25].

NPE can also be helpful in anticipating and identifying complications of surgical ligation of the ductus arteriosus, such as post-ligation cardiac syndrome (PLCS). PLCS is characterized by systemic hypotension secondary to myocardial impairment, oxygenation failure, and increased need for ventilatory support. The echocardiography-guided management resulted in a lower incidence of ventilatory failure, less inotropic support, and a trend toward less oxygenation failure [26].

Persistent pulmonary hypertension

Hypoxemic respiratory failure with signs of transductal right-to-left shunting (difference in pre- and postductal oxygen saturation ≥ 5%) and systemic hypotension is the common clinical presentation of a patient with persistent pulmonary hypertension of the newborn (PPHN). PPHN is associated with both left ventricular (LV) and right ventricular (RV) failure. Increased RV afterload potentially leads to systolic and diastolic myocardial impairment. LV preload is impeded by dilation of the right ventricle, decreased RV output and right-to-left transductal shunting, resulting in decreased LV output. Hypoxia and acidosis may further deteriorate myocardial performance. It is important to be informed about (imminent) ventricular failure in patients with PPHN, since the treatment of systemic hypotension, by increasing systemic vascular resistance, might further impair the myocardial performance, resulting in lower cardiac output. NPE can be used to assess the severity of PPHN and estimate the risk of mortality or the need for support with extracorporeal membrane oxygenation (ECMO) in order to timely transfer the patient to an ECMO center. Being informed about myocardial performance is important in patients with PPHN, since hemodynamic management will be quite different in the presence of ventricular failure [27-31].

Renal injury

Preterm newborns have an immature urinary tract and, consequently, an increased risk for acute kidney injury (AKI) in the neonatal period. Early recognition of AKI is hampered by the lack of specific tests for the neonatal population, as well as by the limitation of traditional markers, such as creatinine or urine output, to reflect early injury. The discovery of new urinary biomarkers may allow an earlier diagnosis, better renal function monitoring, as well as to adapt the therapeutic approach and to improve prognosis [32].

Metabolomic analysis has bet on the dosing of urinary biomarkers to trace different metabolic profiles in neonates of different gestational ages, as well as neonates with intrauterine growth restriction (IUGR), for example [32].

Studies have revealed that the measurement of urinary markers such as kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL) are associated with AKI and mortality in very low birth weight as well as decreased renal function in patients with congenital obstructive nephropathies [32]. Other studies have demonstrated that urinary dosing of N-acetyl-β-D-glucosaminidase (NAG) may be used as a predictor of renal ischaemic damage in perinatal asphyxia. These 3 markers were also found in newborns exposed to aminoglycosides; however, after adjusting for potential confounders, only KIM-1 showed a strong correlation with proximal tubular injury and exposure to gentamicin [32].

Two prospective pediatric cardiac surgery cohorts demonstrated the usefulness of α1 microglobulin, α1-acid glycoprotein and albumin in the early identification of AKI in patients undergoing cardiac surgery, with a peak 6 hours after cardiac surgery, giving additional information on prognosis and duration of hospitalization [33]. Homovanillic acid sulfate, a dopamine metabolite, was identified as a marker of AKI with high sensitivity and specificity in pediatric cardiac surgery patients.

Some urinary biomarkers suggestive of renal tubular injury were associated with aminoglycosides exposure before serum creatinine elevation in two neonatal studies (including preterm newborns) [32].

In one study, investigators identified, by applying urinary proteomic analysis, a panel of 51 peptides associated with obstructive nephropathies [32]. In another study, the ^{1}H-NMR-based metabolic profiling of urine allowed the authors to distinguish the urinary profile of children with nephropathies from healthy children. These differences were related to alterations of purine and pyridine and the urea cycle. This type of urine analysis can be a promising, non-invasive technique for classifying and monitoring nephropathies in children [34]. Proteomic analysis of specific markers may predict clinical evolution, as the need for surgery or spontaneous resolution with high precision. In the specific case of posterior urethra valves, a study

found an association between 13 peptides in patients who evolved to renal failure [32].

Other studies advocate the use of cystatin C as a more sensitive marker than creatinine for glomerular filtration rate and the use of tables, age-dependent, with serum creatinine centiles to earlier identify newborns with AKI, especially extreme low birth weight and term asphyxiated neonates [35]. Additionally, they found that cystatin C measured in the amniotic fluid was a sensitive marker in the prenatal detection of fetuses with obstructive uropathy [32].

Although still on an experimental basis, analysis and early identification of several biomarkers associated with kidney injury may help modify the paradigm of the definition of neonatal AKI, as well as detect drug-induced renal injury earlier and improve prognosis [32, 35]. However, reference intervals for renal biomarkers are still needed to support its clinical application [35].

Newborn screening

NBS is a public health program that has the goal of screening all infants, shortly after birth, for conditions that are treatable, but frequently not clinically evident in the newborn period.

Whole-genome sequencing determines the order of all the nucleotides in an individual's DNA and can determine variations in any part of the genome [36]. In the next decade, widespread application of pediatric whole-genome sequencing could lead to improvement of the NBS, as this technique has the ability to identify gene variants that will predict preventable and/or treatable conditions during the newborn period and early childhood. It could lead to an increase in the number of disorders identified by the NBS, as well as the identification of genetic variants that relate to a higher risk for the development of specific diseases.

Despite its predictive advantage, the indications for the use of whole-genome sequencing should be carefully sought, as certain non-genetic diseases, such as congenital hypothyroidism, cannot be diagnosed by this technique. Also, its global implementation could raise monetary questions, as it represents a high financial burden for the economy. Other limitations could be ethical and social implications and the communication of clinically relevant variants to families and clinicians [36].

On the other hand, in a recent study concerning the NBS of lysosomal disorders [37], a group of authors proposed an analytic algorithm to detect positive cases of Krabbe disease, muco-polysaccharidosis and Pompe disease based on tandem mass spectrometry. In this study, they found out that automated integration of covariate-adjusted reference intervals of amino acids and acylcarnitines and population results, combined with second-tier tests, could improve the false-positive rate of NBS for lysosomal disorders to a sustainable level near-zero. This could lead to a significant reduction in the number of false-positive tests and reduce the cost associated with the monitoring needed for these patients [37].

Despite its unquestionable clinical value, NBS identifies only a small part of inborn errors of metabolism [38]. The metabolomics profile could contribute to extending metabolic information to achieve an accurate diagnosis and to discover new inborn errors of metabolism. There are a lot of studies and interest in this area. For example, a Canadian research group, using a metabolomics approach, found 15 different isoforms/analogs of globotriaosylceramide and 22 isoforms/analogs of galabiosylceramide in the urine of untreated Fabry patients. This discovery contributed to providing new insights into the pathophysiology of Fabry disease and its mechanisms.

In order to reduce false-positive rates of traditional techniques of NBS, a group of researchers proposed a novel approach based on nanospray ionization analysis associated with high-resolution mass spectrometry. This technique allowed screening of galactosemia by detection of hexose and hexose-phosphate in urine. These results support the important added value of metabolomics for improving NBS [38].

Perinatal asphyxia

Perinatal asphyxia is an important cause of neonatal morbidity or death, and the applicability of metabolomics in this area has been debated. Adenosine diphosphate (ADP) and adenosine monophosphate (AMP) accumulate during asphyxia, generating accumulation of adenosine, inosine and hypoxanthine [14]. These substrates are channeled to purine catabolism, leading to generation of uric acid. In the re-oxygenation period, free radicals are produced concomitantly to uric acid formation, which is claimed as an indicator of severity of perinatal asphyxia [14].

In different studies [16], the urinary metabolome of survivors was clearly different from that of neonates that died in the first week of life, with

these differences being already present at birth [17]. Banupriya et al. showed that the excretion rate of urinary proteins (specifically glutarate, mehtylmalonate, 3-hydroxybutyrate and orotate), urinary malondialdehyde (MDA) and urinary uric acid were related to perinatal asphyxia severity and associated brain damage [14]. Also, Noto et al. [39], in 2016, suggested that there are dynamic changes over time in the urine metabolome of newborns with perinatal asphyxia treated with hypothermia. Lactic acid, taurine, lysine and mannitol have been found to be persistently decreased over time, as opposed to citric acid, lactose and galactose, which were increased [39].

This can indicate that a specific metabolomic fingerprint can relate to irreversible asphyxia-related alterations, being useful in the recognition of early markers of perinatal asphyxia and allowing better monitoring during therapeutic hypothermia, concerning optimal cooling temperatures, duration, rewarming regimens and mechanisms and individualization of therapies [17]. Metabolomics could be of great prognostic value, helping to distinguish metabolite combinations associated with death/worse neurological outcomes or less severe injury and better outcomes [17].

Sepsis and shock

Sepsis

Sepsis is a frequent cause of neonatal morbi-mortality, especially in the more susceptible preterm newborn. Current biomarkers used for diagnostic purposes lack accuracy and reliability, and results from blood microbiological cultures are often delayed. Metabolomics could provide new pathways in the early diagnosis, tailored management and prognosis of sepsis, by defining novel sensible biomarkers [17]. The urinary metabolic profile has been used in different studies: metabolite D-serine resulted as a good predictor for antifungal treatment response, reducing itself during therapy [17, 40] and, in another study [1, 41], metabolite variations disappeared at the end of the symptoms.

Shock

Transthoracic echocardiography, electrical biosensing technologies (bioimpedance and bioreactance), and transpulmonary ultrasound dilution are feasible and applicable methods to measure cardiac output in newborns [42]. Hemodynamic monitoring with simultaneous measurement of arterial blood pressure and cardiac output are very important tools in the assessment of shock. It is crucial to detect the low cardiac output in the compensated stage of shock (normal or high blood pressure) and not to wait to intervene only after systemic hypotension occurs (uncompensated stage of shock) [43]. The interpretation of both cardiac output and arterial blood pressure helps to select the optimal cardiovascular drug, based on the presumed etiology of impaired perfusion and oxygenation. Integrating clinical assessment with NPE and regional (cerebral and intestinal) oxygenation monitoring using NIRS resulted in a shorter time for clinical recovery in critically ill infants with cardiovascular compromise [44, 45].

Bronchopulmonary dysplasia

BPD is a multifactorial disease with well-known risk factors like genetic susceptibility, IUGR, nutritional deficits, oxygen toxicity, pulmonary inflammation and direct mechanical injury caused by mechanical ventilation [12, 46-48]. Nowadays, research aims to find ways to individualize lung-protective interventions to prevent development of BPD [12].

Volatile organic compounds

Measuring volatile organic compounds (VOCs) has been increasingly used in adult respiratory medicine. The aim of using VOCs in preterms is to predict BPD at an early stage of the disease, enabling preventive strategies for BPD on an individual basis. One technique that has gained substantial traction is the eNose, which enables real-time analyses of the patterns of selected VOCs in complex gas mixtures [49]. It does not allow measurement of individual VOCs but uses pattern recognition to capture composite VOC mixtures by cross-reactive sensors, called a breath-print [50]. This device can be used at the bedside and provides instant results, which is so highly needed for predicting BPD at an early age. Given the multifactorial etiology of BPD, analysis of exhaled breath of preterm infants might allow quantifying the prognostic accuracy of individual and combinations of VOCs in exhaled breath. As BPD has several pathophysiological links to lung injury in adults, it is expected that the VOCs might also be equipped to detect markers of BPD [12]. One of the challenges will be the collection

of breath in preterm infants as the minute volume ventilation is quite low and there is a relatively high flow bias delivered by the devices used for respiratory support. To date, there is no prediction model based on clinical characteristics or biomarkers with accurate discriminating ability to detect BPD at an early stage [12].

Neonatal pharmacology, drugs, xenobiotics and pharmacometabolomics

Drug dosing, safety and efficiency in the neonatal population are usually extrapolated from adult and pediatric populations, as there is a lack of studies and efficiently proven therapeutics in newborns. The absence of significant data, especially in extreme preterm, and the limited blood sampling options for pharmacokinetic (PK) studies are factors that contribute to this problem [51].

The main factors currently used for the stratification of drug doses in neonates are gestational age and weight. However, drug response and toxicity remain highly variable. Numerous studies have tried to find other methods to predict bloodstream levels and clinical responses to commonly used drugs in NICUs, such as antibiotics and narcotics [2, 51].

The need to change from a population-based to an individualized treatment has led to multiple studies of PK and pharmacodynamics (PD) in numerous drug classes. This approach would enable to predict the response to treatment and minimize adverse effects [52-55].

Differences between newborns and adult or pediatric patients include not only age and size but also the immaturity of enzymatic systems, which are not taken into account in most drug dosing recommendations [56].

The understanding of PK and PD seems to be the first step in an individualized dosing strategy. Obstacles to this knowledge seem to be inter-individual variability of either PK or PD in this population. Clinical stability and clinical factors such as mechanical ventilation, hypothermia and hypoxia affect PD. PK variability correlates with body composition, protein binding capacity and organ's and enzymatic system's maturity [51, 53, 54].

One example of the unique neonatal pharmacology is the variability in cytochrome P450, which is responsible for the metabolism of numerous drugs. Low levels of CYP3A4 expression seem to be responsible for a decreased clearance of benzodiazepines in preterm infants [55].

Genetic factors can also justify inter-individual variability in the clinical response to weight-based drug regimens. Polymorphisms in genes encoding drug transport proteins or drug receptors have been associated with the variability in the response to specific drugs such as opioid agents [51-53].

Metabolomics has been shown to play an important role in predicting drug toxicity, metabolism and response. Several studies made a correlation between metabolites and drug adverse effects such as postacetaminophen hepatotoxicity, gastrointestinal lesion induced by non-steroid anti-inflammatory drugs and nephrotoxicity of aminoglycosides [2, 56, 57].

Pharmacometabolomics is an emerging science that combines the use of metabolites with numerous pharmaceutical fields such as drug research and development. The analysis of the metabolic phenotype of an organism provides a dynamic view of the interaction between genetics, microbiome and environment, which could be crucial in clinical trials to improve patients' selection. The use of this tool would allow for an effective pretrial candidate selection, optimizing drug efficacy and safety. The implementation of these techniques in clinical trials would contribute to a better understanding of metabolic dynamics, drug interaction and interindividual heterogeneity [58, 59].

PK and PD in the newborn differ largely from the adult population. The combination of these fields with pharmacometabolomics could be the answer to a better understanding of the individual metabolic profile and interactions in this population. For example, some animal studies found a correlation between urine metabolites and steroid response in newborns with BPD. Numerous studies have been made to analyze and predict treatment responses in respiratory distress syndrome and PDA, which would enable a more specific and targeted drug use [58, 60-63].

The role of pharmacometabolomics in predicting drug toxicity has increased over the years and is applied to numerous fields. The study of urinary metabolites such as taurine, betaine and trimethylamine N-oxide in acetaminophen overdose correlates with different patterns of liver injury. Some specific metabolite panels are associated with toxic nephropathy; this analysis allows for early detection of nephrotoxicity, prior to clinical manifestations. Monitoring those metabolites could be useful during treatment with drugs commonly used in neonatology, such as gentamicin [64, 65].

Numerous methods have been developed for the analysis of metabolites. Although urine metabolite analysis in the newborn is easily accessible and non-invasive, other methods have been used, such as imaging mass spectrometry, as it allows for specific tissue analysis [66, 67].

Antibiotics

The relationship between dose and antimicrobial effect in neonates is highly variable due to the different growth and maturation, as well as changes in hepatic and renal function. Clearance of these drugs has a large inter-individual variation, with the key determinants being the patient's size, maturation and renal function [68].

Therapeutic drug monitoring (TDM) has been useful in the comparison of drug dose recommendations and serum antibiotic concentration. This method allows for individual drug adjustment resulting in early detection of toxic or under-therapeutic drug dosages. TDM leads to higher effectiveness and safety in antibiotic use and has been applied to numerous classes such as aminoglycosides and vancomycin [69, 70].

Different models have been used to predict the optimal dosage of renal eliminated antibiotics. Wilbaux et al. found that the most common parameters used to determine the ideal drug dose included body weight, body surface, gestational age, postnatal age and renal function. The use of these models helped to adjust antibiotic dosage, such as gentamicin, where preterm newborns were in need of higher doses and wider intervals to achieve optimal serum concentrations [68, 71].

However, as mentioned above, it is challenging to determine renal function in neonates. Recent models have found that the commonly used parameters, such as serum creatinine, were insufficient to determine drug dose and found variations in drug concentration in patients with critical conditions, such as sepsis or hypoxic-ischemic encephalopathy [72, 73].

Co-administration of other drugs, for instance, non-steroid anti-inflammatory, with antibiotics, such as aminoglycoside and vancomycin, have been shown to modify their serum concentration. Fuchs et al. found a negative correlation between dopamine administration and gentamicin clearance [71, 74, 75].

Leroux et al. studied the application of a model-based patient-tailored dose of vancomycin which took into account four patient covariates: birth weight, current weight, postnatal age and serum creatinine concentration within 48 hours of starting treatment. Other authors have studied the application of a model-based individualized drug dose using similar clinical data and found an overall improvement in achieving in-target serum concentrations. The systematic application of model-based dosing in NICU could help improve these clinical tools, leading to an individualized antibiotic regimen in newborns [76-78].

Metabolomics may also play a role in predicting aminoglycosides renal adverse effects. A study made in newborn rats compared urine metabolites following the administration of gentamicin and showed that those with gentamicin-induced nephrotoxicity presented a distinct pattern of urinary metabolites such as an increase in glucose, galactose, N-acetylglucosamine, myoinositol, butanoic acid, 3 hydroxybutirate and a decrease in citrulline, pseudouridine [2, 79].

Opioids

Morphine is the most commonly used opioid in NICU, but the drug dosage necessary to obtain analgesic effect is widely variable. Dose adjustments are based on clinical aspects, in addition to pain and sedation scoring systems. Numerous factors contribute to those differences, such as genetic polymorphisms, and postnatal maturation of enzymatic systems. Chau et al. studied the interaction of single nucleotide polymorphisms and neonatal clinical factors and found an association between UGT1A9 and anxiety or depressing behavior at 18 months and a higher incidence of externalizing behavior in newborns with catechol-O-methyltransferase rs4680 genotype [80]. The variability in morphine response has been linked to genetic polymorphisms in the morphine metabolizing enzyme, UDP-glucuronosyltransferases (UGT2B7, UGT1A6) and the mu-opioid receptor. An example is the *UGT2B7* –900G>A polymorphism, which increases drug metabolism [53, 80]. Matic et al. concluded that a combined *OPRM1* 118A>G and *COMT* 472G>A genotype could be a predictor of the need for rescue morphine in newborns on mechanical ventilation [81].

Fentanyl is the second most commonly used opioid in NICU, Norman et al. found variations in drug concentration and half-life with a significant impact of weight, volume of distribution and clearance [53, 82].

Numerous electronic tools have been developed in order to predict the individual dose required taking into account factors such as size, age and maturation. Vinks et al. developed a precision dosing platform for bedside use, which integrates morphine dose exposure and serum levels with clinical response evaluated by pain scales, heart rate and respiratory rate. The systematic use of such tools would enable gathering large PK and clinical data in newborns and allow for a more precise and individualized dose adjustment [83].

Caffeine

Caffeine has been prophylactically used in the management of apneas in preterm babies with less than 34 weeks of gestational age. It has been shown that, in some infants, a high caffeine loading dose is associated with negative effects on the infant's brain development [84]. On the other hand, low caffeine concentrations may lead to insufficient apnea treatment and increased use of invasive mechanical ventilation, posing a higher risk for BPD and neurodevelopmental impairment [85]. The exact molecular mechanisms underlying the benefits of caffeine administration have not been elucidated; it is likely that genomic and metabolomics heterogeneity influences optimal patient dose due to infant-specific caffeine metabolism and susceptibility risk [86-88]. Investigation of the genomic variation in caffeine metabolism in preterms can be used to optimize and individualize caffeine dosing regimens [12]. Several candidate genes have been suggested based on the known genetic associations with caffeine (e.g., cytochrome P450 enzymes, adenosine receptors) [86]. The analysis of genomic variation in caffeine's metabolism could be an important step to select which newborns would benefit from the use of caffeine as well as the optimal dosage for each individual [12].

Neonatal nutrition

Nutrition plays an important role in human development and can affect the quality of life in several ways [89]. Overweight, obesity and the risk of metabolic syndrome are known to be correlated with either insufficient or excessive fetal and neonatal nutrition. Newborns are classified as adequate for gestational age (AGA), large for gestational age (LGA) or small for gestational age (SGA), when they are between the 10th and 90th percentile, above the 90th percentile, or below the 10th, respectively. Also, despite being AGA or SGA, they can have IUGR, which can lead to future increased risk of metabolic and cardiovascular diseases.

BM represents the optimal source for neonatal nutrition, being able to modify its composition according to neonatal needs, especially in terms of gestational age or lactation stage. Metabolomics represents an ideal tool to analyze BM and the composition of different commercially available formula milks (FMs), allowing their improvement to resemble as much as possible BM composition [17].

In 2016, Dessì et al. analyzed through GC-MS and characterized the urine metabolite profiles of newborns fed with either BM or FM, finding that they were different between the AGA, LGA, SGA and those with IUGR [89]. This study reinforced the importance of the quality of nutrition in the first days of life.

Metabolomics can also help to detect the presence of drugs and contaminants in BM. This could help determine its safety in specific conditions or maternal exposure to environmental toxics [17].

Conclusions

Precision medicine is an evolving science that has led to multiple findings in different areas. This field allows clinicians to look at specific characteristics of an individual, which could be used to overcome the lack of knowledge present, nowadays, in neonatal medicine.

As we enumerated above, research is being developed in numerous areas, which could give neonatologists new information to improve diagnosis, adapt the choice of treatment and predict prognosis in specific patients, thus optimizing the outcome of care.

How will this new research be integrated in clinical practice is a question which remains unanswered. Although some areas are already being used in neonatologist's daily activity, others, like genomics and metabolomics, seem to be limited to the investigational field. Even though the groundwork in such fields seems promising, its clinical utility and availability is still unknown.

As for the clinical practice, non-invasive monitoring, such as NIRS or bedside echography, has gained a critical role, as it provides valuable information on individual hemodynamics and

response to treatment. These tools have been increasingly applied to multiple fields like neurologic, respiratory and cardiovascular monitoring.

Another personalized tool used in NICU's clinical practice is TDM, which has been very important in guiding antibiotic regimens or in neonatal seizure treatment. This useful instrument gives the neonatologist an indirect look at the PK and PD of individual newborns, allowing for the optimization of drug therapy without the risk of toxicity.

The goal of this science is to evolve from a "one-size-fits-all" to a more tailored and personalized approach, which seems a promising and critical tool for the future and evolution of neonatal medicine. As this review states, the creation of a worldwide database, with the purpose of sharing patient data and outcomes, could be an important step for this evolving science, as it would allow the study of large populations, which remains a concerning limitation regarding neonatal research.

Declaration of interest

The Authors declare that they do not have any conflict of interest.

References

1. Antonucci R, Atzori L, Barberini L, Fanos V. Metabolomics: the "new clinical chemistry" for personalized neonatal medicine. Minerva Pediatr. 2010;62(3 Suppl 1):145-8.
2. Fanos V, Barberini L, Antonucci R, Atzori L. Pharma-metabolomics in neonatology: is it a dream or a fact? Curr Pharm Des. 2012;18(21):2996-3006.
3. Ma X, Yang F, Hua Z. Genetic diagnosis of neonatal-onset seizures. Genes Dis. 2019;6(4):441-7.
4. Milh M, Cacciagli P, Ravix C, Badens C, Lépine A, Villeneuve N, Villard L. Severe neonatal seizures: From molecular diagnosis to precision therapy? Rev Neurol. 2016;172(3):171-3.
5. Yang L, Kong Y, Dong X, Hu L, Lin Y, Chen X, Ni Q, Lu Y, Wu B, Wang H, Lu QR, Zhou W. Clinical and genetic spectrum of a large cohort of children with epilepsy in China. Genet Med. 2019;21(3):564-71.
6. Tataranno ML, Vijlbrief D, Dudink J, Benders M. Precision Medicine in Neonates: A Tailored Approach to Neonatal Brain Injury. Front Pediatr. 2021.9:634092.
7. Bahado-Singh R, Vishweswaraiah S, Aydas B, Mishra NK, Guda C, Radhakrishna U. Deep Learning/Artificial Intelligence and Blood-Based DNA Epigenomic Prediction of Cerebral Palsy. Int J Mol Sci. 2019;20:2075.
8. Tataranno ML, Perrone S, Longini M, Coviello C, Tassini M, Vivi A, Calderisi M, deVries LS, Groenendaal F, Buonocore G, Benders MJNL. Predictive Role of Urinary Metabolic Profile for Abnormal MRI Score in Preterm Neonates. Dis Markers. 2018:4938194.
9. Kraaijenga JV, Hutten GJ, de Jongh FH, van Kaam AH. Transcutaneous electromyography of the diaphragm: A cardio-respiratory monitor for preterm infants. Pediatr Pulmonol. 2015;50(9):889-95.
10. Beck J, Reilly M, Grasselli G, Qui H, Slutsky AS, Dunn MS, Sinderby CA. Characterization of Neural Breathing Pattern in Spontaneously Breathing Preterm Infants. Pediatr Res. 2011;70:607-13.
11. Kraaijenga JV, de Waal CG, Hutten GJ, de Jongh FH, van Kaam AH. Diaphragmatic activity during weaning from respiratory support in preterm infants. Arch Dis Child Fetal Neonatal Ed. 2017;102(4):F307-11.
12. Onland W, Hutten J, Miedema M, Bos LD, Brinkman P, Maitland-van der Zee AH, van Kamm AH. Precision Medicine in Neonates: Future Perspectives for the Lung. Front Pediatr. 2020;8:586061.
13. Frerichs I, Amato MB, Van Kaam AH, Tingay DG, Zhao Z, Grychtol B, Bodenstein M, Gagnon H, Böhm SH, Teschner E, Stenqvist O, Mauri T, Torsani V, Camporota L, Schibler A, Wolf GK, Gommers D, Leonhardt S, Adler A; TREND study group. Chest electrical impedance tomography examination, data analysis, terminology, clinical use and recommendations: consensus statement of the TRanslational EIT developmeNt stuDy group. Thorax. 2017;72(1):83-93.
14. Mussap M, Antonucci R, Noto A, Fanos V. The role of metabolomics in neonatal and pediatric laboratory medicine. Clin Chim Acta. 2013;426:127-38.
15. Georgakopoulou I, Chasapi SA, Bariamis SE, Varvarigou A, Spraul M, Spyroulias GA. Metabolic changes in early neonatal life: NMR analysis of the neonatal metabolic profile to monitor postnatal metabolic adaptations. Metabolomics. 2020;16(5):58.
16. Bardanzellu F, Fanos V. How could metabolomics change pediatric health? Ital J Pediatr. 2020;46:37.
17. Fanos V, Antonucci R, Barberini L, Noto A, Atzori L. Clinical application of metabolomics in neonatology. J Matern Fetal Neonatal Med. 2012;25(Suppl 1):104-9.
18. Boode WP. Individualized Hemodynamic Management in Newborns. Front Pediatr. 2020;8:580470.
19. van Laere D, van Overmeire B, Gupta S, El-Khuffash A, Savoia M, McNamara PJ, Schwarz CE, de Boode WP; European Special Interest Group 'Neonatologist Performed Echocardiography' (NPE). Application of NPE in the assessment of a patent ductus arteriosus. Pediatr Res. 2018;84(Suppl 1):46-56.
20. Boode WP, Kluckow M, McNamara PJ, Gupta S. Role of neonatologist-performed echocardiography in the assessment and management of patent ductus arteriosus physiology in the newborn. Semin Fetal Neonatal Med. 2018;23(4):292-7.
21. McNamara PJ, Sehgal A. Towards rational management of the patent ductus arteriosus: the need for disease staging. Arch Dis Child Fetal Neonatal Ed. 2007;92(6):F424-7.
22. El-Khuffash A, James AT, Corcoran JD, Dicker P, Franklin O, Elsayed YN, Ting JY, Sehgal A, Malikiwi A, Harabor A, Soraisham AS, McNamara PJ. A Patent Ductus Arteriosus Severity Score

Predicts Chronic Lung Disease or Death before Discharge. J Pediatr. 2015;167(6):1354-61.e2.
23. Fink D, El-Khuffash A, McNamara PJ, Nitzan I, Hammerman C. Tale of Two Patent Ductus Arteriosus Severity Scores: Similarities and Differences. Am J Perinatol. 2018;35(1):55-8.
24. Carmo KB, Evans N, Paradisis M. Duration of indomethacin treatment of the preterm patent ductus arteriosus as directed by echocardiography. J Pediatr. 2009;155(6):819-22.e1.
25. Bravo MC, Cabañas F, Riera J, Pérez-Fernández E, Quero J, Pérez-Rodríguez J, Pellicer A. Randomised controlled clinical trial of standard versus echocardiographically guided ibuprofen treatment for patent ductus arteriosus in preterm infants: a pilot study. J Matern Fetal Neonatal Med. 2014;27(9):904-9.
26. Jain A, Sahni M, El-Khuffash A, Khadawardi E, Sehgal A, McNamara PJ. Use of targeted neonatal echocardiography to prevent postoperative cardiorespiratory instability after patent ductus arteriosus ligation. J Pediatr. 2012;160(4):584-9.e1.
27. Skinner JR, Hunter S, Hey EN. Haemodynamic features at presentation in persistent pulmonary hypertension of the newborn and outcome. Arch Dis Child Fetal Neonatal Ed. 1996;74(1):F26-32.
28. Sehgal A, Athikarisamy SE, Adamopoulos M. Global myocardial function is compromised in infants with pulmonary hypertension. Acta Paediatr. 2012;101(4):410-3.
29. Aggarwal S, Natarajan G. Echocardiographic correlates of persistent pulmonary hypertension of the newborn. Early Hum Dev. 2015;91(4):285-9.
30. Patel N, Mills JF, Cheung MM. Assessment of right ventricular function using tissue Doppler imaging in infants with pulmonary hypertension. Neonatology. 2009;96(3):193-9.
31. Malowitz JR, Forsha DE, Smith PB, Cotton CM, Barker PC, Tatum GH. Right ventricular echocardiographic indices predict poor outcomes in infants with persistent pulmonary hypertension of the newborn. Eur Heart J Cardiovasc Imaging. 2015;16(11):1224-31.
32. Joshi M, Montgomery K, Giannone P, Bauer J, Hanna M. Renal injury in neonates: use of "omics" for developing precision medicine in neonatology. Pediatr Res. 2017;81(1-2):271-6.
33. Deverajan P, Kwawczeski CD, Nguyen MT, Kathman T, Wang Z, Parikh CR. Proteomic identification of early biomarkers of acute kidney injury after cardiac surgery in children. Am J Kidney Dis. 2010;56(4):632-42.
34. Atzori L, Antonucci R, Barberini L, Locci E, Cesare Marincola F, Scano P, Cortesi P, Agostiniani R, Weljie A, Lai A, Fanos V. 1H NMR-based metabolic profiling of urine from children with nephrouropathies. Front Biosci. 2010;2:725-32.
35. Allegaert K, Smits A, van Donge T, van den Anker J, Sarafidis K, Levtchenko E, Mekahli D. Renal Precision Medicine in Neonates and Acute Kidney Injury: How to Convert a Cloud of Creatinine Observations to Support Clinical Decisions. Front Pediatr. 2020;8:366.
36. Yang L, Chen J, Shen B. Newborn Screening in the Era of Precision Medicine. Adv Exp Med Biol. 2017;1005:47-61.
37. Minter Baerg MM, Stoway SD, Hart J, Mott L, Peck DS, Nett SL, Eckerman JS, Lacey JM, Turgeon CT, Gavrilov D, Oglesbee D, Raymond K, Tortorelli S, Matern D, Mørkrid L, Rinaldo P. Precision newborn screening for lysosomal disorders. Genet Med. 2018;20(8):847-54.
38. Mussap M, Zaffanello M, Fanos V. Metabolomics: a challenge for detecting and monitoring inborn errors of metabolism. Ann Transl Med. 2018;6(17):338.
39. Noto A, Pomero G, Mussap M, Barberini L, Fattuoni C, Palmas F, Dalmazzo C, Delogu A, Dessì A, Fanos V, Gancia P. Urinary gas chromatography mass spectrometry metabolomics in asphyxiated newborns undergoing hypothermia: from the birth to the first month of life. Ann Transl Med. 2016;4(21):417.
40. Dessì A, Liori B, Caboni P, Corsello G, Giuffrè M, Noto A, Serraino F, Stronati M, Zaffanello M, Fanos V. Monitoring neonatal fungal infection with metabolomics. J Matern Fetal Neonatal Med. 2014; (Suppl 2):34-8.
41. Sarafidis K, Chatziioannou AC, Thomaidou A, Gika H, Mikros E, Benaki D, Diamanti E, Agakidis C, Raikos N, Drossou V, Theodoridis G. Urine metabolomics in neonates with late-onset sepsis in a case-control study. Sci Rep. 2017;7:45506.
42. Boode WP. Advanced Hemodynamic Monitoring in the Neonatal Intensive Care Unit. Clin Perinatol. 2020;47(3):423-34.
43. Boode WP, Van Der Lee R, Eriksen BH, Nestaas E, Dempsey E, Singh Y, Austin T, El-Khuffash A; European Special Interest Group 'Neonatologist Performed Echocardiography (NPE). The role of Neonatologist Performed Echocardiography in the assessment and management of neonatal shock. Pediatr Res. 2018;84(Suppl 1): 57-67.
44. Amer R, Kalash R, Seshia MM, Elsayed YN. The Impact of Integrated Evaluation of Hemodynamics on Management of Preterm Infants with Late-onset Compromised Systemic Circulation. Am J Perinatol. 2017;34(10):1011-9.
45. Elsayed YN, Amer R, Seshia MM. The impact of integrated evaluation of hemodynamics using targeted neonatal echocardiography with indices of tissue oxygenation: a new approach. J Perinatol. 2017;37(5):527-35.
46. Morrow LA, Wagner BD, Ingram DA, Poindexter BB, Schibler K, Cotten CM, Dagle J, Sontag MK, Mourani PM, Abman SH. Antenatal Determinants of Bronchopulmonary Dysplasia and Late Respiratory Disease in Preterm Infants. Am J Respir Crit Care Med. 2017;196(3):364-74.
47. Jensen EA, Foglia EE, Schimdt B. Evidence-Based Pharmacologic Therapies for Prevention of Bronchopulmonary Dysplasia: Application of the Grading of Recommendations Assessment, Development, and Evaluation Methodology. Clin Perinatol. 2015;42(4):755-79.
48. Ibrahim J, Bhandari V. The definition of bronchopulmonary dysplasia: an evolving dilemma. Pediatr Res. 2018;84(5):586-8.
49. Dragonieri S, Schot R, Mertens BJ, Le Cessie S, Gauw SA, Spanevello A, Resta O, Willard NP, Vink TJ, Rabe KF, Bel EH, Sterk PJ. An electronic nose in the discrimination of patients with asthma and controls. J Allergy Clin Immunol. 2007;120(4):856-62.
50. de Vries R, Dagelet YWF, Spoor P, Snoey E, Jak PMC, Brinkman P, Dijkers E, Bootsma SK, Elskamp F, de Jongh FHC, Haarman

EG, In 't Veen JCCM, Maitland-van der Zee AH, Sterk PJ. Clinical and inflammatory phenotyping by breathomics in chronic airway diseases irrespective of the diagnostic label. Eur Respir J. 2018;51(1): 1701817.

51. Lewis T. Precision therapeutics in the NICU: why are we missing the mark? J Perinatol. 2018;38(5):444-6.
52. Engbers AGJ, Flint RB, Völler S, de Klerk JCA, Reiss IKM, Andriessen P, Liem KD, Degraeuwe PLJ, Croubels S, Millecam J, Allegaert K, Simons SHP, Knibbe CAJ. Enantiomer specific pharmacokinetics of ibuprofen in preterm neonates with patent ductus arteriosus. Br J Clin Pharmacol. 2020;86(10):2028-39.
53. Euteneuer JC, Kamatkar S, Fukuda T, Vinks AA, Akinbi HT. Suggestions for Model-Informed Precision Dosing to Optimize Neonatal Drug Therapy. J Clin Pharmacol. 2019;59(2):168-76.
54. Momper JD, Wagner JA. Therapeutic Drug Monitoring as a Component of Personalized Medicine: Applications in Pediatric Drug Development. Clin Pharmacol Ther. 2014;95(2):138-40.
55. Fanni D, Ambu R, Gerosa C, Nemolato S, Castagnola M, Van Eyken P, Faa G, Fanos V. Cytochrome P450 genetic polymorphism in neonatal drug metabolism: role and practical consequences towards a new drug culture in neonatology. Int J Immunopathol Pharmacol. 2014;27(1):5-13.
56. Eirakaiby M, Dutilh B, Rizkallah M, Boleij A, Cole J, Aziz R. Pharmacomicrobiomics: the impact of human microbiome variations on systems pharmacology and personalized therapeutics. OMICS. 2014;18(7):402-14.
57. Sieber M, Hoffmann D, Adler M, Vaidya VS, Clement M, Bonventre JV, Zidek N, Rached E, Amberg A, Callanan JJ, Dekant W, Mally A. Comparative analysis of novel noninvasive renal biomarkers and metabolomic changes in a rat model of gentamicin nephrotoxicity. Toxicol Sci. 2009;109(2):336-49.
58. Mussap M, Loddo C, Fanni C, Fanos V. Metabolomics in pharmacology – a delve into the novel field of pharmacometabolomics. Expert Rev Clin Pharmacol. 2020;13(2):115-34.
59. Antonucci R, Pilloni MD, Atzori L, Fanos V. Pharmaceutical research and metabolomics in the newborn. J Matern Fetal Neonatal Med. 2012;25(Suppl 5):22-6.
60. Beger RD, Dunn W, Schmidt MA, Gross SS, Kirwan JA, Cascante M, Brennan L, Wishart DS, Oresic M, Hankemeier T, Broadhurst DI, Lane AN, Suhre K, Kastenmüller G, Sumner SJ, Thiele I, Fiehn O, Kaddurah-Daouk R; for "Precision Medicine and Pharmacometabolomics Task Group" – Metabolomics Society Initiative. Metabolomics enables precision medicine: "A White Paper, Community Perspective". Metabolomics. 2016;12(10):149.
61. Lewis T, Chalise P, Gauldin C, Truog W. Pharmacometabolomics of Respiratory Phenotypic Response to Dexamethasone in Preterm Infants at risk for Bronchopulmonary Dysplasia. Clin Transl Sci. 2019;12(6):591-9.
62. Fabiano A, Gazzolo D, Zimmermann LJ, Gavilanes AW, Paolillo P, Fanos V, Caboni P, Barberini L, Noto A, Atzori L. Metabolomic analysis of bronchoalveolar lavage fluid in preterm infants complicated by respiratory distress syndrome: preliminary results. J Matern Fetal Neonatal Med. 2011;24(Suppl 2):55-8.
63. Atzori L, Barberini L, Lussu M, Murgia F, Noto A, Mercuro G, Bassareo P, Puddu M, Antonucci R, Neroni P, Tumbarello R, Fanos V. Metabolomics & Patent Ductus Arteriosus diagnosis: is 1H-NMR (nuclear magnetic resonace) spectroscopy of urine at birth predictive as ultrasound? In: Selected Abstracts of the 7th International Workshop on Neonatology, Cagliari (Italy), October 22–26, 2011. J Matern Fetal Neonatal Med. 2011;24(Suppl 2):I. [Abstract].
64. Evans WE, Relling MV. Moving towards individualized medicine with pharmacogenomics. Nature. 2004;429(6990):464-8.
65. Katsila T, Patrinos GP. Pharmacometabolomics: Applications and Challenges. Curr Pharmacogenomics Person Med. 2015;13:9-13.
66. Lossl P, van de Waterbeemd M, Heck AJR. The diverse and expanding role of mass spectrometry in structural and molecular biology. EMBO J. 2016;35(24):2634-57.
67. Jiang H, Zeng J, Zheng N, Kandoussi H, Peng Q, Valentine JL, Lange RW, Arnold ME. A convenient strategy for quantitative determination of drug concentrations in tissue homogenates using a liquid chromatography/tandem mass spectrometry assay for plasma samples. Anal Chem. 2011;83(16):6237-44.
68. Wilbaux M, Fuchs A, Samardzic J, Rodieux F, Csajka C, Allegaert K, van den Anker JN, Pfister M. Pharmacometric Approaches to Personalize Use of Primarily Renally Eliminated Antibiotics in Preterm and Term Neonates. J Clin Pharmacol. 2016;56(8):909-35.
69. Hurkacz M, Nowakowska JM, Paluszyńska D, Królak-Olejnik B. Individualization of treatment with gentamicin in neonates based on drug concentration in the blood serum. Dev Period Med. 2019;23(1):21-7.
70. Touw DJ, Westerman EM, Sprij AJ. Therapeutic Drug Monitoring of Aminoglycosides in Neonates. Clin Pharmacokinet. 2009;48(2):71-88.
71. Fuchs A, Guidi M, Giannoni E, Werner D, Buclin T, Widmer N, Csajka C. Population pharmacokinetic study of gentamicin in a large cohort of premature and term neonates. Br J Clin Pharmacol. 2014;78(5):1090-101.
72. Frymoyer A, Meng L, Bonifacio S, Verotta D, Guglielmo B. Gentamicin pharmacokinetics and dosing in neonates with hypoxic ischemic encephalopathy receiving hypothermia. Pharmacotherapy. 2013;33(7):718-26.
73. Sherwin CMT, Kostan E, Broadbent RS, Medlicott NJ, Reith DM. Evaluation of the effect of intravenous volume expanders upon the volume of distribution of gentamicin in septic neonates. Biopharm Drug Dispos. 2009;30(5):276-80.
74. Allegaert K, Anderson BJ, van den Anker JN, Vanhaesebrouck S, de Zegher F. Renal drug clearance in preterm neonates: relation to prenatal growth. Ther Drug Monit. 2007;29(3):284-91.
75. Allegaert K. The impact of ibuprofen or indomethacin on renal drug clearance in neonates. J Matern Fetal Neonatal Med. 2009;22(Suppl 3):88-91.
76. Leroux S, Jacqz-Aigrain E, Biran V, Lopez E, Madeleneau D, Wallon C, Zana-Taïeb E, Virlouvet AL, Rioualen S, Zhao W. Clinical Utility and Safety of a Model-Based Patient-Tailored Dose of Vancomycin in Neonates. Antimicrob Agents Chemother. 2016;60(4):2039-42.
77. Mehrotra N, Tang L, Phelps S, Meibohm B. Evaluation of vancomycin dosing regimens in preterm and term neonates

using Monte Carlo simulations. Pharmacotherapy. 2012;32(5): 408-19.

78. Frymoyer A, Stockmann C, Hersh AL, Goswami S, Keizer RJ. Individualized Empiric Vancomycin Dosing in Neonates Using a Model-Based Approach. J Pediatric Infect Dis Soc. 2019;8(2):97-104.
79. Aggelina A, Syggelou A, Chalkias A, Papalois A, Xanthos T, Iacovidou N. Metabolomics in Experimental Neonatology. J Pediatr Neonatal Care. 2015;2(4):00086.
80. Chau CMY, Ross CJD, Chau V, Synnes AR, Miller SP, Carleton B, Grunau RE. Morphine biotransformation genes and neonatal clinical factors predicted behaviour problems in very preterm children at 18 months. EBioMedicine. 2019;40:655-62.
81. Matic M, Simons SH, van Lingen RA, van Rosmalen J, Elens L, de Wildt SN, Tibboel D, van Schaik RH. Rescue morphine in mechanically ventilated newborns associated with combined OPRM1 and COMT genotype. Pharmacogenomics. 2014;15(10): 1287-95.
82. Norman E, Kindblom JM, Rane A, Berg A, Schubert U, Hallberg B, Fellman V. Individual variations in fentanyl pharmacokinetics and pharmacodynamics in preterm infants. Acta Paediatr. 2019;108(8):1441-6.
83. Vinks AA, Punt NC, Menke F, Kirkendall E, Butler D, Duggan TJ, Cortezzo DE, Kiger S, Dietrich T, Spencer P, Keefer R, Setchell KDR, Zhao J, Euteneuer JC, Mizuno T, Dufendach KR. Electronic Health Record (EHR)-Embedded Decision Support Platform for Morphine Precision Dosing in Neonates. Clin Pharmacol Ther. 2020;107(1):186-94.
84. McPherson C, Neil JJ, Tjoeng TH, Pineda R, Inder TE. A pilot randomized trial of high-dose caffeine therapy in preterm infants. Pediatr Res. 2015;78(2):198-204.
85. Vliegenthart R, Miedema M, Hutten GJ, van Kaam AH, Onland W. High versus standard dose caffeine for apnoea: a systematic review. Arch Dis Child Fetal Neonatal Ed. 2018;103(6):F523-9.
86. Cornelis MC, El-Sohemy A, Campos H. Genetic polymorphism of the adenosine A2A receptor is associated with habitual caffeine consumption. Am J Clin Nutr. 2007;86(1):240-4.
87. Pirastu N, Kooyman M, Robino A, van der Spek A, Navarini L, Amin N, Karssen LC, Van Duijn CM, Gasparini P. Non-additive genome-wide association scan reveals a new gene associated with habitual coffee consumption. Sci Rep. 2016;6:31590.
88. Thorn CF, Aklillu E, McDonagh EM, Klein TE, Altman RB. PharmGKB summary: caffeine pathway. Pharmacogenet Genomics. 2012;22(5):389-95.
89. Dessi A, Murgia A, Agostino R, Pattumelli MG, Schirru A, Scano P, Fanos V, Caboni P. Exploring the Role of Different Neonatal Nutrition Regimens during the First week of Life by Urinary GC-MS Metabolomics. Int J Mol Sci. 2016;17(2):265.