HA Convention 2016
Master course

How to Handle Abnormal Newborn Metabolic Screening Results – Causes, Management and Follow up

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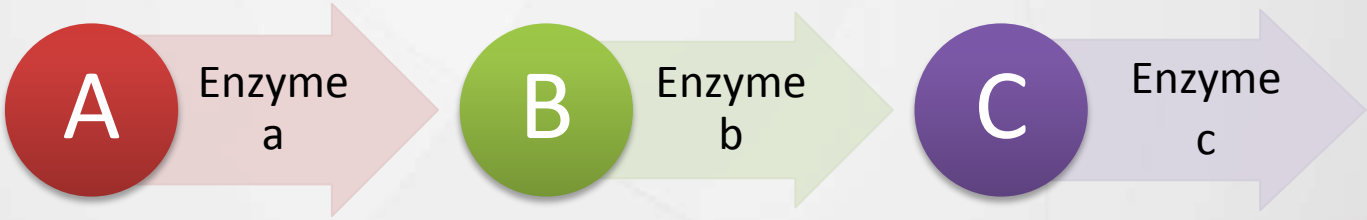
How to Handle Abnormal Newborn Metabolic Screening Results – Causes, Management and Follow up

- "Inborn errors of metabolism" (IEM)
  - a class of genetic disorders with defects of metabolism which are mostly due to single gene defects resulting in defective function of particular enzymes that are essential for conversion of substrates into products.



IEM disorders cause inadequate essential metabolites or accumulation of toxic intermediary metabolites for the body

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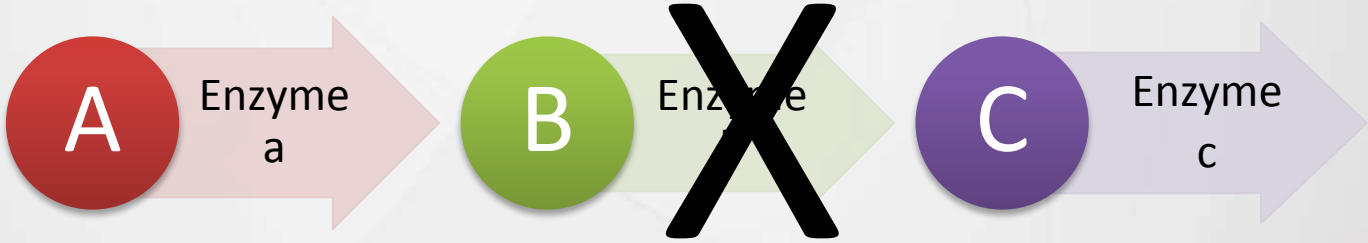

IEM disorders cause inadequate essential metabolites or accumulation of toxic intermediary metabolites for the body

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Need to know all IEM disorders??

NO

Not all IEM disorders are included in a newborn metabolic screening programme

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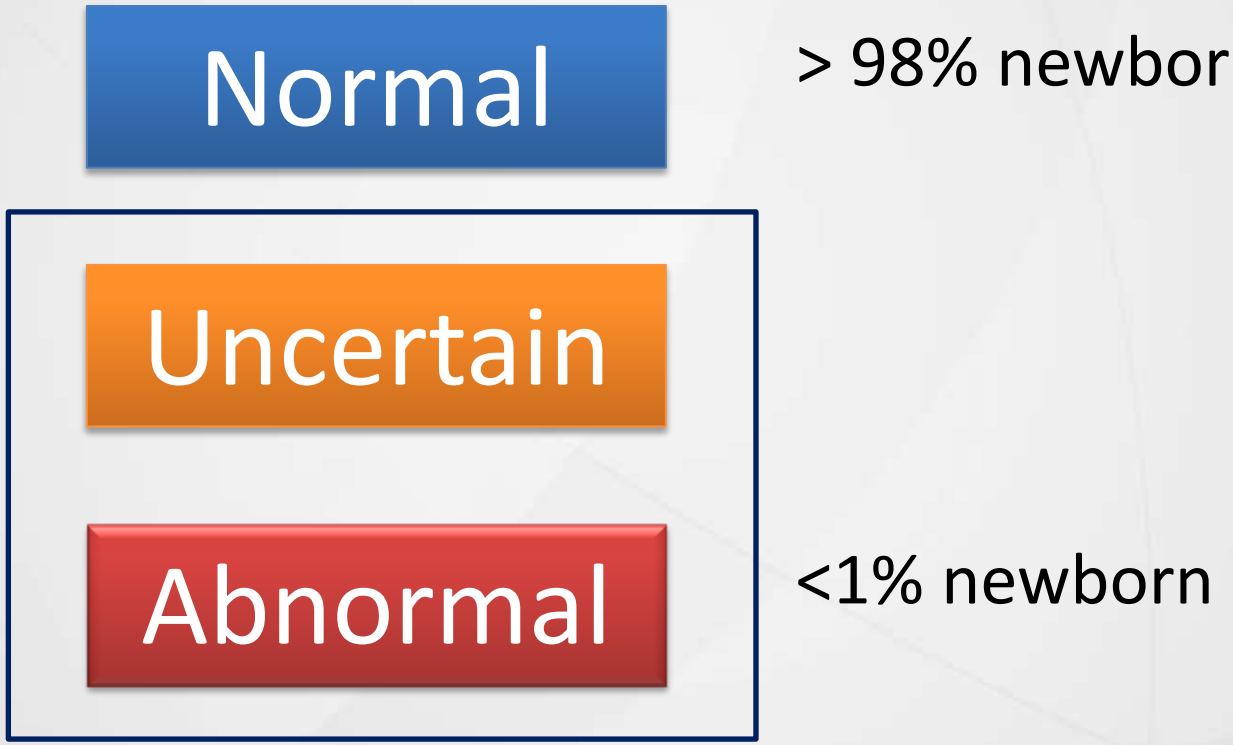
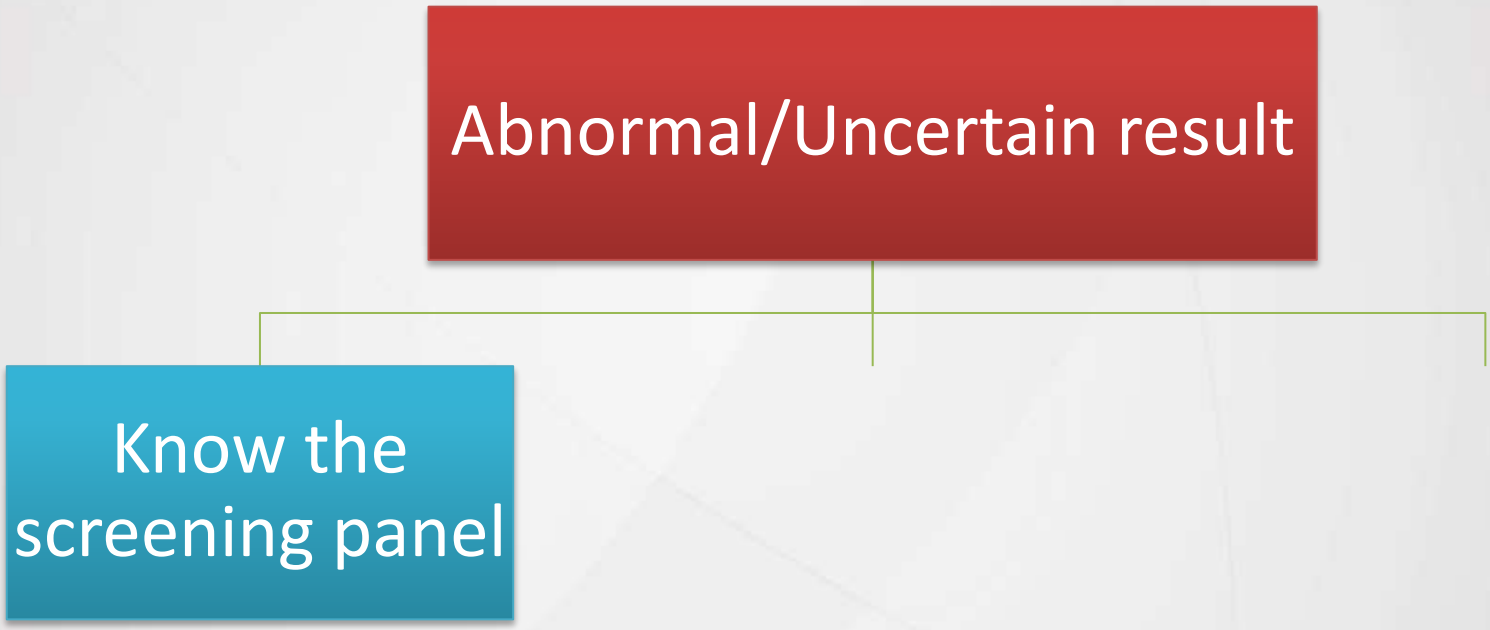
Newborn Metabolic Screening Results



> 98% newborn

<1% newborn

What do you need to know when handling Abnormal Newborn Metabolic Screening Results



Know the Screening Panel

1. What is the tested analytes

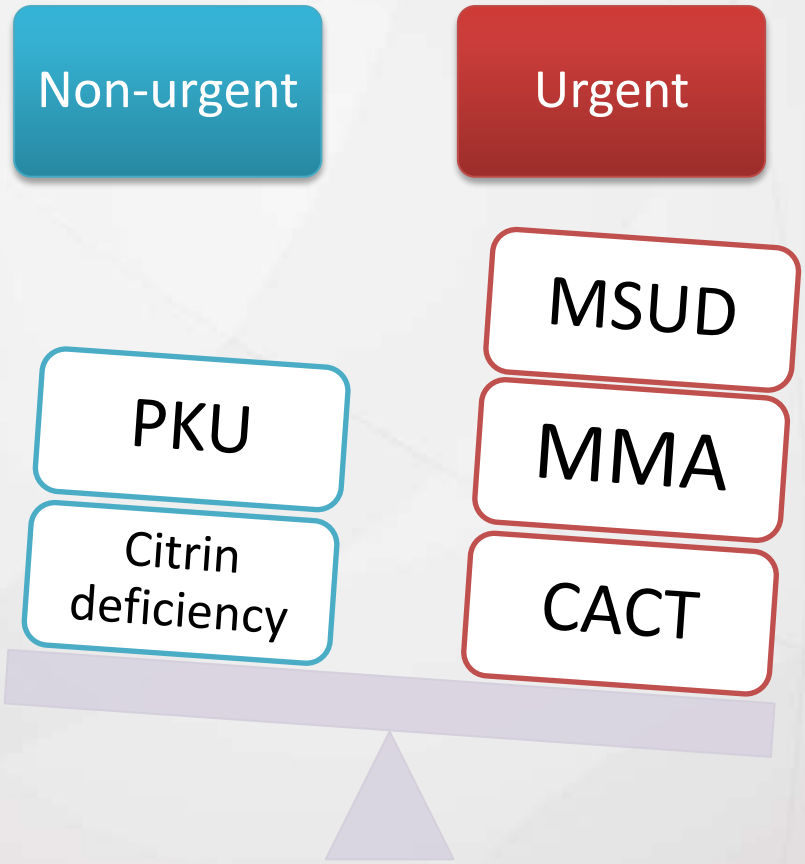
Know the Screening Panel

Amino acid					
Alanine	Citrulline	Leucine/isoleucine	Methionine	Ornithine	Valine
Arginine	Glycine	Phenylalanine	Proline	Tyrosine	Succinylacetone*

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

Know the Screening Panel

1. What is the tested analytes
2. What are the IEM disorders being screened



Know the Screening Panel

Inborn errors of metabolism categories	
Amino acid disorders	Phenylketonuria, Maple syrup urine disease, Citrullinemia type 1, Argininosuccinic aciduria, Homocystinuria, Tyrosinemia type 1, Arginase deficiency, Defects of biopterin cofactor biosynthesis and regeneration, Citrullinemia type 2
Organic acid disorders	Propionic acidemia, Isovaleric acidemia , Glutaric acidemia type 1 , Methylmalonic aciduria , Beta-ketothiolase deficiency, Multiple carboxylase deficiency
Fatty acid oxidation disorders	Carnitine uptake defect, Medium-chain acyl-CoA dehydrogenase deficiency, Very long-chain acyl-CoA dehydrogenase deficiency, Carnitine Acylcarnitine translocase deficiency, Carnitine palmitoyltransferase I /II deficiency

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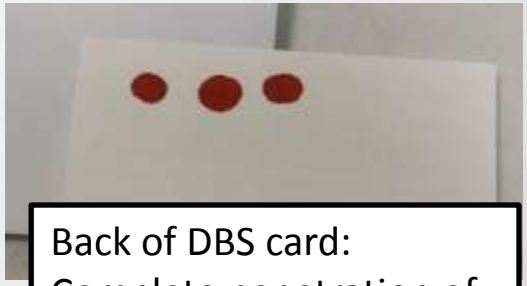
Know the Screening Panel

1. What is the tested analytes
2. What are the IEM disorders being screened
3. What are the factors affecting the levels of tested analytes
    1. Blood spots quality
    2. Timing of collection
    3. Baby's condition, feeding condition, liver function, medication

One big blood drop per circle, no layering

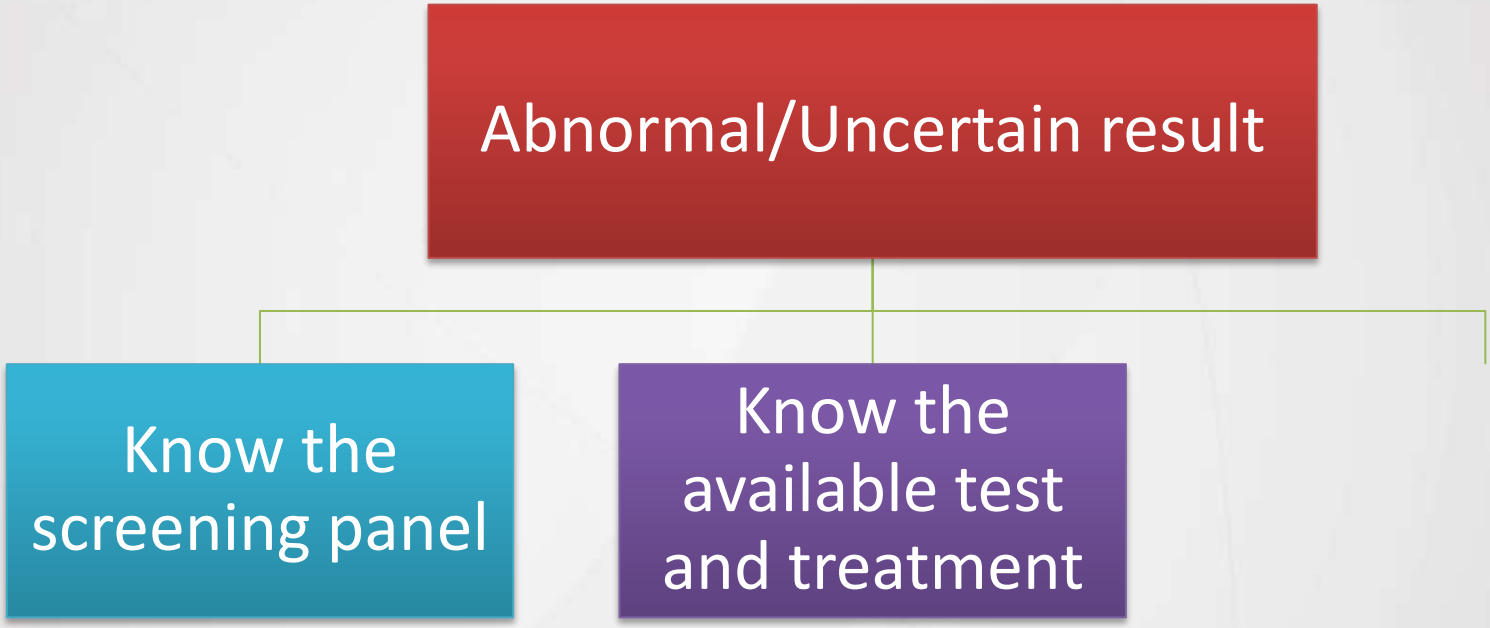


Back of DBS card: Complete penetration of blood drop

Know the Screening Panel

1. What is the tested analytes
2. What are the IEM disorders being screened
3. What are the factors affecting the levels of tested analytes
4. What are the limitations of the screening test
    1. The very mild variant of IEM disorders may not be picked up
    2. False negative (e.g. citrin deficiency)

What do you need to know when handling Abnormal Newborn Metabolic Screening Results



Know the available test and treatment

- Testing: loading testing, confirmatory testing (biochemical, genetics testing)
- Dietary modification: special milk formula, tailored made TPN
- Medications: e.g. carnitine supplement, cofactor supplement (e.g.biotin), anti-hyperammonaemia medication etc
- Treatment for acute decompensation: NICU support, availability of haemodialysis

Know the available test and treatment

ACMG ACT sheet

American College of Medical Genetics **ACT SHEET**

Newborn Screening ACT Sheet

[Elevated C5-DC Acylcarnitine]

Glutaryl-CoA Dehydrogenase Deficiency

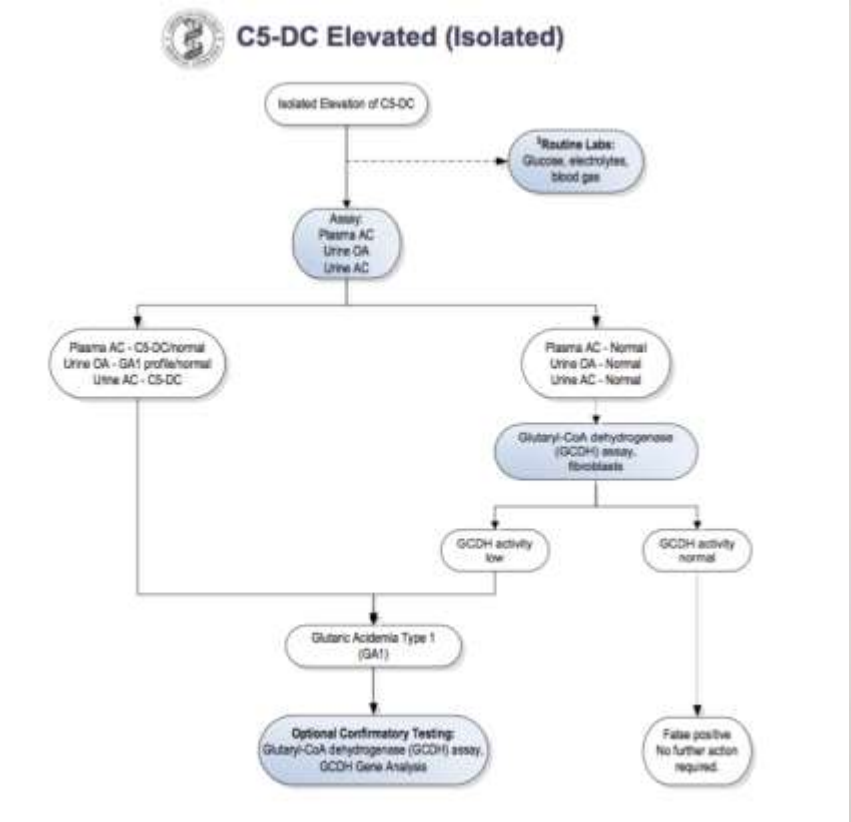
Differential Diagnosis: Glutaric aciduria (GA-1)

Condition Description: GA-1 is caused by a defect of **glutaryl-CoA dehydrogenase** which limits the metabolism of glutaryl-CoA to crotonyl-CoA, resulting in increased glutaric acid or its metabolites that are toxic.

YOU SHOULD TAKE THE FOLLOWING ACTIONS:

- Contact family **IMMEDIATELY** to inform them of the newborn screening result.
- Consult with pediatric metabolic specialist.
- Evaluate the newborn for macrocephaly and muscle hypotonia, initiate confirmatory/diagnostic testing as recommended by metabolic specialist.
- Refer to metabolic specialist to be seen as soon as possible but not later than three weeks.
- Educate family about diagnostic possibilities, complexity of diagnostic work-up and the possibility of neurodegenerative crisis with an intercurrent infectious illness.
- **IMMEDIATE** treatment with IV glucose is needed for intercurrent infectious illness.
- Report findings to newborn screening program.

ACMG algorithm



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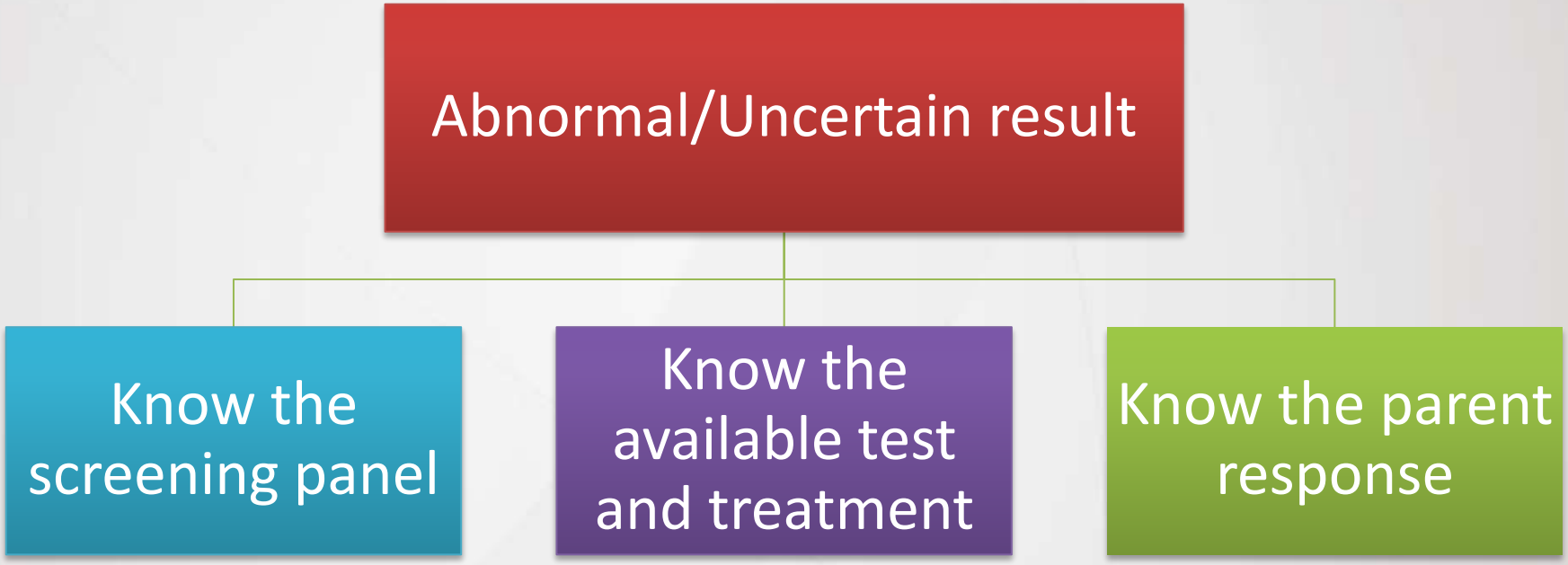

Know the parent response

- Anxious about the result
- Mis-understand the condition
- Worried about acute decompensation in all cases

Informed the parents one day before clinic available if it is non-urgent

CASE EXAMPLE FOR ILLUSTRATION

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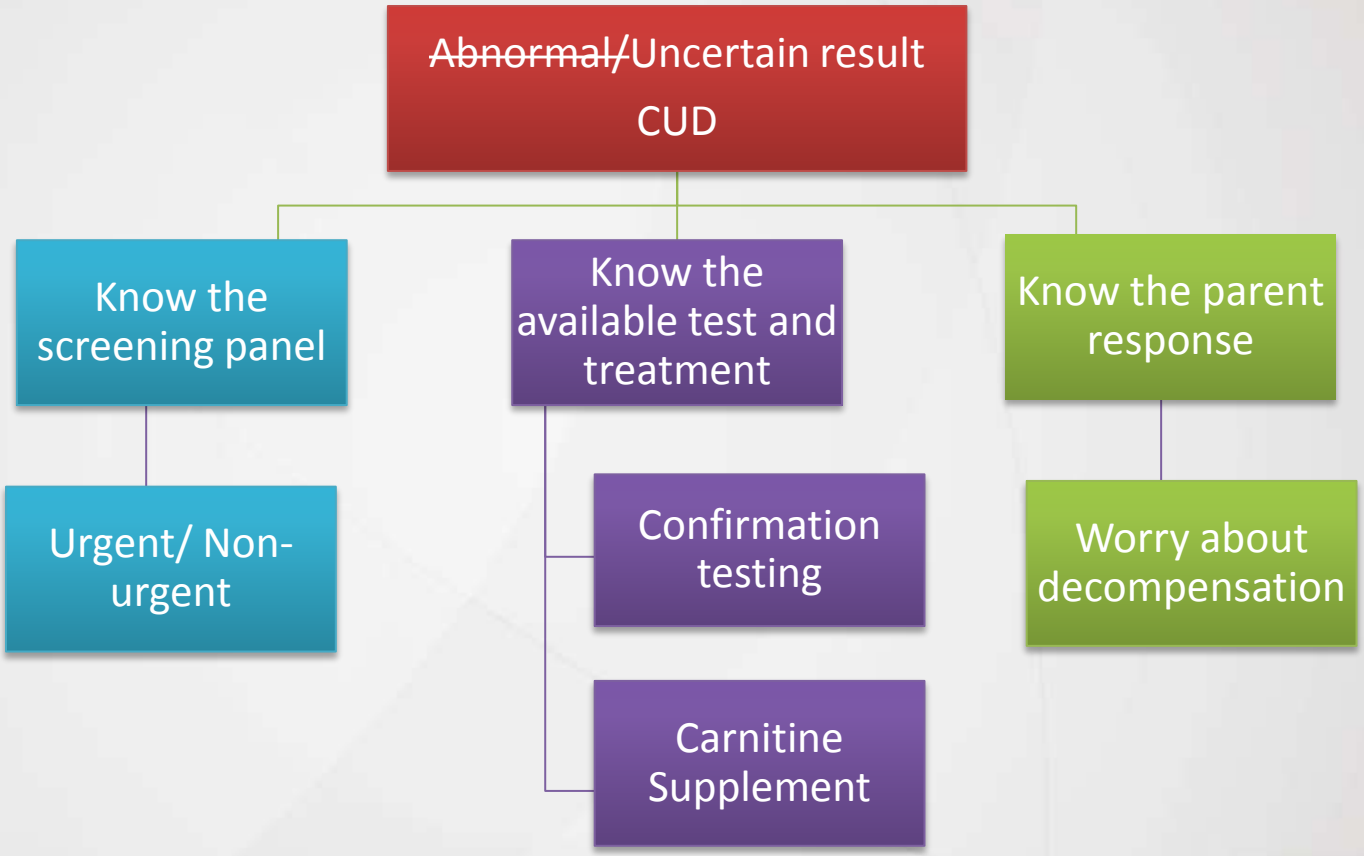
CASE 1

- Term, BW 3Kg, Male, exclusive breast feeding, discharged home on day 2
- Day 2 screening result available on Friday evening:
  - Free Carnitine: C0 5.6 (cut-off >6.0)
  - Acylcarnitine: normal pattern
  - Amino acid: normal pattern
- DDX: Carnitine Uptake Defect (CUD)

CASE 1 – Suspected CUD



Call and inform parent the screening result immediately and assess the patient's condition, ask them to come back to NBS clinic on Monday or come back when they have suspicious of clinical deterioration

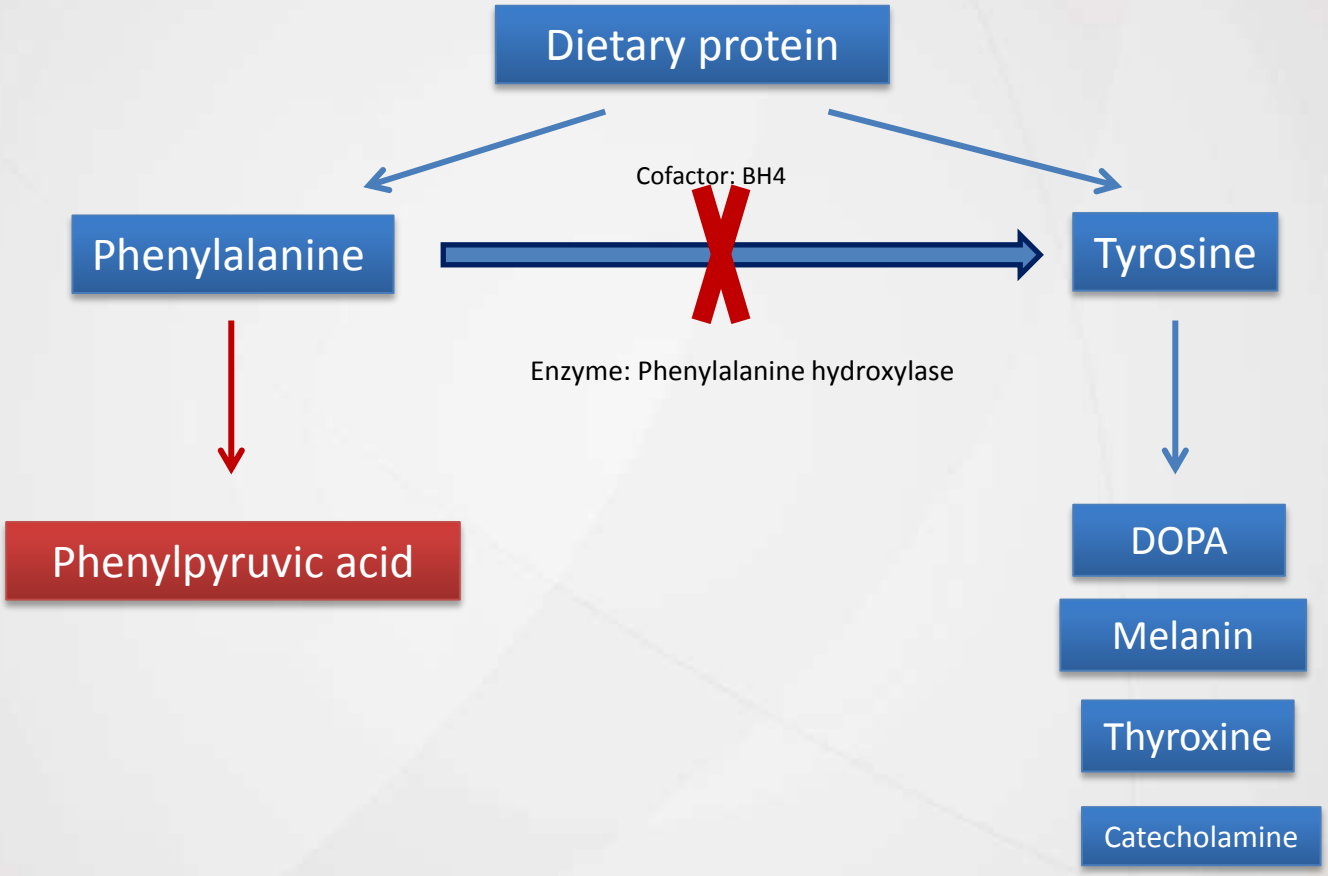
CASE 1 - Progress

- Baby was stable and feeding well
- Repeated DBS:
  - C0 >8.0
  - Acylcarnitine normal profile
  - Mother carnitine was normal
- Discharged home

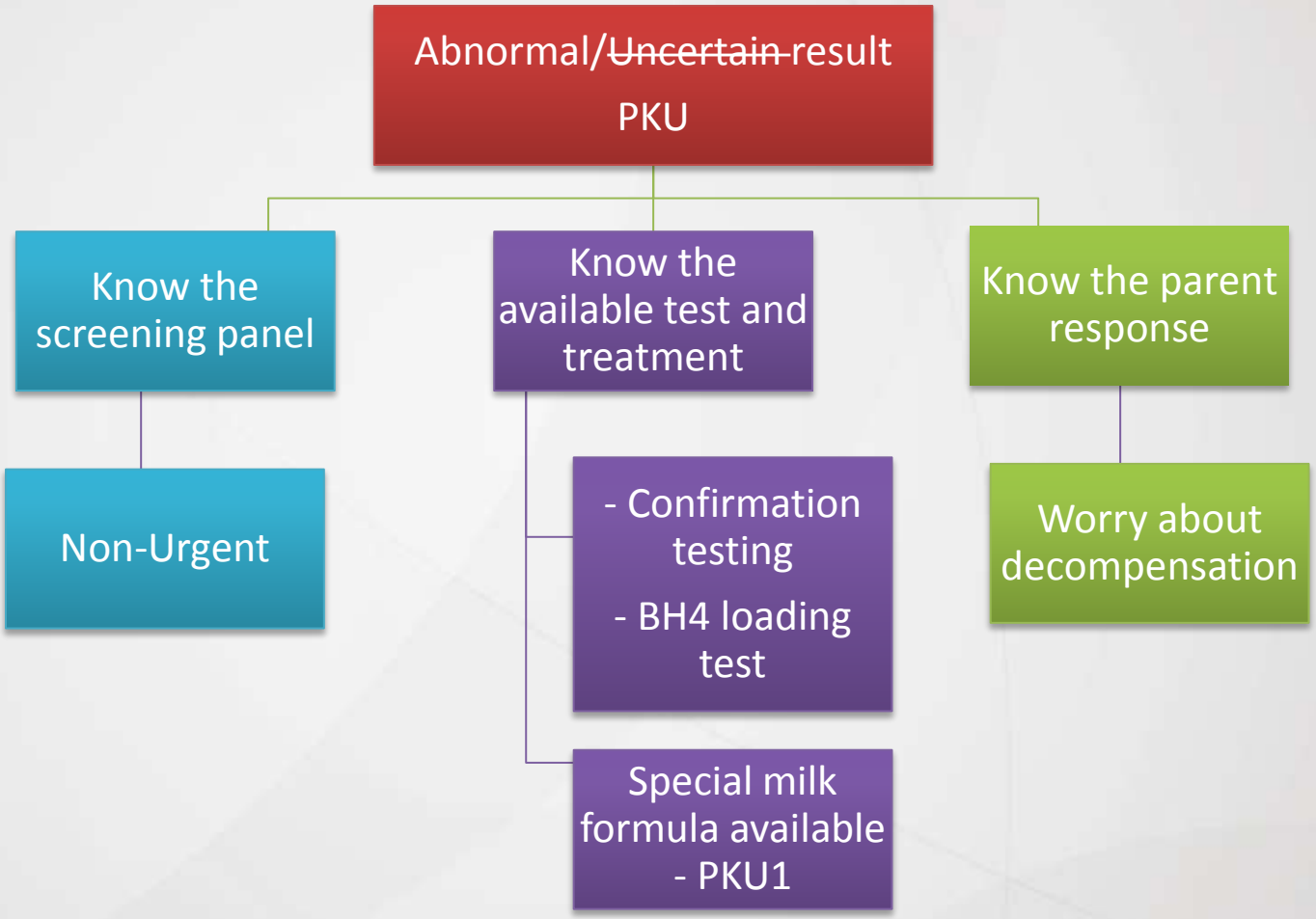
CASE 2

- Term, BW 3Kg, Male, discharged home on day 2
- Day 2 screening result available on Friday evening:
  - Acylcarnitine: normal pattern
  - Amino acid: raised Phenylalanine >1000, all other aminoacids normal
- DDX: Phenylketonuria

Phenylalanine metabolism



CASE 2 - PKU



Call and inform parent the screening result on Sunday and ask them to come back to NBS clinic on Monday

CASE 2 - PKU

Carnitine Analysis for Inborn Metabolic Disease

Serum Free Carnitine	53.5	umol/l	19.3 - 53.9

Serum acylcarnitines pattern

No abnormal pattern detected.

Plasma amino acids

455767-8

Amino acid	Concentration [umol/l]		Age-specific reference range
Alanine	279		[152-547]
Allo-isoleucine	1		[0-5]
Arginine	72		[10-140]
Argininosuccinic acid	<1		[0-8]
Asparagine	55		[23-112]
Aspartic acid	4		[0-24]
Citrulline	38		[1-46]
Cystathionine	<1		[0-3]
Glutamic acid	38		[5-150]
Glutamine	391		[254-823]
Glycine	203		[127-341]
Histidine	82		[41-125]
Isoleucine	71		[22-107]
Leucine	96		[49-216]
Lysine	177		[48-284]
Methionine	24		[7-47]
Ornithine	77		[10-163]
Phenylalanine	1948	H	[26-91]
Serine	124		[69-187]
Threonine	107		[35-226]
Tryptophan	42		[0-79]
Tyrosine	47		[24-115]
Valine	249		[74-321]

Gas chromatographic analysis of urinary organic acids

Phenylalanine metabolites including phenyllactic, 3-phenylpyruvic and phenylacetic acids were markedly elevated.

High phenylalanine level on biochemical testing

-> Dx: Phenylketonuria (PKU)

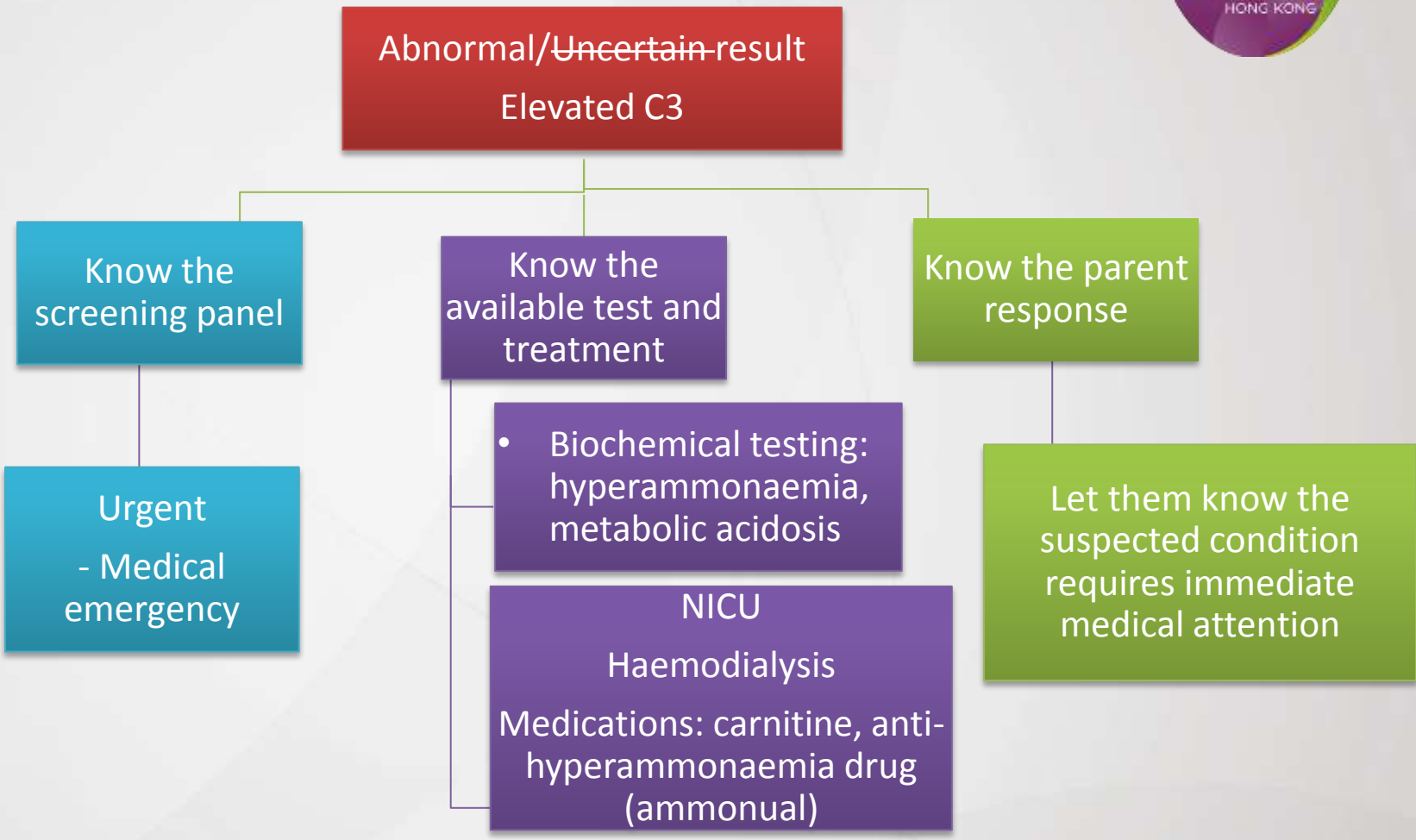
Case 2 - Management

- Confirmatory testing : PAH gene detected mutation
- Parents: carrier
- BH4 loading test: negative
- Treatment: Low protein (low phenylalanine diet), PKU formula

CASE 3

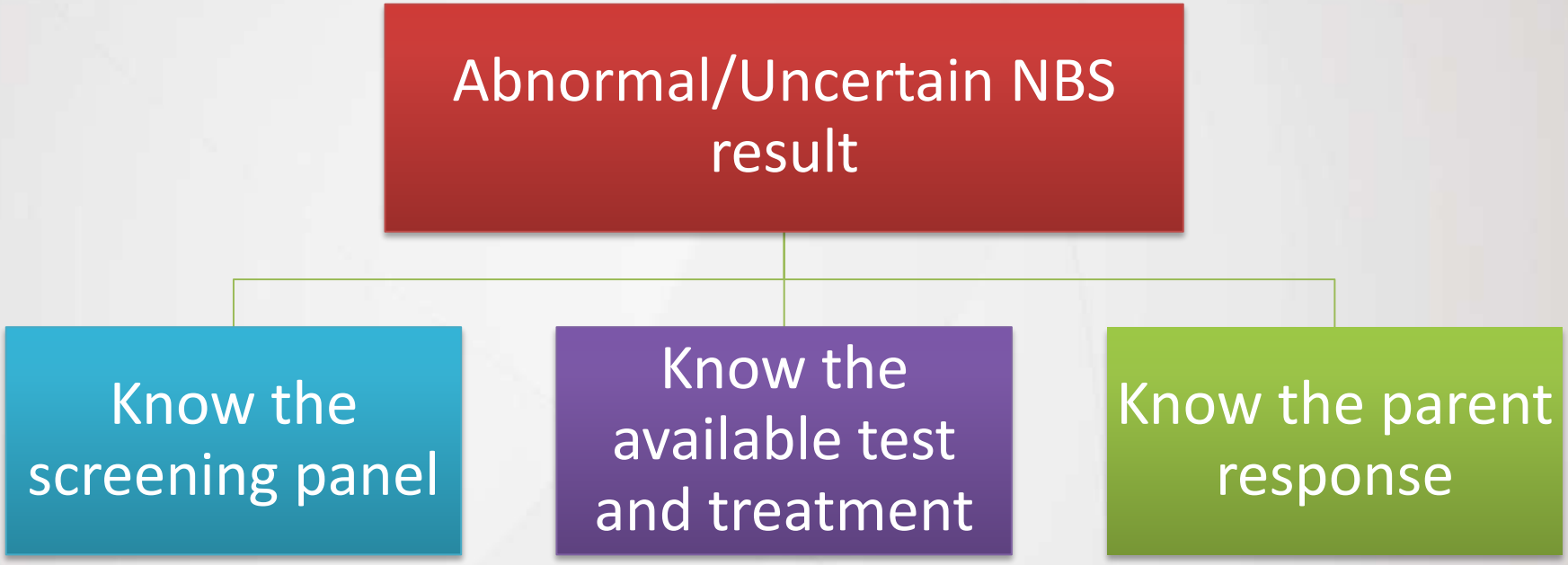
- Term, BW 3Kg, Male, discharged home on day 2
- Day 2 screening result available on Friday evening:
  - Acylcarnitine: elevated C3
  - Amino acid: normal pattern
- DDX: Propionic acidemia (PA); Methylmalonic acidemias (MMA) including defects in B12 synthesis and transport; maternal severe B12 deficiency.

CASE 3 – elevated C3



Call and inform parent the screening result immediately when result available
Ask them to bring baby back for admission asap (That night!!)

Take Home Message – Management of NBS result



Work closely with the NBS lab, neonatologist, and chemical pathologist

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END OF PRESENTATION
THANK YOU

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