Expanded Newborn Metabolic Screening:

Should This Be Implemented in Hong Kong?

Paediatric Services

Hospital Authority Convention 2014

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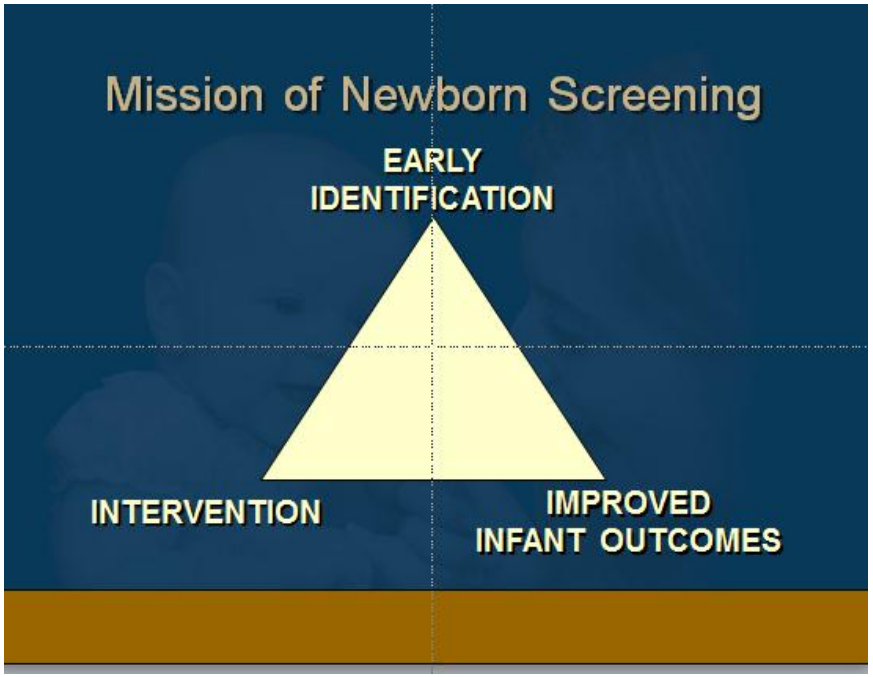
Expanded Newborn Metabolic Screening: Should Be Implemented in Hong Kong

Overview

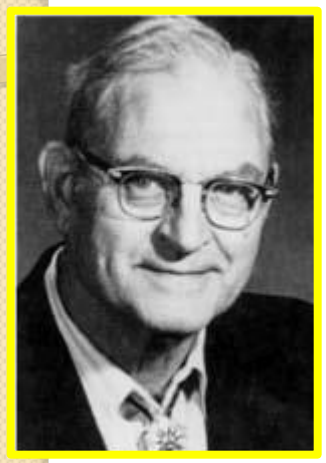
1. Introduction to newborn screening (NBS)
2. Expanded newborn screening & Tandem mass spectrometry (MS/MS)
3. Newborn screening in other parts of the world
4. Pilot program : Joshua Hellmann Metabolic Screening Program CUHK
5. Working towards a universal territory wide newborn screening program

Screening

- a test performed on asymptomatic individuals that allows for early detection, therapeutic intervention & decreased morbidity/ mortality from the disease
- e.g. pap smear – cervical cancer
- Newborn Screening (NBS) – screening performed on babies in the newborn period



History of Newborn screening started in 1961



Robert Guthrie
(1916-1995)

- Introduced the first newborn screening in USA for Phenylketonuria (PKU)
- Dried blood spot (DBS)
- Bacterial inhibition assay

A bacterial culture with phenylalanine antagonist

Excess phenylalanine in PKU patients can be determined based on the amount of bacterial growth

Phenylketonuria

Phenylalanine ----------> Tyrosine

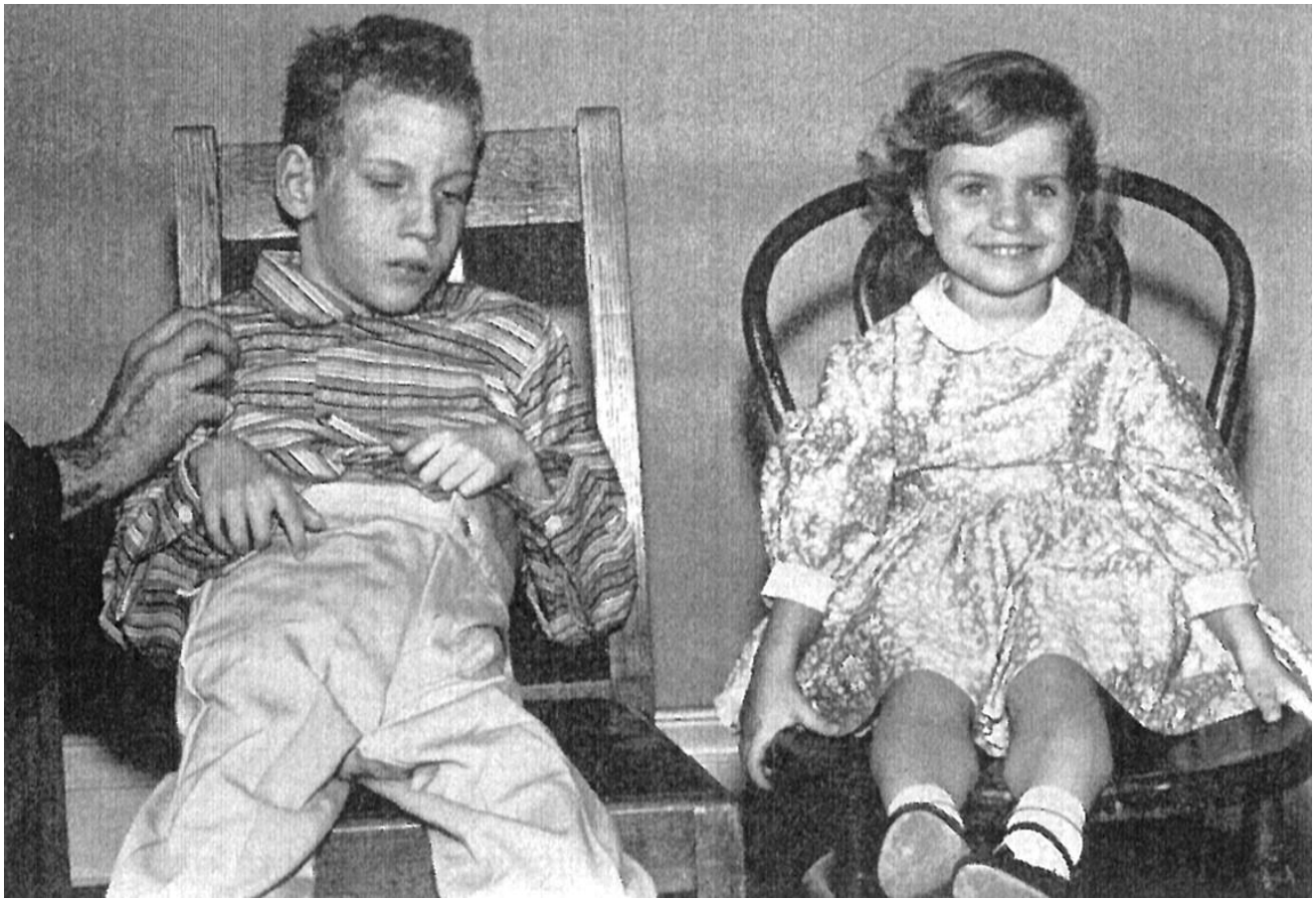
Because a child with PKU lacks the normally functioning enzyme necessary to break down phenylalanine (PHE), it accumulates in the blood and body tissues.

This excess PHE can prevent normal brain development and result in mental retardation.

Boy with untreated PKU

PKU siblings

pre & post newborn screening



Development of Newborn screening over the next 30 years (1960-1990)

More disorders added

- Congenital hypothyroidism
- Cystic fibrosis
- Congenital adrenal hyperplasia
- Biotinidase
- Hemoglobinopathy
- Hearing

- Important condition
- Acceptable treatment available
- Facilities for diagnosis & treatment
- Difficult to recognize early
- Suitable screening test
- Natural history known
- Cost-effective to diagnose & treat

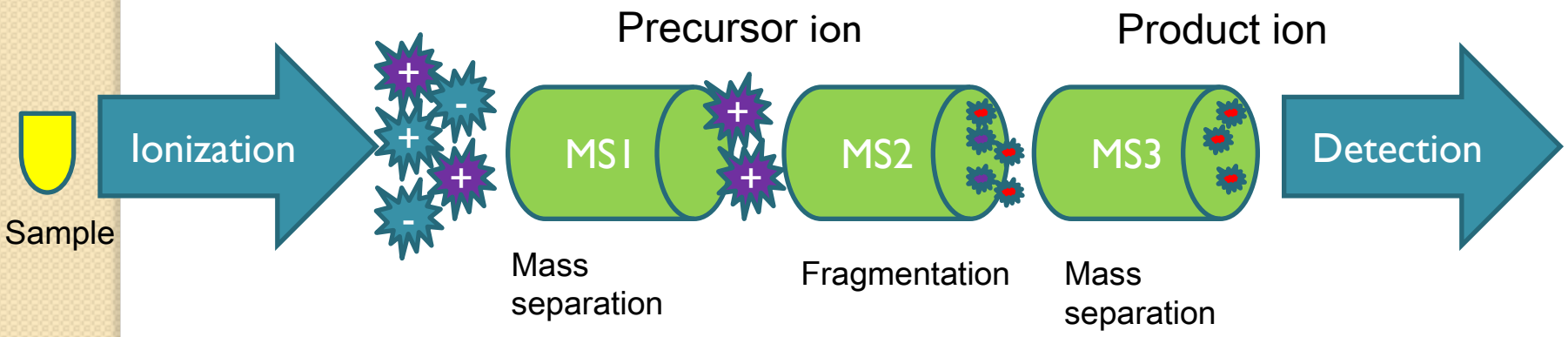
Wilson & Junger criteria 1968

1990's
Expansion of Newborn screening

- Technology driven
- Tandem mass spectrometry
- (MS/MS)
- revolutionized newborn screening

How does Tandem Mass Spectrometry MS/MS work?

- tandem = one following the other
- mass spectrometry (MS) = an analytical technique that produces spectra of the masses of molecules comprising a sample of material

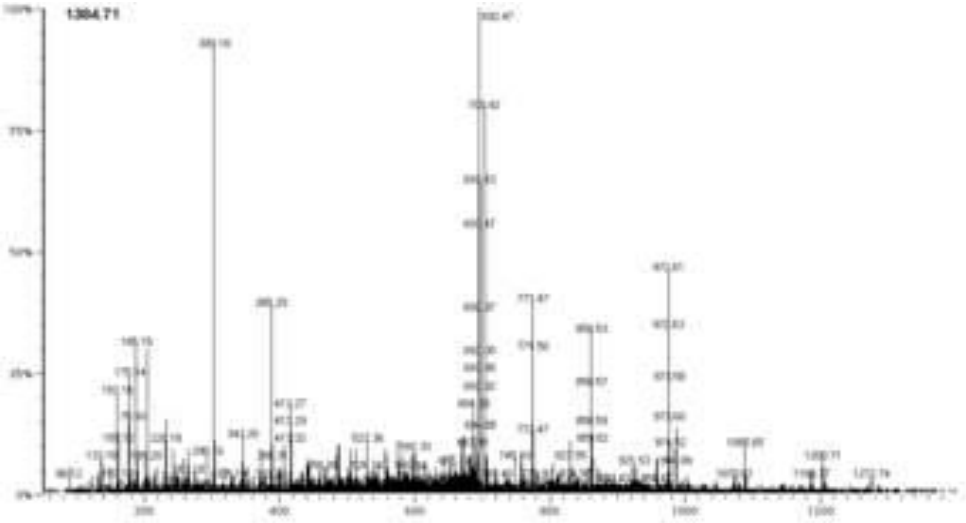


molecules determined based upon their mass-to charge(m/z)ratio

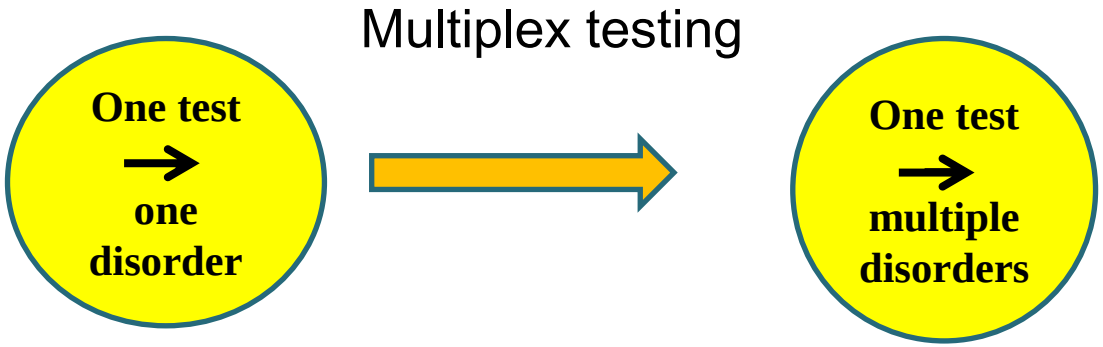
Metabolites measured by MS/MS

Amino acids
Alanine
Arginine
Citrulline
Glycine
Leucine/Isoleucine
Methionine
Ornithine
Phenylalanine
Proline
Tyrosine
Valine
Succinylacetone

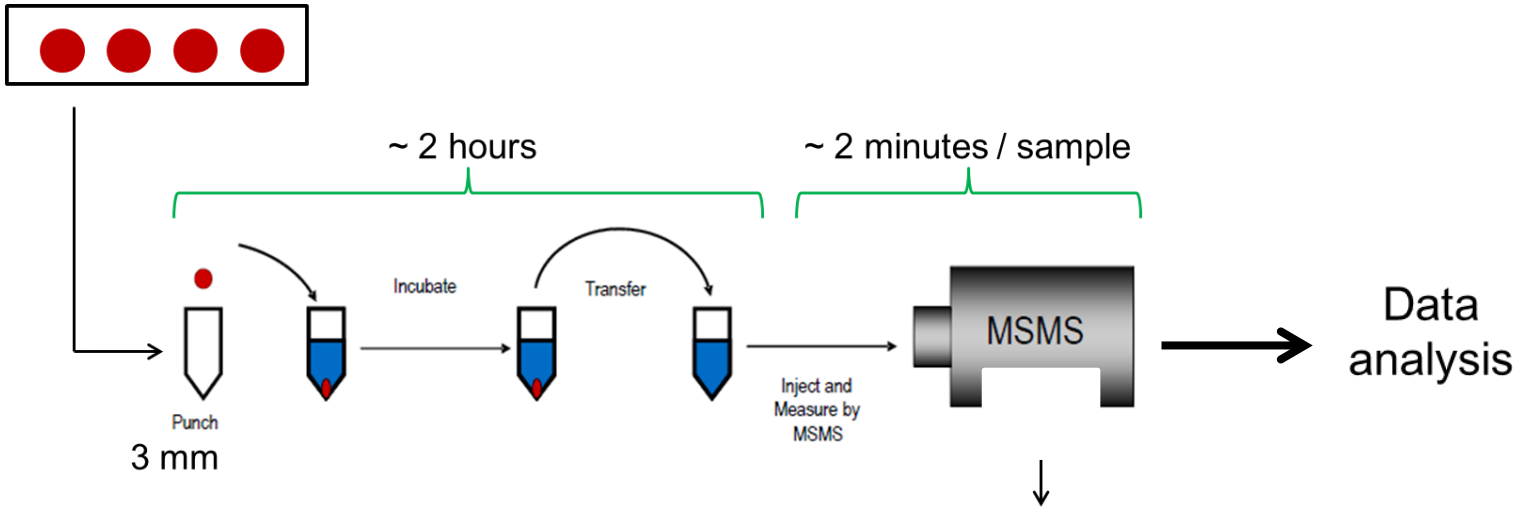
Acylcarnitines		
C0	C6DC	C14:2
C2	C8	C14OH
C3	C8:1	C16
C3DC/C4OH	C10	C16:1
C4	C10:1	C16OH
C4DC/C5OH	C10:2	C16:1OH
C5	C12	C18
C5:1	C12:1	C18:1
C5DC/C6OH	C14	C18:2
C6	C14:1	C18OH



Tandem Mass Spectrometry (MS/MS)



- simultaneous, rapid analysis & detection of many disorders
- a high degree of precision & accuracy



Targeted towards Inborn errors of metabolism (IEM)

Fatty Acid Oxidation Disorders

1. ***Primary carnitine deficiency (Carnitine update defect, CUD) 卡尼丁缺乏症**
2. ***Medium-chain acyl-CoA dehydrogenase deficiency (MCAD) 中鏈醯輔酶A去氫酶缺乏症**
3. ***Very long-chain acyl-CoA dehydrogenase deficiency (VLCAD) 極長鏈醯輔酶A去氫酶缺乏症)**
4. *Long-chain hydroxyl-acyl-CoA dehydrogenase (LCHAD) 長鏈醯輔酶A去氫酶缺乏症
5. *Trifunctional protein deficiency (TFP) 三種功能蛋白缺乏症
6. **Short-chain acyl-CoA dehydrogenase deficiency (SCAD)**
7. **Carnitine palmitoyltransferase I deficiency (CPT1)**
8. **Carnitine palmitoyltransferase II deficiency (CPT2)**
9. **Carnitine-acylcarnitine translocase deficiency (CACT)**
10. **Multiple acyl-CoA dehydrogenase deficiency (GA 2)**
11. Medium/short-chain hydroxyl-acyl-CoA dehydrogenase deficiency (M/SCHAD)

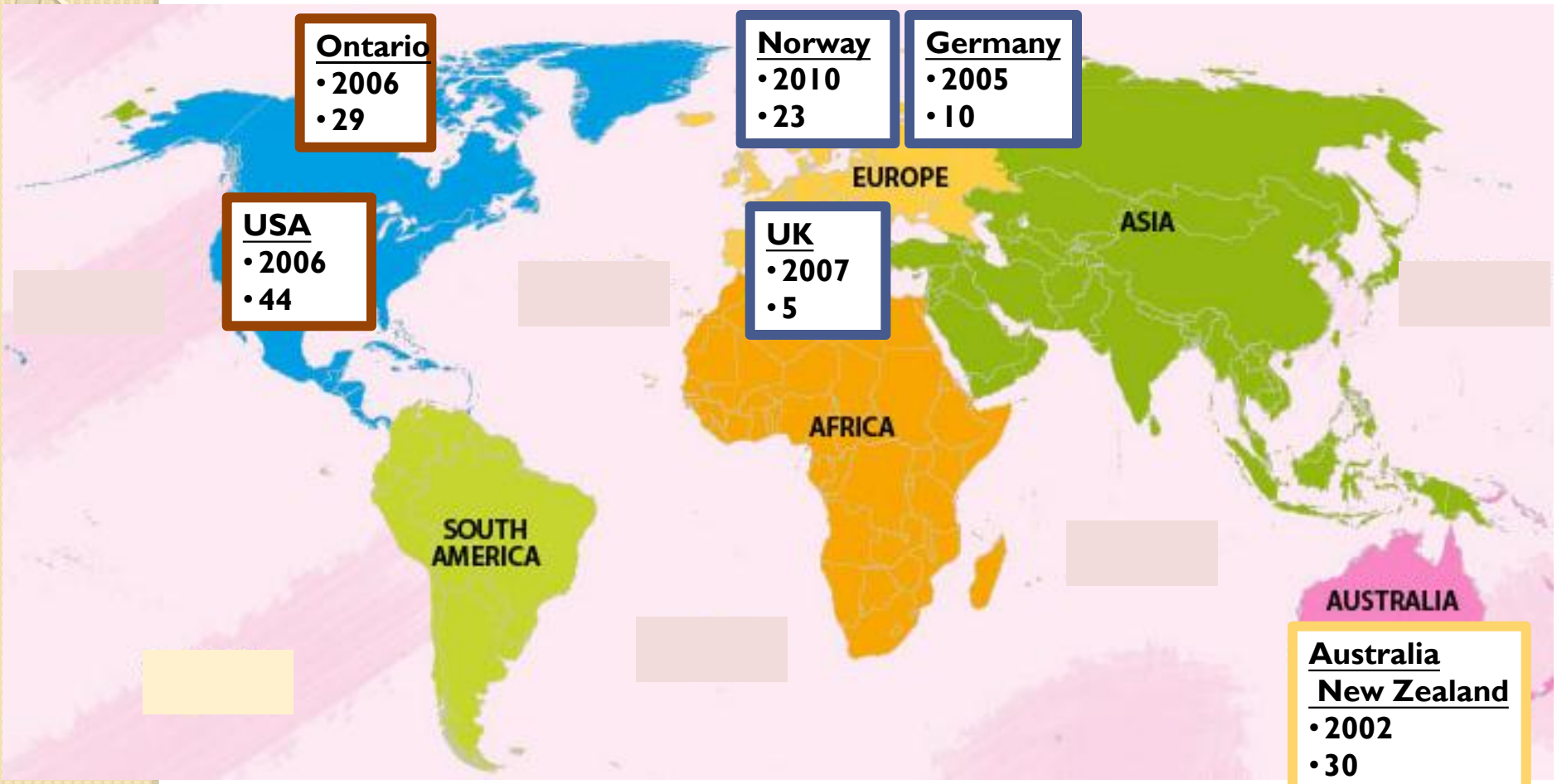
Organic Acid Disorders

1. ***Propionic acidaemia (PA) 丙酸血症**
2. ***Methylmalonic aciduria (MUT, cbl A/B) 甲基丙二酸血**
3. ***Isovaleric acidaemia (IVA) 異戊酸血症**
4. ***ß-ketothiolase deficiency (BKT) 酮硫解酶缺乏症**
5. ***Glutaric acidaemia type 1 (GA1) 戊二酸血症第1型**
6. ***3-Hydroxy-3-methylglutaryl-CoA lyase deficiency (HMG) 三羥基三甲基戊二酸血症**
7. ***Multiple carboxylase deficiency (MCD) 多發性羧化胸缺乏症**
8. *3-Methylcrotonyl-CoA carboxylase deficiency (3MCC)
3-甲基巴豆醯輔酵素羧化酵素缺乏症
9. 2-Methyl-3-hydroxybutyric aciduria (2M3HBA)
10. Malonic aciduria
11. 3-Methylglutaconic aciduria type I (3MGA)
12. Isobutyryl-CoA dehydrogenase deficiency (IBG)
13. 2-Methylbutyryl-CoA dehydrogenase deficiency (2MBG)
14. **Cbl C/D**

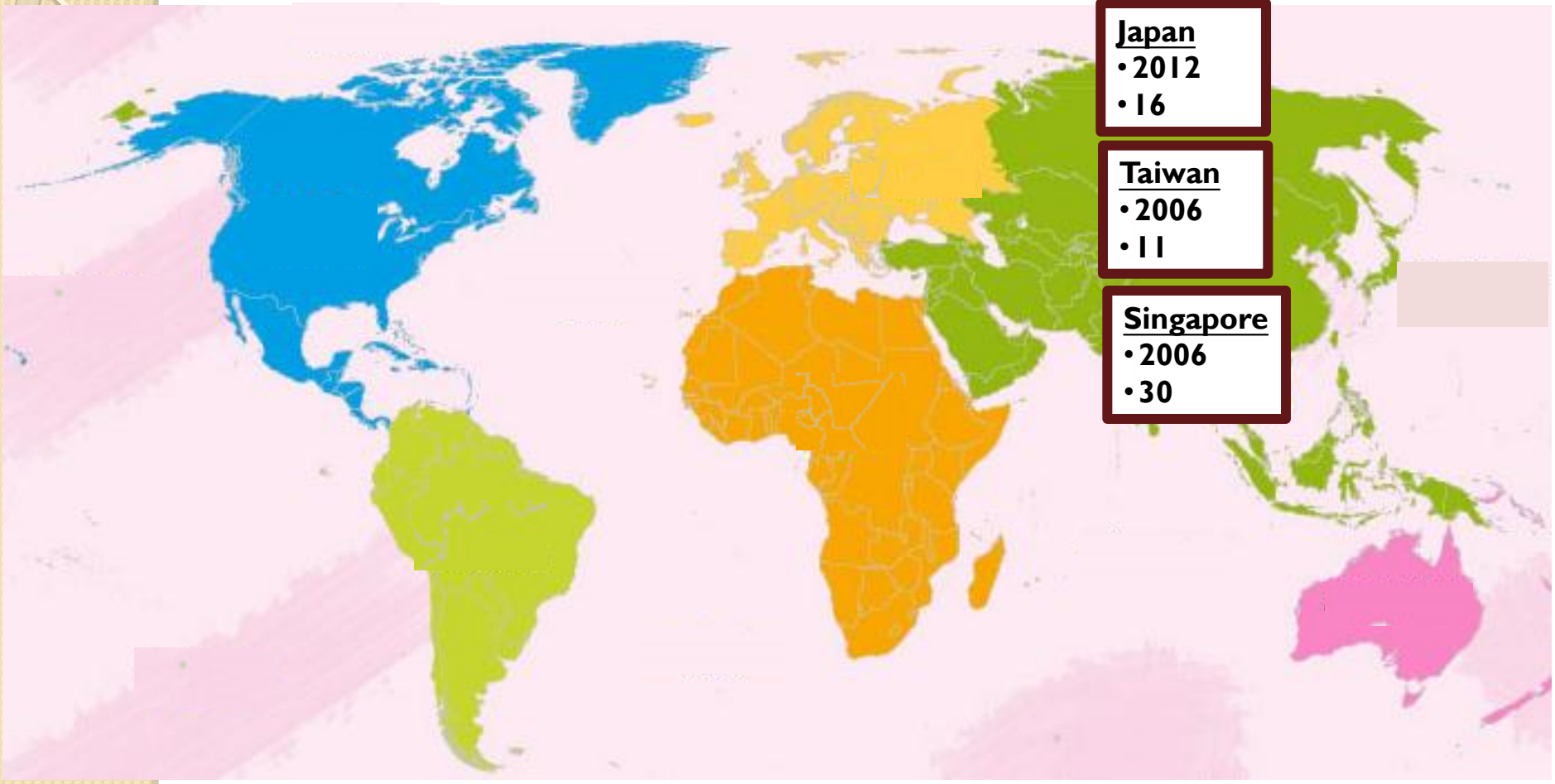
Amino Acid Disorders

1. ***Phenylketonuria (PKU) 苯丙酮尿症**
2. ***Maple syrup urine disease (MSUD) 楓糖尿病**
3. ***Citrullinaemia type 1 瓜氨酸血症1型**
4. ***Argininosuccinic aciduria 精胺丁二酸酶缺乏症**
5. ***Homocystinuria 高胱氨酸尿症**
6. ***Tyrosinaemia type 1 酪氨酸血症1型**
7. **Arginase deficiency**
8. **Defects of biopterin cofactor biosynthesis or regeneration**
9. **Citrullinaemia type 2 (Citrin deficiency)**
10. Hypermethionaemia

Newborn screening in North America, Australia and Europe (Expanded)



Newborn screening in some Asian countries (Expanded)



Newborn screening in Asia Pacific Region (Not expanded)

Approximately half of all births world wide

Consolidating newborn screening efforts in the Asia Pacific region
by the Working Group of the Asia Pacific Society for Human Genetics

Table 1 Summation of screening statistics reported by participants at the 2nd Conference on Consolidating Newborn Screening Efforts

Country	Population†	Annual births†	NDBS initiated	National Coverage	Disorder	Analyte	Methodology	Residual Specimen Storage
Bangladesh	162 M	3.40 M	1999	<5%	CH	TSH	RIA; FIA	Air conditioned room; duration not decided
China	1.35 B	18.29 M	1981	~59%	CH	TSH	FIA	4℃; ≥5 yrs; some labs store at -20℃
					PKU	PHE	BIA	
				N/A	Various Metabolic	Various	MS/MS (3-28 conditions)	
India	1.20 B	26.79 M	2007[1]	<1%	CH	TSH	FIA	-20℃; 5 yrs
					CAH	17-OHP	FIA	
			2007[2]	~86% (local coverage)	CH	TSH	FIA	1 yr; time N/A
					CAH	17-OHP	FIA	
					G6PD-deficiency	G6PD	FIA	
			2008[3]	~70% (local coverage)	CH	TSH	EIA	6-20℃; indefinitely
					CAH	17-OHP	EIA	
					G6PD-deficiency	G6PD	EIA	
					CF	IRT	EIA	
					GAL	Galactose + enzyme	Total galactose + transferase enzyme	
					Various Metabolic	Various	MS/MS (45 conditions)	
Indonesia	230 M	4.17 M	2000	<1%	CH	TSH	RIA	4℃; 2 wks
Laos	6.3 M	0.17 M	2008	~7%	CH	TSH	N/A	Room temperature; time N/A
Mongolia	2.7 M	0.05 M	2000[4]	~6%	CH	TSH	RIA	Room temperature; 5 years
					CAH	17-OHP	RIA	
Pakistan	181 M	5.40 M	2007	<1%[5]	CH	TSH	IRMA	Room temperature; time N/A
Palau	0.02 M	~300	2009	~50%	Uses Philippine panel excluding G6PD-deficiency (see information below)			Room temperature; duration not decided
Philippines	92.0 M	2.25 M	1996	28%	CH	TSH	FIA	Room temperature; duration not decided
					CAH	17-OHP	FIA	
					GAL	GAL-1-P	Spot Test	
					PKU	PHE	Enzyme colorimetric	
					G6PD-deficiency	G6PD	Enzyme flourometric	
Sri Lanka	20.2 M	0.36 M	2005	2.8%[6]	CH	TSH	IRMA	4℃; duration not decided
Vietnam	88.1 M	1.5 M	1998	~7%[7]	CH	TSH	ELISA; FIA	4℃; 1 yr then room temperature (air-conditioned) for 2 yrs (3 yrs total)
					CAH	17-OHP	ELISA	
					G6PD-deficiency	G6PD	Enzyme	

Newborn screening in China (Not expanded)

2nd largest number of births in the world

Newborn Screening in China: Phenylketonuria, Congenital Hypothyroidism and Expanded Screening

Xuefan Gu,[1]*MD, PhD*, Zhiguo Wang,[2]*MD*, Jun Ye,[1]*MD*, Lianshu Han,[1]*MD*, Wenjuan Qiu,[1]*MD, PhD*

Abstract

This study was to investigate the current status of neonatal screening in China, to further clarify the incidences of hyperphenylalaninemia (HPA) and congenital hypothyroidism (CH). From 2000 to 2007, a total of 17,961,826 newborns had been screened for HPA and 1527 cases were detected, giving a HPA prevalence of 1:11,763. At the same time, 18,284,745 newborns had also been tested for CH, with 8918 cases being detected (1:2050). It is remarkable that the mean number of newborns screened per year had increased 5 times between 2000 and 2007. In Shanghai, 116,000 newborns were screened using tandem mass spectrometry and 6 different were detected. The overall prevalence of an inborn errors of metabolism identified was 1 in 5800 healthy newborns, with hyperphenylalaninemia being the most common. Neonatal screening had developed rapidly in China in recent years, and a pilot study using tandem mass spectrometry has been started. The biggest challenge is still to increase coverage to the entire country, especially in the mid-western area.

Ann Acad Med Singapore 2008;37(Suppl 3):107-10

- variable coverage in different provinces
- 50% of newborns have access to NBS for Phenylketonuria & Congenital hypothyroidism
- Expanded newborn screening for inborn errors of metabolism available in few major hospitals

Current Newborn screening in Hong Kong

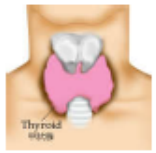
Clinical Genetic Service Information Leaflet on Newborn Screening

The Genetic Screening Unit of Department of Health provides newborn screening

Target:
Babies born in Hong Kong public hospitals

Conditions screened:

1. Glucose-6-phosphate Dehydrogenase (G6PD) Deficiency
2. Congenital Hypothyroidism



Reason:

- No obvious symptoms at the early stage
- Early detection and treatment could help to prevent physical and mental impairment in these babies

Fee: Free

Method: Testing baby's umbilical cord blood

If result normal :

Parents will **not** be informed

If result abnormal:
Parents will be informed within 2 weeks:

1. **Confirmed Glucose-6-phosphate Dehydrogenase (G6PD) Defciency**
   Parents will be informed and counselled by Genetic Screening Unit or hospital staff

2. **Congenital Hypothyroidism**
   *Suspected Congenital Hypothyroidism
   Parents will be informed by Genetic Screening Unit or hospital staff for reassessment, including blood taking and physical examination

   *Confirmed Congenital Hypothyroidism
   Baby will be referred to the hospital for further management

Babies born in private hospitals

Are also entitled to the screening

Parents could consult their Obstetricians or Paediatricians for further information

Hotline : 2361 9979
Website: http:// www.cgs.dh.gov.hk

Rev. 2010

- Started in 1984
- Coverage 99%
- Prevented kernicterus from G6PD deficiency & mental retardation from Congenital hypothyroidism
- Hearing screening started 2007

Should we implement Expanded newborn screening in Hong Kong?

- Should we follow the world trend?
- Is there the need locally? Do we have IEM patients that can be picked up by NBS?
- Do we have the technology?
- Can we effectively treat/manage patients that are picked up by newborn screening?
- Can we afford it?
- Is it cost-effective?

- Is there the need locally?
- Do we have IEM patients that can be picked up by newborn screening?

IEM Patients in Hong Kong

Inborn errors of metabolism
local incidence & disease spectrum

ELSEVIER

Clinica Chimica Acta 313 (2001) 195–201

www.elsevier.com/locate/clinchim

Overview of common inherited metabolic diseases in a Southern Chinese population of Hong Kong

Nelson L.S. Tang [a,*], Joannie Hui [b], L.K. Law [a], K.F. To [c], T.W.L. Mak [d], K.L. Cheung [b], Peter Vreken [c,*], Ronald J.A. Wanders [c], T.F. Fok [b]

Table 1. Major categories of metabolic diseases diagnosed in Prince ofWales Hospital

Category of metabolic diseases	Number of families
Organic aciduria	14
Fatty acid oxidation defect	5
Urea cycle disorders	3
Amino acid disorders	3[a]
Storage diseases (include various types of mucopolysaccharidosis, glycogen storage diseases and also Mucolipidosis type II and Niemann-pick type C)	10
Peroxisomal diseases (X-linked adrenoleukodystrophy and Zellweger syndrome)	6
Mitochondrial disease (include Kearns–Sayre syndrome, Complex I deficiency and Leigh's syndrome)	7

a The three families of amino acid disorders had phenylketonuria, tyrosinemia and cystinuria. However,

- PWH
- 1997-2000 (3y)
- 40 cases
- 14 Organic aciduria
- 5 Fatty acid oxidation disorder
- 3 Amino acid disorders

Chinese Medical Journal 2011;124(7):983-989

Original article

Analysis of inborn errors of metabolism: disease spectrum for expanded newborn screening in Hong Kong

Han-Chih Hencher Lee, Chloe Miu Mak, Ching-Wan Lam, Yuet-Ping Yuen, Angel On-Kei Chan, Chi-Chung Shek, Tak-Shing Siu, Chi-Kong Lai, Chor-Kwan Ching, Wai-Kwan Siu, Sammy Pak-Lam Chen, Chun-Yiu Law, Morris Hok-Leung Tai, Sidney Tam and Albert Yan-Wo Chan

- 3 hospitals (QMH, QEH & PMH)
- 2005-2009 (4y)
- 43 cases
- 5 Organic aciduria
- 8 Fatty acid oxidation disorder
- 30 Amino acid disorders

- IEM incidence 1 in 4122 live births

Joint Metabolic clinic Prince of Wales Hospital since 1997

IEM
Symptomatic presentation

Paediatricians + Chemical Pathologists

diagnostic work up

- patient management
- multi-disciplinary intervention (Dietetics)
- follow up
- Genetic counseling
- Prenatal diagnosis

Over 150 families with various confirmed IEM

Some IEMs are amenable to simple treatment !!!

- if these IEMs can be diagnosed and treated early especially before patients become ill, their outcome would be so much better
- in some instances even life saving

Sudden death after mild illness from Carnitine transporter defect

Consent obtained from parents

Holocarboxylase Synthetase deficiency

→ rash & severe metabolic acidosis

Consent obtained from parents

Glutaric Aciduria I → Acute encephalopathy

Hyperphenylalanaemia (Atypical PKU) due to 6 Pyrovyl tetrahydropterin synthase (PTPS) deficiency

→ developmental delay & movement disorder

Benefits of Expanded newborn screening

- early detection of potentially life threatening conditions
- early treatment & prevention of harmful sequelae
- reduce morbidity & mortality
- reduce burden to family & society (cost of non-productivity, institution care, medical cost)

change the natural history of a number of IEM conditions

Life saving

Harms of Expanded Newborn Screening

Cost Effectiveness

Problems/ Risks/ Harms of Expanded newborn screening

- Not diagnostic
  - Any presumptive positive result requires confirmation
- Misconceptions
  - Not all IEMs have been screened for
- False positives (Parental anxiety)
  - "It was scary and when I found out my daughter was fine I felt like we'd gone through a lot for nothing."
  - I'm willing to face the risk of a false-positive. I would rather have my world shaken for a brief period of time than to lose my baby forever.
  - Newborn screening saves lives; that's enough for me.
- False negatives (Missed diagnosis)
  - Variable disease severities – absence of biochemical abnormalities in the newborn period
- Symptomatic presentation before result of NBS available
- The right 'not to know'
- Labelling – diagnosis of benign conditions
- Unanticipated outcomes – maternal conditions unraveled

Cost - effectiveness of Expanded NBS

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Expanded Newborn Screening: Outcome in Screened and Unscreened Patients at Age 6 Years

Bridget Wilcken, Marion Haas, Pamela Joy, Veronica Wiley, Francis Bowling, Kevin Carpenter, John Christodoulou, David Cowley, Carolyn Ellaway, Janice Fletcher, Edwin P. Kirk, Barry Lewis, Jim McGill, Heidi Peters, James Pitt, Enzo Ranieri, Joy Yaplito-Lee and Avihu Boneh

Pediatrics 2009;124;e241; originally published online July 20, 2009;
DOI: 10.1542/peds.2008-0586

- Cohort study in Australia
- Comparing outcome for IEM patients at 6y before and after expanded NBS
- Expanded newborn screening provides better outcome with fewer deaths and fewer clinically significant disabilities

Cost-Effectiveness of Expanded Newborn Screening in Texas

1Alberta Health Services, Edmonton, Alberta, Canada; 2The University of Texas at Austin, Austin, TX, USA

Value in Health 15(2012) 613-621

- Expanded newborn screening does result in additional expenses to the payer, but it also improves patient outcomes by preventing avoidable morbidity and mortality
- The screened population benefits from greater QALYs (quality adjusted life years) as compared with the unscreened population
- Overall, expanded newborn screening in Texas was estimated to be a cost-effective option as compared with unexpanded newborn screening

Pilot program :

The Chinese University of Hong Kong

Joshua Hellmann Foundation

Newborn Metabolic Screening Program

Joshua Hellmann Foundation for Orphan Disease
夏約書孤兒症基金會

香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

Joshua Hellmann Foundation
Newborn metabolic screening program
The Chinese University of Hong Kong

- a collaborative effort from 3 clinical departments (Obstetrics, Paediatrics, Chemical Pathology) at the Prince of Wales Hospital
- donated funding from Joshua Hellmann Foundation for Orphan disease
- voluntary participation self financed
- babies from both public & private hospitals

- started July 2013
- DBS cards collected & sent to the Screening lab at the Prince of Wales Hospital
- MS/MS run 5 days a week
- turn around time from 1-3 days
- multiple logistics logistics logistics logistics logistics problems to overcome

Joshua Hellmann Foundation for Orphan Disease
夏約書孤兒症基金會

香港中文大學醫學院 Faculty of Medicine The Chinese University of Hong Kong

Joshua Hellmann Foundation Newborn metabolic screening program The Chinese University of Hong Kong Preliminary results

- up till April 2014 (10 months)
- screened over 4500 infants
- majority have normal results
- recall rate ~ 0.5
- turn around time 1-3 days

- True positives : 4 cases

1. elevated C5
   Dx: 2-Methylbutyryl-CoA dehydrogenase deficiency (benign)
2. elevated C5-OH/C4-DC
   Dx: ? 3 -Methylcrotonyl-CoA carboxylase deficiency (maternal)
3. elevated C8
   Dx: Medium chain acylCoA dehydrogenase deficiency
4. decreased C0
   Dx: ? Carnitine transporter defect

HK needs expanded NBS

Technology is available
Logistics is not impossible to work through

IEM babies need to be diagnosed at the earliest instance to ensure the best possible treatment outcome

The way forward-

- Working towards a territory wide Expanded newborn screening program

Aim :
Every newborn baby in HK gets expanded newborn screening

- Public health program & policy
- Working group (multidisciplinary) formed 2013
- Members from

  Clinical Genetic service (Department of Health)

  Paediatrics, Obstetrics, Chemical Pathology (Hospital Authority)

  Clinicians

  Laboratory staff

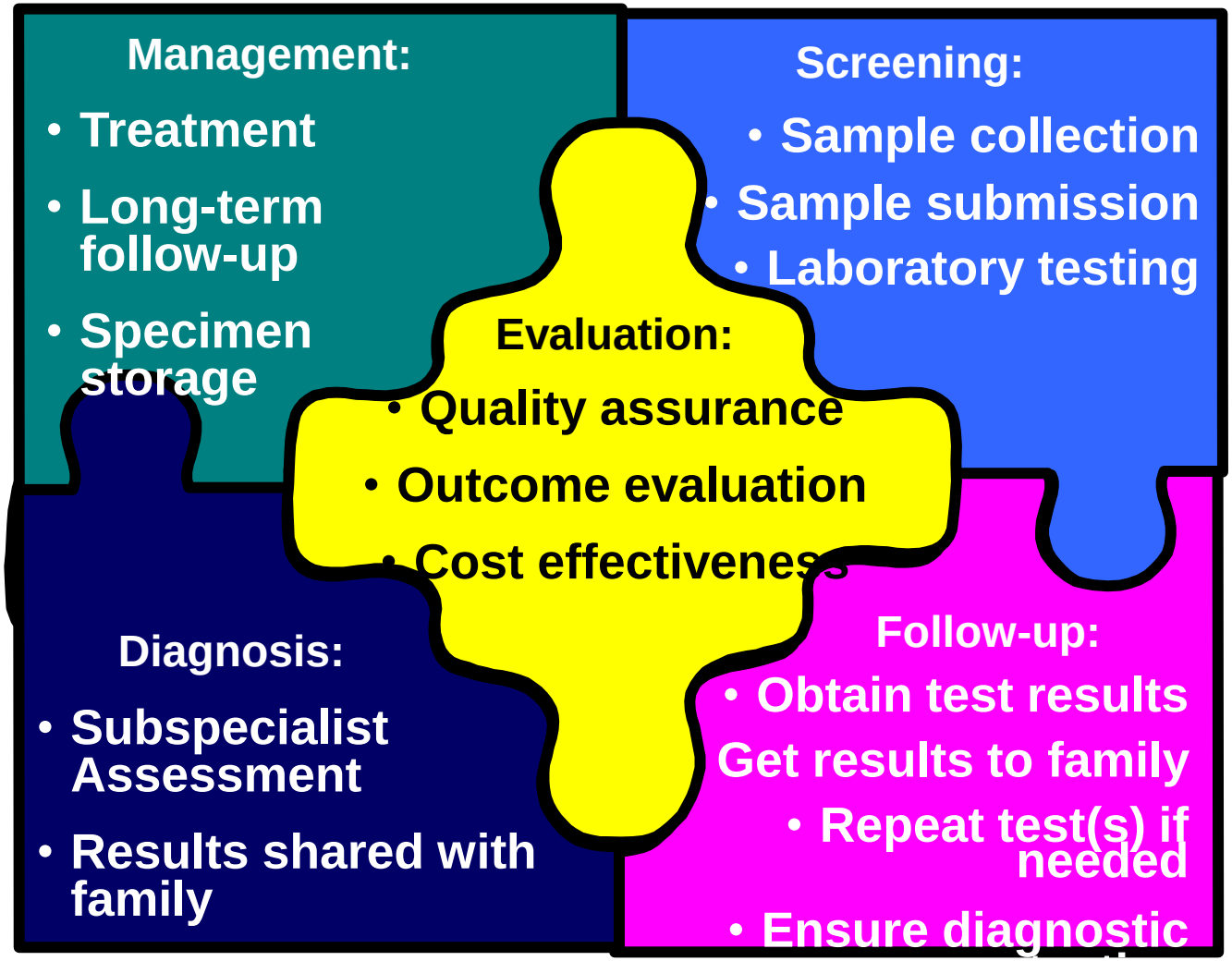
  Public health personnel

  Ethicists, Patient support groups

Screening is more than a test ……

Components of newborn screening

Sampling
Screening
Reporting
Referring
Follow-up
Evaluation



HA core values

Kevin /31y
American
Photographer

My PKU Life

http://www.youtube.com/watch?v=W2ipJAliBc8

Hau Yin /6y
Chinese
Student

http://programme.rthk.hk/rthk/tv/programme.php?name=tv/parentinghandbook&d=2014-04-14&p=6226&e=254615&m=episode

All babies have equal rights to live healthy lives

Expanded NBS is one such platform to ensure a good start for them

Acknowledgment

Department of Paediatrics

- CK Li
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- TY Leung
- Y Cheng
- O Chan
- J Lai

All patients & families who teach us IEM & trust us with their IEM