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Review

Role of Genomics in Neonatal Care and Research—A Narrative Review

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Abstract

There is a high prevalence of genetic abnormalities that significantly contribute to overall morbidity and mortality in neonates. Since early diagnosis is crucial for the optimal administration of conventional and customized medications, neonatal acute care has the most significant potential to benefit from genomic medicine. Genome sequencing has been demonstrated to have diagnostic, therapeutic and informational value in many investigations. With underlying genetic disorders, genome sequencing has the power to change the way newborn care is provided completely. However, due to existing healthcare disparities, genomic medicine requires cautious implementation to guarantee equitable access for disadvantaged groups. Hence, its clinical application is still challenging.

Keywords

Genomic medicine; genome sequencing; whole exome sequencing; neonatal research

1. Introduction

A cell's genome is its genetic material, or deoxyribonucleic acid (DNA), and the field of genomics studies genomes and DNA sequences [1]. Over the past ten years, genomics has developed tremendously in medicine.

There was a quick advancement following the use of diagnostic exome sequencing in patients in 2010 [2]. To find genes linked to phenotypic features, genomics research (GR) is currently effectively identifying genes, genomic areas, as well as the structure and function of the genome [1]. This opens up new possibilities for the diagnosis and treatment of genetic illnesses. Genomic research aims to sequence, compile, and annotate genomic and transcriptome (RNA) data using computer tools, bioinformatics, and DNA-based technologies [3].

Additionally, the scope can be extended to include other molecular-based techniques, such as recombinant DNA technology, sequencing, and cloning [4].

Many different kinds of genetic disorders are described in neonates. When a single gene alters and results in an illness, this is known as a single-gene condition. Some examples are Hemophilia, Tay-Sachs illness, sickle cell anemia, Marfan syndrome, and cystic fibrosis. When there are additional or missing chromosomes or fragments of chromosomes, chromosomal abnormalities arise. An extra chromosome number 21 is the source of the most prevalent chromosomal abnormality, Down syndrome. Aberrant chromosomes can occur accidentally or be inherited from a parent. Since environmental influences and genetic predispositions combine to generate multifactorial or complex disorders, it is more difficult to identify potential risk factors. Spina bifida, cleft lip or palate, and heart abnormalities are a few examples. When the unborn child is exposed to substances known as "teratogens" during pregnancy, it might result in teratogenic illnesses. During the first trimester, while all of the organs are developing, babies are extremely sensitive. Alcohol, narcotics, lead, excessive radiation exposure, some medications, infections, and poisonous substances are examples of teratogens [4-7].

1.1 Genetic Illnesses Can Be Tested for in Two Ways

1. Screening tests that determine the likelihood that your child will have specific genetic abnormalities. The goal of carrier screening is to determine if either parent has a genetic mutation for an inherited illness that could be passed on to the child. A saliva sample can also be used for this procedure. Although it can be completed during pregnancy, the ideal time to complete this test is before pregnancy. It is currently not feasible to screen for every disorder that might be inherited, even though this test can check for multiple illnesses at once. Prenatal genetic screens are a series of tests conducted in the first and second trimesters to assess the risk for the unborn child using ultrasounds and mother blood samples. Prenatal genetic screenings are tests performed in the first and second trimesters to determine the baby's chance of developing specific common genetic abnormalities. These tests use ultrasounds and blood samples from the mother. Down syndrome and specific birth abnormalities like spina bifida are two examples. Cell-free DNA screening, also known as noninvasive prenatal testing (NIPT), is a blood test examining placental DNA in the mother's blood. This is most frequently used in high-risk pregnancies and checks for the most prevalent chromosomal abnormalities, including trisomy 18 and Down syndrome [1, 4, 5].

2. Diagnostic tests which can detect if certain genetic disorders are present in the baby. Pregnancy-related diagnostic tests are used to determine whether the unborn child has Down

syndrome or cystic fibrosis, among other genetic abnormalities. Neural tube anomalies, such as spina bifida, can also be detected by specific diagnostic tests. When a skilled doctor performs diagnostic tests, they are usually safe procedures. Nonetheless, there is little chance of complications with any surgery, including a higher chance of miscarriage. Typical diagnostic examinations consist of a sample of tissue extracted from the placenta during the first trimester is tested via chorionic villus sampling (CVS). Testing a sample of amniotic fluid extracted from the womb during the second trimester is known as amniocentesis [1, 6, 7].

To check for genetic diseases, fetal blood sampling, or percutaneous umbilical blood sampling (PUBS), takes a blood sample from the baby's umbilical cord. This is typically done when chorionic villus sampling or amniocentesis is not feasible. Using cells taken from an amniocentesis or CVS, prenatal chromosomal analysis (Karyotype) is a frequent genetic test that can identify significant chromosome variations, such as an additional or missing chromosome or a change in how the chromosomes are assembled. Prenatal Chromosomal Microarray Analysis (CMA) is a more thorough test that looks for additional or missing chromosomes in cells from an amniocentesis or CVS. These extra or absent components could be too little to be seen on a karyotype. Whole-exome sequencing (WES), or fetal genomic sequencing, is a diagnostic procedure that examines nearly every gene in a fetus with severe prenatal disorders [1, 4-7].

Screening and diagnostic tests are optional, but they help determine whether a newborn truly has a specific genetic condition. All women, including those without established risk factors, can access them.

With the high prevalence of genetic abnormalities contributing significantly to overall morbidity and mortality, neonatal acute care dealing with critically ill population groups has the most potential to benefit from genomic medicine (GM) since optimal administration of both conventional and tailored medicines depends on early diagnosis [4]. Numerous studies have shown the diagnostic, therapeutic, personal, and informational utility of genome sequencing (GS) not only for critically sick newborns with underlying genetic abnormalities but also for their families [4, 5]. GS has the potential to revolutionize neonatal treatment. However, using GM in clinical treatment is tricky since it exacerbates health disparities and necessitates careful application to ensure fair access for vulnerable populations [6, 7]. In this review, we explore the role of genomics in neonatal care and future implications.

2. Materials and Methods

2.1 Objective

This narrative review aims to provide a comprehensive overview of genomics's current understanding and applications in neonatal care and research, highlighting its potential benefits, challenges, and implications for future practice.

2.2 Inclusion Criteria

- Peer-reviewed articles focusing on genomics in neonatal care, including genetic screening, personalized medicine, and genetic disorders.
- Studies and reviews published in English that contribute to the understanding of genomics in neonatology.

2.3 Exclusion Criteria

- Non-peer-reviewed literature, such as editorials and opinion pieces.
- Studies not focused on human neonatal populations, animal studies, or laboratory-based research.

2.4 Literature Search Strategy

A comprehensive literature search was conducted using PubMed, Embase, Web of Science, and Scopus databases. The search will incorporate MeSH terms and relevant keywords, including: "Genomics", "Genetic Disorders", "Whole exome sequencing" "Newborn Care", "Neonatology", & "Research". The search employed Boolean operators (AND, OR) to ensure comprehensive coverage. Two reviewers independently screened the search results for relevance. They assessed the titles and abstracts, followed by a full-text evaluation of potentially eligible articles. Discrepancies are resolved through discussion or consultation with the third reviewer.

Articles published between 1st January 2010 and December 31, 2023 were considered. A total of 64 research papers were included for narrative review.

2.5 Data Extraction and Analysis

Key information extracted from the selected articles included Author(s) and publication year, Study type and design, Population characteristics, Key findings related to genomic applications in neonatal care, and Identified challenges and future directions.

2.6 Synthesis of Information

The extracted data were synthesized through thematic analysis, resulting in categorized findings on the Background of the development of the field of Genomics, Distinctiveness of Neonatal Genomics, socioeconomic overview in UAE, current scope, barriers of implementation, and future potential of genomics in neonatal care with integration of Artificial intelligence.

2.7 Limitations

This review acknowledges potential biases due to the selected literature and the subjective nature of narrative synthesis.

2.8 Ethical Considerations

No ethical approval was required for this review, as it utilized published literature.

3. Background of the Development of the Field of Genomics

DNA plays a significant role in storing genetic information and encoding proteins that are dependable for transmission from parents to children. The linear order of DNA nucleotides determines the kind and quantity of proteins a given genome encodes. This phenomenon explains an organism's physiological capabilities [1, 3, 4].

Due to the advancement of other omics techniques and next-generation sequencing technology, genomics is on the verge of a revolution. These systems can handle lengthy genomic sequences by dividing them into manageable chunks of DNA, which can then be assembled into entire chromosomes and analyzed by automated sequence analyzers [2].

As whole-genome sequences are now accessible, a new area of study known as comparative genomics has emerged, enabling the confirmation of predicted genes and the discovery of new ones. Genes essential to particular cellular activities and intergenic (non-coding) areas that control gene expression can be found using high-throughput genomics technology [4, 6].

In genomics, the recombinant DNA (rDNA) technology is essential. Using this technique, an outside DNA fragment is inserted into a carrier that can replicate independently- called "cloning." A piece of viral DNA, bacterial plasmids, yeast artificial chromosomes, etc., can all be components of a carrier molecule. Gene and genomic libraries can be created using the rDNA technique for additional research. Afterward, a genomic library can be cloned and kept alive in an appropriate cloning vector to eventually be digested and analyzed using next-generation sequencing technology that provides speed and scalability [4, 6].

The multidisciplinary area of bioinformatics has grown due to the development of increasingly advanced and potent computer tools. Bioinformatics tools are helpful in assembling and analyzing large amounts of genomic data. The specificity for compiling and analyzing sequence data at a previously unheard-of depth and size has significantly expanded over the past few years due to the advent of new bioinformatics resources [1, 6, 7].

Newborn screening (NBS) has undergone constant technological improvement and advancement since it was first used in clinical practice in the 1960s. Tandem mass spectrometry (TMS) has been employed for NBS since 1989 [8]. It can identify more inborn errors of metabolism (IEM) in a single examination according to its technological advantages [9]. However, due to the complexity and wide range of clinical symptoms, the diagnosis of IEM frequently necessitates further auxiliary tests, such as identifying disease-causing gene variants. As a result, TMS-NGS, or next-generation sequencing (NGS) after TMS, has taken center stage in infant illness screening initiatives [10]. Nonetheless, several issues remain, including the number of illnesses requiring screening. Twenty-nine screening conditions were identified by the American College of Medical Genetics (ACMG) [11]. Due to the lengthy turnaround time of NGS testing and the comparatively high rate of false positives, diagnosis and intervention are frequently postponed. Furthermore, it is impossible to overlook the high expense of NGS testing. NGS has recently contributed to significant advancements in many medical fields because of the quick development of sequencing and the drop in costs. It can be utilized for population screening in addition to aiding in the diagnosis and focused treatment of illnesses. Furthermore, genomic sequencing has demonstrated potential utility in newborn screening, including whole genome sequencing (WGS), exome sequencing (ES), and gene panel sequencing [12-14].

4. Distinctiveness of Neonatal Genomics

Significant morbidity, frequently lasting a lifetime, and genetic diseases cause infant death. The leading causes of infant mortality in the United States are now reported to be genetic [15, 16]. Over the past several decades, obstetric care and neonatology advancements have reduced morbidity and mortality from other perinatal conditions (e.g., surfactant administration for respiratory distress syndrome). Finding the underlying genetic diagnoses is the first step in using precision medicine techniques to reduce death from genetic illnesses. Due to limited access to GS, up to 25% of severely ill newborns in Neonatal Intensive Care Units (NICUs) may have an undetected genetic abnormality [17-20].

In general, a genetic abnormality may be hypothesized as the underlying cause of a severely unwell newborn with an unknown diagnosis, and the infant may be evaluated for genetic screening. According to prior research, multiple congenital anomalies (or a single significant anomaly with accompanying syndromic features) and severe organ system abnormalities of unknown etiology related to neurology, metabolism, or other areas may be considered specific phenotypic criteria in the neonatal period to prioritize for GS [21-23]. For newborns (less than one-year-old) with one or more congenital abnormalities, the American College of Medical Genetics and Genomics has released a current evidence-based guideline on GS [24].

It's crucial to remember that specific clinical characteristics linked to genetic abnormalities might not manifest until later in life and that nonspecific clinical observations may be present during the neonatal period. When a critically unwell newborn presents without an apparent nongenetic reason, GS should ideally be viewed as a comprehensive diagnostic test.

For severely ill newborns with suspected genetic abnormalities and their families, rapid genetic screening offers several possible advantages. A quick genetic diagnosis can be accomplished from GS. A weighted average diagnosis rate of 36% was found in a recent evaluation of 31 studies involving rapid GS in pediatric and newborn patients in intensive care units [4]. Also, there is a chance that GS will result in changes to clinical management (clinical utility); a weighted average shift in management rate of 27% was reported in the same review [4]. A genetic diagnosis may impact the goals of care, workup, and treatment of the condition.

Furthermore, access to etiology-specific research, such as natural history studies and clinical trials of novel precision medicines, may be made possible by a genetic diagnosis. Nondiagnostic GS has occasionally been linked to changes in management [25]. A genetic diagnosis may have an impact on prognosis and reproductive counseling; for instance, it may affect the risk of recurrence for the latter and developmental delay/intellectual disability for the former. Additional patient-reported advantages for the child and family may also result from a genetic diagnosis [26].

Lastly, recent research has shown that GS is cost-effective in the NICU [25, 27]. Therefore, despite not everyone in one’s healthcare system has equitable access to genomic medicine, GS currently offers the most immense potential to improve NICU patients' medical care.

5. Socio-Economic Overview of the UAE in the Context of Neonatal Genomic Studies

The United Arab Emirates (UAE) has a distinct socioeconomic status, marked by high-income levels, quick expansion, and significant investments in healthcare facilities. Neonates and their families face both possibilities and challenges when cutting-edge medical technology like neonatal genomics, which uses genomic testing to evaluate and comprehend a newborn's genetic

composition, is integrated into this socioeconomic setting. This is becoming increasingly important in early diagnosis, personalized treatment plans, and the prevention of serious diseases. In the UAE, this is particularly relevant given the high rates of consanguinity (inter-family marriages), which increase the risk of genetic disorders. Genetic disorders are the fourth-highest cause of death in the UAE, and the nation is ranked sixth among 193 countries in terms of the prevalence of birth defects, mainly due to genetic causes [28].

The UAE government has supported initiatives to introduce advanced genetic screening and testing, including newborn screening programs focusing on conditions like metabolic disorders, hearing loss, and other congenital diseases [29].

Neonatal genetic testing is frequently covered by the government's comprehensively beneficial health insurance program for Emiratis. Given the high prevalence of genetic illnesses in the population due to consanguinity, these families would consider genomic testing a crucial preventive health intervention. The availability of the technology may vary depending on the medical facility and the ailment being evaluated. Still, for the most part, the cost is not a concern for Emirati families. Families of expatriates: Neonatal genomics is more difficult for foreigners to get. Even while there are top-notch medical facilities, the price of sophisticated genetic testing can be too pricey for those without full health insurance. Many foreigners may only think about genome testing if a physician recommends it or if there is a family history of genetic illnesses. Lower-income expatriate families may be particularly concerned about the out-of-pocket costs associated with these tests [30, 31].

Moving forward with neonatal genetic testing is frequently a joint decision between parents and medical professionals. Emirati households may have more group decision-making, as extended family members may also be involved in healthcare choices. The choice may be more personal or motivated by a nuclear family for expatriates, especially those who do not have many support systems in the United Arab Emirates.

Currently, the Emirati Genome Programme is a nationwide initiative that uses genomic data to enhance the health of the UAE population by identifying and profiling UAE citizens' genes to help prevent and treat chronic illnesses. National Neonatal Screening Program has been in place since 2010, and under this program, more than 95% of newborns in the United Arab Emirates were screened for 16 diseases [29-31].

By finding genes that cause disease in the Arab population and increasing public knowledge of genetic diseases, the Centre for Arab Genomic Studies (CAGS) also seeks to prevent genetic disorders in Arab nations. They also try to resolve any social, legal, and ethical problems that genetic medicine can bring up. The UAE has set up many genomic medicine centers, including the Abu Dhabi Genome Center and the Dubai Genome Center, to enhance healthcare in the nation by offering genomic services and research facilities. To increase the precision and economy of genomic testing, these centers are also developing novel technologies. Additionally, the UAE has set up a registry of clinical trials and research and a record of people with genetic abnormalities [29-31].

6. Current Scope

Many critically ill infants with genetic diseases have unique disease mechanisms associated with pathogenic genomic variants that are rare or novel due to reduced reproductive fitness and that disrupt the function and/or anatomy of multiple organs [32, 33]. Despite this, many physiologically supportive clinical practices of neonatal intensive care help improve these patients' survival. The

clinical utility and desired effects of whole exome sequencing (WES) and whole genome sequencing (WGS) on active and long-term clinical management for pediatric patients <1 year of age with 1 or more congenital anomalies are supported by an evidence-based clinical practice guideline from the American College of Medical Genetics and Genomics (ACMG) [24].

NICUs have realized how important it is to identify the genetic causes of newborn disorders through diagnostics in order to personalize care, determine prognosis, estimate the probability of a reproductive recurrence, and enhance child outcomes [30, 34]. NICUs have started switching from a phenotype-first to a genotype-first approach by partnering with geneticists, genetic counselors, obstetricians, genomicists, and bioinformaticians. The advancements in genome sequencing technology, particularly the reduction in turnaround time [35], computational strategies for identifying pathogenic variants [36], and lower sequencing costs also contribute to this approach. In critically unwell newborns, a quicker and more accurate prediction and the quick discovery of personalized therapy choices are achievable when rapid trio WES and WGS are incorporated into early diagnostic testing [35, 37].

Furthermore, a genotype's first diagnosis provides a family's estimated reproductive recurrence risk for subsequent pregnancies, the surviving proband, and siblings. For NICU patients with congenital abnormalities, epileptic encephalopathy caused by thiamine metabolism malfunction syndrome is an excellent illustration of the diagnostic and therapeutic utility of WES and WGS. While environmental variables, trauma, and infections are linked to epileptic encephalopathies, genetic etiologies play a significant role in their etiology and prevalence [38, 39]. There are differences in the genetic causes due to purifying selection. If a monogenic etiology is found in a baby with extremely fast WGS, precision therapy may be necessary [40]. The significance of incorporating rapid or ultra-rapid WGS for critically unwell newborns with congenital anomalies, such as epileptic encephalopathies, metabolic problems, and structural birth malformations, is well reported in many case studies [40, 41]. Examples of types of genomic testing and their rationale are illustrated in Table 1 [42].

Table 1 Examples of types of genomic testing and their rationale [42].

Test	Specific example	Rationale
Tests for Prenatal conditions	Human expanded alpha-fetoprotein (AFP) screening for Open neural tube defects (spina bifida, anencephaly), Down syndrome and other chromosomal defects, Abdominal wall defects and Twins etc.	Determination of fetal illness
Newborn screening	Metabolic (e.g. phenylketonuria, tyrosinemia, classic galactosemia, maple syrup urine disease), endocrine (e.g. congenital Hypothyroidism, congenital adrenal hyperplasia), Hemoglobin problems (Sickle cell anemia, B-thlassemia, Hemogobin SC disease) and other disorders (Cystic	To ascertain whether a newborn is suffering from a condition that is known to impair development and health

	fibrosis,Spinal muscular atrophy, severe combined immunodeficiency etc.)	
For establishing Diagnosis	Checking the level of creatine kinase (CK) in cases with Duchenne muscular dystrophy	Accurately diagnose a condition and support clinical judgment
Predictive testing	Huntington's disease-causing HTT gene test and breast cancer-causing BRCA gene test	Estimate the chance of contracting an illness
Testing for Carrier detection	Cystic Fibrosis testing using the CFTR gene	Determine the probability of inheriting a hereditary illness
Pharmacogenomics Testing	TPMT gene testing to predict the likely response to immunosuppressive treatments with thiopurines and the test for the expected response to the anticoagulant warfarin is the vitamin K epoxide reductase complex subunit 1 (VKORC1)	Ascertain the ideal medication regimen and dosage based on an individual's metabolic response
Testing for Research	Using genome-wide association studies (GWAS) to ascertain whether a variant is linked to a trait	Advanced knowledge of the fundamental causes of disease

7. Potential Barriers to Implementation of Genomic Science in Neonatal Care

Obstacles to fair access exist at several stages of the GM implementation process, and it's critical to recognize that racism may present challenges at each stage [43, 44]. Genetic heritage is not the same as race or ethnicity because race and ethnicity are social constructs rather than biological ones [45]. Nevertheless, there are racial and ethnic disparities in health care.

Neonatal care providers must first determine whether GS is a suitable test and suspect that a hospitalized infant has an underlying genetic disease. In community and/or rural NICUs, where newborns from lower-income households, underserved areas, and/or racial and ethnic minority populations are frequently cared for, access to clinical geneticists or genetic counselors to help with this procedure may be limited for clinicians [46, 47]. Healthcare professionals who have not had formal training in clinical genetics may be uninformed about genetics and genomics, and they struggle to recognize infants who may have genetic diseases and harbor conflicting opinions regarding genetic testing [48, 49]. Furthermore, newborns of non-European descent may not appear to have similar traits and dysmorphic features as the Northern European population due to genetic dissimilarity [50]. GS must then be authorized and made available in clinical settings. While there are many different contexts in which newborn critical care is provided (rural and urban, community and academic), big academic referral facilities are the primary locations for GS because they have the means and know-how to manage this process in an environmentally responsible manner. In community and/or rural NICUs without genetic screening (GS), infants may be sent to referral facilities for extensive genetic testing or receive limited or no genetic testing. This could result in further financial strain on families and increased healthcare expenditures. In NICUs where GS is offered, institutional committee and/or insurance permission is frequently needed before testing may begin [51, 52].

A practitioner must obtain consent and offer pre-test counseling to the infant's family before ordering GS. When available, clinical geneticists or GCs perform this frequently, and non-genetics providers (NGPs) could find the procedure awkward. Furthermore, because of institutional racism and past injustices, families belonging to racial and ethnic minorities may be more inclined to harbor hostility towards genetic testing and/or the healthcare system [43-45].

8. Future Potential of Genomics in Clinical Care and Research

Genomics is expected to have a bright future due to advancing cutting-edge technology for de novo sequencing, assembly, and sequence data processing. However, these developments are anticipated to also present new difficulties. The first and most challenging problem is developing bioinformatics techniques to integrate omics data, which could aid in forecasting how a genome can influence various phenotypic features in multiple contexts [1, 4, 53].

Advances in genomics research are becoming more numerous as genetic engineering progresses. A special mention should go to the CRISPR-Ca9 technology for practical genome engineering. Among the most effective methods for inducing specific mutations throughout the entire genome [1, 34, 53]. Using CRISPR-Cas9, a genome-editing technology, one can modify nucleotide sequences and investigate the relationship between specific mutations at many loci and a certain phenotype in any desired cell line [53].

Our knowledge of applying GS in NICUs and other pediatric critical care settings will continue to be refined through ongoing research and implementation initiatives. However, it's clear that rWGS-based precision medicine benefits newborns in intensive care units significantly in terms of diagnostic and clinical utility and cost-effectiveness. This data will usher in a new age of widely used precision medicine informed by rWGS for newborns in NICUs. It would be ideal if professional associations released guidelines endorsing rWGS as a first-line diagnostic test for critically unwell newborns with illnesses of unclear etiology. One of the leading open questions is how much genome sequencing should be done in NICUs.

When genomic sequencing was used in 46% of admissions to a regional NICU, the Newborn Sequencing in Genomic Medicine and Public Health (NSIGHT2) trial demonstrated diagnostic and clinical efficacy [37]. It first measured the significance of negative genomic sequencing. More research is required to determine the ideal scope of use at various NICU levels.

Currently, available research continues to underestimate the frequency of single locus genetic disorders in neonates admitted to intensive care units. A high percentage of undiscovered genetic disorders, many of which had excellent prognoses, were discovered in an unpublished study of postmortem newborns [54, 55]. The speed at which genetic illnesses are being found and the quality of WGS are increasing. Using a combination of long- and short-read WGS may result in a 5-15% increase in diagnostic yield [56]. The cost of long-read WGS is higher than that of short-read WGS. It is significantly better at characterizing copy number variants (CNVs) and single nucleotide variants (SNVs) than only detecting SNVs. The evolving picture of these variants shows that they are often more complex than previously thought and are often combination events involving insertions, rearrangements, and deletions at a single locus. Additionally, read assembly will replace read alignment in the near future to provide assembled individual genomes [57]. This is likely to result in an additional 5-15% increase in yield, especially in racial and ethnic groups that were not represented in the existing reference human genome. Digital, automated ethnic ancestry

delineation in short-read WGS and subsequent alignment to the best of a large selection of heterogeneous reference genomes may serve as a bridge to genome assemblies [58].

The benefits of combining WGS with functional omics, including proteomics, metabolomics, and RNAseq [59], are increasingly recognized as we approach a new era of integrated clinical omics. It is not yet possible to estimate the pathogenicity of a very large number of variations at this time. These are primarily intronic or intergenic. However, it is possible to assess the functional implications of these variations because of these omics technologies. Identifying unresolved cases and creating new databases of functional omics-annotated variants are the two applications of this technology. There won't be many variants of unknown significance left in the end [58, 59].

9. Role of Artificial Intelligence in Genomic Medicine

The application of artificial intelligence (AI) to enhance scalability and boost acceptance of precision medicine and quick genome sequencing in neonates in intensive care units is another topic that is picking up steam. Furthermore, AI can provide algorithm-based, automated Electronic Health Record (HER) warnings that are set off in newborns who are at a high risk of dying and who are very likely to have an underlying genetic condition [60]. Intensivists and neonatologists can significantly benefit from it, especially in hospitals lacking a full complement of subspecialists and super specialists, where there may be delays in administering the best treatments for extremely uncommon genetic illnesses.

AI technologies will be pivotal in enabling most NICUs affiliated with birthing hospitals to adopt rWGS-based precision medicine. Accelerated genetic therapy development will be the most fascinating breakthrough in the future. Effective gene therapy is A remarkable achievement in treating Spinal Muscular Atrophy type 1 (SMA1). Unmatched natural history studies of particular infant-onset genetic diseases result from the growing use of rWGS. These studies speed up drug development by identifying endpoints and indications and providing real-world evidence for submitting investigational new drug applications to the US Food and Drug Administration (FDA) [61].

In the absence of quick genome sequencing, most infant-onset genetic illnesses were either not previously known to exist or could not be diagnosed in most cases. Therefore, many hereditary diseases for which it was impossible to develop pharmaceuticals now have viable treatment approaches, such as genome editing, gene therapy, antisense oligonucleotides, small molecules, and repurposing FDA-approved medications. Natural history studies will help us not only with improved therapies but also with prognosis prediction for critically ill infants as well as parent communication and patient stratification within genetic disorders, as is currently done in cases with Duchenne Muscular Dystrophy and Cystic Fibrosis.

It is imperative to apply rWGS for fetal diagnosis and to screen newborns for genetic illnesses using rWGS [62]. Prenatal exome sequencing is recommended in cases of particular fetal abnormalities, according to the opinions of the professional society [63-67]. The integration of genome sequencing into NICU clinical care is highly prioritized due to factors such as genetic heterogeneity of fetal and neonatal phenotypes, the overrepresentation of novel and rare genomic variants in the NICU population, the high fraction of affected infants in NICUs with undiagnosed congenital anomalies or metabolic disorders, the significant contribution of genetic disorders to infant morbidity and mortality, and the demonstrated ability of rWGS/rWES to change clinical management and identify individualized therapeutic strategies [54, 68, 69]. The Genomic Learning

Healthcare System (GLHS) for NICUs will require input from a variety of stakeholders, including parents, payers, bioinformaticians, geneticists, genetic counselors, neonatologists, obstetricians, pediatric subspecialists, developmental biologists, and investigators of model organisms. Additionally, the system will require participation from clinical investigators, genomicists, and institutional leaders, as well as experts in strategies to rescue variant-encoded disruption (e.g., with gene therapy, anti-sense oligonucleotides, repurposed drugs approved by the FDA, small molecules, or genome editing) [36, 70-75].

Facilitating a cultural shift among providers from phenotype- to genotype-first diagnosis; creating governance structures that can respond to novel ethical and operational questions; standardizing genomic and phenotypic data in EHRs; developing more dependable computational and functional evaluation of novel and rare variants of significance that are clinically actionable; and creating consent strategies that allow the inclusion of a patient's clinical and genomic data while maintaining patient confidentiality are some of the challenges associated with the implementation of GLHS [36, 75-83]. NICUs have, nevertheless, a long history of implementing implementation science to improve quality and, more recently, launching value-based quality programs [84].

10. Conclusion

In the research setting, where a critically ill infant can be diagnosed using the newest technologies in less than a day, genomic medicine is a potentially powerful diagnostic tool in NICUs. However, in real-world clinical care, many critically ill infants, and disproportionately racial and ethnic minority infants, do not have access to GS. Ensuring sick newborns have fair access to genetic medicine is a vital need. Predicting the risk of reproductive recurrence for parents and surviving probands is also made possible by genomic diagnostics. By integrating genome sequencing into best practices for neonatal intensive care, deploying a genomic learning healthcare system will reduce neonatal and infant mortality through quality improvement.

Author Contributions

Subhranshu Sekhar Kar: Conceptualization, methodology, Software, Writing-Original draft preparation. Rajani Dube: Conceptualization, Methodology, Software, Formal analysis, Validation. Biji Thomas George: Methodology, Formal analysis, Reviewing and Editing, Validation. Malay Jhancy: Resources, Methodology, Formal analysis, Reviewing and Editing. Approval of the version of the manuscript to be published: All authors.

Competing Interests

The authors declare no conflict of interest.

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