Diagnosis of ‘possible’ mitochondrial disease: an existential crisis

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ABSTRACT
Primary genetic mitochondrial diseases are often difficult to diagnose, and the term ‘possible’ mitochondrial disease is used frequently by clinicians when such a diagnosis is suspected. There are now many known phenocopies of mitochondrial disease. Advances in genomic testing have shown that some patients with a clinical phenotype and biochemical abnormalities suggesting mitochondrial disease may have other genetic disorders. In instances when a genetic diagnosis cannot be confirmed, a diagnosis of ‘possible’ mitochondrial disease may result in harm to patients and their families, creating anxiety, delaying appropriate diagnosis and leading to inappropriate management or care. A categorisation of ‘diagnosis uncertain’, together with a specific description of the metabolic or genetic abnormalities identified, is preferred when a mitochondrial disease cannot be genetically confirmed.

INTRODUCTION
Primary mitochondrial disorders (PMD) are genetic metabolic disorders that directly impair normal mitochondrial structure or function including electron-transport chain (ETC) activity.3 They are due to mutations in either maternally inherited mitochondrial DNA (mtDNA) or one of hundreds of nuclear DNA (nDNA) genes that encode components involved in mitochondrial structure and function. PMDs can present at any age and be multisystemic or selectively involve only a single organ. They can present as a well-defined canonical syndrome or a constellation of phenotypes, although typically at least one ‘red-flag’ symptom is usually present at disease onset.2

With advances in next-generation sequencing (NGS) and the discovery of a multitude of new disease genes, the ability to diagnose PMDs has improved enormously compared with just a few years ago. The diagnosis still remains challenging due to heterogeneous manifestations combined with limitations of currently available biochemical and genetic testing methods. Despite recent advances, many individuals with suspected mitochondrial disease may remain without a confirmed genetic diagnosis, presenting a challenge to the clinician in establishing a mitochondrial disease diagnosis and in knowing how to categorise, counsel and manage the patient with a suspected PMD where a genetic diagnosis is not yet possible.3–7

These limitations contribute to continued variation in diagnostic categorisation of patients depending on the opinion of the treating provider.3 Diagnostic terms such as ‘unlikely’, ‘possible’ or ‘probable’ mitochondrial disease, originally proposed as part of research diagnostic criteria3–7 were developed prior to genetic advances and may end up being inaccurate and misleading to patients and care providers, impacting or limiting proper counselling and the pursuit of further diagnostic testing. The complex and variable clinical presentation of mitochondrial diseases means that many unexplained disorders could conceivably have a mitochondrial aetiology, so if a concrete alternative diagnosis cannot be made using conventional investigations, there is a tendency to use the label ‘possible’ mitochondrial as a working diagnosis until an alternative emerges. Patients and families may inadvertently be burdened by the fear of the progressive nature of PMDs, the potential complications and early demise, as PMDs have no known cure. Thus, a diagnosis of ‘possible’ mitochondrial disease may do more harm than good and consequently a new categorisation for these patients is necessary.

Mitochondrial disease can no longer be diagnosed on the basis of phenotypic features alone
A high index of suspicion for the possibility of a mitochondrial disease is appropriate when there is multisystem involvement or the presence of so-called ‘red-flags’ such as stroke-like episodes in a non-vascular distribution (seen in Mitochondrial Encephalomyopathy, Lactic Acidosis and Stroke (MELAS) syndrome), bilateral symmetric T2-weighted hyperintense MRI lesions in the basal ganglia and/or brainstem (Leigh syndrome) or chronic progressive external ophthalomoplegia (CPEO) and myopathy. Some of these ‘red-flag’
symptoms were the subject of a previous review. However, the growing list of genetically confirmed mitochondrial diseases has also led to an expanding list of variable phenotypes that should be suspected in the differential diagnosis of PMD, some of which are outlined in Table 1.12–14

In contrast, genetic testing has revealed that non-mitochondrial disorders may present with symptoms suggestive of mitochondrial disease. Without confirmatory genetic evidence, an erroneous diagnosis of a PMD may be made. For example, myopathy with ophthalmoplegia may also be seen in some cases of congenital myopathies with mutations in MYH2,15 MTM1 in male patients and female carriers,16 DNLM2222 and recessive RYR1 mutations18–22 as well as in late-onset nemaline myopathy23 and in congenital myasthenia caused by mutations in CHAT encoding the choline acetyltransferase.24 Similarly, patients with branched-chain organic acidurias can manifest with non-haemodynamic strokes,25 as can patients with congenital disorders of glycosylation.26 Bilateral striatal necrosis (with MRI lesions resembling those observed in Leigh syndrome) has been reported with genetic mutations in the nuclear pore proteins NUP6227 and RANBP228 or in the cyclic nucleotide phosphodiesterase PDE8B.29 Many of these disorders may also be associated with secondary mitochondrial dysfunction on biochemical testing as discussed later and illustrated in Table 2. Clinicians clearly need to exercise caution when considering mitochondrial disease, in order not to narrow the differential too quickly simply based on aspects of the clinical phenotype and astutely ensure that even ‘red flag’ features of a PMD are placed in the correct context of the patient’s comorbid symptoms, family history and course of disease.
Biochemical diagnostic tests remain imperfect

Consensus criteria to help standardise the evaluation of patients with potential PMD, outlining a streamlined approach and reviewing the strengths and limitations of many of the current testing modalities were suggested in 2015 by the Mitochondrial Medicine Society (MMS), an international group of clinicians specialising in mitochondrial disease. This exercise aimed to decrease the variability that exists in approaches used by clinicians to diagnose PMD, outlining a streamlined approach and discussed in detail in the supplementary material (online supplementary testing).

<table>
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Box 1 Limitations of testing

Current Limitations of biochemical testing

- Imperfect sensitivity and specificity.
- Secondary mitochondrial dysfunction leading to abnormal results.
- Interlab variability of methods and reference ranges.
- Challenges with tissue processing.
- Current limitations of genetic testing
- Incomplete understanding of the role of the entire genome in mitochondrial function.
- Novel genes still being identified.
- Interpretation of nuclear and mtDNA variants of uncertain significance.
- Lack of understanding of tissue-specificity of mtDNA mutations.
- Unclear relevance of low heteroplasmy levels of pathogenic mtDNA mutations mtDNA deletions and depletions may be observed in non-mitochondrial disease.

Biochemical diagnostic tests remain imperfect

Consensus criteria to help standardise the evaluation of patients with potential PMD, outlining a streamlined approach and reviewing the strengths and limitations of many of the current testing modalities were suggested in 2015 by the Mitochondrial Medicine Society (MMS), an international group of clinicians specialising in mitochondrial disease. This exercise aimed to decrease the variability that exists in approaches used by clinicians to diagnose PMD.

When a mitochondrial disorder is suspected, biochemical screening in blood, urine and cerebrospinal fluid remain the initial tests of choice quickly followed by NGS of mtDNA and nDNA from white blood cells, with additional genetic studies in muscle when needed, particularly in adult-onset cases. Whole exome sequencing (WES) is useful, and along with whole genome sequencing is quickly becoming the first or second line testing modalities were suggested in 2015 by the Mitochondrial Medicine Society (MMS), an international group of clinicians specialising in mitochondrial disease. This exercise aimed to decrease the variability that exists in approaches used by clinicians to diagnose PMD.

Histopathological, biochemical and genetic analysis of tissue including muscle remain important tools to further delineate the phenotype and ascertain the relevance of any genetic variants identified in blood, but should no longer be considered first or second line tests when suspicion of a PMD is high and appropriate genetic testing is available. Select disorders, such as CPEO, may warrant the need for further diagnostic testing in muscle. Additional considerations regarding these tests have been reviewed previously and are summarised below and in box 1 and discussed in detail in the supplementary material (online supplementary testing).
Challenges with biochemical testing
Biochemical studies in blood and urine such as lactate, amino acids, organic acids and including the recently identified biomarkers growth differentiation factor 15 and fibroblast growth factor 21 (FGF21), along with functional assays in various tissues such as ETC enzyme analysis, all have less than optimal sensitivity and specificity, especially when interpreted in isolation from the clinical context.30–35
Abnormalities on ETC enzyme analysis may occur for a multitude of reasons outside of PMD including secondary mitochondrial dysfunction from other causes such as other genetic diseases, limb immobility and in liver failure from non-mitochondrial causes.37–38 The list of other genetic disorders where some degree of secondary mitochondrial dysfunction in various tissues is seen seems ever-growing (table 2) and includes spinal muscular atrophy,39 X linked adrenoleukodystrophy,40 Phelan-McDermid syndrome, Down syndrome, Zellweger syndrome, the ‘rasopathies’ (disorders caused by mutations in the Ras-MAPK pathway) and a variety of other conditions.41–46 Causes of this secondary dysfunction have been discerned for very few of these disorders and the extent of mitochondrial dysfunction is variable and may not meet the diagnostic criteria threshold for ‘definite’ mitochondrial disease.47 Therefore, evidence of biochemical dysfunction on functional testing alone, especially when mild or moderate, should not lead to a conclusive diagnosis of PMD.42 45 47–49 When used with rigour, mitochondrial disease criteria may help the clinician selectively better stratify truly high-risk patients.50 However, mitochondrial disease diagnostic criteria were all developed at a time prior to the advent of NGS, when only limited genetic testing was available, and strongly emphasised the importance of abnormal biochemical findings in tissue.10 50 51 This inevitably led to many patients being diagnosed with ‘possible’ mitochondrial disease.

Challenges with genetic testing
The advent of rapid, relatively low cost, NGS technologies has allowed for a genetic diagnosis to be made in many more patients with PMD. A growing number of nuclear genes has been associated with mitochondrial function (1500 to-date)52 53 although only around 350 or so have firmly been linked to causing human mitochondrial disease.1 54 55 With more routine use of WES, new variants of unknown significance (VUS) add to the diagnostic load may mistakenly be attributed to cause a patient’s phenotype.56 These issues and others are discussed in further detail in the supplementary material (online supplementary testing) but lead to the clear concern that simply testing the mitochondrial genome in leucocytes is not always adequate and that mtDNA testing including quantification and deletion analysis in other tissues (skeletal muscle, liver, buccal, urine sediment) may be needed. Furthermore, even though many defects in mtDNA maintenance may be diagnosed by WES, there remains a significant number in which the causative genes remain unknown. Muscle or liver biopsy (depending on the phenotype), along with reliable assessment of mtDNA copy number compared with age specific control ranges and/or long PCR for multiple deletions, are needed to diagnose these patients.

Despite the current limitations of genetic testing, the need for genetic confirmation of a PMD diagnosis is becoming a necessity. The number of phenocopies identified together with the less than perfect specificity of biochemical studies raises the concern of a mistaken diagnosis and the potential of missing a separate treatable disease. Accurate genetic diagnosis of a PMD allows care providers and affected families to better understand the condition, for the provision of appropriate genetic counselling, and for the development of targeted therapies. For some PMDs where the natural history is better known, clinicians and families can more accurately predict the disease course and provide appropriate clinical management and preventative care.57 The need for a genetic diagnosis in PMD is now essential for eligibility in clinical trials. Preimplantation genetic diagnosis for nuclear and mtDNA disorders and mitochondrial donation techniques also requires a prior confirmed genetic diagnosis.

Ending a ‘possible’ diagnosis of mitochondrial disease
Previously established diagnostic criteria,9–11 developed prior to advances in genetic testing, relied heavily on biochemical functional tests. They were intended to serve as research categorisation tools in the era of only a basic understanding of mtDNA as it relates to mitochondrial illness and prior to our knowledge of any but a handful of the hundreds of nuclear genes that are now known to cause mitochondrial disease. In addition, they were often not adhered to in the strictest fashion by clinicians. These diagnostic categorisations subsequently infiltrated the clinic and many more patients began to be labelled as having ‘possible’ mitochondrial disease. Others have received the diagnosis of ‘mitochondrial myopathy’ because of abnormalities seen in muscle histology or microscopy alone, even though this finding may exist due to other genetic, metabolic or neurodegenerative diseases.

While genetic testing has improved, it is not currently possible to confirm the diagnosis at a genomic level in every case. Some patients may have a coincidentally identified pathogenic mtDNA mutation with low levels of heteroplasmy or a VUS in a nuclear gene bioinformatically predicted to impact mitochondrial function that may make a clinician consider a ‘possible’ mitochondrial disease diagnosis.

Given that patients with symptoms suggestive of mitochondrial disease may or may not ultimately have a PMD, it is increasingly important to establish better diagnostic criteria or at least a unified approach to categorising these patients, to avoid significant variability in diagnostic labelling, genetic counselling and management. With the growing number of clinical, biochemical and genetic phenocopies of PMD being identified, it has become prudent that a definitive diagnosis of mitochondrial disease should only be provided when a confirmed pathogenic genetic defect has been identified. Utmost caution must be used when providing a diagnosis based on biochemical abnormalities in tissue alone and the strictest application of biochemical
diagnostic criteria is needed. Patients with strong biochemical and clinical evidence for a PMD should be periodically re-evaluated as diagnostic testing advances.

There is a clear concern that a diagnosis of ‘possible’ mitochondrial disease may result in harm. First and foremost, some patients who receive a diagnosis of a ‘possible’ or ‘suspected’ mitochondrial disease may not recognise the importance of such a diagnosis and remain carrying this label for many years without having their symptoms periodically reassessed and a more specific diagnosis investigated as knowledge and diagnostic tools improve. Over time, the categorisation of ‘possible’ is often dropped by some providers and non-mitochondrial specialists providing routine care for the patient. Some families may cling to the diagnosis even after having had a different genetic disease confirmed, as it is the diagnosis they have become most familiar with over time. Testing for another disorder may be delayed from the clinician’s side if they are not aware of this diagnostic uncertainty. Other treatable disorders may not be diagnosed or may be delayed.

A diagnosis of ‘possible’ mitochondrial disease may also create an unfounded fear of worsening morbidity and mortality. Certain families of patients given a diagnosis of ‘possible’ mitochondrial disease often overlook the uncertainty of the diagnosis and become overly concerned that they or a family member may manifest all of the symptoms a patient with a PMD may develop, including neurodegeneration or early death, even in instances where their symptoms are relatively mild.

Last, patients with a diagnosis of ‘possible’ mitochondrial disease may receive inappropriate care or be overmedicalised. Counselling of disease expectations and management may vary based on how patients are categorised. Unnecessary medical interventions may be offered to some during times of catabolic stress. Some medications may not be used due to a concern of potential mitochondrial toxicity. New symptoms that a patient may manifest may inappropriately be explained away by the underlying diagnostic label rather than looking for other potentially treatable causes. These and other concerns are summarised in box 2.

Some of these very issues and challenges are outlined in example cases provided in the supplementary material (online supplementary cases). In addition to the disorders outlined in box 2, the online supplementary cases illustrate instances where a patient may have symptoms suggesting the possibility of mitochondrial disease, often with biochemical abnormalities suggesting mitochondrial dysfunction, but the final diagnosis is not a PMD. Diagnosis is often delayed due to the mistaken diagnosis. Examples include a manganese transporter disorder with bilateral basal ganglia hyperintensities and elevated FGF21 levels (Case 1), oculopharyngeal muscular dystrophy with ragged red and cytochrome c oxidase (COX)-negative fibres (Case 2), Lesch-Nyan syndrome with putaminal and thalamic abnormalities, lactic acidosis and reduced Complex I enzymatic activity in muscle (Case 3) and Niemann-Pick Type C with Complex I deficiency leading to a delay in being prescribed Miglustat (Case 4). In some of these instances, mitochondrial functional testing was notably abnormal, meeting biochemical diagnostic criteria for a mitochondrial disease. In contrast, select other cases (Cases 5–8) illustrate a delayed PMD diagnosis due to limitations of genetic testing in blood, findings of low levels of heteroplasmy or findings of a VUS. Case 5 illustrates an instance of a female with MELAS-like symptoms. Other cases (Cases 6–8) show the challenges in interpreting nuclear and mtDNA VUS.

### Box 2 Potential harms arising from a diagnosis of ‘possible’ mitochondrial disease

- Ending diagnostic odyssey prematurely.
- Missing potentially treatable disorders.
- Psychological burden of mitochondrial disease diagnosis: parent/patient fear of progressive or degenerative disorder.
- Inaccurate recurrence risk counselling.
- Inappropriate preventative care.
- Unnecessary medical interventions at times of catabolic stress.
- Avoidance of needed medications owing to fear of mitochondrial toxicity.
- Inappropriate reproductive decisions taken.

### Box 3 Terminology to avoid when a mitochondrial diagnosis is uncertain

- ‘Possible,’ ‘probable’ or ‘suspected’ mitochondrial disease.
- Mitochondrial myopathy.
- Mitochondrial cytopathy.
- Mitochondrial metabolism disorder.
- Defect of mitochondrial metabolism.

### Recommendations

In patients without a confirmed genetic diagnosis, there is a need for clinicians and the mitochondrial disease community to use diagnostic labels that clearly state that the diagnosis is uncertain even when mitochondrial dysfunction has been identified. A category of ‘genetic diagnosis uncertain; mitochondrial biochemical dysfunction or mitochondrial genetic variant of unknown significance identified’ is preferable to a diagnosis of ‘possible’ or ‘probable’ or ‘suspected’ mitochondrial disease. Other terminology that should be avoided is listed in box 3. Depending on the clinical situation, patients may be further stratified into a ‘high risk’ for a PMD to guide management.

Our proposal to use a diagnostic label of ‘genetic diagnosis uncertain’ for all such cases would allow clinicians and patients to remain actively engaged in the diagnostic journey, review the prior data periodically and take advantage of technological advances in genetic testing and new disease descriptions. Conducting relevant screening of other systems and monitoring for other organ involvement would allow better definition of the phenotype and not overlook disease progression. The clarity of the diagnostic label may prevent inappropriate or unnecessary care and allay fears of a progressive or degenerative disease.

Further categorisation of selected patients as possible ‘high risk’ for a PMD would allow for closer monitoring for mitochondrial disease-related systemic comorbidities or extra cautions during times they are at risk of metabolic decompensations. If the phenotype is especially suggestive of a PMD, it may be appropriate to manage such a patient as if they have a genetically confirmed PMD for the time being—especially if they have previously experienced metabolic decompensation during times of illness or medical stress. Unexpected, acute changes in clinical status warrant thorough medical evaluation including laboratory testing to investigate potential mitochondrial dysfunction. However, the ‘diagnosis uncertain’ designation would prevent any misunderstanding among medical teams. If the phenotype is not as suggestive of a PMD, it may be prudent...
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to avoid overmedicalisation of the patient and simply continue more routine monitoring.

As diagnostic standards for mitochondrial disease continue to evolve, these patients should remain under the care of a clinician who can assist in providing up-to-date recommendations regarding further testing. The MMS has such recommendations available online at http://www.mitosoc.org.

CONCLUSION

Despite advances in diagnostic techniques and molecular genetics, a subset of patients with suspected mitochondrial disease remains without a confirmed genetic diagnosis. The path these patients take to receiving a diagnosis is arduous and, at times, circuitous. Newer NGS-based genetic studies offer the ability to streamline the approach to diagnosis for some patients. Others remain with a constellation of symptoms, findings of mitochondrial dysfunction on functional testing and no clear pathogenic genetic mutation. Patients diagnosed with a ‘possible’ mitochondrial disease might be found to have a non-mitochondrial genetic disorder once new testing modalities are used. A mistaken diagnosis of mitochondrial disease may prematurely end their diagnostic journey, overmedicalise their care and potentially limit access to appropriate treatments for the actual underlying condition. To alleviate this dilemma, such patients would be better served by clinicians avoiding the diagnostic term ‘possible’ mitochondrial disease.

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Contributors

SP, AK and AG conceived the presented idea and prepared a document outline including needed supplementary material. SP, AK, AG and SR developed and supervised the manuscript. SP, AK, AG, ES, PFC, JC, BHC, RLD, MJF, CF, RH, MKK, MM, SM, EMM, RM, VN, MS, HS, SS, CS, MT, DRT, JF and SR commented on, approved and helped expand the presented idea, drafted and revised portions of the manuscript including supplementary materials and commented on and approved the final draft.

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