A Delphi-based consensus clinical practice protocol for the diagnosis and management of 3-methylcrotonyl CoA carboxylase deficiency

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Abstract

3-MCC deficiency is among the most common inborn errors of metabolism identified on expanded newborn screening (1:36,000 births). However, evidence-based guidelines for diagnosis and management of this disorder are lacking. Using the traditional Delphi method, a panel of 15 experts in inborn errors of metabolism was convened to develop consensus-based clinical practice guidelines for the diagnosis and management of 3-MCC screen-positive infants and their mothers. The Oxford Centre for Evidence-based Medicine system was used to grade the literature review and create recommendations graded from A (evidence level of randomized clinical trials) to D (expert opinion).

Panelists reviewed the initial evaluation of the screen-positive infant–mother dyad, diagnostic guidelines, and management of diagnosed patients. Grade D consensus recommendations were made in each of these three areas. The panel did not reach consensus on all issues. This consensus protocol is intended to assist clinicians in the diagnosis and management of screen-positive newborns for 3-MCC deficiency and to encourage the development of evidence-based guidelines.

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Expanded newborn screening (NBS) by tandem mass spectrometry has greatly increased the number of inborn errors of metabolism detectable in the neonatal period
[1]. However, not all of the conditions identifiable and recommended for inclusion in newborn screening programs are well characterized [2,3]. This is not entirely surprising as many of these disorders are individually rare and the affected patients typically came to medical attention through the diagnostic study of patients with severe clinical symptoms. With respect to phenylketonuria (PKU), after the implementation of widespread NBS for PKU in the 1960s it was realized that elevations of phenylalanine comprise a spectrum from mild hyperphenylalaninemia to classic PKU, or may even involve another enzyme system (and treatment plan) entirely, i.e. disorders in tetrahydrobiopterin metabolism [4]. This history is repeating itself as the NBS panel is expanded to include many additional conditions that were first described in severely affected patients but may also present a spectrum of severity. One of the most common of these disorders is 3-methylcrotonyl CoA carboxylase (3-MCC) deficiency (EC 6.4.1.4) an inborn error of leucine metabolism (Fig. 1).

Traditionally children with 3-MCC deficiency were detected during the evaluation of mental retardation or metabolic disturbances including ketoacidosis, hypoglycemia, or Reye syndrome [5]. However in addition to these severe or life threatening complications, 3-MCC deficiency has also been reported in asymptomatic individuals or as nonspecific fasting intolerance with normal neurological outcome [6–11]. Most infants detected by newborn screening appear clinically normal and remain healthy, and a number of apparently healthy affected mothers have been ascertained through their infant’s newborn screen [13–15]. This has raised the question whether 3-MCC deficiency constitutes a disease or merely a biochemical phenotype. However, one child diagnosed on NBS and lost to follow-up presented with profound ketoacidosis during an intercurrent illness at age three years [16]. Another family has also been reported with four affected siblings suggesting a broad range of presentation that may include both asymptomatic and severe disease within even the same family; a two-year-old child had a fatal initial acute presentation including profound carnitine deficiency, one otherwise normal sibling had an episode of fasting intolerance, and two siblings were asymptomatic [12]. These and other cases have raised suspicion that 3-MCC deficiency might constitute a predisposition to disease, similar to medium chain acyl-CoA dehydrogenase (MCAD) deficiency, requiring a second trigger such as metabolic stress to produce a symptomatic phenotype [17].

3-MCC deficiency is one of the most common inborn errors of metabolism detectable in neonatal screening programs (1/36,000 births) [18], and establishing the diagnosis can be both costly and medically invasive, in some cases requiring a skin biopsy to establish fibroblast cultures for enzyme assay. At present clinicians are unable to predict which affected infants are at risk for serious sequelae of 3-MCC deficiency, or even which of the symptoms historically described in 3-MCC deficiency are actually secondary to this diagnosis at all. This situation has elicited a need for guidelines and standards for the diagnosis and management of screen-positive infants.

We undertook a comprehensive review of the literature in order to assess the strength of the available medical evidence with respect to diagnosis and management of 3-MCC deficiency, and to standardize recommendations for medical practitioners for the evaluation and care of screen-positive infants and their mothers.

**Method**

The Oxford Centre for Evidence-based Medicine system was used to grade the literature review, with levels of evidence graded from 1 (systematic reviews with homogeneity of randomized controlled trials) to 5 (expert opinion without explicit critical appraisal). These levels were used to create grades of recommendations from A (consistent level 1 evidence) to D (level 5 evidence) [19].

It was immediately clear that there was a paucity of data available to establish evidence-based clinical practice protocols. Case reports and a limited number of case series were available; all studies were retrospective [5,13,14]. A consensus panel was thus convened to review the available data and develop clinical practice protocols using Delphi. Delphi is a consensus method developed by the Rand Corporation to utilize expert opinion for forecasting when insufficient information is available to make a knowledge-based decision [20]. The Delphi process is being used in medicine with increasing frequency. A critical review of the use of the Delphi process in medicine finds it useful for “harnessing the opinions of an often diverse group of experts on practice-related problems” [21]. Delphi is particularly well suited to the development of consensus-based guidelines [22].

In the traditional Delphi process, panelists review available knowledge and answer a survey concerning the issue in question. The survey is scored to determine the variation in opinion on questions, then returned to the

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**Fig. 1. Metabolism of leucine into 3-methylcrotonyl CoA and related metabolites.**
Results

Evaluating the screen-positive infant

Diagnostic testing for the infant

This panel strongly endorsed the recommendations for the initial contact and evaluation of screen-positive infants listed on the American College of Medical Genetics ACT sheet [24] (consensus score 1.8, 100% consensus). This includes a recommendation that all screen-positive infants undergo analysis of urine organic acids and plasma acylcarnitine for further diagnosis of 3-MCC or to identify other metabolic disorders known to present with elevations in C5OH including: beta-ketothiolase deficiency, biotinidase deficiency, holocarboxylase synthase deficiency, 2-methyl-3-hydroxybutyric acidemia, 3-methylglutaconic acidemia, or 3-hydroxy-3-methylglutaryl (HMG)-CoA lyase deficiency. A biotinidase enzyme assay should be done if this was not done on the newborn screen. Recommendations made by our panel for the testing of screen-positive infants and their mothers are slightly more inclusive than the ACT sheet, and are summarized in Table 1. Of note, the ACT sheet does not contain recommendations regarding urine acylglycine analysis for 3-methylcrotonylglycine (3-MCG), and quantitation of this metabolite is not yet universally included in the acylglycine analysis panel offered by most laboratories. Careful examination of urine organic acid profiles with GC–MS for 3-MCG is important for the diagnostic work up of at risk patients. However, this is complicated by the recent identification of partial 3-MCC deficient cases with only trace amounts or even absence of 3-MCG in urine [25].

Well-appearing infants. Previously four of eight affected newborns demonstrated significant carnitine deficiency

<table>
<thead>
<tr>
<th>Management of the screen-positive infant and mother</th>
<th>Consensus score*</th>
<th>% Concurrency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended for all infants:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine organic acid and plasma acylcarnitine analyses</td>
<td>1.8</td>
<td>100</td>
</tr>
<tr>
<td>Biotinidase (if not done on NBS)</td>
<td>1.6</td>
<td>100</td>
</tr>
<tr>
<td>For well-appearing infants:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma carnitine analysis (other laboratories per clinician preference)</td>
<td>0.85</td>
<td>77</td>
</tr>
<tr>
<td>For ill-appearing infants:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma carnitine</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>CBC, electrolytes/glucose, pH/blood gas, NH₃, urinalysis and liver function tests</td>
<td>0.9–1.4</td>
<td>77–100</td>
</tr>
<tr>
<td>For all mothers:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine organic acid analysis</td>
<td>1.4</td>
<td>85</td>
</tr>
<tr>
<td>Plasma acylcarnitine analysis</td>
<td>1.4</td>
<td>85</td>
</tr>
<tr>
<td>Plasma carnitine analysis</td>
<td>0.8</td>
<td>62</td>
</tr>
</tbody>
</table>

*Consensus score $\geq 1 =$ agree, $0 =$ neutral, $\leq -1 =$ disagree.
when confirmatory testing was done [13]. A majority of panelists recommended a plasma carnitine analysis on the initial visit (consensus score 0.9, 77% consensus). Most panelists did not consider additional testing on the initial evaluation necessary on well-appearing children; a minority recommended additional testing including electrolytes/glucose, urinalysis and ammonia (consensus score for testing −0.7 (31% consensus), −0.8 (23% consensus), and −0.8 (31% consensus), respectively).

**Ill-appearing infants.** By contrast, if the infant appears ill (particularly manifesting signs or symptoms such as lethargy, abnormal tone, poor feeding, seizures, vomiting, and others that might suggest another disorder in the differential diagnosis of elevated C5OH such as holocarboxylase synthase deficiency), the panel recommended a full range of additional testing including plasma carnitine quantitation, complete blood count with differential, electrolytes with glucose, plasma ammonia concentration, blood pH or more complete blood gas evaluation, and urinalysis (consensus score 0.9–1.4 for these items, 77–100% consensus).

**Diagnostic testing for the mother**

For a number of screen-positive infants the origin of the abnormal metabolites found in the infant are from placental transfer of maternal metabolites secondary to unrecognized maternal 3-MCC deficiency [14]. Thus metabolic analysis of the mother in addition to the infant is recommended. There was consensus that the mother should undergo a urine organic acid analysis (consensus score 1.4, 85% consensus), and that adding a plasma acylcarnitine profile would quantify the extent of the mother’s C5OH elevation compared to her newborn’s (consensus score 1.4, 85% consensus). The group did not reach consensus regarding whether a plasma carnitine analysis was recommended on the initial evaluation of the mother; a majority would recommend this test but it did not rise to the level of a consensus recommendation (consensus score 0.8 62% consensus).

**Establishing diagnostic criteria**

Mild to moderate persistent elevations of 3-MCC metabolites (particularly C5OH) are relatively common on follow-up testing. There is a paucity of data regarding the correlations between the degree of metabolite elevation and diagnosis or metabolic risk. Among screen-positive infants the initial C5OH levels did not differentiate between affected and unaffected infants [13]. The presence of small amounts of 3-OH isovaleric acid in urine is not necessarily diagnostic, as this finding occurred transiently in two infants with normal enzyme activity in lymphocytes (although fibroblast assay was not done) [13]. Thus evaluation of the significance of persistently elevated metabolites is best done in the clinical context of the individual patient and the pattern of abnormal metabolites, and in consultation with the diagnostic laboratory. Although any elevation of any 3-MCC metabolite on any single or combination of metabolic tests might be significant, special consideration should be given to the clinical significance of metabolite levels higher than twice the upper end of the normal reference range (see Table 2). (Recommendation grade D, expert opinion based).

**Symptomatic infant**

In the presence of clinical symptoms it is appropriate to initiate treatment and pursue confirmatory testing. Signs/symptoms previously reported in affected infants/children include poor feeding, vomiting, lethargy, apnea, abnormal tone, hyperreflexia, seizures, failure to thrive, developmen-

<table>
<thead>
<tr>
<th>Establishing diagnostic criteria</th>
<th>Consensus score</th>
<th>Score</th>
<th>% Concurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>When mother’s metabolites normal, and asymptomatic infant’s metabolites inconclusive: Consider repeating infant metabolic testing in one month before going to enzyme assay</td>
<td>1.0</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>When mother’s metabolites abnormal, and the asymptomatic infant is formula-fed: Repeat infant metabolic testing in one month to verify clearing of maternal metabolites</td>
<td>1.1</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>When mother’s metabolites abnormal, and the asymptomatic infant is breast-fed: Repeat infant metabolic testing after weaning to verify clearing of maternal metabolites</td>
<td>1.2</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>When metabolic studies appear clearly diagnostic: Diagnosis based on metabolites alone requires consultation with diagnostic 3-MCC deficiency can sometimes be diagnosed based on metabolic levels alone, in consultation with the diagnostic laboratory director and depending on the specific metabolites and degree of elevation</td>
<td>1.5</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>In most cases, it is preferable to verify the diagnosis with enzyme assay</td>
<td>1.2</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>In most cases it is reasonable to assay enzyme activity in lymphocytes</td>
<td>1.2</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>When the lymphocyte assay is normal but any clinical suspicion persists, it is reasonable to repeat enzyme assay in fibroblasts</td>
<td>1.2</td>
<td>100</td>
<td></td>
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</tbody>
</table>

*a Consensus score $\geq 1 = $ agree, 0 = neutral, $-1 = $ disagree.
tal delay, and fasting intolerance [5]; however outcomes studies are needed in order to determine the true range of symptoms actually attributable to 3-MCC deficiency.

**Asymptomatic infant, mother’s metabolites normal**
When the asymptomatic infant’s follow-up metabolic studies are inconclusive and mother’s metabolic studies are normal, the clinician may consider repeating the metabolic studies in the infant in a month to determine if they normalize with liver maturity (consensus score 1, 93% consensus).

**Asymptomatic infant, mother’s metabolites abnormal**
When the mother’s and the formula-fed infant’s metabolites are both abnormal, there was agreement that the infant’s metabolic studies should be repeated in approximately one month to verify that the infant’s levels are normalizing as the prenatally transferred metabolites are cleared (consensus score 1.1, 93% consensus). Because of the possibility that maternal metabolites may be transferred to the infant via breast milk, in the case of the asymptomatic breast-fed infant of an affected mother, it is appropriate to consider repeating diagnostic laboratories again in the infant after weaning (consensus score 1.2, 92% consensus).

**Diagnostic metabolites persistently inconclusive**
There was consensus that 3-MCC deficiency can sometimes be diagnosed based on metabolite levels alone, in consultation with the clinical biochemical genetics laboratory, and depending on the specific metabolites and degree of elevation (consensus score 1.1, 85% consensus). However, particularly given the dearth of data on enzyme assay results in infants with mild to moderate elevations of metabolites, it is preferable to confirm the diagnosis based on enzyme assay whenever possible (consensus score 1.5, 85% consensus).

**Confirmation of laboratory diagnosis**
Two infants have demonstrated relatively normal enzyme activity in lymphocytes (63% and 1.5 SD below the mean, respectively), but significant deficiency of enzyme activity in fibroblasts [12,26]. In the absence of other compelling circumstances it is reasonable to assay enzyme activity in lymphocytes as a first choice (consensus score 1.2, 100% consensus), but there was also consensus that if there are persistent concerns about the status of the infant with a normal lymphocyte assay, consideration should be given to repeating the enzyme assay in fibroblasts (consensus score 1.2, 100% consensus).

Genotype does not appear predictive of phenotype or metabolic risk [15,27]. Thus DNA analysis is not yet helpful in the management of affected patients (recommendation grade C) but if available might aid in the confirmation of questionable cases. It is not known if persistent mild elevation of 3-MCC metabolites might reflect the carrier state.

**Treatment of the affected individual**

**Management of intercurrent illness**
There is concern that individuals diagnosed with 3-MCC deficiency by newborn screening may be susceptible to the metabolic stress associated with inadequate caloric intake during intercurrent illnesses (whether or not they are symptomatic when well) [5,6,11–13]. Thus, the staple of management is the prevention of energy deprivation during metabolic stresses, such as intercurrent illnesses, and emergency protocol letters and medical alert devices are recommended for diagnosed patients.

The New England Consortium of Metabolic Programs has created a list of emergency recommendations for the management of acute illness in patients diagnosed with 3-MCC deficiency [28] (consensus score 1.3, 100% consensus). These recommendations detail strict attention to oral intake to maintain adequate calories when oral feeding is adequate, and also for intravenous glucose sufficient to prevent catabolism when oral intake is impaired by illness. The recommendations also call for the administration of carnitine and treatment of acidosis and hypoglycemia. This panel would add the caution to these recommendations that 10% dextrose should be administered intravenously with appropriate electrolytes (isotonic for bolus fluids and half or quarter-normal saline plus appropriate potassium for maintenance fluids) (see Table 3).

**Administration of supplemental carnitine**
Administration of supplemental carnitine has increased excretion of abnormal acylcarnitines in some (but not all) case studies, but has not resulted in clinical improvement except for repleting carnitine deficiency [11,29,30]. Carnitine deficiency was reported in four of eight affected infants diagnosed by newborn screening on initial presentation by Koeberl et al. [13], and profound free carnitine deficiency has also been reported in one affected mother [14].

**Carnitine-deficient children and mothers.** Carnitine deficiency has been implicated in cardiomyopathy and death in children affected with 3-MCC deficiency [12,31]. This panel recommended that plasma carnitine concentration should be monitored in affected individuals, and that supplemental carnitine should be initiated when free carnitine levels are low (consensus score 1.5, 100% consensus).

**Symptomatic children and mothers.** Carnitine levels frequently fall during intercurrent illnesses, specifically when adequate free carnitine is most needed provide energy from fat oxidation and recycle CoA from fatty acyl CoA intermediates [32]. Since previously symptomatic individuals may have already demonstrated susceptibility to fasting stress, the panel recommended that they receive carnitine supplementation regardless of plasma carnitine levels to keep their carnitine pool continuously replete (consensus score 1.1, 86% consensus for infants/children and 0.93, 79% consensus for mothers, respectively). Signs/symptoms
described in affected children were previously stated. Reported signs/symptoms in affected mothers have included fasting or protein intolerance, myopathy, weakness, elevated liver enzymes and fatty liver, and fatigue and weakness especially during pregnancy [13,14]. Carnitine levels were not reported in these mothers, although another asymptomatic mother in that case series was reported to have profound carnitine deficiency [14]. It is also not known if these cases should cause concern that maternal 3-MCC deficiency might increase the risk for pregnancy complications.

Asymptomatic children and mothers. In the absence of studies suggesting a clinical benefit, no consensus was reached regarding recommending administration of supplemental carnitine to asymptomatic children or mothers when monitored free carnitine levels are normal (consensus score 0.14, 46% consensus, and −0.3, 21% consensus, respectively). Nearly half of panelists did advocate the use of carnitine even in asymptomatic children, but this did not rise to the level of a consensus recommendation at this time.

Leucine restriction

No randomized controlled studies of leucine-restricted diets have been published, and the efficacy of such diets is unknown. Specifically, the role of diet in asymptomatic children to prevent symptoms has not been studied. Seven affected infants remained symptom free on leucine or protein-restricted diets; one 35 week gestation diet-treated infant demonstrated developmental delays at 2 years of age [13]. Four affected mothers identified through their infants’ abnormal screens appeared normal despite having consumed an unrestricted diet throughout life, although one mother reported significant emesis with minor illnesses or after high protein meals [13]. An additional four affected mothers reported by Gibson et al. [14] identified through their infant’s newborn screen consumed regular protein diets and were cognitively normal, although as previously noted two mothers had symptoms of unknown origin including myopathy, weakness, elevated liver enzymes and fatty liver in one and fatigue and weakness especially during pregnancy in the other. Normal dietary intake of protein did not seem to harm index patients who were normal until presenting with fasting intolerance; affected siblings of index patients on normal diets have generally been healthy or have demonstrated fasting intolerance [5–7,9,11,12]. Given the nutritional deficiencies that can be associated with protein-restricted diets and the potential to increase risk of catabolism if energy stores are depleted from dietary restriction, the use of leucine or protein-restricted diets in this disorder merits careful study. Leucine-restricted diets have not demonstrated efficacy in improving mental retardation or motor abnormalities in symptomatic children [30].

Table 3

<table>
<thead>
<tr>
<th>Recommendations for management of affected infants and mothers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Management of the affected infant and mother</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Emergency management recommendations as per the New England</td>
</tr>
<tr>
<td>Consortium</td>
</tr>
<tr>
<td>Prevention of fasting stress is the staple of management for</td>
</tr>
<tr>
<td>both symptomatic and asymptomatic infants</td>
</tr>
</tbody>
</table>

Carnitine supplementation is recommended for:

- Carnitine deficient mothers and infants/children 1.5 100
- Carnitine sufficient symptomatic infants/children 1.1 86
- Carnitine sufficient symptomatic mothers 0.9 79
- Carnitine sufficient asymptomatic infants/children 0.1 43
- Carnitine sufficient asymptomatic mothers −0.3 21

Leucine or protein-restricted diets are NOT recommended for:

- Asymptomatic infants/children 1.3 85
- Asymptomatic mothers 1.3 85
- Symptomatic infants/children 0.3 58
- Symptomatic mothers 0.3 36

Decisions regarding restricted diets in symptomatic infants/children should be individualized based on severity of symptoms, response to a diet trial or other factors 1.1 92

Decisions regarding restricted diets in symptomatic mothers should be individualized based on severity of symptoms, response to a diet trial or other factors 1.2 92

Prudence suggests recommending goal protein intake as per the ADA for age (rather than unlimited) 0.3 54

Biotin supplementation is NOT currently indicated 1.3 92

Biotin supplementation in the absence of a clinical effect is NOT currently indicated 0.7 85

Italics signify that a majority of respondents agreed, but the recommendation did not rise to the level of consensus.

*a Consensus score $1 = agree, 0 = neutral, $-1 = disagree.
Asymptomatic infants/children. In the absence of clinical trials or additional data regarding the efficacy of leucine or protein-restricted diets, most panelists felt restricted diets were not necessary for asymptomatic infants and children (consensus score 1.0, 91% consensus). However, this consensus belies some relatively strong divergence of opinion on both sides and this issue requires re-visiting as additional outcomes data become available. Regarding both infants and mothers, a majority of panelists felt that even in the cases where a formal protein restriction is not recommended, prudence dictates recommending goal protein intake as per the American Dietary Association recommendation rather than excessive protein intake, but this recommendation did not reach the level of consensus (consensus score 0.3, 58% consensus).

Symptomatic infants/children. The group did not reach consensus regarding the value of diet for symptomatic children (consensus score 0.3, 58% consensus). The official recommendation concludes that decisions regarding restricted diets in symptomatic children should be individualized based on severity of symptoms, response to a diet trial or other factors (consensus score 1.1 91% consensus).

Affected mothers. There was consensus that leucine-restricted diets were not indicated for asymptomatic mothers (consensus score 1.4, 100% consensus) but the panel did not reach consensus regarding symptomatic mothers (consensus score 0.3, 36% consensus). Decisions regarding restricted diets in symptomatic mothers should be individualized based on severity of symptoms, response to a diet trial or other factors (consensus score 1.2, 92% consensus).

Glycine administration

Case reports have noted variable results regarding the effect of glycine administration. Some studies have found that supplemental glycine results in increased excretion of 3-methylcrotonyl glycine, while others have not found a persistent effect; no studies have observed clinical improvement of symptoms on treatment and no randomized clinical trials have been published [11,29,30].

Asymptomatic or symptomatic infants and mothers. In the absence of clinical trials or additional data regarding efficacy of supplemental glycine, the panel did not consider supplemental glycine necessary at this time (consensus score 1.3, 92% consensus).

Biotin supplementation

Randomized clinical trials of biotin are lacking. Biotin responsiveness has been rarely reported in 3-MCC deficiency; based on at least one report of responsiveness a biotin trial may be considered [33]. It is possible that biotin treatment might falsely normalize the results of the lymphocyte enzyme assay in biotin-responsive individuals, thus a biotin trial would best be considered after enzyme assay. There is no data suggesting continuing biotin is helpful in nonresponders.

Symptomatic and asymptomatic infants and mothers. Panelists agreed there is no data to support endorsing biotin treatment in the absence of a clinical effect (consensus score 0.7, 85% consensus).

Discussion

Evidence-based clinical protocols are the preferred method for medical management recommendations. For 3-MCC deficiency, there are insufficient clinical data on which to base recommendations for the management of screen-positive infants. Applying the Delphi consensus process, however, a protocol was designed to guide clinicians caring for screen-positive infants by sharing the opinions of their peers. The staple of treatment in this protocol is the prevention of fasting/metabolic stress. Most of the consensus recommendations reach only grade D, based on case reports/series and expert opinion.

The Delphi consensus process was selected for several reasons. The process is specifically designed for situations in which the existing literature is insufficient to provide evidence-based answers. In addition, the anonymous standardized format tends toward a “mean” opinion on survey items in advance of the face to face meeting, rather than toward more extreme ideas or vocal personalities. Delphi also provides a means to formally measure consensus as a “score” or “percentage”, information frequently lacking in consensus documents, and can provide a “line item” analysis of consensus on specific recommendations. Finally, the survey style means the process of formal consensus can be obtained quickly once the literature review is completed and survey written. A Delphi consensus project should seek to avoid bias in selection of the consensus panel. In some cases a panelist with particular expertise may find their opinion “diluted” by the group mean, but there is some mechanism to control for this in the face to face meeting when the panelist can present additional information to fellow panelists. Delphi is particularly adaptable to medicine for developing consensus-based clinical practice guidelines and we hope to see its use increased for developing protocols for other rare disorders for which we do not yet have sufficient data to develop evidence-based practice guidelines. This document is not intended to replace clinician judgment, and can not apply to every individual case or condition which may arise. It does not address the potential for inconsistent interpretations between diagnostic laboratories regarding which metabolites at what levels they consider clinically significant. The clinician should consult the literature and research specialists in 3-MCC deficiency for updated information. These recommendations should be superseded by clinical trials and or frequently updated
through active collection of short and long-term follow-up data.

References


[21] References