Newborn Screening in Hong Kong: Practice, Methodologies and Emerging Frontiers

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Editorial Note:

Newborn screening (NBS) is one of the most successful public health programmes in modern paediatrics, allowing pre-symptomatic detection and timely treatment of conditions that would otherwise cause death or lifelong disability. Over the past four decades, the Hong Kong NBS programme has evolved from cord-blood screening for 2 conditions into a comprehensive service covering inborn errors of metabolism, severe combined immunodeficiency, spinal muscular atrophy, congenital hypothyroidism and glucose-6-phosphate dehydrogenase deficiency, with a total number of 34 conditions screened. This review revisits the development, laboratory practice and methodologies of NBS in Hong Kong, places it in an international context, and explores emerging developments such as genomic newborn screening and candidate conditions that may be considered for future screening. We welcome any feedback or suggestions. Please direct them to Dr CHAN Chun Hei Toby of Education Committee, the Hong Kong College of Pathologists. (e-mail: cch191@ha.org.hk). Opinions expressed are those of the authors or named individuals, and are not necessarily those of the Hong Kong College of Pathologists.

Introduction

Population-based newborn screening (NBS) began in the early 1960s when Dr. Robert Guthrie developed a bacterial inhibition assay for phenylketonuria (PKU) using dried blood spots (DBS) collected on filter paper, establishing the operational model that underpins NBS to this day. (1) The guiding philosophy of any screening programme remains the principles of Wilson and Jungner — the condition should be an important health problem, there should be an accepted and effective treatment, facilities for diagnosis and treatment should be available, there should be a recognisable latent or early symptomatic stage, a suitable and acceptable test should exist, the natural history should be adequately understood, and the cost should be balanced against benefit. (2)

In Hong Kong, a publicly funded NBS programme has been in place since 1984, and has expanded substantially in the past decade following the introduction of tandem mass spectrometry (TMS) and molecular testing. (3, 4) With the increasing availability of disease-modifying and potentially curative therapies for an expanding list of rare diseases, NBS has entered a period of rapid change. This review summarises the current state of NBS in Hong Kong and considers where the field may be heading.

Learning Objectives

This review serves to 1) trace the development of newborn screening in Hong Kong, with a focus on inborn errors of metabolism, severe combined immunodeficiency, spinal muscular atrophy, congenital hypothyroidism and G6PD deficiency; 2) describe how the NBS laboratory in Hong Kong Children's Hospital operates, the methodologies used for each condition, and their common false positives, false

negatives and pitfalls; 3) NBS programme in an international context; and 4) review developments in newborn genome sequencing and discuss emerging candidate conditions as future screening targets.

The Development of Newborn Screening in Hong Kong

The history of NBS in Hong Kong up to 2016 was reviewed previously in this bulletin. (5) In brief, a free-of-charge, territory-wide Neonatal Screening Programme for congenital hypothyroidism (CHT) and glucose-6-phosphate dehydrogenase (G6PD) deficiency has been provided since March 1984 under the Neonatal Screening Unit of the Clinical Genetic Service, Department of Health; a distinctive and enduring feature of the programme is the continued use of umbilical cord blood, rather than a heel-prick dried blood spot, as the primary specimen for CHT and G6PD screening. (5, 6) Universal newborn hearing screening was added in all public hospitals with maternity service in 2007. (5) The present review focuses on developments since 2016 — in particular the outcome of the territory-wide pilot study for inborn errors of metabolism (IEM), its subsequent roll-out and the addition of new conditions.

Expanded newborn screening for inborn errors of metabolism

As described previously, a government-initiated "Pilot Study of Newborn Screening for Inborn Errors of Metabolism" was launched on 1 October 2015 at two public birthing hospitals — Queen Elizabeth Hospital and Queen Mary Hospital — following the 2015 Policy Address. (3, 5) The 18-month pilot ran in two phases: Phase I (October 2015 to March 2016) covered 21 IEM, and Phase II (April 2016 to March 2017) covered 24 IEM. Of 15,138 newborns screened, nine IEM cases were confirmed, giving a collective incidence of 1 in 1,682 — higher than the previously estimated local figure and higher than that reported in many other places. (3) The pilot concluded that IEM could not be considered rare in Hong Kong.

Four criteria were agreed for the selection of conditions: screening capability (availability of accurate, reliable screening, diagnostic testing and laboratory capability); clinical significance (seriousness and number of cases encountered locally); availability of effective treatment; and favourable outcome after early treatment. (3) Following the pilot, the same protocol was adopted for territory-wide extension, which was phased in across all eight public birthing hospitals and completed in October 2020. (4) The number of conditions screened has expanded over time, from 21 (2015) to 24 (April 2016), 26 (October 2019), and 30 conditions as of July 2025. The prevalence of IEM in Hong Kong was 1 in 2674. (4)

Severe combined immunodeficiency and spinal muscular atrophy

The programme has since broadened beyond metabolic disorders. Screening for severe combined immunodeficiency (SCID) commenced as a pilot in October 2021 and became a routine service in April 2023. Screening for spinal muscular atrophy (SMA) was piloted from October 2023 to March 2025 and has been provided routinely since April 2025.

Service integration and enhancement of cord-blood screening

On 1 July 2023, the Department of Health’s Newborn Screening Laboratory (which performed cord-blood CHT and G6PD screening) was integrated into the Hospital Authority’s NBS laboratory, consolidating the territory’s newborn screening under a single centralised laboratory service in Hong Kong Children’s Hospital. Bringing cord-blood CHT and G6PD screening together with the dried blood spot (DBS) IEM platform created opportunities to enhance both legacy assays using the dual-sample design.

For *congenital hypothyroidism*, a second-tier DBS thyroid function test was introduced to reduce false-

positive recalls from the primary cord-blood assay, reducing unnecessary follow-up investigations and parental anxiety while preserving case detection.

For G6PD deficiency, the classification and reporting framework was updated in 2026 to align with the latest 2022 WHO classification of G6PD variants, (7, 8), and introduced G6PD genotyping for transfused newborns in whom the enzymatic assay is unreliable.

Extension to private hospital

The 2024 Policy Address committed the Government to "start extending the scope of the HA's newborn screening programme to cover newborn babies delivered in private hospitals". (9) Following this, extension of the programme to private hospitals has been ongoing.

The Newborn Screening Laboratory in Hong Kong Children's Hospital

The Hong Kong programme operates as a centralised laboratory service located in Hong Kong Children's Hospital. For IEM, SCID and SMA, heel-prick dried blood spots (DBS) sample is collected, while cord-blood is used for CHT and G6PD screening. DBS specimen is typically collected at 24–72 hours of life. The spots must be allowed to dry for at least three hours at room temperature in a horizontal position, away from direct sunlight, moving air or any enclosed container, and the card end-flap must be closed only after the specimen is completely dry. A common cause of suboptimal specimen quality is closing the flap or stacking and packing the card before the blood spot has dried, which can cause cross-contamination and compromise the assay. DBS specimens are transported to the NBS laboratory in Hong Kong Children's Hospital by designated daily courier.

At the time of writing, the NBS scope covers 34 conditions. (**Table 1**).

Screening results are analyzed, interpreted and reported by Chemical Pathologist with relevant experience in newborn screening. Screen-positive cases are recalled for clinical assessment, repeat testing and confirmatory investigations by the respective paediatric specialist team. (3, 4)

Condition-Specific Methodologies, Recommendations and Pitfalls

Inborn Errors of Metabolism

First-tier screening for IEM uses non-derivatised Flow Injection Analysis-Tandem Mass Spectrometry (FIA-MS/MS) method. Biotinidase activity, galactose-1-phosphate uridylyltransferase (GALT) activity and 17-hydroxyprogesterone (17-OHP) are measured by DELFIA immunoassay. As of July 2025, the panel comprises 30 conditions across organic acidaemias, aminoacidopathies, fatty acid oxidation disorders and other disorders (**Table 1**). (4, 10)

A key strength of the Hong Kong programme is its tiered screening design. Second-tier biochemical testing by liquid chromatography–tandem mass spectrometry (LC-MS/MS) was introduced for congenital adrenal hyperplasia (steroid profiling) from April 2016 and for methylmalonic acid, methylcitric acid and total homocysteine from January 2021, substantially reducing false-positive recalls. (4) In addition, a second-tier molecular genetic screening test using a custom AmpliSeq next-generation sequencing (NGS) panel was introduced from September 2021 for six IEM and extended in October 2022 to eight IEM, maximising screening specificity and providing rapid genotypic information at the time of recall. (11) The recall rate improved from 0.26% to 0.12% after the introduction of second-tier testing. (4)

The epidemiology and performance of the Hong Kong IEM programme have been reported in a seven-

year review of 125,688 newborns screened between October 2015 and December 2022. (4) The recruitment rate was 99.5%; 47 IEM cases were confirmed, giving an incidence of 1 in 2,674, with 78.7% of affected babies asymptomatic at the time the screening result became available. (4) The overall recall rate was 0.23%, positive predictive value 15.9% (rising to 33.3% by 2022), specificity 99.8% and sensitivity 74.6%. (4) Carnitine uptake deficiency (CUD) was the most common condition (1 in 13,965), followed by citrin deficiency (citrullinaemia type II), which has a Southern Chinese founder variant (*SLC25A13* c.852_855del) and a high carrier frequency. (4)

Screen-positive IEM are recalled for clinical assessment and biochemical confirmation. The confirmatory work-up is tailored to the suspected disorder and the analyte pattern, and typically combines repeat or extended biochemical testing with targeted genetic analysis. Biochemical investigations may include plasma acylcarnitines, plasma amino acids, urine organic acids, urine purines and pyrimidines, urine fractional excretion of free carnitine, total homocysteine, vitamin B12, blood gas, ammonia, lactate, glucose, electrolytes, complete blood count, liver and renal function tests, and, where indicated, tissue biopsy for cell-specific enzymatic testing.

A number of IEM are **time-critical**, meaning that acute symptoms or potentially irreversible damage can develop within the first week of life and that early recognition and treatment can reduce the risk of morbidity and mortality. (12) Such conditions are highlighted in **Table 1**. For these disorders, the time elapsed between specimen collection and result reporting is itself critical, and any avoidable delay can have serious consequences. One example is classical neonatal propionic acidaemia, the affected newborn can become symptomatic (vomiting and respiratory distress) on the first day of life, and deteriorated rapidly if left untreated. (13) To expedite NBS, the Hong Kong programme has implemented several measures to accelerate overall reporting, including an optimised DBS collection schedule in the postnatal ward, a daily designated transport courier, and laboratory analysis and reporting during public holidays over long holiday periods.

Several pitfalls are well recognised. Citrin deficiency is prone to false-negative screening because relevant metabolite elevations may not be present when the DBS is taken early in the first few days of life; clinicians should remain alert to the possibility even after a normal screen, particularly in babies presenting with prolonged neonatal jaundice. (3, 4) Maternal IEM (for example maternal CUD or maternal PKU) may also produce abnormal newborn results, and NBS may incidentally identify affected mothers. (3)

Congenital Hypothyroidism

CHT is screened using cord-blood thyroid-stimulating hormone (TSH) as the primary screening marker, with add-on reflex testing of free thyroxine (FT4). A second-tier DBS TSH measurement has been introduced to reduce false positives. In an in-house retrospective evaluation of cord-blood screen-positive cases, applying a DBS TSH cut-off (<9.7 mIU/L as negative) retained 100% sensitivity while reducing false positives by 55%. This dual-sample approach represents a distinctive convergence of the legacy cord-blood programme and the modern DBS platform.

Screen-positive newborns are recalled for a confirmatory serum (venous) sample for TSH and FT4; treatment is generally initiated when serum TSH is grossly elevated (e.g. exceeds 20 mIU/L), or when FT4 is low with an elevated TSH, with borderline elevations retested at intervals. A substantial proportion of screen-detected cases — approximately 17–40% — represent transient CHT; recognised causes include prematurity, iodine deficiency or excess, transplacental TSH-receptor-blocking antibodies, maternal antithyroid drugs, and monoallelic *DUOX2*/*DUOXA2* variants. (14)

Where CHT with a gland in situ is investigated genetically, a molecular cause is identifiable in at least 42% of cases. (15) Prematurity, low birth weight and maternal thyroid disease are common contributors to false-positive recalls and to a delayed TSH rise that may necessitate a second screen. (16) Conversely, because the Hong Kong programme is a primary-TSH approach, infants with central (secondary) hypothyroidism — in whom TSH is not elevated —may not be detected, and clinicians should remain alert to this possibility on clinical grounds. (17)

G6PD Deficiency

G6PD deficiency is screened by a quantitative enzyme assay on cord-blood. An important methodological caveat is that the assay measures total NADPH-generating activity, which reflects the combined activity of G6PD and 6-phosphogluconate dehydrogenase (6PGD) rather than G6PD alone, and the result could be influenced by factors such as anaemia, thalassaemia, reticulocytosis, leukocytosis, prior transfusion and sex-chromosome aneuploidy.

In 2026 the Hong Kong programme updated its G6PD classification and reporting, moving from the older WHO classification to a percentage activity-based framework aligned with the 2022 WHO update, applying a threshold of <45% for screen-positive (deficient). For newborns who have been transfused — in whom enzyme activity is unreliable — genotyping by a next-generation sequencing panel is used, as it is unaffected by transfusion.

Confirmatory work-up may include the G6PD/6PGD ratio testing and genotyping. Counselling centres on avoidance of oxidative triggers that can precipitate acute haemolysis: fava beans (broad beans), naphthalene-containing mothballs, and certain medications. (18, 19) Pharmacogenomic prescribing is informed by the 2022 Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline, which identifies high-risk drugs to be avoided in G6PD-deficient individuals — including rasburicase, pegloticase, dapsone, methylene blue, toluidine blue, and primaquine and tafenoquine at standard antimalarial doses — while other agents such as nitrofurantoin carry intermediate risk and should be used with caution. (18) The Chinese expert consensus on newborn screening, diagnosis and treatment of G6PD deficiency provides regionally relevant guidance. (19)

Severe Combined Immunodeficiency

SCID is screened by quantification of T-cell receptor excision circles (TREC) on DBS. The laboratory uses a custom designed multiplex droplet digital PCR assay that simultaneous detect *SMN1*, *SMN2*, TREC and the reference gene *RPP30*. (20) A common cause of false-positive (low TREC) results is prematurity, as the T-cell repertoire matures with gestational age. The *RPP30* reference gene is used to confirm adequacy of DNA amplification, a low TREC with *RPP30* failure would invalidate the result. The fully automated high-throughput quadruplex droplet digital PCR method has been described elsewhere. (20) Screen-positive infants are referred for confirmatory lymphocyte subset analysis by flow cytometry, immunoglobulin measurement and complete blood count.

Spinal Muscular Atrophy

SMA is screened by detecting the homozygous deletion of SMN1 exon 7, with concurrent determination of SMN2 copy number, by droplet digital PCR. Approximately 95–98% of SMA patients have a homozygous SMN1 exon 7 deletion detectable by this method; the remaining 2–5% are compound heterozygotes carrying an intragenic point variant, who cannot not be detected by the screening method. (20) The measurement of SMN2 copy number, which is a key prognostic modifier, provides timely information at the time or call, and informs treatment decisions. Confirmatory testing is by multiplex ligation-dependent probe amplification (MLPA).

The clinical urgency of SMA screening reflects the availability of effective pre-symptomatic therapies: the antisense oligonucleotide nusinersen, the gene therapy onasemnogene abeparvovec, and the small-molecule risdiplam. (21-23) Because a substantial proportion of motor neurons may be lost in the first weeks of life, early treatment is critical, and SMA is designated a **time-critical** condition in the ACMG guideline (12)

Newborn Screening in International Context

The pace and breadth of NBS varies considerably between jurisdictions, reflecting differences in disease prevalence, healthcare financing, governance and medical practice.

Mainland China. NBS in China began in Shanghai in 1981, and in 2000 NBS for CHT and PKU was defined by law as the minimum mandatory conditions. (24, 25) By the end of 2018 there were 238 screening centres and the screening rate exceeded 97.5%, with more than 15 million newborns screened annually. (25) G6PD deficiency is screened in some provinces, especially in the south (e.g. Guangdong, Guangxi, Yunnan, Hainan and Chongqing) where it is prevalent, and TMS-based expanded screening, which began at pilot centres in 2004, is now offered across nearly 30 provinces. (24, 25) Recently, a large scale NBS study for SCID, SMA and X-linked agammaglobulinemia involving 103,240 newborns was conducted. (26)

Taiwan. Taiwan's NBS programme began in 1985 with PKU and CHT. (27) It has been a pioneer in newborn screening, being the first to introduce NBS for Pompe disease in 2005 and switching to a multiplex MS/MS assay covering Pompe, MPS I, Gaucher and Fabry disease in 2015, which was subsequently expanded to an 8-plex assay adding MPS II, MPS IIIB, MPS IVA and MPS VI in 2018. (27, 28) X-linked adrenoleukodystrophy was added in 2016. (27) SCID and SMA were added in the year of 2012 and 2017 respectively.(29, 30) More recently, Taiwan has also piloted screening for emerging conditions including AADC deficiency and Duchenne muscular dystrophy. (31, 32)

Europe. The European landscape is highly heterogeneous; across EU Member, up to 43 conditions is included in some of the national panel, yet only CHT and PKU are screened universally. (33) The NBS practices vary widely in the EU, which raises concerns regarding equal access to healthcare and the promotion of health outcomes. (33). Since 2024, EU-level momentum for NBS harmonisation has accelerated markedly, driven by two European Parliament Research Service studies modelling the health-economic impact of EU-wide guidelines. (33, 34)

Australia and New Zealand. In Australia, some state screens up to 32 target conditions in its programme, with minor difference and varying paces of adoption of new conditions. (35) SCID and SMA screening were recommended for introduction in 2020 and is now universally provided. (35 - 38) Recent additions approved through the national health-technology-assessment pathway include tyrosinaemia type I, sickle cell disease, X-linked adrenoleukodystrophy and biotinidase deficiency, while MPS I and MPS II are under active assessment. New Zealand's programme, operating since 1969, screens more than 20 conditions, added SCID in 2017 and commenced SMA screening in February 2025. (39, 40)

United States. In the United States, the Recommended Uniform Screening Panel (RUSP) — provides the national standard, comprising 40 core and 26 secondary conditions. (41, 42) Individual states ultimately determine their own panels, leading to wide variation (for example, California screens over 80 conditions). (43) Key recent RUSP additions include SCID (2010), critical congenital heart disease (2011), Pompe disease (2015), MPS I and X-ALD (2016), SMA (2018), MPS II (2022), GAMT

deficiency (2023), infantile Krabbe disease (2024), and Duchenne muscular dystrophy and metachromatic leukodystrophy (2025). (41, 44) The pace and pattern of adoption of these additions vary considerably between states. (45)

Across regions, SCID and SMA have been the two most rapidly adopted recent additions, although the timing varies widely. Hong Kong's introduction of SCID (2023) and SMA (2025) places it broadly in line with other programmes.

Newborn Genome Sequencing

A major frontier in NBS is the use of genome or exome sequencing to screen newborns directly for hundreds of treatable genetic conditions — so-called genomic newborn screening. Several large projects are now underway or completed internationally.

Completed and ongoing projects

The pioneering BabySeq Project (Boston, USA) randomised newborns to receive genomic sequencing in addition to standard NBS; in its first phase, around 11% of apparently healthy newborns were found to carry a variant indicating risk of a childhood-onset monogenic disorder. (46) The successor BabySeq2 study, with a diversity-focused design across multiple US cities, is ongoing. (46, 47) The GUARDIAN study in New York also aims to screen for 100000 newborns for 156 conditions with established interventions, initial study findings involving the first 4000 newborns has reported a screen-positive rate of 3.7% including treatable conditions that are not currently included in standard NBS. (48) North Carolina has conducted a statewide observational study of expanded genomic NBS (the Early Check program) covering 169 high actionability genes, of 1979 newborn screeded, 2.5% (n = 50) was screened positive, with eventually 1.4% (n = 28; 28/1979) confirmed as true positive. (49) The BeginNGS program (Rady Children's) is a single-group, multicentre, adaptive clinical trial that aims to pre-identify all pathogenic/likely pathogenic variant targets associated with around 2000 severe childhood genetic disease before sequencing the subject, the trial is adaptive to allow accumulating results to make the trial more efficient, informative, equitable and ethical by addition/removal of SCGD and genetic variants, population enrichment, etc., in order to maximize positive predictive Value of gNBS. (50). A pilot clinical trial of BeginNGS for 412 SCGD in a neonatal intensive care unit setting reported a true positive rate of 4.2% and positive predictive value of 100%. (51).

In United Kingdom, the Generation Study (Genomics England and NHS England) aims to sequence 100,000 newborns and screen for 922 gene-condition pairs. (52, 53)

In Australia, the BabyScreen+ pilot and the broader GenSCAN consortium are studying feasibility, cost-effectiveness, ethical and equity considerations. (37, 54) Of the initial 1000 newborns screened, 1.6% (n = 16) were identified as having high-chance results; of these, only one could be detected by standard NBS. (54)

In Europe, the Screen4Care project is developing a genetic NBS panel of treatable conditions alongside digital diagnostic tools, the final list of genes, the TREAT-panel, includes 245 genes. (55). As of February 2026, the project has enrolled 6,433 babies, with sequencing completed for approximately 3,500 samples, the project is expected to conclude in 2027. (56)

In China, the China Neonatal Genome Project (CNGP) was launched in 2016 as a leading initiative in

technological innovation. In March 2022, a consensus guideline for national gNBS program was published.(57) A number of regional studies has been conducted. (58) In the largest study conducted involving 29 601 newborns, 2.7% (n = 813) was screened positive, with a positive predictive value of 50.4%. About 1 in every 500 newborns would be benefited from the addition of newborn sequencing. (59)

Key findings, limitations and unresolved issues

These projects consistently show that genomic screening can identify at-risk infants who could not be detected by conventional biochemical NBS, and that the two approaches are complementary rather than interchangeable. (48) However, important limitations and unresolved issues remain: variants of uncertain significance and the difficulty of variant interpretation at scale; incomplete penetrance and variable expressivity, which complicate prediction of whether and when disease will develop; the handling of secondary or incidental findings; the ethical, legal and social implications, including informed consent, data privacy, the child's future autonomy and equity of access; cost and cost-effectiveness; and the fundamental question of which genes and conditions should be included on a screening panel. International efforts such as the International Consortium on Newborn Sequencing (ICoNS) are working toward consensus on these questions. (60) Genomic NBS is not yet part of routine practice in Hong Kong, and any future implementation would need to address these scientific, ethical and resource considerations.

Conditions Screened Elsewhere but Not Yet in Hong Kong

A number of conditions are screened in other jurisdictions but are not (yet) part of the Hong Kong panel.

Hearing loss with concurrent deafness-gene screening

Although Hong Kong has provided universal newborn hearing screening since 2007, mainland China has pioneered concurrent newborn hearing and deafness-gene genetic screening (5, 61, 62) The panel generally targets specific pathogenic variants in *GJB2, SLC26A4, MT-RNR1* and *GJB3*. (61, 62) A nationwide study of 1.2 million neonates found that genetic screening detected 13% more hearing-impaired infants than hearing screening alone and identified about 0.23% of newborns predisposed to aminoglycoside-induced ototoxicity (largely through the *MT-RNR1* m.1555A>G variant) who almost universally pass conventional hearing screening. (63) The capacity to identify infants at risk of preventable, irreversible drug-induced hearing loss — allowing lifelong avoidance of aminoglycosides — is arguably the most compelling rationale for combining genetic with audiological screening. (61, 63)

X-linked adrenoleukodystrophy (X-ALD)

X-ALD is screened by measuring C26:0-lysophosphatidylcholine (C26:0-LPC) on DBS, with reflex molecular testing of the *ABCD1* gene, and was added to the US RUSP in 2016. Early identification allows monitoring for adrenal insufficiency and for the cerebral form, which is treatable by haematopoietic stem cell transplantation (HSCT) or gene therapy when detected pre-symptomatically. (64) Pitfalls include false positives from peroxisomal biogenesis disorders and other conditions (such as Zellweger spectrum and contiguous-gene deletion syndromes), the absence of a genotype–phenotype correlation and the detection of female heterozygotes. (64, 65) A pilot in a Southern Chinese population (Guangzhou) involving 43,653 newborns has identified 7 hemizygous males, 7 heterozygous females, and 2 were diagnosed with other peroxisomal disorders.(66)

Although C26:0-LPC is the universal first-tier marker, the analytical and molecular workflow varies considerably between programmes, and no single algorithm has been standardised internationally. First-tier quantification is performed by flow-injection tandem mass spectrometry (FIA-MS/MS) in most US states, whereas a few states use liquid chromatography–tandem mass spectrometry (LC-MS/MS) directly; cut-offs and the choice of second-tier or even third-tier screening method with LC-MS/MS, and/or genetic screening tests are variable in different programs. (64-68) The Netherlands implemented a male-restricted protocol in which an "X-Counter" PCR assay genetically distinguishes the sexes so that female newborns are excluded before further testing. (68) This heterogeneity reflects unresolved trade-offs between false-positive rate, turnaround time, cost, and whether to report female carriers at all.

Lysosomal storage disorders (LSDs)

Several LSDs can be screened by multiplex enzyme assay on DBS, including Pompe disease (acid α-glucosidase), MPS I (α-L-iduronidase), MPS II, Fabry, Gaucher and Krabbe disease. (28, 69) A major and recurrent pitfall in East Asian populations is the high frequency of pseudodeficiency alleles, which cause low enzyme activity without disease and inflate false positives, and the predominance of late-onset forms among screen-positive cases. (28, 69, 70) Enzyme replacement therapy (and, for some conditions, transplantation) is available for several of these disorders.

Metachromatic leukodystrophy (MLD)

MLD is a lysosomal disorder caused by biallelic ARSA variants leading to arylsulfatase A deficiency and toxic sulfatide accumulation, with progressive demyelination of the central and peripheral nervous system; the late-infantile form is usually fatal within a few years of symptom onset. It can be screened by a multi-tier algorithm — first-tier quantification of C16:0-sulfatides on DBS by LC-MS/MS, second-tier ARSA enzyme activity and a third tier ARSA genetic testing. (71, 72) Treatments such as HSCT and gene therapy are effective when administered pre-symptomatically. (73) MLD was recently added to RUSP in December 2025. (41)

Duchenne muscular dystrophy (DMD)

DMD can be screened using creatine kinase-MM (CK-MM) on DBS as a first-tier marker, with molecular confirmation. It was also recently added to RUSP in December 2025, following the availability of exon-skipping antisense therapies and gene therapy. (41) Pilot programmes in Chinese populations have been reported. (32) However, in 2025, following three incidences of death due to acute liver failure after the administration of Elevidys (one of the gene therapy option for DMD), extensive FDA investigations were conducted. Eventually, the safety information of the therapy were reviewed, resulting in substantial labeling revisions for Elevidys, including the addition of a Boxed Warning describing the risk of serious liver injury and acute liver failure, including fatal outcomes, and the removal of the indication for non-ambulatory patients with DMD. (74) Although gene therapy represents an innovative game-changing option for many uncommon diseases, it should be emphasized that the safety profile of these novel treatment should not be overlooked.

Cystic fibrosis (CF)

CF is screened by first-tier immunoreactive trypsinogen (IRT), followed by IRT/DNA or more complex IRT/DNA/sequencing algorithms; it is on the RUSP and routinely screened in many Caucasian regions. While the incidence in Caucasian population is up to 1 in 2500 – 3500, the incidence in Asian is much lower, estimated at 1 in 300,000 in Hong Kong and 1 in 350,000 in Japan. (75) This roughly hundred-fold lower disease burden materially weakens the cost-effectiveness argument for universal CF

screening locally.

Emerging Candidate Conditions

The arrival of disease-modifying and potentially curative therapies is reshaping which conditions merit screening, as treatability is a core screening criterion. Several candidates are of particular relevance to Hong Kong's predominantly Southern Chinese population.

Aromatic L-amino acid decarboxylase (AADC) deficiency

AADC deficiency, caused by *DDC* variants, is of special interest because of a Southern Chinese founder variant, IVS6+4A>T (c.714+4A>T). (31) It can be screened by measuring 3-O-methyldopa (3-OMD) on DBS by MS/MS, integrable into existing TMS workflows, and a Taiwanese pilot has demonstrated feasibility. (31) The gene therapy eladocagene exuparvovec received European Medicines Agency approval in 2022 and US Food and Drug Administration approval in November 2024, making AADC deficiency a strong candidate for future screening.

Ornithine transcarbamylase (OTC) deficiency

OTC deficiency, an X-linked urea cycle disorder, is of particular clinical importance because the neonatal-onset male form presents with catastrophic, often lethal hyperammonaemic crisis in the first days of life, so that pre-symptomatic detection could be life-saving. The screening performance with the commercial biochemical TMS panel by raised glutamine/lysine level and/or low citrulline level is suboptimal.(76) Direct measurement of orotic acid enables NBS for OTC deficiency. (77)

Wilson disease

Wilson disease (*ATP7B* gene) is of particular relevance to East Asian populations, in whom the estimated prevalence (1 in 5400) is substantially higher than in Western populations (1 in 30,000). (78, 79) Effective treatment is available, and proof-of-concept DBS biomarker approaches have been described. (80-82) The Washington State, USA, was the first to conduct a pilot NBS study using a novel multiplexed LC-MS/MS proteomic assay, which included Wilson disease as one of the target conditions. (81)

Congenital cytomegalovirus infection

A further emerging candidate is congenital cytomegalovirus (cCMV) infection, the leading non-genetic cause of childhood sensorineural hearing loss, for which early antiviral treatment can preserve hearing. cCMV is screened by detecting viral DNA in body fluid. However, there has been ongoing debates over the cost-effectiveness and sample choice (some prefers saliva, which is not the standard NBS sample). (83)

Conclusion

Over four decades, newborn screening in Hong Kong has grown from cord-blood screening for two conditions into a consolidated, multi-tier, territory-wide programme covering inborn errors of metabolism, SCID, SMA, congenital hypothyroidism and G6PD deficiency, with a total of 34 conditions screened. The programme's multi-tier biochemical and molecular design have improved positive predictive value while controlling recall rates. NBS scope vary widely across the globe. Looking ahead, further expansion of biochemical screening to cover locally prevalent disease such as AADC deficiency, OTC deficiency and Wilson disease should be prioritized. Genomic newborn screening represents unique opportunity to detect presymptomatic newborn before it is too late. Continued evidence review, attention to the ethical and resource implications, and robust laboratory quality

assurance will be essential to ensure that future expansion remains aligned with the founding principles of screening.

Table 1. NBS scope in the Hong Kong Programme

Category	Conditions
Inborn Errors of Metabolism (IEM)	**Beta-ketothiolase deficiency** **Glutaric acidaemia type I** **Isovaleric acidaemia** **Methylmalonic acidaemia (methylmalonyl-CoA mutase deficiency)** **Methylmalonic acidaemia, cblA type** **Methylmalonic acidaemia, cblB type** **Methylmalonic acidaemia and homocystinaemia, cblC type** **Multiple carboxylase deficiency** **Propionic acidaemia** **3-hydroxy-3-methylglutaryl-CoA lyase deficiency** Argininaemia **Argininosuccinic acidaemia** **Citrullinaemia type I** **Citrullinaemia type II (citrin deficiency)** Phenylalanine hydroxylase deficiency Homocystinuria **Maple syrup urine disease** Tyrosinaemia type I 6-pyruvoyl-tetrahydropterin synthase deficiency **Carnitine-acylcarnitine translocase deficiency** **Carnitine palmitoyltransferase II deficiency** Carnitine uptake deficiency **Glutaric acidaemia type II** **Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency** **Medium-chain acyl-CoA dehydrogenase deficiency** **Mitochondrial trifunctional protein deficiency** **Very long-chain acyl-CoA dehydrogenase deficiency** Biotinidase deficiency **Classic galactosaemia** **Classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency**
Severe Combined Immune Deficiency (SCID)	Severe Combined Immune Deficiency
Spinal Muscular Atrophy (SMA)	**Spinal Muscular Atrophy**
Congenital hypothyroidism (CHT)	Congenital hypothyroidism
G6PD deficiency	**G6PD deficiency***

Bold *denotes a time-critical condition, in which acute symptoms or potentially irreversible damage can develop within the first week of life and for which early recognition and treatment can reduce morbidity and mortality.*

** G6PD deficiency is not included in RUSP. Locally, G6PD deficiency is considered as a time-critical condition.*

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