

# Office of Population Health Genomics

Paper:  
Framework for adding new tests  
for conditions within the Newborn  
Screening protocol

**Purpose:** To provide a discussion paper for consideration concerning a framework for adding new tests for conditions within the newborn screening protocol.

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## **Framework for adding new conditions to the Newborn Screening protocol**

Addition of new conditions to the newborn screening protocol should depend on whether the condition in question meets the principles of early disease detection as proposed by Wilson and Junger.<sup>1</sup> The US have recently evaluated the evidence for a total of 84 conditions that may be screened for in newborns.<sup>2</sup> The UK also reviewed the evidence for neonatal screening for inborn errors of the metabolism in 1997<sup>3,4</sup> and their website; <http://www.library.nhs.uk/screening/SearchResults.aspx?catID=8205&pgIndex=0&> indicates these policies were reviewed in 2005 and no changes were made.

The US approach was to develop an instrument to quantitatively evaluate the features of conditions under consideration for inclusion in a uniform screening panel by applying a weighted scoring system.<sup>2</sup> The ACMG expert group included participants with expertise in various areas of subspecialty medicine and primary care, health policy, law, ethics and public health, as well as consumers, who worked together with a steering committee and several expert work groups. A two-tiered approach was taken to assess and rank conditions. Firstly, conditions were analysed according to the evaluation criteria. These data were then compared against the evidence base for each screening criterion. The establishing principles, choice of conditions and evaluation criteria are given in Appendix 1. Conditions were finally scored, ranked and placed into three categories; 1) the core panel, 2) secondary targets (conditions that are part of the differential diagnosis of a core panel condition); and 3) not appropriate for newborn screening (either no newborn screening test is available or there is poor performance with regard to multiple other evaluation criteria). The 84 conditions and their relative rank and category are given in table 1.

The British approach involved the conduct of two systematic reviews commissioned by the Health Technology Assessment Programme of the National Health Service.<sup>3 4</sup> The brief was to review inborn errors of the metabolism and recommend tests for inclusion in a screening panel. The UK recommended continued screening for PKU and congenital hypothyroidism and suggested that screening for medium-chain acyl CoA dehydrogenase deficiency, glutaric aciduria type 1, profound biotinidase deficiency and congenital adrenal hyperplasia should also be considered. (Screening for cystic fibrosis is currently being introduced in the UK, but was not considered in this review). It was recommended that screening for galactosaemia should be discontinued due to lack of evidence. The UK HTA review concluded that there was insufficient evidence for the widespread introduction of tandem mass spectroscopy technology into the newborn screening program.

In 2004, a further HTA review was published on the clinical effectiveness and cost-effectiveness of inborn errors of metabolism using tandem mass spectrometry. This found that there was sufficient evidence for using tandem MS for PKU and MCAD and that other disorders should not be included, even though the marginal cost was relatively small, until there was sufficient evidence that early diagnosis using tandem MS was beneficial.<sup>5</sup> A trial is currently being undertaken to examine the effectiveness of MCAD screening using TMS and data are also being gathered to help the National Screening Committee explore the most effective and efficient way of making decisions about other rare inherited disorders, such as amino acid metabolism disorders. An initial report is expected in 2006.

<http://www.ucl.ac.uk/news-archive/archive/April-2005/latest/newsitem.shtml?NewBorn>

One of the main differences between the two reports is the variety and size of the expert panels. One of the highlights of the US report was the inclusion of consumer/community involvement - an aspect that did not appear in the UK report. Consumer involvement in health care decision-making

is becoming more important and community consultation should be considered in newborn screening decision-making.

The UK report looked in much greater detail at the issue of economic evaluation whereas the US report largely concentrated on the cost of the screening test per baby and gave little information about the screening method, treatment cost or cost per life-year saved. A comparison of the criteria used to evaluate conditions for newborn screening is given in Appendix 2.

These divergent recommendations illustrate the importance of reviewing the evidence relevant to newborn screening in Australia, conducting further research and pilot screening trials where necessary. Criteria 8 of the US Establishing Principles states that “Centralized health information data collection is needed for longitudinal assessment of disease-specific screening programs.” Such data are required in Australia to estimate the utility of a screening program and to evaluate screening programs. The current Human Genetics Society of Australasia (HGSA) Policy on newborn screening is given in Appendix 3.

While the US system cannot be transplanted directly to the Australian situation because of our differing demography and the different economics of newborn screening is unlikely to be successfully replicated in Australia because of the relatively small group of people with an interest in newborn screening, the order of the ranked conditions is likely to be similar in Australia, (with a few notable exceptions such as haemoglobinopathies) and therefore provides useful information regarding the likelihood of conditions being added to the newborn screening protocol in Australia. The conditions are listed in rank order in table 1.

## **Action plan**

A Steering Committee be formed comprising:

- Major organizations with interest and involvement (HGSA-RACP Joint NBS Subcommittee)
- Genetic Alliance
- AHMAC AG on genetic testing and human gene patents

The steering committee should consider:

- finalise the criteria to be used for selecting conditions for the newborn screening panel,
- decide upon the conditions to be considered,
- organise a review of the evidence for screening for each of these conditions,
- facilitate pilot screening projects,
- facilitate the collection of longitudinal data to evaluate the screening program.

**Table 1 – Current Newborn screening recommendations listed against all conditions considered by the US Newborn Screening Panel in their rank order**

<i>Condition</i>	Screening recommended in:		
	<i>Austral ia</i>	United States	United Kingdom
Medium-chain acyl-CoA dehydrogenase deficiency	X	Core panel	X
Congenital hypothyroidism	X	Core panel	X
Phenylketonuria	X	Core panel	X
Neonatal hyperbilirubinemia (Kernicterus)		Core panel	
Biotinidase deficiency		Core panel	X*
Sickle cell anemia		Core panel	Some areas
Congenital adrenal hyperplasia		Core panel	X *
Isovaleric acidemia	X	Core panel	
Very long-chain acyl-CoA dehydrogenase deficiency	X	Core panel	
Maple syrup urine disease	X	Core panel	
Classical galactosaemia	X	Core panel	
HB S/β-thalassemia		Core panel	
HB S/C disease		Core panel	
Long-chain L-3-OH acyl-CoA dehydrogenase deficiency	X	Core panel	
Glutaric acidemia type I	X	Core panel	X
3-OH 3-CH3 glutaric aciduria	X	Core panel	
Trifunctional protein deficiency	X	Core panel	
Multiple carboxylase deficiency	X	Core panel	
Benign hyperphenylalaninemia		Core panel	
Methylmalonic acidemia (mutase deficiency)	X	Core panel	
Homocystinuria (due to CBS deficiency)	X	Core panel	
3-Methylcrotonyl-CoA carboxylase deficiency	X	Core panel	
Hearing loss		Core panel	
Methylmalonic acidemia (Cb1, A,B)	X	Core panel	
Propionic acidemia	X	Core panel	
Carnitine uptake defect	X	Core panel	
Galactokinase deficiency		Core panel	
Glucose-6-phosphate dehydrogenase deficiency		Core panel	
B-Ketothiolase deficiency	X	Core panel	
Citrullinemia	X	Core panel	
Argininosuccinic acidemia	X	Core panel	
Tyrosinemia type I	X	Core panel	
Short-chain acyl-CoA dehydrogenase deficiency		Core panel	
Tyrosinemia type II	X	Core panel	
Glutaric acidemia type II	X	Core panel	
Medium/short-chain L-3-OH acyl-CoA dehydrogenase deficiency		Core panel	
Cystic fibrosis	X	Core panel	X
Variant haemoglobinopathies (including Hb E)		2° target	
Human HIV infection		2° target	
Defects of bipterin cofactor biosynthesis		2° target	
Medium-chain ketoacyl-CoA thiolase deficiency		2° target	
Carnitine palmitoyltransferase II deficiency	X	2° target	
Methylmalonic acidemia		2° target	
Arginemia		2° target	
Tyrosinemia type III		2° target	
Defects of bipterin cofactor regeneration		2° target	
Malonic acidemia		2° target	
Carnitine: acylcarnitine translocase deficiency	X	2° target	

Isobutyryl-CoA dehydrogenase deficiency		2° target	
2-Methyl 3-hydroxy butyric aciduria		2° target	
Carnitine palmitoyltransferase I deficiency (liver)	X	2° target	
2-Methylbutyryl-CoA dehydrogenase deficiency		2° target	
Hypermethioninemia		2° target	
Dienoyl-CoA reductase deficiency		2° target	
Galactose epimerase deficiency		2° target	
3-Methylglutaconic aciduria		2° target	
Severe combined immunodeficiency		2° target	
Congenital toxoplasmosis		2° target	
Familial hypercholesterolemia (heterozygote)		2° target	
Carnitine palmitoyltransferase I deficiency (muscle)	X	2° target	
Citrullinemia type II		2° target	
Ornithine transcarbamylase deficiency		Not recommended	
Guanidinoacetate methyltransferase deficiency		Not recommended	
Wilson disease		Not recommended	
Diabetes mellitus, insulin dependent		Not recommended	
Neuroblastoma		Not recommended	
Arginine: glycerine amidinotransferase deficiency		Not recommended	
Turner syndrome		Not recommended	
Adenosine deaminase deficiency		Not recommended	
Carbamylphosphate synthetase deficiency		Not recommended	
Alpha 1-antitrypsin deficiency		Not recommended	
Congenital cytomegalovirus infection		Not recommended	
Duchenne and Becker muscular dystrophy		Not recommended	
Fragile X syndrome		Not recommended	
Congenital disorder of glycosylation type 1b		Not recommended	
Smith-Lemli-Opitz syndrome		Not recommended	
Biliary atresia		Not recommended	
Hurler-Scheie disease		Not recommended	
X-linked adrenoleukodystrophy		Not recommended	
Fabry disease		Not recommended	
Creatine transport defect		Not recommended	
Lysosomal storage diseases		Not recommended	
Pompe disease		Not recommended	
Krabbe disease		Not recommended	

## **Appendix 1 – Basis of US Newborn Screening Panel <sup>2</sup>**

### Establishing principles

The following basic principles were developed as a framework for defining the criteria by which to evaluate conditions and make recommendations.

1. Universal newborn screening is an essential public health responsibility that is critical to improve the health outcome of affected children.
2. Newborn screening policy development should be primarily driven by what is in the best interest of the affected newborn, with secondary consideration given to the interests of unaffected newborns, families, health professionals, and the public.
3. Newborn screening is more than testing. It is a coordinated and comprehensive system consisting of education, screening, follow-up, diagnosis, treatment and management, and program evaluation.
4. The medical home and the public and private components of the screening programs should be in close communication to ensure confirmation of test results and the appropriate follow-up and care of identified newborns.
5. Recommendations about the appropriateness of conditions for newborn screening should be based on the evaluation of scientific evidence and expert opinion.
6. To be included as a primary target condition in a newborn screening program, a condition should meet the following minimum criteria:
  - a. It can be identified at a phase (24 to 48 hours after birth) at which it would not ordinarily be clinically detected;
  - b. A test with appropriate sensitivity and specificity is available for it; and
  - c. There are demonstrated benefits of early detection, timely intervention and efficacious treatment of the condition being tested.
7. The primary targets of newborn screening should be conditions that meet the criteria listed in number 6 above. The newborn screening program also should report any other result of potential clinical significance.
8. Centralized health information data collection is needed for longitudinal assessment of disease-specific screening programs.
9. Total quality management should be applied to newborn screening programs.
10. Newborn screening specimens are valuable health resources. Every program should have policies in place to ensure confidential storage and appropriate use of specimens.
11. Public awareness, coupled with professional training and family education, is a significant program responsibility that must be part of the complete newborn screening system.

### Choosing conditions

The conditions chosen for evaluation were included for one or more of several reasons:

1. They are included in private, state, or national newborn screening programs;
  2. They are coincidentally revealed by some of the technologies used in newborn screening;
  3. They were identified by members of the expert group as worthy of consideration;
  4. They were identified by disease-specific advocacy organizations;
- and/or
5. They were included in the differential diagnosis of a screening result for another condition.

In the course of collecting information, all conditions were subject to reconsideration. Eighty-four conditions were chosen for consideration.

### Developing evaluation criteria and their comparative values

The uniform panel working group developed the criteria by which conditions were to be evaluated. These were modified subsequently by the expert group. Criteria were divided into three main categories that covered aspects of the condition:

1. The clinical characteristics (e.g., incidence, burden of disease if not treated, phenotype in the newborn);
2. The analytical characteristics of the screening test (e.g., availability, features of the platform); and
3. The diagnosis, treatment and management of the condition in both acute and chronic forms (this criterion includes the availability of health professionals experienced in diagnosis, treatment, and management).

Within each of these categories, several component criteria were developed (resulting in a total of 19 criteria) for assigning the comparative value or score. The scoring system recognizes the strengths and limitations of each condition and summarizes them in a ranking system. Thus, a low score in a particular area does not necessarily mean that screening for that condition will never be conducted. In fact, low scores could be radically overruled by scientific evidence of new advances in testing and treatment, and they should be recognized as opportunities for targeted research endeavors and subsequent reconsideration of the condition for inclusion. The criteria that were developed to differentiate the appropriateness of conditions for newborn screening include some that have a highly objective scientific basis and others that are associated with more subjective aspects. To the extent possible, the expert group relied on the scientific literature to provide the information on which its recommendations are based. However, some criteria have significant subjective aspects that require the consideration of more than just scientific and expert opinion. For example, issues of cost were considered but were not viewed as central in the analyses of the scientific literature. Cost is an example of a subjective criterion because it is a contextual concern and can be measured only against the value of the outcome.

## Appendix 2

### Comparison of screening criteria for the United States and United Kingdom<sup>2, 6</sup>

#### The Condition

##### *United States*

Criteria	Categories	Score
Incidence of Condition	> 1:5,000	100
	>1:25,000	75
	> 1:50,000	50
	>1:75,000	25
	<1:100,000	0
Signs & symptoms clinically identifiable in the first 48 h	Never	100
	< 25% cases	75
	< 50% cases	50
	< 75% cases	25
	Always	0
Burden of disease (natural history if untreated)	Profound	100
	Severe	75
	Moderate	50
	Mild	25
	Minimal	0

##### **United Kingdom**

1. The condition should be an important health problem
2. The epidemiology and natural history should be well understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage.
3. All the cost-effective primary prevention interventions should have been implemented as far as practicable.
4. If carriers of a mutation are identified as a result of screening the natural history of people with this disease, this status should be understood, including the psychological implications.

## The Test

### United States

Does a sensitive and specific screening algorithm already exist?	Yes	200
	No	0
Test characteristics Yes = apply score; No = zero	Detectable in neonatal blood spots or by a simple in-nursery physical method	100
	High throughput > 200/day/FTE	50
	Overall analytical cost < \$1 per test/condition	50
	Multiple analyses relevant to one condition in same spot	50
	Other conditions detected by same analyses	50
	Multiple conditions detected by the same analytes	50
	Multiple conditions detected by the same test (multiplex pattern)	200

### United Kingdom

5. There should be a simple, safe, precise and validated screening test
6. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed
7. The test should be acceptable to the population
8. There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals.
9. If the test is for mutations the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested, should be clearly set out.

## The Treatment

### United States

<i>The Treatment</i>		
Availability of treatment	Treatment exists and is widely available in most communities	50
	Treatment exists but availability is limited	25
	No treatment is available or necessary	0
Cost of treatment	Expensive (> \$50,000/patient/year)	
	Inexpensive (< \$50,000/patient/yer)	
Potential efficacy of existing treatment	To prevent ALL negative consequences	200
	To prevent MOST negative consequences	100
	To prevent SOME negative consequences	50
	Treatment efficacy not known	0
Benefits of early intervention (INDIVIDUAL OUTCOME)	Clear evidence that early intervention resulting from newborn screening optimizes outcome	200
	Some evidence that early intervention resulting from newborn screening optimizes outcome	100
	No evidence that early intervention resulting from newborn screening optimizes outcome	0
Benefits of early intervention (FAMILY & SOCIETY)	Early intervention provides clear benefits to family and society (education, understanding prevalence, natural history and cost effectiveness)	100
	Early intervention provides some benefits to family and society	50
	No benefits to society	0

### United Kingdom

10. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.

11. There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered.

12. Clinical management of the condition and patient outcomes should be optimized in all health care providers prior to participation in a screening programme.

## The Screening Program

### United States

<i>The Screening Program</i>		
Early diagnosis and treatment prevent mortality	Yes	100
	No	0
Availability of diagnostic confirmation	Wide	100
	Limited	50
	Poor	0
Acute management	Providers of acute management widely available	100
	Limited availability of qualified providers of acute management	50
	Acute management available in city in a few centres	0
Simplicity of therapy	Management at primary care or family level	200
	Requires periodic involvement of a specialist	100
	Requires regular involvement of a specialist	0

### United Kingdom

13. There should be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an ‘informed choice’ (eg Down’s syndrome) there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.

14. There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/intervention) is clinically, socially and ethically acceptable to health professionals and the public.

15. The benefit from the screening programmed should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment).

16. The opportunity cost of the screening programmed (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (ie value for money)

17. There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards

18. Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme

19. All other options for managing the condition should have been considered (eg improving treatment, providing other services), to ensure that no more cost effective intervention could be introduced or current interventions increased within the resources available.

20. Evidence-based information, explaining the consequences of testing, investigation and treatment, should be made available to potential participants to assist them in making an informed choice.

21. Public pressure for widening the eligibility criteria for reducing the screening interval and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public.

22. If screening is for a mutation the programme should be acceptable to people identified as carriers and to other family members.

## Appendix 3

### HGSA-RACP Newborn Screening Joint Subcommittee

#### POLICY STATEMENT 2004 - NEWBORN BLOOD-SPOT SCREENING <sup>7</sup>

##### 1 General recommendations

Newborn screening is recommended provided that:

- 1.1 There is benefit for the baby from early diagnosis (benefit to the family may also benefit the baby);
- 1.2 The benefit is reasonably balanced against financial and other costs;
- 1.3 There is a reliable test suitable for newborn screening;
- 1.4 There is a satisfactory system in operation to deal with diagnostic testing, counselling, treatment and follow-up of patients identified by the test.

##### 2 Organisation of programs

- 2.1 The screening program comprises the sum of the operations necessary to ensure that all babies are offered testing, all necessary follow-up is done, all cases found are adequately treated and there are appropriate quality management and program evaluation processes in place.
- 2.2 The current policy of public funding for newborn screening programs should be retained. They should be organised and controlled within the public health sector. It is recommended that the organisers of the screening program take advice about the general operation of the screening program from multidisciplinary expert sources.
- 2.3 The organisers of the screening program should facilitate development and implementation of nationally recognised newborn screening standards, policies and guidelines.
- 2.4 Screening programs should provide a seamless system of care that coordinates and involves community- and hospital-based providers, tertiary-care centres and paediatric subspecialty clinics.
- 2.5 Health professionals and the public should be kept well informed about screening programs. Specifically, written information and the opportunity for discussion must be provided for parents before testing, and health professionals should be provided with comprehensive guidelines describing all aspects of the screening program including correct sample collection procedure.
- 2.6 Health care authorities have a responsibility to ensure that tests are available to all babies born in their region.
- 2.7 For each baby born, an individual or individuals must be identified as responsible for providing information about the test, offering the test, obtaining appropriate consent, collecting the sample and completing any requested follow-up.
- 2.8 A system should be in place to ensure the community- and hospital-based providers know which samples have been received by the screening laboratory. Special care must be taken to ensure that a sample is collected from each baby or refusal of testing is documented and notified to the screening laboratory. An acceptable way of achieving this is for the empty screening test card (with demographic information but no blood sample) to be returned to the laboratory with the documented refusal.
- 2.9 Regular assessments of screening program performance should be undertaken and must include test sensitivity, specificity, positive predictive value, timeliness of reporting, and outcome of diagnosed patients. Outcome assessment should include short and long-term evaluation and may be based on a surrogate measurement in disorders that are well understood.

### 3 Laboratory services

- 3.1 Screening tests should be carried out in large centralised laboratories, so that costs can be kept low, expertise rapidly gained and kept, and for low prevalence disorders, sufficient data are available for assay performance assessment and program audit.
- 3.2 Laboratories should have appropriate accreditation. External assessors should review programs to ensure that suitable tests, quality assurance, cut-off points, follow-up procedures and screening audit processes are in operation.
- 3.3 The HGSA should ensure that quality control programs are available Australasia-wide for each test employed on a routine service basis.
- 3.4 The screening laboratory director is responsible for ensuring the correct performance and interpretation of the test, ensuring that the baby's doctor, treating midwife or parents are informed of any abnormal result and of the appropriate action to be taken. The director should ensure that responsibility for further action is formally handed over to an appropriate healthcare professional.

### 4 Legal and ethical considerations

- 4.1 Participation in a newborn screening program should not be mandatory. Parents should be informed of the availability of testing. If after discussion the parents refuse to have their newborn tested, they should sign a statement that they are fully informed about the test and the consequences of not testing.
- 4.2 The screening program should have appropriate policies and procedures to ensure that the privacy and confidentiality of the patient and family are carefully protected.
- 4.3 If a newborn screening test is investigational or being developed and the benefits and risks are yet to be demonstrated, separate consent and/or more detailed information may be required and this should be discussed with appropriate ethics and advisory committees.
- 4.4 A separate HGSA policy covers the storage and use of newborn screening sample cards. All programs should develop their own detailed policy following the suggestions in the HGSA policy and include:
- 4.5 Following completion of newborn screening testing, cards should be stored securely for such period of time as is determined by the screening program taking into account legal requirements and local pathology service guidelines for samples.
- 4.6 Further use of the stored samples for purposes other than screening program audit requires either written permission from the individual, the parents or guardian, or a legally binding directive, or appropriate ethics committee approval for research studies.
- 4.7 The written information provided for parents should include information about the storage and potential uses of residual samples.

### 5 Research

- 5.1 Screening programs should support research related to current and potential newborn screening, including laboratory and community aspects. Such research should be conducted in line with local ethics and advisory committee recommendations and particularly consider the benefits to families which can arise from non-anonymised studies and what permission might be required for such studies.
- 5.2 Pilot studies should be undertaken to demonstrate the safety, effectiveness, validity and clinical utility of tests for additional disorders and new testing technologies.

### 6 Recommendations for screening for specific disorders

- 6.1 When assessing whether a particular disorder should be added to the screening program of a region, the appropriate cost comparison is the cost of adding the disorder versus not adding it.

- 6.2 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.
- Phenylketonuria (PKU).
  - Primary congenital hypothyroidism (CH).
  - Cystic fibrosis (CF).
- 6.3 Screening is recommended for the following conditions depending on local circumstances. There is a demonstrated benefit or likely benefit from early diagnosis, there are suitable tests and treatment, and follow-up services are available. The benefit may or may not be balanced against financial and other costs depending on the available technology, the frequency of the disorder in the region and other factors.
- Biotinidase deficiency
  - Congenital Adrenal Hyperplasia
  - Galactosaemias
  - Haemoglobinopathies
  - Disorders of amino acid, organic acid and fatty acid metabolism covered by tandem mass spectrometry\*.
- 6.4 Screening is currently not recommended for the following conditions. 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.
- ADA deficiency
  - Duchenne muscular dystrophy
  - Familial hypercholesterolaemia II
  - G6PD deficiency
  - Haemochromatosis
  - Lysosomal storage disorders
  - Neuroblastoma
  - Toxoplasmosis

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