In response to “Letter to the Editor, Management of Ophthalmologic Manifestations of Mitochondrial Diseases”

Author Names and affiliations

Sumit Parikh, MD, Associate Professor of Neurology, Center for Child Neurology, Cleveland Clinic Children’s Hospital, Cleveland, OH

Amy Goldstein, MD, Assistant Professor of Pediatrics, Division of Child Neurology, Children’s Hospital of Pittsburgh, Pittsburgh, PA

Amel Karaa, MD, Assistant in Pediatrics, Division of Genetics, Massachusetts General Hospital, Boston, MA

Mary Kay Koenig, MD, Associate Professor of Pediatrics, Division of Child and Adolescent Neurology, University of Texas Medical School at Houston, Houston, TX

Irina Anselm, MD, Assistant Professor of Neurology, Boston Children’s Hospital, Boston, MA

Catherine Brunel-Guitton, MD, FRCPC, FCCMG, Associate Professor of Pediatrics, University of Montreal, Quebec, Canada

John Christodoulou, Neurodevelopmental Genomics Research Group, Murdoch Childrens Research Institute, and Department of Paediatrics, Melbourne Medical School, University of Melbourne, Melbourne, Australia

Bruce H. Cohen, MD, Professor of Pediatrics, Neurodevelopmental Science Center, Children's Hospital Medical Center of Akron, Akron, OH

David Dimmock, MD, Medical Director, Rady Children’s Institute for Genomic Medicine, San Diego, CA

Gregory M. Enns, M.B., Ch.B., Associate Professor of Pediatrics, Department of Pediatrics, Division of Medical Genetics, Stanford University Lucile Packard Children’s Hospital, Palo Alto, CA

Marni J Falk, MD, Associate Professor of Pediatrics, Division of Human Genetics, Department of Pediatrics, The Children’s Hospital of Philadelphia and University of Pennsylvania Perelman School of Medicine, Philadelphia, PA

Annette Feigenbaum, MD, Division of Clinical and Metabolic Genetics, The Hospital for Sick Children and University of Toronto, Toronto, Canada; Department of Pediatrics, University of California San Diego and Rady Childrens Hospital, San Diego, California.

Richard E. Frye, MD, PhD, Department of Pediatrics, University of Arkansas Medical Sciences, Little Rock AR

Jaya Ganesh, MD, Associate Professor of Pediatrics, Department of Pediatrics, Division of Genetics, Cooper Medical School at Rowan University, Camden, NJ

David Griesemer, MD, Professor of Pediatrics, Division of Neurology, Levine Children's Hospital, Charlotte, NC

Richard Haas, MB, BChir, MRCP, Professor of Neurosciences and Pediatrics, Departments of Neurosciences and Pediatrics, University of California San Diego, La Jolla, CA 92093; and Rady Children's Hospital, San Diego, CA 92123

Rita Horvath, MD, PhD, Professor of Neurogenetics, Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, UK

Mark Korson, MD, Genetic Metabolic Center for Education, Salem, MA

Michael C Kruer, MD, Associate Professor of Child Health, Neurology & Genetics, University of Arizona College of Medicine, Phoenix, AZ

Michelangelo Mancuso, MD, PhD, Department of Experimental and Clinical Medicine, Neurological Clinic, University of Pisa, Pisa, Italy

Shana McCormack, MD, Division of Endocrinology and Diabetes, Children's Hospital of Philadelphia, Philadelphia PA

Marie Josee Raboisson, MD, Department of Cardiology, CHU Sainte-Justine. Montreal, Quebec, Canada

Tyler Reimschisel, MD, MHPE, Associate Professor of Pediatrics and Neurology, Vanderbilt University Medical Center, Nashville, TN

Ramona Salvarinova, MD, MHSc, FRCPC, FCCMG, Clinical Assistant Professor, Division of Biochemical Diseases, BC Children's Hospital, British Columbia, Canada

Russell P. Saneto, DO, PhD, Professor of Neurology and Adjunct Professor of Pediatrics, Seattle Children's Hospital/University of Washington, Seattle, WA

Fernando Scaglia, MD, Professor, Department of Molecular and Human Genetics, Baylor College of Medicine and Texas Children's Hospital, Houston, TX

John Shoffner, MD, Neurology, Biochemical & Molecular Genetics, Atlanta, GA

Peter W. Stacpoole PhD, MD, Professor of Medicine, Biochemistry and Molecular Biology, University of Florida College of Medicine, Gainesville, FL

Carolyn M Sue, Professor and Director of Neurogenetics, Department of Neurology and Kolling Institute, Royal North Shore Hospital, St Leonards, Australia

Mark Tarnopolsky, MD, PhD, Professor of Pediatrics and Medicine, McMaster University, Hamilton, Ontario

Clara Van Karnebeek, Department of Pediatrics, Academic Medical Centre, University of Amsterdam, Amsterdam, NL; Department of Pediatrics, Centre for Molecular Medicine, University of British Columbia, Vancouver CA

Lynne A Wolfe, MS, CRNP, BC, Undiagnosed Diseases Network, National Institutes of Health, Bethesda, MD

Zarazuela Zolkipli Cunningham, MBChB, MRCP, Division of Neurology, The Children's Hospital of Philadelphia, PA 19104.

Shamima Rahman, FRCP, PhD, Professor of Paediatric Metabolic Medicine, Mitochondrial Research Group, UCL Great Ormond Street Institute of Child Health, London, UK.

Patrick F. Chinnery, FRCP, FMedSci, Professor of Neurology & Head of Department, Department of Clinical Neurosciences & MRC Mitochondrial Biology Unit, University of Cambridge, UK

Corresponding author
Sumit Parikh, Cleveland Clinic, 9500 Euclid Avenue, S60, Cleveland, OH 44195. 216-444-1994. Fax: 216-445-9139. Email: parikhs@ccf.org

To the Editor,

We thank Dr. Newman and colleagues for their careful reading of our manuscript and for their additional recommendations.

We agree that creating a single set of guidelines covering the multitude of systemic and neurological manifestations of mitochondrial diseases is difficult, and that the recommendations will inherently not apply to every situation or every patient. However, the Delphi methodology we used allowed us to synthesize what were sometimes diverse views, and thereby to present a consensus based on the experience of a panel of mitochondrial disease physicians. This approach has been shown to be most valuable when there is limited objective evidence base, as for mitochondrial disorders.

In regard to the concern of whether a neuro-ophthalmologist is required for routine care of these patients, the writing group considered that such a specialist, if accessible by the patient, would be the ideal physician to monitor the ophthalmological manifestations of the disease. A neuro-ophthalmologist would also be the best person to determine the need for subspecialty ophthalmology referrals. It is important to note that this was only a recommendation, and not considered to be essential for each and every patient.

With regard to the monitoring of intraocular pressure, while it should be an integral part of every general eye exam, some members of the consortium have noted that this portion of the examination is not always performed in some pediatric patients. For this reason, an additional statement was included to recommend this testing be done when necessary.

We agree that lubrication is required to prevent the keratopathy that occurs with corneal exposure in some mitochondrial patients, and not only due to the inappropriate spread of tears. We also agree that it would be wise for affected and unaffected LHON mtDNA mutation carriers to avoid cigarette smoking and excessive alcohol use, although the evidence that well-established LHON deteriorates with smoking or excess alcohol is limited. The seventh recommendation was included to alert the clinician to the presence of LHON plus phenotypes, with some authors feeling that a periodic neurologic exam may detect pre-clinical symptoms, and a follow-up electrocardiogram may detect a pre-excitation syndrome not apparent on the first examination.

It is important to stress that our recommendations were not a universal view held by all of the authors and rather a consensus statement reflecting the majority. This approach has both strengths and weaknesses. Inevitably this means that the outcome of the review was dependent on the authors who engaged the process. To address this, we did make an open invitation to interested clinician-members of the Mitochondrial Medicine Society to participate. However, most importantly, the consensus describes a ‘current state of play’, which definitely should be revised as additional objective information comes to hand.

We therefore welcome their additional comments, and look forward to incorporating these suggestions in any future revised version of the criteria.

Sumit Parikh, on behalf of all the authors