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## Editorial

# Implementation of Newborn Screening Programme for Inborn Errors of Metabolism in Hong Kong – Progress and Challenges

The successful implementation of the *Newborn Screening Programme for Inborn Errors of Metabolism* in Hong Kong is another major milestone towards delivery of high standard paediatric care to locally born Hong Kong children. Newborn screening (NBS) aims at the earliest possible recognition of diseases to prevent the most serious consequences by timely intervention. Individuals who are affected by these rare inborn errors of metabolism (IEM) can be diagnosed at the earliest instance where by with available treatment and with continued disease monitoring, these patients' outcome and long term prognosis are deemed to be entirely different compared to their historic counterparts when the same diseases may be diagnosed only after catastrophic clinical presentation often leading to poor outcome or after symptomatic presentation when irreversible damages have already taken place. Expansion of Newborn screening with the use of tandem mass spectrometry (MS/MS) for the early detection and treatment of IEM conditions is considered one of the most notable advancements in public health in the 21st century.<sup>1</sup>

Delivery of services to IEM patients in Hong Kong has taken on a steady and gradual developmental process over the last 20 years. While a number of the necessary investigations for diagnosis and monitoring may not have been available locally, recognition of possible IEMs was not simple nor straight forward either due to the lack of clinical experiences 20 years ago. With collaborative and conjoint effort from clinicians, pathologists and patients support groups, the service model and the needs of this highly specialised group of patients become known to the society and the governmental funding bodies. Tang & Hui shared in their paper titled '20 years after discovery of the causative gene of primary carnitine deficiency, how much more have we known about the disease' the journey of making the diagnosis of the first Primary carnitine deficiency (also known as Carnitine uptake deficiency) patient in Hong Kong at the time when very little was known about the disease.<sup>2,3</sup> As it now turned out, Carnitine uptake deficiency is a potentially very treatable IEM condition with carnitine supplementation and is one of the most prevalent IEM in the Chinese population with over 1,000 cases diagnosed and treated all over China. Carnitine uptake deficiency is also one of the more frequent IEM conditions detected from our local screening programme.

Upon the announcement in the Chief Executive's 2015 Policy Address, the Hong Kong Special Administrative Region's *Newborn Screening Programme for Inborn Errors of Metabolism* was launched as a pilot programme at 2 government birthing hospitals in October of the same year. It was a dream realised for many generations of local metabolic physicians and pathologists who have contributed zealously and unconditionally in laying down years of ground work for the development of this specialty. At the end of the 18 months' pilot programme, a comprehensive report was submitted to and reviewed by the government who then decided for full implementation of the programme in a stepwise fashion to involve babies born in all public birthing hospitals in Hong Kong. This full report prepared by The Task Force on the Pilot Study of Newborn Screening for Inborn Errors of Metabolism published in this issue as a formal documentation reviewed the course of events surrounding the pilot programme and discussed all the important clinical findings.<sup>4</sup> A total of 9 IEM cases were confirmed from the pilot programme giving an incidence of 1 in 1,682 which is higher than the original estimation confirming that IEMs is indeed not rare in Hong Kong.

The case reports published in this issue help to highlight the value of newborn screening in the early diagnosis of asymptomatic conditions that will not manifest with symptoms until years later when irreversible damage especially on cognition may have occurred. The first published local case of Homocystinuria alerted us that conditions that have been considered extremely rare locally do occur and only through newborn screening may the true incidence of these rare and often difficult to diagnose IEM conditions be known. The report on the 2 cases of Cobalamin C deficiency, one diagnosed in the pre and the other in the post newborn screening era illustrates the entirely different clinical course between these 2 infants. Although

the baby with Propionic acidemia was not picked up through newborn screening, with increasing awareness among the local paediatric community, this baby's condition was rapidly diagnosed and managed.

In the ideal world, a good screening programme is one that produces minimal false positives and no false negatives. Yet false positive and false negative results are part and parcel of any screening programme. There are multiple factors involved in causing false positive results in IEM screening programs. False positive results are frightening to families, causes extra workload for clinicians and are financially burdensome to the health care system. To improve diagnostic specificity without reducing diagnostic sensitivity, most NBS laboratories develop second tier tests to measure additional metabolites that either strongly support the presumption of a true positive case or refute the notion that the patient has the disorder. Yeung et al shared their local experience of the clinical utility of a second tier testing for Congenital adrenal hyperplasia (CAH) – a condition known to have high recall rate based on the measurement of the primary analyte 17-hydroxyprogesterone. The authors proposed that by adding second-tier steroid profiling with liquid chromatography-tandem mass spectrometry (LC-MS/MS), this can significantly reduce false positive rate and avoid unnecessary recalls in newborn screening for CAH.<sup>5</sup> While second tier testing is effective in reducing false positive recalls, the authors cautioned that false negatives can still occur and genuine cases of CAH can still be missed despite second tier testing. This scenario was presented by Wong et al in their case report titled 'Newborn screening pitfalls: A missed case of salt-losing type of congenital adrenal hyperplasia'. The important lesson here is that a negative newborn screening result does not rule out the conditions completely. In the right clinical context, it remains important for clinicians to exercise their clinical judgement on investigating for conditions that have normal screening results and not be falsely reassured.

After completion of the screening procedures, residual dried blood spot (DBS) cards are usually stored for quality assurance purposes. Protocols vary among different laboratories on storage periods which can range between few months to indefinitely. In addition to quality assurance purpose, stored cards are a valuable resource as they represent a complete population and are extremely useful for establishing reference intervals or carrier frequencies in the population - a rich resource for many potential biomedical research and public health epidemiological studies. However, with the sensitive information derived from stored DBS cards, secondary usage especially for research purposes need to be carefully planned and deliberated. Here is this issue, Ngan & Li discussed the ethical issues surrounding DBS cards storage and its secondary use after newborn screening. Issues on informed consent, privacy and confidentiality concern, returning research results and public transparency were discussed.<sup>6</sup>

With advances in modern day technology on computerisation, automation and sensitivity of analytical instruments, newborn screening (NBS) tests have been rapidly proliferating in recent years. Furthermore, the demands for new tests have partly been driven by improvements in known (e.g. haematopoietic stem cell transplant, enzyme replacement therapy) as well as new innovative treatment options (e.g. chaperone therapy, read-through of premature stop codons, gene therapy). NBS tests for Lysosomal storage diseases, X-linked Adrenoleukodystrophy, Severe combined immunodeficiency and Spinal muscular atrophy are some examples that have been added to different countries' existing screening panel. In this issue, Leung et al reviewed a decade of international experiences on Severe combined

immunodeficiency (SCID) newborn screening using T-cell receptor excision circle.<sup>7</sup> SCID, asymptomatic at birth but often fatal in the first few years of life fulfils criteria for screening. Confirmation of diagnosis is relatively straightforward and with the availability of early haematopoietic stem cell transplantation, prognosis of affected patients is much improved through early detection from newborn screening. SCID was added to the disorders recommended for newborn screening in the USA in 2010.<sup>8</sup> How far and how fast should Hong Kong move in terms of addition of these newer NBS tests. In addition to issues surrounding the disease itself and testing technology, financial and ethical justifications for the introduction of these new NBS tests would need to be properly addressed, discussed and planned among all the involved stakeholders prior to consideration for addition to the existing screening panels.

No doubt newborn screening saves lives. Towards the end of 2020, Hong Kong will celebrate its 5th year of implementation of *Newborn Screening Programme for Inborn Errors of Metabolism* when all babies born in the public birthing hospitals will be covered by the screening programme. While embracing the benefits that this programme brings to the affected IEM children in Hong Kong, there is continued improvement work on many different aspects of the screening programme. Quoting from Bridget Wilcken, the pioneer of newborn screening from Australia's review article on Fifty years of newborn screening, I would like to share her concluding statement – *'With care, the benefits of screening should burgeon – if only we can learn from the past experience and proceed at a good pace - not too fast, not too slowly.'*<sup>9</sup>

**J Hui**  
Guest Editor

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