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Commentary

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Newborn screening in South Africa: the past, present, and plans for the future

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Abstract

Worldwide, comprehensive newborn screening (NBS) now includes a clinical examination at birth, hearing screening, pulse oximetry measurement for congenital heart defects, and biochemical screening to identify congenital disorders early in life, preventing irreversible damage, early mortality and enhancing overall health outcomes. This article provides a comprehensive overview of biochemical NBS in South Africa, outlining the history, current status, and future plans for NBS expansion. In South Africa, NBS is fragmented, with some investigations included in neonatal health assessments. Historically, biochemical NBS pilot projects in the country in the 1960s and 1980s focused on phenylketonuria and congenital hypothyroidism (CH). Despite showing initial promise, these programmes were discontinued, largely due to competing health priorities. The current status of biochemical NBS in South Africa is discussed, both for the state and private healthcare sectors, which collectively screen approximately 0.5% of births annually. While recent clinical guidelines provide for a national biochemical NBS programme, implementation has been limited, and guideline adherence remains a challenge. A brief report of a two-day meeting held in Cape Town in February 2023 focusing on biochemical NBS for South Africa is provided. The meeting addressed the importance of NBS, technology requirements, and the need for a comprehensive demonstration project for biochemical CH NBS. Key challenges identified included early newborn post-delivery discharge, technical, logistical, and infrastructure issues, as well as limited financial and human resources. Meeting recommendations included the establishment of a National Advisory Panel for Biochemical NBS, and the development and implementation of a demonstration project for CH biochemical NBS in two provinces.

Keywords: Biochemical newborn screening, congenital hypothyroidism, rare diseases, South Africa

INTRODUCTION

Biochemical newborn screening (NBS) is a series of tests undertaken during the first hours or days of life to screen for congenital disorders (CDs). Some CDs, defined as abnormalities in structure or function present from birth, are immediately obvious, while others, such as many inborn errors of metabolism (IEM) and rare diseases, are not[1,2]. By the time some conditions manifest, ranging from hours, weeks, or months after birth, disease progression may already have caused irreversible damage, resulting in lifelong intellectual and other disabilities, or premature death[3]. This highlights the importance of early identification and referral for treatment in asymptomatic patients before the disease manifests, to arrest disease progression. Collectively, CDs contribute substantially to global mortality, especially more common conditions including congenital heart defects (CHD) and haemogloinopathies, such as thalassemia and sickle cell disease (SCD)[4].

Biochemical NBS began with phenylketonuria (PKU) screening using a bacterial inhibition assay developed by Robert Guthrie, to estimate phenylalanine concentration in dried blood spots. The test was first introduced in the USA in 1963[5-7] and then extended nationwide[8,9]. Early diagnosis of PKU enables immediate adoption of a low phenylalanine diet which minimises the accumulation of phenylalanine and prevents seizures, stunted growth, delayed development, and irreversible intellectual disability[10]. The development of tests suitable for mass screening of congenital hypothyroidism (CH), congenital adrenal hyperplasia (CAH), and cystic fibrosis (CF) followed in the late 1970s[11-13]. With the introduction of tandem mass spectrometry (MS) in the 1990s, the number of known biochemical NBS conditions increased rapidly[14-16]. Today, biochemical NBS is available for a multitude of treatable conditions including IEMs, endocrine-, haemoglobin-, immune-, and other genetic disorders. The United States Recommended Uniform Screening Panel [RUSP (https://www.hrsa.gov/advisory-committees/heritable-disorders/rusp)] now includes biochemical/genetic screening for a minimum of 35 core and 26 secondary conditions (identified unintentionally when screening for core conditions), with similarly expanding panels in other

developed countries[17,18]. The definition of NBS has also been broadened to include screening for critical (CHD) and hearing loss, in addition to the head-to-toe clinical examination of the newborn prior to discharge and biochemical and/or genetic NBS[4,18,19].

Biochemical NBS is now standard practice in most high-income countries (HIC) and some low- and middle-income countries (LMIC), supported by compelling evidence of improved health outcomes and financial benefits[3,18,20]. In many LMIC, including South Africa (SA), biochemical NBS is limited or unavailable. The United Nations Sustainable Development Goal (SDG) 3 targets for 2030 seek to reduce neonatal- and under-5 mortality to fewer than 12 and 25 deaths per 1,000 live births, respectively[21]. To meet these targets, all countries must consider addressing CDs comprehensively, which includes universal biochemical NBS.

The aim of this article is to provide a comprehensive overview of the history, current status and plans underway for expanding biochemical NBS implementation in SA. This includes a brief report of a two-day meeting on NBS for SA, which was held in Cape Town in February 2023.

OVERVIEW OF SOUTH AFRICA

Situated at the southern point of Africa, SA is classified as an upper middle-income country. The population of 60.6 million is spread across nine provinces, covering a geographic area of 1.2 million km^2[22]. Approximately 68% of the population is urbanized, with 25% living in the province of Gauteng and 19% in KwaZulu Natal (KZN)[22]. Around a million live births are recorded annually, and in 2021, 17.5% of births were to mothers aged ≥ 35 and 11.5% to mothers aged 10-19 years[23]. Neonatal (NMR), infant (IMR), and under-5 mortality rates (U5MR) were 12, 21, and 28 per 1,000 live births, respectively, in 2020[24]. The South African fertility rate is 2.34 births per woman, with life expectancy at birth of 64.2 years for females and 59.2 for males[22,23]. The country has been severely impacted by HIV/AIDS, with an estimated 13.9% of the population (8.45 million) living with HIV (2022), and the largest number of people enrolled in antiretroviral treatment (ART) globally. High AIDS-related mortality combined with the effective HIV Prevention of Mother to Child Transmission (PMTCT) programme[25] has resulted in a younger population demographic, with 20% (17 million) of the population aged ≤ 15 years and only 9% (6 million) aged ≥ 60[22].

The dual health system implemented in SA is one of the most disproportional globally, with 84% of the population reliant on state services and 16% on private medical services, with the latter consuming a majority share of available healthcare resources[26]. The establishment of the National Health Insurance, a funding mechanism for universal health coverage to redress inequalities, has been hampered by a lack of resources and, most recently, by the COVID-19 pandemic which diverted funding and human capacity to the pandemic emergency response[27-33].

Community genetic services in SA have been neglected in the last 20-30 years due to competing health priorities[27,34-36]. Inadequate financial and human resources and ineffective use of available infrastructure prevent an appropriate response to the growing health need of CDs, as the country transitions epidemiologically[34]. While significant reductions in child mortality have been achieved through targeted health interventions (e.g., PMTCT for HIV, expanded programme of immunisation, improved maternity care, *etc.*), improvements to the IMR and U5MR have slowed since 2011[37], highlighting the need to address other health issues[34,38,39]. In SA, as seen globally, the number and rate of CDs are estimated to be decreasing, but the proportion of CD-related deaths is increasing[40]. To achieve further reductions in child mortality, CDs must be prioritised, including the implementation of cost-effective, universally available biochemical NBS[41,42].

NEWBORN SCREENING IN SOUTH AFRICA

History of biochemical NBS in SA

Biochemical NBS for PKU was investigated in SA in the mid-1960s through a state-funded pilot project using phenistix testing in Johannesburg (1964-1967), followed by a more comprehensive pilot from 1979-1981 and a formal programme from 1981-1986 in Pretoria[43]. However, in 1986, the biochemical NBS programme for PKU and other amino acidopathies was discontinued as it was deemed "neither cost-effective nor justifiable, especially against the background of other, more pressing health priorities"[43-46].

A case was made for biochemical NBS of CH in SA in the late 1970s following the global application of radio-immunoassay to assess thyroid function[47]. This condition is a prime candidate for biochemical NBS in SA due to its high birth prevalence (1 in 4,000 or 0.25 per 1,000 live births), the availability of screening and follow-up diagnostic tests with standard, low-cost (in comparison with many other IEMs) levothyroxine treatment to prevent disease progression[23,48]. Clinical onset ranges from days, weeks to months after birth, depending on the cause and extent of thyroid dysfunction, by which time intellectual deficits are irreversible regardless of subsequent thyroid replacement therapy[49]. Diagnosis of CH may also be significantly delayed depending on clinical awareness and experience.

Several biochemical NBS pilot studies for CH were implemented in Pretoria from 1979-1981 (13,146 newborns screened, 2 cases diagnosed clinically) and from 1981-1986 (45,577 newborns screened, 11 diagnosed)[47-49]. A Cape Town pilot project from 1982-1984 screened 28,000 neonates with 6 positive cases confirmed[48,50]. These pilots indicated that NBS for CH was cost-effective and a "nation-wide unified screening programme" was recommended[48]. However, without guaranteed adequate follow-up and intervention for positive cases, caution was advised, and further investigation was suggested to ensure cost-effectiveness[46].

The first national workshop on CH was held in Cape Town in 1987, with a subsequent meeting in Johannesburg in 1992[46], where CH biochemical NBS data for 1990-1992 from four locations (Cape Town, Durban, Johannesburg, and Pretoria) were presented. A total of 65,545 neonates (3.56% of total births) were screened, with 12 confirmed CH cases[46].

As indicated earlier, global advancements improved the sensitivity, reliability, and coverage of biochemical NBS through tandem MS in the 2000s, leading to an increase in the number of treatable genetic conditions that could be screened simultaneously[51]. However, in SA, biochemical NBS remained limited. From 1999-2006, a pilot study funded by the International Atomic Energy Agency (IAEA) screened 42,000 newborns for CH and 13,000 for other IEMs across 12 hospitals in three provinces using tandem MS at North-West University (NWU) in Potchefstroom[52]. Results from this pilot study and subsequent testing indicated that CH, biotinidase deficiency, propionic acidaemia, and galactosemia [due to galactose-1-phosphate uridyl transferase (GALT) deficiency] are most commonly encountered with biochemical NBS. Unfortunately, this pilot study did not result in a national biochemical NBS programme[53], but expertise and services at NWU were preserved by offering biochemical NBS to the private healthcare sector on a "fee for service" basis. Since 2016, a major medical aid scheme in SA has begun to reimburse biochemical NBS costs, albeit from members' medical savings accounts. Several other schemes have followed suit. In the period between January 1998 and September 2023, a total of 125,888 samples (0.5% of all births in SA) were screened by NWU for 22 conditions, with 80 diagnoses in total, including 16 CH cases [Table 1].

An audit of the CH biochemical NBS programme implemented by the Peninsula Maternal and Neonatal Service (PMNS) [The PMNS included: Groote Schuur Hospital (GSH), Mowbray Maternity Hospital

Table 1. Summary of biochemical NBS results, Centre for Metabolomics, North-West University, January 1998-September 2023. All 125,888 samples (equivalent to 0.5% of births in South Africa) were screened using a panel of 22 conditions

year	Project	Total samples	Total positive	PA	MMA	IVA	GAI	BIOT	PKU	GALT	CH	CAH	CF	3-MCC	TYRI	TFP/LCHAD	CUD	OTC	MADD/GAII
				RUSP core conditions														Secondary conditions	
1998	Government	445	0																
1999	Government	4,903	0																
2000	Government	8,410	1								1								
2001	Government	10,674	1								1								
2002	Government	8,886	0																
2003	Government	11,399	1								1								
2004	Government	12,665	1								1								
2005	Government	11,933	0																
2006	Government	3,121	0																
2007	Private	106	0																
2008	Private	1,325	0																
2009	Private	1,163	3					1			2								
2010	Private	871	3			1						1	1						
2011	Private	811	0																
2012	Private	951	5		1			1			1	1	1						
2013	Private	1,770	1	1															
2014	Private	2,897	9				1	1 + 1*	1	1	3								1
2015	Private	3,442	6	1	1	1				2		1							
2016	Private	4,245	1								1								
2017	Private	5,486	1										1						
2018	Private	5,596	8					4		2	1			1					
2019	Private	5,567	5								3				1			1	
2020	Private	5,346	11	3		1		3		1	1	1	1						
2021	Private	5,362	13	2 + 3*			1			2			1			1	2	1	
2022	Private	4,702	5						1	2			1					1	
2023	Private	3,812	5					3	1					1					
Total		125,888	80	10	2	3	2	14	3	10	16	4	6	2	1	1	2	3	1

*Indicates cases unconfirmed via further review following initial positive screening. PA: Propionic acidaemia; MMA: methylmalonic acidaemia; IVA: isovaleric acidaemia; GAI: glutaric acidaemia type I; BIOT: biotinidase deficiency; PKU: phenylketonuria; GALT: galactosaemia due to GALT deficiency; CH: (primary) congenital hypothyroidism; CAH: congenital adrenal hyperplasia; CF: cystic fibrosis; 3-MCC: 3-methylcrotonyl-CoA carboxylase deficiency; TYRI: tyrosinemia type I; TFP/LCHAD: trifunctional protein deficiency/long-chain hydroxyacyl-CoA dehydrogenase deficiency; CUD: carnitine uptake disorder; OTC: ornithine transcarbamylase deficiency; MADD/GAII: multiple acyl-CoA dehydrogenase deficiency/glutaric acidaemia type 2. A RUSP "secondary condition" is identified unintentionally when screening for one of the core conditions; or as a consequence of confirmatory testing for an out-of-range result of a core condition.

(MMH), New Somerset Hospital (NSH) and six MOUs. The PMNS was initiated in 1987 and has subsequently been disbanded and subdivided into three regions] in Cape Town was undertaken for the period January 2000-December 2004[54]. Of the 140,507 neonates screened using cord blood, 13 CH cases were confirmed, at an average review age of 62 days. A crude costing indicated a cost of ZAR22 per CH screening or ZAR221,552.96 per detected case (equivalent to US$3.89 and US$39,213 in 2004 using historic ZAR:US$ exchange rates), but the study did not include comparable associated lifetime cost of care for undetected cases[54]

Current status of NBS in South Africa

NBS is considered a component of community genetic services in SA, as indicated in the 2021 Clinical Guidelines for Genetic Services published by the National Department of Health (NDOH)[55]. These Guidelines provide for NBS, specifying that "All newborns must have a postnatal examination (three to six days postnatal) to identify CDs missed at birth or discharge"[55]. It lists considerations, including hearing and vision assessments, checking of oxygen saturations within 24 h of birth, growth and development, and potential false positive/negative assessment at birth. Biochemical NBS is included as a "progression" of broader NBS, important for all newborns when it prevents significant, irreversible morbidity and/or mortality. Neonates screening positive should be referred for diagnostic confirmation, genetic counselling, and management. The Clinical Guidelines also recommend further studies to determine which conditions should be included in the biochemical NBS programme and indicate that an initial minimum panel should include CH, CAH, CF, galactosaemia (due to GALT deficiency), glutaric aciduria type 1, and propionic acidaemia[55].

While the current guidelines provide for biochemical NBS, the implementation thereof and adherence to previous guidelines have been limited, and to date, no progress reports have been issued[56-61].

NBS in the private sector

In the private health sector of SA[26], biochemical NBS is led by NWU, implementing a panel of 22 conditions and providing services to private laboratories countrywide. Samples are taken via a minimally invasive heel prick of the newborn between 1 and 7 days after birth/before discharge. Next Biosciences, a private laboratory in SA, assists with the follow-up of abnormal screening results, including patient support and counselling, timely and relevant secondary testing, and precise sampling.

The recent establishment of the CHM Biobank for rare diseases at NWU will further underpin biochemical NBS efforts, providing a legal framework and infrastructure for the long-term storage of samples and an accompanying registry for secure data storage[62,63]. A patient-initiated rare disease registry is under development by Rare Diseases South Africa (RDSA), a patient-based advocacy Non-Profit Organisation, in collaboration with the NWU Biobank.

NBS in the state sector

In the state sector, biochemical NBS for CH is available using cord blood at birth at a number of facilities in the Western Cape (formerly the PMNS), screening an estimated 38,000 or 3.8% of total births annually (H. Vreede, Personal Communication)[54]. While this project was initially facilitated via the Red Cross War Memorial Children's Hospital, the National Health Laboratory Service (NHLS) is now supporting this project in the interim, while long-term continuity and expansion of the project are considered.

NBS for South Africa meeting, Cape Town, February 2023

Following the previous biochemical NBS meetings held in SA in 1987 and 1992[46,48], momentum was lost during subsequent decades due to the necessary response required for other healthcare priorities, most

notably HIV/AIDS. In mid-2022, a group of key South African stakeholders involved in, or enthusiastic about expanding biochemical NBS, voiced the need for renewed national commitment and an appropriate plan for the future. Led by RDSA, together with key individuals from NWU, the University of Cape Town (UCT), NHLS, and several global organisations, a meeting was held from 21-22 February 2023 in Cape Town. The two-day meeting was collectively funded by the joint NBS Task Force of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), the International Society for Newborn Screening (ISNS), the South African Inherited Metabolic Disorders Group (SAIMDG), and industry partners PerkinElmer and Labsystems Diagnostics Oy.

Day 1 was attended by 97 participants (45 in-person, 52 virtually) including clinicians, nurses, medical scientists, academic researchers, government officials/policy makers, patient advocacy groups, and international experts. A series of presentations ensured a common understanding of the benefits of biochemical NBS, its current status, lessons learned from other LMIC (Nigeria and Philippines), testing capacity, technology and infrastructure requirements, and potential costs and health outcomes of biochemical NBS.

Day 2 was a closed meeting for key national and provincial policy makers to plan a way forward for biochemical NBS in SA. Key issues discussed included: biochemical NBS as a component of comprehensive NBS; the importance of initiating biochemical NBS simply and building on existing programmes to minimise costs and promote "home-grown" sustainability; learning from experiences of other health programmes, such as PMTCT[64], and ensuring integration of the biochemical NBS pathway, which starts and ends with the patient, including treatment management for identified individuals.

Identified challenges to biochemical NBS in SA include: early discharge of newborns post-delivery (from 6 hours after birth); technical challenges in optimal sample collection and methodology (cord blood versus heel prick, appropriate cut-off levels, *etc.*); high rates of patients lost to follow-up; lack of accountability at all levels of current practice; inadequate resources allocated (human and financial), and poor logistics for the biochemical NBS pathway, including communicating test results and accessibility of genetic counselling for patients.

Recommendations from the two-day meeting included:

1. The establishment of a National Advisory Panel for biochemical NBS in SA.

2. Development, funding, and implementation of a comprehensive demonstration project for biochemical CH NBS in two provinces in SA (Limpopo and Western Cape Provinces), including all relevant components of the CH biochemical NBS pathway and an assessment of all expenses. This will be preceded by a preliminary feasibility study in the two provinces to gather relevant data for the demonstration project[65,66].

3. Present project results to NDOH with a proposed action plan for progressive implementation of CH biochemical NBS in SA.

4. In the interim, provincial health services are encouraged to fully implement NBS recommendations for hearing/visual assessments, critical CHD screening, and a comprehensive physical examination prior to discharge post-delivery[55].

To date, the meeting report (available from www.rarediseases.co.za) has been distributed to all sponsors and participants and written support from NDOH has been obtained for the biochemical CH NBS demonstration project. Funding is being sought to enable preliminary feasibility work on the provincial demonstration projects in 2024.

CONCLUSION

It has been over 50 years since biochemical NBS was first considered in SA, with little progress achieved to date, leaving the country far from a universal biochemical NBS programme. The country has a responsibility to fully investigate expanding services for biochemical NBS, starting with CH. For the estimated 250 babies born annually with CH in SA, amounting to 12,500 over the last 50 years - the lack of early detection and treatment has resulted in them living with preventable, life-long intellectual disability and other health issues. These patients require full-time care and special education, rendering them unable to actively participate in society. This results in considerable personal and economic burdens.

South Africa is at the point where the value of biochemical NBS needs to be fully and urgently considered to further reduce the burden of childhood mortality and morbidity. Globally, biochemical NBS is considered to "increase in importance" as the IMR drops < 20 per 1,000 live births and needs to be "in place for it to drop to < 10 per 1,000"[18]. Without biochemical NBS, babies affected by CH, IEMs, and other rare diseases and CDs will be left behind, dying prematurely or facing a lifetime of disability. It remains an imperative that biochemical NBS is fully investigated in SA, both within the context of the SDGs and beyond.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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