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Citation	**SM Journal of Clinical Pathology, 2016, v. 1 n. 1, article no. 1001**
Issued Date	**2016**
URL	**http://hdl.handle.net/10722/224840**
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Research Article

Cost-Effectiveness Analysis of Newborn Screening for Organic Acidemias in Hong Kong

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Abstract

Aim: This study assesses the cost-effectiveness of population-wide organic acidemias newborn screening in Hong Kong from the public healthcare provider's perspective.

Methods: A decision tree was established to model the effect of screening birth cohort in Hong Kong in 2009 compared with no screening. Life-time costs and benefits were considered. Screening test performance, outcome probabilities and costs were obtained from the international literature and local sources. A yearly discount rate of 5% was applied to costs and benefits. Incremental Cost-Effectiveness Ratio (ICER) was calculated per life year gained (overall) and per life year gained without mental retardation.

Results: The ICER per life year gained for all newborns is -HK$1,300,177 and the ICER per life year gained without mental retardation is -HK$983,333, for screening as compared with no screening strategy.

Conclusion: Newborn screening for organic acidemias is shown to be highly cost-effective for avoidable mortality and mental retardation development.

Introduction

Inborn Errors of Metabolism (IEM) are a class of genetic diseases involving genes which code for enzymes or transporters in metabolism. Patients with IEM produce defective enzymes or transporters from defective genes. This hinders metabolic pathways which convert substrates into desirable products, leading to (1) failure in synthesizing essential biochemical compounds; and/or (2) accumulation of substances that are toxic or could interfere with normal physiological function and may contribute to morbidity and mortality.

Individual cases of IEM are rare but collectively, IEM diseases are prevalent [1]. The cumulative incidence rate varies among countries from 1 in 784 live births in United Kingdom [1] to 1 in 9300 in Japan [2]. Ethnicity-related discrepancies by country is in part due to variation of IEM panels being used for screening, impeding direct comparison [3].With a greater understanding of the pathophysiology and the availability of emerging biochemical and molecular diagnostic tools, more types of IEM are being identified [4].

Depending on the pathogenesis and the metabolic pathway affected, classical IEM is grossly classified into different groups: amino acidemias, organic acidemias (OA), and fatty acid oxidation defects. Of the various types of IEM diseases, OA most frequently occur among severely ill children [5].

Although clinical presentations of OA involve multiple body systems, OA predominately affects the central nervous system. If OA is not treated, patients may develop irreversible brain damage, leading to mental retardation. Long-term management requires a low-protein-high-energy diet with amino acid supplements which are free from the problematic precursor amino acids. Response to treatment for OA is generally good, particularly among neonates before onset of symptoms [4,6]. As supported in multiple studies [7-9], early identification by screening and timely intervention significantly improves clinical outcomes.

In recent years, the use of tandem mass spectrometry (TMS) allows screening of multiple diseases from one test. Chace, et al. [10] demonstrated the use of TMS in IEM screening using dried blood spots (DBS). Confirmatory testing can be performed with analysis of plasma amino acids, plasma acylcarnitines and urine organic acids; and genetic diagnosis by DNA sequencing [3].

This screening strategy has multiple advantages. Firstly, TMS has high sensitivity (99%) and specificity (99.995%) for most IEM diseases [11-13]. Secondly, only a 0.3 ml whole blood sample is needed for the DBS card; this amount is comparatively small and attainable from neonates [12].

In addition, it has the potential of accommodating high-throughput environment for newborn screening, as it requires only 3 minutes to screen 30 diseases [11]. Furthermore, the cost of test reagents is low. Despite relatively high installation and setup costs; the incremental marginal cost was calculated to be about $10 USD per birth screen [12].

Newborn screening has been shown to be cost-effective in various studies [16]. These studies are specific to the local situation, in terms of disease of interest, disease epidemiology, healthcare cost, study perspective, and treatment and management models. These studies used various methodological approaches and implementation strategies, reported on a unique panel of diseases and disease incidence. Service delivery costs were obtained from the healthcare provider. Hence, newborn screening cost-effectiveness analyses may not be transferrable from one country or locality to another.

In Hong Kong, incidence for classical IEM was estimated to be 1 in 4,122 [17]. Universal newborn screening provided by Department of Health for genetic defects has been limited to G6PD deficiency and congenital hypothyroidism. The screening strategy in China (using TMS-based platform) has shown potential for adoption in Hong Kong and may guide development of higher neonatal screening standards. Lee, et al. [18] found that TMS-based expanded IEM screening to be cost effective for hyperphenylalaninemia in Hong Kong. Inclusion of OA in newborn screening requires economic justification. The cost-effectiveness of such programme in Hong Kong has yet to be addressed in scientific research papers. Hence, this study assessed the cost-effectiveness of additionally including OA to an existing TMS-based newborn hyperphenylalaninemia screening platform.

Materials and Methods

Perspective and setting

This study takes the perspective of a Hong Kong public healthcare provider. Only direct costs related to the screening programme and utilization of health care services: cost of confirmation test, consultation, and management costs are considered in this model. As TMS platform is already in place for hyperphenylalaninemia

screening, there is no installation and setup cost. Reagent cost for screening test is negligible for additionally include OA, due to the nature of the TMS-screening strategy (one test for screening multiple diseases). The monetary values in 2009 are used and a discount rate of 5% per year is applied for both costs and benefits [19].

Cases Based on a Local Inborn Errors of Metabolism Study

This study is based on a study previously conducted by Lee, et al. [17] to estimate the incidence and disease spectrum of classical IEM, including OA. Five years of laboratory records (2005 to 2009) were retrieved to identify IEM cases from three regional chemical pathology laboratories in Hospital Authority (HA) [17]. These cases were reviewed and confirmed by genetic analysis. Eventually, 43 IEM cases, of which 5 cases were classified as OA, met the inclusion criteria.

Incidence for classical IEM in Hong Kong was then estimated to be 1 in 4,122 [17]. The identified OA patients are followed up in this study. With the approval from Kowloon West Cluster Research Ethics Committee of the HA, and the Institutional Review Board, service utilization for these patients was retrospectively retrieved from the Clinical Management System. Five-year records of hospitalization, consultation, and imaging service were retrieved for utilization review and costing. Costs were based on "charges for non-eligible persons (NEP)" [20] of HA; average annual cost was subsequently calculated.

Decision tree model

A decision tree model was established to compare TMS-based screening versus no-screening strategy in the cohort of newborn babies in 2009. The model considered possible pathways and associated probabilities and outcomes (Figure 1).

For the screening group: for test-positive subjects, confirmation tests and genetic analysis were included to distinguish between true positive and false positive. Sensitivity and specificity of the confirmation tests were assumed to be 100% each. True positives were expected to be picked up for prompt treatment. It was assumed that a specialist out-patient visit was required quarterly for follow-up and prescription.
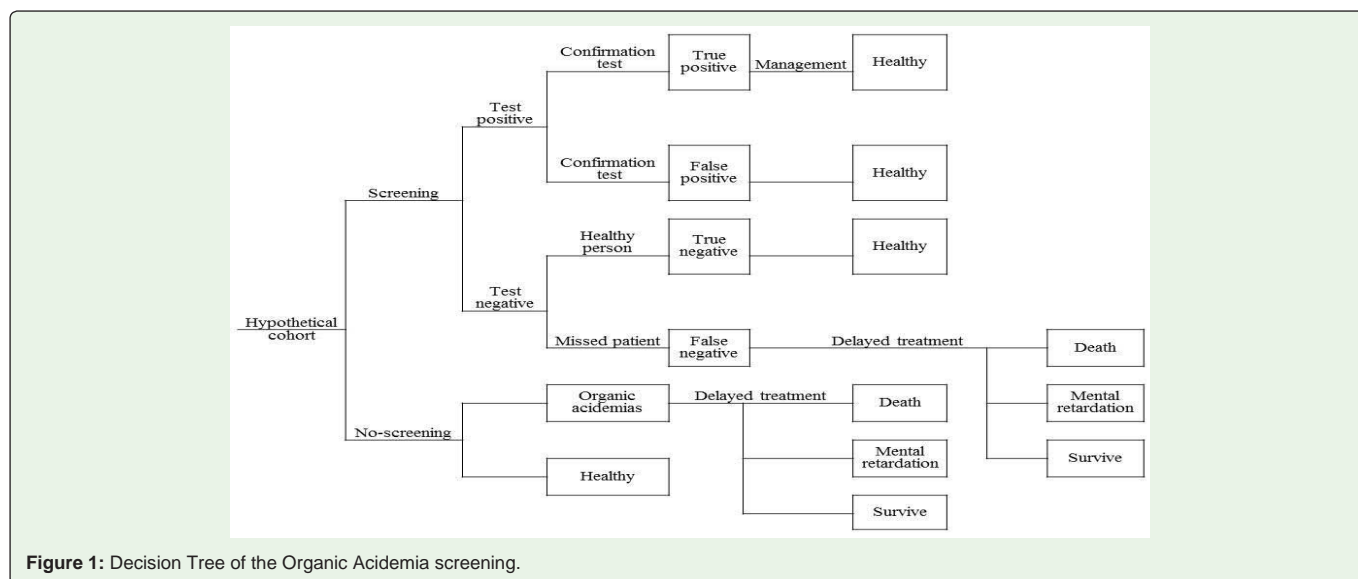

Figure 1: Decision Tree of the Organic Acidemia screening.

Table 1: Summary of major estimates used for calculation of outcomes and costs in the decision tree pathways.

Parameter	Estimates	References
Discount Rate	5%	[19]
Birth Cohort 2009		
- Cohort size	82,100	
- Life Expectancy	79.8 years	[21]
Disease Burden of Organic Acidemias		
- Incidence	1 in 35,534	[17]
- Mortality rate		
Early detection	0%	Assumption
Late detection:		
- Year 0 to Year 1	10.54%	[22]
- Year 1 to Year 2	2.79%	[22]
- Year 2 to Year 5	3.02%	[22]
- Year 5 to Year 15	1.44%	[22]
- Year 15 to Year 80	0.93%	[22]
- Probability of developing of mental retardation		
Early detection	0%	Assumption
Late detection		
- Year 1 to Year 2	8.64%	[22]
- Year 2 to Year 5	11.20%	[22]
- Year 5 to Year 15	6.80%	[22]
- Year 15 to Year 80	2.49%	[22]
Screening Test (Tandem Mass Spectrometry)		
- Sensitivity	99%	[3]
- Specificity	99.995%	[3]
Confirmation Test (Genetic Investigation)		
- Sensitivity	100%	Assumption
- Specificity	100%	Assumption
- Cost	HKD $20,100	Hospital Authority
Treatment for Organic Acidemias		
- Compliance to treatment	100%	Assumption

Screening test-negative subjects were either healthy (true negative) or missed OA (false negative). The latter would be identified when clinical symptoms arise.

For no screening group: OA patients were identified only when clinical symptoms arise. These types of patients, like missed OA, were regarded as having delayed treatment. Age-specific event probabilities were applied to these subjects to calculate the total number of life years lost and the total number of life years with mental retardation up to life expectancy. Life-time management cost was calculated as summation of average annual management cost up to life expectancy.

The cohort was assumed to be homogenous in terms of OA risk, complication rate and response to treatment, and was expected to undergo either population-wide TMS OA screening strategy or no screening. The compliance rate was assumed to be 100% with no drop-outs.

Given the severe nature of complications [10], the treatment compliance rate was assumed to be 100%. Medication use for any detected cases was assumed to be same across cases. Despite good response to treatment for OA among neonates [4,6], published data on treatment effectiveness is limited. Therefore, treatment effectiveness for avoiding mortality and/or mental retardation in early detected cases is both assumed to be 100%.

Estimates were obtained from published research on MEDLINE/PubMed, and from local sources. Rare diseases like OA are usually studied as case series and observational studies. Data quality was ensured by two criteria (1) applicability with the Hong Kong context: data from Hong Kong is preferred to China, then Asia and international; (2) reliability of data: sample size and length of the study.

Cost-effectiveness analysis

The primary outcome is the incremental cost-effectiveness ratio (ICER): ICER per life year gain (overall), and ICER per life year gain without mental retardation. It is calculated by the formula: [ICER = $\Delta C / \Delta E$], where, ΔC = the difference in total cost between screening and no screening for OA; and, ΔE = the difference in effectiveness [(i) cost per life-year gained (overall); (ii) cost-per life year gained without mental retardation]

The ICER threshold is set at per capita gross domestic product (GDP) of 2009, which is HK$233,239 per life-year gained [22].The World Health Organization [19] recommends that, a programme is (1) highly cost-effective if ICER is less than GDP per capita; (2) cost-effective if ICER falls between one and three times GDP per capita; or (3) not cost-effective if ICER is greater than three times GDP per capita.

Results

Use of estimates

The major estimates for calculation of life years and costs in different decision tree pathways, extracted from published search on MEDLINE/PubMed and from local sources, are summarized in Table 1.

Table 2: Cost involved in screening group (stratified).

Cost (HK$)	OA subjects		Healthy Subjects		
	True Positive	False Negative	True Negative	False Positive	
Confirmation	20,100	/	/	20,100	
Management	86,547+	/*	/	/	
Cost per case	106,647	/*	/	20,100	
Number of cases	2.29	/*	82,093.58	4.10	
Total per group (HK$)	243,939+	99,552*+	0	82,508	
				Subtotal:	426,000

+Discounted at 5% yearly discount rate.

*Management cost for false negative group is separately calculated.

NB: Cost per case = cost of confirmation + cost of management

Total cost per group = cost per case × number of cases

No screening group

Disease outcome: In the no screening group, the expected numbers of OA outcomes is 2.31(out of 82,000). This was derived by incidence rate (0.0028%). From age-specific event probabilities, number of discounted life years lost is 7.40 while discounted number of life years with mental retardation development is 9.79.

Cost: Service utilization for the 5 OA cases identified in a local IEM study [17] was retrospectively retrieved. Utilization data including number of days of in-patient stays, number of out-patient consultation, and number of imaging service orders were retrieved. Average annual management cost per person based on NEP charges was HK$261,609. Using annual discount rate of 5%, the life time cost of the no screening group was expected to be HK$9,955,222.

Screening group

Disease outcome: From the incidence of OA, the expected number of OA cases is 2.31. Test sensitivity (true positive rate) further divide the cases into expected number of true positives (TP) category (n = 2.29), and false negative (FN) category (n = 0.02). Likewise, from the specificity (true negative rate), the expected number of true negatives (TN) can be calculated (n = 82093.58), and the remaining cases belong to false positive (FP) cases (n = 4.10).

Assuming that all true positives (TP) cases are treated in time, i.e. no OA related death or mental retardation; and that all FN are incorrectly identified, the expected total number of life years lost is 0.07 (discounted), and the expected number of life years with mental retardation is 0.10 (discounted) for screening group.

Cost: For TP cases, it is assumed that each case would have consultation quarterly. The life-time discounted management cost for each case is HK$86,547. For FN cases, the expected life-time management cost is the sum of the discounted cost of each life year up to their expected life years: HK$99,552.Costs for each group is calculated in Table 2, adding up to the group total of HK$426,000.

Incremental cost-effectiveness ratio: Incremental cost is then calculated to be -HK$9,529,223. Discounted benefits from screening were 7.33 life years saved, and 9.69 life years without mental retardation. Hence, the ICER per life year gained is -HK$1,300,177 and the ICER per life year gained without mental retardation is -HK$983,333. As both figures fall below the cost-effectiveness

threshold, population-wide TMS screening strategy is economically justified.

Discussion

Cost-effectiveness analysis

Inclusion of OA in newborn screening is found to be cost-effective. This finding is comparable to other existing IEM cost-effectiveness analysis. A Canadian study [23] also assessed the ICER per life year gain of expanding TMS-based newborn screening, from Phenylketonuria alone to 21 IEM diseases, including OA. In their study, the healthcare cost was also considered up to 80 of age, which is similar to our study. They also concluded that TMS is cost-effective when screening for a wider variety diseases.

Most economic analyses for TMS-based screening strategy for OA also target other IEM diseases. The profile and choice of control group varies among studies. Schoen et al. [15] compared life-time treatment cost and outcomes for expanded TMS screening covering more than 5 IEM diseases (including two types of OA), with those of no screening, and estimated the cost per Quality-Adjusted Life Year (QALY) saved to be HK$45,451. (USD$5,827) Another study [14] considering life-time cost per QALY was estimated to be HK$90,168 (USD$11,560) expanded TMS-based screening from 7 disorders to 27 disorders. In Wisconsin, the cost per QALY was calculated as HK$118,966 (USD$15,252) for screening programme expanded from medium-chain acyl-coA dehydrogenase diseases alone to include OA and fatty acid oxidation disorders [24].

All ICERs calculated among studies reached their respective cost-effectiveness thresholds. Although it is apparent that cost-effectiveness analysis from other localities may not be directly applicable to Hong Kong. Some variation is likely due to different evaluation approaches or a more contextualized environment.

Limitation of the study

This study was highly contextualized for practical purpose. It considered the occasion of additionally including OA screening to an existing TMS-based hyperphenylalaninemia screening platform. With low cost margin for screening procedure, costs difference between two groups mainly reflects the impact of early OA identification.

This study is heavily based on another local study [17], in which OA subjects were identified and followed-up. Subjects were all children, so their service utilization record was limited. Due to limited data on the management cost of OA, annual cost was averaged from 5-year period and was assumed to be uniform across the life time. Changes in annual management cost in OA subjects were not accounted for in this study.

In the case of OA, the long-term cost of morbidity may even be higher. The Centers for Disease Control and Prevention in United States estimated the average lifetime cost for persons with mental retardation to be USD$1,014,000, at 3% discounted rate for future costs [25]. Among cost categories, direct medical costs only account for 13.8% of the total costs. Productivity loss to society contributes over 75% of the total life-time cost [25].There is inadequate data to calculate social and long-term care cost in Hong Kong. For the current model, from the public healthcare provider perspective and the length of study period, this large portion of unrealized societal cost is not considered.

Another major challenge for researches of rare diseases is the lack of data. Ideally, estimates of disease costs, incidence, and outcomes would be derived from a single cohort by following them up throughout their lifetime. Nevertheless, such study is rarely feasible in practice. Most publications about rare diseases are presented as case reports, case series or observational studies, in which only descriptive figures recorded from observed subjects.

For practical reasons, IEM studies often estimate incidence and disease outcomes by observation and projection. This may underestimate the incidence as cases are picked up mostly by clinical suspicion. Such strategy misses asymptomatic, mild, atypical or late-onset cases. As demonstrated by the experience of TMS-based screening in Australia [26], the prevalence of IEM, excluding phenylketonuria, was adjusted from 8.6-9.5 per 100,000 births to 15.7 per 100,000 upon implementation of screening. The effect of increased detection of asymptomatic or mild cases was not addressed in the study, but this is of significant importance to the screening programme.

This study considers OA as a group of diseases. As OA is rare and longitudinal studies of OA patients are even rarer, the probabilities of outcomes were obtained based on a relatively small number of published observations. The diversity of clinical presentation and level of severity were yet to be addressed. The outcomes of OA were also simplified in the model, in which only two major adverse events were considered: mortality and development of mental retardation. Other outcomes, for example, seizure or acute symptoms were not considered. Therefore, the benefit from screening may have been underestimated in this model.

There is also ambiguity about effectiveness of treatment. Although it has been known that OA subjects have good response to treatment [6], details and statistics on treatment efficacy are yet to be published. The period of onset during which treatment improve outcome has yet to be studied, hence was not incorporated in the model.

Future studies

This study is, to the understanding of the authors, the first economic evaluation of TMS-based platform for newborn OA screening. This study has solely considered OA. In future studies, cost-effectiveness can be calculated for more than one disease group; and incorporate existing G6PD deficiency and congenital hypothyroidism screening programmes in Hong Kong.

Cipriano, et al [23] performed a cost-effectiveness analysis on TMS-based newborn screening for up to 21 IEM diseases. By step-wise addition of diseases to the existing screening program, they calculated the ICER and determined the optimal condition in which the greatest number of diseases that could be identified. It is believed that this study is potential to be a pilot model for a bigger project to have a better picture of overall cost-effectiveness of TMS-based screening strategy; and to establish the optimal framework of newborn IEM screening in Hong Kong.

Conclusion

Cost-effectiveness of newborn screening for OA was analysed using a decision tree with a 5-year cohort. With screening, ICER per life year gained and per life year gained without mental retardation are -HK$1,300,177 and -HK$983,333 respectively compared with no screening strategy, which are both less than GDP per capita. Population-wide screening is shown to be highly economically favourable to avoid mortality and mental retardation from a public healthcare provider's perspective.

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Citation: Ng HL, Mak CM and Johnston JM. Cost-Effectiveness Analysis of Newborn Screening for Organic Acidemias in Hong Kong. SM J Clin Pathol. 2016;1(1):1001.

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Citation: Ng HL, Mak CM and Johnston JM. Cost-Effectiveness Analysis of Newborn Screening for Organic Acidemias in Hong Kong. SM J Clin Pathol. 2016;1(1):1001.

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