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The United Mitochondrial Disease Foundation proudly presents...

Mitochondrial Medicine 2018: Nashville

Family Program: June 29 - 30, 2018
LHON Program: June 28 - 29, 2018

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Mitochondrial Medicine 2018: Nashville

Family Program: June 29 - 30, 2018
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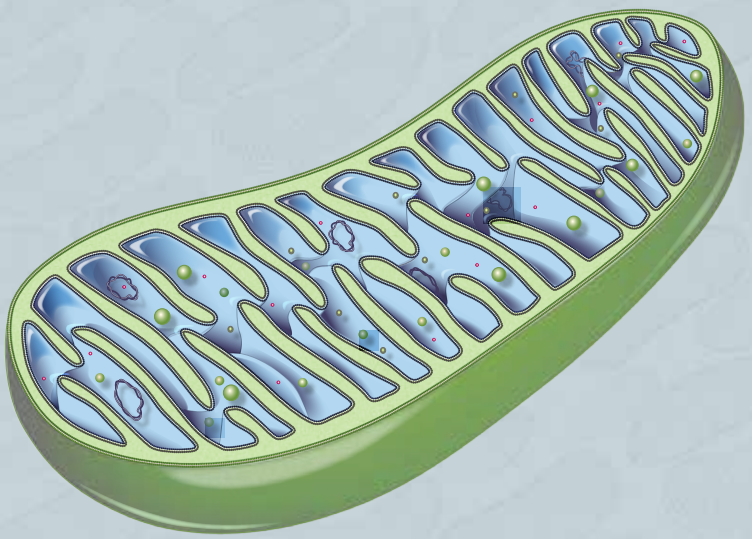

Stealth BioTherapeutics is committed to the development of therapies for mitochondrial disease and is a proud supporter of the mitochondrial foundations and their communities.

To learn more about our work, please visit StealthBT.com

Mitochondrial Medicine 2018: Nashville

Special Announcements

Name Badges
All attendees must wear a name badge to all course functions.

Exhibits
Exhibits will be open in the Hermitage Lobby during all breaks and lunches.

Evaluation Forms
Please complete the symposium evaluation forms and return them to the registration desk at the closing of the symposium on Saturday. We appreciate your comments and find them very useful for future planning. By filling out the evaluation form, your name will be entered into a drawing to win a FREE registration for Mitochondrial Medicine 2019.

Each session has an additional "session" evaluation form. Please complete one for each session you attend to help us evaluate the speaker and topic. Please return them to the registration desk on Saturday or hand to the session volunteer as you exit.

The Doctor is In

This is a very special program that gives families an opportunity to meet one-on-one with some of the world's top experts in mitochondrial medicine. You are able to reserve one 15 minute session. Sign up sheets will be available on Thursday evening from 6:00pm to 8:00pm and starting again early Friday. After the sessions start, sign ups will continue in the "Doctor is In" room until all sessions are filled. Please note, discussions with physicians in the "Doctor is In" forum are informal and do not establish a doctor-patient relationship. NOTE: We are including Genetic Counselors this year to try something new.

Teen Social Activities

Hang out with your crew! Join other mito-teens and their siblings! Lots of new activities this year and plenty of time to chat with new and old friends.

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Mitochondrial Medicine 2018: Nashville

Special Announcements

Patient/Family Networking

If you cannot find a session to your liking during any of the time slots on Friday and/or Saturday, there will be several options to sit back, relax and gather with new found friends or old acquaintances during the meals and breaks.

Lunch

Lunches will be held in the Hermitage DEF.

Friday Night Banquet and Awards Ceremony

Scientific and family program attendees are invited to attend the Friday Night Banquet and Award Ceremony in the Heritage Ballroom.

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SCHEDULE

Mitochondrial Medicine 2018: Nashville

Family Program Schedule

Thursday, June 28, 2018

6:00pm - 8:00pm	**12th Annual Adult Gathering** *Moderators: AACT Leadership*
11am - 12:30pm	**LHON Community Connection Networking** LHON attendees will get to know the people behind the voices
12:30pm - 1:30pm	**LHON Luncheon** *(Hermitage F)*
1:30pm - 2:30pm	**LHON - Welcome and Assistive Technology Update** *Lissa Poincenot*
2:30pm - 3:30pm	**Living with LHON: Sports** *Molly Knox*
3:30pm - 4:00pm	Break
4:00pm - 5:15pm	**LHON Journeys** *Maria Johnson*
5:15pm - 5:30pm	**LHON - Thursday Closing Remarks** *Molly Knox*
4:00 pm	**TEEN & YOUNG ADULT - Painting to Music with Nancy Ostrowski, Movies, and Games**
5:30pm - 8:00pm	**Symposium Mitochondrial Family "Mixer" Reception!** (All Patients/Families and LHON attendees will come together to enjoy an evening to network with each other prior to the meeting beginning)

Mitochondrial Medicine 2018: Nashville

Family Program Schedule

Friday, June 29, 2018

7:00am	Registration & Continental Breakfast
8:00am - 8:10am	**Welcome and Clinical Trials Session** (Combined with Scientific, Clinician, Patient, Family and LHON Attendees) *Brent Fields, Chuck Mohan, Philip Yeske, PhD*
8:10am - 8:40am	**History of Clinical Trials in Mitochondrial Disease** *Bruce H. Cohen, MD*
8:40am - 9:45am	**Clinical Trial Updates Session 1: Small Molecule Approaches** - *Bruce Cohen, MD* • Mitochondria Disease Program Update - *Reenie McCarthy, Chief Executive Officer, Stealth BioTherapeutics* • Safety, Efficacy, and Pharmacodynamics of Omaveloxolone in Mitochondrial Myopathy Patients (MOTOR Trial-Reata): Part 1 Results - *Karen Lindhardt Madsen, PhD, University of Copenhagen* • The KHENERGY study: an exploratory, double-blind, randomized, placebo-controlled, two-way cross-over phase II trial in m.3243A>G patients - *Jan Smeitink, CEO Khondrion*
9:45am - 10:15am	Break
10:15am - 11:40am	**Clinical Trial Updates Session 2: Vision Disorders** *Moderators: Lissa Poincenot and Nancy Newman, MD* • Overview of Mitochondrial Vision Disorders - *Nancy Newman, MD* • GenSight: What we have Done, What we are Doing - *Barrett Katz, MD* • Santhera's Real World Experience with Idebenone in LHON. Update on Programs - *Xavier Lloria, Medical Affairs Director, Santhera Pharmaceuticals* • Stealth Development Update - *Jim Carr, PharmD, Chief Clinical Development Officer, Stealth BioTherapeutics* • Vision Disorder Panel Q&A
11:40am - 11:45am	Mini-Break (LHON Families may leave for other sessions)
11:45am - 12:00pm	**Pre-Clinical Data Updates** *Philip Yeske, PhD* • L1333 - Mitochondrial disease treatment opportunity by NAD+ modulation and mitochondrial biogenesis - *Magnus Hansson, PhD, NeruoVive*
12:00pm - 12:30pm	**Planning an Externally-led Patient-Focused Drug Development Meeting** • EL-PFDD Meeting Background - *James Valentine* • EL-PFDD Mitochondrial Disease Plan - *Philip Yeske, PhD* • EL-PFDD Meeting Timeline and Q&A
10:30am - 11:30am	**ALL – What is Mitochondrial Disease and What to Expect (Mito Basics)** *Tyler Reimschisel, MD*

Most family sessions are 45-60 minutes long unless otherwise stated.

SCHEDULE

SCHEDULE

10:30am - 11:30am	**ALL – Nutritional Interventions in Mitochondrial Disorders** B*arbara Marriage, PhD, RD*
10:30am -11:30am	**ALL – Grief Throughout Life** *Dr. Tracy Hills, DO and Amanda Borchik, MDiv*
11:30am - 12:30pm	**ALL – Cardiology Issues in the Mitochondrial Patient** *Justin Godown, MD*
11:30am - 12:30pm	**ADULT – Ask the Mito Doc Panel** *Moderator: UMDF Staff* *Panel Speakers: Zarazuela Zolkipli Cunningham, MD; Sumit Parikh, MD; Andrea Gropman, MD; and Amel Karaa, MD*
11:45am - 12:45pm	**LHON Scientific Q&A** *Moderator: Lissa Poincenot - Speaker: Nancy Newman, MD* **LHON Community Update, Group Photo and Closing Remarks** *Lissa Poincenot*
12:30pm - 2:00pm	Lunch – Networking by Geographic
2:00pm - 3:00pm	**ALL – Yoga and Relaxation**
2:00pm - 3:30pm	**ADULT – Navigating Social Security Disability Panel** *Moderator: Donald E. Garrison, JD - Panel Speakers: Carol Rabideau, LCSW; John P. Garner, JD, Social Security Disability Attorney; Tim Takacs, JD, Certified Elder Law Attorney; and Joy and Bryan Krumdiack*
2:00pm - 5:00pm	**Living with Mitochondrial Disease - Patient Panel Sessions** *James Valentine*
2:00pm - 2:15pm	**Overview and Initial Polling Questions on Demographics**
2:15pm - 2:35pm	**Parent Perspective on the Burdens of the Disease** (Focusing on Pediatric/Youth Neurologic Issues) Panelists: 2:15-2:20 - Ann Korsen (NJ) 2:20-2:25 - Annett Cotte (GA) 2:25-2:30 - Stacy Taylor (MD) 2:30-2:35 - Heather Thornbury (FL)
2:40pm-3:05pm	**Parent Perspective on Management of Care** (Focusing on Pediatric/Youth Neurologic Issues) Panelists: 2:40-2:45 - Carrie Mullin (PA) 2:45-2:50 - Lori Martin (TX) 2:50-2:55 - Cheryl Porter (GA) 2:55-3:00 - Gwen Lopez-Cohen (CT) 3:00-3:05 - Anne Tuccillo (VA)
3:05pm - 3:25pm	**Q&A (Polling time)**
3:25pm - 3:35pm	Break

Most family sessions are 45-60 minutes long unless otherwise stated.

3:35pm - 4:00pm Myopathies)	**Adult Patient Perspective on the Burdens of the Disease** (Focusing on Adults with Mito Panelists: 3:35-3:40 - Laura Prudhomme-Gaupp (LA) 3:40-3:45 - Devin Shuman (PA) 3:45-3:50 - Deborah Bricker Parsons (GA) 3:50-3:55 - Rachel Schanzenbach (VA) 3:55-4:00 - Alysse Delotte (FL)
4:05pm - 4:35pm	**Adult Patient Perspective on Management of Care** (Focusing on Adults with Mito Myopathies) Panelists: 4:05-4:10 - Kristen Schroeder (CT) 4:10-4:15 - Deborah Carman (IL) 4:15-4:20 - Sharon Shaw Reeder (AZ) 4:20-4:25 - Nicole DeJean (LA)
4:30pm - 5:00pm	**Q&A (Polling time) and wrap up**
3:30pm - 4:30pm	**ALL - Tips and Transitions for Caregivers of Children with Medical Complexity** *Michaela Ibach, MD and Sarah Wilkerson, CPNP*
6:00pm	Reception
7:00pm	Banquet Celebration for Scientific, LHON, and all Family Attendees Awards Ceremony

Saturday, June 30, 2018

7:30am	Continental Breakfast
8:30am	**Patient Registries - MDCR, MSeqDR EConsent Review, Leigh Syndrome Patient Registry, and Workshop** *Philip Yeske, PhD; Elizabeth McCormick, MS, CGC; Mary Kay Koenig, MD* (Hands-on workshop time with families. Workshop will remain open until break)
9:30am - 10:30am	**ALL - Managing Sleep Issues in the Mitochondrial Patient** *Althea Robinson Shelton, MD, MPH*
9:30am - 10:30am	**ALL - Advocacy Session** *Cliff Gorski, David Faughn and Jenny Hobbs*
10:30am	BREAK
11:00am - Noon	**ALL – Mitochondrial Disease of Non-Genetic Origin** *Kendall Wallace, PhD and Bruce H. Cohen, MD*
11:00am - Noon	**ALL - Physical, Occupational, and Speech Therapies and the Mitochondrial Disease Patient** *Karen Coker, PT, DPT, CWS, WCC, C/NDT, FACCWS; Missy Bryan, OTD, OTR/L, ATP, CPST; and C. Melanie Schuele, PhD, CCC-SLP*
Noon - 1:30pm	LUNCH

Most family sessions are 45-60 minutes long unless otherwise stated.

SCHEDULE

1:30pm - 2:30pm	**CHILD – Ask the Mito Doc Panel** *Moderator: UMDF Staff* *Panel Speakers: Mary Kay Koenig, MD; Richard Haas, MD ; Russell Saneto, DO, PhD; and Annette M. St. Pierre-MacKoul, MD*
1:30pm - 2:30pm	**ALL – Additional Patient Registry Time Workshop** *UMDF Staff*
1:30pm - 2:30pm	**ALL - Practical Strategies to Enhance Independence Workshop** *Terena Scott*
1:30pm - 2:30pm	**Adult AND Young Adult – Genetics 101 Talk** *Tyler Reimschisel, MD* *Note: The slides for this talk will be similar to the "What is Mito" talk from Friday but with Q&A time specific to Adult and Young Adult questions.*
2:30pm - 3:00pm	BREAK
3:00pm - 4:30pm	**Closing Session – What's on the Horizon!** **Scientific Meeting Highlights and Upcoming Clinical Trial Updates** *Amy Goldstein, MD; Philip Yeske, PhD* NAMDC Study Updates – *Kris Englestad* Other company updates - TBD
4:30pm	Adjourn

Most family sessions are 45-60 minutes long unless otherwise stated.

Save the Date!

Mitochondrial Medicine 2019: Washington DC

Scientific Program: June 26 - 29, 2019
Family Program: June 28 - 29, 2019
UMDF "Day on the Hill": Thursday, June 27, 2019

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Mitochondrial Medicine 2018: Nashville

TEEN Sessions Schedule

TEEN SCHEDULE

Friday, June 28, 2018

9:00am	**Getting to Know You**
9:30am	**Healthy Lifestyle** *Dr. Zarazuela Zolkipli Cunningham will do a fun, interactive talk about staying fit and making use of physical therapies*
10:30am	Break
11:00am	*** STEM** Cooking up a Storm - Nitrogen / It's Electric - Circuitry COOKING UP A STORM (25-minute Demonstration) Learn about the three basic ingredients of weather - water, air, and temperature - and investigate what weather events are created when these ingredients are combined in different recipes. Standards: Earth and Space Science: Atmosphere IT'S ELECTRIC! (50-minute STEM Learning Lab) Partners collaborate on challenges that include building series and parallel circuits to make a light bulb glow, a motor spin, and a fan turn into a flying saucer. Standards: Physical Science: Energy, Motion
Noon	Lunch
1:00pm	**Line Dancing**
2:00pm	**Advocating** *Led by two of our teens - Advocating in government and for yourself*
3:00pm	Break
3:30pm	**Movies/Rest**
4:00pm	**Prom Prep**
6:00pm	**Prom, Dinner, Dancing and Fun**

Saturday, June 29, 2018

9:30 AM	**Meditation Yoga**
10:30 AM	Break
11:00 AM	**Dating and Relationships** (High School and Beyond) **Movies/Games** (Middle School)
12:00 PM	Lunch
1:30 PM	**Teen Informational Round Table with Mitochondrial Specialists** *Dr. Amy Goldstein from CHOP in Philadelphia will have an informal Q&A chat with our teens and young adults. Dr. Grainne Gorman and Physiotherapist Jane Newman from the United Kingdom will also join the round table discussion.*
2:30	**Games and Keeping in Touch**

Mitochondrial Medicine 2018: Nashville

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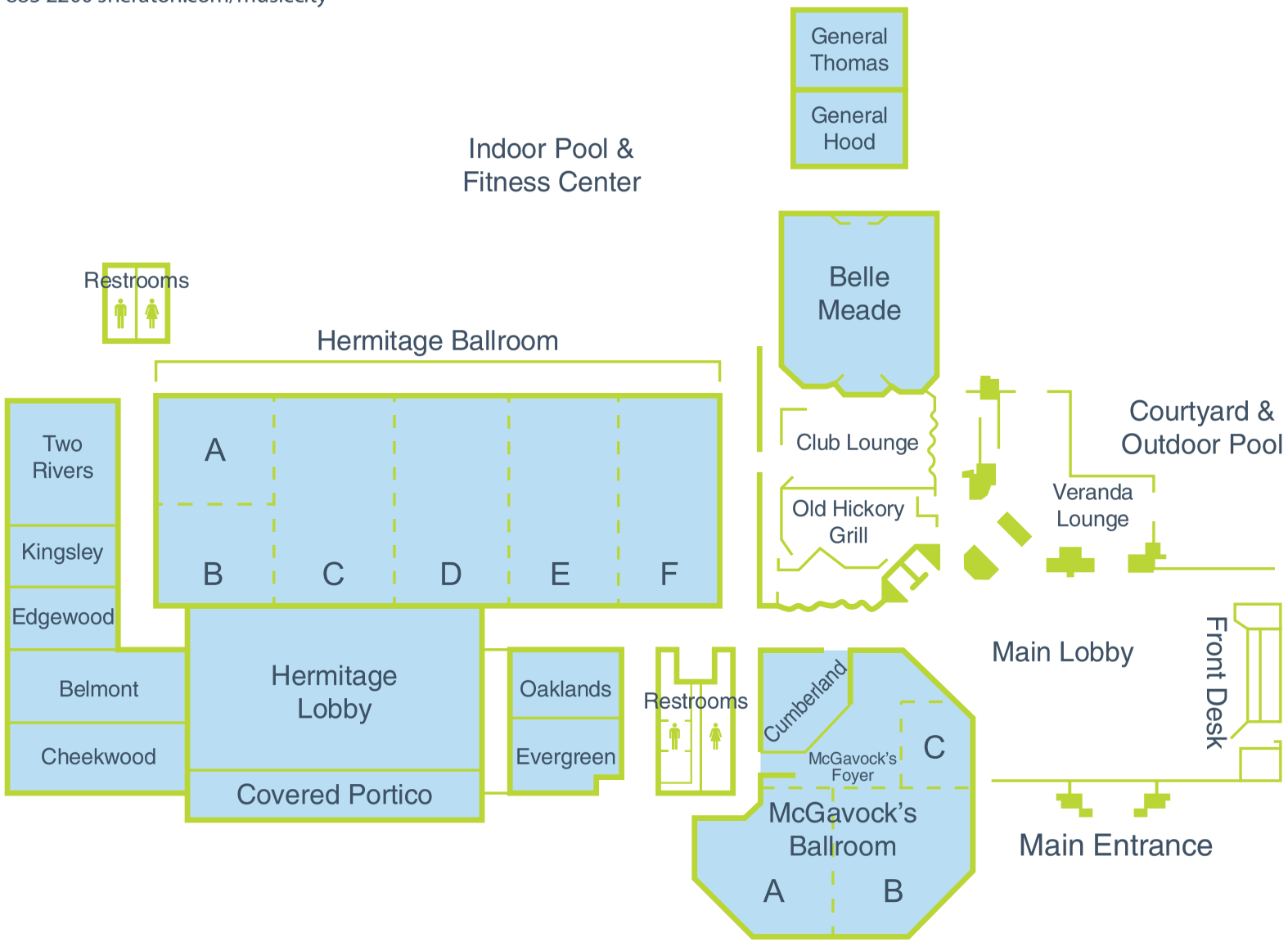

Mitochondrial Medicine 2018: Nashville

Family Program Faculty

- **Amanda Borchik, MDiv**
  Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, TN
- **Missy Bryan, OTD, OTR/L, ATP, CPST**
  Belmont University, Nashville, TN
- **Bruce H. Cohen, MD**
  Akron Children's Hospital and Medical Center, Akron, OH
- **Karen Coker, PT, DPT, CWS, WCC, C/NDT, FACCWS**
  Tennessee State University, Nashville, TN
- **Kris Engelstad, MS, CGC**
  NAMDC, Columbia University, New York, NY
- **John P. Garner, JD**
  Social Security Disability Attorney and Retired Judge, Franklin, TN
- **Donald E. Garrison, JD**
  Retired Social Security Administrative Law Judge, Franklin, TN
- **Justin Godown, MD**
  Vanderbilt University School of Medicine, Nashville, TN
- **Amy Goldstein, MD**
  Children's Hospital of Philadelphia, Philadelphia, PA
- **Cliff Gorski**
  UMDF Director of Communications, Pittsburgh, PA
- **Andrea L. Gropman, MD FAAP, FACMG**
  Children's National Medical Center, Washington, DC
- **Tracy Hills, DO**
  Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, TN
- **Jenny Hobbs**
  Co-Founder of Advocates for Medically Fragile Kids NC, Pfafftown, NC
- **Michaela Ibach, MD**
  Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, TN
- **Maria Johnson**
- **Amel Karaa, MD**
  Massachusetts General Hospital, Boston MA
- **Molly Knox**
- **Mary Kay Koenig, MD**
  UT Health/Children's Memorial Hermann Hospital, Houston, TX
- **Joy and Bryan Krumdiack**
  AACT, Bellingham, WA
- **Barbara Marriage, PhD, RD**
  Abbott Nutrition, Columbus, OH
- **Elizabeth McCormick, MS, CGC**
  Children's Hospital of Philadelphia, PA
- **Nancy J. Newman, MD**
  Emory Eye Center, Atlanta, GA
- **Sumit Parikh, MD**
  The Cleveland Clinic, Cleveland, OH
- **Lissa Poincenot**
  UMDF LHON Ambassador, San Diego, CA
- **Carol Rabideau, LCSW**
  Vanderbilt Kennedy Center, Nashville, TN
- **Tyler Reimschisel, MD MHPE**
  Vanderbilt University School of Medicine, Nashville, TN
- **Althea Robinson Shelton, MD, MPH**
  Vanderbilt University Medical Center, Nashville, TN
- **Russell Saneto, DO, PhD**
  Seattle Children's Research Institute, Seattle, WA
- **Melanie Schuele, PhD, CCC-SLP**
  Vanderbilt University Medical Center, Nashville, TN
- **Terena Scott**
  Certified Orientation and Mobility Specialists, Ukiah, CA
- **Tim Takacs, JD, Elder Law Attorney**
  Takacs McGinnis Elder Care Law, Hendersonville, TN
- **James E Valentine**
  Hyman, Phelps & McNamara, P.C., Washington, DC
- **Kendall B. Wallace, PhD**
  University of Minnesota Medical School, Duluth, MN
- **Sarah Wilkerson, CPNP**
  Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, TN
- **Philip Yeske, PhD**
  UMDF Science & Alliance Officer
- **Zarazuela Zolkipli Cunningham, MBChB, MRCP**
  Children's Hospital of Philadelphia, PA

Note: Clinical Trial Speakers and PFDD Panelists are listed on the schedule.

Mitochondrial Medicine 2018: Nashville

Special Thanks to Our Supporters!

The United Mitochondrial Disease Foundation gratefully acknowledges the following organizations for their support of Mitochondrial Medicine 2018:

Akron Children's Hospital

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Edith L. Trees Charitable Trust

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Homie's Hope

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Summit Health Pharmacy

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Mitochondrial Medicine 2018: Nashville

Exhibitors

Thank you to the following exhibitors for attending:

Agilent Technologies

Akron Children's Hospital

Baylor Genetics

ChemRx

Epic4Health/Tishcon Corp.

GeneDx

Homie's Hope

Iliad Neurosciences

Miracles For Mito

MitoAction

MNG Laboratories

NAMDC

NeuroNeeds

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Exhibitors

PALS

PerkinElmer Genomics

Permobil

Quten Research

Rare Genomics Institute

Reata Pharmaceuticals

Santhera Pharmaceuticals

Solace Nutrition

Stealth BioTherapeutics

Summit Health Pharmacy

ThriveRx

Undiagnosed Disease Network

UT Center of Excellence

Thank you also to any exhibitors who have been added since the printing of this syllabus.

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Thursday, June 28, 2018

12th Annual Adult Gathering

Hosted by the
Adult Advisory Council Team (AACT)

UNITED MITOCHONDRIAL DISEASE FOUNDATION®

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ADULT ADVISORY COUNCIL TEAM (AACT)

AACT Purpose: To represent and serve the unique needs of the affected adult community and to ensure that those needs are adequately represented to UMDF resulting in enhanced services to the affected adult population. AACT is a liaison to the UMDF Board of Trustees whom will assess and evaluate, provide advice and guidance, and make recommendations to UMDF on all adult related issues and/or needs.

For UMDF to have parity between the affected adult community and the affected pediatric community to ensure equal representation and service to the affected adult population, and to provide better service, support and assistance to adults with mitochondrial disease.

AACT Serves:

- Adults with mitochondrial disease 18 years of age and older.
- Adults suspected of having mitochondrial disease 18 years of age and older.
- Adult's support system: spouse; partner; siblings; other family members; friends.
- Affected adults with affected child(ren) and parent(s) with affected child(ren).

The Team

Joy Krumdiack, AACT Co-Chair, Washington

Gail Wehling, AACT Co-Chair, Illinois

Devin Shuman, AACT Young Adult Chair, Nevada

Kailey Danks, Toronto, Canada

Whit Davis, North Carolina

Nicole & Lillian DeJean, Louisiana

Debra Fox, Arizona

Rev. David Hamm, Maryland

Christy Koury, North Carolina

Terry Livingston, Florida

David McNees, Ohio

Linda Ramsey, New York

Sharon Reeder, Arizona

Jennifer Schwartzott, New York

Gregory Yellen, Maryland

Medical Advisors

Bruce H. Cohen, M.D., Akron Children's Hospital

Amy Goldstein, M.D., Children's Hospital of Philadelphia

Established in 2006, the purpose of AACT is to represent, serve and support the unique needs of the affected adult mitochondrial community and to ensure that those needs are adequately represented to UMDF resulting in enhanced services to the affected adult population. ACCT does not work independently but in conjunction with UMDF to provide advice, guidance and make recommendations working with and through UMDF.

The following five arenas were identified and created by AACT as our primary areas of special interest and focus. Under each arena we have listed objectives but AACT is not limiting itself as we continue to work hand-in-hand with UMDF to better understand the many facets and unique needs of the affected adult mitochondrial community and its support system.

Arena #1: Collateral & Communication
Objectives:
*To assess and recommend any changes, updates and/or revisions need to be made to UMDF collateral with respect to the word adult(s), their unique issues, their stories, and to put more adult and young adult faces in the forefront or equal to a child(ren). *Evaluate the need to develop new materials. *Raise awareness about the adult and young adult mitochondrial population through their personal stories and photos.

Arena #2: Website, Internet & Social Media
Objectives:
*Effective use of the AACT website as a means of education and communication between UMDF, AACT, and the adult and young adult mitochondrial community. *Effective use of social media. *To host special educational webinars.

Arena #3: Outreach & Education
Objectives:
*To provide adult resources to help adults and young adults navigate in the medical world. *To provide institutions and physicians that diagnose, treat and support the affected adult and young adult mitochondrial population (per request.) *Continue to educate the mitochondrial community, the public, and the medical community. *In conjunction with UMDF, oversee any-and-all adult and young adult related issues and/or needs.

Arena #4: UMDF Mitochondrial Medicine Symposium
Objectives:
*Assess and make recommendations to ensure adequate number of adult and young adult sessions. *Create networking and social opportunities for adults and young adults. *To provide and share information of special interest, resources, news and updates. *Assist UMDF at Regional Symposiums.

Arena #5: Development of New Materials & Adult Mitochondrial Community
Objectives:
*Evaluate the need to develop new materials on behalf of the adult and young adult mitochondrial community. *Continue to assist UMDF in developing a comprehensive adult and young adult database, patient registries and library. *Continue to be an advocate on behalf of the affected adult mitochondrial community.

Please visit our AACT Website & Pages on the UMDF Website at: www.umdf.org

Click On: Find Support Resources & Click On: Adult Advisory Council Team

Contact the Council at: Connect@umdf.org or 888-317-8633

May 2018

Notes

Friday, June 29

Notes

Morning Session

Welcome and Clinical Trials Session

Brent Fields, Chuck Mohan, Philip Yeske, PhD

UNITED MITOCHONDRIAL DISEASE FOUNDATION®

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Mitochondrial Disease-Focused Industry-Sponsored U.S. Clinical Trials Update June 2018

Here is a brief summary of industry-sponsored, US-based mitochondrial disease-focused clinical trials as of June 2018:

Pediatric Mitochondrial Disorders Clinical Trials

BioElectron Technology Corporation, formerly Edison Pharmaceuticals (BioE-743, formerly EPI-743)- BioE-743 is administered orally, passes into the brain, and works by regulating key enzymes involved in the synthesis and regulation of energy metabolism. A pediatric-focused Phase 2b trial of BioE-743 was completed at the end of 2014 and BioElectron continues to analyze trial data, meet with regulatory authorities worldwide and prepare for a next set of clinical trials across a number of mitochondrial disorders. https://clinicaltrials.gov/ct2/show/NCT01721733 (not actively recruiting)

Adult Mitochondrial Disorders Clinical Trials

Reata Pharmaceuticals (RTA 408, omavaloxolone)- In preclinical studies RTA 408 was shown to target inflammatory, metabolic, and mitochondrial pathways by inducing Nrf2 and suppressing NF-kB. Unlike other drugs in development for the treatment of mitochondrial disease, RTA 408 directly affects mitochondrial function and energy production in muscle cells. In 2015, Reata launched a Phase 2 clinical trial (the MOTOR study) to evaluate the efficacy, safety, and pharmacodynamics of RTA 408 in the treatment of adult patients with mitochondrial myopathy. In an analysis of top-line data, Reata reported in March 2018 that omaveloxolone failed to sufficiently separate from placebo in the MOTOR study, with patients in the treatment group not performing better than those treated with placebo during exercise testing (peak work), the primary endpoint, or in the 6-minute walk test, the secondary endpoint. No safety concerns were identified and the highest dose tested of omaveloxolone (160 mg) reduced heart rate and blood lactate levels in the submaximal exercise test, which are indicative of improved mitochondrial function. No additional trials for mitochondrial disease are planned by Reata at this time. https://clinicaltrials.gov/ct2/show/NCT02255422 (not actively recruiting)

Stealth BioTheapeutics (MTP-131, elamipretide)- MTP-131 is a small molecule peptide designed to penetrate the cellular and outer mitochondrial membrane and target cardiolipin, which is found exclusively in the inner mitochondrial membrane. MTP-131 has been shown to positively impact dysfunctional mitochondria in nonclinical studies, with no effect in healthy mitochondria. In June 2016 Stealth reported positive preliminary findings on topline data from a Phase 1/2 study to evaluate safety, tolerability and efficacy of MTP-131 to treat mitochondrial myopathy in adult patients with genetically-confirmed mitochondrial disease (MMPOWER study). A follow-on Phase 2 trial (MMPOWER-2) focused on subcutaneous efficacy launched returned positive data in 2017. In anticipation of a Phase 3 trial in 2018, Stealth has launched a 1-year observational study (RePOWER) from which Phase 3 participants will be recruited. That Phase 3 trial (MMPOWER-3) is now underway at multiple clinical sites with a goal of enrolling over 200 participants. Top-line data from MMPOWER-3 are anticipated in Q1 2019. https://clinicaltrials.gov/ct2/show/NCT03323749 (enrolling by invitation)

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Mitochondrial Disease-Focused Industry-Sponsored U.S. Clinical Trials Update

June 2018

Ophthalmic Mitochondrial Disorders Clinical Trials

Santhera Pharmaceuticals (Raxone®, Idebenone)- Raxone is an approved drug in Europe for the treatment of Leber's Hereditary Optic Neuropathy (LHON). While Raxone is not approved for treatment in the US, Santhera is conducting a Phase IV study (LEROS) as an open-label interventional study of the use of idebenone for patients with LHON up to 5 years after clinical onset. https://clinicaltrials.gov/ct2/show/NCT02774005 (actively recruiting)

GenSight Biologics (GS010)- GS010 is an investigational gene therapy being evaluated in multiple clinical trials for the treatment of Leber's Hereditary Optic Neuropathy (LHON). In the REVERSE Phase 3 clinical trial, GS010 was evaluated the safety and efficacy of a single intravitreal injection of GS010 (rAAV2/2-ND4) in 37 subjects whose visual loss due to the 11778-ND4 mutation commenced between 6 and 12 months prior to study treatment. The primary endpoint was the ETDRS visual acuity (quantitative score) at Week 48 after intravitreal injection. GenSight reported in April 2018 a clinically meaningful improvement of +11 ETDRS letters in both eyes- an unexpected improvement in the untreated eye suggests a bilateral treatment effect that needs to be further investigated. GS010 is currently being investigated in two additional ongoing Phase 3 trials, RESCUE and REFLECT, while patients in REVERSE continue to be followed for another 4 years. RESCUE is a randomized, double-masked, sham-controlled Phase III trial designed to evaluate the safety and efficacy of a single intravitreal injection of GS010 in subjects affected by LHON with < 6 months of onset of vision loss. GenSight expects to report topline data for RESCUE in the third quarter of 2018. REFLECT is a randomized, double-masked, placebo-controlled Phase III trial evaluating the safety and efficacy of bilateral injections of GS010 in patients with < 1 year of onset of vision loss in LHON. The first patient in REFLECT was treated in March 2018.

REVERSE: https://clinicaltrials.gov/ct2/show/NCT02652767 (not actively recruiting)
REFLECT: https://clinicaltrials.gov/ct2/show/NCT03293524 (actively recruiting)
RESCUE: https://clinicaltrials.gov/ct2/show/NCT02652767 (not actively recruiting)

Stealth BioTheapeutics (MTP-131, elamipretide)-Stealth launched in June 2016 a Phase 2 trial focused on front-of-the-eye delivery of MTP-131 for Leber's Hereditary Optic Neuropathy (LHON), with topline data expected in late 2018. https://clinicaltrials.gov/ct2/show/NCT02693119 (not actively recruiting)

Among the most important things that patients and family members can do to contribute to the development of treatments and cures is to sign up for the Mitochondrial Disease Community Registry (MDCR), a central repository for patient-derived data that provides registrants with full control of who can see and analyze their de-identified data as well as who can make contact with them about relevant research studies.

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Notes

Morning Session

History of Clinical Trials in Mitochondrial Disease

Bruce H. Cohen, MD

Notes

Morning Session

Clinical Trial Updates Session 1: Small Molecule Approaches

Bruce Cohen, MD

- Mitochondria Disease Program Update - *Reenie McCarthy, Chief Executive Officer, Stealth BioTherapeutics*

- Safety, Efficacy, and Pharmacodynamics of Omaveloxolone in Mitochondrial Myopathy Patients (MOTOR Trial-Reata): Part 1 Results - *Karen Lindhardt Madsen, PhD, University of Copenhagen*

- The KHENERGY study: an exploratory, double-blind, randomized, placebo-controlled, two-way cross-over phase II trial in m.3243A>G patients - *Jan Smeitink, CEO Khondrion*

Notes

Clinical Trial Updates Session 2: Vision Disorders

Moderators: Lissa Poincenot and Nancy Newman, MD

- Overview of Mitochondrial Vision Disorders - *Nancy Newman, MD*
- GenSight: What we have Done, What we are Doing - *Barrett Katz, MD*
- Santhera's Real World Experience with Idebenone in LHON. Update on Programs - *Xavier Lloria, Medical Affairs Director, Santhera Pharmaceuticals*
- Stealth Development Update - *Jim Carr, PharmD, Chief Clinical Development Officer, Stealth BioTherapeutics*
- Vision Disorder Panel Q&A

Notes

Morning Session

Pre-Clinical Data Updates

Philip Yeske, PhD

- L1333 - Mitochondrial disease treatment opportunity by NAD+ modulation and mitochondrial biogenesis - *Magnus Hansson, PhD, NeruoVive*

Notes

Morning Session

Planning an Externally-led Patient-Focused Drug Development Meeting

- EL-PFDD Meeting Background - *James Valentine*
- EL-PFDD Mitochondrial Disease Plan - *Philip Yeske, PhD*
- EL-PFDD Meeting Timeline and Q&A

Notes

Morning Session

What is Mitochondrial Disease and What to Expect (Mito Basics)

Tyler Reimschisel, MD

Mitochondrial Disease: What is it and What to Expect

UMDF Mitochondrial Medicine 2018
Nashville, TN
June 29, 2018

Tyler Reimschisel, MD, MHPE
Vice Chair for Education, Department of Pediatrics
Associate Professor of Pediatrics & Neurology
Director, Division of Developmental Medicine
and the Center for Child Development
Director, Vanderbilt Consortium LEND

Disclosure

Tyler Reimschisel, MD, MHPE receives research support from Shire Pharmaceutical. The content of this presentation does not relate to the research supported by Shire Pharmaceutical.

Learning Objectives

At the completion of this presentation, attendees should be able to:

1. Compare and contrast mitochondrial disease with mitochondrial inheritance.
2. Discuss the genetics of mitochondrial diseases, including features unique to mtDNA (polyplasmy, heteroplasmy, & threshold effect).
3. Discuss the typical clinical features and laboratory manifestations of mitochondrial diseases.

Case

- 17-year-old girl with new onset seizures
- After the seizure, she is asleep
- So cannot obtain history
- Initial labs
  - Glucose: normal
  - White blood cell count (infection): normal
  - Acidotic

Case: Additional History

- Past medical history: hearing loss
- Family history:
  - Mother deceased from strokes & epilepsy
  - Maternal grandmother deceased from strokes
  - Multiple family members with hearing loss

Case: Additional Labs

- Lactate = 9.7 (0.5-2.2); repeat =7.3
- Liver enzymes (AST & ALT): normal
- CK: normal
- Plasma amino acids: elevated alanine
- Urine organic acids
  - Lactate > 1000 (<101)
  - Pyruvate > 500 (<31)
- mtDNA mutation analysis: A3243G mutation
- Diagnosed with MELAS and placed on mitochondrial cocktail (including arginine)

Case: Follow Up

- 8 months later: right-sided stroke
- 13 months later: left-sided stroke
- Seizures treated with Keppra
- Recurrent strokes with accumulating physical impairment

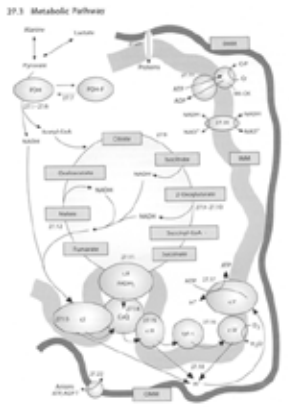
Definition of "Mitochondrial Cytopathy"

Although multiple biochemical reactions in a variety of metabolic pathways occur within the mitochondria, the term "mitochondrial cytopathy" refers to diseases that are caused by primary or secondary dysfunction of the respiratory chain

Human Cell

From https://gcps.desire2learn.com

Respiratory Chain



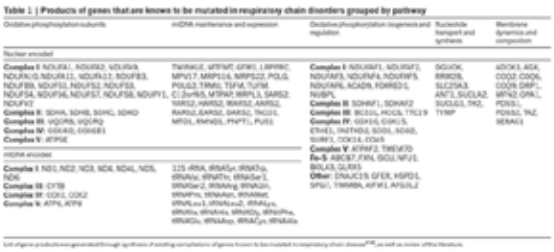
From Blau, *Physician´s Guide to the Laboratory Diagnosis of Metabolic Diseases*, 2003

Respiratory Chain Complexes

Complex I	Complex II	Complex III	Complex IV	Complex V
NADH dehydrogenase - ubiquinone oxidoreductase	Succinate dehydrogenase - ubiquinone oxidoreductase	Ubiquinone - cytochrome C oxidoreductase	Cytochrome C oxidase	ATP synthase
45 subunits • 7 mtDNA encoded	4 subunits • 0 mtDNA encoded	10 subunits • 1 mtDNA encoded	19 subunits • 3 mtDNA encoded	19 subunits • 2 mtDNA encoded

- 2 electron carriers (coenzyme Q10 and cytochrome C)
- 60 additional nucleus-encoded enzymes for assembly and function of subunits
- Estimated to include about 1000 genes total

Genes Mutated in Mitochondrial Cytopathies



Vafai and Mootha. Nature (491) 2012.

Mitochondrial DNA

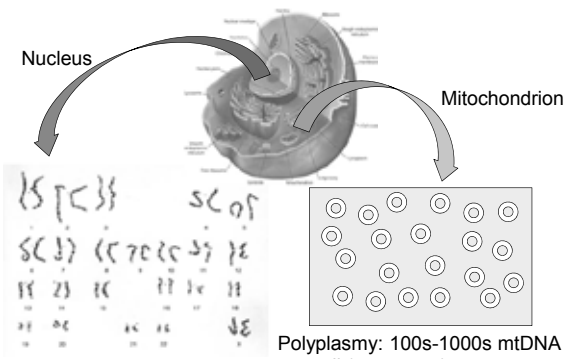
- 16,569 base pairs
- 37 genes
  - 24 genes for translation
    - 2 rRNAs
    - 22 tRNAs
  - 13 encode subunits of respiratory chain

Figure 3. Mutations in the Human Mitochondrial Genome That Are Known to Cause Disease.

From DiMauro et al. *Seminars in Neurology* 2003;21(3):254.

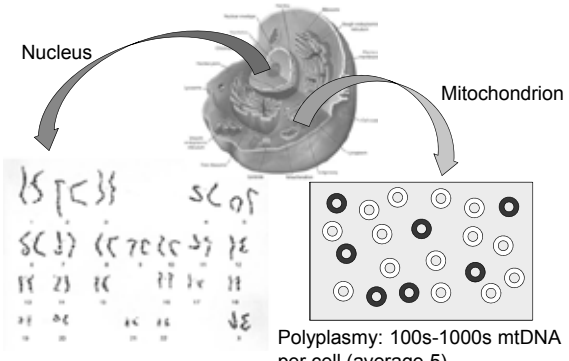
Mitochondrial DNA

- Maternal inheritance
  - Mitotic segregation is random
  - All offspring of mother will inherit abnormal mitochondria if in germline
    - Variable dose of abnormal mtDNA
  - No offspring of affected males will inherit abnormal mitochondria
    - Case report of paternal inheritance (Schwartz et al. NEJM 2002;347:576)



23 pairs of chromosomes

Polyplasmy: 100s-1000s mtDNA per cell (average 5)



23 pairs of chromosomes
Up to two alleles per gene

Polyplasmy: 100s-1000s mtDNA per cell (average 5)
Heteroplasmy: cell with mixed normal and mutated genomes

Threshold Effect

- Minimum number of mutated mtDNA that must be present to cause OXPHOS dysfunction
- Abnormal phenotype develops when threshold is exceeded (most common with skewed heteroplasmy)
- Threshold is lower in tissues with higher oxidative requirements (brain, muscle, retina, heart, kidney, endocrine glands)

mtDNA Genetics and Clinical Variability

- Determinants of clinical variability
  - Type of mutation
  - Percentage of mutated mtDNA
  - Varying heteroplasmy in different tissues
  - Variable threshold in different tissues
  - Mutations can accumulate over time
- Ubiquitous mutations can have tissue-specific manifestations
  - Deafness from 12S rRNA mutation
  - Cardiomyopthy due to $tRNA^{Ile}$ mutations
  - Optic atrophy due to NADH dehydrogenase (complex I) mtDNA mutations

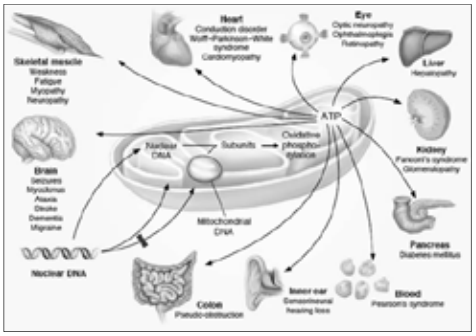
Inheritance of Mitochondrial Cytopathies

- mtDNA mutations
  - Sporadic (esp. large scale deletions)
  - Maternal inheritance
- Nuclear DNA mutations
  - Autosomal dominant
  - Autosomal recessive
  - X-linked (*DDP1* mutation → deafness-dystonia syndrome)

Progressive External Ophthalmoplegia

- Large deletion in mtDNA
  - Sporadic
  - Weakness, exercise intolerance, ophthalmoplegia, ptosis
  - Lactic acidosis, ragged red fibers
- Autosomal dominant forms
  - Various mutations
    - *Twinkle* (mitochondrial DNA helicase)
    - *ANT1* (adenine nucleotide translocator)
    - *POLG1*
  - Proximal limb weakness, peripheral neuropathy, hearing loss, cataracts, depression, endocrine dysfunction
- Autosomal recessive form
  - Cardiomyopathy and ophthalmoplegia
  - Mutations of tyrosine phosphorylase - PEO + MNGIE

Clinical Presentations of Mitochondrial Disease



Johns DR. N Engl J Med 1995;333:638-44

Common Clinical Manifestations

- Brain
  - Seizures
  - Myoclonus
  - Ataxia
  - Stroke
  - Intellectual disability
  - Dementia
  - Migraines
- Neuromuscular
  - Neuropathy
  - Weakness
  - Fatigue
  - Myopathy
- Cardiac
  - Cardiomyopathy
  - Conduction block
  - Dysrhythmias/WPW
- Ears
  - Sensorineural hearing loss
- Eyes
  - Optic atrophy
  - Ophthalmoplegia
  - Pigmentary retinopathy
  - Cataracts
  - Ptosis
- Blood
  - Anemia
- Gastrointestinal
  - Dysmotility
  - Pancreatitis
- Liver
  - Hepatopathy
- Kidney
  - Fanconi syndrome
  - Glomerulopathy
- Endocrine
  - Short stature
  - Diabetes mellitus
  - Hypoparathyroidism
  - Hypothalamic hypogonadism
  - Adrenal insufficiency

Laboratory Manifestations of Mitochondrial Cytopathies

- Screening with basic labs (complete blood count, comprehensive metabolic panel, CK level, lactate, pyruvate, uric acid
- Biochemical labs: plasma amino acids, urine organic acids, acylcarnitine profile
- Neurodiagnostic studies: brain MRI with spectroscopy, EEG, EMG/nerve conduction, rarely muscle biopsy

Possible Laboratory Manifestations

- Complete blood count (CBC)
  - White blood cells, red blood cells, platelets
  - Low individual cell lines
  - All cell lines decreased (pancytopenia)
- Comprehensive metabolic panel (CMP)
  - Acidosis
  - Elevated BUN and creatinine (kidney disease)
  - Elevated liver enzymes
  - Low calcium
- Increased CK

Possible Laboratory Manifestations

- May have elevated lactate (plasma, cerebrospinal fluid)
  - May have chronic elevation
  - May only be elevated pre- and/or post-prandial
- May have elevated alanine
- May have elevated pyruvate
- May have sbnormalities on urine organic acids
- May have low carnitine

Possible Laboratory Manifestations

- Aminoaciduria (Fanconi syndrome)
- UOA: Krebs cycle intermediates, dicarboxylic acids, tiglyglycine, ethylmalonate, 3-methylglutaconate, 2-methylsuccinate, butyrylglycine, isovaleryl glycine
- Carnitine can be low

Laboratory Manifestations

- Electroencephalogram (EEG)
  - No specific abnormalities
  - May show propensity to seizures
  - Rarely see electrographic seizure
- Electromyography (EMG)
  - May show muscle disease (myopathy)
- Nerve conduction study
  - May show nerve disease (neuropathy)

Brain MRI: Leigh Syndrome

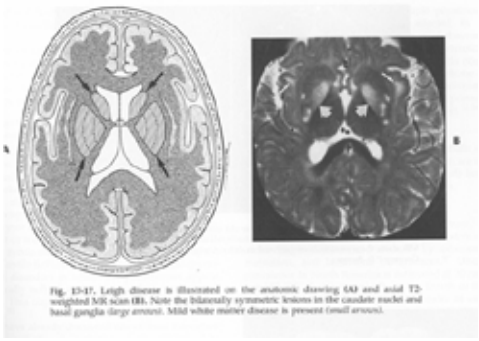


Fig. 17-17. Leigh disease is illustrated on the anatomic drawing (A) and axial T2-weighted MR scan (B). Note the bilaterally symmetric lesions in the caudate nuclei and basal ganglia (*large arrows*). Mild white matter disease is present (*small arrows*).

From Osborn. *Neuroradiology*, 2000

Brain MRI

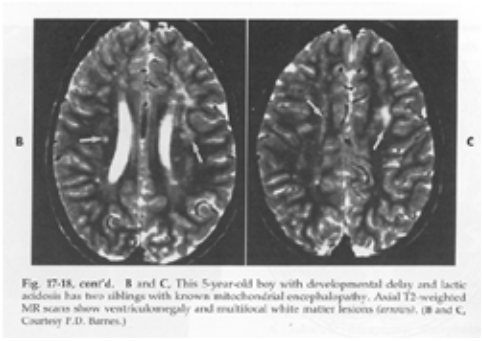


Fig. 17-18, cont'd. B and C, This 5-year-old boy with developmental delay and lactic acidosis has two siblings with known mitochondrial encephalopathy. Axial T2-weighted MR scans show ventriculomegaly and multifocal white matter lesions (*arrows*). (B and C, Courtesy F.D. Barnes.)

From Osborn. *Neuroradiology*, 2000

Muscle Biopsy*

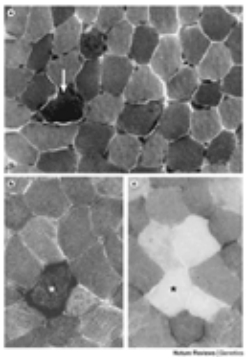


Figure 4 | **Muscle phenotypes of OXPHOS disorders.** **a** | Ragged-red fibres (RRFs) revealed by the modified Gomori trichrome stain. Abnormal deposits of mitochondria appear as reddish blotches in the subsarcolemmal or intermyofibrillar space (arrow). **b**, **c** | Serial sections of a muscle biopsy from a patient with a mitochondrial DNA (mtDNA) single deletion. In **b**, the RRF (white asterisk) is highlighted by the histochemical stain for succinate dehydrogenase, an enzyme entirely encoded by nuclear DNA. In **c**, the same fibre shows no activity for cytochrome *c* oxidase, an enzyme containing ten subunits encoded by nuclear DNA and three encoded by mtDNA (see text). (Courtesy of Eduardo Bonilla, Columbia University.)

(From Smeitink et al. Nature Reviews: Genetics 2001;2:342)

Cardiac Manifestations

- Electrocardiogram (ECG or EKG)
  - Conduction abnormalities
- Echocardiogram
  - Cardiomyopathy

United Mitochondrial Disease Foundation

Mitochondrial Disease Community Registry

www.umdf.org/registry

Who?
Patients, caregivers & family members
Confirmed diagnosis ***NOT*** required

Why?
Need patient data collected over time in order to improve diagnoses and develop treatments

Key
Registrants have full control of privacy settings

- Allow, deny or “ask me”
- Who can see anonymous data
- Who can analyze anonymous data
- Who can contact you about research studies and clinical trials

Notes

Morning Session

Nutrition for Mitochondrial Disease Patients

Barbara Marriage, PHD, RD

Nutritional Interventions in Mitochondrial Disorders

Mitochondrial Medicine 2018
Nashville
Barbara Marriage PhD RD
Abbott Nutrition

Objectives

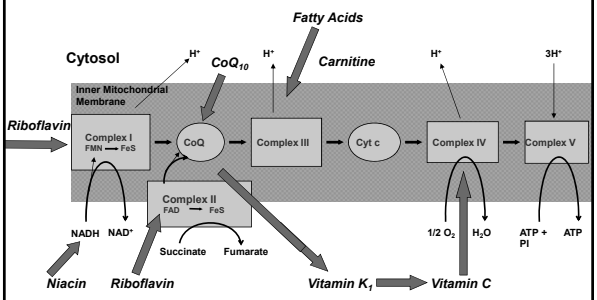
- Rationale for the use of nutritional cofactors and vitamin therapy
- Evidence (or lack thereof) of clinical efficacy
- Practices/consensus on clinical use
- General guidelines – fasting, exercise, hydration
- Use of the ketogenic diet
- Future?

Why are they so difficult to diagnose and treat?

- Any disease manifestation
- Any degree of severity
- Any age of onset
- Any mode of inheritance
- Any organ or tissue

Munnich 1996

Cofactor Treatment



Rationale for Cofactor and Vitamin Therapy

- Cofactor role in respiratory chain
- Bypass blocked component of the respiratory chain
- Stimulate enzyme activity (Vitamin B1 or B2)
- Antioxidant activity (Vitamin C, E Lipoic Acid
- Alternate energy source
- Scavenger for free fatty acids and organic acids
- Improve muscle bulk (creatine)

Shotgun Approach

Mitochondrial Cocktail

- Riboflavin
- Thiamine
- Niacin
- Folinic acid
- Vit C and Vit K
- Lipoic Acid
- Creatine
- Carnitine
- L-arginine
- CoQ_{10}

Role of Vitamins

Riboflavin

- Riboflavin is involved in the energy production for the electron transport chain
- By-pass Complex 1 defect - building block in Complex I and II
- Bernsen et al (1993)[1]
  - 5 patients with complex 1 deficiency
  - 2 pure myopathy, 3 encephalomyopathic
  - Clinical improvement in myopathic form
  - Normalized complex 1 activity in muscle –no correlation with clinical symptoms

[1]*Bernsen P et al Treatment of complex 1 deficiency with riboflavin J Neurol Sci 1993 118: 181-187*

Role of Vitamins

Riboflavin

- Scholte (1995)[1]
  - 3 subjects - Higher endurance power in exercise testing
  - Increase in Complex 1 activity from 16 to 47% in 1 patient 2 years later
- Ogle et al (1997)[2]
  - Complex 1 deficiency
  - Case report of clinical improvement during 3 years of therapy
- Dosage 50 to 400 mg/day

[1]*Scholte et al Riboflavin responsive complex-1 deficiency Biochim et Biophys Acta 1995 1271:75-83*

[2]*Ogle et al Mitochondrial myopathy with tRNA (Leu(UUR) mutation and complex 1 deficiency responsive to riboflavin J Pediatr 1997 130: 138-145*

Role of Vitamins

Thiamine

- Conversion of pyruvate to acetyl CoA in metabolism
- Enhance pyruvate entry into mitochondria

Niacin

- Co-enzyme forms of niacin NAD and NADP
- Role in energy transfer reactions

Used in combination with other cofactors

Role of Vitamins

Folinic Acid (Leucovorin or Deplin)

- **Reduced form of folic acid (5-methyl - tetrahydrofolate)**
- **Natural transport form of folate that crosses the blood-brain barrier**
- **Case reports suggesting mitochondrial disease my lead to secondary cerebral folate deficiency [1,2]**
- **Reason – inadequate ATP for active folate transport**
- **CSF folate deficient patients – 5 to 25 mg tid**

[1]Ramaekers et al. Mitochondrial complex 1 encephalomypathy and cerebral 5- methyltetrahydrofolate deficiency. Neuropediatrics 2007 38: 184-187

[2]Garcia-Cazorla et al. Secondary abnormalities of neurotransmitters in infants with neurological disorders. Dev Med Child Neurol 2007 49: 740- 744

Role of Vitamins

Vit C and Vit K

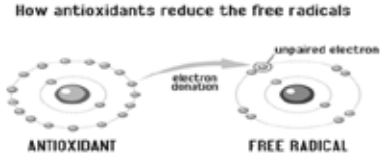
- **Role of Vit C as an antioxidant**
- **Case report of complex III deficiency - Vit K_3 (40 mg daily) and vitamin C (4 g daily) improved the clinical picture (measured by 31P NMR)[1]**
- **Improvement was not sustained and other patients with complex III deficiency myopathy failed to respond[2]**
- **Vit K3 (menadione) –hyperbilirubinemia and hemolytic anemia**

[1]Eleff et al 31NMR study of improvement in oxidative phosphorylation by Vit K3 and C in a patient with a defect on Complex III in skeletal muscle. Proc Natl Acad Sci 1984 81:3529-3533

[2]Andreu et al. Exercise intolerance due to mutations in the cytochrome b gene of mitochondrial DNA N Engl J Med. 1999 341 1037–1044

Role of Antioxidants

- **Mitochondrial dysfunction leads to oxidative stress**
- **Alpha lipoic acid, Vit C and Vit E have been used individually or as part of a mitochondrial cocktail**
- **Case reports have described some benefit –but in combination with other therapies such as CoQ_{10}, riboflavin, creatine etc.**



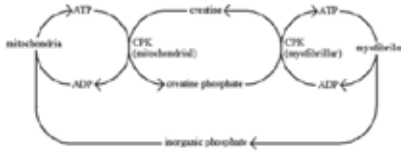
Creatine

- Combines with phosphate to form PCr
- PCr is a source of high energy phosphate
- Reduction of PCr has been found in skeletal muscle of mitochondrial patients
- Randomized controlled trial in adult patients showed benefits[1]
  - 5g bid for 2 weeks followed by 2g bid for 1 week
  - Increase in high-intensity isometric anaerobic and aerobic power

[1]*Tarnopolsky M et al A randomized, controlled trial of creatine monohydrate in patients with mitochondrial cytopathies Muscle Nerve 1997 20:1502-1509*

Creatine

- Positive results have been reported in 4 studies
- No benefit has been reported in 2 studies
- Dosage **Adult 10 g/day divided in 2 doses**
  Children 0.1 g/kg /day divided in 2 doses



Carnitine

- Carrier across the mitochondrial membrane
- Case reports in combination with other supplements have shown possible benefits in some mitochondrial patients[1-3]

[1]*Zaffanello M , Zamboni G Therapeutic approach in a case of Pearson's syndrome Minera Pediatr 2005 57: 143-146*

[2] *Mermigkis C et al Medical treatment with thiamine, coenzyme Q, vitamin E and C and carnitine improved obstructive sleep apnea in an adult case of Leigh disease Sleep Breath 2013 17:1129-1135*

[3]*Artuc R et al Biochemical monitoring of the treatment in paediatric patients with mitochondrial disease JIMD 1998 21:837-845*

L-arginine

- Initial study showing IV L-arginine (500 mg/kg/dose) decreased severity of stroke-like symptoms in patients with MELAS[1]
- Decrease in clinical severity and frequency of stroke-like episodes with oral L-arginine (150-300 mg/kg/day)[2]

Koga et al Effects of L-arginine on the acute phase of strokes in 3 patients with MELAS Neurology 2002 58: 827-828

Koga et al L-arginine improves the symptoms of strokelike episodes in MELAS Neurology 2005 64: 710-712

Coenzyme Q_{10}

- Electron carrier in the electron transport chain
- Potent reactive oxygen species (ROS) scavenger
- Most popular in treatment of mitochondrial disorders
- Well documented safety, even at dosages of 2 g/day
- Frequently used in combination with other cofactors
- Commercially available in the form of ubiquinol – increased absorption compared with the oxidized form

Coenzyme Q_{10} Clinical Evidence

- 12 patients - 1 year mitochondrial cocktail
  - CoQ_{10} 5mg/kg, B Vitamins, Vit C and K plus carnitine
- Significant increase in ATP synthetic capacity in lymphocytes
- Improvement clinically?
- Exposure of control lymphocytes in vitro to individual components of the cocktail showed only CoQ_{10} increased ATP synthesis

Marriage B et al Cofactor treatment improves ATP synthetic capacity in patients with oxidative phosphorylation disorders Mol Genet Metab 2004 81:263-272

Coenzyme Q_{10} Clinical Evidence

- 16 patients CoQ_{10} Vit K, Vit C riboflavin, thiamine and niacin
  - 1 to 4 periods of treatment (2 months each)
  - Large increase in serum CoQ_{10} concentrations
  - Independent measurements of oxidative metabolism to assess efficacy
  - No objective clinical improvement

Matthew et al Coenzyme Q10 with multiple vitamins is generally ineffective in the treatment of mitochondrial disease 1993 43: 884

Coenzyme Q_{10} Clinical Evidence

- 16 patients CoQ_{10} (120 mg/day), creatine (3 g/day) and lipoic acid (300 mg/day)
  - Randomized placebo controlled crossover study
  - Lower resting lactate and biomarkers of oxidative stress
  - Decline in peak ankle dorsiflexion strength

Rodriguez et al Beneficial effects of creatine, Coenzyne Q10 and lipoic acid in mitochondrial disorders Muscle Nerve 2007 35:235-242

Coenzyme Q_{10} Clinical Evidence

- Literature is not conclusive in regards to efficacy
- Effective in CoQ_{10} deficiencies
- Some formulations poorly absorbed
- Small sample size
- Variability in outcome variables and clinical features
- Evidence of CoQ_{10} therapy reviewed in 2007[1] and 2014[2]

[1] *Haas RH The evidence basis for coenzyme q therapy in oxidative respiratory disease Mitochondrion 2007 S137-S145*

[2] *Garrido –Maraver J et al Coenzyme Q10 Therapy Mol Syndromolgy 2014 :187-197*

Coenzyme Q_{10}

- Reports of benefit of CoQ_{10}
- Placebo-controlled double blind trial still missing
- First randomized controlled trial ongoing[1]
  - 6 months
  - CoQ_{10} 10 mg/kg/day Max 400 mg/day
  - Multivitamin and mineral supplement (Centrum Kids Complete)

[1]Stacpoole P et al Design and implementation of the first randomized controlled trial of coenzyme Q10 in children with primary mitochondrial disease Mitochondrion 2012 12: 623-629

Dichloroacetate (DCA)

- Potent lactate lowering drug
- Open label study - 7 years demonstrated a variable response *(Barshop 2004)*
- Randomized double-blind placebo controlled crossover study in MELAS patients terminated due to DCA toxicity –peripheral neuropathy *(Kaufmann 2006)*
- Orphan drug status –compassionate use
- 10 to 50 mg/kg bid

What is the evidence?

Neurotherapeutics. Apr 2013; 10(2): 307–319.

Review of Clinical Trials for Mitochondrial Disorders: 1997–2012

Douglas S. Kerr[a]

It should be clear from the series of clinical trials summarized here that anecdotal case reports or common medical practice of specific therapies for mitochondrial disorders are insufficient for evidence-based medicine. When subjected to controlled trials, formerly advocated therapies have not usually been proven to be effective and/or may have unacceptable side effects. This is borne out particularly by experience with DCA, creatine, and CoQ10.

What is the evidence?

Treatment for mitochondrial disorders

Gerald Pfeffer[1,2], Kari Majamaa[3], Douglass M Turnbull[4], David Thorburn[5], Patrick F Chinnery[1]

[1]Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, UK. [2]Clinician Investigator Program, University of British Columbia, Vancouver, Canada. [3]Institute of Clinical Medicine, Department of Neurology, University of Oulu, Oulu, Finland. [4]Mitochondrial Research Group, The Medical School, Newcastle University, Newcastle Upon Tyne, UK. [5]Murdoch Children's Research Institute, Royal Children's Hospital, Victoria, Australia

Authors' conclusions

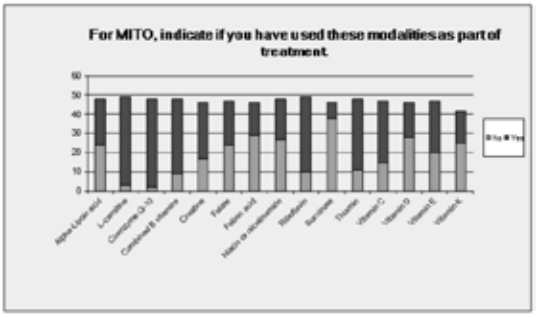
Despite identifying eight new trials there is currently no clear evidence supporting the use of any intervention in mitochondrial disorders. Further research is needed to establish the role of a wide range of therapeutic approaches. We suggest further research should identify novel agents to be tested in homogeneous study populations with clinically relevant primary endpoints.

Citation: Pfeffer G, Majamaa K, Turnbull DM, Thorburn D, Chinnery PF. Treatment for mitochondrial disorders. *Cochrane Database of Systematic Reviews* 2012, Issue 4. Art. No.: CD004426. DOI: 10.1002/14651858.CD004426.pub3.

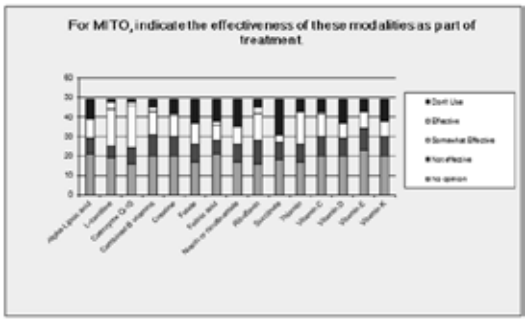
Survey of Metabolic Specialists

- Conducted in October 2012
- Invitations sent to members of SIMD and GMDI and posted on Metab-L and PNO listservs
- 152 began the survey; 78 completed
- Asked about the use and effectiveness of a number of dietary supplement and nutritional interventions used for IEM
  - Primary and secondary NBS panel
  - Others (e.g., mitochondrial disorders)

Survey Results of SIMD and GMDI members



Effectiveness of cofactors and vitamins



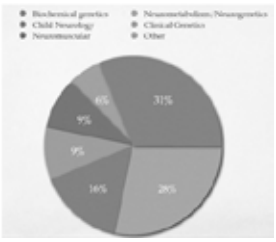
Practice patterns of Metabolic Physicians

Practice patterns of mitochondrial disease physicians in North America. Part 2: treatment, care and management

Sumit Parikh [a,b], Amy Goldstein [1], Mary Kay Koenig [c], Fernando Scaglia [d], Gregory M. Enns [e], Russell Saneto [f], for the Mitochondrial Medicine Society Clinical Directors Working Group, Other members of the MMS, Clinical Director's Work Group Irina Anselm [1], Abigail Collins [2], Bruce H. Cohen [3], Suzanne D. DeBrosse [4], David Dimmock [5], Mami J. Falk [6], Jaya Ganesh [7], Carol Greene [8], Andrea L. Gropman [9,10], Richard Haas [11], Stephen G. Kahler [12], John Kamholz [13], Fran Kendall [14], Mark S. Korson [15], Andre Mattman [16], Margherita Milone [17], Dmitriy Niyazov [18], Phillip L. Pearl [19], Tyler Reimschisel [20], Ramona Salvarinova-Zivkovic [21], Katherine Sims [22], Mark Tarnopolsky [23], Chang-Yong Tsao [24], Johan van Hove [25], Laurence Walsh [26,27], Lynne A. Wolfe [28]

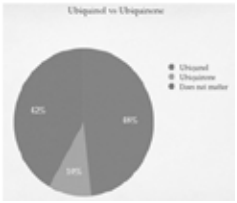
Survey Results

- 32 completed all surveys
- Similarities in practice but lack of consensus
- Items used most
  - CoQ_{10} 100%
  - L-arginine for strokes 100%
  - L-carnitine 94%
  - Creatine 75%



Survey Results

- 50% started on a cocktail, 50% individual supplement
- 60% unique combination
  - >9 9%
  - 6-9 19%
  - 3-6 63%
  - <3 9%
- 9% CoQ_{10} alone



Consensus Criteria Working Group

- Intravenous IV L-arginine should be administered in acute setting of stroke in MELAS
- CoQ_{10} should be offered to most patients with mitochondrial disease
  - Reduced CoQ_{10} is most bioavailable form
  - Plasma or leukocyte CoQ_{10} levels are helpful in monitoring absorption and adherence to treatment

Sumit Parikh, Irina Anselm, Bruce Cohen, Salvatore DiMauro, Marni Falk, Carol Greene, Andrea Gropman, Richard Haas, Michio Hirano, Phil Morgan, Mark Tarnopolsky, Kathie Simms, Johan Van Hove, Lynne Wolfe

Consensus Criteria Working Group

- Lipoic acid and riboflavin should be offered
- Folinic acid should be considered with CNS manifestation and routinely administered to those with documented CSF deficiency
- L-carnitine should be administered when there is a deficiency
- When beginning supplement therapy, begin one at a time if possible
- ….need for evidence-based guidelines

Parikh S et al Diagnosis and Management of mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society Genetics in Medicine 2014 (online publication)

What about a High Carbohydrate Diet ?

- Support
  - Glycolytic Rate is increased in mitochondrial disease
  - Dextrose IV fluids may present catabolism in metabolic crisis
  - Low glycemic carbohydrates may improve health outcomes

What about a High Carbohydrate Diet ?

- Concerns
  - Glucose infusions may precipitate metabolic crisis
  - Glucose dysregulation common in mitochondrial disease
    - Diabetes mellitus (MELAS)
    - Hypogylcemia in some patients (more common in children)

Ketogenic Diet in Mitochondrial Disorders

- How does it work?
  - Increased production of antioxidants
  - Activation of ATP sensitive potassium channels by mitochondrial metabolism
  - Inhibition of mammalian target of rapamycin pathway
  - Inhibition of glutamatergic excitatory synaptic transmission

Danial et al How does the Ketogenic Diet work? Four Potential Mechanisms J Child Neur 2013 28: 1027-1033

Ketogenic Diet in Mitochondrial Disorders

Epilepsy in Mitochondrial Disorders

- **Prevalence not known**
- **Seizures reported to occur in 35 to 60% of biochemically confirmed mitochondrial disease** *(Debray 2007; Khurana 2008)*
- **33% of patients with refractory seizures had mitochondrial dysfunction** *(Parikh 2008)*

Use of Ketogenic Diet

- **Kang (2007) reported safe and effective use in MRC defects**
  - **14 patients - 9 pts CI, 1 CII, 3 CIV, 1 CI & IV**
  - **10/14 seizure-free or > 50% reduction**
  - **4/14 no benefit**
- **Lee (2008) reported positive response in 18/24 pts**
  - **48 patients – 35 CI, 1 CII, 11 CIV, 1 CI & IV**
  - **24 with intractable seizure**
  - **12/18 seizure free; 6/18 > 50-90%**

Use of Ketogenic Diet

Case reports

- **MELAS-seizure free w KD + suppls** *(Steriade 2014)*
- **POLG-related epilepsy - successful use of LGI diet** *(Martikainen 2012)*
- **Ohtahara Syndrome and MRC complex I - seizure free until KD d/c'd** *(Seo 2010)*
- **Landau-Kleffner w MRC complex I—"dramatic improvement"** *(Kang 2006)*

Ketogenic Diet is Controversial

- Conflicting reports in animal models
- May not be tolerated in mitochondrial patients
- Mito patients may have elevated triglycerides
- Mito patients may have decreased fatty acid oxidation

What should the Macronutrient Profile Be?

- No scientific data to support specific ratios of carbohydrate, protein and fat
- Assess for relative under-nutrition
  - Consider intake, expenditure and absorption
  - If needed –gastrostomy tube or parental nutrition
  - Treat swallowing disorders, altered gut motility, behavioral feeding issues and GI reflux

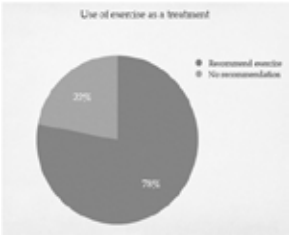
Nutritional Guidance

- Monitor for essential micronutrient deficiency
  - Multiviatmin supplement is safe and may help prevent deficiencies
  - NARP, LHON –may add a multiviatmin with lutein
- Avoid fasting and encourage frequent small meals
- Increase fluid intake with heat and metabolic stress

General Guidelines

Exercise

- **Some evidence that exercise leads to improvement in mitochondrial function and heteroplasmy shift in favor of healthy mitochondrial DNA**
- *(Jeppseen 2006; Taivassalo 2005; Tarnoplolsky 2009)*



General Guidelines

Nutrition

- **No specific diet (Exceptions)**
  - **Complex 1 deficiency and seizures (Ketogenic diet)?**
  - **Slow gut motility – limit of excessive fatty foods**
- **Limit fasting**
  - **Small frequent meals may be recommended**
- **Hydration**
  - **IV therapy if unable to maintain oral intake**
- **Use of Supplements**

Future?

- **EPI-743 study for Leigh Syndrome**
  - **Failed primary outcome**
- **Idebenone –approved in EU for LHON**
- **Dichloroacetate (DCA) PDH deficiency**
- **Nicotinic Acid (B3)**
- **N-acetylcysteine and Vitamin E**

Martinelli et al EPI-743 reverses the progression of the pediatric mitochondrial disease – Genetically defined Leigh Syndrome Mol Genet Metab 2012 107: 383-388

Resources

- Parikh S et al *A Modern Approach to the Treatment of Mitochondrial Disease* Curr Treat Options Neurol 2009 :414-430.
- Parikh S et al *Diagnosis and Management of mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society* Genetics in Medicine 2014 (online publication)
- DiMauro S and Rustin P *A critical approach to the therapy of mitochondrial respiratory chain and oxidative phosphorylation disease* Biochem Biophy Acta 2009 1159-1167
- Camp K et al *Nutritional interventions in primary mitochondrial disorders: Developing an evidence base* Molecular Genetics and Metabolism 2016 187-206

Questions?

Thank You

Notes

Morning Session

Grief Throughout Life

Dr. Tracy Hills (Vanderbilt Palliative Care Team)
and Rev. Amanda Borchik, MDiv

Notes

Grief Throughout Life

- Mitochondrial Disorder and Grief throughout Life
- Developmental understanding of grief
- Anticipatory Grief
- Stages of Grief
- Complicated Grief
- Impact of grief on siblings
- Impact of grief on spouses
- Impact of grief on values and beliefs

Notes

Morning Session

Cardiology Issues in the Mitochondrial Patient

Justin Godown, MD

Cardiology Issues in the Mitochondrial Patient

Justin Godown, MD
June 29th, 2018

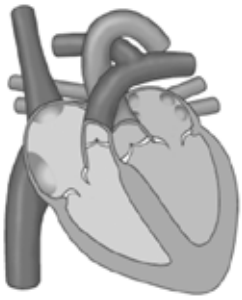
Goals

- Provide an overview of cardiac complications of mitochondrial disease
  - Brief review of cardiac physiology
  - Why is the heart at risk?
  - Forms of cardiac disease
- Screening
- Warning signs
- What can you do to advocate for yourself

Cardiac physiology

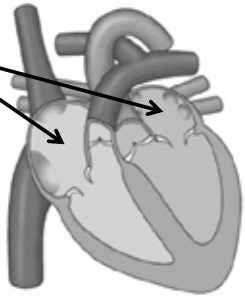
- Heart functions to deliver oxygen to tissues of the body

Cardiac physiology

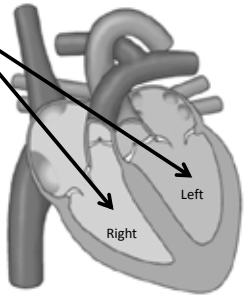


4 chambers

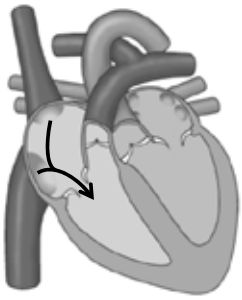
Cardiac physiology



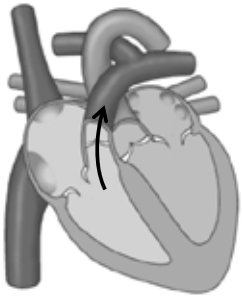
Cardiac physiology



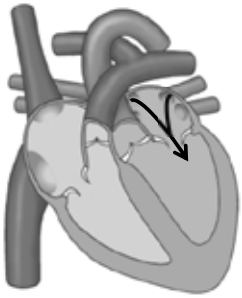
Cardiac physiology



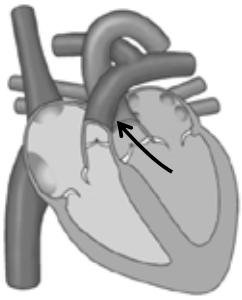
Cardiac physiology



Cardiac physiology

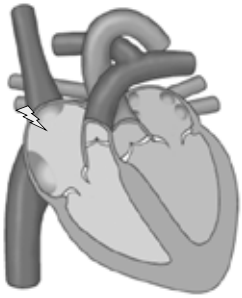


Cardiac physiology



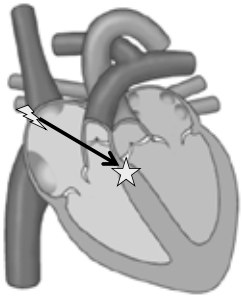
Cardiac physiology

- Conduction system



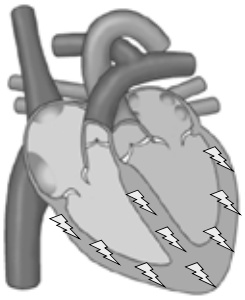
Cardiac physiology

- Conduction system



Cardiac physiology

- Conduction system



Why is the heart at risk?

- Mitochondria produce energy for cells in the form of ATP

- Mitochondrial diseases impair energy production
- Brain, heart, and skeletal muscle are markedly energy dependent
  - These systems can be significantly impacted by mitochondrial disease
  - Heart muscle has the highest density of mitochondria

Forms of cardiac disease

- Cardiomyopathy
- Abnormal heart rhythm

What is cardiomyopathy?

- Cardiomyopathy
  - A disease of the heart muscle
- Multiple different forms
  - Hypertrophic (58%)
  - Dilated (29%)
  - Left ventricular non-compaction (13%)
- Why is this important
  - The presence of cardiomyopathy significantly impacts survival*

1. Scaglia, et al. Pediatrics 2004, Vol 114 (4)
2. Holmgren, et al. Eur Heart J. 2003. 24(3)

Cardiomyopathy: How common is it?

Cardiomyopathy in children with mitochondrial disease

Clinical course and cardiological findings

D. Holmgren[a]*, H. Wåhlander[a], E.O. Eriksson[a], A. Oldfors[b], E. Holme[c], A. Tulinius[a]

European Heart Journal
2003, Vol 24, p 280-288

Clinical Spectrum, Morbidity, and Mortality in 113 Pediatric Patients With Mitochondrial Disease

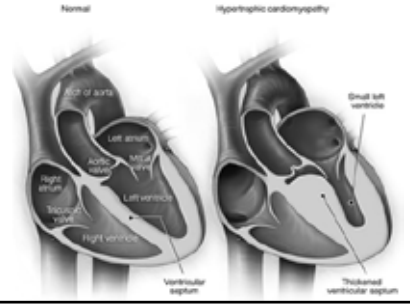
Fernanda Scaglia, Jeffrey A. Towbin, William J. Craigen, John W. Belmont, E. O'Brien Smith, Stephen H. Neish, Stephanie M. Ware, Jill E. Hunter, Susan D. Fernbach, Georgianne D. Vladutiu, Lee-Jun C. Wong, Hannes Popp

Pediatrics
2004, Vol 114 (4)

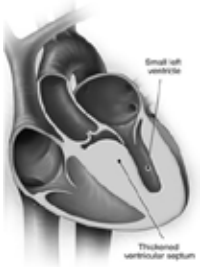
- Cardiomyopathy estimated to occur in 20-40% of patients with "known" mitochondrial disease
- Potentially underestimate the incidence
  - May be the only presenting symptom

Hypertrophic cardiomyopathy

- Abnormal thickening of the heart muscle

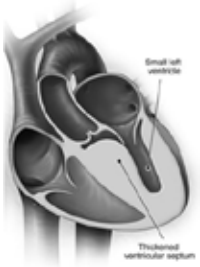


Hypertrophic cardiomyopathy



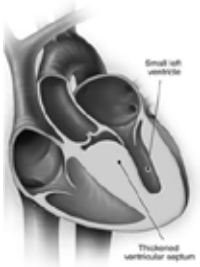
- Problems associated with HCM
  - Scar formation
    - Increased risk of arrhythmia
    - Risk of sudden death
  - Obstruction
  - Mitral valve regurgitation
  - Symptoms
    - Chest pain
    - Shortness of breath
    - Fainting
    - Palpitations

Hypertrophic cardiomyopathy



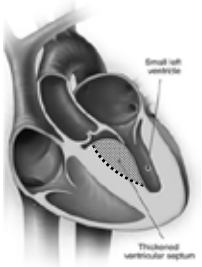
- Management Goals
  - Relieve symptoms
  - Prevention of sudden death

Hypertrophic cardiomyopathy



- Medications
  - Beta blocker
    - Slows heart rate
    - Increases filling
    - May decrease obstruction
  - Indicated for symptoms

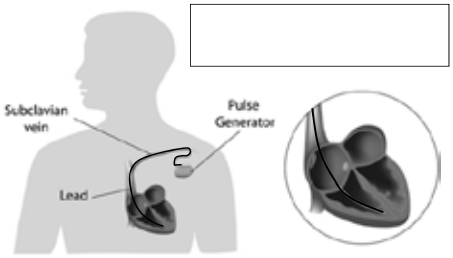
Hypertrophic cardiomyopathy



- Septal myectomy
  - To relieve obstruction
    - Not common in mitochondrial disease
  - May help symptoms

Hypertrophic cardiomyopathy

- Risk assessment
  - Defibrillator placement
    - Primary vs. secondary prevention

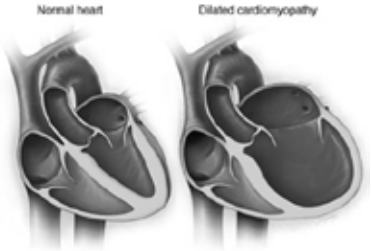


Hypertrophic cardiomyopathy

- Risk assessment
  - Holter monitoring
  - Exercise testing
  - Family history
  - Unexplained fainting
  - Thickness of ventricular muscle (>3cm)

Dilated cardiomyopathy/LVNC

- Weakening of the heart muscle
  - Decreased function
  - Thinning of the ventricular walls and dilated chambers



Dilated cardiomyopathy/LVNC

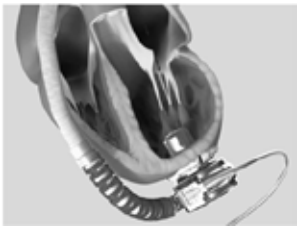
- Symptoms (heart failure)
  - Fatigue
  - Shortness of breath
  - Swelling
  - Weight gain
  - Fainting
  - Palpitations
  - Chest pain
  - Sudden death

Dilated cardiomyopathy/LVNC

- Medications
  - Diuretics (i.e. lasix)
  - ACE inhibitors (i.e. lisinopril)
  - Beta blockers (i.e. carvedilol)
  - Spironolactone
  - Digoxin
  - Anticoagulation

Dilated cardiomyopathy/LVNC

- Ventricular assist devices
  - Option as destination therapy
  - Bridge to heart transplant



*HeartWare HVAD

What about heart transplant?

Heart transplantation outcomes in children with mitochondrial disease

Jeffrey G Weiner, A Nicole Lambert, Cary Thorn, Matt Hall, Jonathon H Soslow, Tyler E Reimschisel, David W Bond, Debra A Dodd, Brian Feingold, Justin Godown.

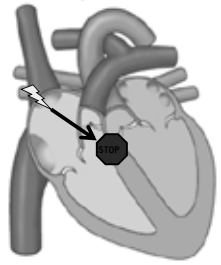
- May be an option for select patients
- 47 children with mitochondrial disease
- Overall outcomes no different compared to patients without mitochondrial disease
  - Increased morbidities
    - Longer ICU LOS
    - Longer time on ventilator
    - Increased incidence of stroke

Abnormal heart rhythm

- Heart block
- Supraventricular arrhythmias
  - Pre-excitation/Wolff Parkinson White (WPW)
- Ventricular arrhythmias
  - Ventricular tachycardia

Heart block

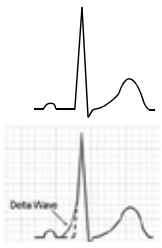
- Interruption of the electrical impulse
  - Usually at the AV node
  - May result in slow conduction or complete block

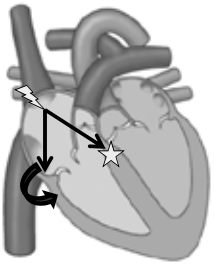


  - Loss of AV synchrony
  - Ventricles pace themselves
  - Slow heart rate
- May develop slow or suddenly
- Treatment
  - Pacemaker

Pre-excitation

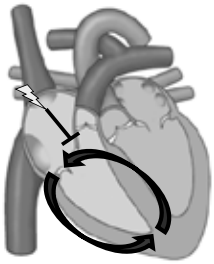
- Accessory conduction pathway
  - Abnormal depolarization of ventricle
  - Risk of SVT





SVT

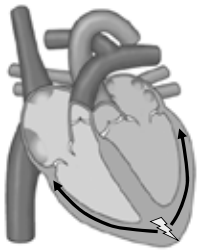
- A re-entry circuit within the conduction system
- Heart rate independent of pacemaker
- Sudden onset of tachycardia



- Treatment
  - Medications
  - EP study
  - Ablation

Ventricular tachycardia

- Abnormal heart rhythm originating from the ventricles
  - Can be fast
  - Risk of sudden death



- Treatment
  - Medications
  - +/- Ablation
  - ICD

Screening?

- Standard part of ongoing assessment for patients with mitochondrial disease
  - Routine testing
    - 12-lead EKG
    - Echocardiogram
    - Holter monitor (ambulatory EKG)
  - Other testing options
    - Catheterization
    - Cardiac MRI
    - EP study

Screening?

- How often is screening needed?
  - No guidelines
  - Annual for those without evidence of cardiac disease
  - More frequent if concerns
    - Abnormal findings
    - Symptoms
- Goal
  - Early detection and treatment

Notes

Metabolic crisis

- Cardiac function can worsen with metabolic crisis
- May precipitate heart failure
- Avoidance and early treatment important
- Reasonable to screen for cardiac involvement during and after metabolic crisis

How can you advocate for yourself?

- Routine cardiology evaluation important
  - Including testing (even if asymptomatic)
- Don't ignore symptoms
- Avoidance or early treatment of metabolic crisis
  - Cardiac re-evaluation during and following
- Ask questions

Questions?

Justin.Godown@vanderbilt.edu

Notes

Morning Session

Ask the Mito Doc Panel - Adult

Moderator: UMDF Staff

Panel Speakers: Zarazuela Zolkipli Cunningham, MD; Sumit Parikh, MD; Andrea Gropman, MD; and Amel Karaa, MD

Notes

Afternoon Session

Navigating Social Security Disability

Moderator: Donald E. Garrison, JD
Panel Speakers: Carol Rabideau, LCSW; John P. Garner, JD, Social Security Disability Attorney; Tim Takacs, JD, Certified Elder Law Attorney; and Joy and Bryan Krumdiack

Disability Benefits

Carol Rabideau, LCSW

United Mitochondrial Disease Foundation Symposium

Mitochondrial Medicine 2018: Nashville, TN

June 29 & 30, 2018

Agenda

Disability Programs

- Definition
  - Social Security Disability Income (SSDI)
  - Supplemental Security Income (SSI)
- Eligibility & Benefits
- When does a person qualify?
- When and how to apply
- How to appeal a decision

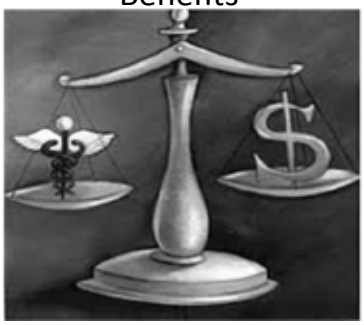
Social Security Administration Disability Programs

- Provide benefits to adults who are unable to engage in substantial gainful activity (SGA) due to a disability (physical or mental).
- Blindness - there are special rules.
- SSI children's benefit category - has a different definition of disability.

www.ssa.gov/disability/professionals/bluebook/ChildhoodListings.htm

Disability Program (SSDI & SSI) Benefits

Health Insurance



Financial Income

SSDI Program Description

- Social Security Disability Insurance **(SSDI)**
  - An insurance program of the U.S. government funded by payroll taxes
  - Provides benefits for people who become disabled before retirement age
  - Has no means/resource-testing
  - Can pay benefits for children, disabled adult children and disabled widow(er)s, if their condition meets definition of disability.

Social Security Disability Insurance (SSDI) Eligibility

- You must be able to prove you are **medically disabled**
- You must have earned required work **"credits"**
  - You worked long enough
  - You earned enough money during your work history

Earning Work Credits

- There is a minimum $ amount required to earn work credit
- Calculated annually & amount increases each year
- Can earn a maximum of 4 credits per year
- It doesn't matter in which quarters you do the work.

YEAR	Dollar Amount for One Work "CREDIT"	FOR MAXIMUM CREDITS (4) PER YEAR
2017	$1300	$5,200
2018	$1320	$5,280

How Many Work Credits are Needed to Qualify?

- Determined by your age
- Understanding work history requirements *handout*: *"Duration of Work Test"* https://www.disabilitysecrets.com/page10-13.html
- There is an exception to these rules for certain blind applicants. *Handout: "Rules if Blind"* https://www.ssa.gov/pubs/EN-05-10052.pdf

SSDI - What Are the Benefits?

- **Monthly financial benefit** is calculated on earnings

	Amount
Most SSDI recipients receive	$1,700
The average SSDI payment in 2018	$1,200
The maximum disability benefit in 2018	$2,788

- **Insurance** – **Medicare** after a 24 month waiting period
- **Children's Benefit** – The children of a parent who is receiving SSDI also get benefits (children <18 or children 18+ who are disabled)

SSI Program Description

- Supplemental Security Income **(SSI)**
  - Is a low income program - intended to alleviate poverty, funded from general revenues rather than dedicated tax
  - Is means-tested (resource limits)
  - Has no prior-work requirement
  - No benefits for dependents - pays benefits only to blind or disabled individuals.

Type Benefit	Paid To
Disabled Child	disabled children <age of 18
Disabled Adult	disabled persons aged 18 or older.

Resource Limits for SSI

Resource Limits	January 2018
Individual/Child	$2,000
Couple	$3,000

The following resources are not counted for SSI

- **home** & the **land** where you live
- **household goods** and **personal effects**
- **burial spaces** for you/immediate family
- **burial funds** for you/spouse, each = or <$1,500
- **life insurance policies** = or <$1,500
- **Achieving a Better Life Experience (ABLE)** account $100,000 max http://www.ablenrc.org/about/what-are-able-accounts
- **one vehicle**
- **retroactive SSI or Social Security benefits** for up to nine months after you receive them
- **grants, scholarships, fellowships, or gifts** for educational expenses for 9 months after receipt

www.ssa.gov/ssi/text-income-ussi.htm

SSI – Benefits

- **Monthly income** is available to the eligible
  - adult
  - child
  - couples
  - an essential person under some circumstances
- **Insurance: Medicaid** benefits are available in most states to SSI recipients without a waiting period

SSI Monthly Federal Benefit Rates (FBRs) and Living Arrangements

SSI benefit amounts and state supplemental payment amounts vary based upon your income, living arrangements, and other factors. https://www.ssa.gov/ssi/text-general-ussi.htm

Live alone or pay your share of food and housing costs	January 2018
Individual/Child	$750
Couple	$1,125
Live in the household of another	**January 2018**
Individual/Child	$750
Couple	$750
Live in a Medical Institution	**January 2018**
Individual/Child	$30

Some States supplement the Federal SSI benefit with additional payments. https://www.ssa.gov/ssi/text-living-ussi.htm

SSDI or SSI

- When you apply for disability benefits, you are automatically evaluated for both programs.
- There is a screening tool on SSA website http://ssabest.benefits.gov/
- You could be eligible for both if
  - Your SSDI check is less than $750 per month, *and*
  - You meet the resource limits of $2000

When Do You Qualify for Disability?

- You can qualify for disability benefits when :
  - your condition can be considered severe
  - you are unable to engage in substantial gainful activity (SGA).
  - Your condition has lasted twelve months or more, or is expected to last twelve months or more, or results in death.
  - *See handout "Definition of Disability and the Determination Process*"

How Much is Substantial Gainful Activity?

YEAR	NON-BLIND	BLIND
2017	$1,170	$1,950
2018	$1,180	$1,970

If you are unable to make the amounts above on a monthly basis because of a medical impairment, you may be eligible for disability benefits.

How To Apply

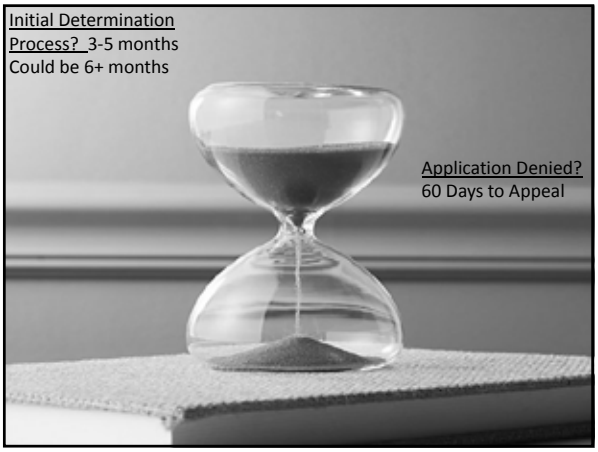
- Three options
  - **Online** application (SSDI only) https://www.ssa.gov/disability/disability.html
  - **Call** 1-800-772-1213 or TTY 1-800-325-0778 if deaf or hard of hearing
  - **Call or visit** your **local** Social Security office – important to make appointment first
- The Disability Starter Kit
  - Fact sheet
  - Checklist *See handout: "Checklist to Apply"*
  - Worksheet

Compassionate Allowance Program

- SSA maintains a list of diseases/conditions that clearly meet their statutory standard for disability.
- Some of the types of Mitochondrial Disease are on the Compassionate Allowances List
- Can reduce SSA application wait time
- Still must go through normal application process.

Types of Mitochondrial Disease on SSA Compassionate Allowance List

- Alpers Disease
- Glutaric Acidemia - Type II
- Leigh's Disease
- Myoclonic Epilepsy with Ragged Red Fibers Syndrome
- NFU-1 Mitochondrial Disease
- Pearson Syndrome



What if You Are Denied Benefits?

- Use the SSI appeal form https://secure.ssa.gov/apps6z/iAppeals/ap001.jsp
- Who can file an appeal?
  - You or an attorney or other benefits specialist
- Who to trust?
  - A professional who is experienced and knowledgeable and known by others.
  - Check with your disability organization, social worker at your medical center, other families.

Thank You!

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2018

Securing today and tomorrow

If You're Blind Or Have Low Vision — How We Can Help

SocialSecurity.gov

If you're blind or have low vision

If you're blind, we have special rules that allow you to receive benefits when you are unable to work.

We pay benefits to people who are blind under two programs: the Social Security Disability Insurance program and the Supplemental Security Income (SSI) program. The medical rules we use to decide whether you are blind are the same for each program. Other rules are different. We explain the different rules for each program below.

You can get disability benefits if you're blind

You may qualify for Social Security or SSI disability benefits if you're blind. We consider you to be blind if your vision can't be corrected to better than 20/200 in your better eye or if your visual field is 20 degrees or less in your better eye for a period that lasted or is expected to last at least 12 months.

You can get disability benefits even if you're not blind

If your vision doesn't meet Social Security's definition of blindness, you may still qualify for disability benefits if your vision problems alone, or combined with other health problems, prevent you from working. For Social Security disability benefits, you must also have worked long enough in a job where you paid Social Security taxes. For SSI payments based on disability and blindness, you need not have worked, but your income and resources must be under certain dollar limits.

How you qualify for Social Security disability benefits

When you work and pay Social Security taxes, you earn credits that count toward future Social Security benefits.

If you're blind, you can earn credits anytime during your working years. Credits for your work after you become blind can be used to qualify you for benefits if you don't have enough credits at the time you become blind.

Also, if you don't have enough credits to get Social Security disability benefits based on your own earnings, you may be able to get benefits based on the earnings of one of your parents or your spouse.

For more information about Social Security disability benefits, contact us to get *Disability Benefits* (Publication No. 05-10029). This booklet also is available in Braille and other formats.

Disability freeze

There is a special rule that may help you get higher retirement or disability benefits someday. You can use this rule if you are blind but aren't getting disability benefits now because you are still working. If your earnings are lower because of your blindness, we can exclude those years when we calculate your Social Security retirement or disability benefit in the future. Because Social Security benefits are based on your average lifetime earnings, your benefit will be higher if we don't count those years. We call this rule a "disability freeze." Contact us if you want to file for this "freeze."

You can get SSI disability payments

SSI payments are based on need. Your income and resources must be less than certain dollar limits. The income limits vary from one state to another. You need not have worked under Social Security to qualify for SSI. Ask your local Social Security office about the income limits in your state and contact us for *Supplemental Security Income (SSI)* (Publication No. 05-11000). This booklet is also available in Braille and other formats.

You can work while receiving benefits

Rules, called "work incentives," make it easier for people receiving disability benefits to work.

People getting Social Security disability benefits can continue to receive their benefits when they work as long as their earnings are not more than an amount set by law.

If you're receiving Social Security disability benefits and you're blind, you can earn as much as $1,970 a month in 2018. This is higher than the earnings limit of $1,180 a month that applies to disabled workers who aren't blind. The earnings limits usually change each year.

Additionally, if you're blind and self-employed, we don't evaluate the time you spend working in your business as we do for people who aren't blind. This means you can be doing a lot of work for your business, but still receive disability benefits, as long as your net profit averages $1,970 or less a month in 2018.

Work figured differently beginning at age 55

If you are age 55 or older, and blind, we use determination rules about work for you that are different from the rules we use for people who aren't blind. After age 55, even if your earnings exceed $1,970 a month in 2018, benefits are only suspended, not terminated, if the work you're doing requires a lower level of skill and ability than what you did before you reached 55. We'll pay you disability benefits for any month your earnings fall below this limit.

Different work incentives apply to people getting SSI.

For more information about all the work incentives for people who receive either Social Security disability or SSI disability, contact us and ask for *Working While Disabled — How We Can Help* (Publication No. 05-10095). This booklet is also available in Braille and other formats. You can also read ***www.socialsecurity.gov/redbook***.

Special services for people who are blind or have low vision

Some services and products are designed specifically for people who are blind or have low vision.

Social Security notices

You can choose to receive notices from us in one of the following ways; just let us know which you prefer:

- Standard print notice by first-class mail;
- Standard print notice by certified mail;
- Standard print notice by first-class mail and a follow-up telephone call;
- Braille notice and a standard print notice by first-class mail;
- Microsoft Word file on a data compact disc (CD) and a standard print notice by first-class mail;
- Audio CD and a standard print notice by first-class mail; or

- Large print (18-point size) notice and a standard print notice by first-class mail.

To select one of these options, please:

- Visit our website at ***www.socialsecurity.gov/notices*** and follow the steps provided;
- Call us toll-free at **1-800-772-1213**. If you are deaf or hard of hearing, you may call our TTY number at **1-800-325-0778**; or
- Write or visit your local Social Security office.

If you already have requested notices in one of the seven formats, but need us to provide a particular Social Security document in your preferred format, please let us know.

If you'd like to receive notices in another way, please call us at **1-800-772-1213,** or visit your local Social Security office so we can begin processing your request. If we're unable to approve your request, we'll send you the reason in writing and tell you how to appeal the decision.

If you have a question about a Social Security notice, you may call us toll-free at **1-800-772-1213** to ask for the notice to be read or explained to you.

Publications available in alternative formats

We make all of our publications available in multiple formats, including Braille, audio cassette tapes, compact discs, or enlarged print on request. And, most of our publications are currently available in audio format on our website, ***www.socialsecurity.gov/pubs.***

To request copies of these publications in alternative formats, you can:

- Go to our website, ***www.socialsecurity.gov/pubs/alt-pubs.html***, to order online.
- Call us toll-free at **1-800-772-1213**. If you are deaf or hard of hearing, you may call our TTY number, **1-800-325-0778**.
- Mail, call, or fax your request to the Braille Services Branch at the Social Security Administration:

  — Mailing address:
  Social Security Administration
  Office of Printing and Alternative

  Media Services
  6401 Security Boulevard
  Room 1305 Annex Building
  Baltimore, MD 21235

  — Phone numbers:
  410-965-6414
  TTY number: **1-800-325-0778**
  Fax number: **410-965-6413**

Please have the following information available when you contact us:

- Title and publication number for the pamphlet or fact sheet you want;
- Your preferred format (Braille, audio cassette tape, compact disc, or enlarged print); and
- Name, mailing address, and telephone number for the person to whom we should send the requested publication.

Contacting Social Security

There are several ways to contact Social Security, including online, by phone, and in person. We're here to answer your questions and to serve you. For more than 80 years, Social Security has helped secure today and

tomorrow by providing benefits and financial protection for millions of people throughout their life's journey.

Visit our website

The most convenient way to conduct Social Security business from anywhere at any time, is to visit ***www.socialsecurity.gov***. There, you can:

- Create a *my* Social Security account to review your *Social Security Statement*, verify your earnings, print a benefit verification letter, change your direct deposit information, request a replacement Medicare card, get a replacement SSA-1099/1042S, and more;
- Apply for Extra Help with Medicare prescription drug plan costs;
- Apply for retirement, disability, and Medicare benefits;
- Find copies of our publications;
- Get answers to frequently asked questions; and
- So much more!

Call us

- If you don't have access to the internet, we offer many automated services by telephone, 24 hours a day, 7 days a week. Call us toll-free at **1-800-772-1213** or at our TTY number, **1-800-325-0778**, if you're deaf or hard of hearing.
- If you need to speak to a person, we can answer your calls from 7 a.m. to 7 p.m., Monday through Friday. We ask for your patience during busy periods since you may experience a higher than usual rate of busy signals and longer hold times to speak to us. We look forward to serving you.

Securing today
and tomorrow

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Social Security Administration

Checklist For Online Adult Disability Application

This checklist will help you gather the information you may need to complete the online adult Disability application process. We recommend you print this page to use while you gather your information. We hope you find our online application easy and convenient.

Birth and Citizenship Information
If you were born outside the United States or its territories:
- Name of your birth country at the time of your birth (it may have a different name now)
- Permanent Resident Card number (if you are not a U.S. Citizen)

Marriage and Divorce
- Name of current spouse and prior spouse (if the marriage lasted more than 10 years or ended in death)
- Spouse(s) date of birth and SSN (optional)
- Beginning and ending dates of marriage(s)
- Place of marriage(s) (city, state or country, if married outside the U.S.)

Names and Birth Dates of Children Who
- Became disabled prior to age 22, or
- Are under age 18 and are unmarried, or
- Are aged 18 to 19 and still attending secondary school full time

U.S. Military Service
- Type of duty and branch
- Service period dates

Employer Details for Current Year and Prior 2 Years (not self-employment)
- View your Social Security Statement online at: www.ssa.gov/myaccount
- Employer name
- Employment start and end dates
- Total earnings (wages, tips, etc.)

Self-Employment Details for Current Year and Prior 2 Years
- View your Social Security Statement online at: www.ssa.gov/myaccount
- Business type and total net income

Direct Deposit

Domestic bank (USA)
- Account type and number
- Bank routing number

International Bank (Non-USA)
- International Direct Deposit (IDD) bank country
- Bank name, bank code, and currency
- Account type and number
- Branch/transit number

Name, address and phone number of someone we can contact who knows about your medical condition(s) and can help you with your claim

List of your medical conditions

Information about Doctors, Healthcare Professionals, Hospitals and Clinics
- Names, addresses, phone numbers, patient ID numbers, and dates of examinations and treatments
- Names and dates of medical tests you have had and who sent you for them
- Names of medications (prescriptions and non-prescriptions), reason for medication and who prescribed them

Information about other medical records that may be available from vocational rehabilitation services, workers compensation, public welfare, prison or jail, an attorney or lawyer, or another place

Job History
- Date your medical condition began to affect your ability to work
- Type of jobs (up to 5) that you had in the 15 years before you became unable to work because of your medical condition
- Dates you worked at those jobs, if available
- Type of duties you did on the longest job you had

Education and Training
- Highest grade in school completed and date you completed it
- Name of special job training, trade school or vocational school and date completed
- Special education school name, city and state, and date completed

We may contact you for additional information after you submit your online application.

Social Security Office of Policy - Trends in the Social Security and Supplemental Security Income Disability Programs

https://www.ssa.gov/policy/docs/chartbooks/disability_trends/overview.html

Definition of Disability and the Determination Process

Section 223(d)(1) of the Social Security Act defines "disability" in an adult as

1. Inability to engage in any substantial gainful activity by reason of any medically determinable physical or mental impairment which can be expected to result in death or which has lasted or can be expected to last for a continuous period of not less than 12 months;[6] or
2. In the case of an individual who has attained age 55 and is blind (within the meaning of "blindness" as defined in section 216(i)(1)), inability by reason of such blindness to engage in substantial gainful activity requiring skills or abilities comparable to those of any gainful activity in which he has previously engaged with some regularity and over a substantial period of time.

The Social Security Administration (SSA) makes a decision on whether an individual is disabled using a five-step sequential evaluation process. An outline of the process follows.

1. Is the individual engaging in substantial gainful activity? If yes, deny. If no, proceed to step 2.
2. Is the impairment severe and does it meet the duration requirement? If no, deny. If yes, proceed to step 3.
3. Does the impairment meet, or equal in severity, one of the medical listings? If yes, allow. If no, proceed to step 4.
4. Can the individual perform his or her past work? If yes, deny. If no, proceed to step 5.
5. Can the individual (considering his or her age, education, and prior work) perform any other work? If yes, deny. If no, allow.

This five-step framework is followed by all SSA adjudicators in making disability decisions for adults at all levels of the administrative process.

The definition of disability and the sequential evaluation process for SSI children (under the age of 18) is similar to that for adults, but the severity requirement is more strict. For children, the impairment(s) must cause "marked and severe functional limitations," which means that the child's impairment must meet, medically equal, or be functionally equal to the listings

Notes

Duration of Work Test

You must have worked the following number of years (or earned the following number of credits) to qualify for SSDI.

Became Disabled At Age	Number of Credits You Need	Number of Years of Work
21 through 24	6	1.5
24 through 31	6 to 18	1.5 to 4.5
31 through 42	20	5
44	22	5.5
46	24	6
48	26	6.5
50	28	7
52	30	7.5
54	32	8
56	34	8.5
58	36	9
60	38	9.5
62 or older	40	10

www.disabilitysecrets.com/page10-13.html

CAN MY TRUST BUY ME A HOUSE? CREATING AND ADMINISTERING SPECIAL NEEDS TRUSTS

Timothy L. Takacs
Certified Elder Law Attorney

TAKACS MCGINNIS
ELDER CARE LAW

HISTORY

Special Needs Trusts

THIRD-PARTY & SELF-SETTLED TRUSTS

Third-Party Trusts

- Established by a grantor who desires to set aside assets in a trust for a blind or disabled child or any blind or disabled individual under age 65.
  - *At least part of the grantor's motive is to attain Medicaid eligibility for the grantor.*
- Created for Another
  - *Where the Grantor Seeks Public Benefits*

Self-Settled Trusts

- Created by or for the Public Benefits Recipient
  - *Self-settled trusts are usually established to protect the proceeds of a personal injury settlement or inheritance.*

Supplemental Security Income

- Supplemental Security Income and the Special Needs Trust
  - *Distributions from a Special Needs Trust*
  - *Supplemental Needs*
  - *The Benefit Amount*
  - *Earned Income*
  - *"In-kind" Support and Maintenance (ISM)*

Trusts under OBRA '93

Trusts under OBRA '93

- 42 U.S.C § 1396(d)(4)(A)
  - *A trust containing the assets of an individual who is disabled and meets certain criteria.*
  - *Trust is established by the individual, a grandparent, parent, guardian/conservator, or a court.*
  - *Available only to disabled individuals under age 65.*
- (d)(4)(C)

Trusts under OBRA '93

- 42 U.S.C § 1396(d)(4)(A)
- (d)(4)(C)
  - *A trust containing the assets of an individual who is disabled and meets certain criteria.*
  - *Trust is established and managed by a non-profit association.*
  - *A separate account is maintained for each beneficiary of the trust.*

The Five-Step Trust Process

1. Creation
2. Tax Recognition
3. Funding
4. Administration
5. Distribution

The Five-Step Trust Process

4. Administration

- *Understanding Fiduciary Obligations*
- *Back-End Duties of a Fiduciary*
- *How to Stay Compliant*

The Five-Step Trust Process

5. Distribution

- *Front-End Services*
- *What are "Special Needs"?*
- *Developing a Care Plan for the Beneficiary*

ADMINISTRATION OF SPECIAL NEEDS TRUSTS

Typical Problems

Ethical Issues

- Questions to consider:
  - *Is the trustee competent in this area of practice?*
  - *How is trust administration carried out?*
- Can a trust pay for a gift from the beneficiary?
  - *Example: Adult son wants a truck*

Your State Medicaid Agency

- Is your state hostile to special needs trusts?
- Will your state impose unreasonable or unrealistic requirements?
  - Example: Will your state demand regular accounts, approvals of expenditures from the trust, or use of settlement funds to reimburse Medicaid benefits that were expended prior to the beneficiary's receipt of the funds?
- How often and how much information should you provide to your state Medicaid agency?

Investing Trust Funds

- The trustee exercises fiduciary responsibility in investing the money in each special needs trust.
  - *Should you act as your own investment advisor?*
  - *How often should you change investments?*

Can a Special Needs Trust be used to buy a home?

- The trust cannot be used for payment of the SSI beneficiary's basic needs, such as food and shelter and medical care.
- Money used for those purposes are considered "income" for purposes of determining the beneficiary's eligibility to receive SSI and Medicaid.
- The money can be used to purchase a home for the beneficiary.
  - *The home will be part of the remainder of the trust, and will be deeded over to whoever is designated to receive the balance of the trust fund after the beneficiary dies; OR*
  - *If the beneficiary dies, the home would be subject to the Medicaid payback provision and the home may be lost.*

Can My Special Needs Trust Buy Me a House?

- When computing household operating expenses for ISM, the following 10 items are the only ones used in the applicable computations:
  1. *Food*
  2. *Mortgage (including insurance required by the mortgage holder)*
  3. *Real property taxes*
  4. *Rent*
  5. *Heating fuel*
  6. *Gas*
  7. *Electricity*
  8. *Water*
  9. *Sewer*
  10. *Garbage removal*

Setting and Collecting Fees

- How much should a trust charge?
  - Set-up fee: Tiered fee structure
- Is there a minimum investment requirement?
- Annual Fee
  - Percentage or
  - Flat fee or
  - Both
- K-1 Tax Form Preparation
- Closing Fee

Front-End Services

- Interaction with the trust officers
- Long-term relationship with the beneficiary and the attorney-in-fact
- "Welcome Packet" provided to trust beneficiary, guardian or attorney-in-fact
- Follow-up contacts made to trust beneficiary and guardian or attorney-in-fact
- Office visits
- Care manager visits (as appropriate)

INCOME AND ITS EFFECT

on

Special Needs Trusts

EXAMPLE 1:
Unearned Income

EXAMPLE 2:
Earned Income

CONCLUSION
- Drafting the trust is the easy part.
- Identifying the appropriate trustee, trust administration, trust distributions, and public benefits challenge disabled individuals, trustees, and their attorneys.

Notes

References

- Takacs McGinnis Elder Care Law
  www.tn-elderlaw.com
- Omnibus Reconciliation Act of 1993 (OBRA'93), 42 U.S. Code § 1396p(d)(4)
- POMS
  https://secure.ssa.gov/apps10/poms.nsf/Home?readform
- Vista Points Special Needs Trust
  www.vistapoints.org

Notes

Afternoon Session

Living with Mitochondrial Disease - Patient Panel Sessions

James Valentine

Notes

Afternoon Session

Parent Perspective on the Burdens of the Disease

Panelists:
2:15-2:20 - Ann Korsen (NJ)
2:20-2:25 - Annett Cotte (GA)
2:25-2:30 - Stacy Taylor (MD)
2:30-2:35 - Heather Thornbury (FL)

Notes

Afternoon Session

Parent Perspective on Management of Care

Panelists:
2:40-2:45 - Carrie Mullin (PA)
2:45-2:50 - Lori Martin (TX)
2:50-2:55 - Cheryl Porter (GA)
2:55-3:00 - Gwen Lopez-Cohen (CT)
3:00-3:05 - Anne Tuccillo (VA)

Notes

Afternoon Session

Adult Patient Perspective on the Burdens of the Disease

Panelists:
3:35-3:40 - Laura Prudhomme-Gaupp (LA)
3:40-3:45 - Devin Shuman (PA)
3:45-3:50 - Deborah Bricker Parsons (GA)
3:50-3:55 - Rachel Schanzenbach (VA)
3:55-4:00 - Alysse Delotte (FL)

Notes

Afternoon Session

Adult Patient Perspective on Management of Care

Panelists:
4:05-4:10 - Kristen Schroeder (CT)
4:10-4:15 - Deborah Carman (IL)
4:15-4:20 - Sharon Shaw Reeder (AZ)
4:20-4:25 - Nicole DeJean (LA)

Notes

Afternoon Session

Tips for the Caregiver

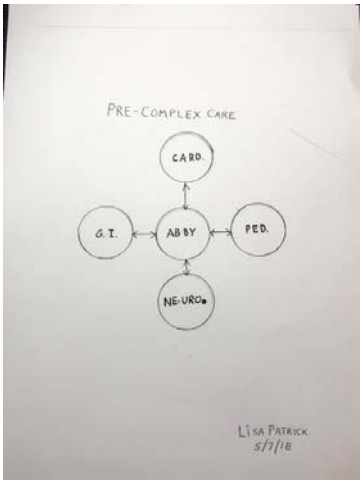
Michaela Ibach, MD and Sarah Wilkerson, CPNP

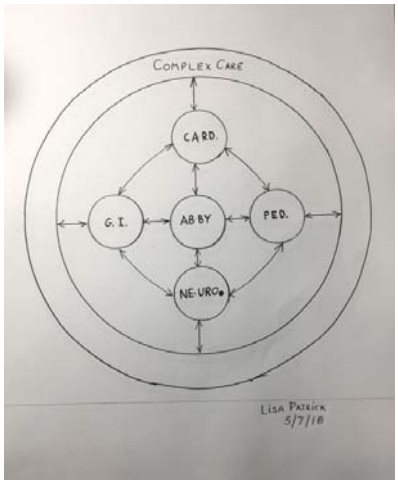
Tips and Transitions for Caregivers of Children with Medical Complexity

UMDF Symposium 2018

What is Complex Care?

- Our team follows kids with multisystem, life long chronic illness.
- We partner with families to navigate the Vanderbilt Health care system, and work together with you to provide goals directed care for your child.
- We seeks to improve continuity of care by following children over time, including during hospital admission and after discharge
- Our team consists of 2 doctors, 2 NP's, 3 nurses, a pharmacist, social worker, dietician and program coordinator
- https://www.childrenshospitalvanderbilt.org/program/complex-care




COMPLEX CARE
CARD.
G. I.
ABBY
PED.
NE-URO.
LISA PATRICK
5/7/18

palliative
people
care
life
patients
illness
disease
think
chronic
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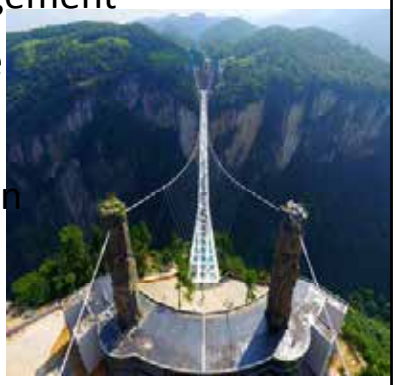
Pediatric Palliative Care

- Pain & symptom management
- Navigating goals of care
- Decision-making
- Complex communication
- Transitions in care

- What PPC is NOT!



Complex Care + Palliative Care

Tips for Caregivers

- Communication
- Preparing for the future
- Self-care

Communication...with yourself

- How do you best appreciate receiving information?
  - Details or big picture?
  - Written or oral?
- How far ahead do you think?
  - Looking down the road or one step at a time?

Okay, what else?

- What is your history?
- What do you value?

Communication…with a healthcare team

- Who's who ?
- What's best?
- A word about certainty

So what does that look like practically?

- Find your co-advocates
- Remember who's who
- Have some communication tools
- Ask!
- Practice awareness in decision making

Planning for the future

When your child turns 18 years old, apply for SSI (Social Security Insurance)

Prior to 18 years old, the financial assets of the family weigh more heavily than disability of the child. However, once the child is an adult, the disability often holds more weight than the finances of the guardian, making it easier to receive benefits.

Medicaid transition to Medicare

- Once an adult child qualifies for SSI, you can apply for Medicaid benefits.
- Sometime between 21 and 22 years of age, there will be a transition to Medicare.
- Medicare has some benefits over Medicaid, namely that your adult child can be seen by specialty providers at Vanderbilt Main Campus(does not take Medicaid).
- Drawbacks include that you may require a supplemental plan and coverage for things like PDN, decrease.

Planning for the future

- Conservatorship vs Health Care Surrogate
- What is conservatorship?
- a court-approved and court supervised legal relationship between a competent adult (known as a conservator in TN; as a guardian in other states) and an adult who needs assistance in decision-making.

Planning for the future

- The court has the final decision-making responsibility and authority in those areas, such as health care, living arrangements and/or finances, for which conservatorship has been deemed necessary. A conservator acts as the agent of the court.

Health Care Surrogate

- A health care surrogate is an adult who is appointed to make healthcare decisions for and individual that cannot make decisions for him/herself.
- Appointed by a physician or NP
- Requires reappointment of the HCS during every hospital stay/ER visit.
- Proposed surrogate reasonably appears to be better able to make decisions in accordance with the **wishes of the patient** or in accordance with the **best interest of the patient**

HCS

- The physician, not the individual, decides whether a surrogate is needed and who will take on that role.
- Preference for the selection of the surrogate is given in the following order:
  - The person's spouse
  - The person's adult child
  - The person's parent or stepparent
  - The person's adult sibling
  - Any other adult relative
  - Any other adult.

Durable Power of Attorney

- A durable power of attorney (DPOA) is a legal document that gives someone authority to make decisions on behalf of another individual.
- Must be in writing and notarized
- In order for the DPOA to be valid, the individual must be considered competent at the time s/he signs the document.

DPOA

- Benefits:

The individual remains competent in the eyes of the law; the person who holds the DPOA can assist and act on behalf of the individual; and the court is not involved in the individual's life.

- Drawbacks:

Since the individual remains competent, he/she can make potentially unsound choices.

Can be revoked by the individual at any time

Special Needs Trust

- a legal plan for placing funds and other assets in the control of a trustee for the benefit of an individual with a disability. The trust protects an individual's assets without requiring that s/he be declared incompetent by a court

Pros of a Special Needs Trust

- Can keep person eligible for government programs like SSI and Medicaid and help pay for services and care over and above what the government provides.
- Funds used to create a SNT are tax-deductible.
- Ensures that funds are used for the care of the person with a disability – This is especially comforting when there is a concern that the person with a disability could be influenced or taken advantage of in matters concerning money.
- Funds are not available to creditors or for paying judgments – The money is used only for the care of the person with a disability.

Disadvantages of a Special Needs Trust

- Cost

  Annual fees and high cost at set up
- Lack of Independence

  The beneficiary has to request funds from the trustee and the trustee has complete discretion as to whether the request is appropriate based on the terms laid out in the trust.
- Medicaid Payback

CHOICES program

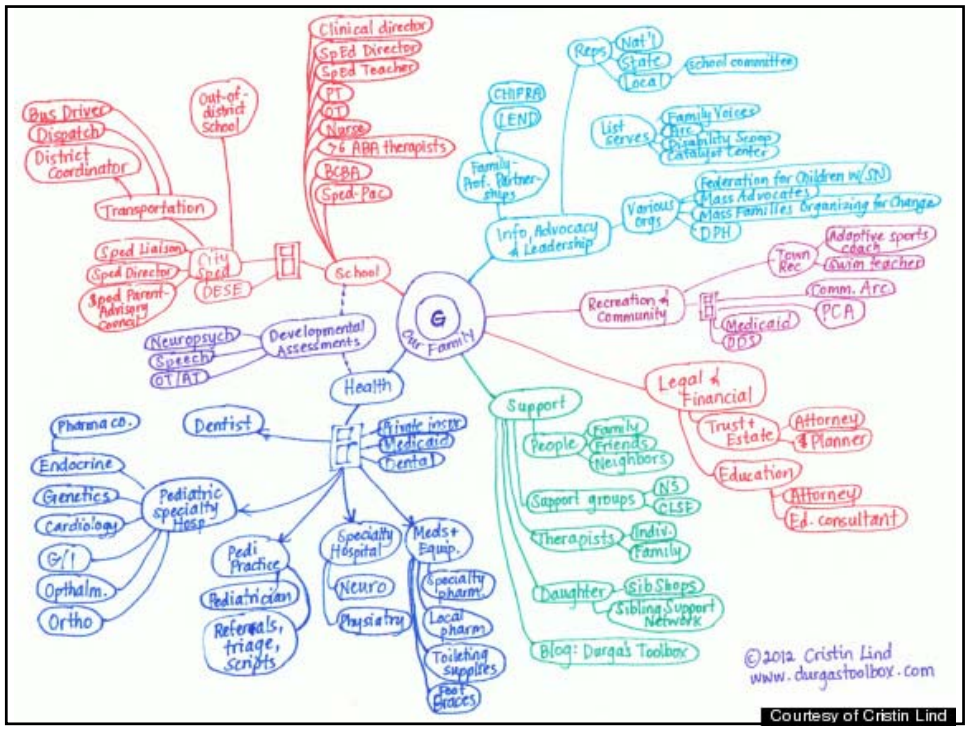
- Nursing facility services and home and community-based services (HCBS) for adults 21 years of age and older with a physical disability
- Can provide things like attendant care visits (4 hours or longer), in home respite care, inpatient respite care, meal delivery, assistive technology, minor home modifications

ECF Choices Waiver

- New long term care waiver for people with developmental and intellectual disabilities
- Apply online by completing the self-referral from on TennCare's website

https://www.tn.gov/didd/employment-and-community-first-choices.html

- To find out if your state has a waiver, go to www.medicaidwaiver. org



A few words about self care

- The basics
- Awareness
- Acknowledgement

Resources

- The Dougy Center https://www.dougy.org
- Courageous Parents Network https://courageousparentsnetwork.org

Caring for siblings

- Review article published in the NYT on 2/12/18, discussing findings of Dr. Mandleco (Professor emerita studying siblings of children with disabilities) and Emily Incledon (clinical psychologist)
- Extensive literature review
- Findings: Several key strategies and interventions associated with better mental health of siblings of children with special needs

Caring for siblings

- education about the illness, with participating in support groups and attending recreational camps designed for kids with sick siblings
- A sense of being supported by family members and peers
- Maintaining as much normalcy as possible.

Caring for siblings

- Siblings learn compassion and empathy towards those who have a disability
- There's evidence to suggest that this experience shapes many siblings into resilient, helping, caring adults, and may shape some of their career choices as well.

Caring for siblings

- https://www.nytimes.com/2018/02/12/well/family/caring-for-siblings-of-sick-or-disabled-children.html

Resources

- Vanderbilt Kennedy Center
  - Programs for siblings
  - Social work services
    - Referral services to individuals and families
  - Help with IEP and Vocational Training (Return to work Program)
    - Contact person is Joann Ball
    - Can your child work?
    - In TN, adult children can stay in the public school system until they are 21 (this must be spelled out in your IEP)

Resources

- ARC Conservatorship Handbook
- Tennessee Disabilities pathfinder
  https://www.tn.gov/cdd/projects-and-initiatives/.../tennessee-disability-pathfinder.html
- Area agency on Aging and Disability

Advocacy

- Volunteer Advocacy Project
- Tnstep.org
  - Both of these organizations help with IEP and school (educating and empowering parents.)
- Tennessee Justice Center
  - Help with appealing Medicaid if there is a denial

Questions?

- We would love to hear from you!
- We have created a google poll for you give us any “pearls” that have helped you in your journey
- https://docs.google.com/forms/d/e/1FAIpQLScLKznTwUSBo8UDry-evvMbyrKgK-o6g89MeY_KoHgwLWy5AQ/viewform

Notes

Saturday, June 30

Notes

Morning Session

Patient Registries - MDCR, MSeqDR EConsent Review, Leigh Syndrome Patient Registry, and Workshop

Philip Yeske, PhD; Elizabeth McCormick, MS, CGC; Mary Kay Koenig, MD

Mitochondrial Disease Community Registry

Our Disease. Your Information. The Community's Best Hope for Treatments and Cures

A novel participant-centric registry built on Genetic Alliance's Platform for Engaging Everyone Responsibly (PEER)

June 2018 Update

UNITED MITOCHONDRIAL DISEASE FOUNDATION℠
HOPE. ENERGY. LIFE.

Genetic Alliance

Mitochondrial Disease Community Registry

www.umdf.org/registry

Who?
Patients, caregivers & family members
Confirmed diagnosis ***NOT*** required

Why?
Need patient data collected over time in order to improve diagnoses and develop treatments

Key
Registrants have full control of privacy settings

- Allow, deny or "ask me"
- Who can see anonymous data
- Who can analyze anonymous data
- Who can contact you about research studies and clinical trials

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PLEASE REGISTER & SHARE!

Mitochondrial Disease Community Registry

- Goals for a Patient-Populated Registry
  - Keywords: Sustainable, Compatible, Valuable
  - UMDF as steward, not owner
    - Registrants should have full control of who may see their data, analyze their data and who may contact them
  - Patient-populated in order to cast a wider net
    - Complementary, NOT competitive to NAMDC
  - Collect contact and health information
    - Collection of health information over time (longitudinal)
    - Ability to accept study/trial proposals from researchers, query the database and supply de-identified data

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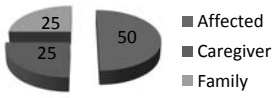
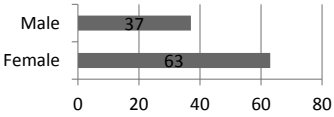
MDCR Current Status

- Launched August 2014
- June 2018: ~2,300 registrants
- Single static survey
  - ~100 Q's/~50K Responses
  - Baseline demographics
  - Diagnostic State
  - Opinions on patient-centered drug development
- International: 46 countries represented!
  - ~89% from the US

% Registrants



Biological Gender



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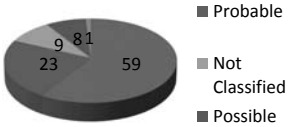
MDCR Data Snapshots

Self-Reported Diagnostic State



***Sample* of Mitochondrial Disease Types Currently Represented in MDCR**

Mitochondrial DNA Mutation Syndromes
LHON, LHON+, MELAS, MERRF, MIDD, MILS, NARP

Mitochondrial DNA Deletion Syndromes
CPEO, KSS, ADOA

Nuclear Gene Disorders
Leigh's, MNGIE, Alper's, SANDO

Biochemical Disorders
Complex I, Complex II, Complex III, Complex IV, Complex V, CoQ Deficiency

System-Based Disorders
Encephalomyopathy, Encephalopathy, Mitochondrial Myopathy

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DO YOU KNOW ?

someone with Leigh syndrome?

*If so, **you can help** change the course of this disease.*

Anyone with diagnosis of Leigh syndrome qualifies to be part of the Leigh syndrome patient registry. The Leigh syndrome patient registry will create a highly-secure, highly-protected international database of patients with Leigh syndrome.

THE REGISTRY HAS TWO MAIN GOALS:

1. **Collect valuable information about the medical status of patients to increase the understanding of how the disease progresses.**
   Imagine knowing what the potential future looks like for your Leigh syndrome patient.

2. **Serve as a resource to researchers conducting clinical trials.**
   Allowing access to the patient community will help speed up the process of locating potential patients for clinical trials.

To learn more and enroll visit **PEOPLEAGAINSTLEIGHS.ORG**
and click on the link for the Leigh Syndrome Patient Registry.

Principal Investigator: Mary Kay Koenig, MD

Contact Information:

The UT Mitochondrial Center of Excellence
6410 Fannin Street, Ste. 732
Houston, TX 77030
Phone- 713-500-7164, Option 4
Fax- 713-500-0719

UT Mitochondrial Center of Excellence

UTHealth
The University of Texas Health Science Center at Houston
Medical School

IRB NUMBER: HSC-MS-14-0907
IRB APPROVAL DATE: 06/08/2015

Notes

Morning Session

Managing Common Sleep Issues in Mitochondrial Disease Patients

Althea Robinson Shelton, MD, MPH

Managing Common Sleep Issues in the Mitochondrial Patient

Althea Robinson Shelton, M.D., M.P.H.
Sleep Division-Neurology Dept.
Vanderbilt University

Objectives

- Review sleep complaints and prevalence
- Discuss sleep disordered breathing (SDB)and treatment
- Discuss Insomnia and Treatment
- Review restless legs syndrome (RLS)

Abnormal Sleep

- Adults and children present to the sleep clinic with 3 main symptoms:
  1. Trouble falling asleep or staying asleep (insomnia)
  2. Excessive daytime sleepiness
  3. Abnormal events or episodes at night (snoring, apneic episodes, seizures, sleepwalking, leg kicks, etc.)

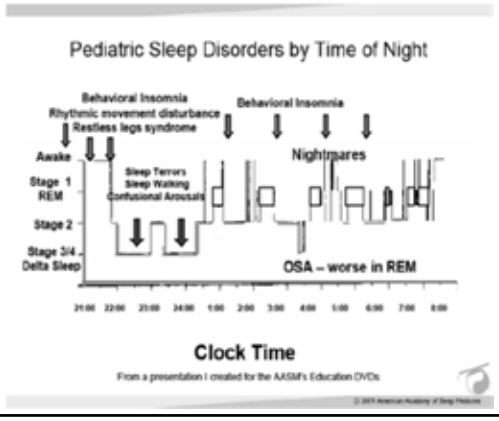
Pathophysiology of Sleep Disorders

The Most Common Sleep Disorders

1. **Insomnia**
2. **Obstructive Sleep Apnea (OSA)**
3. Narcolepsy
4. **Restless Legs Syndrome (RLS)**

Others include

- parasomnias (sleepwalking, night terrors,
  - REM-behavior disorder),
  - **circadian rhythm disorders**,
  - nocturnal seizures,
  - others



Prevalence of Pediatric Sleep Disorders

- Insomnia (aka sleeplessness) 10-25%
  - Behavioral insomnia of childhood – toddler, preschool 25%?, Teens – 10%?
- Rhythmic movement disturbance (head-banging, body rocking)
  - Age: 9 mos-4 yr; common (15 → 3%)
- NREM parasomnia
  - Confusional arousals ⇔ night terrors (3%)
  - Sleep walking ⇔ agitated sleep walking (2% weekly-monthly)
- Delayed sleep phase – 7% teens
- Obstructive sleep apnea 2% (habitual snoring – 10%)
  - Other types of sleep disordered breathing*
- Restless legs syndrome 0.5-2%
- Narcolepsy with cataplexy 0.05% (1/2000)

*Central apnea and hypoventilation are rare and usually associated with other complex conditions

© 2015 American Academy of Sleep Medicine

Sleep disordered breathing (SDB)

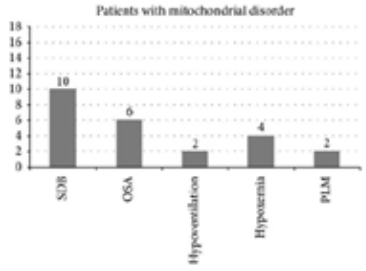
- Respiratory disorders occurring exclusively in sleep or exacerbated by sleep
  - Primary snoring
  - Upper airway resistance syndrome
  - Sleep induced hypoxemia
  - **Obstructive sleep apnea (OSA)**
  - **Central sleep apnea (CSA)**
  - **Sleep related Hypoventilation**

Sleep disturbance in Mitochondrial Disorder (MD)

- Both nuclear DNA and mitochondrial DNA mutations were associated with abnormal sleep patterns.
- Most patients exhibited SDB (87%)
  - 26% had CSA
  - 11% had OSA
- Twenty-four patients (51%) showed decreased ventilatory drive in response to hypoxia
  - Not necessarily related to muscle weakness

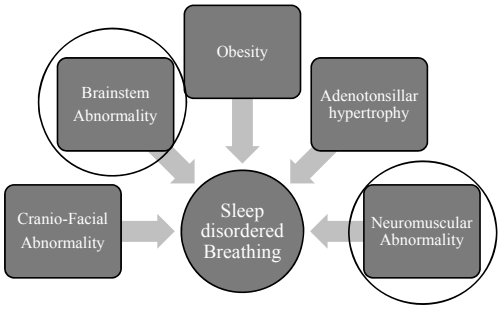
Ramazeni and Stacpoole, 2014

SDB in Children with MD



Mosquera et al., 2014

Pathophysiology of SDB



Neuromuscular Dysfunction

- Forty-five (45) percent of pediatric patients with MD first present with a neuromuscular problem
  - Degree of impairment is not well defined
- Fatigue and hypotonia were the most prevalent symptoms reported in children
- SDB and neuromuscular disease (NMD) are highly associated

Obstructive Sleep Apnea (OSA)

- OSA is defined as partial or complete upper airway obstruction during sleep, associated with at least 1 of the following:
  - Sleep disruption
  - Hypoxemia (low oxygen)
  - Hypercapnia (elevated CO2)
  - Daytime symptoms

Central Sleep Apnea (CSA)

- CSA is characterized by a lack of drive to inspire
  - No associated respiratory effort
  - No inhalation, chest or abdomen movement
- Brain doesn't send proper signals to the muscles that control your breathing

Sleep-related Hypoventilation

- Nocturnal hypoventilation develops because of weak inspiratory muscles
  - Typically begins during rapid eye movement (REM)
- As muscle weakness progresses, nocturnal hypoventilation often includes non-REM sleep
  - Increases the patient's risk for daytime hypoventilation

Katz et al., 2009 and Panitch et al., 2009

Presentation and Symptoms

- **Nocturnal Symptoms**
  - Snoring and/or noisy breathing
  - Apneic pauses and/or gasping
  - Paradoxical movement of chest wall and abdomen during breathing
  - **Restless sleep**
  - **Sweating during sleep**
  - Mouth breathing
  - **Abnormal sleeping positions**
  - **Multiple night awakenings**

Presentation Of Symptoms

- **Daytime symptoms**
  - **Morning headache**
  - **Nausea**
  - Excessive daytime sleepiness
  - Fatigue
  - **ADHD like activity**
  - **Increased Irritability**

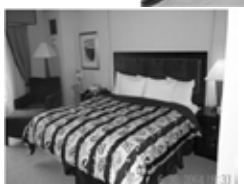
Recommendations for MD

- Polysomnogram (PSG) should be considered at baseline in every patient **at diagnosis** to assess for sleep disturbances, central or obstructive apnea, and nocturnal hypoventilation.
- Patients even with mild abnormalities should be referred to a sleep specialist

Parikh et al., 2017

Objective Sleep Measures: PSG

- PSG is gold standard for detecting sleep apnea, periodic leg movements of sleep, parasomnias, and nocturnal seizures (when video-EEG added)



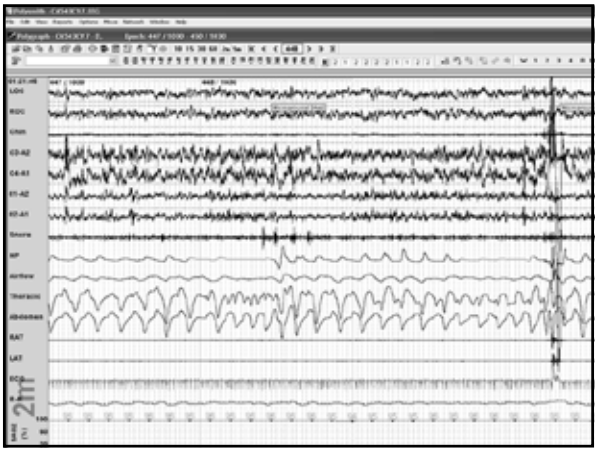
✓**How perform PSGs in children???**

✓Experienced sleep techs who use child-friendly terminology

✓Create picture books to help prepare children for the sleep study experience

✓Quiet play activities, stickers, activity books

Zaremba, Barkey, Mesa, Sanniti, Rosen. Making polysomnography more "child friendly:" a family-centered care approach. J Clin Sleep Med, 2005



Positive Airway Pressure (PAP)

Continuous Positive Airway Pressure (CPAP)

- **Single pressure** that remains consistent throughout the night
- Comfort feature called C-flex
- Most use a Ramp setting

Bi-Level Positive Airway Pressure (Bi-PAP)

- **Two pressure settings**: the prescribed pressure for inhalation (ipap), and a lower pressure for exhalation (epap)
- Allow the patient to get more air in and out of their lungs
- Breath timing feature

PAP Therapy

- Effective therapy, but adherence is a major barrier
  - ***Parent and family support are key***
  - Easier to implement if nasal/oropharyngeal obstruction is optimized

PAP habituation

- Always a challenge
  - –20% drop out rate
  - –Parent report overestimate use
  - –Variable adherence (30-70%)
  - –No difference for fixed vs bi-level PAP

PAP Habituation: It's a Process

- Place on face/no flow
- Add headgear
- Introduce flow
- Increase time with mask in place
  - –Awake, distracted
  - –Falling asleep

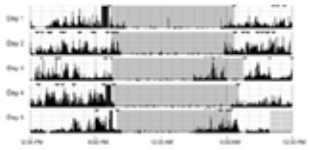
Treatment of Insomnia: Behavioral and Pharmacological Approaches

Assessment of Insomnia: Key points

- Ask about bedtime, wake time, awakenings
- Is there a regular bedtime?
- Is there a bedtime routine?
- Are there any habits (caffeine, stimulating activities before bed) that can be interfering with sleep?
- Are there any medications or psychiatric comorbidities that can be interfering with sleep?
- **Is there evidence of a primary sleep disorder (such as obstructive sleep apnea) contributing to insomnia?**

Objective Sleep Measures: Actigraphy

- Actigraphy is a promising technique for measuring sleep patterns and responses to treatment in children, especially those with neurodevelopmental disorders (AASM, 2007)
- Does require parents to keep accurate sleep diaries as actigraph needs to be interpreted in context of when child went to bed



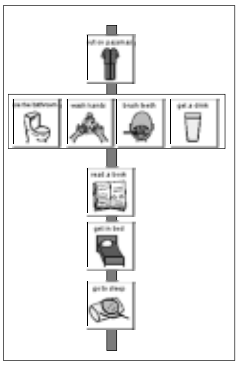
Components of Successful Sleep "Sleep Hygiene"

- Daytime habits:
  - Exercise
  - Abundant light
  - Avoid caffeine
  - Limit naps
  - Selective bedroom use
- Evening habits
  - Calming Activities
  - Less light
  - Limit electronic video games, etc
- Sleep environment
  - Temperature
  - Texture
  - Sound
  - Minimal light
- Bedtime
  - Routine
  - Regular Bedtime/Waketime
  - Timing
  - Amount

Visual schedules clarify bedtime routines

Time for bed

- ☐ Put on pajamas
- ☐ Use the bathroom
- ☐ Wash hands
- ☐ Brush teeth
- ☐ Get a drink
- ☐ Read a book
- ☐ Get in bed and go to sleep



The Bedtime Pass

Sleep Problems and Daytime Behavior

- Behavioral treatment of sleep problems in children with a developmental disorder and challenging daytime behavior reduces parental stress, increases parents' satisfaction with their own sleep, their child's sleep, and heightens their sense of control and ability to cope with their child's sleep

  (Wiggs L, British J Health Psychology, 2001)

Insomnia- Pharmacological Treatment

- Best used after behavioral treatments have been tried unsuccessfully, and in combination with behavioral therapies
- Whenever possible, choose a medication that will treat a comorbidity such as epileptic seizures, anxiety, or a mood disorder
- Start at low doses, as children with developmental disabilities may be more susceptible to adverse effects and be less able to communicate them effectively

Insomnia- Pharmacological Treatment

- Epilepsy: Most antiepileptic medications are sedating, and maximizing nighttime dose can promote sleep.
  - Avoid valproic acid
- Bipolar disorder, irritability, aggression, self-injurious behavior: sedating atypical neuroleptics such as respiridone
- Anxiety or depression: sedating antidepressants
- Primary insomnia: **melatonin**, clonidine, diphenhydramine, benzodiazepines

Restless Legs Syndrome (RLS) New Diagnostic Criteria

- **Essential Four Criteria**
  - **U**rge/sensation in legs
  - **R**est increases symptoms
  - **G**ets better with motor activity
  - **E**vening symptoms are worse

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RLS in Children

- Essential Four Criteria
  - **U**rge/sensation in legs
  - **R**est increases symptoms
  - **G**ets better with motor activity
  - **E**vening symptoms are worse

  and
- ***"a description in [the child's] own words that is consistent with leg discomfort"***

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Notes

Descriptions by Children

- The RLS sensations described: *have to move, need to kick, pain/hurts, 'like bugs crawling, weird/funny feelings, and tingling.*
- Two main descriptors:
  - **Need to Move/Kick.**
  - **Pain as a description of RLS Sensations**

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Therapy of RLS

- First line– Dopaminergic Agents
  - L-Dopa, ropinirole, pramipexole
- Second line –
  - Opioids
  - ***Anticonvulsants – gabapentin, pregabilin***
  - ***Benzodiazepines – clonazepam, diazepam***
  - ***Iron Therapy***

Notes

Morning Session

Advocacy Session

Cliff Gorski, David Faughn and Jenny Hobbs

Notes

Morning Session

Mitochondrial Disease of Non-Genetic Origin

Kendall Wallace, PhD and Bruce H. Cohen, MD

Notes

Morning Session

Physical, Occupational, and Speech Therapies and the Mitochondrial Disease Patient

Karen Coker, PT, DPT, CWS, WCC, C/NDT, FACCWS;
Missy Bryan, OTD, OTR/L, ATP, CPST;
and C. Melanie Schuele, PhD, CCC-SLP

Physical Therapy and Mitochondrial Disease

Karen Coker, PT, DPT, CWS, WCC, C/NDT, FACCWS

Physical Therapy

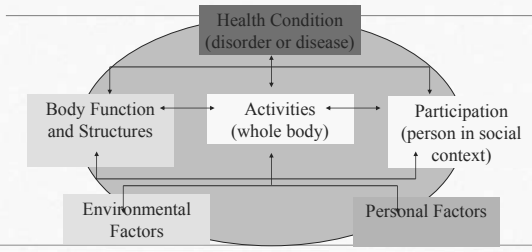
- Evaluation
- Standardized Assessments
  - Peabody Developmental Motor Scales
  - Bayley Scales of Infant and Toddler Development
- Treatment Planning
- Child/Parent/Therapist Goals

Mitochondrial Myopathy Helps

- No FDA-approved medication that target specifically mitochondrial disease
- Vitamin cocktails are prescribed to boost cell function
  - Creatine, Riboflavin, coenzyme Q, L-carnitine (specialized amino acid)
  - May improve fatigue and energy levels in some people
- Diet modifications
- Avoid stress
- Avoid extremes in heat and cold
- Medications to treat symptoms
- **Physical Therapy/OT/SLP**
  - Range of motion, improve dexterity, energy management, conservation

https://www.ninds.nih.gov/Disorders/All-Disorders/Mitochondrial-Myopathy-Information-Page

International Classification of Functioning, Disability, and Health (ICF)



5

Characteristics treated often by PT

- Muscle weakness and atrophy (muscle bulk shrinkage)
- Developmental delay
- Lethargy and Exercise Intolerance
- Low muscle tone (hypotonia)/scoliosis
- Ataxia
- Altered control over breathing
- Stroke symptoms

PT enhances Participation in life

- Friedreich's Ataxia
  - Spinocerebellar degeneration
  - Frataxin production is limited (protein that functions in the mitochondria)
  - Onset age 5 to 15 with rapid progression; may also have late onset
  - Loss of coordination, fatigue, muscle loss, visual impairment, hearing loss, aggressive scoliosis, diabetes, heart conditions, unaffected mental abilities

http://www.muscle.ca/about-muscular-dystrophy/types-of-neuromuscular-disorders/friedreichs-ataxia/

Friedreick's Ataxia PT/OT HELPS

- Loss of coordination COORDINATION EXERCISES/COMPENSATION
- Fatigue, muscle loss ENERGY CONSERVATION
- Visual impairment REFERRAL, SAFETY TRAINING
- Hearing loss REFERRAL

Mitochondrial Myopathy

- Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS)
  - Onset in childhood to early adulthood
  - Causes recurrent stroke-like episodes, migraine-type headaches, vomiting and seizures, can lead to permanent brain damage.
  - Common: PEO (progressive external opthalmoplegia, general muscle weakness, exercise intolerance, hearing loss, diabetes, short stature

https://www.mda.org/disease/mitochondrial-myopathies/types

Friedreick's Ataxia PT/OT HELPS

- Aggressive scoliosis POSITIONING, BRACING, EXERCISES
- Diabetes ENCOURAGE PROPER DIET AND EXERCISE
- Heart conditions MONITOR DURING ACTIVITY
- Unaffected mental abilities RESPECT

Scoliosis Bracing

Milwaukee brace

Boston Brace (left)
TLSO (right)

Considerations while treated by PT

Encephalomyopathy

- Migraines, Seizures
- Intellectual disability
- Visual issues: eye itself (retinopathy) or parts of brain involved in vision (optic nerve atrophy)
- Sensorineural Hearing loss: damage to cochlea in inner ear or the auditory nerve
- Neuropathy
- Other co-morbidities

Mitochondrial disease

- Diabetes
- Heart conduction block (arrhythmia) or cardiomyopathy (heart muscle weakness)
- Respiratory muscle weakness
- Gastrointestinal problems
- Kidney problems

Characteristics treated often by PT
Muscle weakness and atrophy

Posture and Torso Alignment System

For flexible kyphosis and lordosis, hypotonia, weak trunk, difficulty maintaining midline and sitting balance

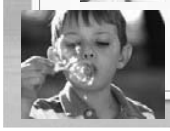
- Improved posture and core strength
- Improved respiratory capacity
- Increased sensory awareness
- Reduced torso deviation
- Gentle shoulder retraction
- Gentle scapular stabilization

Characteristics treated often by PT
Positioning

https://www.google.com/search?q=positioning+children+with+muscledefs=1C1KMZB_enUS625US625&source=lnms&tbm=isch&sa=X&ved=0ahUKEwiXo47K457ThAhWGy1MKHdSbAvcQ_AUICigB&biw=1280&bih=939

Characteristics treated often by PT
Lethargy and Exercise Intolerance

- Weakness in muscles that support breathing
- Altered control over breathing



Characteristics treated often by PT
Developmental delay

- Due to muscle weakness and brain abnormalities
- Longer time to reach motor milestones, speech and learning difficulties

https://www.google.com/search?q=positioning+children+with+muscledefs=1C1KMZB_enUS625US625&source=lnms&tbm=isch&sa=X&ved=0ahUKEwiXo47K457ThAhWGy1MKHdSbAvcQ_AUICigB&biw=1280&bih=939

Characteristics treated often by PT
Low muscle tone (hypotonia)

https://www.google.com/search?q=physical+therapy+hypotonia&defs=1C1KMZB_enUS625US625&source=lnms&tbm=isch&sa=X&ved=0ahUKEwiFkaGbjL_hAhUGAhoKHWC2pQ_AUICigB&biw=1280&bih=939

Typical Motor Milestones

1 Month: Momentary head elevation with minimal forearm support in prone

2 Months: head elevation to 45 degrees in prone; prone on elbows with elbows behind shoulders

4 Months: Rolls prone to side and side to supine

6 Months: Sits Independent

8-9 Months: Belly crawls and Creeps

10 – 15 Months: begin to walk unassisted, squat

2 years: Runs well

3 years: Rides tricycle, kicks ball

4 years: stand on tip toes

5 years: skips, dresses self

https://www.google.com/search?q=1C1KMZB_enUS625US625&biw=1280&bih=939&tbm=isch&sa=1&ei=vyi4W7vfJ8zm5gLB3aHACw&q=typical+motor+milestones&oq=typical+motor+milestones&gs_l=img.3.0i24l3.9001383897910.9086042.6.14.1.1.1.0.186.1100.15j1.14.0...0...1c.1.64.img..0.25.1229...0j46761j35i39k1j0i30k1j0i67k1.0.DTTIEEJPd-I

Characteristics treated often by PT
Ataxia

- Associated with mitochondrial encepahlomyopathy
- Balance and coordination dysfunction increases falls chances
- Vision loss due to optic atrophy or retinopathy causes visual impairment.

Thanks so much!

References

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- http://www.medicalsymptomsguide.com/mitochondrial-disease.html
- http://www.umdf.org/wp-content/uploads/2017/03/Mitochondria-Capaldi.pdf
- https://www.genpharmservices.com/aspire-educational-series-mitochondrial-myopathy-mm-part-13/

References

- http://www.mitoaction.org/
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- http://www.umdf.org/
- https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Mitochondrial-Myopathy-Fact-Sheet

Occupational Therapy and Adaptive Equipment for Mitochondrial Disorder

Missy Bryan, OTD, OTR/L, ATP, CPST

Conflict of Interest Statement

- The presenter has no financial relationship with any of the manufacturers or suppliers of products shown in the presentation.
- Equipment photos in the presentation are examples of the variety of equipment, but not an endorsement for any of the specific products.
- The array of equipment shown in this presentation is only a limited sample of equipment that is available.

Occupational Therapy

- What – Therapeutic use of everyday life activities
- Why – To enhance or enable participation in roles, habits, and routines
- Where – Home, school, workplace, community

Occupations

- Activities of daily living
- Rest and sleep
- Education
- Work
- Play
- Leisure
- Social participation

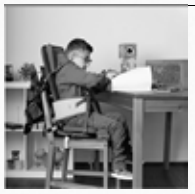
Approaches

- Address symptoms
- Remediate – enhance skill or performance to facilitate participation
- Modify – adapt activity or technique to enhance participation or independence
- Prevent – develop strategies to prevent decreased participation

Assistive Technology

- Positioning chairs
- Adaptive equipment for activities of daily living
- Bathing and toileting equipment
- Car seats
- Wheelchairs
- Standers, gait trainers, and walkers (see physical therapy)
- Commercial products to high-end medical equipment

Adaptive Seating



Adaptive Equipment for Activities of Daily Living

Bathing and Toileting

Adaptive Car Seats

Walkers and Standers

Wheelchairs

Tips for Selecting Adaptive Equipment

- Work with therapist and DME supplier who are familiar with equipment
- Make decisions as a team
- Consider short term and long term needs
- Consider low tech and high tech options
- Try the products out when possible
- Consider how product will integrate into your routine

References (in order of appearance)

- https://www.fireflyfriends.com/us/goto-seat
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- http://www.inspiredbydrive.com/product/contour-wrap-around-bath-support/
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- http://www.inspiredbydrive.com/product/aqualift
- http://www.inspiredbydrive.com/product/spirit-plus-car-seat/

References (in order of appearance)

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- http://www.merrittcarseat.com/
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- https://i1.wp.com/easystand.com/wp-content/uploads/2016/01/Bantam-Medium-Nick.jpg?fit=3370%2C3370&ssl=1
- http://www.jenx.com/product/multistander/
- https://www.convaid.com/ez-rider/
- http://www.sunrisemedical.com/manual-wheelchairs/zippie/rigid-wheelchairs/zone#prettyPhoto
- http://www.quantumrehab.com/ilevel-power-chairs/

Notes

Afternoon Session

Ask the Mito Doc - Child

Moderator: UMDF Staff
Panel Speakers: Mary Kay Koenig, MD; Richard Haas, MD ; Russell Saneto, DO, PhD; and Annette M. St. Pierre-MacKoul, MD

Notes

Afternoon Session

Practical Strategies to Enhance Independence Workshop

Terena Scott

Notes

Afternoon Session

Genetics 101

Tyler Reimschisel, MD

Genetics 101

UMDF Mitochondrial Medicine 2018
Nashville, TN
June 29, 2018

Tyler Reimschisel, MD, MHPE
Vice Chair for Education, Department of Pediatrics
Associate Professor of Pediatrics & Neurology
Director, Division of Developmental Medicine
and the Center for Child Development
Director, Vanderbilt Consortium LEND

Disclosure

Tyler Reimschisel, MD, MHPE receives research support from Shire Pharmaceutical. The content of this presentation does not relate to the research supported by Shire Pharmaceutical.

Learning Objectives

At the completion of this presentation, attendees should be able to:

1. Compare and contrast mitochondrial disease with mitochondrial inheritance.
2. Discuss the genetics of mitochondrial diseases, including features unique to mtDNA (polyplasmy, heteroplasmy, & threshold effect).
3. Discuss the typical clinical features and laboratory manifestations of mitochondrial diseases.

Case

- 17-year-old girl with new onset seizures
- After the seizure, she is asleep
- So cannot obtain history
- Initial labs
  - Glucose: normal
  - White blood cell count (infection): normal
  - Acidotic

Case: Additional History

- Past medical history: hearing loss
- Family history:
  - Mother deceased from strokes & epilepsy
  - Maternal grandmother deceased from strokes
  - Multiple family members with hearing loss

Case: Additional Labs

- Lactate = 9.7 (0.5-2.2); repeat =7.3
- Liver enzymes (AST & ALT): normal
- CK: normal
- Plasma amino acids: elevated alanine
- Urine organic acids
  - Lactate > 1000 (<101)
  - Pyruvate > 500 (<31)
- mtDNA mutation analysis: A3243G mutation
- Diagnosed with MELAS and placed on mitochondrial cocktail (including arginine)

Case: Follow Up

- 8 months later: right-sided stroke
- 13 months later: left-sided stroke
- Seizures treated with Keppra
- Recurrent strokes with accumulating physical impairment

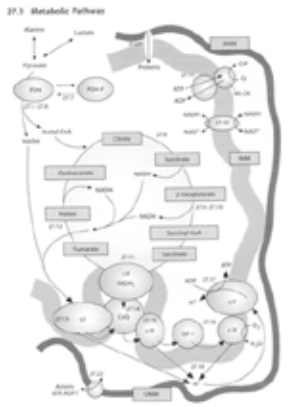
Definition of "Mitochondrial Cytopathy"

Although multiple biochemical reactions in a variety of metabolic pathways occur within the mitochondria, the term "mitochondrial cytopathy" refers to diseases that are caused by primary or secondary dysfunction of the respiratory chain

Human Cell

From https://gcps.desire2learn.com

Respiratory Chain



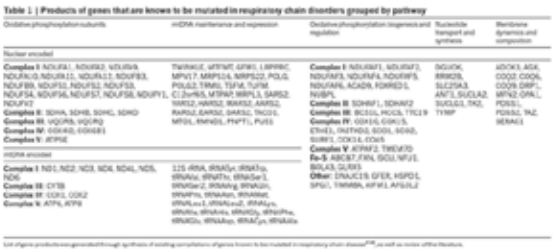
From Blau, *Physician´s Guide to the Laboratory Diagnosis of Metabolic Diseases*, 2003

Respiratory Chain Complexes

Complex I	Complex II	Complex III	Complex IV	Complex V
NADH dehydrogenase - ubiquinone oxidoreductase	Succinate dehydrogenase - ubiquinone oxidoreductase	Ubiquinone - cytochrome C oxidoreductase	Cytochrome C oxidase	ATP synthase
45 subunits • 7 mtDNA encoded	4 subunits • 0 mtDNA encoded	10 subunits • 1 mtDNA encoded	19 subunits • 3 mtDNA encoded	19 subunits • 2 mtDNA encoded

- 2 electron carriers (coenzyme Q10 and cytochrome C)
- 60 additional nucleus-encoded enzymes for assembly and function of subunits
- Estimated to include about 1000 genes total

Genes Mutated in Mitochondrial Cytopathies



Vafai and Mootha. Nature (491) 2012.

Mitochondrial DNA

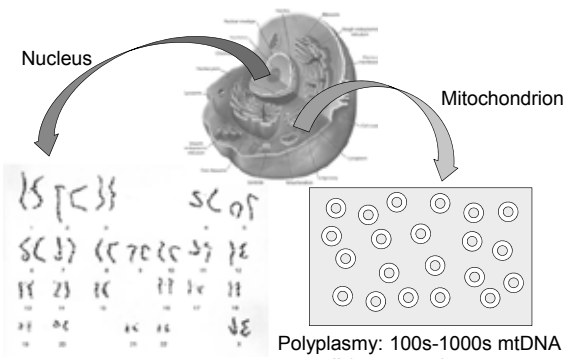
- 16,569 base pairs
- 37 genes
  - 24 genes for translation
    - 2 rRNAs
    - 22 tRNAs
  - 13 encode subunits of respiratory chain

Figure 3. Mutations in the Human Mitochondrial Genome That Are Known to Cause Disease.

From DiMauro et al. *Seminars in Neurology* 2003;21(3):254.

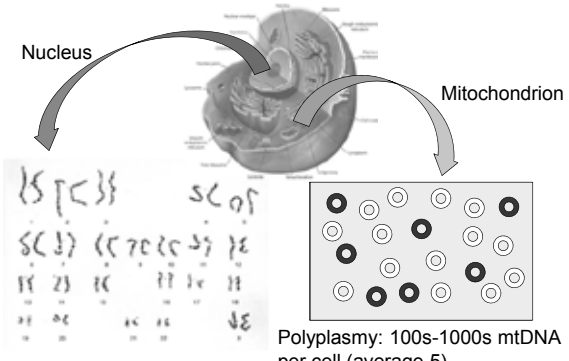
Mitochondrial DNA

- Maternal inheritance
  - Mitotic segregation is random
  - All offspring of mother will inherit abnormal mitochondria if in germline
    - Variable dose of abnormal mtDNA
  - No offspring of affected males will inherit abnormal mitochondria
    - Case report of paternal inheritance (Schwartz et al. NEJM 2002;347:576)



23 pairs of chromosomes

Polyplasmy: 100s-1000s mtDNA per cell (average 5)



23 pairs of chromosomes
Up to two alleles per gene

Polyplasmy: 100s-1000s mtDNA per cell (average 5)
Heteroplasmy: cell with mixed normal and mutated genomes

Threshold Effect

- Minimum number of mutated mtDNA that must be present to cause OXPHOS dysfunction
- Abnormal phenotype develops when threshold is exceeded (most common with skewed heteroplasmy)
- Threshold is lower in tissues with higher oxidative requirements (brain, muscle, retina, heart, kidney, endocrine glands)

mtDNA Genetics and Clinical Variability

- Determinants of clinical variability
  - Type of mutation
  - Percentage of mutated mtDNA
  - Varying heteroplasmy in different tissues
  - Variable threshold in different tissues
  - Mutations can accumulate over time
- Ubiquitous mutations can have tissue-specific manifestations
  - Deafness from 12S rRNA mutation
  - Cardiomyopthy due to $tRNA^{Ile}$ mutations
  - Optic atrophy due to NADH dehydrogenase (complex I) mtDNA mutations

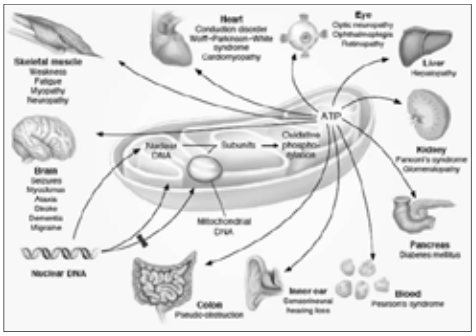
Inheritance of Mitochondrial Cytopathies

- mtDNA mutations
  - Sporadic (esp. large scale deletions)
  - Maternal inheritance
- Nuclear DNA mutations
  - Autosomal dominant
  - Autosomal recessive
  - X-linked (*DDP1* mutation → deafness-dystonia syndrome)

Progressive External Ophthalmoplegia

- Large deletion in mtDNA
  - Sporadic
  - Weakness, exercise intolerance, ophthalmoplegia, ptosis
  - Lactic acidosis, ragged red fibers
- Autosomal dominant forms
  - Various mutations
    - *Twinkle* (mitochondrial DNA helicase)
    - *ANT1* (adenine nucleotide translocator)
    - *POLG1*
  - Proximal limb weakness, peripheral neuropathy, hearing loss, cataracts, depression, endocrine dysfunction
- Autosomal recessive form
  - Cardiomyopathy and ophthalmoplegia
  - Mutations of tyrosine phosphorylase - PEO + MNGIE

Clinical Presentations of Mitochondrial Disease



Johns DR. N Engl J Med 1995;333:638-44

Common Clinical Manifestations

- Brain
  - Seizures
  - Myoclonus
  - Ataxia
  - Stroke
  - Intellectual disability
  - Dementia
  - Migraines
- Neuromuscular
  - Neuropathy
  - Weakness
  - Fatigue
  - Myopathy
- Cardiac
  - Cardiomyopathy
  - Conduction block
  - Dysrhythmias/WPW
- Ears
  - Sensorineural hearing loss
- Eyes
  - Optic atrophy
  - Ophthalmoplegia
  - Pigmentary retinopathy
  - Cataracts
  - Ptosis
- Blood
  - Anemia
- Gastrointestinal
  - Dysmotility
  - Pancreatitis
- Liver
  - Hepatopathy
- Kidney
  - Fanconi syndrome
  - Glomerulopathy
- Endocrine
  - Short stature
  - Diabetes mellitus
  - Hypoparathyroidism
  - Hypothalamic hypogonadism
  - Adrenal insufficiency

Laboratory Manifestations of Mitochondrial Cytopathies

- Screening with basic labs (complete blood count, comprehensive metabolic panel, CK level, lactate, pyruvate, uric acid
- Biochemical labs: plasma amino acids, urine organic acids, acylcarnitine profile
- Neurodiagnostic studies: brain MRI with spectroscopy, EEG, EMG/nerve conduction, rarely muscle biopsy

Possible Laboratory Manifestations

- Complete blood count (CBC)
  - White blood cells, red blood cells, platelets
  - Low individual cell lines
  - All cell lines decreased (pancytopenia)
- Comprehensive metabolic panel (CMP)
  - Acidosis
  - Elevated BUN and creatinine (kidney disease)
  - Elevated liver enzymes
  - Low calcium
- Increased CK

Possible Laboratory Manifestations

- May have elevated lactate (plasma, cerebrospinal fluid)
  - May have chronic elevation
  - May only be elevated pre- and/or post-prandial
- May have elevated alanine
- May have elevated pyruvate
- May have sbnormalities on urine organic acids
- May have low carnitine

Possible Laboratory Manifestations

- Aminoaciduria (Fanconi syndrome)
- UOA: Krebs cycle intermediates, dicarboxylic acids, tiglyglycine, ethylmalonate, 3-methylglutaconate, 2-methylsuccinate, butyrylglycine, isovaleryl glycine
- Carnitine can be low

Laboratory Manifestations

- Electroencephalogram (EEG)
  - No specific abnormalities
  - May show propensity to seizures
  - Rarely see electrographic seizure
- Electromyography (EMG)
  - May show muscle disease (myopathy)
- Nerve conduction study
  - May show nerve disease (neuropathy)

Brain MRI: Leigh Syndrome

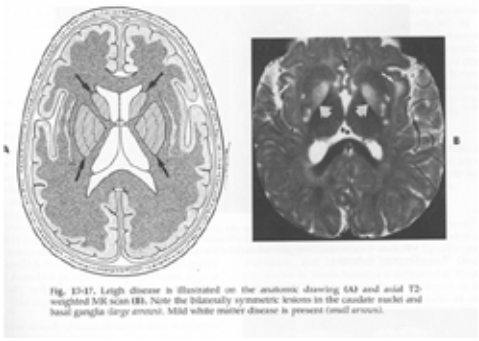


Fig. 17-17. Leigh disease is illustrated on the anatomic drawing (A) and axial T2-weighted MR scan (B). Note the bilaterally symmetric lesions in the caudate nuclei and basal ganglia (*large arrows*). Mild white matter disease is present (*small arrows*).

From Osborn. *Neuroradiology*, 2000

Brain MRI

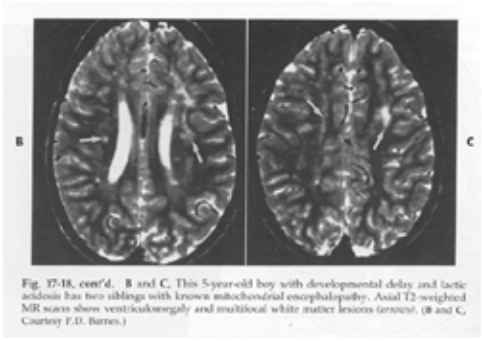


Fig. 17-18, cont'd. B and C, This 5-year-old boy with developmental delay and lactic acidosis has two siblings with known mitochondrial encephalopathy. Axial T2-weighted MR scans show ventriculomegaly and multifocal white matter lesions (*arrows*). (B and C, Courtesy F.D. Barnes.)

From Osborn. *Neuroradiology*, 2000

Muscle Biopsy*

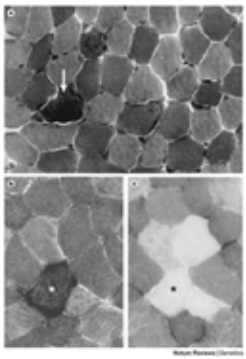


Figure 4 | **Muscle phenotypes of OXPHOS disorders.** **a** | Ragged-red fibres (RRFs) revealed by the modified Gomori trichrome stain. Abnormal deposits of mitochondria appear as reddish blotches in the subsarcolemmal or intermyofibrillar space (arrow). **b**, **c** | Serial sections of a muscle biopsy from a patient with a mitochondrial DNA (mtDNA) single deletion. In **b**, the RRF (white asterisk) is highlighted by the histochemical stain for succinate dehydrogenase, an enzyme entirely encoded by nuclear DNA. In **c**, the same fibre shows no activity for cytochrome *c* oxidase, an enzyme containing ten subunits encoded by nuclear DNA and three encoded by mtDNA (see text). (Courtesy of Eduardo Bonilla, Columbia University.)

(From Smeitink et al. Nature Reviews: Genetics 2001;2:342)

Cardiac Manifestations

- Electrocardiogram (ECG or EKG)
  - Conduction abnormalities
- Echocardiogram
  - Cardiomyopathy

United Mitochondrial Disease Foundation

Mitochondrial Disease Community Registry

www.umdf.org/registry

Who?
Patients, caregivers & family members
Confirmed diagnosis ***NOT*** required

Why?
Need patient data collected over time in order to improve diagnoses and develop treatments

Key
Registrants have full control of privacy settings

- Allow, deny or “ask me”
- Who can see anonymous data
- Who can analyze anonymous data
- Who can contact you about research studies and clinical trials

Notes

Afternoon Session

Closing Session – What's on the Horizon! Scientific Meeting Highlights and Upcoming Clinical Trial Updates

Amy Goldstein, MD; Philip Yeske, PhD
NAMDC Study Updates – Kris Englestad
Other company updates - TBD

Notes

UMDF Funded Grant Projects

UNITED MITOCHONDRIAL DISEASE FOUNDATION®

HOPE. ENERGY. LIFE.

2017 UMDF Grant Recipients

Chairman's Award
Prashant Mishra, MD, PhD
University of Texas Southwestern Medical Center
Children's Research Institute
$100,000

"Identification of SLC Family Members as Predictive Biomarkers for Mitochondrial Disease"
The development and validation of blood based biomarkers for mitochondrial disease remains a top priority in the research community. This project investigates the potential use of specific solute carrier (SLC) family members in blood serum as novel predictive biomarkers of mitochondrial disease. Preliminary data generated in Dr. Mishra's lab indicates that SLC family members are not only altered in the disease setting, but could also serve as therapeutic development targets.

New and Early Principal Investigator Award
Rustum Karanjia, MD, PhD
Doheny Eye Center
UCLA
University of Ottowa
$100,000

"Photopic Negative Response as an Objective Biomarker in Mitochondrial Disease"
Many forms of mitochondrial disease have eye-related symptoms, including LHON, DOA, Leigh Syndrome and MELAS. There is a significant and need for better measurements of eye function as it relates to disease progression. Dr. Karanjia intends to measure eye cell electrical activity over 18 months in affected individuals utilizing Photopic Negative Response (PhNR). This data will help to validate PhNR as a potential biomarker for optic nerve function in mitochondrial disease patients.

Postdoctoral Fellowship Award
Melissa Anne Walker, MD, PhD
Massachusetts General Hospital
$100,000

"A Single Blood Draw Test of Mitochondrial Disease"
here are currently no consensus biomedical tests for mitochondrial disease due to its complex and diverse nature, a situation which makes effective diagnosis and treatment extremely challenging. The goal of Dr. Walker, working in the lab of Dr. Vamsi Mootha, is to develop a rapid, facile blood test for mitochondrial activity based on a single blood draw. Preliminary data points to a simple, inexpensive test that could be applied in any standard clinical laboratory. The funds provided by the UMDF will allow for continued development and validation of this assay in both healthy controls as well as affected individuals with a genetically confirmed diagnosis of mitochondrial disease.

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2016 UMDF Grant Recipients

Short Summaries by Phil Yeske, PhD

Chairman's Award

Nicola Brunetti-Pierri, MD, FACMG, Associate Investigator, Telethon Institute of Genetics and Medicine (Italy), "*Phenylbutyrate Therapy for Pyruvate Dehydrogenase Deficiency, Small Clinical Study Award*" - 1 year/$25,000

This grant, winner of the 2016 Chairman's Award for highest rated research proposal after peer review, is a clinical study of a new potential therapy for pyruvate dehydrogenase complex (PDHC) deficiency by lowering lactate levels. This project comes 5 years after Dr. Brunetti-Pierri received a UMDF grant to first test phenylbutarate on patient cells. Subsequent animal model studies confirmed the promising in vitro data that resulted from the first grant, and now a pilot clinical trial will be carried out across multiple centers in Italy. Positive results from the pilot study would lead to a larger study directed toward PDHC deficiency patients.

Brendan J. Battersby, Ph.D., Research Director, Biomedicum Helsinki, Research Programs Unit-Molecular Neurology, University of Helsinki (Finland), "*Investigating the Pathogenesis of C12orf65 Deficiency in Mitochondrial Translation and Mitochondrial Disease*" - Principal Investigator Award, 2 years/$70,000

The goal of this research project led by Dr. Battersby is to address a significant gap in mechanistic knowledge within the mitochondrial field- ribosome function and translation. The outcome of this work could provide unique insights into the broad range of mitochondrial disease symptoms that result from mutations in the C12orf65 gene.

Alessandro Bitto, Ph.D., Department of Pathology, University of Washington Medical Center (USA), "*Molecular Mechanisms for Suppression of Mitochondrial Disease by Acarbose, Postdoctoral Fellowship Award*" - 2 years/$70,000

Dr. Bitto, under the mentorship of Dr. Matt Kaeberlein, will evaluate an FDA-approved drug called acarbose for efficacy in a translational mouse model of Leigh Syndrome. The drug impacts mTOR signaling, an important mitochondrial function pathway whose understanding could open up a broad therapeutic strategy for mitochondrial disease.

Adam Hughes, Ph.D., Assistant Professor of Biochemistry, University of Utah School of Medicine (USA), "*Quality Control of Unimported Mitochondrial Precursor Proteins, Principal Investigator Award*" - 2 years/$100,000

Utilizing yeast models, Dr. Hughes intends to explore the link between loss of mitochondrial membrane potential and mis-targeted mitochondrial proteins. That the accumulation of such proteins and their associated "waste disposal" is a source of mitochondrial pathology is a novel and intriguing premise that could open up many new avenues in future research.

Leo Nijtmans, Ph.D., Radboud University Medical Centre, Nijmegen (Netherlands), "*Mitochondrial Complexome Profiling Provides a Novel Tool to Diagnose and Understand Complex I Deficiency*" - Principal Investigator Award, 1 year/$40,000

Complex I disorders are some of the most common types of mitochondrial disease. Dr. Nijtmans will utilize a profiling technique to study protein interactions within Complex I using patient cell lines. The results will provide insight into Complex I assembly and function, and could ultimately lead to new therapeutic targets for investigation.

George A. Porter, Jr., MD, Ph.D., Assistant Professor, Department of Pediatrics, Division of Cardiology, University of Rochester Medical Center (USA), "*Manipulating the Permeability Transition Pore to Ameliorate Neonatal Heart Failure*" - Principal Investigator Award, 2 years/$100,000

Many types of mitochondrial disease have associated cardiomyopathies. In this translational research project Dr. Porter will test potential therapies for cardiomyopathies in a mouse model. Success in this project would initially open the possibility for treating neonates with bioenergetics disorders, and eventually have potential for more broadly treating mitochondrial disease patients with Complex I disorders.

Eric A. Shoubridge, Ph.D., Professor and Chair, Department of Human Genetics, Montreal Neurological Institute, McGill University (Canada), "*Interrogating the Mitochondrial Interactome Using BioID, Principal Investigator Award*" - 2 years/$75,000

Dr. Shoubridge's project will identify functional networks within the mitochondria based on the analysis of protein-protein interactions. In addition to the potential for revealing new insights into mitochondrial disease, the availability of a mitochondrial protein interactome will be a generally useful resource for addressing basic questions regarding mitochondrial structure and function in both a normal and diseased state.

Zarazuela Zolkipli Cunningham, MBChB MRCP, Division of Neurology,The Children's Hospital of Philadelphia (USA), "*Development and Validation of a New Outcome Measure in Mitochondrial Disease*" - Small Clinical Study Award, 1 year/$25,000

Dr. Zolkipli Cunningham and collaborators aim to develop a new outcome measure for mitochondrial myopathy that is specifically designed for use in Phase II/III clinical trials. The patient perspective will be critical to the project, helping to ensure that meaningful measures are developed over the full range of disease state- from early ambulatory to late non-ambulatory. Recognizing the urgent need for improved clinical trial endpoints, the development of this scale will build upon existing scales and tools.

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2015 UMDF Grant Recipients

Short Summaries by Phil Yeske, PhD

Chairman's Award

John Christodoulou, PhD, Children's Hospital at Westmead, New South Wales, Australia.
"Utility of FGF21 and GDF15 as Diagnostic and Prognostic Biomarkers of Mitochondrial Respiratory Chain Disorders." - $100,000 over 2 years

Dr. Christodoulou will validate optimal methodology in a clinical diagnostic laboratory setting to determine the utility of measuring FGF-21 and GDF-15 as biomarkers of pediatric mitochondrial disease. This has become a major question in the field, as to how potentially useful in terms of sensitivity and specificity these biomarkers are for mitochondrial disease.

Daniel F. Bogenhagen, MD, Department of Pharmacological Sciences, Stony Brook University.
"Kinetics of Mitochondrial Complex Assembly." - $100,000 over 2 years

Dr. Bogenhagen is utilizing mass spectrometry techniques to study the assembly map of the mitoribosome as well as the mitochondrial respiratory complexes. The improved understanding of both of these mitochondrial construction projects will enhance the diagnosis and future therapy of mitochondrial disorders.

Peter W. Stacpoole, PhD, MD, Department of Medicine, University of Florida.
"Validation of an Observer Reported Outcome (ObsRO) Measure of Home Functionality in Children with Pyruvate Dehydrogenase Complex Deficiency (PDCD)." - $24,898 for 1 year

Dr. Stacpoole, in response to a specific request from the FDA for information from the patient or patient family to aid in regulatory decisions, has developed an innovative computer tool to track home functionality of pediatric PDCD patients. The pilot study in 10 PDCD families will test the feasibility of the survey instrument and refine it as needed for its eventual use in a planned Phase III trial of dichloroacetate (DCA). If the trial shows DCA is found safe and effective, it could lead to this drug being designated as the first FDA-approved therapy for PDCD.

Dr. Atif Towheed, PhD, Department of Pathology and Laboratory Medicine, Children's Hospital of Philadelphia.
"Allotopic RNA Rescue of LHON Mouse Model." - $70,000 over 2 years

The goal of Dr. Towheed's work is to develop a novel gene therapy strategy for the treatment of Leber hereditary optic neuropathy (LHON) utilizing a mouse model developed in the labs of Dr. Douglas C. Wallace. If this therapeutic approach is successful it could inhibit the onset of the optic nerve pathology.

Sara M. Nowinski, PhD, Department of Biochemistry, University of Utah.
"Characterizing the Function of the Atypical Mitochondrial Kinase ADCK3." - $70,000 over 2 years

The studies in Dr. Nowinski's grant will improve the understanding of ADCK3 function in the synthesis of coenzyme Q and cerebellar ataxia. Additionally, better treatment strategies for mitochondrial disease could be developed in the future if new roles for ADCK3 are identified.

Anu Suomalainen Wartiovaara, MD, PhD, University of Helsinki, Finland.
"Vitamins B as Therapy for Disorders with mtDNA Instability." - $100,000 over 2 years

Dr. Suomalainen Wartiovaara will utilize a mouse model to build upon preliminary results indicating that vitamins B, especially B3 (Niacin) play key metabolism regulatory roles in patients with mitochondrial myopathies. Pre-clinical data generated in mice will inform the creation of a follow-up human clinical trial on the impact of Niacin supplementation for the alleviation of symptoms due to mitochondrial disease.

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2014 UMDF Grant Recipients

Short Summaries by Steven G. Bassett, PhD

Chairman's Award

Hubert Smeets, PhD, Department of Genetics and Cell Biology, Maastricht University, The Netherlands - $25,000 for 1 year
"Development of an autologous myogenic stem cell therapy for carriers of a heteroplasmic mtDNA mutation, a proof of principle study in m.3243A>G mutation carriers."
Dr. Smeets has developed a process using transplantation of a patient's own muscle stem cells that have been freed of mitochondrial DNA mutations. The resulting formation of normal muscle fibers promises to set the stage for significant new therapies for mitochondrial disease.

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Carlos Moraes, PhD, Department of Neurology, University of Miami Miller School of Medicine - $120,000 over 2 years
"Developing specific mitochondrial nucleases to eliminate mutant mtDNA."
Dr. Moraes has developed a process for removing disease-causing mitochondrial DNA mutations from affected mitochondria. Extension of this research seems likely to lead to the development of gene therapies for human mitochondrial disease.

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Michael James Bell, MD, University of Washington DC - $25,000 for 1 year
"Improving CNS delivery of brain antioxidants after acute metabolic decompensation in mitochondrial disease."
Dr. Bell will investigate a combination of two FDA-approved drugs for their effectiveness in treating children and young adults with Leigh's Syndrome. This work has the potential to improve brain function in patients with a mitochondrial disease for which there are currently no proven treatments.

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Francisca Diaz, PhD, Department of Neurology, University of Miami Miller School of Medicine - $80,000 over 2 years
"Modulation of GSK3 activity and enhancement of glycolysis to maintain neuronal survival in Complex IV deficient mice."
Dr. Diaz is using a much studied mouse model in which a mitochondrial respiratory enzyme has been deactivated in nerve cells. She will study the effectiveness of modulating glucose metabolism as a treatment for these mice, with the potential for extending this therapy to human mitochondrial disease patients.

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Scot Leary, PhD, Department of Biochemistry, University of Saskatchewan - $120,000 over 2 years
"Targeted delivery of copper to mitochondria: investigating its therapeutic potential for the effective treatment of patients with mutations in SCO1 and SCO2."
Dr. Leary is investigating therapies for copper delivery to mitochondria in patients with impaired ability to synthesize a vital mitochondrial respiratory enzyme that requires copper as a building block. This research could lead to the development of early intervention therapies for mitochondrial disease.

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Erin Seifert, PhD, Department of Pathology, Thomas Jefferson University, Philadelphia - $120,000 over 2 years
"Pathogenesis of myopathies caused by mitochondrial phosphate carrier mutations."
Dr. Seifert is studying mutations that severely affect the delivery of phosphate for ATP synthesis in the mitochondria of skeletal muscle and the heart. This foundational research will provide new insights into important mechanisms responsible for mitochondrial disease.

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2013 UMDF Grant Recipients

Short Summaries by Steven G. Bassett, PhD

Chairman's Award
James Stewart, PhD, Max Planck Institute for the Biology of Ageing, Cologne, Germany - $90,000 over 2 years
"Using mtDNA mutator mouse-derived lineages to generate mouse models of human mitochondrial diseases."
By working with mice that are prone to mitochondrial mutations, Dr. Stewart will develop new genetic models of human disease. Once established, these mouse models can be used for the development of new drug therapies.

Alberto Sanz-Monterro, PhD, University of Tampere, Tampere, Finland - $100,000 over 2 years
"A Genome-wide RNAi Screening to Identify New Genes Involved in Mitochondrial Diseases."
Dr. Sanz-Monterro will use a well-understood fruit-fly model to discover previously unknown genetic defects that can cause mitochondrial disease. Many mitochondrial disease patients have not had a specific genetic mutation linked with their disease, and this research will help to fill that gap.

Rajesh Ambasudhan, PhD, Sanford-Burnham Medical Research Institute, La Jolla, California - $84,000 over 2 years
"A Human Reprogrammed-Cell Model of MELAS."
Dr. Ambasudhan will obtain skin cells from MELAS patients and reprogram them as nerve cells to be grown in culture. This "disease-in-a-dish" model will be used to gain insights into mitochondrial dysfunction in MELAS and other mitochondrial diseases.

Natalie Niemi, PhD, University of Wisconsin, Madison, Wisconsin - $75,000 over 2 years
"Utilizing dynamically regulated phosphorylation as a means to modulate mitochondrial metabolism."
Dr. Niemi will study mechanisms that activate enzymes in the mitochondria, with the goal of understanding how this regulation is impaired in mitochondrial disease. This could lead to new therapeutic options for mitochondrial disease patients.

Gerald Shadel, PhD, Yale University Medical School. - $120,000 over 2 years (co-funded by UMDF and MitoCon)
"Characterization of disease-specific mitochondrial stress-signaling pathways in vivo as potential therapeutic targets for mitochondrial diseases."
Dr. Shadel will use a mouse model to identify important stress signaling pathways than can then be related to mitochondrial dysfunction in humans. This could enable repurposing of existing therapeutics as well as development of new therapies.

2013 Clinical Fellowship Training Award

Amel Karaa, MD, Harvard Medical School and Massachusetts General Hospital, Boston MA - $70,000 for 1 year

"Hypogonadotropic hypogonadism in mitochondrial disease: prevalence, phenotypic heterogeneity and hormonal spectrum variations in a tertiary hospital cohort."

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2012 UMDF Grant Recipients

Short Summaries provided by Steven G. Bassett, PhD

Chairman's Award

Carla Giordano, MD, PhD, University of Rome - $108,000 over 2 years (co-funded by UMDF and MitoCon)

"Estrogen mediated regulation of mitochondrial biogenesis and functions: possible therapeutic implications for Leber's hereditary optic neuropathy."

Dr. Giordano will use phytoestrogens, plant compounds with estrogenic properties, to enhance mitochondrial energy metabolism. This research could result in effective treatments for a progressive mitochondrial disease that severely impairs vision.

William James Craigen, MD, PhD, Baylor College of Medicine - $100,000 over 2 years

"Testing Gene Therapy in an Animal Model of Mitochondrial Respiratory Chain Disorders."

Dr. Craigen's lab is developing procedures using viruses to deliver the correct genetic information to mice that have defective mitochondria, in an attempt to greatly improve their energy metabolism. This could lead to the development of an effective gene therapy for young mitochondrial disease patients.

Mariana G. Rosca, MD, Case Western Reserve University - $100,000 over 2 years

"Rescuing complex I defective mitochondria and target organs with methylene blue."

Dr. Rosca is developing a treatment that could bypass a defective mitochondrial enzyme, enhancing energy metabolism. Improving the performance of mitochondria in this way could address a defect that is responsible for a third of all mitochondrial disease cases.

Javier Torres-Torronteras, PhD,Vall d'Hebron Research Institute, Barcelona, Spain - $93,000 over 2 years

"Preclinical studies for the gene therapy of mitochondrial neurogastrointestinal encephalomyopathy (MNGIE). Long-term follow-up and use of adeno-associated viral vectors."

Dr. Torres-Torronteras will investigate the effectiveness of a gene therapy that he developed for use in mice with mitochondrial disease. This research will aid in determining the best approaches for treating human mitochondrial disease with gene therapy.

David A. Sinclair, PhD, Harvard Medical School - $80,000 over 2 years

"Ultra-high-throughput screening for mitochondrial enhancers as novel targets for treating mitochondrial diseases."

Dr. Sinclair will screen a large number of genes for their ability to enhance mitochondrial energy metabolism. Applying his findings to cell culture models of various mitochondrial diseases could lead to the discovery of new treatments.

Nuno Raimundo, PhD, Yale University School of Medicine - $50,000 over 1 year

"Mechanisms and treatment of mitochondrial deafness."

Dr. Raimundo has developed an animal model for the study of hearing loss due to a mutation in mitochondrial DNA. The insights gained from this research could lead to the prevention and treatment of a type of deafness that is linked to mitochondrial malfunction.

2012 Clinical Fellowship Training Award

Lisa Emrick, MD, Baylor College of Medicine, Houston, TX - $60,000 over 1 year

"Characterization of Neurologic Deficits and Response to Treatment in Patients with MELAS and other Mitochondrial Disorders."

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2011 UMDF Grant Recipients

Short Summaries provided by Steven G. Bassett, PhD

Chairman's Award
Brett A. Kaufman, PhD, Department of Animal Biology, University of Pennsylvania - $120,000 for 2 years
"Regulatory mechanisms governing TFAM-mediated mtDNA copy number control."
Dr. Kaufman research could lead to therapies that would increase the number of copies of normal mitochondrial DNA in patients with specific types of mitochondrial disease.

Chairman's Award
Nicola Brunetti-Pierri, MD, Telethon Institute of Genetics and Medicine, Fondazione Telethon, Rome, Italy - $120,000 for 2 years
"Therapeutic Interventions for Pyruvate Dehydrogenase Deficiency."
Dr. Brunetti-Pierri is seeking safe and effective treatments for a genetic condition that causes deficiencies of an important enzyme in the energy pathway of mitochondria.

Miguel Garcia-Diaz, PhD, Department of Pharmacological Sciences, Stony Book University, New York - $100,000 for 2 years
"Deficiencies of tRNA maturation and the pathogenesis of mitochondrial diseases."
Dr. Garcia-Diaz will study the regulation of mitochondrial transfer RNAs, molecules that are intrinsic to synthesis of the energy metabolism enzymes in mitochondria.

Ying Dai, MD, PhD, Department of Neurology, Beth Israel Deaconess Medical Center, Boston - $80,000 for 2 years
"Driving Selection Against Heteroplasmic Mitochondrial DNA Mutations by Enhancing Mitophagy."
Dr. Dai hopes to develop a mechanism whereby mitochondria with abnormal mutated mitochondrial DNA will be eliminated from cells, with the goal of restoring normal function.

2011 Clinical Fellowship Training Award

Anna-Kaisa Niemi, MD, PhD, Stanford University Medical Center, Stanford, CA - $75,000 for one year
"Redox imbalance in methylmalonic acidemia mut0 subtype"

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2010 UMDF Grant Recipients

Cornelius Boerkoel, MD, PhD, University of British Columbia, Vancouver - $130,348
Spinocerebellar ataxia with axonal neuropathy: defining the mitochondrial component

Robert Jensen, PhD, Johns Hopkins School of Medicine, Baltimore, MD - $110,000
DCMA and Barth syndromes—similar diseases caused by defects in mitochondrial protein import?

Ingrid Tein, MD, Hospital for Sick Children, Toronto, Canada - $75,000
Pilot study to investigate the efficacy of L-arginine therapy on endothelium-dependent vasodilation & mitochondrial metabolism in MELAS syndrome

2009 UMDF Grant Recipients

Christoph Handschin, PhD, Institute of Physiology, University of Zurich - $130,000
Mitochondrial dysfunction, exercise intolerance and myopathy in skeletal muscle-specific PGC-1a-deficient mice

Michael Murphy, PhD, Medical Research Council Dunn Human Nutrition Unit, Cambridge, UK - $110,000
Development of a Novel Mass Spectrometric Approach to Measure Mitochondrial Oxidative Damage In Vivo

Sarika Srivastava, PhD, Harvard Medical School - $90,804
Investigating the Rescue of Mitochondrial Dysfunction by SIRT1 and Calorie Restriction

Patrick O'Farrell, PhD, Biochemistry & Biophysics, University of California, San Francisco - $81,857
Selecting for Transformation with Mitochondrial

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UMDF Grant Recipients 1998-2008

2008

$126,563	Stuart Smith, PhD, DSc	*Children's Hospital & Research Center at Oakland*
$116,428	Bridget Elizabeth Bax, PhD	*St. George's University of London*
$100,469	Beverly A. Rzigalinski, PhD	*Virginia College of Osteopathic Medicine*
$100,000	Deepa Vinay Dabir, PhD	*University of Helsinki*
$99,998	Timothy E. Shutt, PhD	*University of California - Los Angeles*
$99,998	Sion L. Williams, PhD	*University of Miami*
$99,990	Rebeca Acin-Perex, PhD	*Weill Medical College, Cornell University*
$98,300	Elizabeth Ann Amiott, PhD	*University of Utah*
$83,334	Leo Joseph Pallanck, PhD	*University of Washington*

2007

$157,450	Mindong Ren, PhD	*New York University School of Medicine*
$118,648	Michael King, PhD	*Thomas Jefferson University*
$114,189	Patrice Hamel, PhD	*Ohio State University*
$111,779	Brett H. Graham, MD, PhD	*Baylor College of Medicine*
$110,000	Konstantin Khrapko, PhD	*Beth Israel Deaconess Medical Center/Harvard Medical School*
$100,000	Ludivine Walter, PhD	*Cornell University*
$99,000	Paul Cobine, PhD	*University of Utah*
$98,340	Ann Saada (Reisch), PhD	*Hadassah Hebrew University Medical Center*
$94,481	Tina Wenz, PhD	*University of Miami*
$86,250	Paolo Pinton, PhD	*University of Ferrara*
$60,500	Orly Elpeleg, MD	*Hadassah Hebrew University Medical Center*

2006

$125,000	Brian H. Robinson, PhD	*Hospital for Sick Children, Toronto, Canada*
$125,000	Thomas W. O'Brein, PhD	*University of Florida*
$1122,720	Håkan Westerblad, MD, PhD	*Karolinska Institute, Sweden*
$115,000	Haya Loberboum-Galski, PhD	Hebrew University of Jerusalem
$110,000	Zaza Khuchua, PhD	*Vanderbilt University Medical Center*
$98,500	Stephane Chiron, PhD	*University of California - San Diego*
$98,457	Michael J. Palladino, PhD	*University of Washington DC*
$98,000	Doron Rapaport, PhD	*Institute for Physiological Chemistry, Germany*
$88,850	Vishal Gohil, PhD	*Massachusetts General Hospital*
$43,494	John Gordon Lindsay, PhD	*University of Glasgow*

2005

$ 110,980	Linda Spremulli, PhD	*University of North Carolina, Chapel Hill*
$ 86,455	Jan-Willem Taanman, PhD	*University College London, UK*
$162,878	Patrick Chinnery, PhD	*University of Newcastle upon Tyne*
$126,500	Elena Rugarli, MD	*Telethon Institute of Genetics and Medicine, Naples, Italy*
$94,000	Luca Scorrano, MD, PhD	*Dulbecco-Telethon Institute, Padova, Italy*
$141,027	Michael Frohman, MD, PhD	*Stony Brook University, Stony Brook, NY*
$70,525	Tal Mia Lewin, PhD	*University of North Carolina at Chapel Hill*
$116,133	Mair Churchill, PhD	*University of Colorado Health Sciences Center*
$109,991	Richard Haas, MB, B.Chir.	*University of CA San Diego*

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UMDF Grant Recipients 1998-2008

2004

$128,000	David Chan, MD, PhD	*California Institute of Technology, Pasadena, CA*
$108,305	Miriam Meisler, PhD	*University of Michigan, Ann Arbor, MI*
$99,360	Volkmar Weissig, PhD, ScD	*Northeastern University, Boston, MA*
$90,200	Vamsi Mootha, MD	*Massachusetts Institute of Technology*
$88,852	Joseph Garcia, MD, PhD	*University of Texas SW Medical Center at Dallas,*
$88,000	Stefan Strack, PhD	*University of Iowa, Carver College of Medicine*
$44,000	Brian Robinson, PhD	*Hospital for Sick Children, Toronto, Canada*
$34,179	Gregory Enns, MB, ChB	*Stanford University, Stanford, CA*
$33,776	Ramon Marti, PhD	*Fundacio Institut Hospital Universitari Vall d'Hebron, Barcelona, Spain*

2003

$100,000	Immo Scheffler, PhD	*University of California, San Diego, La Jolla, CA*
$100,000	Mikhail Alexeyev, PhD	*University of South Alabama, Mobile, AL*
$90,000	Matthew Freeman, PhD	*Laboratory of Molecular Biology – M.R.C., UK*
$83,400	Koji Okamoto, PhD	*University of Utah, Salt Lake City, UT*
$76,780	Bernard Lemier, PhD	*University of Alberta, Edmonton, Alberta, Canada*
$50,000	Giovanni Manfredi, MD, PhD	*Weill Medical College of Cornell University*

2002

$81,574	Philip Schwartz, PhD	*Children's Hospital of Orange County*
$66,000	Yidong Bai, PhD	*University of Texas Health Science Center*
$61,389	Tanja Taivassalo, PhD	*Institute for Exercise & Environmental Medicine*
$41,085	Jose Hernandez-Yago, PhD	*Institute for Cell Research, Valencia, Spain*

2001

$33,000	Min-XIn Guan, PhD	*Cincinnati Children's Hospital Medical Center*
$15,000	Brian Robinson, PhD	*The Hospital for Sick Children, Toronto, Canada*
$12,000	Edwin Kirk, MD	*Sydney Children's Hospital, Randwick, New South Wales, Australia*

2000

$36,719	Dikoma Shungu, PhD	*Columbia University*
$18,281	George Perry, PhD	*Case Western Reserve University*

1999

$31,137	Cecilia Giulivi, PhD	*University of Minnesota*
$30,000	John Shoffner, MD	*Horizon Molecular Laboratory*
$8,863	Brian Robinson, PhD	*The Hospital for Sick Children, Toronto, Canada*

1998

$5,000	Carolyn Bay, MD	*Children's Hospital of Washington DC*
$30,000	Richard Boles, MD	*Children's Hospital of Los Angeles*