Exploration of clinical and ethical issues in an expanded newborn metabolic screening programme: a qualitative interview study of healthcare professionals in Hong Kong

Olivia MY Ngan *, Ching Janice Tam, CK Li

ABSTRACT

Introduction: The Newborn Screening Programme for Inborn Errors of Metabolism (NBSIEM) enables early intervention and prevents premature mortality. Residual dried bloodspots (rDBS) from the heel prick test are a valuable resource for research. However, there is minimal data regarding how stakeholders in Hong Kong view the retention and secondary use of rDBS. This study aimed to explore views of the NBSIEM and the factors associated with retention and secondary use of rDBS among healthcare professionals in Hong Kong.

Methods: Between August 2021 and January 2022, semi-structured interviews were conducted with 30 healthcare professionals in obstetrics, paediatrics, and chemical pathology. Key themes were identified through thematic analysis, including views towards the current NBSIEM and the retention and secondary use of rDBS.

Results: After implementation of the NBSIEM, participants observed fewer patients with acute decompensation due to undiagnosed inborn errors of metabolism. The most frequently cited clinical utilities were early detection and improved health outcomes. Barriers to rDBS storage and its secondary use included uncertain value and benefits, trust concerns, and consent issues.

Conclusion: This study highlighted healthcare professionals' concerns about the NBSIEM and uncertainties regarding the handling or utilisation of rDBS. Policymakers should consider these concerns when establishing new guidelines.

Hong Kong Med J 2024;30:120–9
https://doi.org/10.12809/hkmj2210234

[1,2] **OMY Ngan *,** PhD
[3] **CJ Tam,** MSc (Medical Genetics), BNurs
[4,5] **CK Li,** MD, FRCPCH

[1] *Medical Ethics and Humanities Unit, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China*
[2] *Centre for Medical Ethics and Law, The University of Hong Kong, Hong Kong SAR, China*
[3] *Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, China*
[4] *Department of Paediatrics, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, China*
[5] *Hong Kong Hub of Paediatric Excellence, The Chinese University of Hong Kong, Hong Kong SAR, China*

* Corresponding author: olivian1@hku.hk

This article was published on 9 Apr 2024 at www.hkmj.org.

New knowledge added by this study

- After implementation of the Newborn Screening Programme for Inborn Errors of Metabolism, participants observed fewer patients with acute decompensation due to undiagnosed inborn errors of metabolism.
- The obligation to know more about a child's health and the drive for an altruistic contribution to science were factors supporting the retention of residual dried bloodspots (rDBS) for secondary research use.
- Uncertain value and benefits of rDBS, along with concerns regarding trust, privacy, and consent, were cited as barriers to the retention of rDBS for secondary research use.

Implications for clinical practice or policy

- The retention of rDBS requires inherent trust based on public support, with strict clinical and ethical parameters.
- Concerns about privacy and consent issues related to genomic information should be addressed before next-generation sequencing is integrated into clinical care for newborns.

Introduction

Inborn errors of metabolism (IEM) are rare genetic diseases arising from congenital deficiencies of certain enzymes or cofactors. The accumulation of excessive toxic substances and the absence of essential metabolites may damage vital organs, impair normal metabolism, or increase risks of morbidity and mortality. A small proportion of IEM cases can be diagnosed and treated early through dietary interventions. Patients substantially benefit from early diagnosis and appropriate disease monitoring.

The incidence of IEM in Hong Kong is 1 in 1682 newborns.[1] In response to public health

concerns, a territory-wide free voluntary Newborn Screening Programme for IEM (NBSIEM) was implemented for all newborns born in public birthing units, beginning in 2017.[2] This programme covers 27 conditions, including severe combined immunodeficiency (SCID).[3] Spots of blood are collected from newborns within 24 to 72 hours after birth, preferably following 24 hours of milk feeding, using a heel prick test; these samples are discarded after hospital laboratories perform quality control and assurance monitoring (online supplementary Table 1).

The materials on dried bloodspots provide clinical benefits and lifelong healthcare research opportunities that are advantageous to individuals and the population. However, the retention and use of residual DBS (rDBS) has led to controversies regarding privacy, transparency, consent, misuse of, and unauthorised access to information, unclear research purposes, and the absence of data management and governance protocols.[4] Despite these concerns, it is common for rDBS to be routinely stored and used for research purposes in some regions. For example, in Denmark, a nationwide newborn screening programme was implemented in 1975; it currently screens for 17 diseases.[5] Samples are stored indefinitely with consent in the Danish Newborn Screening Biobank at the State Serum Institute.[6] Similarly, a programme in the Netherlands screens for 31 conditions.[7] Although participation is voluntary, the participation rate has reached 99.3%.[8] In the Netherlands, rDBS samples are stored for 1 year to facilitate quality control. Most samples are stored for an additional 4 years for secondary uses, such as disease-specific biomedical research and patient-specific diagnostic purposes, after the acquisition of parental consent.[9] The International Society for Neonatal Screening compared national newborn screening policies, revealing great variation in programme acceptance, consent procedure, storage, and length of storage.[8] The Society's findings highlight the importance of incorporating local views during policy development.

Two empirical studies in Hong Kong revealed that parents were unaware of the expanded newborn screening programme and the potential value of rDBS.[10,11] The secondary use of rDBS in medical and health research is well-supported, mainly on the basis of altruism. However, participation does not provide direct individual benefits. Factors contributing to parental support towards retention and secondary use of rDBS include parental consent and trust in the relevant authority. If explicit permission is obtained, parents are more willing to contribute their child's rDBS card. An opt-out approach and broad consent for unspecified use were considered unfavourable options.[11] Although multiple rDBS-focused studies in Hong Kong have included public stakeholders, few have assessed the attitudes of healthcare professionals (HCPs)[12]; none have been conducted since implementation of the territory-wide screening programme. To address this gap, the present study explored views of the NBSIEM and the factors associated with retention and secondary use of rDBS cards among HCPs in Hong Kong.

探討擴大初生嬰兒代謝病篩查計劃的臨床和倫理問題：香港醫護人員訪談研究

顏妙融、譚靜、李志光

引言：初生嬰兒代謝病篩查計劃能夠在病徵出現之前檢測異常，及早介入和作出治療，預防嬰兒猝死。在初生嬰兒腳板採集的乾血點樣本是科研重要資源，然而有關本地持分者如何看待儲存及使用乾血點樣本的資料較少。本研究旨在探討香港醫護人員對初生嬰兒代謝病篩查計劃的看法，以及他們對儲存及使用乾血點樣本作科研用途的意見。

方法：2021年8月至2022年1月期間，30名在公私營醫療機構工作的婦產科、兒科和化學病理學科醫護人員獲邀參加半結構性訪談，分別就目前初生嬰兒代謝病篩查計劃和儲存及使用乾血點樣本作科研相關用途發表意見。我們利用主題分析法找出關鍵主題。

結果：在推行初生嬰兒代謝病篩查計劃後，醫護人員觀察到未診斷代謝異常的患者出現急性失代償的情況有所減少。最常被提及的臨床效用是讓醫護人員和家長及早發現疾病和改善健康情況。儲存及使用乾血點樣本作科研用途存有隱憂，包括不確定相關用途對初生嬰兒是否帶來益處，當中亦衍生信任和個人資料收集等問題。

結論：本研究顯示，醫護人員對於初生嬰兒代謝病篩查計劃以及乾血點樣本的處理及使用存在隱憂。政策制定者在訂立新指引時應考慮這些擔憂。

Methods

Sampling and recruitment

Semi-structured interviews were conducted among 30 HCPs in obstetrics, paediatrics, and chemical pathology practising in eight public and two private institutions in Hong Kong between August 2021 and January 2022. Purposeful sampling was used to select key stakeholders involved in the NBSIEM according to disciplines and responsibilities. Initial invitations were sent through the two local medical universities (ie, The University of Hong Kong and The Chinese University of Hong Kong) and associated hospitals. Referrals via snowballing were also performed to recruit additional participants.

The study inclusion criteria were academics and HCPs (eg, medical, nursing, and laboratory staff) involved in IEM-related research or clinical work. Individuals who did not meet the criteria were excluded. Overall, this study recruited participants who were involved in recruitment and counselling within the NBSIEM, laboratory data analysis and interpretation, or academic research related to IEM.

Each participant received a detailed description of the research. All participants gave written informed consent before taking part in the study. The second author conducted the interviews at locations convenient for participants, such as meeting rooms, offices, and coffee shops. The interview length ranged from 37 to 71 minutes. Upon completion of the interview, each participant received a supermarket voucher for HK$200.

Interview guide

A semi-structured topic guide was developed based on existing literature concerning newborn screening and ethical considerations (Table).[4,11-15] Prior to data collection, the guide was reviewed by a senior paediatrician to ensure its content validity, relevance, clarity, and cultural sensitivity.

Data analysis

Interviews were digitally recorded, transcribed verbatim in the original language (Cantonese), and then translated into English. Transcripts were anonymised and assigned an identification code. The interviewer and another member of the research team reviewed the transcription accuracy. Two independent researchers read and coded the transcripts and audio recordings via thematic analysis, in which textual data were coded and labelled in an inductive manner. New thematic codes that did not fit into predetermined categories were created and refined, as necessary. Codes were compared and discussed among research members until a consensus was reached. Reflexivity was maintained during the discussion and data analysis process. The entire research team identified emerging themes from the early and intermediate stages of interviews, then recruited HCPs to represent each new theme until theoretical saturation was achieved (ie, no new themes emerged in the discussions and existing themes were consistently observed).

Results

Interviewee characteristics

Thirty HCPs were recruited and interviewed. The study sample was diverse. Among the interviewees, 15 (50.0%) were doctors and 13 (43.3%) were nurses or midwives; 13 (43.3%) worked in obstetrics and gynaecology and 13 (43.3%) worked in paediatrics; 28 worked in the public sector (93.3%); and 14 (46.7%) had >10 years of clinical experience (online supplementary Table 2). Two major thematic themes were identified, namely, views towards the current NBSIEM and views towards the retention and secondary use of rDBS. Illustrative quotations are used to support the themes.

Theme 1: views towards the current newborn screening programme

Perceived clinical utility

The implementation of the NBSIEM was a public health achievement, and interviewees showed a positive attitude towards the programme. Early detection and improved health outcomes were the most commonly reported clinical utility outcomes (n=21, 70.0%). Some interviewees, primarily paediatric HCPs, noted a difference between the periods before and after territory-wide test implementation. Before NBSIEM, it was not uncommon for doctors working in intensive care units to encounter cases of acute decompensation due to undiagnosed IEM. Considering the broad phenotypes involved in IEM, such conditions may not be recognised in early stages.

TABLE. Sample interview questions[4,11-15]

Themes	Probing questions
Current local practices in NBSIEM	1. What is your role in the NBSIEM? How long have you been involved in this role? Please tell me your clinical triage routine. 2. Where did you learn about the NBSIEM? What do you know about the test(s)? 3. What have your experiences been in terms of counselling and consent? 4. What is your opinion of the consent procedures for the NBSIEM? 5. Have you ever encountered parental anxiety about false-positive or uncertain results? What are the psychological impacts on parents if their newborn has a (false) positive test result? 6. Overall, what are your views towards the NBSIEM?
Views towards the retention and secondary use of rDBS	1. Residual dried bloodspots cards contain a wealth of DNA material that has substantial implications for researchers and newborns. Are you aware of the use of these cares for research purposes beyond their routine use? 2. Would you support the retention and secondary use of rDBS? What are your views and concerns? 3. What is an optimal consent approach for the retention and secondary use of rDBS? 4. In the literature, there has been discussion regarding the roles of healthcare providers in reporting research findings. Do doctors and researchers have any obligation to report incidental or secondary findings to parents?

Abbreviations: NBSIEM = Newborn Screening Programme for Inborn Errors of Metabolism; rDBS = residual dried bloodspots

'I have been working in the ward for ages and observed that many patients with IEM deteriorated to an irreversible stage. With this NBSIEM, we can screen out IEM cases and offer treatment. The patients achieve normal development like others. In other words, the screening helped many people.' (Interview 25, paediatric nurse)

Affected families previously endured a long wait for diagnosis before the NBSIEM; there was a substantial psychological burden involved. Parental distress was observed.

'From hospital admission to disease diagnosis, it takes 2 weeks. The whole process involved hospital transfer from the (suspected IEM clinic) to the specialised team at (Hong Kong) Children's Hospital, conducting blood investigation, and making a diagnosis.' (Interview 20, paediatric doctor)

Some limitations were noted, including false-positive and false-negative results, as well as call-back rates. Interviewees cited the reduction of recall caseloads as an advantage associated with implementation of second-tier tests.

'It is best if we can eliminate the false-positives. To achieve this purpose, we implement aggressive second-tier testing. Our pathologists also make stringent interpretations. Without pathologists working in laboratories, clinicians can only draw reference from the pre-set levels.' (Interview 30, pathology doctor)

Screening panel

The programme covers 27 conditions, including SCID.[3] Interviewees generally agreed that the benefits of screening for lethal IEM conditions outweigh the costs of screening, despite the very low incidence of IEMs. When asked about their views on the current panel, interviewees emphasised that disease selection must be based on public health principles, supported by Wilson and Jungner's screening criteria.[16] Diseases in the panel should be treatable and have a high prevalence in Hong Kong.

'I support the NBSIEM. I believe (the experts) came up with the 27 conditions based on robust considerations, including incidence and prevalence, availability of treatment, mortality prevention, cost-effectiveness, etc. It is beneficial to patients.' (Interview 13, obstetrics and gynaecology doctor)

Healthcare professionals have encountered parents who have completed the publicly funded IEM test and selected an additional private IEM test solely based on the number of conditions. For such parents, the underlying motivation is that 'screening more conditions is perceived to be more definitive'.

'If I were a mother with a child, I would like to know whether my child was affected by these diseases. The more conditions the panel includes, the better. One can prevent the onset of disease. Parents are helpless when diseases occur suddenly.' (Interview 24, obstetrics and gynaecology doctor)

'Some mothers compared the list of conditions between the public and private sectors. I am talking about the difference between 26 and 30 conditions, respectively. They would rather pay out of pocket and send the baby to retake the test in the private sector.' (Interview 16, obstetrics and gynaecology academic)

One paediatrician questioned whether a genetic test with a larger number of conditions contributes to enhanced parental control and confidence regarding the newborn's health. She was aware of some urine tests available in the direct-to-consumer market that screen for so-called 'non-diseases'—short-/branched-chain acyl-coenzyme A dehydrogenase and 3-methylcrotonyl-coenzyme A carboxylase deficiency—although such conditions do not require follow-up. She highlighted the importance of periodically reviewing conditions on the panel according to locality-specific factors, including disease prevalence, clinical sensitivity and specificity, treatment, and cost-effectiveness.

'Running an analysis on a rDBS card is not difficult. What is more challenging is the post-analysis follow-up. Compared with other NBSIEMs, the United States screens for the greatest number of conditions, maybe 40, while the United Kingdom screens for five conditions. Instead of adding conditions, should we also consider taking out some (non-disease) conditions from the list?' (Interview 27, paediatric doctor)

Source of information

Three HCPs (10.0%) reported that most Hospital Authority staff received NBSIEM information through departmental seminars and training sessions, which prepared them to complete the consent procedure with parents. When asked about their understanding of IEMs, knowledge levels varied among frontline staff involved in the NBSIEM. Some were uncertain what the test evaluated.

'What is it (NBSIEM) testing for...? Is it checking for chromosomal defects? Or is it checking for lack of (metabolites)?' (Interview 15, obstetrics and gynaecology nurse)

Some also mistakenly thought that the NBSIEM analysed genes.

'It is a filter paper with some dried bloodspots, testing IEM genes.' (Interview 29, obstetrics and gynaecology doctor)

Some frontline staff wanted additional information beyond the procedure. They felt unprepared for questions about the diseases, symptoms, test procedures, and care for patients with IEMs. They felt anxious or uncomfortable explaining these aspects to parents with some level of understanding.

'After implementing this programme, what the patients will undergo, where they will be referred to,

what to do with a confirmed diagnosis… to be honest, I learned everything from the protocol. In actual settings, parents asked many practical questions, such as "what to be cautious about during daily care"—I do not know how to answer them. These are not common diseases observed in the ward, but we are asked to counsel parents.' (Interview 24, obstetrics and gynaecology doctor)

A senior doctor responsible for providing educational seminars noted that training should not be an isolated event; periodic refresher training should be provided.

'We provide intensive training for nurses, all of them. (In the training), we give clear explanations, conduct videotaping (for review), and address inquiries and questions. In addition, we also plan to host refresher courses every few years. Hong Kong requires more observation before moving forward.' (Interview 27, paediatric doctor)

Experience with parental counselling and consent procedure

Interviewees felt that the educational pamphlet and consent material are easy to read. During parental counselling, HCPs were prepared to answer parents' enquiries. Most parents supported the NBSIEM. Parents wanted to identify IEM conditions in their newborns because they felt that early detection could facilitate autonomous decision-making related to their child and other family members.

'I observed that most parents enrol in the NBSIEM as they would like to know sooner if their babies are affected. If a diagnosis is confirmed, we run a genetic test to predict the risk of recurrence. Only a few refuse to take part in the programme.' (Interview 23, paediatric doctor)

Midwives played an important role in obtaining parental consent in antenatal clinics. Refusals of the current NBSIEM are infrequent. Five frontline staff (16.7%) involved in the recruitment process observed that only a small number of parents, who were sceptical about medical interventions or had religious affiliation–based reservations, declined to join the programme.

'Some people who advocate minimal medicalisation do not consent to procedures in our hospital. For example, they refuse vaccinations and vitamin K injections.' (Interview 10, obstetrics and gynaecology nurse)

Participants involved in recruitment recognised that informed consent procedures were intended to enable parents to make informed choices. The current opt-in consent approach allows HCPs to obtain explicit permission from parents. The participants observed that parents, especially Hong Kong Chinese individuals, were vocal about the patient's right to know.

'Nowadays, patients put a strong emphasis on patient's rights, thinking that "you need my consent before carrying out a procedure".' (Interview 5, obstetrics and gynaecology nurse)

In particular, six HCPs (20.0%) speculated that opt-in consent was more accepted by parents and thus easier to obtain. It provided parents with a sense of personal control by allowing them to give explicit permission. Opt-in consent has been used in many medical settings. It is more familiar to and accepted by community members with respect to studies of genetic material.

'Must I choose a consent model for handling genetic materials? It would be an opt-in approach.' (Interview 6, obstetrics and gynaecology doctor)

Seven HCPs (23%) felt that consent was needed because of the invasiveness of the procedure, but some HCPs felt that the procedure involved minimal harm.

'(The phlebotomists) perform an invasive procedure on the infant, which may cause discomfort or pain. Opt-in is preferable to an opt-out approach. (Interview 27, paediatric doctor)

'It is just a heel prick test and will not affect the baby. I cannot see the downsides (of the screening).' (Interview 16, obstetrics and gynaecology academic)

Opt-in consent was perceived to be more efficient. There may be opposition to an opt-out approach. Some HCPs (n=6, 20.0%) felt that an opt-out approach would increase sample sizes and contribute to advances in medical research.

'Inborn errors of metabolism would be a prevalent issue, and therefore, opt-out is better than the opt-in approach. Like an human immunodeficiency virus test with an opt-out approach, one can refuse to take the test for a valid reason. There are treatments for IEMs; opt-out is a desirable consent model.' (Interview 24, obstetrics and gynaecology doctor)

One doctor pondered the adoption of different methods in obtaining informed consent because opt-in and opt-out approaches are 'like two sides of the same coin'. He stated that the key aspect of selecting an appropriate consent approach is the parental counselling process. He also emphasised that the consent procedure is not absent from the opt-out approach and that effective communication remains important.

Disclosure of confirmed results of inborn errors of metabolism to affected families

When a confirmed IEM diagnosis was disclosed to an affected family, parents often felt shocked, stressed, and guilty about having an 'abnormal' baby. They then began to explore the financial implications; for example, some worried about treatment costs and uncertainties. Counselling is limited to discussing the diagnosis; it also includes psychological support through follow-up care involving a multidisciplinary team.

'Many families were worried when they heard about the IEM diagnosis, as they knew it was a life-long condition. It is tough to handle (bad news). Their child will be different from other peers, and finances will be affected. They must self-finance the drugs.' (Interview 28, paediatric nurse)

On some occasions, the NBSIEM is beneficial to the newborn and has implications for the entire family. Some interviewees reported disclosing an IEM result relevant to the mother, rather than the infant. In one case, the HCP informed the involved family members and provided follow-up care for the newborn's siblings.

'Sometimes, a secondary finding is related to the mother instead of the child. When maternal blood contamination is present (the baby is not affected), the mother is referred to relevant specialists for medical follow-up.' (Interview 23, paediatric doctor)

'We had a positive result for citrullinemia deficiency. The newborn had three brothers and a sister with the same disease. Now we are following them.' (Interview 27, paediatric doctor)

Theme 2: acceptance of retention and secondary use of residual dried bloodspots

Motivations for storage

Interviewees were asked about their views of rDBS storage. Healthcare professionals supported the long-term storage of rDBS through the NBSIEM to facilitate advances in public health epidemiology, forensic purposes, familial disease analysis, and development of other screening tests. Some HCPs highlighted the importance of rDBS in supporting scientific advances. Stored rDBS could be used to enhance healthcare management and clinical testing, such as establishment of local reference standards.

'We did not know how to define the cut-off values at first. Within the United States, the cut-off values differ by state. The initial cut-off values we chose may not reflect local needs. Residual dried bloodspots (storage) is essential to develop a large data pool that supports a control pool when technology advances.' (Interview 19, pathology doctor)

Healthcare professionals observed that most parents demonstrated substantial interest in knowledge about their children. They thought that parents would like to have the right to obtain medical information regarding their children.

'I believe that most parents would agree to save (their) genetic material...perhaps... they would not mind if the laboratory preserved the DNA material and let them know the findings of future screening tests.' (Interview 17, paediatric doctor)

Barriers to storage

Uncertain value of retention

Four HCPs (13.3%) were worried that the public lacked an understanding of how rDBS could generate knowledge. This lack of awareness may be linked to an unwillingness among parents to permit the use of their children's rDBS samples.

'Many laypeople may not understand why they should engage in research studies. They may be reluctant to take part in research studies due to their own beliefs.' (Interview 3, obstetrics and gynaecology nurse)

Two-fifths of HCPs (n=12) questioned the need for the long-term storage programme.

'Several ongoing studies on population genetics use a wide-consent approach, supported by government funding. Does every newborn have to provide data (to support this research)? I doubt it.' (Interview 18, paediatric doctor)

'With strong opposition, I dissent to the storage (of rDBS) as I see no value at all. Perhaps it offers convenience for research, but it provides no personal benefits.' (Interview 30, pathology doctor)

Interviewees believed that genetic material is very stable and does not easily degrade, despite long storage periods. Although storage is possible, some concerns were raised about its cost-effectiveness.

'I heard researchers (scientists) mention that proper sample storage incurs a considerable cost.' (Interview 13, obstetrics and gynaecology doctor)

No direct benefit to patients or parents

Around one-fourth of HCPs (n=7, 23.3%) would only support clinical research if the findings could be used to help their children and patients. Parents were not expected to be interested in research, especially if it did not provide direct clinical benefit to their children.

'Parents care about whether the disease can be treated or not. Knowledge of disease aetiology is only relevant to public health or research institutes.' (Interview 2, obstetrics and gynaecology nurse)

'Would I receive the data if I donated a sample? I would donate a sample if the researcher would return the data. I must know every single conclusion or diagnosis from data generated using the rDBS. I would refuse if no data were returned.' (Interview 13, obstetrics and gynaecology doctor)

Trust and privacy concerns regarding responsible authorities

Another recurring theme was trust in the context of primary privacy concerns, such as data leakage and misuse of private information generated from sensitive genetic materials.

'It may not be desirable to store (genetic materials) for a long time. The longer it is stored, the more concerns arise. Immediate disposal would be more reassuring in terms of the protection of privacy.' (Interview 12, paediatric nurse)

'Some people may steal genetic information (rDBS cards) for illegal (or unauthorised) purposes.' (Interview 12, paediatric nurse)

Obligation to return research findings

Generally, around 30% of the interviewed doctors and researchers (n=9) believed they have a duty to warn research participants upon finding abnormalities, enabling parents to take appropriate action after receiving relevant test results, including secondary findings.

'There is an obligation to inform the patients (of medically actionable findings) because we work in this profession. First, we do no harm. If a significant finding warrants medical attention, we should be responsive and responsible.' (Interview 24, obstetrics and gynaecology doctor)

Issues with obtaining consent for storage purposes

The importance of consent was acknowledged, but there was disagreement concerning the need for broad or specific consent. Interviewees frequently noted that broad consent is convenient for researchers.

'Our understanding of IEMs or diagnostic tests increases as time goes by. The advantage of broad consent is that we do not need to obtain consent when new technology evolves. Like the recently added SCID, we do not need to redesign or implement a new consent procedure again when adding new conditions to the panel.' (Interview 9, paediatric doctor)

Despite the view that broad consent may permit more efficient use of biospecimens and relevant data, there were concerns about public acceptance. Some interviewees stated that it would be challenging to obtain consent for all future research and explain the need for a change in consent approach.

'Broad consent implies uncertainty in the research scope, which leads to parental concern. Parents are uncertain how the rDBS will be used or handled. I feel uneasy during counselling. I am not sure how their blood will be used in a research project, but in short, it will be helpful.' (Interview 7, paediatric doctor)

'Broad consent entails an unknown. As such, parents might be unwilling to sign the consent form (and contribute the rDBS).' (Interview 27, paediatric doctor)

For HCPs, the legitimacy and scope of consent are key considerations. Specific consent is commonly exercised in clinical or research procedures in Hong Kong. It is recognised as the most appropriate procedure because it ensures patients receive information about the study. A few interviewees mentioned that no existing framework recommends the use of broad consent; thus, they favoured the use of specific consent.

'Specific consent may not provide sufficient coverage of all possible research. If there is a breach in the protocol, it may bring about ethical and legal issues.' (Interview 26, obstetrics and gynaecology doctor)

'I found that specific consents were more protective for HCPs.' (Interview 15, obstetrics and gynaecology nurse)

'I have never sought ethical approval for broad consent from institutional research boards.' (Interview 28, paediatric nurse)

The level of public knowledge regarding the NBSIEM requires further analysis. Education and counselling might be intended to address problems that arise from long-term storage. One doctor emphasised that proper counselling on tests involving genetic material should be considered best practice. Some interviewees expressed a desire to prepare themselves to address parents' concerns.

'The drawbacks of the NBSIEM should be discussed, apart from privacy and personal genetic information. Parents should be aware that there are many unknowns in genetics. (As medical professionals) we have, of course, fewer concerns. Suppose I have to conduct genetic counselling for an IEM test. In that case, I will cover all the aspects, including the basic understanding of genetics, even if it is a selected target gene panel. I do not see much difference in terms of counselling across all forms of genetic tests.' (Interview 9, paediatric doctor)

Discussion

This study explored the voices of HCPs from various backgrounds and discussed clinical and ethical issues during the early implementation phase of the NBSIEM. Similar to professionals in the United Kingdom,[13] HCPs in Hong Kong did not exhibit extensive knowledge and awareness of IEM conditions, which may have detrimental effects on patient-centred care. First, parental autonomy might be undermined because parents are not adequately informed about the test procedure and conditions. Second, a lack of understanding regarding IEMs can lead to suboptimal clinical care. Children with IEMs attend multiple specialist clinics to manage multiple co-morbidities. Caregivers encounter difficulties, such as miscommunication or inconsistent information about medications or dietary restrictions, when attending non–IEM-specific clinics.[14] They face numerous psychosocial challenges in caring for their children,[15,17] and increased awareness of these stressors among healthcare providers could improve communication for the entire family. More than four-fifths of individuals in Hong Kong attend medical services at public hospitals,[18] and many parents are expected to participate in the NBSIEM. The establishment of training or educational interventions and a centralised pipeline to coordinate care are

essential considerations for patient-centred care that focuses on caregivers of children with IEMs. Because hospitals are expanding screening for other uncommon disorders, such as SCID,[19] the results of the present study may inform the development of a family-oriented framework for IEM management.

Development of the current NBSIEM was based on a stringent infrastructure and second-tier testing pipeline.[20] Samples with borderline or ambiguous results were sent for further genetic tests to confirm the diagnosis and carrier status. Carnitine deficiency, citrin deficiency, methylmalonic acidaemia, and glutaric aciduria type I are examples of diseases with relatively high incidences of false-positives or false-negatives.[1,21] After the implementation of stringent second-tier tests, the recall rate has declined to 0.3% to 0.4%, similar to the standards of international IEM programmes.[22] This work has been successful, and the retention of rDBS to create a large-scale genetic biobank will be the next focus of public health dialogue.

It is important to note that territory-wide biobanks are not common; biobank platforms in Hong Kong currently are operated by individual hospitals or institutions. A notable example is Children of 1997, a population-based birth cohort study of local infants.[23] Other existing platforms include disease-oriented biobanks,[24] which support quality assurance and conduct epidemiology studies; they also identify risk factors, novel molecular markers, and genetic variants associated with diabetes and related complications. The establishment of biobanks at separate institutions has led to non-standardised informed consent practices. Many ethical and legal issues remain unresolved in efforts to harmonise all regional biobanks. Public awareness of the value of rDBS has been low[11]; improvements in public acceptance and engagement are needed for broad support of rDBS storage or biobanks.

The present study highlighted common ethical, legal, and social concerns as barriers to the storage of rDBS. Trust and low awareness of the potential value of rDBS were cited as primary barriers. In contrast to the assumptions of HCPs, parents generally agree with academic researchers and doctors accessing their children's rDBS and health data after explicit consent has been provided.[11] The optimal consent model for the use of rDBS outside of screening purposes depends on cultural and social characteristics that vary among regions. In the past three decades, some countries have stored rDBS without consent, leading to public controversy and lawsuits.[25] Considering these situations, the retention of rDBS requires inherent trust based on public support, with strict clinical and ethical parameters. Essential factors in establishing trust are consent to participate in the NBSIEM, as well as consent for rDBS retention and secondary uses; questions remain regarding the optimal approach to obtaining consent.[25] Other factors involved in decision-making concerning rDBS retention and secondary uses include timing of consent, adequate communication and discussion of potential uses, protection of privacy, and responsible governance.[9,11,26] These factors should be considered in public policy initiatives.

Concerns about privacy issues and discrimination related to genomic information will be amplified as next-generation sequencing is integrated into clinical care for newborns.[27,28] In South Korea, next-generation DNA sequencing has been evaluated for use in primary newborn screening.[29] In the United Kingdom, Genomics England plans to offer whole-genome sequencing to newborns, identifying actionable genetic conditions that may impact infants in early childhood.[30] There is evidence that sequencing data provides information about conditions not currently assessed in newborns, as well as information with unclear clinical significance.[29] The previous regime agreed that it was appropriate to disclose incidental research findings if they would directly benefit the child after considering risk and benefit. However, this approach may differ in cultural and social settings when considering the child's future and non-therapeutic genomic information.

Limitations and strengths of the study

Most participants in this study were HCPs working in the public sector; they may have different views regarding clinical utility, value, and perceived cost-benefit, compared with stakeholders from other healthcare settings. However, this study used various sampling strategies to recruit a heterogeneous group of HCPs with diverse specialities, roles, and responsibilities in the screening programme, as well as years of experience. A longitudinal study would provide long-term insights concerning the NBSIEM. Knowledge of heterogeneous IEMs and perception of rDBS storage among HCPs could be analysed via quantitative methods.

Conclusion

This study highlighted HCPs' concerns about the NBSIEM and uncertainties regarding the handling or utilisation of rDBS. Policymakers should consider these concerns when establishing new guidelines. Future investigations should explore parents' experiences with screening for rare metabolic conditions and communication of positive results.

Author contributions

Concept or design: OMY Ngan.
Acquisition of data: CJ Tam.
Analysis or interpretation of data: All authors.
Drafting of the manuscript: OMY Ngan, CJ Tam.

Critical revision of the manuscript for important intellectual content: CK Li.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors declared no conflicts of interest.

Acknowledgement

The authors thank all healthcare professionals who participated in the study.

Funding/support

This research was supported by the Direct Grant for Research from the Faculty of Medicine at The Chinese University of Hong Kong (2020/2021) [Ref No.: 2020.081]. The funder had no role in study design, data collection/analysis/interpretation or manuscript preparation.

Ethics approval

The research was approved by the Survey and Behavioural Research Ethics Committee of The Chinese University of Hong Kong (Ref No.: SBRE-20-846). All participants provided written consent for interview and publication of the study.

Supplementary material

The supplementary material was provided by the authors and some information may not have been peer reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by the Hong Kong Academy of Medicine and the Hong Kong Medical Association. The Hong Kong Academy of Medicine and the Hong Kong Medical Association disclaim all liability and responsibility arising from any reliance placed on the content. To view the file, please visit the journal online (https://doi.org/10.12809/hkmj2210234).

References

1. The Task Force on the Pilot Study of Newborn Screening for Inborn Errors of Metabolism. Evaluation of the 18-month "Pilot Study of Newborn Screening for Inborn Errors of Metabolism" in Hong Kong. Hong Kong J Paediatr (new series) 2020;25:16-22.
2. Belaramani KM, Chan TC, Hau EW, et al. Expanded newborn screening for inborn errors of metabolism in Hong Kong: results and outcome of a 7-year journey. Int J Neonatal Screen 2024;10:23.
3. Hospital Authority. Newborn Screening Programme for Inborn Errors of Metabolism (IEM). October 2023. Available from: https://www21.ha.org.hk/smartpatient/SPW/MediaLibraries/SPW/SPWMedia/Education-pamphlet_NBS-IEM_Eng-(Oct-2023).pdf?ext=.pdf. Accessed 27 Mar 2024.
4. Ngan OM, Li CK. Ethical issues of dried blood spot storage and its secondary use after newborn screening programme in Hong Kong. Hong Kong J Paediatr (new series) 2020;25:8-15.
5. Lund A, Wibrand F, Skogstrand K, et al. Danish expanded newborn screening is a successful preventive public health programme. Dan Med J 2020;67:A06190341.
6. Nordfalk F, Ekstrøm CT. Newborn dried blood spot samples in Denmark: the hidden figures of secondary use and research participation. Eur J Hum Genet 2019;27:203-10.
7. Jansen ME, Klein AW, Buitenhuis EC, Rodenburg W, Cornel MC. Expanded neonatal bloodspot screening programmes: an evaluation framework to discuss new conditions with stakeholders. Front Pediatr 2021;9:635353.
8. Loeber JG, Platis D, Zetterström RH, et al. Neonatal screening in Europe revisited: an ISNS perspective on the current state and developments since 2010. Int J Neonatal Screen 2021;7:15.
9. Jansen ME, van den Bosch LJ, Hendriks MJ, et al. Parental perspectives on retention and secondary use of neonatal dried bloodspots: a Dutch mixed methods study. BMC Pediatr 2019;19:230.
10. Mak CM, Lam CW, Law CY, et al. Parental attitudes on expanded newborn screening in Hong Kong. Public Health 2012;126:954-9.
11. Hui LL, Nelson EA, Deng HB, et al. The view of Hong Kong parents on secondary use of dried blood spots in newborn screening program. BMC Med Ethics 2022;23:105.
12. Mak CM, Law EC, Lee HH, et al. The first pilot study of expanded newborn screening for inborn errors of metabolism and survey of related knowledge and opinions of health care professionals in Hong Kong. Hong Kong Med J 2018;24:226-37.
13. Moody L, Atkinson L, Kehal I, Bonham JR. Healthcare professionals' and parents' experiences of the confirmatory testing period: a qualitative study of the UK expanded newborn screening pilot. BMC Pediatr 2017;17:121.
14. Siddiq S, Wilson BJ, Graham ID, et al. Experiences of caregivers of children with inherited metabolic diseases: a qualitative study. Orphanet J Rare Dis 2016;11:168.
15. Zeltner NA, Landolt MA, Baumgartner MR, et al. Living with intoxication-type inborn errors of metabolism: a qualitative analysis of interviews with paediatric patients and their parents. JIMD Rep 2017;31:1-9.
16. Petros M. Revisiting the Wilson–Jungner criteria: how can supplemental criteria guide public health in the era of genetic screening? Genet Med 2012;14:129-34.
17. Grant S, Cross E, Wraith JE, et al. Parental social support, coping strategies, resilience factors, stress, anxiety and depression levels in parents of children with MPS III (Sanfilippo syndrome) or children with intellectual disabilities (ID). J Inherit Metab Dis 2013;36:281-91.
18. Hospital Authority. Hospital Authority Strategic Plan 2022-2027: Towards Sustainable Healthcare. Available from: https://www.ha.org.hk/haho/ho/ap/HA_StrategicPlan2022-2027_Eng_211216.pdf. Accessed 16 Dec 2021.
19. Leung D, Lee PP, Lau YL. Review of a decade of international experiences in severe combined immunodeficiency newborn screening using T-cell receptor excision circle. Hong Kong J Paediatr (new series) 2020;25:30-41.
20. Tsang KY, Chan TC, Yeung MC, Wong TK, Lau WT, Mak CM. Validation of amplicon-based next generation sequencing panel for second-tier test in newborn screening for inborn errors of metabolism. J Lab Med 2021;45:267-74.
21. Hennermann JB, Roloff S, Gellermann J, Grüters A, Klein J. False-positive newborn screening mimicking glutaric aciduria type I in infants with renal insufficiency. J Inherit Metab Dis 2009;32 Suppl 1:S355-9.

22. la Marca G. Mass spectrometry in clinical chemistry: the case of newborn screening. J Pharm Biomed Anal 2014;101:174-82.
23. Schooling CM, Hui LL, Ho LM, Lam TH, Leung GM. Cohort profile: 'Children of 1997': a Hong Kong Chinese birth cohort. Int J Epidemiol 2012;41:611-20.
24. Ng IH, Cheung KK, Yau TT, Chow E, Ozaki R, Chan JC. Evolution of diabetes care in Hong Kong: from the Hong Kong Diabetes Register to JADE-PEARL Program to RAMP and PEP Program. Endocrinol Metab (Seoul) 2018;33:17-32.
25. Cunningham S, O'Doherty KC, Sénécal K, Secko D, Avard D. Public concerns regarding the storage and secondary uses of residual newborn bloodspots: an analysis of print media, legal cases, and public engagement activities. J Community Genet 2015;6:117-28.
26. Hendrix KS, Meslin EM, Carroll AE, Downs SM. Attitudes about the use of newborn dried blood spots for research: a survey of underrepresented parents. Acad Pediatr 2013;13:451-7.
27. Pereira S, Robinson JO, Gutierrez AM, et al. Perceived benefits, risks, and utility of newborn genomic sequencing in the BabySeq project. Pediatrics 2019;143(Suppl 1):S6-13.
28. Johnston J, Lantos JD, Goldenberg A, et al. Sequencing newborns: a call for nuanced use of genomic technologies. Hastings Cent Rep 2018;48 Suppl 2:S2-6.
29. Woerner AC, Gallagher RC, Vockley J, Adhikari AN. The use of whole-genome and exome sequencing for newborn screening: challenges and opportunities for population health. Front Pediatr 2021;9:663752.
30. Biesecker LG, Green ED, Manolio T, Solomon BD, Curtis D. Should all babies have their genome sequenced at birth? BMJ 2021;375:n2679.