

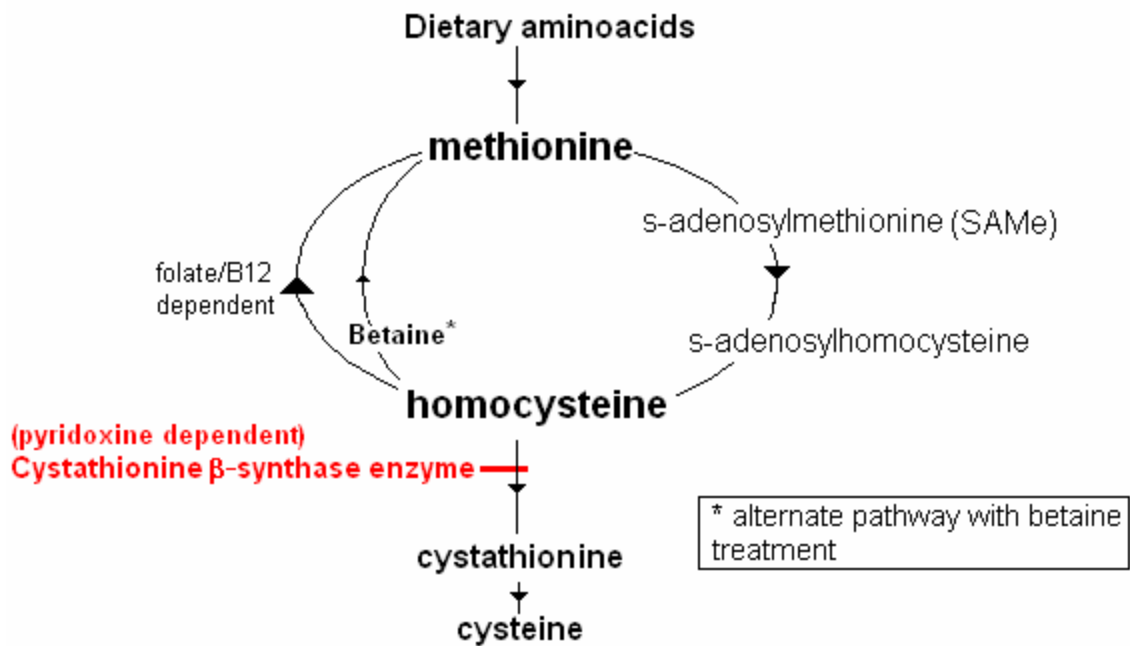
**Elevated methionine (Met);  
homocystinuria, methionine adenosyl transferase I & III deficiencies**

**First Newborn screening result**

**Met elevated, > 2 mg / dL, possibly homocystinuria**

**Repeat newborn screening result**

**Met elevated, possibly homocystinuria**



### History and examination

**History** will probably be unrevealing. Attention should be given to family history of mental retardation, mental illness, dislocated ocular lens, severe myopia and early onset thrombo-embolism.

**Examination** should reveal a clinically normal neonate.

**It is essential to refer to a metabolic center to ensure that the child and family receive the necessary metabolic evaluation.**

**Contact the metabolic physician for elevated methionine**

ENSURE THAT THE REPEAT NEWBORN SCREENING SAMPLE IS SENT TO THE NEWBORN SCREENING LABORATORY AND THE RESULT OBTAINED AS SOON AS POSSIBLE.

(Go to **NNSGRC** for the state labs)

## **Discussion with parents for elevated Met**

Response to a reported newborn screening result must be undertaken in two parts;

1. Initial contact with the family, often by phone, to inform them of the newborn screening result
2. Meeting with the family at the office.

### **Initial communication,**

Many parents want to know what the result is testing positive for and are reassured if their doctor has knowledge of Homocystinuria or has taken the time and made the effort to find out about the condition when informing the family (see **commonly asked questions**). If the test result is equivocal it is important to let the family know that their child may be ENTIRELY normal but will require repeat blood testing until the definitive testing either confirms the diagnosis or demonstrates another disorder or determines that the test was a false positive (transient methionine increase).

Note that a positive test may represent other rare conditions, including the probably benign disorder known as **Methionine adenosyl transferase deficiency (MAT I & III)**. The metabolic physician will determine this when making the evaluation (see **Contact metabolic physician for elevated Met**).

### **In the office**

Many parents do not understand newborn screening, the need to treat their apparently healthy baby.

Parental anxiety will be high and it is important to reassure them that

- Their child is healthy and if treated will be able to avoid many of the problems.
- Failure to aggressively treat a baby with Homocystinuria can result in problems, particularly mental retardation and serious eye problems.

Treatment for Homocystinuria depends on whether the individual is pyridoxine (vitamin B6) responsive or not but usually includes a low-methionine diet. Vitamin B6 can be very helpful and is an essential component of treatment, particularly in those with a good response. The diet consists of a methionine-free essential amino acid formula and very low protein foods.

**Further counseling, treatment and a more detailed assessment and testing of the infant is required; therefore **contact metabolic physician****

## Contact metabolic physician for markedly elevated Met

Your local metabolic physician can be found via [metabolic physicians and specialists](#)

The metabolic physician's role

- Provides you with information on homocystinuria.
- Discusses, in further detail, the meaning of the test result with the family.
- Starts appropriate [treatment](#).
- Provides supportive counseling for the family.
- Undertakes [definitive investigations](#) to determine if the child has :-
  - Homocystinuria
  - Methionine adenosyltransferase (MAT) deficiency type I or III
  - Glycine N-methyltransferase deficiency
  - S-adenosylhomocysteine hydrolase deficiency
  - Transient hypermethioninemia
- Provides genetic / prenatal counseling.

Return to [discussion with parents for elevated Met](#)

## Commonly asked questions

### **1. What is homocystinuria?**

Homocystinuria is a disorder caused by excess of the methionine derived amino acid homocysteine. The defect is in the enzyme responsible for metabolizing homocysteine to compounds that can be excreted in the urine. This enzyme is known as cystathionine  $\beta$ -synthase. Excess homocysteine damages connective tissue leading to problems in the eyes with myopia and lens dislocation, skeletal system (particularly osteoporosis) and cardiovascular system (marked predisposition to atherosclerotic disease). Mental retardation and behavioral problems also occur.

### **2. How and when will we know if my baby has homocystinuria?**

If your baby's newborn screening result showed a Met level  $> 2$  mg / dl, he or she probably has homocystinuria or MAT deficiency (which is probably not at all harmful). If the result was 1-2 mg /dl your baby could still have homocystinuria but the finding might also be transient (false positive). The newborn screening test will be repeated and additional tests will be undertaken to help determine if your baby has homocystinuria or not. Typically the results of these tests take up to 4 days to come back. Depending on the test results, additional testing can take a variable amount of time to confirm the diagnosis. If the diagnosis of homocystinuria is confirmed, a trial of treatment with vitamin B6 will be undertaken to determine if your baby has the B6 responsive variant or not.

### **3. How did my baby get this?**

Homocystinuria is an autosomal recessive disorder. This means that your baby has two mutated genes, one from the mother and one from the father. Having only one mutated gene (a carrier) does not affect a person at all.

### **4. What does it mean for my child?**

If your baby has homocystinuria, he or she should stay on a special low methionine diet, or other treatment, throughout life. This will help to prevent or minimize the complications of this condition.

### **5. What is the treatment? Does it work? Is the diet difficult to do/expensive?**

Homocystinuria is primarily treated by either a low methionine diet, a large amount of vitamin B6 or both. Children with homocystinuria cannot eat as much protein as other children and must have their feeds supplemented with a special methionine-free formula. This diet is very effective at preventing the complications of homocystinuria. Most babies and children get used to this diet. Later on, additional therapies such as the drug betaine may be used.

### **6. What about my other children/future children?**

Since homocystinuria is an inherited condition it is important to have your other children tested. Children from the same father and mother as the affected infant have a 1 in 4 (25%) chance of having homocystinuria and, though it is less likely if they are well, some individuals remain relatively asymptomatic or very mildly affected for some time.

Since there is a risk for having a future child with homocystinuria it is important to let your obstetrician and pediatrician know that you have a child with homocystinuria if you are planning future pregnancies so that they may discuss the options with you and prepare accordingly.

## Definitive Investigations

### **1. Plasma and urine amino acids and plasma total homocysteine**

The cardinal biochemical features of homocystinuria are markedly increased concentrations of plasma homocystine, total homocysteine, and methionine and increased concentration of urine homocystine.

**\*\*NOTE** The blood for plasma amino acids should be processed immediately, then deproteinized and the supernatant frozen until analysis.

The metabolic laboratory may also carry out additional testing including :-

### **2. Enzyme assay**

This is carried out in skin fibroblasts and is the classical definitive diagnostic method. It is important to note though, that while activity levels may help to indicate whether or not the patient may be B6 responsive, the enzyme activity levels do not appear to correlate with the clinical severity of the condition.

### **3. Molecular testing**

Mutation testing for common disease causing mutations is commonly carried out and to a limited degree may help in determining the subtype of homocystinuria as well as aiding future pregnancy related questions. Full sequence analysis for private family mutations is available. [Go to genetests.](#)

## Treatment

**Vitamin B6 (pyridoxine) therapy.** All patients identified by newborn screening should be challenged with pyridoxine (vitamin B6) before treatment with diet begins. If B6-responsiveness is shown, treatment with pyridoxine in a dose of approximately 200 mg/day, or the lowest dose that produces the maximum benefit, should be given. Pyridoxine may also be included despite evidence of B6-nonresponsiveness.

**Dietary treatment.** The majority of B6-responsive patients also require a protein-restricted diet for metabolic control. B6-nonresponsive neonates require a methionine-restricted diet with frequent metabolic monitoring. This diet should be continued indefinitely.

Dietary treatment reduces methionine intake by restricting natural protein intake. However, to prevent protein malnutrition, a methionine-free amino acid formula supplying the other amino acids is provided. The amount of methionine required is calculated by a metabolic dietitian and is supplied in natural food and in special low-protein foods and is monitored on the basis of blood concentrations of homocystine/total homocysteine and methionine. The best results occur in patients identified by newborn screening and treated shortly after birth in whom the plasma homocystine concentration is maintained below 11  $\mu\text{mol/L}$  (preferably, no higher than 5  $\mu\text{mol/L}$ ).

**Betaine treatment.** Treatment with betaine provides an alternate remethylation pathway to convert excess homocysteine to methionine (see figure) and may help to prevent complications **but is not appropriate for infants.**

**Folate and vitamin B12 supplementation.** Folate and vitamin B12 optimize the conversion of homocysteine to methionine by methionine synthase (see figure), thus helping to decrease homocysteine levels. The diet contains much folate and B12, so this should not be a problem. Nevertheless, plasma B12 and RBC folate levels should be obtained semi-annually in treated patients to identify low levels that may require specific B12 and/or folate supplementation.

## Repeat Newborn screening result

### **Normal repeat newborn screening result.**

If the first screen showed a markedly elevated level of Met ( $> 4$  mg / dl), a normal second screen result is reassuring BUT may not rule out homocystinuria. Therefore the metabolic physician may want to await the results of more definitive tests.

If the first screen was only mildly elevated however, the newborn screening increase was probably transient (false positive).

Once the metabolic team has confirmed that the infant does not have homocystinuria, it is essential to reassure the family that their baby is well and that they should treat their baby as entirely normal. Many people can be made anxious by a false positive result and counseling may be appropriate. If the metabolic physician remains concerned, however, then he/she will discuss this further with you and may consider further evaluation. It is important to remember, however, that this does not mean that the baby has homocystinuria but only that the metabolic doctor is taking an extra cautious approach until definitive results are available to keep the baby safe and well.

### **Abnormal repeat newborn screen result.**

An elevated Met on the second sample is very suspicious of homocystinuria and further evaluation by the metabolic doctor is definitely required.

See **Met elevated, probable homocystinuria** discussions in first newborn screening result section.