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Policy

Title

Recommendations for Screening for Specific Disorders

Document Number	2019PL02
Publication Date	August 2019
Replaces	2017 PL02
Review Date	August 2022

Preamble

These recommendations have been developed by an expert Australasian group based on experience and literature review. There is considerable interest from the general community and health care professionals in screening for additional conditions. From 2010 in New Zealand, and 2018 in Australia there is a formal process for recommending disorders for addition to the screening panel. The evidence base to support extending the program to include new conditions is variable.

Conditions are classified according to a hierarchy, based on the following aspects:

- there is a demonstrated benefit from early diagnosis,
- the benefit is balanced against financial and other costs,
- there are suitable tests available
- follow-up services are available.
- the ability of technology (screening and diagnostic) to identify whom to treat
- the availability and proven effectiveness of treatment
- the frequency of the disorder in the region and the situation without screening.

The recommendations are intended to apply only to bloodspot screening of the whole population in the neonatal period. Other testing, for example wider genetic testing in sick/premature newborns and other screening, for example for familial hypercholesterolemia (FH) in older children is outside the scope of the recommendations, hence FH is in category 3 because there isn't a reliable test in the newborn period not because FH screening may not be valuable.

The selection of disorders and their categorisation is complex and must balance goods and harms of screening, hence while screening for a disorder may have poor sensitivity the benefit to the detected patients may outweigh that disadvantage. Costs and benefits are also a consideration which will vary between jurisdictions depending for example on the prevalence of the disorder and

the ability of the particular healthcare system to diagnose conditions in an appropriate timeframe without screening.
When a new disorder is considered for addition to a screening panel it may be appropriate to perform a pilot programme designed to inform the decision and protocols of the screening.
While screening is designed to detect a particular disorder it may be abnormal levels of other analytes are found and followup of these may be warranted in some circumstances.
Since bloodspot screening by definition screening is in normal healthy infants and there is no condition in which the presence of gene mutations always causes the familiar clinical phenotype screening using a primary molecular genetics test should be undertaken with caution. This does not preclude the use of molecular genetics second tier tests in the presence of an abnormal biochemical phenotype.

Category 1 Screening is highly recommended for the following conditions because there is a demonstrated benefit from early diagnosis, the benefit is balanced against financial and other costs, there are suitable tests, and follow-up services are available. Screening for recommended disorders may not be 100% sensitive but overall there is benefit from the screening. The intention of the newborn screening programme is to detect infantile or early childhood onset conditions and not late or adult onset.

- Aminoacid disorders
    - Argininosuccinic aciduria (ASA lyase deficiency)
    - Citrullinemia (argininosuccinate synthase deficiency, citrin deficiency I and II)
    - Homocystinuria (cystathionine beta-synthase deficiency
    - Maple Syrup Urine Disease (classical and variant)
    - Phenylketonuria (classical, intermediate and pterin defects
- Congenital adrenal hyperplasia (salt wasting) (CAH)
- (Primary) congenital hypothyroidism (CH)
- Cystic fibrosis (CF)
- Fatty Acid Oxidation Disorders
    - Carnitine/acylcarnitine translocase deficiency
    - CPT-1 deficiency (carnitine palmitoyl transferase deficiency 1)
    - CPT-2 deficiency (carnitine palmitoyl transferase deficiency 2)
    - LCHADD (3-hydroxy long chain acyl-CoA-dehydrogenase deficiency)/ TFP (trifunctional protein deficiency)
    - MADD (multiple acyl-CoA dehydrogenase deficiency)/Glutaric acidemia Type 2)
    - MCADD (medium chain acyl-CoA-dehydrogenase deficiency)
    - VLCADD (very long chain acyl-CoA-dehydrogenase deficiency)
- Galactosemias
- Organic acid disorders
    - Glutaryl-CoA dehydrogenase deficiency (glutaric acidemia Type 1)
    - Isovaleric acidemia
    - Methylmalonic acidurias (Mutase deficiency, Cobalamin A&B deficiencies, plus Cobalamin C deficiency and related conditions)
    - Propionic academia
    - Holocarboxylase synthase deficiency
- SCID

Category 2 Screening is desirable for the following conditions, however the benefits may or may not be balanced against costs depending on the ability of the available technology (screening and diagnostic) to identify whom to treat; the availability and utility of treatment,. the frequency of the disorder in the region and other considerations.

- Adrenoleukodystrophy
- Argininemia (arginase deficiency)
- Biotinidase deficiency
- Carnitine transporter defect
- Duchenne muscular dystrophy
- Haemoglobinopathies
- Lysosomal storage disorders
    - Mucopolysaccharidosis Type I (Hurler, Hurler-Scheie and Scheie syndromes)
    - Mucopolysaccharidosis Type II (Hunter syndrome)
    - Mucopolysaccharidosis type VI (Maroteaux-Lamy syndrome)
    - Fabry disease
    - (Infantile) Pompe disease.
    - Krabbe disease
- 3-methylglutaconyl-CoA hydratase deficiency
- SMA (spinal muscular atrophy
- Tyrosinemia type 1 (Fumaryl acetoacetase deficiency)
- Tyrosine aminotransferase deficiency (tyrosinemia Type 2)

Category 3 Screening is currently not recommended for the following conditions where screening tests are not available, or, tests are available but proof of advantage from early diagnosis is absent or uncertain, or the test is unsuitable or does not detect those cases in which there might be an advantage. New knowledge about screening and screening outcome in these conditions should be monitored regularly.

- Bile acid disorders including biliary atresia
- Familial hypercholesterolemia II
- G6PD deficiency
- 3-hydroxy-3-methylglutaryl-CoA lyase (HMGCoA lyase deficiency)
- Beta-ketothiolase deficiency (mitochondrial acetoacetyl-CoA thiolase deficiency)
- Peroxisomal disorders (other than ALD).

Category 4 These conditions have been considered but there is no evidence that screening is useful.

- Cytomegalovirus
- Fragile X
- Haemachromatosis
- Short chain acyl-coA dehydrogenase deficiency
- 3-methylcrotonyl-coA carboxylase deficiency

Table 1 Screening Status August 2109

		NSW	QLD	SA	VIC	WA	NZ
Category 1	Argininosuccinic aciduria (ASA lyase deficiency)	✓	✓	✓	✓	✓	✓
	Citrullinemia (argininosuccinate synthase deficiency, citrin deficiency I and II)	✓	✓	✓	✓	✓	✓
	Homocystinuria (cystathionine beta-synthase deficiency)	✓	✓	✓	✓	✓	✓
	Maple Syrup Urine Disease (classical and variant)	✓	✓	✓	✓	✓	✓
	Phenylketonuria (classical, intermediate and some pterin defects)	✓	✓	✓	✓	✓	✓
	Congenital adrenal hyperplasia (salt wasting) (CAH)	✓					✓
	(Primary) congenital hypothyroidism (CH)	✓	✓	✓	✓	✓	✓
	Cystic fibrosis (CF)	✓	✓	✓	✓	✓	✓
	Carnitine/acylcarnitine translocase deficiency	✓	✓	✓	✓	✓	✓
	CPT-1 deficiency (carnitine palmitoyl transferase deficiency 1)	✓	✓	✓	✓	✓	✓
	CPT-2 deficiency (carnitine palmitoyl transferase deficiency 2)	✓	✓	✓	✓	✓	✓
	LCHADD (3-hydroxy long chain acyl-CoA-dehydrogenase deficiency)/ TFP (trifunctional protein deficiency)	✓	✓	✓	✓	✓	✓
	MADD (multiple acyl-CoA dehydrogenase deficiency)/Glutaric acidemia Type 2)	✓	✓	✓	✓	✓	✓
	MCADD (medium chain acyl-CoA-dehydrogenase deficiency)	✓	✓	✓	✓	✓	✓
	VLCADD (very long chain acyl-CoA-dehydrogenase deficiency)	✓	✓	✓	✓	✓	✓
	Galactosemias	✓	✓	✓		✓	✓
	Glutaryl-CoA dehydrogenase deficiency (glutaric acidemia Type 1)	✓	✓	✓	✓	✓	✓
	Isovaleric acidemia	✓	✓	✓	✓	✓	✓
	Methylmalonic acidurias (Mutase deficiency, Cobalamin A&B deficiencies, plus Cobalamin C deficiency and related conditions)	✓	✓	✓	✓	✓	✓
	Propionic academia	✓	✓	✓	✓	✓	✓
	Holocarboxylase synthase deficiency	✓	✓	✓	✓	✓	✓
	SCID	✓					✓
Category 2	Adrenoleukodystrophy						
	Argininemia (arginase deficiency)	✓	✓	✓	✓	✓	✓
	Biotinidase deficiency						✓
	Carnitine transporter defect	✓	✓	✓	✓	✓	
	Duchenne muscular dystrophy						
	Haemoglobinopathies						
	Mucopolysaccharidosis Type 1 (Hurler, Hurler-Scheie and Scheie syndromes)						
	Mucopolysaccharidosis Type 2 (Hunter syndrome)						
	Fabry disease						
	(Infantile) Pompe disease.						
	Krabbe disease						
	3-methylglutaconyl-CoA hydratase deficiency	✓	✓	✓	✓	✓	
	SMA (spinal muscular atrophy	*					
	Tyrosinemia type 1 (Fumaryl acetoacetase deficiency)	✓	✓	✓	✓	✓	**
	Tyrosine aminotransferase deficiency (tyrosinemia Type 2)	✓	✓	✓	✓	✓	**

* Pilot programme ** Suspended pending introduction of succinylacetone.

Table 2 Regulatory status of recommended disorders. H = historically screened prior to introduction of a formal assessment process, or year of formal approval.

		Australia	NZ
Category 1	Argininosuccinic aciduria (ASA lyase deficiency)	H	H
	Citrullinemia (argininosuccinate synthase deficiency, citrin deficiency I and II)	H	H
	Homocystinuria (cystathionine beta-synthase deficiency)	H	H
	Maple Syrup Urine Disease (classical and variant)	H	H
	Phenylketonuria (classical, intermediate and some pterin defects)	H	H
	Congenital adrenal hyperplasia (salt wasting) (CAH)	2018	H
	(Primary) congenital hypothyroidism (CH)	H	H
	Cystic fibrosis (CF)	H	H
	Carnitine/acylcarnitine translocase deficiency	H	H
	CPT-1 deficiency (carnitine palmitoyl transferase deficiency 1)	H	H
	CPT-2 deficiency (carnitine palmitoyl transferase deficiency 2)	H	H
	LCHADD (3-hydroxy long chain acyl-CoA-dehydrogenase deficiency)/ TFP (trifunctional protein deficiency)	H	H
	MADD (multiple acyl-CoA dehydrogenase deficiency)/Glutaric acidemia Type 2)	H	H
	MCADD (medium chain acyl-CoA-dehydrogenase deficiency)	H	H
	VLCADD (very long chain acyl-CoA-dehydrogenase deficiency)	H	H
	Galactosemias	H	H
	Glutaryl-CoA dehydrogenase deficiency (glutaric acidemia Type 1)	H	H
	Isovaleric acidemia	H	H
	Methylmalonic acidurias (Mutase deficiency, Cobalamin A&B deficiencies, plus Cobalamin C deficiency and related conditions)	H	H
	Propionic academia	H	H
	Holocarboxylase synthase deficiency	H	H
	SCID	Application received	2017
Category 2	Adrenoleukodystrophy		
	Argininemia (arginase deficiency)	H	H
	Biotinidase deficiency		H
	Carnitine transporter defect	H	
	Duchenne muscular dystrophy		
	Haemoglobinopathies		
	Mucopolysaccharidosis Type 1 (Hurler, Hurler-Scheie and Scheie syndromes)		
	Mucopolysaccharidosis Type 2 (Hunter syndrome)		
	Fabry disease		
	(Infantile) Pompe disease.	Application received	Application received
	Krabbe disease		
	3-methylglutaconyl-CoA hydratase deficiency	H	
	SMA (spinal muscular atrophy		
	Tyrosinemia type 1 (Fumaryl acetoacetase deficiency)	H	
	Tyrosine aminotransferase deficiency (tyrosinemia Type 2)	H	

At the time of publication the process for consideration of the addition of SCID is well underway in Australia while applications for Pompe disease are at the initial stage in both jurisdications.