
Practice Patterns and Challenges

Sumit Parikh Md
How is mitochondrial medicine practiced in North America?

Is there consensus?

Is there a need for consensus criteria?
Invitations sent to CNS, SIMD, MMS, metab-l and Child Neurology list-serv members

37 initial volunteers

5 stopped participating

32 completed all surveys
Practice Locations

Little Rock, Arkansas
San Diego, California
Stanford, California
Vancouver, BC, Canada
Hamilton, Ontario, Canada
Aurora, Colorado
Washington, DC
Atlanta, Georgia
Indianapolis, Indiana
New Orleans, Louisiana
Baltimore, Maryland
Bethesda, Maryland
Boston, Massachusetts
Detroit, Michigan
Rochester, Minnesota
Akron, Ohio
Cleveland, Ohio
Columbus, Ohio
Nashville, Tennessee
Houston, Texas
Philadelphia, Pennsylvania
Pittsburgh, Pennsylvania
Seattle, Washington
Milwaukee, Wisconsin
of physicians surveyed, while pediatric trained, see both adults and pediatric patients

81%
New Patient Consult Visit Time

- **< 60 minutes**: 25%
- **60-90 minutes**: 50%
- **90-120 minutes**: 25%

50 minutes
Average time of a follow-up visit
New Patient Preparation Time

- **< 30 minutes**: 16%
- **30-60 minutes**: 38%
- **60-90 minutes**: 19%
- **90-120 minutes**: 13%
- **Variable**: 16%
Mitochondrial clinics require

Time !!!

Prescreening of patients  66%
Advance review of records  94%
Multiple specialty appointments  69%
Additional preparation time >30 minutes  69%
Physician Extenders  90%
Case Review with colleagues  88%

50% cancel visit if no records received
<table>
<thead>
<tr>
<th>Biochemical studies obtained</th>
<th>Physicians surveyed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate</td>
<td>100%</td>
</tr>
<tr>
<td>Organic Acids, urine</td>
<td>100%</td>
</tr>
<tr>
<td>CMP</td>
<td>94%</td>
</tr>
<tr>
<td>Amino Acids, plasma</td>
<td>91%</td>
</tr>
<tr>
<td>Acylcarnitines</td>
<td>84%</td>
</tr>
<tr>
<td>CBC</td>
<td>54%</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>47%</td>
</tr>
<tr>
<td>Pyruvate</td>
<td>38%</td>
</tr>
<tr>
<td>Amino Acids, urine</td>
<td>31%</td>
</tr>
<tr>
<td>CK</td>
<td>28%</td>
</tr>
<tr>
<td>MMA</td>
<td>6%</td>
</tr>
<tr>
<td>Carnitine, urine</td>
<td>3%</td>
</tr>
</tbody>
</table>
Genetic studies obtained

- mtDNA point mutation first: 50%
- mtDNA genome first: 34%
- Nuclear Gene Panel, Selective: 63%
- Nuclear Gene Panel, 100 genes: 38%
- Nuclear Gene Panel, > 100 genes: 15%
- Exome, if needed: 59%

Perceived pressure to perform mtDNA sequencing: 28%
Perception of various laboratories that perform mitochondrial testing

bit.ly/mms paper supplement
<table>
<thead>
<tr>
<th>Percentage</th>
<th>Procedure/Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>53%</td>
<td>Obtain a muscle biopsy when faced with normal biochemistry screening</td>
</tr>
<tr>
<td>46%</td>
<td>Wait until a child is at least a year old prior to obtaining a muscle biopsy (if not longer)</td>
</tr>
<tr>
<td>97%</td>
<td>Prefer the quadriceps muscle</td>
</tr>
<tr>
<td>84%</td>
<td>Obtain at least ETC enzymology, histology and electron microscopy</td>
</tr>
<tr>
<td>31%</td>
<td>Only establish whether an ETC abnormality is significant via diagnostic criteria</td>
</tr>
<tr>
<td>43%</td>
<td>Only measure muscle Coenzyme Q10 levels</td>
</tr>
<tr>
<td>48%</td>
<td>Only obtain mtDNA sequencing, deletion and duplication analysis</td>
</tr>
<tr>
<td>78%</td>
<td>Feel mitochondrial testing in skin is of limited value</td>
</tr>
<tr>
<td>81%</td>
<td>Obtain liver biopsy if there is hepatic disease</td>
</tr>
</tbody>
</table>
63% of physicians surveyed use diagnostic criteria

60% Modified Bernier
20% Nijmegen
20% NAMDC
37% of physicians surveyed require a genetic diagnosis.
100% believe in secondary mitochondrial dysfunction

34% need to treat secondary dysfunction
unsure if Autism related mitochondrial dysfunction is a primary or secondary phenomenon

88%

unsure what symptoms represents mitochondrial autism

78%
A bar chart showing the perceived muscle biopsy false-positive rate based on the survey of physicians.

- **< 5%**: 19%
- **5-10%**: 28%
- **10-20%**: 16%
- **>20%**: 16%
- **Unable to assess**: 19%

The chart represents the percentage of physicians surveyed who perceived the muscle biopsy false-positive rate in different ranges.
% of physicians surveyed

Perceived Muscle Biopsy False-Negative Rate

- < 5%: 3%
- 5-20%: 22%
- 20-30%: 28%
- 30-50%: 6%
- >50%: 19%
- Unable to assess: 22%
Perceived Skin Biopsy False-Negative Rate

- < 5%: 3%
- 5-10%: 3%
- 10-20%: 3%
- 20-40%: 28%
- >40%: 50%
- Unable to assess: 16%
Part 2

Treatment and Preventative Care
Supplement used most commonly

- Creatine: 75%
- Levo-Carnitine: 100%
- CoQ10: 100%
- L-Arginine for strokes: 100%

Physicians surveyed
Start cocktail
Start individual supplement
Ubiquinol vs Ubiquinone

- Ubiquinol: 48%
- Ubiquinone: 10%
- Does not matter: 42%

Diagram showing the percentage of people who prefer Ubiquinol, Ubiquinone, or do not care.
Following CoQ10 levels

- 47% Follow levels
- 53% Do not follow levels
Following CoQ10 levels

- 41% Serum levels
- 47% Leukocyte levels
- 12% No preference
Use of exercise as a treatment

- Recommend exercise: 78%
- No recommendation: 22%
Type of exercise recommended

- 48% Land, water and resistance
- 40% Land and resistance
- 12% Per therapist
### Lab work checked preventatively

<table>
<thead>
<tr>
<th>Test</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrolytes</td>
<td>100%</td>
</tr>
<tr>
<td>Transaminases</td>
<td>100%</td>
</tr>
<tr>
<td>HgbA1C</td>
<td>84%</td>
</tr>
<tr>
<td>Thyroid function</td>
<td>72%</td>
</tr>
<tr>
<td>Amino acids, urine</td>
<td>68%</td>
</tr>
<tr>
<td>CoQ10</td>
<td>56%</td>
</tr>
<tr>
<td>Lipids</td>
<td>52%</td>
</tr>
<tr>
<td>Adrenal function</td>
<td>28%</td>
</tr>
</tbody>
</table>

80% of physicians surveyed obtain screening every 1-2 years.
Preventative Testing obtained routinely

- EKG: 81%
- Echo: 81%
- Ophthalmology: 81%
- Cardiology Consultation: 69%
- Audiograms: 63%
- Sleep studies, if fatigue: 47%
- Immunologic tests: 38%
- Repeat MRI: 22%
- Repeat CSF: 13%
- Stress test: 6%
- Resting metabolic rate: 6%
Clinician Participation Levels

- Educational talks to families: 69%
- Advisory Board: 60%
- Educational talks to physicians: 50%
- Fundraising: 47%
- Political Advocacy: 34%
- Walkathon participation: 28%
Similarities in practice but a general lack of consensus
Agreement in care

Clinic structures and organization

Physician perceptions of various diagnostic laboratories

Care requires significantly more time

Shortage of adult trained experts
Variability in care

Diagnostic approaches used

Extent of testing sent

Interpretation of test results

How a diagnosis of mitochondrial disease is arrived upon

Treatment variability
Officers of the MMS, 2012-2014

Sumit Parikh

Mary Kay Koenig

Greg Enns

Russ Saneto

Amy Goldstein

Fernando Scaglia
Methods to develop consensus

borrowed from Georgianne Arnold

- Evidence-based
- Eminence based (grey heads in the room)
- Committee based (may the strongest personality win)
- NIH style consensus (non-experts decide)
- Individual (I’ll decide)
# Oxford Levels of Evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Type of evidence</th>
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<tbody>
<tr>
<td>1a</td>
<td>Systematic review with homogeneity of randomized control trials</td>
</tr>
<tr>
<td>1b</td>
<td>Individual randomized control trial with a narrow confidence interval</td>
</tr>
<tr>
<td>1c</td>
<td>All or none related outcome</td>
</tr>
<tr>
<td>2a</td>
<td>Systematic review with homogeneity of cohort studies</td>
</tr>
<tr>
<td>2b</td>
<td>Individual cohort study (including low-quality randomized control trials, e.g., &lt;80% follow-up)</td>
</tr>
<tr>
<td>2c</td>
<td>“Outcomes” Research; Ecological studies</td>
</tr>
<tr>
<td>3a</td>
<td>Systematic review with homogeneity of case–control studies</td>
</tr>
<tr>
<td>3b</td>
<td>Individual case–control study</td>
</tr>
<tr>
<td>4</td>
<td>Case-series (and poor-quality cohort and case–control studies)</td>
</tr>
<tr>
<td>5</td>
<td>Expert opinion without explicit critical appraisal, or based on physiology, bench research or “first principles”</td>
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</table>

### Grades of recommendation

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
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<tbody>
<tr>
<td>A</td>
<td>Consistent level 1 studies</td>
</tr>
<tr>
<td>B</td>
<td>Consistent level 2 or 3 studies or extrapolations from level 1 studies</td>
</tr>
<tr>
<td>C</td>
<td>Level 4 studies or extrapolations from level 2 or 3 studies</td>
</tr>
<tr>
<td>D</td>
<td>Level 5 evidence or troublingly inconsistent or inconclusive studies of any level</td>
</tr>
</tbody>
</table>
Delphi Method

“Pooled intelligence enhances individual judgement and captures the collective opinion of a group of experts”

Developing consensus in the absence of sufficient evidence utilizing a committee of 15-25 content experts
1. A modified Delphi consensus study to identify UK osteopathic profession research priorities.
   Rushton AB, Fawkes CA, Carnes D, Moore AP.
   PMID: 24855956 [PubMed - as supplied by publisher]
   Related citations

   Levitt CA, Nair K, Dolovich L, Price D, Hilts L.
   PMID: 24850794 [PubMed - as supplied by publisher]
   Related citations

   PMID: 24845034 [PubMed - as supplied by publisher]
   Related citations

   Freeman E, Seifer SD, Stupak M, Martinez LS.
   PMID: 24841362 [PubMed - as supplied by publisher]
   Related citations

5. Relevant concepts of functioning for patients with systemic lupus erythematosus identified in a delphi exercise of experts and a literature review.
   Leuchten N, Bauernfeind B, Kuttner J, Stamm T, Smolen JS, Pisetsky DS, Aringer M.
Delphi Method

“Pooled intelligence enhances individual judgement and captures the collective opinion of a group of experts”

1. Committee forms subgroups
2. Literature review and data summary
3. Survey
4. Consensus?
5. Items without consensus
6. Survey with group’s responses revealed
7. Consensus?
8. Face-to-face discussion
Delphi Method

<table>
<thead>
<tr>
<th>The Good</th>
<th>borrowed from Georgianne Arnold</th>
</tr>
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</table>

- Quantifiable consensus
- Less personality based; results driven to the group mean
- Leaves room for dissent
- Panel size allows for functional and geographic diversity
Delphi Method

The Bad

borrowed from Georgianne Arnold

- The “Mean” is not Scientific Truth
- Panel selection is a source of bias (having people who all agree)
- Consensus not always reached
- Managing groups of physicians is like “herding a group of cats”
Diagnosis and management of mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society

Sumit Parikh, MD¹, Amy Goldstein, MD², Mary Kay Koenig, MD³, Fernando Scaglia, MD⁴, Gregory M. Enns, MD⁵, Russell Saneto, MD, PhD⁶,⁷, Irina Anselm, MD⁸, Bruce H. Cohen, MD⁹, Marni J. Falk, MD¹⁰, Carol Greene, MD¹¹, Andrea L. Gropman, MD¹², Richard Haas, MB BChir, MRCP¹³, Michio Hirano, MD¹⁴, Phil Morgan, MD¹⁵, Katherine Sims, MD¹⁶, Mark Tarnopolsky, MD, PhD¹⁷, Johan L.K. Van Hove, MD¹⁸, Lynne Wolfe, MS, CRNP¹⁹ and Salvatore DiMauro, MD²⁰
Consensus Criteria

- Biochemical Testing in Blood, Urine and Spinal fluid
- Genetic Testing
- Pathology and Biochemical Testing of Tissue
- Neuroimaging
- Treatment of Acute Stroke
- Exercise
- Anesthesia
- Treatment During Illness
- Treatment with vitamins and xenobiotics
Consensus recommendations for testing blood, urine, and spinal fluid

1. The initial evaluation in blood for mitochondrial disease should include complete blood count, creatine phosphokinase, transaminases, albumin, lactate and pyruvate, amino acids, and acylcarnitines, along with quantitative or qualitative urinary organic acids. *Caution must be taken to ensure that specimens are collected appropriately, especially for lactate and pyruvate measurements.*

2. Postprandial lactate levels are more sensitive than fasting specimens and are preferred when possible. *Caution must be taken to not overinterpret small elevations in postprandial lactate.*

3. The lactate/pyruvate ratio in blood or CSF is of value only when the lactate level is elevated.

4. Quantitative 3MG measurements in plasma and urine should be obtained when possible in addition to urine organic acids in patients being evaluated for mitochondrial disease.

5. Creatine phosphokinase and uric acid should be assessed in patients with muscle symptoms who are suspected of having mitochondrial diseases.

6. Urine amino acid analysis should be obtained in the evaluation of mitochondrial tubulopathy.

7. When CSF is obtained, it should be sent for lactate, pyruvate, amino acid, and 5-methyltetrahydrofolate measurements.

8. Further research is needed regarding other biomarkers such as FGF21, glutathione, and CSF neopterin.
Consensus recommendations for DNA testing

1. Massively parallel sequencing/NGS of the mtDNA genome is the preferred methodology when testing mtDNA and should be performed in cases of suspected mitochondrial disease instead of testing for a limited number of pathogenic point mutations.

2. Patients with a strong likelihood of mitochondrial disease because of a mtDNA mutation and negative testing in blood, should have mtDNA assessed in another tissue to avoid the possibility of missing tissue-specific mutations or low levels of heteroplasmy in blood; tissue-based testing also helps assess the risk of other organ involvement and heterogeneity in family members and to guide genetic counseling.

3. Heteroplasmy analysis in urine can selectively be more informative and accurate than testing in blood alone, especially in cases of MELAS due to the common m. 3243A>G mutation.

4. mtDNA deletion and duplication testing should be performed in cases of suspected mitochondrial disease via NGS of the mtDNA genome, especially in all patients undergoing a diagnostic tissue biopsy.
   a. If a single small deletion is identified using polymerase chain reaction–based analysis, then one should be cautious in associating these findings with a primary mitochondrial disorder.
   b. When multiple mtDNA deletions are noted, sequencing of nuclear genes involved in mtDNA biosynthesis is recommended.

5. When a tissue specimen is obtained for mitochondrial studies, mtDNA content (copy number) testing via real-time quantitative polymerase chain reaction should strongly be considered for mtDNA depletion analysis because mtDNA depletion may not be detected in blood.
   a. mtDNA proliferation is a nonspecific compensatory finding that can be seen in primary mitochondrial disease, secondary mitochondrial dysfunction, myopathy, hypotonia, and as a by-product of regular, intense exercise.

6. When considering nuclear gene testing in patients with likely primary mitochondrial disease, NGS methodologies providing complete coverage of known mitochondrial disease genes is preferred. Single-gene testing should usually be avoided because mutations in different genes can produce the same phenotype. If no known mutation is identified via known NGS gene panels, then whole-exome sequencing should be considered.
**Consensus recommendations for pathology testing**

1. Muscle (and/or liver) biopsies should be performed in the routine analysis for mitochondrial disease when the diagnosis cannot be confirmed with DNA testing.
2. When performing a muscle biopsy, an open biopsy is preferred in the routine analysis for mitochondrial disease, except when the center performing the biopsy is experienced in obtaining an adequate quality and quantity of tissue via a percutaneous biopsy.
3. The vastus lateralis is the preferred site for a muscle biopsy in the evaluation of mitochondrial disease due to this site having been used by most laboratories to establish reference ranges.
4. COX, SDH, NADH-TR, and the combined SDH/COX stain along with EM should be obtained in the routine analysis of tissue for mitochondrial disease; EM is strongly recommended in pediatric patients receiving a tissue biopsy because histological findings are often limited.
5. Mitochondrial hepatopathy may have characteristic findings on liver biopsy histology.
6. When possible, extra tissue should be frozen to allow for additional testing. See Table 1 for special considerations.

**Consensus recommendations for biochemical testing in tissue**

1. Biochemical testing in tissue does not always differentiate between primary mitochondrial disease and secondary mitochondrial dysfunction.
2. When obtaining a biopsy in the evaluation of mitochondrial disease, ETC enzymology (spectrophotometry) of complex I–IV activities in snap-frozen tissue or

**Consensus recommendations for neuroimaging**

1. When the central nervous system is involved, brain magnetic resonance imaging should be performed in the evaluation of a patient suspected of having a mitochondrial disease. MRS findings of elevated lactate within brain parenchyma are useful as well. Neuroimaging cannot by itself be the absolute criterion for disease confirmation.
### Table 1  Tissue collection and processing instructions for mitochondrial tissue biopsies

- The vastus lateralis muscle should typically be biopsied because most laboratories standardize their assays to results from this muscle tissue.
- Avoid muscles that have experienced electromyogram manipulation or severe wasting.
- Avoid infiltrating the muscle with lidocaine or use of isometric muscle clamps.
- Never use electrocautery in the biopsy procedure until after the specimen has been removed.
- Muscle should not be collected in fragments or from subfascial and myotendinous areas.
- Similar cautions need to be followed when liver samples are obtained.
- Tissue obtained during a biopsy should be quickly snap-frozen in liquid nitrogen, and a piece should be fixed in glutaraldehyde for electron microscopy; another specimen is needed if it is being used for polarographic evaluation.
- Proper storage of specimens along with close coordination between pathology and the practitioner collecting the sample are essential to avoid degradation of biochemical enzyme activity.

### Table 2  Points to consider regarding mitochondrial biochemical testing in tissue

- Assays of spectrophotometric quantification of OXPHOS enzyme activities differ across various laboratories and make interlaboratory comparison of test results highly variable\(^{159,160}\).
- The use of simultaneous control samples may help validate most ETC test results in muscle\(^{160}\).
- There is little to no margin between patient ranges and control ranges\(^{161,162}\).
- Enzyme activities around the lowest reference value cannot always be “absolutely” normal or abnormal.
- Electron transport enzyme activity measures are secondarily affected by many factors, with physical inactivity being relevant to most mitochondrial patients\(^{163}\).
- ETC analysis may be completely normal in any tissue tested early in the disease process, especially in mitochondrial DNA depletion and deletion syndromes\(^{164}\).
- Interpretation of mitochondrial biochemical testing results is aided by utilizing established diagnostic criteria to avoid mitochondrial dysfunction being identified in a subjective fashion and interphysician variability in diagnoses provided\(^2\).

ETC, electron transport chain.
Consensus recommendations for the treatment of mitochondrial stroke

1. Stroke-like episodes in primary mitochondrial disease typically have correlating visible magnetic resonance imaging abnormalities.

2. IV arginine hydrochloride should be administered urgently in the acute setting of a stroke-like episode associated with the MELAS m.3243 A>G mutation in the MTTL1 gene and considered in a stroke-like episode associated with other primary mitochondrial cytopathies as other etiologies are being excluded. Patients should be reassessed after 3 days of continuous IV therapy.

3. The use of daily oral arginine supplementation to prevent strokes should be considered in MELAS syndrome.

4. The role of following plasma arginine and citrulline levels and oral citrulline supplementation in the treatment of MELAS requires further research.
**Consensus recommendations for exercise**

1. Exercise-induced mitochondrial biogenesis is an appropriate target to improve function in patients with mitochondrial disease.
2. Endurance exercise can increase mitochondrial enzyme activity in muscle and quality-of-life scores, and can reduce the energy cost of activities of daily living. Resistance exercise can increase muscle strength and recruitment of satellite cells in muscle fibers in mitochondrial patients.
3. A combination of progressive and resistance exercise is optimal for patients with mitochondrial disease and is thought to be safe when instituted in a supervised, progressive fashion with training beginning at a low intensity and duration.
4. Mitochondrial patients should undergo cardiac screening prior to beginning an exercise program.
5. Exercise intolerance is a real phenomenon in patients with mitochondrial disease, but a deconditioned mitochondrial patient should be encouraged to exercise. Physicians should encourage compliance with exercise programs for mitochondrial patients.
6. High-intensity interval training has been shown to induce similar mitochondrial adaptations as compared with endurance exercise in healthy and diabetic adults, but the effectiveness and safety have not been adequately studied in patients with mitochondrial disease.

**Consensus recommendations for anesthesia**

1. Patients with mitochondrial diseases are at an increased risk of anesthesia-related complications.
2. Preoperative preparation of patients with mitochondrial disease is crucial to their perioperative outcome. Patients should minimize preoperative fasting and have glucose added to their perioperative IV fluids, unless they are on a ketogenic diet or have been demonstrated to have adverse reaction to higher glucose intake.
3. Caution must be used with volatile anesthetics because mitochondrial patients may potentially be hypersensitive.
4. Caution must be used with muscle relaxants in those mitochondrial patients with a preexisting myopathy or decreased respiratory drive.
5. Mitochondrial patients may be at a higher risk for propofol infusion syndrome and propofol use should be avoided or limited to short procedures.
6. One should consider slow titration and adjustment of volatile and parenteral anesthetics to minimize hemodynamic changes in mitochondrial patients.
7. Local anesthetics are generally well-tolerated in patients with mitochondrial defects.
8. There is no clear established link between malignant hyperthermia and mitochondrial disease.
Consensus recommendations for treatment during an acute illness

1. Specific decisions about patient management including hospitalization require clinical judgment and should be case-specific. Decisions should reflect the individual patient's presentation as well as an understanding of the etiology for the acute decompensation and the pathophysiology of the underlying mitochondrial disorder.

2. Patients with a mitochondrial disease should carry an emergency care plan that details their underlying disorder and provides management recommendations.

3. Patients with a mitochondrial disease should wear a Medic Alert bracelet.

4. Mitochondrial patients should take precautions to prevent entering catabolism, especially when exposed to medical stressors, including avoiding prolonged fasting and receiving dextrose-containing IV fluids before, during, and after procedures and surgeries. (Dextrose should not be provided or should be provided in limited in quantity as indicated by clinical status in suspected or confirmed disorders of pyruvate metabolism, if the patient is on a ketogenic diet, or the patient has had an adverse response to high glucose delivery.)

5. Evaluation of a mitochondrial patient in the acute setting should include evaluation of routine chemistries, glucose, transaminases, and lactate; all other testing is as clinically indicated, although one must keep in mind the potential for cardiac and neurologic decompensations in these patients.

6. Treatment during acute decompensation should include dextrose-containing IV fluids, stopping exposures to potentially toxic medications, and correction of any metabolic derangements. (Note: dextrose should be provided only in limited in quantity or not at all, as indicated by clinical status in suspected or confirmed disorders of pyruvate metabolism, if the patient is on a ketogenic diet, or the patient has had an adverse response to high glucose delivery.) The IV fluid rate should be based on the clinical situation. Outpatient mitochondrial therapies should be continued when possible.

7. Lipids can be used when needed in mitochondrial patients, even in the presence of secondary fatty-acid oxidation dysfunction.

8. The following medications should be avoided in patients with mitochondrial disease when possible and, if given, they should be used with caution: valproic acid; statins; metformin; high-dose acetaminophen; and selected antibiotics, including aminoglycosides, linezolid, tetracycline, azithromycin, and erythromycin.

9. Repeat neuroimaging should be considered in any mitochondrial patient with an acute change in neurologic status.
Consensus recommendations for vitamin and xenobiotic use

1. CoQ$_{10}$ should be offered to most patients with a diagnosis of mitochondrial disease and not exclusively used for primary CoQ$_{10}$ deficiency.
   a. Reduced CoQ$_{10}$ (ubiquinol) is the most bioavailable form and, when used, dosing should be appropriately modified.
   b. Plasma and/or leukocyte CoQ$_{10}$ levels are helpful in monitoring absorption and adherence to treatment. Plasma levels are more variable and less reflective of tissue levels.
2. ALA and riboflavin should be offered to mitochondrial disease patients.
3. Folinic acid should be considered in mitochondrial disease patients with central nervous system manifestations and routinely administered to those with documented CSF deficiency or with disease states known to be associated with deficiency.
4. L-Carnitine should be administered to mitochondrial disease patients when there is a documented deficiency and levels should be monitored during therapy.
5. When beginning supplement therapy, one should begin one at a time when possible, taking into account a patient’s clinical status.
6. There is no evidence to suggest that one can adjust a person’s diet on the basis of ETC results.
7. Goal levels for most vitamin therapy used are not yet known; it is prudent to replace deficiency states.
Next?

* Preventative Care Guidelines?