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Measures to Improve Newborn Screening System in Korea

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Ⅰ. Introduction

The territory of Korea is 99,392 square kilometers, of which 70% is mountainous area. Korea has a population of 46.8 million. Infant mortality rate of the 1996 birth cohort was 7.7 per 1,000 live births (Table 1).

<Table 1> Socioeconomic Indicators

Classification	Year 1999
Territory	99,392Km^2
Total population(1,000 persons)	46,858
Urban population rate	78.5%(1995)
per capita GDP	$6,947(1998)
Crude birth rate(per 1,000 persons)	13.2
Crude death rate(per 1,000 persons)	5.2
Total fertility rate	1.42
Life expectancy at birth: Male	71.71
Female	79.22
Infant mortality rate(per 1,000 live births)	7.7(1996)
Maternal mortality ratio(per 100,000 live births)	20(1996)

The first among the 10 major causes of infant death was 'Congenital malformation of the heart', accounting 9.1% of the infant deaths. The second cause was 'Sepsis of the newborn', responsible for 8.4% of infant deaths, the third was 'Respiratory distress of the newborn' at 8.3% and the fourth was 'Fetal growth disorder' at 8.0%.

<Table 2> 10 Major Causes of Infant Death (1996 birth cohort)

Classification	%
Congenital malformation of the heart	9.1
Sepsis of the newborn	8.4
Respiratory distress of the newborn	8.3
Fetal growth disorder	8.0
Other symptoms and signs	7.2
Other respiratory disease of the newborn	5.6
Other congenital malformation	3.8
Birth asphyxia	3.5
Other perinatal disease	3.4
Neonatal hemorrhagic disease	3.2
Others	20.9
Cause unknown	18.6

The Ministry of Health and Social Affairs adopted newborn screening for the low-income families in 1991 and expanded in 1997 to cover all newborns. At the beginning of the program 6 diseases were selected for screening. These are congenital hypothyroidism (CH), penylketonurea (PKU), galactosemia (Gal), maple syrup urine disease (MSUD), homocystinuria (HU), and histidinemia (His). The number of screening items had been reduced to two (CH and PKU) since 1995 because other four diseases had been rarely detected and cost-effectiveness issues were raised.

Until now, 1,431,791 newborns were screened by government program. 330 CH and 27 PKU cases were detected, making the detection rate 1 per 4,339 for CH and 1 per 53,029 for PKU. Now, the government program has a ten-year history. The program needs to be reviewed with a view to enhancing effectiveness, efficiency and equity, and related policy measures should be presented for the further improvement of the national newborn screening program.

II. Current status of newborn screening in Korea

1. Neonatal screening program in Korea

Table 3 shows the sources of the screening program fund, which has increased rapidly since 1997. An estimated 40% of the total fund was provided by the central government and other 60% by local governments. Follow-up supports, including special milk, were given only to the low-income families.

〈Table 3〉 Achievement of the Government Screening Program and Sources of Funding

Year	Project budget			Source of fund
	Total cost	Test	Follow up	
1991	297,600	240,000	57,600	Social welfare fund
1992	320,000	281,400	38,600	Central government subsidy Social welfare fund
1993	544,160	491,360	52,800	Central government subsidy, Social welfare fund
1994	757,600	702,674	54,926	Central government subsidy, local government budget Social welfare fund
1995	837,400	766,432	70,968	Central government subsidy, local government budget Social welfare fund
1996	641,980	562,144	79,836	Central government subsidy, local government budget
1997	5,367,673	5,273,700	93,973	Central government subsidy, local government budget
1998	3,910,439	3,768,309	142,070	Central government subsidy(40%), local government budget(60%)
1999	3,890,595	3,748,525	142,070	Central government subsidy(40%), local government budget(60%)
2000	3,849,903	3,641,442	208,461	Central government subsidy(40%), local government budget(60%)

(Unit: thousand won)

Source: 1) MOHW, Internal material, 1991～1999.
2) MOHW, Plan of Family Health and Welfare program, 1991～2000.

Table 4 is a profile of the money spent on the program for the inborn errors of metabolism. A large share (40-60%) of the total cost spent on the program was supported by both central and local governments. The cost spent for screening tests in 2000 was 3,641,442 thousand won or 95% of the total budget. Patients with inherited metabolic diseases detected by the screening program were provided with special milk at government's expense. The cost for the management of patients occupied 5% of the total budget.

〈Table 4〉 Budget for the Inborn Errors of Metabolism (2000)

Classification	Contents	central government subsidy (40%)	Local government budget (60%)
Cost for test	9,500 won × 383,310 persons = 3,641,442	1,456,577	2,184,865
Cost for management of patients			
PKU	2,546,000 won×66 persons = 168,036	67,243	100,823
CH	275,000 won×147 persons = 40,425	16,170	24,265
Total	3,849,903	1,539,990	2,309,913

(Unit: thousand won)

Source: MOHW, Family Health Program Guideline, 2000.

The cost for newborn screening was 8,000 won for 6 kinds of tests in 1991 and 9,500 won for 2 kinds of test in 2000.

〈Table 5〉 Cost for Newborn Screening (1991～2000)

Year	Cost	Test items
2000～1998	9,500	2 kinds: PKU, CH
1997	8,640	2 kinds: PKU, CH
1996～1995	8,000	2 kinds: PKU, CH
1994～1992	14,000	6 kinds: PKU, CH, HU, MSUD, GAL, HIS
1991	8,000	6 kinds: PKU, CH, HU, MSUD, GAL, HIS

(Unit: won)

Source: MOHW, Family Health Program Guideline.
PKU(Penylketonuria), CH(Chronic Hypothyroidism), HU(Homocystinuria), MSUD(Maple Syrup Urine Disease), Gal(Galactosemia), His(Histidenemia)

During the period 1991-1995, 1,431,791 newborns were screened and 330 Congenital Hypothyroidism patients and 27 Penylketonurea patients were detected (Table 6)

〈Table 6〉 Number of Screen-tested Newborns and Detected Patients (1991～1999)

Year	No. of tested Newborns	No. of detected patients	
		CH	PKU
1991	28,286	7	1
1992	20,372	7	0
1993	35,094	8	0
1994	51,045	12	1
1995	74,880	8	2
1996	62,542	6	1
1997	345,013	62	6
1998	416,115	132	7
1999	398,444	88	9
Total	1,431,791	330	27

(Unit: event, person)

Source: MOHW, internal material.

Table 7 shows the distribution of the newborns by the number of tests taken, based on the data from the Korea Family Health and Welfare Association (KFHWA). The government supported two major items. The proportion of the two items decreased from 72.7% in 1998 to 66.2% in 1999.

〈Table 7〉 Distribution of Newborns by the Number of Screening Tests Taken

(Unit: person, %)

No. of screening tests	1998		1999	
	No.	%	No.	%
2 kinds[1)]	20,542	72.7	17,868	66.2
3 kinds	79	0.3	574	2.1
4 kinds	220	0.8	326	1.2
5 kinds[2)]	3,095	10.9	4,601	17.0
6 kinds[3)]	4,338	15.3	3,631	13.5
Total	28,274	100.0	27,000	100.0

Note: 1) 2 kinds (PKU, CH, government provided tests)
2) 5 kinds (PKU, CH, HU, MSUD, Gal)
3) 6 kinds (PKU, CH, HU, MSUD, Gal, His, CAH)
Source: KFPWA, 1999 report on the statistical analysis of the blood collection papers of the screening test, 2000.

According to the KFHWA data, the test rate for CH and PKU was 100%, while those for Gal, HU and MSUD were 31.6%, 30.7% and 30.7% respectively (Table 8).

〈Table 8〉 Test Rate by Test Item[1)] (1999)

(unit: person, %)

Test item	No. of newborn tested	Test rate
PKU	27,000	100.0
CH	27,000	100.0
HU	8,301	30.7
MSUD	8,300	30.7
GAL	8,532	31.6
CAH	4,426	16.4

Note: 1) Result on the sample of 27,000 newborns.
Source: KFHWA, 1999 report on the statistical analysis of the blood collection papers of the screening test, 2000.

According to the survey result on the 76 laboratories participated in external quality assurance program in June 2000, all of them conducted screening on the diseases supported by the government, PKU and CH. However, for other test items, the proportion of laboratories conducted screening test on Gal was 79%, on MSUD 58%, on HU 42%, and on CAH 41% (Table 9). Guthrie method (BIA) was used for PKU at 26 laboratories and ECA/EIA method at 50 laboratories. However, screening laboratories with many screening test cases were found to have often utilized the cheap Guthrie method (Table 9).

〈Table 9〉 Methods of Newborn Screening[1)] (1999)

(Unit: post, %)

Disease	Test items	Methods of newborn screening test					No. of screening laboratory	%
		BIA	ECA /EIA	RIA	Others	Total		
Penylketonuria	Phenylalanine	26	50	-	-	76	76	100.0
Congenital hyperthyroidism	TSH	-	66	10	-	76	76	100.0
	T4	-	18	8	-	26		
Maple syrup urine disease	Leucine	31	-	-	-	31	44	57.9
	Leu, Ile, Val	-	13	-	-	13		
Homocystinuria	Methionine	32	-	-	-	32	32	42.1
Galactocemia	Galactose	13	35	-	-	48	60	78.9
	Galactose-1-PUT	-	7	-	5	12		
Congenital adrenal Hypertrophy	17-OHP	-	31	-	-	31	31	40.8

Note: 1) Survey result from 76 screening laboratories in June 2000.
Source: Survey result on the Inborn errors of metabolism, Quality assurance committee on the Inborn errors of metabolism, 2000.

"Quality Assurance Committee on the Inborn Errors of Metabolism" produced ten test samples—including abnormal one—four times a year (March, June, September, November), sent them to laboratories designated by the government and analyzed the reports they produced (KFHWA, 1999).

In 1997, the committee set a rejection standard regarding laboratory reports based on the external inspection of PKU and CH. According to this standard, more than 1 false negative on the test of PKU and CH or more than 2 false positive on each

item is subject to rejection. A laboratory rejected more than three times within a period of one year may be disqualified as a designated laboratory. The pass rate has been increased recently. Most of the laboratories failed to pass PKU tests were known to have used Guthrie method (Table 10).

〈Table 10〉 Result of External Inspection on Newborn Screening

(Unit: post, %)

Year	Quarter	No of participating laboratories	No of passed laboratories	No of rejected laboratories	Pass rate
1994	1	17	15	2	88.2
	2	17	15	2	88.2
1995	1	22	21	1	95.5
	2	22	17	5	77.3
1996	1	24	24	0	100
	2	24	22	2	91.7
	3	23	22	1	95.7
	4	23	23	0	100
1997	1	74	67	7	90.5
	2	79	76	3	96.2
	3	78	78	0	100
	4	76	67	9	88.2
1998	1	75	45	30	60.0
	2	75	73	2	97.3
	3	76	68	8	89.5
	4	76	69	7	90.8
1999	1	76	74	2	97.4
	2	77	74	3	96.1
	3	78	70	8	89.7
	4	78	75	3	96.2
2000	1	76	74	2	97.4
	2	75	71	4	94.7
Total		1,241	1,140	101	91.9

Note: 10 test samples were produced for inspection each time and conducted test on 8 items on each sample. 8 test items are phenylalanine, TSH, T_4, leucine (Leu, Ile, Val), methionine, galactose, galactose-1-PUT, 17-OHP.
Source: Survey result on the Inborn errors of metabolism, Quality assurance committee on the Inborn errors of metabolism, 2000.

In order to enhance the quality of screening tests, test procedure should be taken concurrently with test sample collection on a daily basis. However, only 10.5% of the total laboratories conducted daily tests, while those undertaken weekly tests occupied 41.9% (Table 11).

〈Table 11〉 Number of Screening Laboratory, by Period of Testing

(Unit: posts, %)

Test period	No. of screening Lab	%
Daily	9	10.5
4～5 times per week	5	5.8
3 times per week	12	13.9
2 times per week	19	22.1
Weekly	36	41.9
Every 10 days	1	1.2
Every other week	2	2.3
Others	2	2.3
Total	86	100.0

Source: KFHWA (Korea Family Health and Welfare Association), Internal material, 2000.

Among the 86 screening laboratories, 25.6% conducted tests on the two items supported by the government. The percentage of laboratories conducted tests on 5 items took up0 32.5% (Table 12).

〈Table 12〉 Number of Screening Laboratory by Test Item (2000)

(Unit: posts, %)

Test Items	No. of screening Lab	%
2	22	25.6
4	6	7.0
5	28	32.5
6	14	16.3
7	15	17.4
8	1	1.2
Total	86	100.0

Source: KFHWA, Internal material, 2000.

Table 13 shows the distribution of the laboratories according to the cost per additional test, which ranges from free of charge to more than 10,000 won per each test item. Proportion of the laboratories by cost were almost evenly distributed, ranging from 'less than 5,000 won (28.1%)', '5,000～less than 10,000 (28.1%)' to more than 10,000 won (26.6%)

〈Table 13〉 Number of the Screening Laboratory by Cost Per Additional Test[1)]

Cost for test	No. of screening Lab	%
Free of charge	10	15.6
Less than 5,000 won	18	28.1
5,000～less than 10,000 won	18	28.1
More than 10,000 won	17	26.6
Others	1	1.6
Total	64	100.0

(Unit: Post, %)

Note: 1) Analysis based on the 64 laboratories except 22 Labs without additional test.

Source: KFHWA, Internal material, 2000.

Ⅲ. Survey results

1. National fertility and family health survey

According to the survey on National Fertility and Family Health, the newborn screening rate was increased from 35.7% in 1994 to 88.8% in 2000. The rate has been higher for rural areas than for urban areas since 1997, presumably due to the active program delivery by health workers at health centers in rural area. The rate was high among the women with a university or higher education (Table 14).

〈Table 14〉 Percentage of married women of 15-44 years of age who have taken screening test on the last childbirth

(Unit: %, person)

Classification	1994	1997	2000
Total	35.7	73.6	88.8(1,351)
Region			
Urban	35.7	73.4	88.4(1,242)
Rural	35.8	74.4	93.0(109)
Education			
Middle school	31.2	65.7	81.5(53)
High school	33.5	71.6	86.7(768)
University and above	43.2	79.0	92.5(530)
Age of mother at delivery			
15～24	36.6	70.2	83.3(201)
25～29	33.9	72.7	90.9(695)
Above 30	39.3	77.3	87.9(455)

Source: 1) Hong MS et al, 『1994 National Fertility and Family Health Survey』, KIHASA, 1994.
2) Cho, NH et al, 『1997 National Fertility and Family Health Survey』, KIHASA, 1997.
3) Kim, SK et al, 『2000 National Fertility and Family Health Survey』, KIHASA, 2000.

Although the government-supported newborn screening tests have expanded to cover all newborns, most women are found to have their newborns taken additional tests at their own expense. Very often, hospitals demand a high cost on an additional test without requesting government to pay for the 2 items due to the complicated reimbursement system. The proportion of self-paid for the newborn screening was 81.0% (Table 15). Therefore, it seems some hospitals have provided two tests free of charge and offset the cost by offering other charged items.

<Table 15> Screening test cost paid by married women aged 15-44 (2000)

(Unit: %, person)

Region	Self-paid	Free of charge	Self-paid+ government	Others	Total
Whole country	81.0	13.5	2.8	2.7	100.0(1,020)
Urban	81.6	12.6	2.9	2.9	100.0(947)
Rural	72.3	25.0	2.7	--	100.0(73)

Source: Kim SK et al, 『2000 National Fertility and Family Health Survey』, KIHASA, 2000.
Note: Government funded only 2 items (Congenital hypothyroidism and PKU).

2. Health center-based survey on the management of inborn errors of metabolism

This study utilized structured questionnaires to conduct a survey covering 241 health centers in June 2000, with the aim of identifying characteristics of the patients detected as having inborn errors of metabolism and of reviewing the status of screening system in Korea. In addition, a supplementary survey was conducted on the families of the patients at an 'association of families of patients with inborn errors of metabolism' to gather information from them (Han, 2000).

In order to identify the number of inborn errors of metabolism, information on the patients was gathered from the survey and other various existing sources. The information was

made into a duplication-free data set by utilizing the ID numbers of the patients. The total number of cases identified through this process was 481, including 378 CHs, 73 PKUs, 11 MSUDs, 7 PAs, 9 UCDs and 3 Gals (Table 16). Most of the cases were those had been identified after 1997 with the expansion of the program.

〈Table 16〉 Distribution of the identified inborn errors of metabolism

(Unit: person)

Year of birth	CH		PKU		MSUD		Propionic Acidosis		Urea cycle disorders		Galactosemia	
	M	F	M	F	M	F	M	F	M	F	M	F
2000[1)]	24	18	1	-	2	-	1	1	-	1	1	-
1999	44	44	9	1	3	-	3	1	3	3	1	1
1998	49	37	3	3	1	-	1	-	1	1	-	-
1997	34	41	4	3	3	-	-	-	-	-	-	-
1996	10	10	1	2	1	-	-	-	-	-	-	-
1995	5	12	4	4	-	-	-	-	-	-	-	-
1994	8	7	1	3	-	-	-	-	-	-	-	-
1993	9	4	0	0	-	-	-	-	-	-	-	-
1992	4	1	2	2	-	1	-	-	-	-	-	-
1991	1	2	0	5	-	-	-	-	-	-	-	-
Before 1990	6	8	11	14	-	-	-	-	-	-	-	-
Total	194	184	36	37	10	1	5	2	4	5	2	1

Note: 1) the patients born from Jan. to May in 2000 only

Among the 260 patients whose time of detection was known, 83.5% were detected within 2 months after having childbirth. Especially the detection rate within 2 month after childbirth was increased rapidly from 23.5% in 1994 to 90% in 1997 (Table 17).

〈Table 17〉 Time of detection of inborn errors of metabolism

(Unit: Person, %)

Year of Birth	Less than 2 months		2 months～less than 1 year		1 year～less than 3 years		More than 3 years		Total	
	N.	%	N.	%	N.	%	N.	%	N.	%
2000	31	96.9	1	3.1	-	-	-	-	32	100.0
1999	59	93.7	4	6.3	-	-	-	-	63	100.0
1998	60	92.3	3	4.6	2	3.1	-	-	65	100.0
1997	45	95.7	2	4.3	-	-	-	-	47	100.0
1996	6	75.0	1	12.5	1	12.5	-	-	8	100.0
1995	8	72.7	1	9.1	2	18.2	-	-	11	100.0
Before 1994	8	23.5	2	5.9	8	23.5	16	47.1	34	100.0
Total	217	83.5	14	5.4	13	5.0	16	6.1	260	100.0

Since 1997, most cases of inborn errors of metabolism were identified through screening tests. However, 48.5% of the total cases in 1994 were identified as a result of abnormal symptom and 30.3% as a result of growth retardation (Table 18).

〈Table 18〉 Causes of the detection of inborn errors of metabolism

(Unit: person, %)

Year of birth	Screening test		Abnormal symptom		Growth retardation		Total	
	N.	%	N.	%	N.	%	N.	%
2000	32	100.0	-	0	-	0	32	100.0
1999	61	96.8	2	3.2	-	-	63	100.0
1998	60	98.4	1	1.6	-	-	61	100.0
1997	47	100.0	-	-	-	-	47	100.0
1996	7	77.8	1	11.1	1	11.1	9	100.0
1995	8	80.0	1	10.0	1	10.0	10	100.0
Before 1994	7	21.2	16	48.5	10	30.3	33	100.0
Total	222	87.1	21	8.2	12	4.7	25.5	100.0
Total	222	87.1	21	8.2	12	4.7	255	100.0

Note: Excluded 5 persons without response.

When family history was asked 258 cases responded. Although the small size of the sample does not allow any generalization, this information will prove to be useful for further studies on the influence of family upon the occurrence of disease. 17.7% of PKU patients and 4.2% of the congenital hypothyroidism cases had a family history associated with these diseases (Table 19).

〈Table 19〉 Distribution of patients with inborn errors of metabolism, by family history

(Unit: person, %)

Family history	CH		PKU		MSUD		PA		UCD		Gal	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Yes	8	4.2	9	17.7	2	33.3	1	16.7	1	25.0	-	-
No	182	95.8	42	82.3	4	66.7	5	83.3	3	75.0	3	100.0
Total	190	100.0	51	100.0	6	100.0	6	100.0	4	100.0	3	100.0

Ⅳ. Problems Identified

- Absence of an organization responsible for coordination and control of national newborn screening services.
- Too many screening laboratories. There are 76 laboratories for newborn screening tests in 2000 in Korea.
- Only two items (CH and PKU) were supported by the government and the cost for additional tests is parent's responsibility. The problem is that the items of screening test are not selected according to the prevalence of diseases and the number of tests, and costs vary widely across medical facilities.
- Follow up treatment and services are not adequate.
-Reimbursement system is very complicated and involves unnecessary administrative processes.

Ⅴ. Recommendations

- Establish an organization responsible for national newborn screening, and provide services such as quality assurance and accreditation of the screening laboratory, technical assistance and research.

- Establish a newborn screening and patient management model consisting of test sample collection system, screening laboratory work system, follow-up retest system and diagnosis and treatment system.

- Reduce the number of screening laboratories from current 76 posts to 3～4 posts by putting strict requirement on the standards and also induced by cost-competitiveness. Adoption of Tandem Mass Screening as an alternative for quality assurance and cost-effective way of improving the current screening method.

- Increase the number of test items that are supported by government from the current two items to more than five items. Costs may not increase much if the Tandem Mass Screening method is introduced.

- Strengthen follow-up management of the identified patients.

- Streamline and simplify the current reimbursement system. There are several alternative methods such as providing coupon, and payment through health insurance system.

- In order to improve the patient management, activities of the health center should be strengthened and supported by the central government based on patient management guidelines and health education materials.

- A dietary guideline for the inborn errors of metabolism was developed as a part of the research. It was based on the analysis of component of the favorite Korean food selected by the patient family association. This guideline should be supplemented and revised in the future.

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