Mitochondrial Disease Roadmap to a Cure
Mitochondrial Disease Community Registry Update

Southeast Regional Mitochondrial Medicine Symposium

April 2017
Guiding Principles of a Roadmap Project

- **Global in scope**
  - Opportunity to identify partners around the world, each with unique capabilities

- **Community-Driven**
  - UMDF would like to steward and manage the project, but broad stakeholder involvement/buy-in is mission critical

- **Leverage knowledge/experience of UMDF SMAB to jump-start the process**
  - Allowed framework to be quickly created

- **An iterative process**
  - Versions will be renewed on a regular basis, reflective of changes in landscape
Why does our community need a Roadmap?

“If you don’t know where you are going, any road will get you there.”

Lewis Carroll (George Harrison, Any Road)

- UMDF’s Mission: “…is to find treatments and cures for Mitochondrial Disease…”
- Desire of the UMDF Board of Trustees
- Timing: Significant progress towards therapeutics, understanding mitochondrial biology, increased interest of pharma, increased government awareness.
- UMDF could be the steward for aligning resources in the most efficient and effective manner

The Roadmap is simply a mechanism for identifying, aligning and mobilizing all the various activities and resources necessary to accelerate the discovery of treatments and potential cures.
Mitochondrial Disease Roadmap
A 3-Pillar Approach

**Diagnosis**
- Increase Awareness
- Improving Diagnoses
- Developing Tools to Measure Mitochondrial Health/Disease

**Therapeutic Development**
- Facilitating Drug Development
- Identifying & Funding Gaps, from Basic Science to Clinical Trials

**Patient Care**
- Personalized Medicine
- Patient/Clinician Education
- Developing Coordinated Care Models
- Establishing Centers of Excellence
Summary Findings - Diagnosis Pillar

Current Landscape
- Challenging due to extreme complexity of disease
- Broad need to better identify and characterize patients

Key Existing Assets
- Patient Registries: NAMDC/RDCRN/MDCR/MSeqDR/Global DBs
- Patient Biobanks: NAMDC/ Mayo (limited)

Key Needs
- Improved diagnostic methods
- Consensus indices to measure mitochondrial health
- Increased patient access to genetic testing

Near-Term UMDF Focus
- MDCR Growth: create infrastructure to support research data
- Improved Patient Biobanking: utilize MDCR to steward biosamples in collaboration with Mayo
Summary Findings - Therapeutic Development Pillar

Current Landscape

- Rapidly advancing activity in both academia and industry
- Committed pool of clinician researchers in place, but shallow and stretched thin, making clinical trial expansion challenging

Key Existing Assets

- Patient registries and biobanks
- UMDF Grants: advance basic, translational and clinical projects
- Availability of translational tools (limited)

Key Needs

- Broad stakeholder consensus on priority research topics
- Development of additional translational tools and validated outcome measures
- Increased collection of natural history data

Near-Term UMDF Focus

- Evolve to increased focus on directed funding of priority topics
- Financially support industry-sponsored pilot clinical investigations
Summary Findings - Patient Care Pillar

Current Landscape
- Small group of highly expert clinicians
- **Complexity of disease demands involvement of many specialties- a difficult reimbursement scenario**

Key Existing Assets
- Handful of Centers of Excellence (CoE) established
- UMDF Grand Rounds

Key Needs
- Validation, standardization, support and oversight of CoE models + additional locations
- Expanded educational tools for patients and clinicians
- Increased advocacy around insurance reimbursement in coordinated care models

UMDF Focus
- **Development of oversight process for Centers of Excellence**
- Collection of patient care experience to support advocacy efforts
Key Assets Aligned to Roadmap

Diagnosis
• Increase Awareness
• Improving Diagnoses
• Developing Tools to Measure Mitochondrial Health/Disease

Therapeutic Development
• Facilitating Drug Development
• Identifying & Funding Gaps, from Basic Science to Clinical Trials

Patient Care
• Personalized Medicine
• Patient/Clinician Education
• Developing Coordinated Care Models
• Establishing Centers of Excellence

Mitochondrial Disease Community Registry
• Multi-stakeholder governance
• Increased data collection
• International deployment

MSeqDR – Genomic Data
• Patient eConsent via MDCR

Scientific Investment Portfolio
• Academic research grants
• Support of MDCR/MSeqDR/NAMDC
• Funding pilot clinical trials

Education
• Online materials
• Symp/Grand Rounds

Patient Care Project
• MMS Project
• Coordinated care
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
Mitochondrial Disease Community 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

[www.umdf.org/registry](http://www.umdf.org/registry)

PLEASE REGISTER & SHARE!
MDCR Current Status

- Launched August 2014
- March 2017: ~2,050 registrants
- Baseline survey
  - ~100 Q’s/~150K Responses
  - Baseline demographics
  - Diagnostic State
  - Opinions on patient-centered drug development
- International: 46 countries represented!
  - ~90% from the US

% Registrants

- 50% Affected
- 25% Caregiver
- 25% Family
MDCR Data Mining Project

Analysis of Data Collected
2014-2016
Demographics

- **Gender**
  - Greater female participation

- **Age**
  - Majority between 20-40
  - Caregivers responding for younger probands
  - 99.7% living

<table>
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<th>My gender (self-identified) is...</th>
<th>No.</th>
<th>Column %</th>
<th>Cumulative %</th>
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<td>308</td>
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<td>99</td>
</tr>
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<td>0.4</td>
<td>99.4</td>
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<td>0.6</td>
<td>100</td>
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<td><strong>839</strong></td>
<td><strong>100</strong></td>
<td></td>
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</table>
Mito Disease Diversity

- Broad syndrome representation
- Disorder vs. Age/Race relationships too thin for substantive conclusions

<table>
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<tr>
<th>mitochondrial dx</th>
<th>asian</th>
<th>white</th>
<th>other rac</th>
<th>2 + races</th>
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<tr>
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<td>0</td>
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<td>2</td>
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<td>CPEO</td>
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<tr>
<td>Encephalomyopathy</td>
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<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Encephalopathy</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
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<tr>
<td>MELAS</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
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<tr>
<td>MNGIE</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
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<tr>
<td>Multiple Respiratory</td>
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<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>NARP</td>
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<td>1</td>
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<td>Total</td>
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<td>1</td>
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<td>13</td>
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<table>
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<tr>
<th>I was diagnosed with (or may have) one of the following</th>
<th>No.</th>
<th>Col %</th>
<th>Cum %</th>
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<td>Alpers syndrome</td>
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<td>0.9</td>
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<tr>
<td>Encephalopathy</td>
<td>11</td>
<td>9.6</td>
<td>10.5</td>
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<tr>
<td>KSS (Kearns-Sayre Syndrome)</td>
<td>20</td>
<td>17.5</td>
<td>28.1</td>
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<tr>
<td>Leukoencephalopathy</td>
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<td>0.9</td>
<td>28.9</td>
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<tr>
<td>LHON (Leber Hereditary Optic Neuropathy)</td>
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<td>0.9</td>
<td>29.8</td>
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<tr>
<td>MELAS</td>
<td>12</td>
<td>10.5</td>
<td>40.4</td>
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<tr>
<td>Myoclonus Epilepsy Ragged-red Fibers</td>
<td>3</td>
<td>2.6</td>
<td>43</td>
</tr>
<tr>
<td>Mitochondrial DNA Depletion Syndrome</td>
<td>11</td>
<td>9.6</td>
<td>52.6</td>
</tr>
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<td>MNGIE</td>
<td>8</td>
<td>7</td>
<td>59.6</td>
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<tr>
<td>Multiple Respiratory Chain Enzyme Deficiencies</td>
<td>25</td>
<td>21.9</td>
<td>81.6</td>
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<tr>
<td>NARP</td>
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<td>5.3</td>
<td>86.8</td>
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<tr>
<td>Pearson syndrome</td>
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<td>1.8</td>
<td>88.6</td>
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<tr>
<td>SANDO</td>
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<td>0.9</td>
<td>89.5</td>
</tr>
<tr>
<td>Sensory Ataxia Neuropathy</td>
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<td>10.5</td>
<td>100</td>
</tr>
<tr>
<td>Total</td>
<td>114</td>
<td>100</td>
<td>100</td>
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</table>
Willingness to Participate in Research

- Generally high willingness/interest in community to HELP with clinical studies

<table>
<thead>
<tr>
<th>Item</th>
<th>Yes</th>
<th>%</th>
<th>No</th>
<th>%</th>
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<tr>
<td>&quot;Do not want to be a guinea pig&quot;</td>
<td>3</td>
<td>0.20%</td>
<td>5</td>
<td>0.33%</td>
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<tr>
<td>&quot;The project was not recommended by a doctor&quot;</td>
<td>1</td>
<td>0.07%</td>
<td>7</td>
<td>0.46%</td>
</tr>
<tr>
<td>&quot;Results may not be kept private or confidential&quot;</td>
<td>0</td>
<td>0.00%</td>
<td>8</td>
<td>0.53%</td>
</tr>
<tr>
<td>&quot;The project will take a lot of time&quot;</td>
<td>0</td>
<td>0.00%</td>
<td>8</td>
<td>0.53%</td>
</tr>
<tr>
<td>&quot;Not paid for taking part&quot;</td>
<td>0</td>
<td>0.00%</td>
<td>8</td>
<td>0.53%</td>
</tr>
<tr>
<td>&quot;The project involves medical tests, like drawing blood or having x-rays&quot;</td>
<td>1</td>
<td>0.07%</td>
<td>7</td>
<td>0.46%</td>
</tr>
<tr>
<td>&quot;The research might reveal something bad&quot;</td>
<td>0</td>
<td>0.00%</td>
<td>8</td>
<td>0.53%</td>
</tr>
<tr>
<td>&quot;No obvious benefit to self or family&quot;</td>
<td>1</td>
<td>0.07%</td>
<td>7</td>
<td>0.46%</td>
</tr>
<tr>
<td>&quot;Worried about privacy&quot;</td>
<td>0</td>
<td>0.00%</td>
<td>8</td>
<td>0.53%</td>
</tr>
<tr>
<td>&quot;Don't know&quot;</td>
<td>3</td>
<td>0.20%</td>
<td>5</td>
<td>0.33%</td>
</tr>
<tr>
<td>&quot;Would rather not say&quot;</td>
<td>1</td>
<td>0.07%</td>
<td>7</td>
<td>0.46%</td>
</tr>
<tr>
<td>&quot;Would rather not say&quot;</td>
<td>1</td>
<td>0.07%</td>
<td>7</td>
<td>0.46%</td>
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</table>

Total: 1509
**Miscellaneous**

- High marks for PEER platform experience
- High interest in sharing of genetic testing results

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**I have access to the results of genetic testing...**

<table>
<thead>
<tr>
<th>I/He/She recall(s)</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>5</th>
<th>0</th>
<th>0</th>
<th>1</th>
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</thead>
<tbody>
<tr>
<td>Genetic testing was performed, I/He/She would be willing to request a copy for this purpose.</td>
<td>0</td>
<td>1</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
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<tr>
<td>I/He/She recall(s) that genetic testing was never done.</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</tr>
<tr>
<td>While I/He/She recall(s) that genetic testing was performed, I/He/She would be willing to request a copy of the report if this would be useful to gathering information concerning the mitochondrial disorder.</td>
<td>0</td>
<td>1</td>
<td>10</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>17</td>
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<tr>
<td>Other (please specify)</td>
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<td>2</td>
<td>5</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Skipped</td>
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<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>3</td>
<td>24</td>
<td>39</td>
<td>7</td>
<td>15</td>
<td>1</td>
<td>89</td>
<td>1</td>
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</tbody>
</table>
Near-Term Growth Initiatives

• Increased MDCR Activity
  – Advisory Board in place and recommended:
    • Philip Yeske, UMDF; Amy Goldstein, CHOP; Michio Hirano, Columbia; Jodie Vento, UPMC; Jodi Wolff, Santhera Pharma
    • Regular communication with registrants- plan developed & data mining project complete
    • More frequent, simple surveys- One launched, one in dev, many conceptualized
    • Broaden type of data collected- expand to include genomic & biosamples

• Increased Partnering/Internationalization
  – MDCR is now ready to be broadly deployed
    • IMP and AMDF also very interested in utilizing PEER
  – Establishes a central global repository of patient-derived data on a single platform
    • Flexible platform ideal for driving large global priorities while also allowing or local customization