

## Issues on Universal Screening for Galactosemia

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### Abstract

Galactosemia is an inborn error of galactose metabolism, caused by an abnormality in the conversion of galactose and uridine diphosphoglucose to glucose-1-phosphate and uridine diphosphogalactose through the action of 3 sequential enzymes: galactokinase (GALK), galactose-1-phosphate uridylyltransferase (GALT), and uridine phosphogalactose 4-epimerase (GALE). The advent of newborn screening brought hope with early diagnosis and prompt treatment. Newborn screening advocates have pushed for inclusion of galactosemia in the newborn screening panel. However, reports of complications despite early treatment have questioned the merits of universal screening. This paper presents issues in favour and against universal newborn screening for galactosemia.

Ann Acad Med Singapore 2008;37(Suppl 3):39-41

**Keywords:** Galactokinase (GALK), Galactose-1-phosphate uridylyltransferase (GALT), Uridine phosphogalactose 4-epimerase (GALE)

### Introduction

Galactosemia is an inborn error of galactose metabolism, caused by an abnormality in 3 sequential enzymes involved in galactose metabolism namely: galactokinase (GALK), galactose-1-phosphate uridylyltransferase (GALT), and uridine diphosphate galactose 4-epimerase (GALE). These enzymes allow the subsequent conversion of galactose into galactose-1-phosphate (GALK), of galactose-1-phosphate and uridine diphosphate-glucose (UDP-glucose) into glucose 1-phosphate and UDP-galactose (GALT), and the interconversion of UDP-glucose and UDP-galactose (GALE).<sup>1</sup> The biochemical consequences of this genetic disorder are abnormally high concentrations of galactose and its metabolites in body tissues and fluids. It is a serious disorder with significant mortality/morbidity should its diagnosis be missed, with mortality understood to be preventable by newborn screening.<sup>2</sup>

There are 3 types of galactosemia based on the deficient enzyme: GALT deficiency (type I), GALK deficiency (type II), and GALE deficiency (type III).<sup>2</sup> Type I (classical galactosemia), the most common type and most severe form, may lead to life threatening complications if not treated promptly with a low galactose diet within a few days after birth.<sup>3</sup> In the first few weeks of life, it may present as poor feeding and weight loss, vomiting, diarrhoea, lethargy

and hypotonia, signs and symptoms of liver dysfunction, bleeding tendencies, cataracts and septicemia.<sup>2</sup> Affected patients are also at increased risk of delayed development, speech difficulties and mental retardation and female patients may experience reproductive problems caused by ovarian failure.<sup>3</sup> The main clinical feature of Type II is cataracts that are usually bilateral and detectable in the early weeks of life and even at birth and in some reports in foetus at 20 weeks' gestation. Type III galactosemia, the most rare type, have an enzyme defect principally in their erythrocytes and have normal growth and development<sup>2</sup> but some patients may present with cataracts, delayed growth and development, mental retardation, liver disease and kidney problems.<sup>3</sup>

Frequency depends on the genetic mix of the population with an overall incidence of 1 in 30,000 to 60,000 for classic galactosemia; less than 1 in 100,000 for type II, and type III appears to be very rare.<sup>3</sup> The incidence of complete absence of epimerase activity was found to be 1:23,000 in Japan.<sup>4</sup>

### Issues in Favour of Universal Screening

Newborn screening, if performed in the first 1 to 2 days of life, provides an opportunity for diagnosis either before or just as the infant presents with symptoms. This early

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diagnosis can lead to an early diet shift to a soy based formula that reduces permanent damage from the immediate impact of high doses of galactose, such as life threatening liver failure and its complication, by cutting short the duration of exposure to the offending metabolites. In a 10 year period, statistical mortality was reportedly reduced more than ten-fold (from 4.6 to 0.3) in galactosemia children as a result of newborn screening.<sup>5</sup>

Some infants may avoid brain damage from the early high doses of galactose, with the result of a normal IQ outcome with no ataxia. If a child with a severe IQ loss, yielding an IQ of 60, does not die, the galactosemia model predicts US\$1,022,000 in additional non-medical and indirect costs.<sup>6</sup> Cost of care of a child with mental retardation may reach up to US\$1,014,000.<sup>7</sup>

Newborn screening is expected to reduce the cost of clinical identification. Currently, most galactosemic infants are hospitalised in neonatal intensive care units with an expected reduced cost per stay of US\$12,000 per child.<sup>5</sup>

Early screening is a cost effective means of reducing infant death. It is a cost-saving intervention which results in both better health outcomes and less total spending, including medical care and other direct costs of care, as well as costs associated with the intervention. From the societal perspective, economic benefits include averted indirect costs or productivity losses from premature mortality or disability.<sup>8</sup>

Costs for screening of galactosemia alone may outweigh its benefits but the addition of galactosemia on an existing newborn screening infrastructure for congenital hypothyroidism, for example, results in net benefits of US\$4.58M with a benefit:cost ratio of 2.0 (Table 1).<sup>9,10</sup>

Despite arguments that the costs of screening for galactosemia alone or in certain combinations with other conditions outweigh the benefits, screening is expected to reduce the cost of clinical identification. Early commencement of treatment does not necessarily prevent complications like neurological defects especially affecting language and ovarian failure,<sup>11</sup> but early diagnosis and intervention can limit early mortality and morbidity from

the disease, minimise the magnitude or severity of complications, help prevent disability, and improve health related quality of life. According to cost calculations from the Washington State newborn screening programme,<sup>5</sup> minor neural damage that reduces IQ ultimately reduces the function of the individual in all areas of life. Without retardation, loss of IQ generates a loss of productivity, which was valued at US\$14,500 per IQ point (year 2000 dollars). Thus, even when the difference in IQ is as small as a few IQ points, a financial loss is incurred for the individual and society. Likewise, they calculate that ovarian failure will require hormone replacement therapy at a cost of US\$360 per year and will mean that the girl will be unable to bear children. A cost for the latter was assigned at US\$21,000. Cataract surgery costs were also estimated at US\$3500 by the Washington report. In the long run, therefore, funding comprehensive newborn screening programmes may save money for society.

### Issues Against Universal Screening

To understand the economics of universal screening for this disease, it is important to decipher the expenditure and gains within the concept of the screening system. On the one hand, expenditure is incurred right from the start of planning and organisation, when stakeholders have to be informed, the strategy defined and consensus attained. Then, the process of educating of professionals and the public starts, together with the implementation of the whole screening system, including issues of testing, quality assurance, counselling and patient tracking/confirmation. For confirmed cases of galactosemia,<sup>5</sup> the costs for patient monitoring and subsequent management must be considered, including training families for food selection and treatment if the child eats inappropriately. If galactosemia screening is added to a cord blood screening programme, then there is a significant cost to change the programme to one of blood collection on filter paper, since cord specimens are unsatisfactory for this testing. These costs include such items as filter paper card development and distribution, training in collection technique, specimen transport, and assignment of collection responsibilities.

Table 1. Cost-benefit Analysis of GAL and in Combination with Other Disorders<sup>9</sup>

Condition(s)	Total costs*	Total benefits*	Net benefits*	Benefit:Cost ratio
Gal	\$ 1.12 M	\$ 0.21 M	\$ (0.9 M)	(0.2)
Gal + CH	\$ 4.80 M	\$ 9.37 M	\$ 4.58 M	2.0
Gal + CH + CAH	\$ 10.91 M	\$ 13.12 M	\$ 2.22 M	1.2
Gal + CH + CAH + PKU	\$ 23.96 M	\$ 19.68 M	\$ (4.27 M)	(0.8)
Gal + CH + CAH + G6PD	\$ 15.89 M	\$ 33.80 M	\$ 17.91 M	2.1
Gal + CH + CAH + G6PD + PKU	\$ 28.94 M	\$ 40.36 M	\$ 11.42 M	1.4

\* computations in US dollars

The expenditure arm of the equation does not stop at that point. Long-term medical outcome costs must also be included. That is, despite early intervention, some galactosemia patients may still suffer from long-term sequelae in the form of developmental delay and cataracts, and 90% of surviving females experience ovarian failure which requires hormonal replacement. There are also costs associated with care giving since caring for a galactosemia child may result in expenses to the family in terms of medical visits, time away from work, etc. Additionally, activities such as food sorting itself can be a time consuming and costly process.

In the case of screening for galactosemia, it should be noted that the incidence of the disease may vary significantly from population to population. For example, the classical type of galactosemia has been found to be low among the Chinese. In Taiwan, it was found to be 1 in 419,286 (personal communication – Hsiao KJ). Additionally, the availability of clinical expertise varies in different countries. The problem with cost-benefit analyses in galactosemia screening is that there are few published reports. Costing reports that are published must make assumptions based on available data relating to incidence, sensitivity and specificity of tests, treatment accessibility, cost and compliance, the value of improved or saved lives and costs for lost productivity. All these considerations vary in different populations, making cost analyses difficult to compare.

In a recent US cost-utility analysis of many newborn screening strategies,<sup>12</sup> the cost-effectiveness of each component of a multi-test newborn screening programme was studied and one of the diseases emphasised was galactosemia. In this study, a detailed economical decision model was used, drawing on sources that included cohort studies, government reports, secondary analyses and others. Using this model, data were extracted to ascertain the probabilities of sequelae for each of the conditions screened, their quality-adjusted survival rates, estimated prevalence, costs for treatment, life expectancy as a result of disability and sensitivity and specificity of screening tests for individual conditions. In addition, the quality-adjusted life years (QALYs), discounted costs and incremental cost-effectiveness ratios were measured. This study found that the incremental cost for adding a screening condition to an ongoing filter paper newborn screening system was negative for all diseases except galactosemia and congenital adrenal hyperplasia. By definition, a negative incremental cost means that screening for these 2 conditions would not save

money over not screening. For galactosemia screening, it was estimated that the cost was US\$94,000 for each QALY.

## Conclusions

It is apparent that many issues have to be considered in implementing a newborn screening programme for galactosemia. The tools and results of cost-effectiveness and cost-utility analyses are important considerations in this process, as well as the impact of societal costs and considerations that may vary among different countries. As a result, each healthcare system must evaluate its priorities according to its own calculations of expenditures, gains and other social factors.

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Financial disclosure: The author/s declare that they have no relevant financial interest in this manuscript.