UK National Screening Committee

# Newborn screening for biotinidase deficiency

## External review against programme appraisal criteria for the UK National Screening Committee (UK NSC)

Version: 1

**Bazian Ltd**

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The UK NSC advises Ministers and the NHS in all four UK countries about all aspects of screening policy. Its policies are reviewed on a 3 yearly cycle. Current policies can be found in the policy database at http://www.screening.nhs.uk/policies and the policy review process is described in detail at http://www.screening.nhs.uk/policyreview

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## Introduction

Biotinidase is an enzyme involved in the recycling of the B vitamin biotin in the body. Biotinidase deficiency is a condition where there is little or no biotinidase activity. It is an autosomal recessive genetic condition caused by mutations in the *BTD* gene which encodes biotinidase.

Biotinidase promotes the release of biotin from proteins found in food such as egg yolk and liver. The released biotin binds to and activates enzymes involved in protein, fatty acid and glucose metabolism. Biotinidase deficiency affects these metabolic processes. Biotinidase also releases biotin from these enzymes, allowing it to be recycled.

The condition is rare, affecting approximately 1 in 60,000 newborns, though no UK prevalence data was available at the last review.

Biotinidase deficiency is classified based on the level of residual biotinidase activity:

- profound biotinidase deficiency - less than 10% of normal biotinidase activity
- partial biotinidase deficiency - between 10% and 30% of normal biotinidase activity

The clinical course of these two categories is quite different. Profound biotinidase deficiency affects about 50% of cases and is the more severe form of the condition. It can result in seizures, ataxia, and vision and hearing deficits. Other consequences include skin rashes, alopecia and breathing difficulties.

Partial biotinidase deficiency is a milder form of this condition. Affected children may experience hypotonia, skin rashes, and hair loss, but these problems may only appear in times of metabolic stress, such as during illness or infection.

The treatment for biotinidase deficiency is lifelong oral supplementation with unbound biotin.

The current UK NSC policy is that population screening for biotinidase deficiency should not be offered in the NHS. A brief review document was produced in 2004. More recently a vignette was produced in 2008 as part of the discussion on a range of issues relating to newborn bloodspot screening. The need for a review was last considered in February 2009 but no document was produced.

The key issues underlying the policy not to screen newborn babies for biotinidase deficiency included:

- the rarity of biotinidase deficiency
- lack of information on the cost effectiveness of screening
- concern about the test (e.g. false positive rate)
- lack of optimisation of other approaches to management
- lack of information on the overall benefit of screening.

**This report**

This report uses evidence published from 2004 to 2012 to update the review of screening for biotinidase deficiency against the UK National Screening Committee (NSC) criteria for appraising the viability, effectiveness and appropriateness of a screening programme (National Screening Committee 2003). This update focuses on evidence relating to screening of newborns in the general population in the UK for biotinidase deficiency as this is the policy under review.

This update report aimed to focus on studies addressing key issues underlying the current policy decision, including:

- prevalence of biotinidase deficiency
- cost effectiveness of screening
- performance of the test
- optimisation of other approaches to management
- overall benefit of screening.

This report includes information from the 2004 NSC report and the 2008 vignette to provide context to the current update.

The update search covered the period January 2004 to 28 May 2012. A total of 309 references were identified, and of these 107 were judged to be potentially relevant. Additional relevant references identified during the preparation of this report have also been included.

A first pass appraisal of the potentially relevant studies at abstract level was followed by a retrieval of selected full text papers. An overview of the most informative and relevant references regarding the individual screening criteria is given below. Guidelines, systematic reviews of the evidence, randomised controlled trials and studies from the UK were prioritised, as were studies addressing key issues identified in the previous report.

Based on the evidence reviewed provisional summary statements have been made about whether each criterion is met, not met, partially met, unclear if met, or is not applicable. These judgements are provisional and should be reviewed by the Expert Panel in the context of all the evidence available.

## Appraisal against UK NSC Criteria

These criteria are available online at http://www.screening.nhs.uk/criteria.

### 1. The condition should be an important health problem

**2004 NSC review:** "*Biotinidase deficiency is a rare condition which leads to progressive neurological deterioration in infancy. It affects less than one in 60,000 babies - no more than 12 cases each year. About half are only mildly affected. Although it is very rare, early recognition of the severe form could prevent neurological damage. Without screening, some but not all severely affected babies will be diagnosed in time to avoid irreversible damage. The number of adverse events that are potentially preventable per year by a screening programme (population with 700,000 births) is possibly 3 - 4.*"

**The condition**

Biotinidase is an enzyme which recycles the B vitamin biotin.[1] Biotin is found in the diet in two forms: free biotin (non-protein bound), and as biotinylated peptides bound to protein. The proteins containing bound biotin are broken down by proteolysis to produce biotinyl-ε-lysine (biocytin) or small biotinyl-peptides. Biotinidase breaks down these smaller molecules to release free biotin.

Free biotin is needed to convert four carboxylase enzymes into their active forms. These carboxylases have roles in a variety of biochemical pathways:

- propionyl-CoA carboxylase (PCC) – needed for protein breakdown
- β-methylcrotonyl-CoA carboxylase (MCC) – needed for protein breakdown
- acetyl CoA carboxylase (ACC) – needed for making fatty acids
- pyruvate carboxylase (PC) – needed for making glucose.

Biotinidase also releases biotin from these enzymes, and in this way biotin is recycled in the body until it is excreted.

Individuals with biotinidase deficiency have abnormally low activity of the biotinidase enzyme. Biotinidase deficiency is separated into two categories based on the level of serum biotinidase activity:

- profound biotinidase deficiency – defined as <10% of the normal enzyme activity
- partial biotinidase deficiency – defined as 10%-30% of the normal enzyme activity

Individuals with biotinidase deficiency have reduced ability to release free biotin from its protein-bound form when ingested in the diet or recycle it from the carboxylases.

Biotinidase deficiency is a genetic condition which shows autosomal recessive inheritance. Biotinidase is encoded by the *Biotinidase* (*BTD*) gene on chromosome 3q25. The gene has a simple structure (4 exons spanning at least 23 kilobases of genomic DNA).

More than 150 mutations have thus far been identified in the *BTD* gene in individuals with profound biotinidase deficiency.[1] This includes a variety of mutations (nonsense, missense, deletions, insertions, duplications and splice junction mutations), with missense mutations the most common.[2]

The mutations are spread throughout the gene. Different combinations of mutations give rise to profound or partial biotinidase deficiency.

Five mutations are reported to account for 60% of the mutations causing biotinidase deficiency (listed in Table 1).[1,3]

**Table 1: Common mutations causing biotinidase deficiency**

| Nucleotide change | Amino acid change | Profound/partial deficiency allele |
|---|---|---|
| c.98_104delinsTCC (G98del3ins) | p.Cys33PhefsX36 (C33FfsX36) | Profound deficiency allele |
| c.1612C>T | p.Arg538Cys (R538C) | Profound deficiency allele |
| c.511G>A; c. 1330G>C (a double mutant allele) | p. Ala171Thr; pAsp444His (A171T; D444H) | Profound deficiency allele |
| c. 1368A>C | p.Gln456His (Q456H) | Profound deficiency allele |
| c. 1330G>C | p.Asp444His (D444H) | Partial deficiency allele (when in the presence of a profound deficiency allele in *trans*). (When present in *cis* with A171T it is a profound deficiency allele, see above) |

The c.98_104delinsTCC mutation causes a frameshift and occurs in at least one allele of about 50% of children with symptomatic biotinidase deficiency in the US. The c.1612C>T mutation is the second most common allele in children with profound biotinidase deficiency in the US, present in about 30% of symptomatic children.[4]

Almost all (98%) of people with partial biotinidase deficiency carry the 1330G>C (D444H) mutation as one of their alleles.[1] Individuals who have this allele plus a profound biotinidase deficiency allele have partial biotinidase deficiency and are expected to have about 20-25% of normal biotinidase activity. Individuals homozygous for this mutation have about 50% of normal biotinidase activity and therefore are not considered as having partial biotinidase deficiency.

In the US, some mutations have been reported to be more common in children identified by newborn screening, with others more common in children ascertained clinically, although there is overlap.[5] This suggests that newborn screening may be identifying individuals who may not have been picked up based on clinical presentation.

The test for biotinidase deficiency is based on serum biotinidase activity level, and not on screening DNA for genetic mutations.

Clinical presentation of profound biotinidase deficiency is reported to be variable, even within families.[4,5]

Symptoms usually appear between 2 to 5 months of age in untreated profound biotinidase deficiency patients, but may not appear until later in childhood.[4] There have been reports of adults identified with profound biotinidase deficiency who are asymptomatic despite not being treated (see Natural History section in Criterion 2).

The first symptoms of profound biotinidase deficiency often affect the nervous system. The majority of children with clinical presentation (over 70%) are reported to have seizures, hypotonia, skin rash or alopecia before diagnosis.[4] Over 75% of untreated children are reported to develop hearing loss, and about 50% have ataxia, developmental delay, conjunctivitis, and visual problems including optic atrophy.[4]

The severity of symptoms of profound biotinidase deficiency may vary from multiple mild seizures and ataxia to severe metabolic compromise leading to coma or death.[4] Children who develop symptoms later in life tend to have motor limb weakness, spastic paresis, and visual problems.[6]

Individuals with partial biotinidase deficiency are reported to be largely asymptomatic but can exhibit symptoms in times of stress, such as infection.[4]

**Studies identified in the update search**

No new studies were identified in the update search which described the prevalence of biotinidase deficiency in the UK. Studies on the prevalence of biotinidase deficiency are described in criterion 2.

Two papers described consequences of biotinidase deficiency in cases occurring in the UK. [7,8]

The first paper described five cases of biotinidase deficiency in the UK, most of whom had seizures, white matter abnormalities, hearing impairment, and problems with vision.[7] The paper did not report if the children had profound or partial biotinidase deficiency. The children presented at a median of 10 weeks (range 1 to 5 months) and diagnosis was at between age 2.5 and 12 months. The median delay between presentation and diagnosis was 5.5 months. The authors suggested that this delay had shown "little improvement" over the preceding decade, but did not provide specific figures for age at diagnosis for all known cases in the UK over time.

The second study described two children with biotinidase deficiency with unusual presentations at around age 2 years.[8] Both children had abnormal brain findings on MRI and neurological problems. One child had acute respiratory failure requiring intubation and ventilation. They had biotinidase activity levels that suggest they had profound biotinidase deficiency (based on the reference figures presented in Table 7 in Criterion 6). These papers are summarised in more detail in Criterion 2.

**Criterion 1: Met.** Untreated profound biotinidase deficiency can have serious consequences such as seizures, hearing and vision loss, and can result in severe metabolic compromise leading to coma or death. No studies assessing UK prevalence were identified in the update search. Figures from screening programmes worldwide suggest that the condition is rare.

## 2. The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage

**2004 NSC report:** *Yes*

**2008 vignette: "***There is no UK prevalence data available apart from a pilot screening study in Scotland where 102,393 babies were screened without finding a case. Prevalence rates reported*

*in Europe for partial and profound biotinidase deficiency combined range from 1 in 20,420 in Spain to 1 in 105,471 in Italy with a combined European prevalence of 1 in 47,486."*

**Epidemiology**

The update search did not identify any new studies which assessed the prevalence or incidence of biotinidase deficiency in the UK. A number of other studies identified in the update search reported on prevalence in other countries (see Table 2).

A narrative review reported that screening for the condition around the world has suggested an incidence of 1 in 137,000 for profound biotinidase deficiency, and 1 in 110,000 for partial biotinidase deficiency – giving an incidence of 1 in 61,000 for biotinidase deficiency overall.[1] Based on these figures the carrier frequency in the general population is estimated to be 1 in 120.

The Swedish study included in Table 2 below suggested that the condition was more common in children of Middle Eastern or African origin.[9] Four of the six children identified in this study with profound biotinidase deficiency were born to parents who were first cousins of Middle Eastern or African origin.

**Table 2: Prevalence of biotinidase deficiency identified in newborn screening programmes**

| Source | Country | Time period | Biotinidase deficiency (overall) | Partial BD | Profound BD |
|---|---|---|---|---|---|
| Newborn screening figures[10] | US | Not stated (pre-2004) | 1 in 61,319 | NR | NR |
| Newborn screening figures [4] | US | 2007-2008 | NR | 1 in 31,000 to 1 in 40,000 | 1 in 80,000 |
| Newborn screening figures[11] | Europe (7 countries) | Up to 2004 | 1 in 47,486<br>(25 in 1,187,153 infants screened) | NR | NR |
| Newborn screening figures[9] | Sweden | 2002-2008 | 1 in 53,000 | 1 in 91,000 | 1 in 127,000 |
| Newborn screening figures[12]* | Brazil | 1995-1999 | 1 in 9,000† | 1 in 16,000*<br>(10 mutation confirmed cases) | 1 in 75,000*<br>(3 mutation confirmed cases) |
| Pilot newborn screening study[13] | Turkey (area where consanguinity common) | 2006-2007 | NR | 1 in 34,378‡ | No cases identified (suggests prevalence <1 in 34,378) |

NR not reported. †The basis on which this figure was calculated was unclear. ‡Only one affected newborn was identified, so this figure may not be reliable. *Based on cases confirmed by serum biotinidase assay and mutation testing; not all screen positives had confirmatory testing so this may be an under-estimate.

**Natural history**

Untreated children with profound biotinidase deficiency usually present within the first few months of life, although they may present later in childhood or adolescence.[1,3,4] There have been cases of asymptomatic adults with untreated profound biotinidase deficiency; the reason for their lack of symptoms is unknown.[1] Clinical presentation of profound biotinidase deficiency is also reported to be variable, even within families.[4,5] The reasons for this are also not known.

Untreated individuals with profound biotinidase deficiency usually develop one or more neurological symptoms (myoclonic seizures, hypotonia, ataxia, developmental delay, vision problems and/or hearing loss) and/or dermatological symptoms (alopecia, eczema, and/or candidiasis). Individuals with partial biotinidase deficiency are usually asymptomatic, but may develop symptoms under stress, such as hypotonia, skin rash, and hair loss.

Many of the papers identified in the update were case reports of children with biotinidase deficiency, these are not summarised here. Studies from the UK are described here, as are the larger case series identified in the update search.

***UK studies***

The update search identified two papers describing the pattern of disease in children with biotinidase deficiency in the UK.[7,8]

One paper described neurological imaging in five children diagnosed with biotinidase deficiency in the UK.[7] Biotinidase deficiency had been detected in plasma or dried blood spots either colourimetrically or by a fluorimetric method. Four of the children were of Pakistani descent, and one of Asian descent. Parents were first cousins for four of the children.

The children presented at a median of 10 weeks (range 1 to 5 months). Age at diagnosis ranged from 2.5 to 12 months.

Four children presented with seizures as a first symptom, and one had abnormal (acidotic) breathing and regression. Eczema and/or alopecia were seen in three children. Three children had learning disabilities or developmental delay, two had frequent seizures, hearing impairment was seen in four children, two children had severe visual problems, and one had mild optic atrophy. One child had limited follow-up data due to recent diagnosis. The children were aged between age 3 months and 12 years 3 months at most recent follow up.

The main imaging findings were white matter abnormalities (all 4 patients with MRI scans) including delayed myelination (3 patients) and enlargement of the ventricular system and/or the extracerebral spaces (4 patients: 3 with MRI scans, 1 with a CT scan). Repeat scans were taken after 7-12 months of biotin treatment in two patients, and they showed improvements in myelination. One of these patients also showed normalisation of inner and outer cerebrospinal fluid (CSF) spaces, while the other showed progressive atrophy and the development of cerebellar cysts. The patient who showed improvement of myelination and CSF spaces with biotin treatment was reported to be developing normally, while the patient with improved myelination but worsening atrophy was severely handicapped.

The authors suggested that biotinidase deficiency should be excluded in all children with unexplained neurological problems.

A second paper described two cases in the UK with unusual clinical and radiological presentations.[8] The children were both from consanguineous Pakistani parents.

One child presented at 22 months with progressive motor weakness and ataxia two months after a diarrhoeal illness. He had sparse hair, spastic paraparesis and neuropathic bladder. Spine MRI showed signal abnormalities in the upper cervical cord extending into the inferior brainstem. Brain MRI six weeks after first neurological symptoms showed symmetrical abnormal signal extending caudally from the medial thalamus into the tectum and periacqueductal grey, dorsal pons, medulla, and dorsal spinal cord. This led to a suspicion of neurometabolic disorder, and testing showed that biotinidase activity was <0.5nmol/mL/min which confirmed severe biotinidase deficiency. Visual evoked potential testing showed moderate bilateral post retinal dysfunction and optical disc pallor.

The patient was treated with 10mg biotin twice daily, and by three years of age he had full motor recovery, but residual speech and cognitive impairment, and bilateral sensorineural hearing loss.

The second patient presented at age 2 years with acute bilateral ptosis, facial diplegia and general lethargy with diurnal variation. She had a history of mild motor delay, and eczema and wheezing associated with intercurrent illness. During investigations she presented with focal seizure and respiratory failure with severe respiratory acidosis which required intubation and ventilation. She was hypotonic with lower limb pyramidal signs. Skin, hair, and eyes were normal.

Her biotinidase level was 0.7nmol/mL/min. MRI showed symmetrical abnormalities in the medulla, dorsal pons, and dorsal midbrain extending upwards. Once biotin 15mg once daily was started she began to recover. At follow up there was still evidence of developmental delay but she was reaching new developmental milestones. A subsequent sibling was treated with biotin 5mg once daily from birth and subsequently found to be affected. This baby was reported to be developing appropriately for age at last follow up.

***Hearing loss***

The update search identified two papers describing the natural history of hearing loss in children with biotinidase deficiency.[14,15]

The first paper reported on audiologic findings in 20 children with profound biotinidase deficiency in Turkey.[14] Three of these children had been diagnosed due to having an older sibling with the disease and were therefore younger at diagnosis (aged up to 2 weeks) than the other 17 children (aged between 2 months and 15 years at diagnosis). The three children diagnosed due to an older affected sibling did not have symptoms at the time of diagnosis, only one of the other 17 children was asymptomatic at the time of diagnosis at age 7 months. The other 16 children had a period of between 1 and 120 months between onset of symptoms and diagnosis.

Sixteen of the children were receiving biotin at the time of hearing testing, while four were tested at the time of diagnosis, including the three children diagnosed at or before age 2 weeks. How long the children taking biotin had been treated for was not reported.

Of the 20 children, 9 had normal hearing (including the three diagnosed early), and 11 showed at least some hearing loss (55%). Two of these children had mild hearing loss, one moderate, two severe, and six profound hearing loss. There was no significant difference between age at onset of symptoms, age at diagnosis, or time from onset of symptoms to diagnosis between the children with and without hearing loss (see Table 3). This may be in part due to the small numbers of children in the study.

**Table 3: Comparison of characteristics of children with biotinidase deficiency and with or without hearing loss**

| | Children with hearing loss (n=11) | Children with normal hearing (n=9) |
|---|---|---|
| Mean age at onset of symptoms (range) | 6.9 months (1 to 60 months) | 18.6 months (1 to 48 months)* |
| Mean age at diagnosis (range) | 21.5 months (2 to 180 months) | 15.4 months (0.1 to 54 months) |
| Mean time from onset of symptoms to diagnosis (range) | 14.5 months (1 to 120 months) | 7.6 months (1 to 20 months)* |

*Excludes children diagnosed due to older sibling and child with no symptoms at diagnosis

Children diagnosed immediately after birth had significantly shorter auditory brainstem response (ABR) latencies in both ears than children who were diagnosed later ($p<0.05$). The authors of the paper note that not all children with biotinidase deficiency develop hearing loss, so they could not be certain that biotin treatment had prevented hearing loss in the children with normal hearing.

A second paper from the same medical faculty in Turkey appeared to report on genotype-phenotype correlation in the same 20 patients.[15] It reported that children were followed up for between 1 to 5 years and did not show any changes in auditory thresholds over this time. The study mainly focused on genotype-phenotype correlation and is described in greater detail below.

***Genotype-phenotype correlation***

The American College for Medical Genetics report that there is still little known about the correlation between genotype and phenotype in biotinidase deficiency.[4] Universal newborn screening makes it more difficult to study genotype-phenotype correlation as all children identified as having biotinidase deficiency would be treated.[5] The screening and main confirmatory test for biotinidase deficiency are based on biotinidase activity rather than testing for mutations, although mutation analysis may be used as a secondary confirmatory test (see Criterion 8). It has also been suggested that treatment should be based on biotinidase activity (rather than on genotype).[1,16] This would mean that the lack of understanding of genotype-phenotype correlation would not directly impact on screening and treatment.

A study from Turkey was identified in the update search that reported on correlation between genotype and hearing phenotype in 20 children with profound biotinidase deficiency.[15] All the children who were diagnosed after with symptom onset and who had hearing loss were homozygous for null mutations in the *BTD* gene. The three children diagnosed and treated shortly after birth all had null mutations but had normal hearing. All children who were diagnosed after symptom onset but who had normal hearing were homozygous for missense mutations that were predicted to result in a defective biotinidase protein. It reported that there were no differences in dietary biotin intake between the children.

These findings suggest the possibility of a genotype-phenotype correlation. The authors cite another study published in 2002 of 26 children with hearing loss, where 16 had two null mutations, and most of the remainder had at least one null mutation. One of the eight children with normal hearing in this study had two null mutations and six had at least one null mutation.

Although these findings also suggest that null mutations may be associated with hearing loss, they also show that this relationship is not clear cut.

***Asymptomatic individuals with biotinidase deficiency***

One paper identified in the update search reported on patients with biotinidase deficiency identified through family studies in index cases.[17] The study assessed family members of 121 individual with biotinidase deficiency detected by newborn screening (84%) or selective metabolic screening (16%). It identified 32 individuals with biotinidase deficiency that had not previously been diagnosed, in the families of 26 index cases (24 identified by newborn screening, 2 with selective metabolic screening).

Seventeen of the 32 had profound biotinidase deficiency (7 parents and 10 siblings) and 15 partial biotinidase deficiency (7 parents and 8 siblings). The average age of the parents on diagnosis was 25.8 years, and for siblings it was 6.8 years.

Only three individuals with profound biotinidase deficiency (17.6%) were found to be symptomatic, they were all siblings of index cases (aged 2.5, 5 and 7 years). One of these children had dermatitis on the elbows; one had ataxia, speech delay and attention deficit disorder; and the third had microcephaly, severe developmental delay, seizures and ataxia. The first two children improved with biotin treatment, while the third child and her affected sibling had only a poor response. One of the affected siblings with partial biotinidase deficiency had a borderline IQ, but none of the others displayed symptoms. None of the affected parents reported symptoms, although two mothers reported periodic hair loss.

These observations suggest that not all patients with biotinidase deficiency, even those with profound biotinidase deficiency, will display symptoms. Previous family studies have also identified similarly asymptomatic adults.[1]

**Summary: Partly met.** The precise prevalence of biotinidase deficiency in the UK remains uncertain. Studies from Europe suggest an overall prevalence of biotinidase deficiency of 1 in about 50,000. One Swedish study suggested that the prevalence of profound biotinidase deficiency in Sweden in newborns was 1 in 127,000 and of partial biotinidase deficiency was 1 in 91,000.

The natural history of the condition appears to be reasonably well understood, although there is limited understanding of genotype-phenotype correlation, which would be needed if screening were to be based on genetic testing. Current newborn screening programmes are based on biochemical testing. A better understanding of why some individuals remain asymptomatic and their prognosis is needed.

A reduced level of biotinidase activity is detectable in affected individuals from birth, before the onset of symptoms (see Criterion 5 for further discussion).

## 3. All the cost-effective primary prevention interventions should have been implemented as far as practicable

**2004 NSC report:** *Not applicable*

**2008 vignette:** "*Not applicable; prenatal diagnosis available but questionable in view of effective treatment."*

There are no new primary prevention interventions that can prevent biotinidase deficiency.

**Summary: Not applicable.**

## 4. If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood, including the psychological implications.

**2004 NSC report:** *Not applicable*

Biotinidase deficiency is an autosomal recessive genetic condition. Screening for biotinidase deficiency is for levels of biotinidase activity rather than for mutations. Testing for mutations may occur in the diagnostic work up of screen positives and these 'positives' may include carriers.

Individuals with <10% of average normal biotinidase activity have profound biotinidase deficiency, and those with 10%-30% of average normal biotinidase activity have partial biotinidase deficiency. A technical guideline on the diagnosis of biotinidase deficiency from the American College of Medical Genetics (ACMG) stated that heterozygous individuals may have about 50% of normal activity.[4] They say that there may be significant overlap in activity among the various groups (those with profound or partial biotinidase deficiency and heterozygous carriers). They say that at least some of the variability is due to clinical status, assay interference, and sample handling artefacts. They did not report whether to what extent carriers are identified by newborn screening in the US.

One paper from Brazil reported that some carriers of profound or partial biotinidase deficiency mutations had been picked up in the newborn screen.[12] They had biotinidase activity of <30% on confirmatory biotinidase testing, and were found to be heterozygotes on mutation testing. This suggests that carriers may be identified in screening, although the study suggested this may have been as a result of poor quality control, for example in the storage and transport of samples.

No papers were identified in the update search specifically addressing the natural history of carriers or the psychological implications of carrier status. Individuals with partial biotinidase deficiency are reported to be largely asymptomatic but may show symptoms under stress (e.g. infection), and even some individuals with profound biotinidase deficiency may be asymptomatic.[4] Heterozygous carriers, who should have higher biotinidase activity than individuals with partial or profound biotinidase deficiency, would not be expected to show symptoms.

Parents whose child is identified as having biotinidase deficiency by newborn screening will be obligate carriers; the same would be true for parents of children with biotinidase deficiency identified through clinical presentation.

**Summary: Not met.** Screening for biotinidase deficiency is for levels of biotinidase activity rather than for mutations, but may identify carriers of the associated mutations. One study from Brazil did report the identification of some carriers by newborn screening (four amongst 21 followed up with mutation testing). Use of an appropriate cut-off threshold for biotinidase activity on screening and appropriate quality control of testing processes should minimise the likelihood of identifying carriers in newborn screening.

No studies in the update search reported on the numbers of carriers identified through newborn screening in Europe or the US, or reported on the natural history or psychological implications of being a carrier.

## 5. There should be a simple, safe, precise and validated screening test

**2004 NSC report:** "*Yes. The neonatal blood spot is used. The biochemical test needed to identify this disorder cannot currently be included in other biochemical screens and would need separate equipment and processes. It could be automated and can be done at relatively low cost. The test itself is believed to be satisfactory."*

"*Probably high sensitivity, >95%, but there would be 0.02% repeat specimen rate and then <10% false positive at clinical referral."*

***2008 Vignette:*** *"Biotinidase analysis on neonatal bloodspots is relatively simple based upon measurement of enzyme activity through release of 4-aminobenzoate (PABA) from biotinyl-4-aminobenzoate and the colorimetric determination of the diazo derivative of PABA.*

*Pre-term infants tend to show low activity and therefore need to be re-tested on a later sample. These methods detect both partial and profound biotinidase deficiency."*

*"The original TMS method uses either biocytin or biotinyl-PABA as substrate, measuring either PABA or biotin by isotope dilution. A semi-quantitative method on blood spots (no stable isotope internal standard, calculation from substrate/product ratio) can be combined with haemoglobinopathy screening or with metabolite screening on the same 3mm blood spot (personal communication Neil Dalton & Charles Turner)*

The update search identified one paper describing recommended procedures for diagnosis of biotinidase deficiency in the US,[4] three papers describing experience with newborn screening programmes in Brazil, Turkey and Sweden,[9,12,13] and one paper describing development of a screening test for use in Cuba.[18]

The American College of Medical Genetics (ACMG) produced a report which ranked newborn screening tests in order of priority of inclusion in a uniform newborn screening panel across US states, and included information on the screening tests.[10] This document suggested that the semi-quantitative or qualitative biotinidase screening test can be performed at high throughput, with 500 to 1,000 samples processed in a day. It suggested that the cost of the test ranged from $0.30 to £1 USD. It noted that the screening test was not part of a multiplex platform such as tandem mass spectrometry (TMS). There were anecdotal reports of cases being detected by TMS acylcarnitine profiling, but this was inconsistent. The screening test for biotinidase deficiency does not detect multiple analytes related to the condition, and does not detect other secondary target conditions.

**Guidelines for biotinidase testing and tests available**

The ACMG issued technical standards and guidelines for the diagnosis of biotinidase deficiency in 2010.[4] This includes recommendations about the initial newborn screening test and confirmatory testing.

It stated that almost all screening programmes in the US are reported to be based on a colorimetric assay of biotinidase activity in dried blood spots.[4] PABA-based assays are reported to be the most commonly used, although there are other methods including a fluorescent technique utilising biotinyl-6-aminquinoline as a substrate which has been used in newborn

bloodspot testing. These alternative methods are said to be more expensive, more time consuming, more difficult to perform and not readily adaptable for use on dried blood spots.[4]

Different US states have been reported to use different newborn screening cut-off points and rescreening and follow up protocols. Some states use qualitative screening results (positive or negative), while others use quantitative enzyme activities and a set cut-off value. The test is a direct assay of biotinidase activity, and is not influenced by biotin in the diet.

For blood spot testing, the ACMG state that the spots need to be dried completely before transport to the laboratory, as humidity or wet samples can result in significant loss of biotinidase activity.[4] About 50% of false positive results are reported to relate to prematurity, and most of the others to mishandling of samples and possibly their exposure to heat and humidity.[4] The effect of transfusion on screening results is not established; it may have an effect on the results of testing for biotinidase deficiency.

For confirmatory biotinidase activity testing, plasma or serum from a whole blood sample is needed, with storage at -80°C until testing. Storage at -20°C results in loss of biotinidase activity. They recommend that blood samples from the parents and an unrelated normal control are selected at the same time and sent together for analysis to aid interpretation of results for the newborn, and to assess sample handling artefacts. They note that in a number of cases where this was not done, a child has been diagnosed with profound biotinidase deficiency and treated for extended periods with biotin before repeat enzyme studies showed that they did not have the condition.

The presence of sulfa drugs is reported to potentially lead to false negatives, but these drugs are reported to be contraindicated in neonates and in pregnancy, and therefore should not be an issue for newborn screening.[4]

The ACMG state that follow-up molecular testing by either targeted mutation analysis or full sequencing of the *BTD* gene is particularly useful for differentiating individuals with profound biotinidase deficiency from partial biotinidase deficiency, and partial biotinidase deficiency from heterozygosity for profound biotinidase deficiency. Most children with partial biotinidase deficiency carry one copy of the D444H mutation and one profound biotinidase deficiency allele. They also recommend gene sequencing in cases where there is any question on the interpretation of biotinidase activity results.

Urine organic analysis in individuals with biotinidase deficiency may show normal or increased 3-hydroxyisovaleric acid and 3-methylcrotonylglycine, and plasma acylcarnitine analysis may show normal or increased C5-OH acylcarnitine.[19] The ACMG state that analysis of urine organic acids by gas chromatography/mass spectrometry or plasma acylcarnitines by liquid chromatography should not be used as the sole test for biotinidase deficiency.[4] This is because as although they may identify characteristic abnormalities seen in people with biotinidase deficiency, these characteristics may also be shared by other disorders and many cases of biotinidase deficiency will also be missed. Therefore biotinidase enzyme assay is always required.

**Performance of newborn screening programmes**

Three studies reported on the performance of newborn screening programmes.[9,12,13] As not all screened babies are further assessed for biotinidase deficiency using confirmatory tests, it is not possible to calculate many sensitivity or specificity of the screening test from this data.

The first paper reported on newborn screening in Sweden.[9] It reported that biotinidase activity was measured in dried blood spots with a semi-quantitative method using biotin-6-

amidoquinoline as substrate. The cut-off value used was initially 25% of the mean activity of all samples measured on that day, and this was lowered to 20% in 2006 to reduce false positives. Infants with a positive screening test provided a second blood spot and blood sample for the assessment of biotinidase activity. If the confirmatory biotinidase assay also showed partial or profound deficiency, mutation analysis was carried out.

Over six years, 24 children screened positive among 637,452 screened newborns and 5,068 adoptive/immigrant children (a recall rate of 1 in 26,771). Thirteen children were confirmed as having partial or profound biotinidase deficiency (1 in 49,425). This equates to 46% of screen positives being false positives (or a positive predictive value for the test of 54%; see Table 4).

**Table 4: Performance of screening test for the identification of biotinidase deficiency in Sweden***

| | **Disease positive** | **Disease negative** | **Totals** |
|---|---|---|---|
| **Test positive** | 13 | 11 | 24 |
| **Test negative** | NA | NA | **642,496** |
| **Totals** | NA | NA | **642,520** |

NA not assessed; this table includes both newborn and adoptive/immigrant children as test positives were not presented separately for these groups

The second study reported the experience with screening for biotinidase deficiency in Brazil between 1995 and 1999.[12] A total of 225,136 babies were screened at a median age of 13 days (range 2 to 30 days). The screening test used a qualitative colorimetric assay on blood spots using biotinyl-p-aminobenzoate as a substrate. In babies suspected of deficiency a confirmatory quantitative colorimetric assay was carried out. Babies with <30% of the mean serum enzyme activity of normal children had direct sequencing.

Of the babies screened 0.12% (272 babies) had absent or low biotinidase deficiency on blood spot screening (about a 1 in 827 recall rate). Of these babies, 240 had confirmatory testing and 36 (15%) had <30% of normal enzyme activity (14 had <10% enzyme activity and 22 had enzyme activity 10%-30% of normal). Therefore 85% of those who had positive screening results had normal biotinidase levels on confirmatory biotinidase activity testing.

Of these 36 babies and their families, 21 had mutation analysis. Based on this, 3 were confirmed as carrying two profound deficiency alleles and having profound biotinidase deficiency, and 10 were confirmed as carrying two partial deficiency alleles and having partial biotinidase deficiency. One was homozygous for a mutation that can cause partial deficiency (1330G>C) and was reported as having partial biotinidase deficiency. The paper reported that these 14 children needed continued biotin treatment. Four children were found to be carriers of only a single profound or partial deficiency allele, and three had no *BTD* mutations identified.

Excluding the 47 babies for whom confirmatory testing was not obtained, and taking positive confirmatory blood sample biotinidase assay and mutation analysis as the gold standard for diagnosis this gives the figures in Table 5 below. The positive predictive value of the screening test based on these figures is 6% (i.e. 94% of positive tests turn out to be false positives on confirmatory testing).

**Table 5: Performance of newborn screening test for the identification of biotinidase deficiency in Brazil**

| | Disease positive | Disease negative | Totals |
|---|---|---|---|
| **Test positive** | 14 | 211 | 225 |
| **Test negative** | NA | NA | 224,864 |
| **Totals** | NA | NA | **225,089** |

NA not assessed

The recall rate for confirmatory testing was reported to be higher than that seen in most other laboratories. This was attributed to inadequate shipping and handling of the samples (failure to rapidly freeze samples and ship on dry ice or to store at -80°C if not processed immediately).

The third study reported in the experience with a pilot programme screening for biotinidase deficiency in an area of Turkey where consanguineous marriages are common.[13] Between 2006 and 2007 a total of 34,378 babies were screened. The screening test used a qualitative colorimetric assay on blood spots with biotinyl-p-aminobenzoate as a substrate. If an abnormal result was obtained with the second blood spot disc, and additional blood spot was requested from the infant. Definitive diagnosis was based on quantitative assessment of enzyme activity in serum samples.

There were reported to be 0.09% false positive results i.e. where the screening test was positive but a second blood sample was negative for biotinidase deficiency – this would equate to about 31 infants. This gave an overall recall rate (true and false positives) of about 1 in 1,074. One newborn was positive on both the first and second bloodspot test, and later serum testing showed the individual to have partial biotinidase deficiency. This suggested a positive predictive value for the screening test of 3% (i.e. 97% of positive screening tests turned out to be negative on confirmatory testing; see Table 6 below).

**Table 6: Performance of newborn screening test for the identification of biotinidase deficiency in Turkey**

| | Disease positive | Disease negative | Totals |
|---|---|---|---|
| **Test positive** | 1 | 31 | 32 |
| **Test negative** | NA | NA | 34,346 |
| **Totals** | NA | NA | **34,378** |

NA not assessed

One narrative review reported anecdotally that there have been cases of profound biotinidase deficiency have been missed by newborn screening.[1] It also reported that although initially biotinidase screening had a low false positive rate compared with other disorders being screened for, this rate has increased markedly. Another paper by the same author reported that the false positive rate in the pilot newborn screening programmes in Virginia and worldwide was 0.001.[6] The cause for the increasing false positive rate was suggested to be most likely to be modifications to screening test methods made by different laboratories and commercial kit manufacturers.[1] Another possible contributor was suggested to be variation between technicians when visual identification of positives is used.

**Development of a newborn bloodspot screening test**

One paper identified in the update search described an adaptation of the PABA method for use in a qualitative colorimetric ultra-microassay for newborn bloodspot screening for biotinidase deficiency.[18] It involved visual inspection of the assay results, with a purple colour indicating normal biotinidase activity, a clear purpose colour indicating low biotinidase activity, and a light yellow colour little or no biotinidase activity. It tested the assay on control samples with known biotinidase activity, as well as heel prick newborn samples from the national phenylketonuria screening programme. It compared the assay with the conventional PABA-based method (not further described).

They found that the adapted method had a minimum detection limit of 2% biotinidase activity, with no colour visible below this level. The new test agreed with conventional test in 785 dried blood samples and reference and control samples with known biotinidase activity. They say that this method has been implemented for national newborn screening in Cuba. The paper did not described to what extent the adapted screening method was similar to that used for screening in other countries.

**Summary: Partly met.** The test is safe as the initial screen uses a newborn bloodspot and confirmatory testing is based on a blood sample, which are unlikely to cause harm to the infant. The test is relatively simple, in that it uses newborn bloodspots, which are already collected in the UK for use in other screening programmes. The confirmatory test requires a blood sample. The diagnostic tests would be likely to already be conducted in UK laboratories for confirmation of clinically identified cases. The screening test does not use tandem mass spectrometry (TMS), and would need to be conducted separately to other newborn screening tests, which means that the process would not be as simple as it could be if TMS were available.

The detection rate and number of false negatives of the screening test were not reported in the literature identified in the update search, and the positive predictive values that are reported vary widely and are dependent on best practice in handling and storage. This suggests that quality control of the screening and follow up testing would be important.

## 6. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed

**2004 NSC report:** "*Yes. Probably high sensitivity, >95%, but there would be 0.02% repeat specimen rate and then <10% false positive at clinical referral."*

No papers were identified in the update search describing the distribution of biotinidase activity amongst newborns in the UK. One paper described test values and cut-offs in the US,[4] three described cut-off values used in European countries,[9,11,20] and two described cut-off values in Brazil and Turkey.[12,13]

The American College for Medical Genetics' (ACMG) technical standards and guidelines report that reference ranges of biotinidase activity have been published.[4] These appear to have been obtained from only relatively small number of individuals (between 21 and 100 in each group). They are summarised in Table 7 below.

**Table 7: Reference biotinidase activities as reported by the ACMG**

| Population group | n | Biotinidase activity ± SD (nmol/min/mL serum) |
|---|---|---|
| Unaffected individuals | 100 | 7.57 ± 1.41 |
| Parents of children with profound BD | 21 | 3.49 ± 0.72 |
| Children with profound BD ascertained by clinical symptoms | 23 | 0.12 ± 0.18 |
| Children with profound BD ascertained by newborn screening | 41 | 0.19 ± 0.16 |
| Individuals with partial BD | 23 | 1.47 ± 0.41 |

BD biotinidase deficiency; n number of individuals tested; SD standard deviation

The ACMG state that before initiating testing each laboratory should establish their own reference ranges for biotinidase deficiency by measuring biotinidase activity for a sample of normal individuals (e.g. 20-50 people), and multiple individuals with profound biotinidase deficiency, partial biotinidase deficiency, and heterozygotes for profound biotinidase deficiency. One narrative review highlighted the importance of laboratories setting appropriate cut-offs for the assay they are using and monitoring these to reduce the rate of false positives.[6]

The ACMG report that full term newborns have 50-70% of the average normal adult biotinidase activity, and therefore a separate reference range should ideally be established for this age group. Preterm infants have lower levels of biotinidase activity.[6]

As noted in Criterion 5 above, different states in the US have been reported to use different newborn screening cut-off points and rescreening and follow up protocols.[4]

For confirmatory testing the ACMG report that biotinidase activity <10% of normal is indicative of profound biotinidase deficiency, and 10%-30% of normal is indicative of partial biotinidase deficiency.

A paper summarising European experience with newborn screening in 2004 reported that six countries had national newborn screening for biotinidase deficiency (Austria, Germany, Hungary, Liechtenstein, Sweden and Switzerland) and four countries had pilot programmes (Belgium, Italy, Spain, and Turkey).[11] Of the seven countries for which details on screening for biotinidase deficiency were available, three countries used colorimetric methods (Austria, Italy, Spain), one used the 'Wolf' method (Switzerland), one used both colorimetric and Wolf methods in different areas (Belgium), one used fluorimetric and colorimetric methods (Germany), and one used an enzymatic method (Sweden). No further details were provided about the methods. One country using the colorimetric method (Austria) used visual inspection to identify positive results, and had a recall rate of 0.014%. Another county (Belgium, Wallonia) using a colorimetric method with an activity of 10% as a cut-off for recall, and had a 0.04% to 0.21% recall rate. Germany used a cut-off of 30% biotinidase activity and had a recall rate of 0.05%, and Sweden used a cut-off of 20% and had a 0.004% recall rate.

The other three countries did not have data on the cut-off used, and only one (Spain) had data on recall rate (0.03%).

An update on newborn screening in Europe reported that eleven European countries had newborn screening for biotinidase deficiency in 2009 (Austria, Belgium, Denmark, Germany, Hungary, Liechtenstein [who take part in Switzerland's screening programme], the Netherlands, Spain, Sweden, Switzerland, and Turkey).[20] All of the countries used a "relatively simple" enzymatic reaction with a colorimetric endpoint. The results were reported to be usually presented as a percentage of the daily mean of all samples tested. The six countries reporting their cut-off limits used values varying from 2.7% (Germany) to 50% (Belgium) of daily mean activity to identify screen positives.

Between one in 30,000 samples (Austria) and one in 111,000 samples (Sweden) were reported to screen positive and require further investigation. The overall prevalence of screen positive results was 1 in 45,000.

A paper providing more detail about newborn screening in Sweden was identified.[9] It reported that biotinidase activity was measured in dried blood spots with a semi-quantitative method using biotin-6-amidoquinoline as substrate. The cut-off value used was initially 25% of the mean activity of all samples measured on that day, and this was lowered to 20% in 2006 to reduce false positives. Infants with a positive screening test provided a second blood spot and blood sample for the assessment of biotinidase activity. If the confirmatory biotinidase assay also showed partial or profound deficiency, mutation analysis was carried out.

A Brazilian study reported that a qualitative colorimetric assay was used as the initial screening test (not further described).[12] It reported that in the confirmatory quantitative biotinidase assay normal serum biotinidase activity was from 4 to 10 µmol PABA formed per mL per minute. Infants with <30% of the mean serum biotinidase activity of normal children had blood taken for confirmatory DNA analysis.

A Turkish study reported that a colorimetric assay was used as the screening test (see Criterion 5 for details).[13] Infants with less than 10% of the mean normal biotinidase activity on confirmatory serum testing were considered to have profound biotinidase deficiency, and those with 10-30% of normal activity were considered to have partial biotinidase deficiency.

**Summary: Not met.** No papers were identified describing biotinidase levels in newborns in the UK or a threshold value based on optimising sensitivity/specificity in a UK population. A laboratory protocol from one children's hospital in the UK suggested that a normal biotinidase activity range for males and females of any age as 3.9 to 18.9nmol/mL/min. One US guideline reported that reference ranges for biotinidase activity have been published, although these seemed to be based on relatively small numbers of individuals.

Different countries in Europe and states within the US appear to use different variations of the newborn screening test, and different cut-offs. A technical guideline from the US and a narrative review highlighted the importance of individual laboratories establishing their own reference ranges for biotinidase activity, setting appropriate cut-offs and monitoring them, particularly to reduce false positives.

The definition of profound biotinidase deficiency as having <10% of normal enzyme activity on confirmatory testing and partial biotinidase deficiency as having 10-30% of normal enzyme activity appears to be widely used.

## 7. The test should be acceptable to the population

**2004 NSC report:** *Yes.*

The update search did not identify any assessments of whether newborn biotinidase screening is acceptable to the UK population. Other conditions are screened for using newborn bloodspot samples in the UK, so at least the initial sample collection may be acceptable.

One paper reported that eleven European countries had newborn screening for biotinidase deficiency in 2009 (Austria, Belgium, Denmark, Germany, Hungary, Liechtenstein [as part of Switzerland's screening programme], the Netherlands, Spain, Sweden, Switzerland, and Turkey).[20] The levels of uptake of these programmes were not reported.

**Summary: Unclear if met.** The update search did not identify any assessments of whether newborn biotinidase screening is acceptable to the UK population. Other conditions are screened for using newborn bloodspot samples in the UK, so at least initial sample collection may be acceptable. Acceptance of a screening programme if proposed should be based directly on the views of parents regarding the test and implications of the tests and follow up treatments being proposed.

## 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

**2004 NSC report:** *Yes.*

As newborn biotinidase deficiency screening is not currently carried out in the UK, there is not currently an agreed UK policy on follow-up investigations.

Documents summarising further diagnostic investigation after positive screening test result were identified for the US.[4,21]

The American College of Medical Genetics (ACMG) has produced an algorithm outlining further diagnostic investigations after newborn screen indicates possible biotinidase deficiency.[21] It suggests that if the child is symptomatic additional testing including glucose, electrolytes, blood gas, lactate, and ammonia can be carried out in parallel with confirmatory testing.

After abnormal newborn screening results a confirmatory serum biotinidase assay is carried out.[21] The ACMG technical guidelines for biotinidase deficiency diagnosis recommend that both parental blood samples and a normal control blood sample are collected simultaneously with the infant's blood sample, and the samples sent together for testing.[4] Serum biotinidase activity <10% of normal is indicative of profound biotinidase deficiency, and 10%-30% of normal is indicative of partial biotinidase deficiency. If a child is found to have normal biotinidase activity on the confirmatory test no further action is required.

The ACMG say that typically for an infant with partial biotinidase deficiency, one parent will have biotinidase activity of about 50% of normal, indicating that they are a carrier for a profound biotinidase deficiency allele, and the other parent will have about biotinidase activity of about 75% of normal, indicating that they are a carrier for the D444H partial biotinidase deficiency allele.[4] If one or both parents have results in the normal range, then mutation analysis is recommended. In infants with biotinidase activity of about 50%, this could indicate either being a carrier for a profound biotinidase deficiency allele or homozygosity for the D444H partial biotinidase deficiency allele. Parental biotinidase activity analysis may be helpful in distinguishing between these, although mutation analysis may still be required.

Newborns have lower mean biotinidase activity than adults, with activity increasing in the first days to weeks of life. One narrative review suggested that term infants normally have about 50-

70% of mean normal activity of adults.[6] The ACMG state that newborns with 50-70% of mean normal activity not usually require retesting at a later date.[4]

The narrative review reported that at 24 weeks of gestation biotinidase activity is about 25% of normal, and increases linearly to term.[6] The ACMG also report that prematurity causes about half of the false positives identified by newborn screening. The ACMG did not specify any different procedures for screening or diagnostic testing in premature infants.

The ACMG reports that targeted mutation analysis or complete gene sequencing is often useful, but may not always be needed, for example where the infant has <10% activity, parental biotinidase activity is consistent with them being carriers of profound biotinidase deficiency alleles, and the normal control sample showed normal biotinidase activity. Sequencing of the *BTD* gene only includes 4 exons, and rapid sequencing of the entire coding sequence and intron-exon junctions is possible. The ACMG suggest that mutation analysis is also useful for family studies and prenatal diagnosis.

The treatment for individuals with biotinidase deficiency is oral free biotin supplementation. Infants can receive biotin supplementation before confirmatory biotinidase activity testing without jeopardising the confirmatory test result because biotin does not affect the activity of biotinidase.

**Summary: Not met.** There is no currently an agreed UK policy on follow-up investigations. Several countries offer newborn biotinidase deficiency screening and policies on further diagnostic investigation were identified from the US. The further investigations outlined in the US (serum biotinidase activity testing and mutation analysis) are similar to those described in studies outlining follow up in newborn screening programmes in other countries and could be the basis for the UK (see Criterion 5).

## 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

**2004 NSC report:** *Not applicable*

Although the condition is genetic the screening test is biochemical, and not for specific mutations.

**Summary: Not applicable.**

## 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

**2004 NSC report:** *Yes.*

The treatment involves lifelong oral supplementation with free (non-protein bound) biotin.[1,3] Affected individuals may also be advised to avoid raw eggs, as they contain avidin which binds to biotin and will stop it being accessible to the body.[16]

Biotin treatment is seen as highly effective and no side effects are reportedly known.[3,5,19] Therefore RCTs of biotin treatment for biotinidase deficiency are likely to be unethical, and none

were identified in the update search. Several narrative reviews and other papers discussed the use of biotin treatment.

Biotin is reported to prevent the development of symptoms in affected children identified by newborn screening, and can improve symptoms in children who present clinically.[3,10] Seizures and biochemical abnormalities are reported to resolve rapidly with biotin treatment, and some white matter abnormalities can resolve on treatment, although some damage may not be reversible.[7,10] For example, developmental delay, damage to the optic nerve and hearing loss may not be reversible with biotin treatment once they have occurred.[3,10] Cutaneous abnormalities are reported to improve within weeks of starting biotin treatment.[6] Symptoms are reported to recur if children do not comply with their biotin treatment.[6]

A narrative review acknowledged that there have been a few short term studies of outcomes of treatment in children with profound deficiency identified by newborn screening, but no long term studies, and that much of what is known is encouraging but anecdotal.[6]

The American College of Medical Genetics report ranking conditions for inclusion in the newborn screening panel reported that biotin treatment scored highly for being simple and widely available, having the potential to prevent all negative consequences of the condition, having clear evidence that early intervention optimises individual outcomes, and being able to prevent mortality by preventing life threatening episodes of metabolic decompensation.[10]

**Effects of early versus late treatment**

One paper identified in the update search compared the outcomes of children diagnosed early versus those diagnosed late. It reported a comparison of children who were diagnosed as a result of newborn screening and children diagnosed after presenting with symptoms or through a family investigation (clinically detected) in Switzerland.[22]

The study aimed to contact the 119 patients with profound biotinidase deficiency that had been identified by tests performed at a children's hospital in Switzerland up to 1998. The tests performed to assess biotinidase activity in the patients were a colorimetric assay and a sensitive high performance liquid chromatography assay. Information could be obtained for 37 of these patients (25 identified by newborn screening, 12 clinically detected; 24 male, 13 female; median age 6.5 years, range 6 months to 20 years). They came from 31 unrelated families. Only one of the 12 clinically detected children had been identified as a result of having an affected relative and not by symptomatic presentation.

The patients' development was assessed in a questionnaire completed by the referring physician, and parental questionnaires (including the Child Behaviour Checklist [CBC] for children older than 3 years and the Vineland Adaptive Behaviour Scales [VABS]). Information on other patient characteristics including biotin supplementation was obtained from laboratory records and a follow-up questionnaire on the child's clinical course which was completed between 6 months and 2 years after diagnosis. Children diagnosed as a result of newborn screening were compared to symptomatic children for residual impairments, social adaptation and behavioural disorders.

Results of this study are summarised in Table 8 below. The average age of the two groups at follow-up was not reported. Fifteen children had less than 1% of normal biotinidase activity, ten identified clinically and five by newborn screening. Twenty two children had between 1% and 10% of normal biotinidase activity, two identified clinically and 20 by newborn screening. Mean age at diagnosis in the clinically detected group was 17.5 months (range 2 months to 4.75 years)

and in the newborn screening group was 11 days (range 5 to 42 days). Mean age at start of biotin treatment was 40 days (range 10 to 158 days). Those detected by newborn screening started biotin at median of 22-23 days old, while those clinically detected started at a median of 1.4 years old for those with <1% residual biotinidase activity and a median of about 102 days for those with <1% residual biotinidase activity.

Most of the children who showed developmental delay were those with biotinidase activity<1% of normal, and who had been detected clinically. All of the children with optic atrophy or hearing impairment were detected clinically, and all had <1% of normal biotinidase activity. Profound visual and hearing problems were significantly more common in the clinically detected group (visual: $p<0.001$; hearing: $p=0.004$). Delays in walking and speaking were also significantly more common in the clinically detected group (walking: $p=0.002$; speaking: $p=0.022$). There was no significant difference in behaviour between the groups (based on CBC or VABS scores).

Three of the clinically detected children needed speech therapy, one needed occupational therapy and five needed physiotherapy. One of the children detected clinically attended a school for children with special educational needs. The two children detected clinically who had biotinidase activity 1-10% of normal had no residual symptoms.

This article suggested that there is little published long term data on the effects of biotin treatment.[22]

**Table 8: Comparison of children with profound biotinidase deficiency diagnosed by newborn screening (NBS) or clinically detected (as a result of symptoms or having an affected relative)**

| | **Biotinidase activity <1% of normal** | | **Biotinidase activity 1%-10% of normal** | |
|---|---|---|---|---|
| | *NBS detected (n=5)* | *Clinically detected (n=10)* | *NBS detected (n=20)* | *Clinically detected (n=2)* |
| **Diagnosis at ≤28 days of age** | 5 (100%) | 0 | 19 (95%) | 0 |
| **Diagnosis at >28 days of age** | 0 | 10 (100%) | 1 (5%) | 2 (100%) |
| **Initially symptomatic** | 0 | 9 (90%) | 0 | 2 (100%) |
| **Median age at start of treatment (range)** | 22 days (10 to 51) | 1.4 years (0.2 to 5) | 23 days (11 to 151) | 102 days (84 to 119) |
| **Developmental milestones** | | | | |
| **Median age at onset of sitting (range)** | 9 months (7 to 12) | 7 months (6 to 19) | 8 months (5 to 9) | 9 (9) |
| **Delayed onset of sitting (>9 months)** | 1 (20%) | 3 (30%) | 0 | 0 |
| **Median age at onset of walking (range)** | 12 months (12 to 14) | 19 months (12 to 24) | 13 months (9 to 18) | 14 months (12 to 14) |
| **Delayed onset of walking (>18 months)** | 0 | 5 (50%) | 0 | 0 |
| **Median age at onset of speech (range)** | 14 months (12 to 14) | 18 months (12 to 60) | 12 months (7 to 20) | 14 months (12 to 14) |
| **Delayed onset of speech (>17 months for first 3 words)** | 0 | 6 (60%) | 4 (40%) | 0 |
| **Impairments (n)** | | | | |
| **Optic atrophy** | 0 | 4 (40%) | 0 | 0 |
| **Hearing aid** | 0 | 4 (40%) | 0 | 0 |
| **Hearing impairment** | 0 | 3 (30%) | 0 | 0 |
| **Ataxia or seizures** | 0 | 0 | 0 | 0 |

**Summary: Met.** Biotin treatment is seen as highly effective and no side effects are reportedly known. Therefore RCTs of biotin treatment for biotinidase deficiency are likely to be unethical, and none were identified in the update search. There are some areas of uncertainty, such the appropriate dose for partial biotinidase deficiency treatment.

There is an effective treatment, oral free biotin supplementation, for patients identified through early detection. There can be substantial delay (years) in diagnosis when relying on symptomatic presentations and one small observational study suggests this delay leads to poorer outcomes.

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

**2004 NSC report:** *Yes.*

Children with profound biotinidase deficiency are treated with lifelong oral biotin supplementation. No evidence-based treatment guidelines for biotinidase were identified in the update search, although several narrative reviews and other papers discussed treatment.

Treatment is also recommended in those with profound biotinidase deficiency even if they are asymptomatic.[1] Biotin supplementation during pregnancy in mothers carrying a baby at risk of biotinidase deficiency can also be considered.[3]

Initially partial biotinidase deficiency was considered not to have clinical consequences and affected children not always offered biotin supplementation.[5] However, some individuals with partial biotinidase deficiency were found to develop symptoms in times of stress, and so biotin is reported to be recommended in this group as well as those with profound biotinidase deficiency.[5,6] One narrative review reported that although biotin treatment seemed the most prudent course in children with partial biotinidase deficiency, a few metabolic specialists still questioned its necessity.[6] It noted that this issue needs more study.

Treatment decisions should be based on enzyme activity.[16] Biotin treatment is reported to not be needed in individuals who are heterozygous for a profound biotinidase deficiency allele, or who are homozygous for the partial biotinidase deficiency allele D444H (and not carrying another biotinidase deficiency mutation), as they should have biotinidase enzyme activity >30% (i.e. not in the profound or partial biotinidase deficiency range).

The doses of biotin used are reported to have been determined empirically.[6] One article reported that treatment for those with those with partial biotinidase deficiency is 1-5mg biotin per day, and for profound biotinidase deficiency is 5-10mg biotin per day.[3] Newborn screening fact sheets from the US also report that doses of 1-5mg biotin per day can probably be used to treat individuals with partial biotinidase deficiency, with higher 5-20mg/day doses used in individuals with profound biotinidase deficiency.[23] One study from Sweden reported that individuals with partial and profound biotinidase deficiency all received 5-10mg biotin per day.[9]

One source reported that a dose of 30mg/day was needed in one individual to resolve dermatitis.[23] One narrative review suggested that more data are needed to determine the dosage of biotin for older children with profound or partial biotinidase deficiency.[16] It reported that all children have tolerated 10mg/day of oral biotin with no side effects, with anecdotal reports that increasing dose to 15-20mg/day resolved hair loss in adolescence in two girls with profound biotinidase deficiency.

This review also recommended yearly ophthalmologic examination, auditory testing, and assessment by a medical geneticist or metabolic specialist for all children with biotinidase deficiency. It also recommended that children with symptoms and residual clinical problems should be seen by the appropriate sub-specialists. Assessment of urinary organic acids was recommended if symptoms return in a treated child, to detect non-compliance with biotin, which is the most common reason. Testing of biotinidase activity was recommended in siblings of affected individuals even in asymptomatic, and in relatives with symptoms consistent with biotinidase deficiency.[16]

In Europe in 2009, 40% of countries which offered newborn biotinidase screening had guidelines about what age children should start treatment.[24]

**Summary: Not met.** No agreed evidence based policies covering which individuals should be offered treatment in the UK were identified in the update search.

Narrative reviews report that treatment is recommended for all children with profound biotinidase deficiency, regardless of whether they have symptoms at the time of diagnosis. Children with partial biotinidase deficiency also appear to be offered treatment, as they may develop symptoms in time of distress. Doses used have been derived empirically, with between 5 and 30mg biotin daily reported as being used in patients with profound biotinidase deficiency, and between 1 and 10mg biotin daily reported as being used in patients with partial biotinidase deficiency.

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

**2004 NSC report:** *Yes.*

The update search did not identify any studies assessing the management of biotinidase deficiency in the UK. Two papers described cases of biotinidase deficiency diagnosed in the UK and these are described in Criterion 2.[7,8] One of these papers reported that the median delay between presentation and diagnosis in the five children assessed was 5.5 months, with diagnosis made between ages 2.5 and 12 months.[7] The authors suggested that this delay had shown "little improvement" over the preceding decade. They but did not provide specific figures for age at diagnosis for all known cases in the UK over time.

**Summary: Unclear if met.** No updated evidence was found on management of biotinidase deficiency in the UK, although one paper from 2004 anecdotally suggested that the delay between presentation and diagnosis had not improved in the previous decade. Studies of interventions that seek to reduce the age at diagnosis (for example awareness raising initiatives) could be useful in this regard.

## 13. (a) There should be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality or morbidity.

**2004 NSC report:** *No.*

The update search did not identify any RCTs of screening for biotinidase deficiency.

In 2004, six European countries had national screening programmes for biotinidase deficiency (Austria, German, Hungary, Liechtenstein, Sweden and Switzerland), and a further four countries had pilot programmes (Belgium, Italy, Spain, and Turkey).[11] In 2009 eleven European countries had newborn screening for biotinidase deficiency (Austria, Belgium, Denmark, Germany, Hungary, Liechtenstein [who take part in Switzerland's screening programme], the Netherlands, Spain, Sweden, Switzerland, and Turkey).[20]

In 2009 infants had their bloodspot taken on average at age 2.8 days, with screening started at 4.8 days, age at start of confirmation 7.6 days, age at end of confirmation 32 days and mean age at starting treatment 12 days. Only 5.3% of infants were symptomatic at the start of treatment. Half of countries reported having materials for parents to explain treatment.

Biotinidase deficiency is one of the core conditions screened for in the US newborn screening programme.[25] This was based on the findings of an expert panel convened by the American College of Medical Genetics used a set of defined criteria relating to the condition, and treatment and the evidence base to score and rank conditions for priority for inclusion in standardised newborn screening panel. Biotinidase deficiency was ranked the fifth highest priority condition for inclusion, and was one of the core panel of conditions which were recommended for mandatory inclusion in state newborn screening programmes.

**Summary: Not met.** The update search did not identify any randomised trials or comprehensive evaluations of the screening programmes in existence.

### 13. (b) Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (eg. Down's syndrome, cystic fibrosis carrier screening), 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

**2004 NSC report:** *Not applicable.*

**Summary: Not applicable.**

### 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

**2004 NSC report:** *Yes.*

No studies were identified in the update search which assessed the acceptability of a biotinidase deficiency newborn screening programme to health professionals and the public in the UK.

In 2006 the American College of Medical Genetics published a report ranking conditions in order of priority for inclusion in standardised newborn screening panel. The panel included individuals from the areas of subspecialty medicine, primary care, health policy, law, public health, and consumers. Biotinidase deficiency was ranked the fifth highest priority condition for inclusion, and was one of the core panel of conditions which were recommended for mandatory inclusion in state newborn screening programmes.

Eleven countries in Europe were reported to provide newborn screening for biotinidase deficiency in 2009.[20]

**Summary: Unclear if met**. No evidence was identified pertaining to the clinical, social or ethical acceptability of a biotinidase deficiency newborn screening programme to health professionals and the public in the UK. Biotinidase deficiency newborn screening is offered in other countries, and was recommended as a core condition for inclusion in newborn screening by an expert panel in the US.

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

**2004 NSC report:** "*Not known as there are a number of false positives."*

No studies were identified in the update search which weighed up the benefit versus the harms of the biotinidase screening programme in a UK setting.

An expert panel convened by the American College of Medical Genetics used a set of defined criteria relating to the condition, and treatment and the evidence base to score and rank conditions for priority for inclusion in standardised newborn screening panel.[10] Biotinidase deficiency was ranked the fifth highest priority condition for inclusion, and was one of the core panel of conditions which were recommended for mandatory inclusion in state newborn screening programmes.

**Summary: Unclear if met.** No studies were identified in the update search which weighed up the benefit versus the harms of the biotinidase screening programme in a UK setting.

## 16. The opportunity cost of the screening programme (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). Assessment against this criteria should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource

**2004 NSC report:** *"Cost estimates varied from 8p per test to 43p per test. Thus the programme costs would be between £56,000 and £301,000; the cost per case detected would be between £4700 and £25,000; the cost per adverse event prevented might be between £14,000 and £75,000. The adverse events are likely to include lifelong severe neurological deficit. Therefore in terms of cost per QUALY the programme could be more attractive than it looks at first glance. However, for such a rare condition it cannot claim a high priority in introduction of new programmes."*

No cost effectiveness analyses from a UK health and social care perspective were identified in the update search.

One paper looked at the costs incurred after a screen positive is identified in European countries in 2009.[26] It found that the average direct cost of confirmation (or rejection) of a positive screening test result was an average of 832 Euros (standard deviation 399 Euros).

A 2006 paper reported the cost of biotinidase screening test in the US to be between $0.30 and $1 USD, and the cost of biotinidase treatment to be $100 to $300 USD annually.[10]

A paper from 2006 reported on a cost-utility analysis for newborn screening strategies in the US.[27] It used a decision model using a societal perspective. The analysis assumed that tandem

mass spectrometry (TMS) would be used to detect multiple conditions, including biotinidase deficiency. It was not clear whether this assumption was used in the analyses looking at cost utility of the individual screening programmes, as TMS is not currently used to screen for biotinidase deficiency.

The model used clinical and administrative data to inform its assumptions, as well as expert opinion if data was not available (summarised in Table 9). Costs were in 2004 US dollars, and included medical and non-medical costs. Discounting rate was 3%. Base case assumptions are.

**Table 9: Base case assumptions in cost-utility analysis of newborn biotinidase screening**

| Variable | Base case assumption |
|---|---|
| Sensitivity | 100% |
| Specificity | 99.98% |
| Prevalence | 1.1 per 100,000 |
| Probability of hearing loss in BD (utility value) | 76% (0.8611) |
| Probability of seizure disorder in BD (utility value) | 70% (not reported) |
| Probability of severe developmental delay in BD (utility value) | 50% (0.3909) |
| Probability of vision loss in BD (utility value) | 50% (0.514) |
| Effectiveness of early screening in prevention BD sequelae | 100% |
| Cost of BD screening test | $1.83 |
| Cost of follow up of a false positive | $300 |
| Cost of caring for a person with BD (lifetime) | $6,592 |
| Cost of deafness | $445,255 |
| Cost of seizure disorder | $216,848 |
| Cost of severe developmental delay | $1,042,110 |
| Cost of blindness | $581,688 |
| Life expectancy for a person with severe developmental delay | 58.6 years (normal expectancy 77.2 years) |

BD biotinidase deficiency

In the base case newborn screening for biotinidase deficiency dominated the option of no screening (i.e. cost less and was more effective). The average cost per person screened was $85 USD, a saving of $13 per person compared to not screening.

Sensitivity analysis showed that biotinidase deficiency screening dominated no screening down to a prevalence of 0.2 per 100,000, a test sensitivity of 13%, specificity of 95.8%, and up to a cost per false positive of $600 and a cost per test of $14. If the chance of blindness from biotinidase deficiency was reduced to less than 40% screening was no longer cost saving.

**Summary: Unclear if met.** No cost effectiveness analyses from a UK health and social care perspective were identified in the update search. One study found that the average direct cost of confirmation (or rejection) of a positive screening test result was an average of 832 Euros (standard deviation 399 Euros) in Europe in 2009. A study assessing cost-utility of newborn

screening in a US setting found that newborn screening for biotinidase deficiency dominated the option of no screening (i.e. cost less and was more effective).

### 17. 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

**2004 NSC report:** "*Raised clinician awareness and easier access to paediatric neurology services may facilitate earlier diagnosis."*

The update search did not identify any studies assessing alternative options to newborn biotinidase deficiency screening. One paper from the UK in 2004 suggested that the delay between presentation and diagnosis has not improved in the previous decade, but did not present figures for previous years. [7]

**Summary: Unclear if met.**

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

**2004 NSC report:** ***"****As for other laboratory screening programmes."*

The UK does not currently have a newborn biotinidase deficiency screening programme, therefore no plan for monitoring or management or quality assurance standards exists.

In 2010 the American College of Medical Genetics issued technical standards and guidelines for the diagnosis of biotinidase deficiency.[4] These guidelines provide some suggestions regarding quality assurance, such as including normal and abnormal control samples when testing plasma or serum for biotinidase activity, validation of assay reagents and assay performance, and training and competency requirements for testing personnel. The ACMG also produce guidelines about what information should be included in the patient reports.

They also state that in the US the Centers of Disease Control and Prevention (CDC) provide an external Newborn Screening Quality Assurance Programme. No external QA was reported to be available for diagnostic testing.

**Summary: Not met.**

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

**2004 NSC report:** *Yes.*

**Summary: Not assessed.**

### 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

**2004 NSC report:** *The [Personal Child Health Record] could be used.*

No UK based information on biotinidase deficiency screening was identified as it is not currently offered in the UK. The Committee in Genetics of the American Academy of Pediatrics has produced fact sheets on conditions screened for in US newborn screening programmes including biotinidase deficiency.[23,28] They are aimed at paediatricians and other healthcare professionals rather than participants.

In Europe in 2009, half of the countries providing newborn biotinidase deficiency screening reported having guidelines about how professionals should inform parents about a positive screening test.[24] Sixty percent of countries had guidelines about who should inform parents about the need for confirmatory tests. Only 10% of countries had guidelines about how professionals should explain the confirmed diagnosis and its overall implications, and none had guidelines about which professionals should be involved in teaching parents about diagnosis and treatment.

**Summary: Not met.** No UK based information on biotinidase deficiency screening was identified as it is not currently offered in the UK.

### 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

**2004 NSC report:** *Not applicable.*

**Summary: Not assessed.**

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

**2004 NSC report:** *Not applicable.*

The screening test is not for a mutation, although it will identify parents as obligate carriers and there may be other carrier or affected family members. Some carriers were reported to be identified by screening in a newborn screening programme in Brazil (see Criterion 4). No studies were identified in the update search which assessed the acceptability of newborn biotinidase screening to carriers or other family members.

**Summary: Unclear if met.**

## Conclusions

**The condition**

- No evidence was identified in the update search on the prevalence of biotinidase deficiency in a UK setting.
- Profound biotinidase deficiency is an important condition as untreated it can result in severe metabolic compromise leading to coma or death. The condition is rare, with an estimated overall prevalence of profound and partial biotinidase deficiency about 1 in 50,000 in Europe.

- The natural history of the condition appears to be reasonably well understood, although there is limited understanding of genotype-phenotype correlation and why some individuals with profound biotinidase deficiency remain asymptomatic.

**The screening programme**

- No studies were identified in the update search assessing: the overall balance of benefits and harms of newborn biotinidase deficiency screening; the cost effectiveness of newborn biotinidase screening in a UK setting; or whether newborn biotinidase screening is acceptable to the UK population.

**The test**

- Screening for biotinidase deficiency is based on testing for the level of biotinidase activity on newborn bloodspots. The test is safe and relatively simple, although it does not use tandem mass spectrometry and would need to be performed separately to other newborn screening tests.
- The detection rate and number of false negatives of the screening test were not reported in the literature identified in the update search. Positive predictive values that are reported vary widely and are dependent on best practice in handling and storage. This suggests that quality control of the screening and follow up testing would be important.
- Different countries use different varying modifications of the newborn screening test, and different thresholds for further investigation. It is important for individual laboratories to establish their own reference ranges for biotinidase activity and set and monitor appropriate cut-offs, particularly to reduce false positives.

**The treatment**

- Biotin treatment is seen as highly effective and no side effects are reportedly known. There are some areas of uncertainty, such the appropriate dose for partial biotinidase deficiency treatment.
- There is an effective treatment, oral free biotin supplementation, for patients identified through early detection. There can be substantial delay (years) in diagnosis when relying on symptomatic presentations and one small observational study identified in the update suggested that this delay leads to poorer outcomes.

**Current management in the UK**

- No studies identified in the update search directly assessed whether other approaches to management of biotinidase deficiency has been optimised in the UK, although one paper from 2004 anecdotally reported that the delay between presentation and diagnosis had not improved in the previous decade.

## Implications for policy

The evidence published since the last policy update has not changed significantly in the key areas of concern identified in previous, and therefore does not suggest the needs to review the UK NSC's policy position on newborn biotinidase deficiency screening.

## Implications for research

Areas where research may be of value include:

- Assessment of the prevalence of biotinidase deficiency in the UK
- Assessment of current management of biotinidase deficiency and treatment outcomes in the UK
- Assessment of the cost-effectiveness of newborn biotinidase deficiency screening in the UK
- Studies assessing interventions to reduce the age at diagnosis (for example awareness raising initiatives)
- Assessment of the long term effects of biotin treatment in children identified by newborn screening and in children identified clinically
- Research into why some individuals with profound biotinidase deficiency remain asymptomatic

# Methodology

## Search strategy

BACKGROUND: The current policy is that screening for biotinidase deficiency should not be offered. A brief review document was produced in 2004. This was based on two HTA reports addressing a broad range of inherited metabolic disease (see full references below).

Seymour et al. Neonatal screening for inborn errors of metabolism: a systematic review. Health Technology Assessment 1997; 1(11)

Pollitt et al. Neonatal screening for inborn errors of metabolism: cost, yield and outcome. Health Technology Assessment 1997; 1(7)

SOURCES SEARCHED: Medline (OvidSP), Cinahl, and the Cochrane Library.

DATES OF SEARCH: January 2004 – May 2012

SEARCH STRATEGY: Medline (OvidSP)

1. Biotinidase Deficiency/ (67)
2. (biotinidase and deficien$).tw. (313)
3. 1 and 2
4. limit 3 to yr="2004-Current" (99)

Similar searches were also carried out in Embase, Cinahl, and the Cochrane Library.

All searches carried out on 28 May 2012.

| **Database** | **Results** |
|---|---|
| Medline | 99 |
| Embase | 205 |
| Cochrane Library | 0 |
| Cinahl | 5 |
| **Total** | **309** |

**Inclusions and exclusions**

The above search strategies retrieved 309 references in total. After duplicate references were removed a total of 202 references were left. The title and abstracts of the remaining citations were scanned for relevance to screening for biotinidase screening.

107 references were deemed to be relevant. They are classified into the following categories.

| **Category** | **Number of references** |
|---|---|
| Recommendations and guidelines | 4 |

| | |
|---|---|
| The condition | 16 |
| Case studies | 34 |
| Possible presentations | 9 |
| Inborn errors | 6 |
| The test | 9 |
| The treatment | 2 |
| Screening for biotinidase deficiency | 5 |
| Newborn screening | 22 |
| **Total** | **107** |

## Quality

A first pass appraisal of the potentially relevant studies at abstract level was followed by a retrieval of selected full text papers. An overview of the most informative and relevant references regarding the individual screening criteria is given below. Guidelines, systematic reviews of the evidence, randomised controlled trials and studies from the UK were prioritised, as were studies addressing key issues identified in the previous report.

No relevant explicitly evidence-based guidelines, systematic reviews, or randomised controlled trials were identified in the update search. Observational studies were therefore included. Conference abstracts and case reports were excluded. Small case series (<10 individuals) were excluded unless they were from the UK. Narrative reviews were used to provide background information.

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10. Newborn Screening: Toward a Uniform Screening Panel and System: Main report. Genetics in Medicine. 2006;8 (5 SUPPL. 1):12S-252S.

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