

# BEYOND SCREENING: CHALLENGES IN MEASURING OUTCOMES

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**Abstract.** There are several important messages for pediatricians concerned with what happens to patients after identification through newborn screening. Particularly important in many of the disorders are the developmental aspects of outcome. There are certain basic assumptions that are essential in improving developmental outcome as a result of newborn screening: 1) newborn screening leads to early case identification; 2) early diagnosis and intervention generally enhance developmental outcome; 3) sustained compliance is crucial for better developmental outcome; 4) increased awareness of other factors improves developmental outcome; 5) periodic developmental monitoring ensures quality follow-up. Even though the Philippine Newborn Screening Program is young, there are already experiences in these areas to draw from. Likewise, there are strategies that can be employed to overcome the challenges in a developing country, which can lead to better follow-up, characterized by desirable critical features of availability, accessibility, affordability, accuracy and adequacy.

## INTRODUCTION

*"So long as little children are allowed to suffer, there is no true love in this world."*

*- Isadora Duncan (1878-1927)*

As the tragedy of September 11, 2001 unfolded claiming thousands of lives in New York City, the Association of Pediatric Societies of the Southeast Asian Region (APSSEAR) unanimously passed a resolution to save lives through the promotion of newborn screening programs at its meeting in Beijing (Santos Ocampo, 2002) (see Appendix A). Newborn screening was first established in the United States in the early 1960s. Since then, other countries in the Asia Pacific region including the Philippines, have adopted newborn screening to identify the thousands of children with inborn errors of metabolism throughout the Region and to institute

prompt interventions. The pediatrician has a key role to play in ensuring that the outcomes of early screening and intervention are maximized to the benefit of the child and the family. While the pediatrician plays a major role in ensuring the health and well-being of a child identified with one of the screening disorders, developmental outcome must be considered one of the major components in evaluating the impact of any newborn screening program.

## BASIC ASSUMPTIONS AFFECTING OUTCOME

### Newborn screening leads to early case identification

By definition, neonatal screening leads to early case identification. The Newborn Screening Program of the Philippines, like those in other developing countries, is still in its infancy. It relies heavily on foreign experiences

Table 1. Results of screening 172,509 newborns in the Philippine Newborn Screening Project (August 2001).

Disease	(+) Screened	Confirmed	False (+)	Recalled	Expired	Incidence
CH	229	47	144	33	6	1: 3,670
CAH	112	21	58	6	28	1: 8,215
PKU	67	4	34	13	16	1:43,127
Gal	16	2	13	1	-	1:86,255
Hcy	6	-	4	1	1	0
Total	430	74	253	54	51	1: 2,331

in developing its framework. Program evaluation is essential to improving and strengthening the program. The Philippine program is primarily the result of efforts of one of the co-authors (CDP) who has worked to develop the program over the past 5 years with minimal resources.

### **Early diagnosis and intervention generally enhance developmental outcome**

Several important studies have focused on the developmental outcome of children identified through newborn screening. Although children with congenital hypothyroidism (CH), congenital adrenal hyperplasia (CAH), phenylketonuria (PKU) and galactosemia (GAL) have occasionally been reported to have developmental difficulties, early intervention resulting from early diagnosis has shown marked improvements in developmental outcome. Sato and Nimi, for example, reported improved prognosis in a study of IQ of 151 patients with CH detected through neonatal screening when compared to children detected clinically before screening began (Sato and Nimi, 1994). Rovet and Erlich have found, in a study of 83 CH patients (almost all with IQ scores in the normal range), that the critical period of thyroid hormone effects on verbal and memory skills appears to be the first two months of life (Rovet and Erlich, 2000). A study by Waggoner showed a greater incidence of developmental delay among galactosemic children who were not treated until after 2 months of age (Waggoner *et al*, 1990). And, likewise, Koch and others have concluded that prompt dietary revisions after early detection of PKU prevent mental retardation and neurodegenerative effects (Koch, 1984).

### **Sustained compliance is crucial for better developmental outcome**

Several studies, including our own observations, have documented the need for periodic developmental assessment as an essential component of newborn screening. Some studies have demonstrated developmental delays and behavioral problems in children despite early diagnosis and intervention. Slight motor delays and difficulties in educational achievement in late childhood were seen on follow-up in children with congenital hypothyroidism studied in Canada (Rovet and Erlich, 2000). On the other hand, others have demonstrated that early treatment and follow-up with high initial doses of medications lead to normal mental development (Bongers-Schokking *et al*, 2002). In the galactosemia patients studied by Waggoner, despite good dietary compliance, 45% of 177 cases at least 6 years

old were developmentally delayed (Waggoner *et al*, 1990). In a younger age group, speech problems with motor coordination, gait, balance, fine motor tremors and ataxia were also seen. Visual perception disturbances and intelligence declining with age have also been observed in some galactosemia patients (Schweitzer *et al*, 1993). Neurological impairment and deviant behavior has also been shown in PKU when phenylalanine levels are not controlled (Smith *et al*, 1998) and PKU children with 'normal' intelligence have been shown, on occasion, to have linguistic delays (Melnick *et al*, 1981).

### **Increased awareness of other factors improves developmental outcome**

The factors that may affect developmental outcome despite early diagnosis and treatment are primarily the prenatal onset and severity of the metabolic condition, as well as therapeutic and dietary difficulties in management. Several have demonstrated that long term outcome in congenital hypothyroidism is determined by a variety of prenatal and postnatal factors (Heyerdahl *et al*, 1991; Dussault, 1994; Rovet and Erlich, 1995). It has also been suggested that some effects of insufficient thyroid hormone early in development may not be reversible even with early detection and treatment, while other effects may be ameliorated by careful monitoring and control of concurrent thyroid hormone levels (Rovet and Erlich, 1995). Others have also demonstrated that the developmental outcome of children with severe congenital hypothyroidism treated earlier with higher initial doses of levothyroxine is now indistinguishable from that of infants with the moderate form of the disease who were used as controls (Glorieux *et al*, 1985; 1992; Dubuis *et al*, 1996). Associations between severity of neonatal hypothyroidism and significantly lower neurological scores and moderate to severe language defects in older children have also been reviewed (Bargagna *et al*, 1999) and socio-economic class has also been noted as a determining outcome factor for some children. In a 1984 study, Hulse also demonstrated that time of diagnosis and socio-economic class were major influences on IQ in CH patients (Hulse, 1984). Similarly, Sato and Nimi concluded that even though there was slight developmental delay in screened patients related to signs of prenatal hypothyroidism and treatment during the first two years, neonatal screening contributed to improved mental prognosis in CH patients (Sato and Nimi, 1994).

In PKU studies, behavioral disturbances and neurologic impairment have been attributed primarily to the burdens of a difficult diet and problems in fully controlling the metabolic abnormality (Smith and Beasley, 1989). They also attributed some problems to residual

neurologic damage. In reviewing PKU studies, Berenbaum also noted that elevations of phenylalanine early in life appear to produce irreversible damage to the nervous system whereas ongoing elevations seem to produce possibly reversible effects on abilities dependent on the frontal lobe (Berenbaum, 1999). Likewise, concurrent phenylalanine concentrations have been shown to affect neuropsychological performance (Brunner *et al*, 1983).

In studies with galactosemia patients, it is theorized that several of the clinical abnormalities may have a prenatal origin because the metabolic disturbance is expressed in the galactosemic fetus (Holton and Leonard, 1994). There is also the possibility of some damage occurring postnatally since blood and urine concentration of galactose metabolites remain slightly raised despite a galactose-restricted diet. Chronic intoxication with galactose metabolites has also been noted as a cause of unsatisfactory outcome in some children (Schweitzer *et al*, 1993).

The importance of prenatal androgens on gender role development in CAH has been noted and studies of patients identified with CAH through newborn screening are providing more information (Berenbaum and Therrell, 1994). Development of behavior typical of males by female subjects has been theorized to result from prenatal androgen exposure. Studies have now confirmed that behavioral masculinization in girls with CAH results from high levels of androgens during fetal development and not postnatally (Berenbaum *et al*, 2000).

#### **Periodic developmental monitoring ensures quality follow-up**

To ensure quality follow-up, the imperative for periodic developmental monitoring cannot be overemphasized. Every program should include adequate provisions for periodic developmental monitoring and strategies used to advocate for newborn screening should emphasize the importance of follow-up and outcome monitoring. The public must not be left with the erroneous impression that screening is sufficient to save babies and subsequent care is unnecessary or of minimal concern. Developmental and behavioral assessments serve as important evaluation guides to assist physicians in adjusting medication dosages and in modifying management approaches. Program protocols for follow-up should be monitored for relevance, appropriateness, and effectiveness. Typically, the barriers to good follow-up are availability of evaluation tools and trained professionals, cultural appropriateness of the evaluation tools and protocols,

and time available for administering follow-up testing. It is essential that these barriers be overcome if the overall newborn screening process is to be successful (where success is measured by quality of patient outcome).

#### **LOCAL EXPERIENCES**

In the Philippine Newborn Screening Program, 22 patients identified and confirmed with CAH, CH, PKU or GAL were assessed using the Denver Developmental Screening II assessment tool (De Guzman *et al*, 2001). These patients were tested at various times from age 0.3 yrs to 4.9 yrs and yielded normal results in 12 children, while 8 were suspect. The fact that not all of the children tested were normal, emphasizes the need for developmental surveillance of patients who are subsequently confirmed and treated as a result of newborn screening. In cases where developmental milestones are missed, treatment strategies should be adjusted. It is important that developmental screening tools are available that can be utilized by general pediatricians, and pediatricians should be aware of their availability and the correct methods of utilization, result interpretation and need for adjustment of patient management plans based on testing results.

#### **CHALLENGES**

##### **Identification of the challenges**

The literature review presented here coupled with testing results in the Philippine Newborn Screening Program have identified a number of impediments to effective follow-up of children confirmed with CH, CAH, GAL, and PKU as a result of newborn screening. Most noticeable is the absence of regular developmental follow-up by competent developmental health professionals. This absence may result for a number of reasons, not the least of which is adequate finances. The availability of simple developmental screening procedures and competent specialists able to administer testing are the best deterrents to these difficulties.

Challenges to quality follow-up may be summarized by the following five A's:

- Awareness (of parents) of the importance of follow-up after disorder identification.
- Availability of competent specialists, e.g. developmentalists, endocrinologists, etc. and simple, brief validated testing instruments.
- Accessibility of competent testing specialists and laboratory facilities for ongoing monitoring.
- Accuracy of data from assessment procedures (*Quality Assurance*).

- *Affordability* of follow-up including adequacy of funds for medicines, tests, procedures and consultations.

### Addressing the challenges

Four decades of newborn screening have provided a wealth of studies on patient outcome, most of them, long term. They deal not only with physical and metabolic effects of the conditions detected, but more importantly, with the developmental outcome of the affected children. Despite differences in materials and methods used, the overriding message is the same – ***early diagnosis and early treatment lead to better patient outcome***. Numerous children are detected, treated, and saved from a lifetime of mental retardation each day from international efforts in newborn screening. Nevertheless, outcome must continually be monitored and outcomes reported if we are to improve our efforts and effectiveness.

Some strategies that should be included in newborn screening program planning beyond the actual screening and follow-up systems include:

- Advocacy, utilizing the same effective campaigns to encourage initial newborn screening to ensure that parents are aware of the urgent need for follow-up.
  - Formation of parent support groups.
- Government support, e.g. the issuance of favorable policies on the nationwide implementation of newborn screening such as AOI-As, 2000 of the Department of Health and funding through national health insurance for continued care of babies with positive results
- Involvement of non-governmental organizations.
  - Donations from business and civic organizations
- Enlistment of all health professionals as advocates. [Note: As an example, please see the *Resolution of the Association of Pediatric Societies of the Southeast Asian Region (APSEEAR)* in Appendix A].
- Development of simple, culturally relevant and non time-consuming tools for assessment.
- Inclusion of follow-up of patients as part of routine child health programs, e.g. Early Childhood Development by UNICEF.
- Training of health professionals for awareness and competencies. (In the Philippine setting, this has been incorporated in the Undergraduate Pediatric Curriculum).
- Legislation for mandatory neonatal screening

whenever and wherever necessary.

### SUMMARY

The basic assumptions underlying all successful newborn screening programs have been discussed along with references to studies pertinent to these assumptions. The basic assumptions are listed below in review:

- Newborn screening leads to early case identification.
- Early diagnosis and intervention enhances developmental outcome.
- Sustained compliance is crucial for better developmental outcome.
- Increased awareness of other factors improves developmental outcome.
- Periodic developmental monitoring ensures quality follow-up.

In order to increase the number of babies with improved morbidity and mortality as a result of newborn screening, follow-up activities must be continually monitored and program adjustments made. This is best accomplished by integrated actions throughout the community. The spirit of community should prevail in all child health professionals.

*“Without the human community, one single human being cannot survive.”*

- *The Dalai Lama, b. 1935*

### REFERENCES

- Bargagna S, Dionetti D, Pinchera A, Marcheschi M, Montanelli L, Presciuttini S, Chiovato L. School attainments in children with congenital hypothyroidism detected by neonatal screening and treated early in life. *Eur J Endocrinol* 1999;140:407-13.
- Berenbaum SA. Neuropsychological follow-up in neonatal screening: issues, methods and findings. *Acta Paediatr Suppl* 1999; 88:83-7.
- Berenbaum SA, Duck SC and Brynk K. Behavioral effects of prenatal versus postnatal androgen excess in children with 21-hydroxylase-deficient congenital adrenal hyperplasia. *J Clin Endocr Metab* 2000; 85: 727-33.
- Berenbaum SA, Therrell BL. Behavioral and follow-up studies of congenital adrenal hyperoplasia. In: Takasugi N, Naruse H, eds. *New trends in neonatal screening*. Sapporo: Hokkaido University Press, 1994:125-7.

- Bongers- Schokking J, Koot H Wiersma D, Verkerk PH, de Muinck Keizer-Schroma SM. Influence of timing and dose of thyroid hormone replacement on development in infants with congenital hypothyroidism. *J Pediatrics* 2002; 36:292-7.
- Brunner RL, Jordan MK, Berry HK. Early-treated phenylketonuria: Neuropsychologic consequences. *J Pediatr* 1983; 102:831.
- De Guzman RPR, Santos Ocampo PD, Padilla CD, Cutiongco EMC, Cavan BCV, Malijan MCB, Sia JM, Villarin H. Denver II screening outcome of Filipino children with metabolic disorders identified through newborn screening. [Abstract]. 4th Asia Pacific Regional Meeting of the International Society for Neonatal Screening and the 1<sup>st</sup> Annual Convention of the Newborn Screening Society of the Philippines Inc, Manila, Philippines, 17-19 October 2001.
- Dubuis JM, Glorieux J, Richer F, Deal C, Dussault J, Van Vliet G. Outcome of severe congenital hypothyroidism – closing the developmental gap with early high dose lebothyroxione treatment. *J Clin Endocrinol Metab* 1996; 81: 222-7.
- Dussault JH. Treatment and long term prognosis of congenital hypothyroid newborns detected by screening programs in North America. In: Takasugi N, Naruse H, eds. New trends in neonatal screening. Sapporo: Hokkaido University Press, 1994; 201-4.
- Glorieux J, Dussault JH, Morissette J, Desjardins J, Letarte J, Guyda H. Follow-up at ages 5 and 7 years on mental development in children with hypothyroidism detected by Quebec Screening Program. *J Pediatr* 1985 107:913-5.
- Glorieux J, Dussault JH, Van Vliet G. Intellectual development at age 12 years of children with congenital hypothyroidism diagnosed by neonatal screening. *J Pediatr* 1992; 121:581-4.
- Heyerdahl S, Kase BF, Lie SO. Intellectual development in children with congenital hypothyroidism in relation to recommended thyroxine treatment. *J Pediatr* 1991; 118:850-7.
- Holton JB, Leonard JV. Clouds still gathering over galactosemia (Commentary). *Lancet* 1994; 344:1242-43.
- Hulse JA . Outcome for congenital hypothyroidism. *Arch Dis Child* 1984; 59:23-30.
- Koch R, Azen C, Friedman EG, Williamson ML, Friedman EG, Williamson ML. Paired comparisons between early treated phenylketonuria children and their matched sibling controls on intellectual and school achievement test results at eight years of age. *J Inher Metab Dis* 1984; 7:86-90.
- Melnick CR, Michals KK, Matalon R. Linguistic development of children with PKU and normal intelligence. *J Pediatr*; 19:269-72.
- Rovet JF, Ehrlich RM. Long-term effects of L-thyroxine therapy for congenital hypothyroidism. *J Pediatr* 1995; 126:380-6.
- Rovet JF, Ehrlich R. Psychoeducational outcome in children with early-treated congenital hypothyroidism. *Pediatrics* 2000; 105 Part 1 of 2: 515-22
- Santos Ocampo PD. Resolution on the promotion of newborn screening. *Bull Assoc Pediatr Soc Southeast Asian Region* 2002; 31:5.
- Sato H, Niimi H. Mental development in children with congenital hypothyroidism detected by neonatal screening in Japan. In: Takasugi N, Naruse H, eds. New trends in neonatal screening. Sapporo: Hokkaido University Press, 1994: 205-8.
- Schweitzer S, Shin Y, Jacobs C, Brodehl J. Long-term outcome in 134 patients with galactosemia. *Eur J Pediatr* 1993; 152:36-43.
- Smith I, Beasley M. Intelligence and behavior in children with early treated phenylketonuria. *Eur J Clin Nutr* 1989; 43(suppl):1-5.
- Smith I, Beasley MG, Wolff OH, Ades AE. Behavior disturbance in 8-year-old children with early treated phenylketonuria. *J Pediatr* 1998; 112:403-8.
- Waggoner DD, Buist NRM, Donnell GN. Long-term prognosis in galactosaemia: Results of a survey of 350 cases. *J Inher Metab Dis* 1990; 13: 802-12.

## Appendix A

### RESOLUTION ON THE PROMOTION OF NEWBORN SCREENING

Whereas, *newborn screening* has been recognized to be a public health activity aimed at the early identification of infants who are affected by certain genetic/metabolic/infectious conditions;

Whereas, early identification of these conditions is particularly crucial, as timely intervention can lead to a significant reduction of morbidity, mortality, and associated disabilities;

Whereas, thousands of children have been saved from mental retardation and death in countries where newborn screening is already a standard component of quality newborn care;

Whereas, advances in technology, have made possible affordable tests for the general population;

Whereas, there is an anticipated shift in burden from the infectious diseases to non-communicable diseases which includes congenital anomalies;

Whereas, cost benefit analysis of screening programs have shown net benefits to the state, the family and to the individual when national screening programs have been implemented;

Whereas, newborn screening in developed countries have achieved almost 100% coverage of its newborn population;

Whereas, newborn screening in some developing countries, is not routinely done or is in varying stages of implementation for its newborn population due to lack of awareness, lack of technology, lack of government support and resources;

Whereas, the Association of Pediatric Societies of the Southeast Asian Region (APSSEAR), has under its responsibility almost half of the world's children;

We, the members of the Executive Committee and Advisory Board of the Association of Pediatric Societies of the Southeast Asian Region do hereby resolve, as it is hereby resolved that;

That the Association of Pediatric Societies of the Southeast Asian Region, through its national pediatric societies,

- ◆ Be a vigilant advocate of newborn screening;
- ◆ Lobby for issuance of a policy on *newborn screening* for its newborn population;
- ◆ Encourage collaboration with their respective ministries of health, in developing strategies to integrate *newborn screening* in their existing delivery of maternal and child health services;
- ◆ Encouraging inclusion of *newborn screening* in the curricula of health professionals;
- ◆ Motivate their pediatrician members to participate actively in awareness campaigns and public health education.

**HUNG-CHI LUE MD**  
President APSSEAR

**MOHD SHAM KASIM MD**  
Secretary-General APSSEAR

cc All members of the Executive Committee and Advisory Board