Pilot Study of Newborn Screening (NBS) for Inborn Errors of Metabolism (IEM) in Collaboration with Department of Health and Hospital Authority

Dr Chloe Mak
Department of Pathology
Princess Margaret Hospital
On behalf of the Task Force of Pilot Study of Newborn Screening for Inborn Errors of Metabolism

Newborn Screening (NBS)
– *the Best Practice of Preventive Medicine*

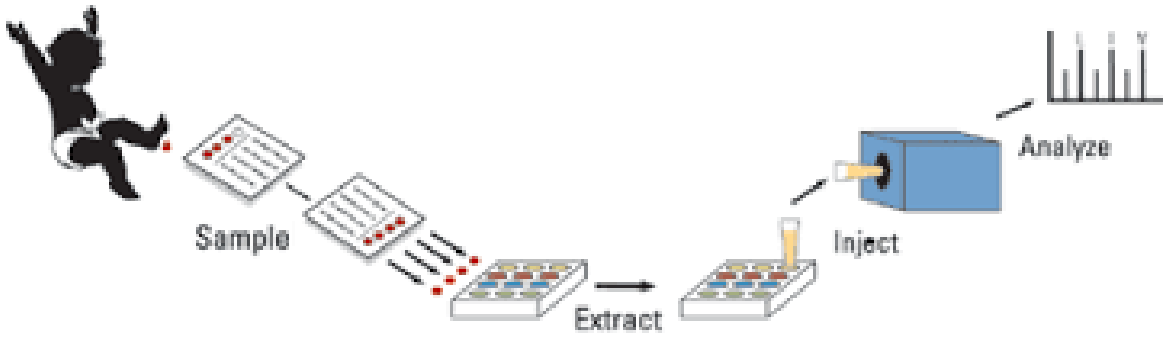
Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

Newborn Screening Portal

NBS identifies conditions that can affect a child's long-term health or survival.

Early detection, diagnosis, and intervention can prevent death or disability and enable children to reach their full potential.

Recent Development in NBS for IEM



Argentina
Armenia
Australia
Austria
Bahrain
Belgium
Brazil
Bulgaria
Canada
Chile
China
Colombia
Costa Rica
Cuba
Czech Republic
Denmark
Egypt
El Salvador
Estonia
Finland
France
Germany
Greece
Greenland
Hungary
Iceland
India
Ireland
Israel
Italy
Japan
Jordan
Kuwait
Latvia
Lebanon
Lithuania
Luxembourg
Malaysia
Mexico
Netherlands
New Zealand
Norway
Oman
Pakistan
Panama
Paraguay
Peru
Philippines
Poland
Portugal
Qatar
Saudi Arabia
Singapore
Slovak Republic
South Africa
South Korea
Spain
Sweden
Switzerland
Taiwan
Thailand
Turkey
Ukraine
United Arab Emirates
United Kingdom
United States
Uruguay

Tandem Mass Spectrometry
One Test Multiple Diseases

Cost per QALYs gained

> US $10,000

Preventable Death & Medicolegal Conflicts

Coroner's Report 2008

(vi) A fourteen year old died of un-diagnosed congenital metabolism defect

The Department of Health, the Hospital Authority, the Faculty of Medicine of various universities and others concerned should carry out a feasibility study to see whether universal check may be carried out on all newborn babies for 'congenital metabolism defect'.

http://www.judiciary.gov.hk/en/publications/coroner_report_july08.pdf

醫健

初生嬰兒

代謝缺乏症普遍

本港初生嬰兒進行的遺傳病篩查，只針對甲狀腺功能不足和蠶豆症。瑪嘉烈醫院病理部發現，嬰兒先天性代謝缺乏症（IEM）相當普遍，在二○○五年至○九年間，就發現四十三宗個案，其中一人更在廿九歲時才被診斷出來，以此推算本港每四千一百二十二名新生嬰兒中，就有一名患者。由於該類疾病可導致智障、肝衰竭、心臟受損和猝死等，故建議擴大初生嬰兒篩選，以及早找出患者和提供適當治療。

四十三宗IEM患者中，包括卅宗屬氨基酸血症、八宗脂肪酸氧化作用缺乏及五宗有機酸血症。五名患者在發病時，已知他們有該類疾病的家族史。患者發病時間由出生至十一歲，而確診為IEM時間則由出生至廿九歲。患者主要出現發育遲緩、黃疸、經常嘔吐、血糖過低、肝衰竭等徵狀，嚴重的甚至可能猝死。

每四千新生嬰一病患

其中兩名患者分別在一九八七年和一九九○年出生，在年幼時已出現大腦麻痺，但他們直至○五年才確定患上其中一類的IEM。另有一名患者是父母的第三胎，之前兩胎都患上同一疾病。

雖然該研究只找出四十三宗IEM個案，但同期出生的嬰兒有卅五萬四千多名，以此推算本港每四千一百二十二名新生嬰兒就有一宗個案，發病率與鄰近地區相若。

負責該研究的醫生指出，該類疾病臨床診斷困難，延遲診斷情況也非罕見，擴大嬰兒篩選可及早找出患者，為家長提供輔導和跟進患者的情況。

擴大篩選及早尋患者

中文大學兒科學系教授韓錦倫表示，IEM的種類很多，主要因身體不能消化某種酵素、碳水化合物或脂肪等，積聚在體內多年才發病，導致心臟衰竭、肌肉萎縮或猝死，故患者發病後求診，醫護人員未必留意到病徵與IEM有關。

韓錦倫指出，即使醫生有懷疑，對患者進行檢驗需時，可能在化驗有結果前，患者已死亡。

他認為，若某類IEM在華人社會普遍，又有治療方法，就值得在進行初生嬰兒篩查，找出患者和提供適當治療。

瑪嘉烈醫院病理部研究建議，擴大新生嬰兒篩查，及早找出先天性代謝缺乏症患者，以便跟進患者和輔導家長。

嬰兒患上先天性代謝缺乏症，會影響身體機能。

醫先知健

先天代謝缺乏症普遍

初生嬰遺傳病篩查不足

本報訊 本港初生嬰兒進行的遺傳病篩查，只針對甲狀腺功能不足和蠶豆症。瑪嘉烈醫院病理部發現，嬰兒先天性代謝缺乏症（IEM）相當普遍，在二○○五年至○九年間，就發現四十三宗個案，其中一人更在二十九歲時才被診斷出來，以此推算，本港每四千一百二十二名新生嬰兒中，就有一名患者。由於該類疾病可導致智障、肝衰竭、心臟受損和猝死等，故建議擴大初生嬰兒篩選，以及早找出患者和提供適當治療。

IEM可致發展遲緩及猝死

四十三宗IEM患者中，包括三十宗屬氨基酸血症、八宗脂肪酸氧化作用缺乏及五宗有機酸血症。五名患者在發病時，已知他們有該類疾病的家族史。患者發病時間由出生至十一歲，而確診為IEM時間則由出生至二十九歲。患者主要出現發展遲緩、黃疸、經常嘔吐、血糖過低、肝衰竭等徵狀，甚至可能猝死。

其中兩名患者分別在一九八七年和一九九○年出生，在年幼時已出現大腦麻痺，但他們直至○五年才確定患上其中一類的IEM。另有一名患者是父母的第三胎，之前兩胎都患上同一疾病。

雖然該研究只找出四十三宗IEM個案，但同期出生的嬰兒有三十五萬四千多名，以此推算，本港每四千一百二十二名新生嬰兒就有一宗個案。

負責該研究的醫生指出，該類疾病臨床診斷困難，延遲診斷情況也非罕見，擴大嬰兒篩選可及早找出患者，為家長提供輔導和跟進患者的情況。

中文大學兒科學系教授韓錦倫表示，IEM的種類很多，主要因身體不能消化某種酵素、碳水化合物或脂肪等，積聚在體內多年才發病，導致心臟衰竭、肌肉萎縮或猝死，故患者發病後求診，醫護人員亦未必留意到病徵與IEM有關。

瑪嘉烈醫院病理部研究建議，擴大新生嬰兒篩查。

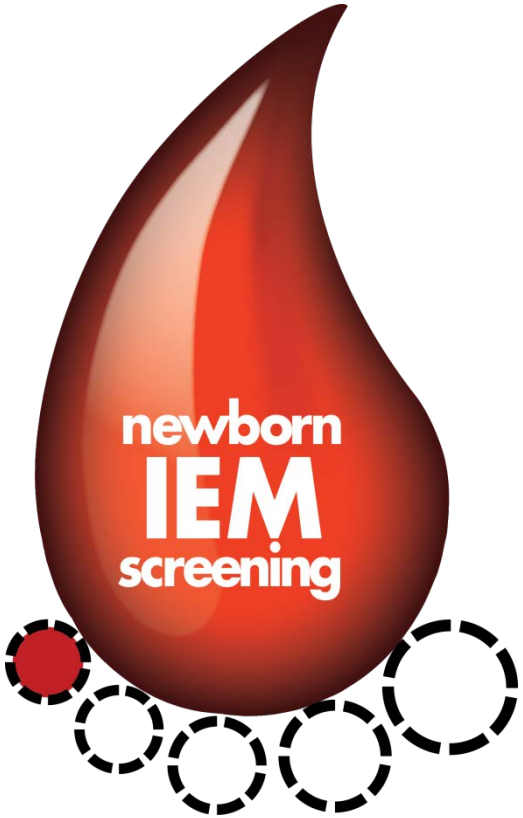
一滴血驗出罕見遺傳病

2015 Policy Address by Chief Executive

191. The DH and the HA have set up a working group to study the feasibility of trying out in the public healthcare system a *screening programme for newborn babies for inborn errors of metabolism*. The working group will study the types of disease to be screened, scientific evidence on the effectiveness of screening, actual arrangements and related recommendations.

http://www.info.gov.hk/gia/general/201501/14/P201501140477.htm

Materials & Methods



Pilot Study of Newborn Screening for Inborn Errors of Metabolism

Memberships

with representatives from the Food and Health Bureau, DH, HA and included disciplines of Clinical Genetics, Paediatrics, Obstetrics, Pathology, Information Technology and Public Health.

Workgroup

- Dr. Dr LIU Shao-haei
- Dr. Derrick AU Kit-sing
- Dr. Ivan LO Fai-man
- Dr. Rebecca LAM Kit-yi
- Dr. LEUNG Kwok-yin
- Dr. Bill CHAN Hin-biu
- Dr. Joannie HUI Chung-ni
- Dr. WONG Kit-fai
- Dr. Michael CHAN Ho-ming
- Dr. Chloe MAK Miu
- Dr. LO Yim-chong
- Dr. Rita HO Ka-wai
- Dr. Edgar HAU Wai-lok
- Mr. Tony TONG Ming-for

- In attendance
- Ms. Fiona CHAU Suet-mui
- Ms. Yvonne TAM Yan-wun
- Dr. Cindy LAI Kit-lim, JP

TaskForce

- Dr. Ivan LO Fai-man
- Dr. Rebecca LAM Kit-yi
- Dr. LEUNG Chau-mau
- Dr. Anna TONG Yee-ha
- Mr. Sam YEUNG Wing-chiu
- Dr. LEUNG Kwok-yin
- Dr. HUI Pui-wah
- Ms. TSANG Siu-ling
- Ms. Grace MA Gar-yee
- Dr. Betty BUT Wai-man
- Dr. Joannie HUI Chung-ni
- Dr. Grace POON Wing-kit
- Dr. Eric YAU Kin-cheong
- Dr. WONG Kit-fai
- Dr. Chloe MAK Miu
- Dr. Karen TSO Ka-pik
- Dr. Edgar HAU Wai-lok
- Ms. Andes AU Wing-mui

Criteria for inclusion of IEM

- Based on classical Wilson and Jungner screening criteria:

	Criteria	***Elaboration***
1	Screening capability	availability of accurate and reliable screening and diagnostic testing; and of laboratory capability
2	Clinical significance	number of cases encountered in our locality
3	Available treatment	efficacy and/or effectiveness of the treatment
4	Early treatment outcome	adequacy of the understanding of the natural history of the condition and its long-term outcome with early treatment

24 diseases in metabolism of carbohydrates, protein, fat and hormones.

	IEM
Organic acid disorders	Multiple carboxylase deficiency
	Glutaric acidaemia type 1
	Methylmalonic acidaemia
	Propionic acidaemia
	Isovaleric acidaemia
	3-hydroxy-3-methylglutaryl-CoA lyase deficiency
	Ketothiolase deficiency
Amino acid disorders	Phenylketonuria
	6-pyruvoyl-tetrahydropterin synthase deficiency
	Argininosuccinic acidaemia
	Maple syrup urine disease
	Citrullinaemia type I
	Citrullinaemia type II
	Tyrosinaemia Type 1
	Homocystinuria

	IEM
Fatty acid oxidation disorders	Carnitine uptake deficiency
	Carnitine-acylcarnitine translocase deficiency
	Carnitine palmitoyltransferase II deficiency
	Medium-chain acyl-CoA dehydrogenase deficiency
	Very long-chain acyl-CoA dehydrogenase deficiency
	Glutaric acidaemia type 2
Others	Congenital adrenal hyperplasia
	Biotinidase deficiency
	Galactosaemia

2-year Pilot Study for NBS IEM

6 months

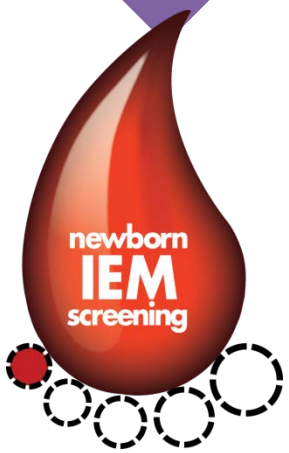
- Apr – Sep 15, Preparatory phase
  - Protocol development, education/training, laboratory set-up

6 months

- Oct 15 – Mar 16, Phase 1 logistic testing
  - 21 diseases, normal babies only

12 months

- Apr 16 – Mar 17, Phase 2 full testing
  - 24 diseases, all babies



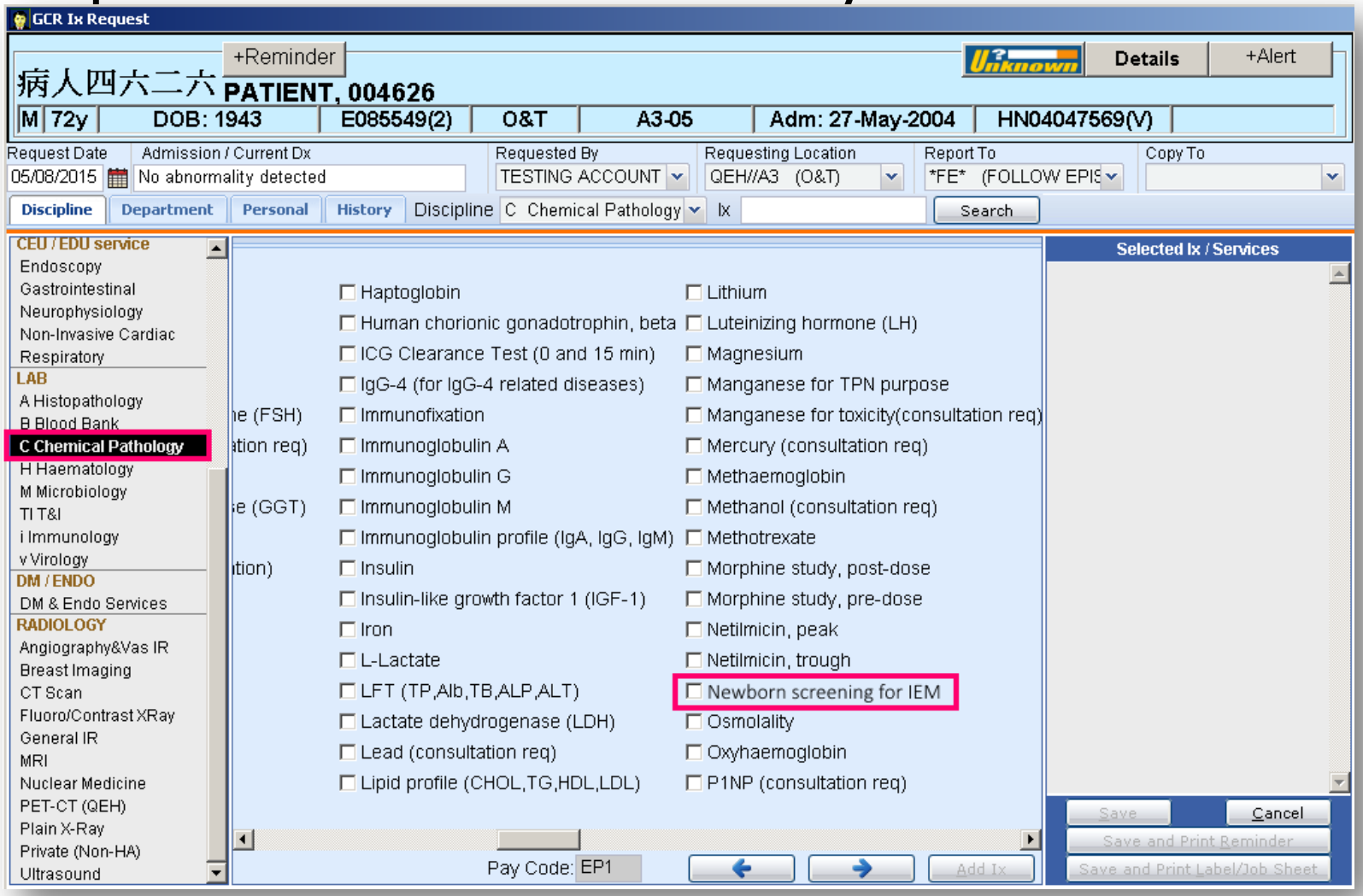
“10 Steps” of the NBS IEM Pilot Study

1. Parental Education
2. Consent
3. Sampling
4. Sample Delivery
5. Sample Testing
6. Reporting
7. Recall, Counseling
8. Confirmatory Testing
9. Treatment & Monitoring
10. Evaluation

初生嬰兒代謝病篩查Youtube link
廣東話版: https://youtu.be/RHK1NOGZkDs
普通話版: https://youtu.be/MLLxJf7RvEQ
英文版: https://youtu.be/JPPFfzUavGQ

GCRS ordering

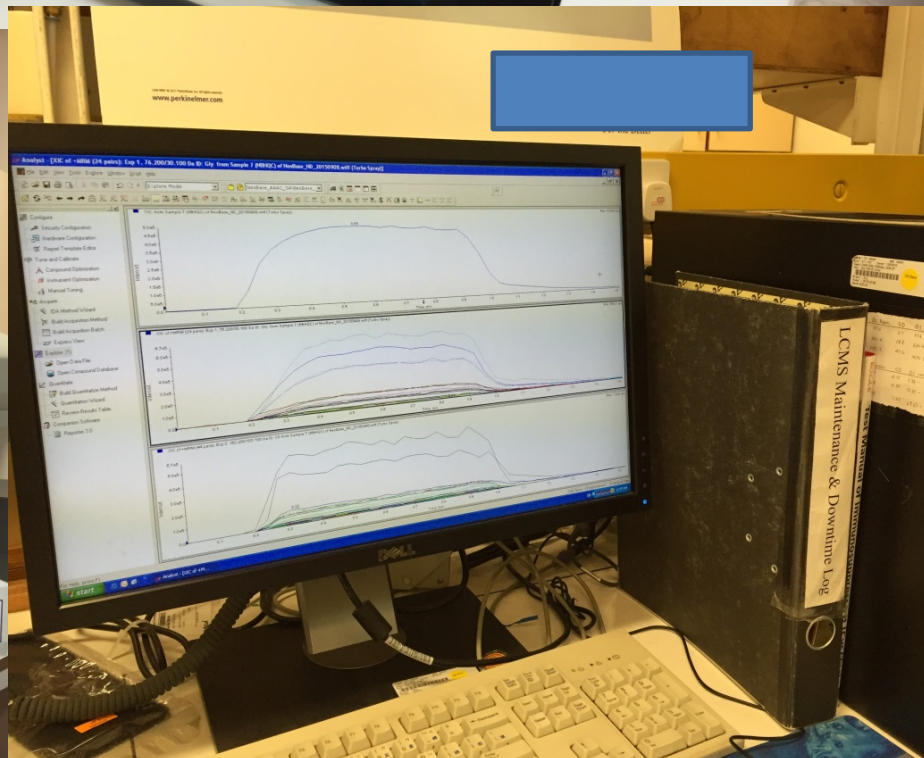
- Request “NBSIEM” in GRCS system.



Whatman 903TM
Whatman 903TM
Whatman 903TM

Select mode
TTV Slave

Agilent Technologies
Agilent Technologies
LCMS Maintenance & Downtime Log


www.perkinelmer.com
LCMS Maintenance & Downtime Log

PMH Production Chemical Pathology cbut051---mm612 LIS V.5.0.1234.7 [LisPmhPrd_cdceap9m dc5_lis_prd]

Patient Request Enquiry Worksheet Signout Report ADA System

F1 CWE F2 NB...

Retrieve Completed
Start Retrieve Request

Worksheet -- NBSIEM ( )

NBSTMS

16C3171651 [redacted] F 1 D Location: QEH/UNK/C9

Collection date: 30/05/16 Request Doctor: DR. WONG MING SUM, ROSANNA

Clinical Dtls: > / = 2250 gram,> / = 37 weeks + 0 day,Chinese,No,No,Normal,No,arnoid,

Birth weight: > / = 2250 gram Gestation: > / = 37 weeks + 0 day Please specify:

Ethnicity: Chinese Please specify:

Parental consanguinity: No

Family history of IEM: No Please specify:

Diet: Normal

Transfusion: No Last transfusion date: Last transfusion time:

Remarks: arnoid, coiari II MALFORMATION

Remarks:

Go to

Next >
< Back
Authorize
Save
Print
Refresh
Exit

NALA	241.89	NARG	13.04	NCIT	19.7	NRCITXLE	0.1877	NRCITARG	1.51	NRORNCIT	3.79	NGLY	334.93		
NMET	21.86	NRMETXLE	0.21	NRMETPHE	0.47	NORN	74.61	NPHE	46.24	NRPHETYR	0.64	NPRO	99.68		
NSA	0.48	NTYR	71.87	NVAL	116.19	NXLE	104.95	NRXLEALA	0.43	NRXLEPHE	2.27	NTCAR	32.5		
NC0	16.14	NC2	11.62	NC3	1.67	NRC3C16	0.9	NRC3C2	0.14	NC3DC4OH	0.03	NC4	0.26		
NRC4C3	0.16	NC5	0.09	NRC5C2	0.01	NRC5C3	0.05	NC5DC	0.06	NRC5DC8	3	NRC5DC16	0.03		
NC5OH	0.14	NRC5OHC8	7	NC51	0.01	NC6DC	0.04	NC6	0.02	NC8	0.02	NC81	0.03		
NRC8C10	1	NC10	0.02	NC101	0										
NC141	0.05	NRC14116	0.03	NC142	0										
NC16OH	0.01	NC161OH	0.04	NC18	0										
NR16OH16	0.01														

SCREENING FOR AMINO ACID DISORDERS:

Result: N

Abnormal Analyte(s):

Diagnosis:

Comments:

SCREENING FOR ORGANIC ACIDEMIAS:

Result: N

Abnormal Analyte(s):

Collection date: 01/06/16 Request Doctor: DR. JALAL KHAIR

Clinical Dtls: > / = 2250 gram,> / = 37 weeks + 0 day,Chinese,No,No,Normal,No/....

Birth weight: > / = 2250 gram Gestation: > / = 37 weeks + 0 day Please specify:

Ethnicity: Chinese Please specify:

Parental consanguinity: No

Family history of IEM: No Please specify:

Diet: Normal

Transfusion: No Last transfusion date: Last transfusion time:

Remarks:

Remarks:

NALA	304.33	NARG	15.66	NCIT	13.1	NRCITXLE	0.1209	NRCITARG	0.84	NRORNCIT	5.42	NGLY	336.37		
NMET	15.84	NRMETXLE	0.15	NRMETPHE	0.32	NORN	71.02	NPHE	48.74	NRPHETYR	0.6	NPRO	126.34		
NSA	0.52	NTYR	81.04	NVAL	113.1	NXLE	108.35	NRXLEALA	0.36	NRXLEPHE	2.22	NTCAR	33.18		
NC0	14.25	NC2	15.39	NC3	0.92	NRC3C16	0.54	NRC3C2	0.06	NC3DC4OH	0.06	NC4	0.14		
NRC4C3	0.15	NC5	0.08	NRC5C2	0.01	NRC5C3	0.09	NC5DC	0.08	NRC5DC8	8	NRC5DC16	0.05		
NC5OH	0.08	NRC5OHC8	8	NC51	0	NC6DC	0.04	NC6	0.01	NC8	0.01	NC81	0.04		
NRC8C10	0.5	NC10	0.02	NC101	0.01	NC102	0	NC12	0.02	NC121	0.02	NC14	0.1		
NC141	0.05	NRC14116	0.03	NC142	0.01	NC14OH	0.01	NC16	1.7	NRC01618	6.36	NC161	0.09		
NC16OH	0.01	NC161OH	0.04	NC18	0.54	NC181	0.65	NC182	0.15	NC18OH	0	NC181OH	0.01		
NR16OH16	0.01														

Date/time Collected : 06/04/2016 10:29
Date/time Arrived : 07/04/2016 13:46

Reference Range

C

NEWBORN SCREENING FOR INBORN ERRORS OF METABOLISM (NBSIEM)

Specimen: Dried blood spots	
Birth weight	> / = 2250 gram
Gestation	> / = 37 weeks + 0 day
Ethnicity	Chinese
Parental consanguinity	No
Family history of IEM	No
Diet	Normal
Transfusion	No

SCREENING FOR AMINO ACID DISORDERS

Result: NORMAL

Remarks: The screening panel includes argininosuccinic acidaemia, citrullinaemia type I, citrullinaemia type II, homocystinuria, maple syrup urine disease,phenylketonuria due to phenylalanine hydroxylase deficiency, 6-pyruvoyl-tetrahydropterin synthase deficiencyand tyrosinaemia type I.

SCREENING FOR ORGANIC ACIDAEMIAS

Result: NORMAL

Remarks: The screening panel includes beta-ketothiolase deficiency, glutaric acidaemia type I, 3-hydroxy-3-methylglutaryl-CoA lyase deficiency, isovaleric acidaemia, methylmalonic acidaemia, multiple carboxylase deficiency and propionic acidaemia.

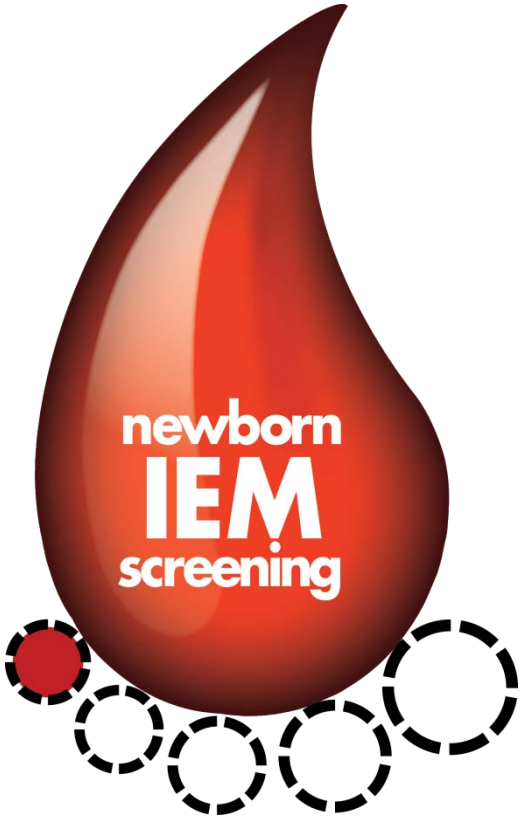
SCREENING FOR FATTY ACID OXIDATION DISORDERS

Result: NORMAL

Remarks: The screening panel includes carnitine uptake defect, carnitine-acylcarnitine translocase deficiency, carnitine palmitoyltransferase II deficiency, glutaric acidaemia type II, medium-chain acyl-CoA dehydrogenase deficiency and very long-chain acyl-CoA dehydrogenase deficiency.

Results

Pilot Study of Newborn Screening for Inborn Errors of Metabolism



Results

- 99% babies were consented to join the Pilot Study.

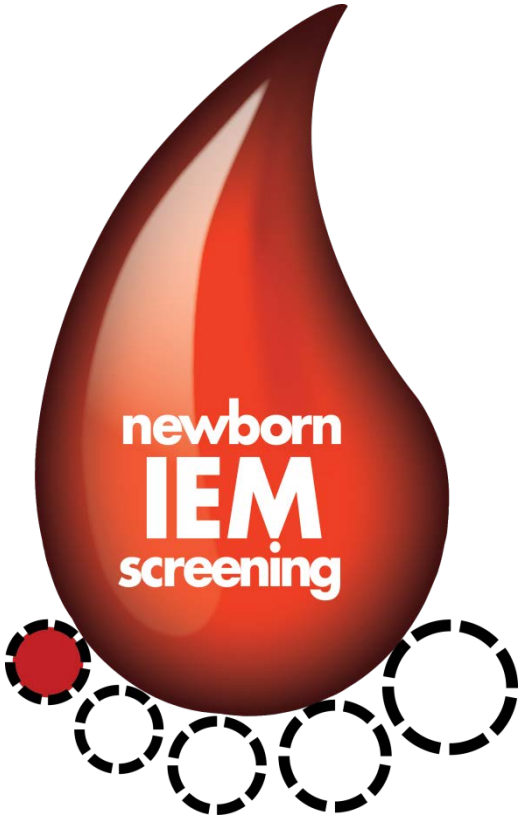
- Detected IEM incidence 1 in 1,700
  - Fatty acid oxidation disorders *(risk of heart failure / sudden death)*
  - Amino acid disorders *(risk of mental retardation / liver failure)*
  - Organic acid disorder *(risk of acute decompensation)*

  - Major outcome: remain asymptomatic & stable upon early management

- False positive 0.33%, true positive 0.06% (5.5 vs 1)
- False negative 0.01%

	Standards for Newborn Blood Spot Screening (2013 UK NBS Program Centre)	Our Output	Pass
1	≥ 99.9% consented babies were tested.	100%	Pass
2	100% timely specimen collection, delivery, reporting	100%	Pass
3	≤ 0.5% invalid samples	0.14%	Pass

Conclusions

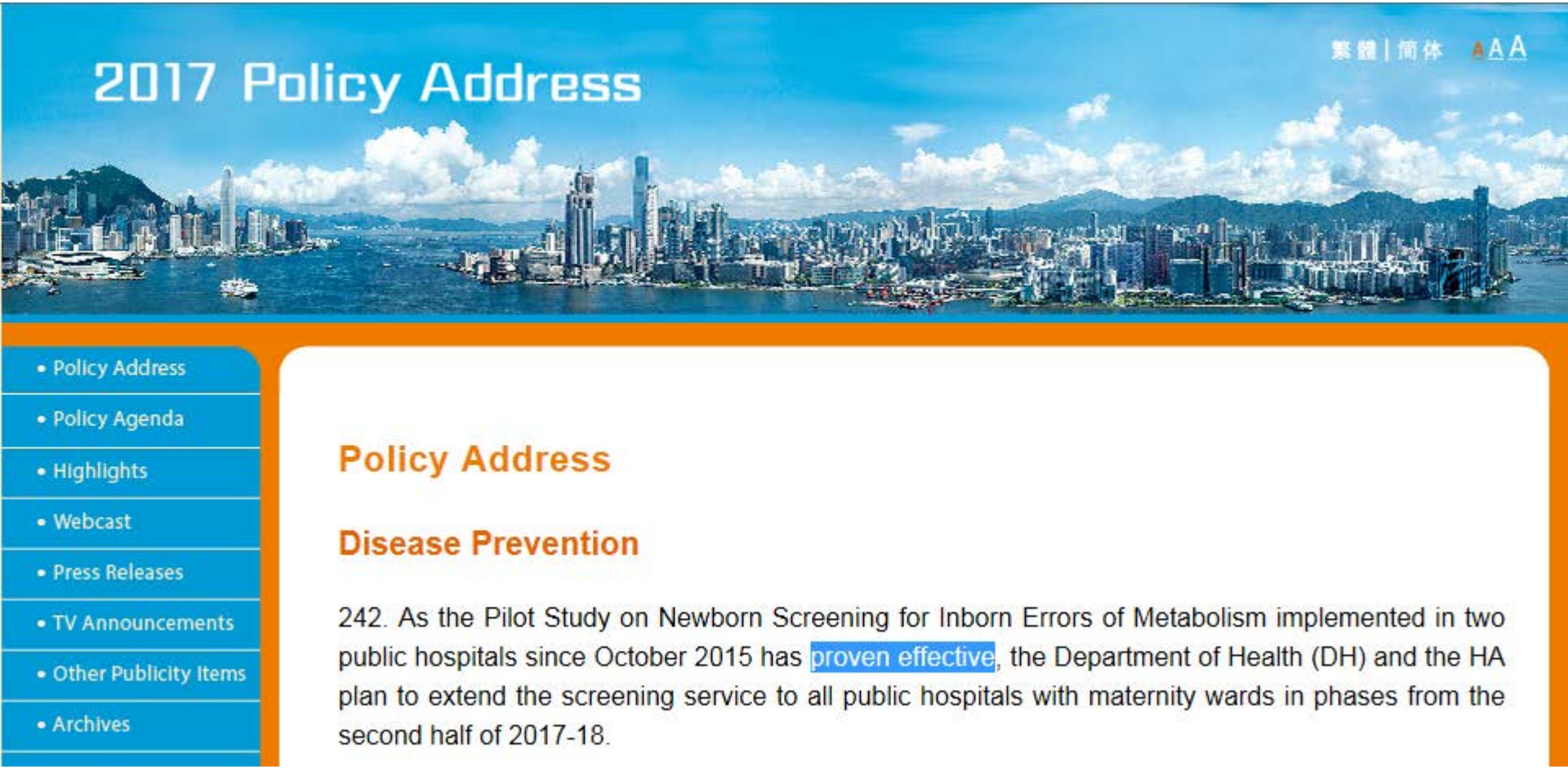


Pilot Study of Newborn Screening for Inborn Errors of Metabolism

Conclusions & Future Directions:

- The operation model is proven effective.
- Parental education and participation is satisfactory.
- IEM collectively is not rare in HK.
- Early detection and treatment save lives.
- Cost-effective study should follow in the long run.
- Potential integration with the Hong Kong Children's Hospital.
- The scope of IEM included can be reviewed on a regular basis to suit the changing needs and advancement of screening technology and treatment modalities.

Conclusions & Future Directions:



Thank God and everyone for NBS

Thank you