

## Original Article

# Ethical Issues of Dried Blood Spot Storage and Its Secondary Use After Newborn Screening Programme in Hong Kong

OMY NGAN, CK LI

### Abstract

The advances in high-resolution tandem mass spectrometry led to a paradigm shift in expanded newborn screening, based on the dried blood spot (DBS). At the time of DBS collection, the quantity of blood collected is always more than sufficient for initial and repeated testing to validate screening results. Thus, the residual DBS for secondary use is almost always available. Current applications of residual DBS for various purposes, including quality assurance and test validation, new screening programme development and evaluation, biomedical research and public health epidemiological studies. However, because of the sensitive information that can be derived from the DBS, the storage and secondary use of residual DBS for research purposes raise several ethical considerations. This paper discusses some issues about the storage and secondary use of residual DBS in newborn settings, including informed consent, privacy and confidentiality concerns, the need for returning research results and public transparency.

### Key words

Bioethics; Dried blood spot; Expanded newborn screening; Hong Kong; Informed consent

### Introduction

Newborn screening is regarded as one of the most successful public health programmes, with clinical benefits that include providing information for family planning, enabling early diagnosis and treatment, and preventing childhood morbidity and mortality. The advances in high-

resolution tandem mass spectrometry led to a paradigm shift in the development of expanded newborn screening, based on the dried blood spot (DBS).<sup>1,2</sup> DBS is a form of sampling, where a few drops of blood are obtained from the heel through a prick and blotted on filter paper. Samples are then analysed via tandem mass spectrometry to determine the concentrations and activity of certain compounds, which allow detection of inborn errors of metabolism (IEM) – rare metabolic diseases caused by the accumulation of toxic metabolites or lack of essential metabolites in the metabolic pathway. The biospecimen in dried samples can be conserved for long periods at ambient temperature or under refrigeration,<sup>3</sup> and have a minimal risk of bacterial contamination or haemolysis. The DBS collection procedures are also inexpensive, reliable for testing, and could be stored and transported easily. It offers an excellent opportunity to explore ground to routinely store and use the residual DBS collected in the newborn screening programme for research purposes. However, because of the sensitive information that can be derived from the DBS, its storage and secondary use raise several ethical considerations.

**CUHK Centre for Bioethics, Faculty of Medicine, The Chinese University of Hong Kong, Shatin, N.T., Hong Kong SAR, China**

OMY NGAN (顏妙融) *PhD*

**Department of Paediatrics, Faculty of Medicine, The Chinese University of Hong Kong, Shatin, N.T., Hong Kong SAR, China**

CK LI (李志光) *MD, FHKAM(Paediatrics), FRCPCH*

**Correspondence to:** Dr OMY NGAN  
Email: [oliviangan@cuhk.edu.hk](mailto:oliviangan@cuhk.edu.hk)

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## Advantages of Storing Residual DBS in the Newborn Settings

Current applications of residual DBS for various purposes include quality assurance and test validation, new screening programme development and evaluation, biomedical research and public health epidemiological studies.<sup>4</sup>

At the individual level, residual DBS has a continued value to the newborn when re-testing or additional testing is required to validate the test results. In particular, newborn infants with IEM often have variable and non-specific clinical presentations and can become acutely ill with severe complications within a short period. These diseases are rare but treatable, where therapeutic options, such as special modified diets, or bone marrow transplantation, may possibly restore normal metabolism with good prognosis. It is recommended that these therapeutic interventions should be implemented prior to the onset of signs. With doctors' poor understanding of uncommon diseases, newborn infants with mild or atypical signs often diagnosed late and thus unable to receive early treatment. Residual DBS could be an effective alternative to identify affected infants at the earliest instance, often before they develop signs and facilitate early treatment to ensure the best possible outcome. For example, studies showed that residual DBS allows an early diagnosis of rare IEM, such as Gaucher disease and lysosomal storage disorder.<sup>5,6</sup> The residual biospecimens can also be used for forensic identification purposes in the case of a missing or deceased child after an unexplained death.<sup>7</sup>

At the institutional level, residual DBS enables quality assurance and control. A newborn screening programme is not a one-time screening but involves multistage procedures, such as confirmation of diagnosis, management, and long-term follow-up. Regular audit and continuous quality improvement of the programme are essential to assess laboratory analytical processes in detecting, reducing, and correcting deficiencies prior to the release of patient results.

At the community, residual DBS foster biomedical research and public health programme development. In the 1990s, many developing countries used residual DBS as a surveillance tool for HIV epidemiology research to monitor the use of antiviral treatment among patients, estimate maternal-infant HIV transmission rates at birth, and perform drug resistance genotyping.<sup>8,9</sup> It is particularly useful to identify HIV-exposed infants so that timely primary paediatric medical care could be provided.<sup>10</sup>

Residual DBS is also an invaluable source for developing a new screening method that requires large sample sizes especially to study rare diseases, characterise genetic variation frequencies, and establish a baseline measure for longitudinal comparisons.

## Ethical Consideration about the Storage and Secondary Use of Residual DBS

Research use of residual DBS has a high societal value at the population level, although the immediate benefit for individual biospecimen donor may not be self-evident. There is some discussion advocating formalising use of residual DBS in a more systematic way as a biobank for future population research,<sup>11</sup> but this practice does not come without disputes.

## Informed Consent

The most frequently discussed concern is informed consent, which is the clinical practice of adhering to the principles of respecting autonomy. Autonomy broadly refers to individual freedom to make an informed choice voluntarily based on self-value and informedness without an undue coercive or deceptive circumstance.<sup>12</sup> In health care practice, the consent procedures usually involve providing specific information about the nature of the research, as well as anticipated risk and benefits. Healthcare providers or researchers has an ethical responsibility not expose biospecimen donors to any uninformed research risk.

The need for informed consent is indisputable, and there are broadly two arguments against waiving informed consent. Firstly, the consent procedures enable individuals to learn what the research entails and what the risks and benefits they may face may be. There is some scholarly debate arguing that residual DBS is considered part of routine care so that consent is unnecessary for any related secondary use.<sup>13</sup> It is, however, essential to note that autonomy entails the notion that biospecimen donors should not be treated as merely means to an end. Consent procedures provide an opportunity allowing parents to express approval or disapproval in storing children's DBS, while also allowing professionals to build up a rapport with them. Secondly, the DBS contains genetic information that can potentially readily identify the donor. Consent procedures allow parents to protect their children's privacy

by restricting the use of residual DBS in some research projects that they may consider to be sensitive or against their moral view.

Approaches for research with residual DBS, or broadly human biospecimens, employ different types of consent procedures and there are three types of consent majorly discussed in the literature, namely – specific, blanket, or broad – consent.<sup>14</sup>

The first type is known as specific consent, where explicit details specific to research are mentioned prior to study enrolment. Parents must be recontacted to obtain new permission for each future study. Residual DBS research, however, rarely takes place in a clearly defined scope such that explicit information often cannot be provided at the study recruitment. Also, it is hard to determine what is an acceptable scope for clarity in specific consent.<sup>15</sup> Adopting the specific consent model is logistically limited in research for such biospecimens, and it may make informed consent too routine, leading to a reflexive denial when subjects are being asked to give consent too often.<sup>16</sup> This approach may cause researchers to spend excessive amounts of time in these practical procedures rather than spending time in conducting research analysis.

Another type is known as blanket consent, which involves a one-time consent to future research without any limitation or oversight.<sup>17,18</sup> This framework is favourable when the future research uses cannot be known at the time of consent and when samples are de-identified that there is no risk or concern about tracing identity to the residual biospecimen donor. It is, however, weak in terms of providing sufficient informedness to research participants.

The third type is known as a generic or broad consent that contains non-specific information with some specified procedural oversight, including governmental regulation, institutional committee review, and researcher integrity and privacy protection training.<sup>17</sup> In this approach, parents have a higher degree of autonomy than the blanket consent as they are allowed to give a propositional agreement in giving out residual DBS on the types of research they would like to join.<sup>19</sup> The flexibility account in the broad consent with some governance to some degree is regarded as ethically acceptable for biospecimen research, although it raises questions as to whether a generic consent with nonspecific information suffices because of the complexities of identifying future research with DBS, and ever-changing nature of genetic advancements.

Empirical research studied the parental understanding of residual DBS from newborn screening and found that

parents of young children lacked knowledge towards the programme and were not familiar with the handling of biospecimens.<sup>20</sup> Some were not even aware of the implemented policy of residual storage and thought that all samples were discarded immediately after clinical use.<sup>21</sup> Parents showed a high level of trust and support towards the storage of DBS, and were willing to give out child's DBS if permission was obtained. In this way, they felt respected and given room to express consent or dissent to research prior to the enrolment.<sup>22,23</sup> Specifically, they preferred being asked to give out consent for researchers to obtain and retain samples for research (an opt-in consent approach) over being assumed and stored, unless parents contact the researchers to have their child's sample removed (an opt-out consent approach).<sup>24,25</sup> Healthcare providers or researcher involved in newborn screening also equally found consent procedure crucial to prevent adverse consequences from newborn screening.<sup>26</sup> Small numbers of Hong Kong healthcare providers working in paediatrics, pathology or obstetrics, however, did not believe that parental consent should be mandatory for baby blood sampling.<sup>27</sup> A possible explanation is that they see drawing blood is normalised as a part of regular clinical care that consent is regarded as not crucial in such a routine setting.

## Privacy and Confidentiality Concern

The storage and secondary use of residual DBS card can lead to privacy and confidentiality concerns when the phenotype or personally identifiable information (e.g., name, ID card number, and date of birth) is not delinked from the collected biospecimen. The solution to alleviate these concerns is to guarantee anonymity grounded in two positions. First, it encourages altruism.<sup>28</sup> Secondly, it protects biospecimen donors against potential bias or disadvantageous social consequences, such as exclusion from insurance.<sup>29</sup> This approach, however, may limit the implications of the storage and secondary use of residual biospecimens. At the individual level, the donor of DBS may no longer directly benefit from the research, since the identity cannot be traced and results returned to parents or their physicians. At the population level, anonymity limits the research utility in transforming residual DBS into broader biobanks research, since DNA analysis gives meaningful implication only when interpreting with health care information. Empirical research studied how parents made a trade-off decision between anonymity and return

of research findings.<sup>24</sup> In the vignette, parents were put in a situation to choose between anonymity for greater privacy protection, and a chance to receive important infant health information if retaining identifiers with the samples. Parents, who are knowledgeable about NBS, lower-income, and received lower education put infant health information at a higher priority than privacy. In other words, parents regarded the importance of benefiting a child's health as more imperative than privacy protections.

Parental attitude towards retaining the child's residual DBS for research purposes was also partly influenced by the question as to who or which entities manage the data and what purposes what these data serve. Parents found confident with research participation selectively when academic institutions lead a project, and are less favourable to give out samples of a child to non-academic institutions, such as commercial enterprises, insurance companies and pharmaceutical companies, with the concern of potential misuse of information.<sup>22,25</sup> Examples of types of research uses that were considered unacceptable include, commercially-oriented research targeting profitable diseases by pharmaceutical and biotechnology companies, research lead to potential discrimination by workplaces, schools, insurance companies, or governmental agencies.<sup>30</sup> Another research studied factors influencing parental decision to enrol in residual DBS research and the vast majority respondents prioritised consent as the most critical factors, distantly followed by privacy and research identity.<sup>22</sup> Parents generally preferred their consent to be sought for every use of the child's DBS, child's identity not linked to the DBS, and research projects conducted by university researchers.

An alternative way not to completely obviate anonymity is to store personal identifier separately from the residual samples and label a unique study identifier to each sample. In this way, it not only enables the adoption of the double-blinded standard that permits unbiased laboratory analyses but also offers the feasibility to retrace participants for returning research findings. This approach requires additional considerations in data management and handling, such as restricting limited research investigators access right to the sensitive information.

## Return of Research Findings

There has been active ethical debate about whether, when, and how residual DBS research findings should be

returned to parents or their physicians, even if there are of no direct medical benefit (e.g., some IEM conditions are incurable, and there is no treatment plan upon returning the results). The underlying arguments supporting the return of research findings are autonomy, beneficence, reciprocity, and empowerment.<sup>31</sup> Some physicians and researchers believe that they are obliged to warn research participants upon finding abnormalities and believe early warning can enable parents to take appropriate actions after receiving relevant test results.<sup>32</sup> The counterargument against returning results concerns the potential violation of the original altruistic intent to help research benefiting for the greater public good instead of wishing for anything in return. Healthcare providers worry that clinically unactionable information might not lead to meaningful clinical implication but rather emotional burden, such as anxiety, and fear of discrimination by parents.<sup>27</sup> They may feel that there is an obligation to avoid harm to parents by not disclosing the information, even though there is a possibility to deprive their right to know.

The discussion about what incidental research findings should be released or not is not new to the paediatric community, and consensus remains elusive. Some ethicists recommended that the information disclosure should be grounded upon the standard of best medical interests, where results that are accurate, has clinical significance to health and has available clinical interventions should be returned.<sup>33</sup> However, for conditions with adult-onset or may have relevance only to the health of other family members is more controversial, since there are also some familial implications in pregnancy planning and concerns about the vulnerability of the child who will grow up with risk information. This approach is consistent with the purpose of newborn screening for early disease detection reducing child morbidity or mortality.

There is now a shift of consensus that physicians and research investigators should be prepared to return findings discovered in the course of the research and meeting an actionability threshold, but they have no ethical obligation to search for such results actively.<sup>34</sup> However, the returning of results should be packaged with a referral for appropriate clinical follow-up. The workload and expertise in genetic counselling of the results at the time of releasing to participants can be significant. How to return the results and who should be responsible for returning of results should be well-planned. The research protocols requesting the use of residual samples should include a clear action plan in returning results.

## Public Transparency

The storage and secondary use of residual DBS without parental consent and public transparency have culminated in lawsuits in the United States and Canada and raised international controversy.<sup>35</sup> In 2009, the Texas State health office retained residual DBS from the mandated disease screening and then used them for research purposes without parental consent. Five families filing against the Texas State Department of Health claimed that uninformed storage and use of NBS for research purposes violated their constitutional protection with unlawful search and seizures and also failed to protect their liberty and privacy interests.<sup>36</sup> The Texas Department of Health later admitted that they had provided 800 de-identified samples without parental consent to the United States Armed Forces for forensics purposes between 2003 and 2007. The lawsuit was settled and led to the destruction of over five million biospecimens and influenced succeeding research practice that parental consent must be sought before retaining residual DBS for storage and secondary use.<sup>37</sup>

Another litigation in British Columbia, Canada took place in 2011.<sup>38</sup> A lawsuit was filed in the Supreme Court of British Columbia against the Provincial Health Services Authority alleging the torts of fraudulent and negligent misrepresentation. The plaintiffs alleged that the Authority knowingly or neglectfully misrepresented the purpose of the collection and storage of the newborn blood samples and subsequently used the samples beyond indicated purposes without explicit parental consent. The court later ruled that the Authority making the unconsented samples available to outside parties for the purpose of medical research was unlawful and tortious that constituted a breach of privacy and fiduciary duty to the plaintiffs. The lawsuit was settled and led to a recent policy revision, where parents now have the right to choose from dissenting storing their children's DBS after the completion of the tests.<sup>39</sup>

## Hong Kong Context

Since 1984, two metabolic conditions, namely congenital hypothyroidism and Glucose-6-Phosphate Dehydrogenase deficiency, are screened under the governmental-subsidised neonatal screening pathway using umbilical cord blood samples under Clinical Genetic Service, Department of Health. A limitation of using umbilical cord blood samples in newborn screening is that it is not suitable for detection of IEM. In 2008, a local

case reported the sudden death of a 14-year-old child resulting from glutaric acidemia type II, confirmed by a post-mortem genetic diagnosis.<sup>40,41</sup> In 2010, 2 year-old boy died of aspiration pneumonia, which was suspected to be related to methylmalonic academia.<sup>42</sup> The two cases of child mortality due to a metabolic disease could have been prevented if earlier diagnoses were made, leading to reconsideration in expanding the screening panel for IEM, which is not yet covered in the universal newborn screening in Hong Kong. The universal congenital hearing impairment screening programme was also introduced and offered in 2007.<sup>43</sup>

In 2012, a first territory-wide prospective study on expanded newborn screening for IEM in two public hospitals was conducted by the University of Hong Kong.<sup>27</sup> The team specifically implemented a 10-step model in delivering quality health service, including parental education, informed consent procedure, DBS collection and handling, laboratory assay, test result reporting, post-test counselling and follow-up, as well as treatment monitoring. Among all 2,440 newborn babies were recruited for newborn screening from October 2012 to August 2014. There were six (0.25%) false-positive cases confirmed by subsequent laboratory findings. No true-positive cases were found.

Starting from July 2013, the Centre of Inborn Errors of Metabolism at The Chinese University of Hong Kong started a private expanded newborn metabolic screening programme.<sup>44</sup> During the period of July 2013 and July 2016, out of a total of 30,488 local newborn babies screened, there were 35 cases with mildly abnormal results and four with markedly abnormal results that were highly suggestive of IEM. Followed by further metabolic investigations, six neonates were subsequently confirmed to have IEM and one had a deficiency in maternal carnitine uptake, which had an incidence of 1 per 4355 births. The false-positive rate was 0.105% (32/30,448). One false-negative result was also identified. In particular, this study incidentally diagnosed a mother with carnitine uptake defect through the abnormal result for her baby in the newborn screening. The mother reported history of good past health during the pregnancy period, and her cardiac function was normal at the time of diagnosis. Later, she was referred to a cardiologist for follow-up.

The feasibility to implement expanded newborn screening for IEM was positively demonstrated, and the government decided to introduce a full-territory wide implementation of the programme in phases to involve all babies born in public hospitals.<sup>45</sup> Under the current

framework, all residual DBS cards will be stored in the laboratory for a minimum of two years according to laboratory accreditation guideline. Once reaching the end of the retention period, blood samples will then be destroyed and disposed of. With informed consent from parents, the laboratory stores the cards longer for medical research after removing all identifying information. With the current annual delivery rate, it is estimated that over 40,000 dried blood spots would be collected yearly. As DBS cards represent a big wealth of data, its proper utilisation in clinical and research settings needs a thorough discussion among different stakeholders.

To date, there is a limited policy consideration about the long-term storage of these biospecimens in Hong Kong, despite its important value for research benefiting the children, pregnant women, and the general public. Policy aspect of managing residual DBS storage and its secondary uses are multifaceted.

First is about biospecimen retention period. In countries where universal newborn screening is currently implemented, the policy regarding the storage practices of newborn bloodspots varies. While some states in the United States destroy the cards after completing the laboratory quality check,<sup>46</sup> other such as Denmark<sup>47</sup> and Canada<sup>48</sup> retain the leftover DBS collected in a routine standard of clinical care and stored for a lengthy period (10 years or more) or indefinitely for research purposes. What is an acceptable timeframe in the local context should be openly discussed, since the decision is likely to be influenced by many factors, for example, public knowledge and awareness, civic involvement, as well as scientific infrastructure.

Second is about the biospecimen data research uses, handling, sharing and management. Hospital Authority is not a research-orientated organisation, and so partnership

with academic and not-for-profit organisations is essential to enhance utility for research. In response to incidental findings not only related to the newborn but also immediate family members, do physicians or researchers have duty of care? What research purposes, other than for clinical service, do residual samples serve or not serve? How should biospecimens be managed and shared among qualified investigators and institutions? These questions remain unanswered and require further exploration among stakeholders.

Third relates to the parallel development of healthcare infrastructure and regulatory oversight aligned with the residual DBS programme. Without compatible support in the clinical settings, including trained medical expertise to act upon abnormal results or access to healthcare services, the limited supporting healthcare services impede the benefit of the biospecimen storage programme. An oversight process for quality assurance and research are equally essential to ensure public transparency and public trust, such as launching an open website. Hospital Authority and the government play vital roles in taking up leadership in developing a regulatory framework.

## Conclusion

We discussed some major ethical issues associated with the storage and secondary use of residual DBS in newborn settings (see Table 1). The discussion highlighted the essence of the informed consent model, privacy and confidentiality framework, returning research results protocol, transparency and public accountability in running a local-wide DBS storage programme and transforming it to a sizeable biobank-like database in supporting biomedical research. Stakeholders' opinion is

**Table 1** Some ethical consideration of dried blood spot (DBS) card storage and its secondary use after the expanded newborn screening programme

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- What are the pros and cons of each informed consent model?
  - What types of research should be allowed to use the residual DBS?
  - How long should the residual DBS be stored?
  - Who has access to the residual DBS? How shall it be shared and managed?
  - Who has the ownership of the residual DBS?
  - Do researchers have the duty to return parents the research findings from DBS? What results should be returned or not returned?
  - What measures should be taken to enhance the transparency and public accountability in newborn screening programmes?
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context-dependent and varies by countries, primarily affected by data sharing and protection policy, consent regulation, and governmental oversight. When the period of residual DBS storage prolongs and formalise as a biobank, the discussion should involve researchers, paediatricians, ethicists, policymakers, and other stakeholders to inform public policy. Normative analysis, such as empirical research among different stakeholders (e.g., parents and ethics committee) is also helpful to inform the development of acceptable research guidelines governing residual DBS in the local context.

## Declaration of Interest

The authors declare that there is no conflict of interest.

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