A New Paradigm for Metabolic Medicine

Mark S. Korson, MD
A Promising Future for Metabolism?

• New diagnostics
• Newborn screening
• New therapies are being developed
• Greater “metabolic awareness”
A Promising Future for Metabolism?

- New diagnostics
- Newborn screening
- New therapies are being developed
- Greater “metabolic awareness” (in pediatrics)
Newborn screening - USA, Nov/2014

Data from Therrell BL et al, 2015
The Problem

- Inadequate # of metabolic clinicians
- Inadequate recruitment of metabolic trainees
- Inadequate training of non-metabolic professionals
The Problem

- Inadequate # of metabolic clinicians
- Inadequate recruitment of metabolic trainees
- Inadequate training of non-metabolic professionals
- Few options for transitioning patients into adult medicine... so they never leave the (pediatric) metabolic clinic
- Identification of adult-onset metabolic disease is poor and inconsistent at best
Inadequate # of metabolic clinicians

Threatens the care of metabolic patients
Inadequate # of metabolic clinicians

Threatens the care of metabolic patients

Threatens the wellbeing of metabolic professionals
Current Approaches - 1

*Increase the # of metabolic clinicians*
Current Approaches - 1

*Increase the # of metabolic clinicians:*

- Funding from industry and disease foundations to help support training in biochemical genetics
Current Approaches - 1

*Increase the # of metabolic clinicians:*

- Funding from industry and disease foundations to help support training in biochemical genetics
- North American Metabolic Academy (NAMA)
Current Approaches - 1

These programs mostly target and educate those who have already chosen a career in genetics.
Current Approaches - 2

How are we going to attract young professionals to a career in metabolic medicine?

What about educating non-geneticists in metabolic diagnosis and management?

What about educating medical students, interns and residents?
MOS
Metabolic Outreach Service
Based at Tufts Medical Center, Boston, MA

2007-2011
More effective CME strategies

1. Active interventions > passive ones
2. Academic “detailing”, educates 1 on 1
3. Using multiple interventions → positive impact
4. Face-to-face strategies followed up with printed materials
5. Talking to a subspecialist is preferred over reading books or journals
Metabolic Outreach Service (MOS)

Began with generous support from:

• Genzyme Therapeutics
• Ucyclyd Pharma
• Shire Human Genetic Therapies
• Sigma-Tau, Inc
• Actelion Pharmaceuticals
• Biomarin Pharmaceutical
• The Baby Lorenzo Gregory Scavio Fund
• Educational workshops
• Scheduled rounds, conferences
• Patient Forums
• Case reviews
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<th>WORKSHOP TOPICS</th>
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<tr>
<td>Metabolic acidosis, hyperammonemia, hypoglycemia</td>
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<td>Metabolic clue: The dietary history</td>
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<td>Metabolic emergencies</td>
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</table>
• Educational workshops
• Scheduled rounds, conferences
• Patient Forums
• Case reviews
- Educational workshops
- Scheduled rounds, conferences
- Patient Forums
- Case reviews
Ellen, Fabry disease
Patient Forums

• Patients and parents speak and share:
  – Their diagnostic journey
  – Living with their disease
  – Perspectives on therapy
  – What doctors do right and what they do wrong
  – Their needs and hopes

Ellen, Fabry disease
Patients don’t talk about facts. They tell a story and people remember stories.

Alena, Maroteaux-Lamy syndrome
Damian - the diagnostic journey

https://www.youtube.com/watch?v=0ufXPYyJres
• Educational workshops
• Scheduled rounds, conferences
• Patient Forums
• Case reviews
Case Reviews

- On-site or long distance
- This is NOT a satellite clinic – it’s about helping clinicians work through their own cases
- In the process, they learn something because they do the work
Case Reviews

- On-site or long distance
- This is NOT a satellite clinic – it’s about helping clinicians work through their own cases
- In the process, they learn something because they do the work

local metabolic competence increases
As of Jun 2011:

- # of educational sessions = 184
- # of patient forums = 49 (15 disorders)
- # of case reviews = 387
As of Jun 2011:

- TOTAL # participants in MOS = 6660
Evaluations (lectures, patient forums)

- Achieved stated goals = 4.84
- Topic relevant = 4.6
- Presentation effective = 4.78
- Audience participation = 4.6
- Overall satisfaction = 4.78

n=699-833
Evaluations

• Would this information change your practice?
  - YES = 734 (91%)
  - NO = 72

• n=806
# RESULTS OF PRE- AND POST-TESTING

**June 29-30, 2010**

<table>
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<tr>
<th>TOPIC</th>
<th>PRE (% correct answers)</th>
<th>POST (% correct answers)</th>
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# of RESPONDENTS 33
Baystate Medical Center

Lecture – Overview of acute metabolic disease

RESULTS OF PRE- AND POST-TESTING

June 29-30, 2010

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Metabolic Lab Tests- # of tests ordered
# Metabolic Lab Tests - # of tests ordered

## AMMONIA

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Onset of MOS
## Metabolic Lab Tests - # of tests ordered

### AMMONIA

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↑

Onset of MOS
Patients as Teachers
First year Biochemistry

MEDICAL COLLEGE OF VERMONT

SUNY DOWNSTATE - BROOKLYN

TUFTS UNIVERSITY SCHOOL OF MEDICINE

BOSTON UNIVERSITY MEDICAL SCHOOL
Patient Forums

They generate interest

From 2000-2007:

- # of 1st year Tufts medical students requesting elective time in the Metabolism Clinic: 0
New interest - *Patient Forums*

They generate interest

2007-2014:
- # of 1st year Tufts medical students requesting elective time in the Metabolism Clinic

18
New interest - Patient Forums

2007-2014:
• 18 electives
• 3 summer projects in the clinic
• a 4th enrolled in the ACMG Summer Scholars program

They generate interest
New interest - *Patient Forums*

- They generate interest

2007-2014:
- 18 electives
- 3 summer projects in the clinic
- A 4th enrolled in the ACMG Summer Scholars program
- 3 declared they want to pursue genetic training
2011…

The Metabolic Outreach Service ended
Missing information

• Long term evidence of retention of information?
• Actual change in thinking or practice?
• Does an interest in metabolism actually lead to a career choice?
Limitations of the MOS

- Labor intensive
- Not exportable
- Impacted the medical students and the trainees mostly, not the attending physicians and subspecialists
Lessons learned from the MOS

1. Don’t teach what you want to teach; better to teach what they want to learn (need to know).
2. Don’t pitch high; pitch real.
3. Don’t teach if a patient can tell a story instead.
4. Repetition over time is a great teaching tool.
5. Learning styles are individual; accommodate as many as possible.
6. Teaching to diagnose is different from teaching to manage.
Lessons learned from the MOS

7. Adult medicine is different from pediatric medicine; adjust accordingly.
8. Attempt to prove that what you teach is being learned.
9. Don’t be afraid to experiment (but learn from it).
10. Attention spans are short. Make it fun. Mix it up.
Lessons learned from the MOS

7. Adult medicine is different from pediatric medicine; adjust accordingly.

8. Attempt to prove that what you teach is being learned.

9. Don’t be afraid to experiment (but learn from it).

10. Attention spans are short. Make it fun. Mix it up.

TEACHING IS GOOD
TEACHING WELL IS POWERFUL
With help

• Jerry Vockley, MD, PhD

• Joe Ogrodnik and Private Investors and Advisors Group (PIAG), Pittsburgh
• Recordati Rare Diseases
• Genzyme Therapeutics
• BioMarin Pharmaceutical
• Solace Nutrition
• Vitaflo

• Organic Acidemia Association
• Fatty Acid Oxidation Support Group
• The Damian Fund
• New England Genetics Collaborative (NEGC)
• **Medical advisory board** of 18 biochemical geneticists, genetic counselors, nurse practitioners, and metabolic dietitians

• **Business management board** of 8 senior executives and entrepreneurs

• **Executive oversight committee** of 6 senior executives and entrepreneurs
To ensure that patients with inborn errors of metabolism (IEMs) are identified, diagnosed and treated.
Mission

To educate and enable healthcare professionals worldwide in order to improve health care for children and adults with genetic metabolic disease.
Mission

To educate and enable healthcare professionals worldwide in order to improve health care for children and adults with genetic metabolic disease.
The Metabolic Community

The Patients and Families
The Metabolic Community

The Patients and Families

Treating Physicians
Focus on Treating Physicians

- US shortage of metabolic expertise:
  - Clinics managing metabolic patients
  - Newborn screening follow-up
  - US military bases (remote)
  - Adult patients lost to follow-up
- Global shortage of metabolic expertise
• Consultation and Clinical Support Service
• Consultation and Clinical Support Service
• Pairing a biochemical geneticist and metabolic dietitian with local providers
• Consultation and Clinical Support Service
• Pairing a biochemical geneticist and metabolic dietitian with local providers
• An “apprenticeship” model
• Consultation and Clinical Support Service
• Pairing a biochemical geneticist and metabolic dietitian with local providers
• An “apprenticeship” model that includes education
• This is not traditional “telemedicine” but a peer-to-peer telehealth outreach
The Metabolic Community

The Patients and Families

Specialists & trainees
Focus on Specialists and Trainees

• Education about metabolic disease is inadequate at all levels
• Specialists need to participate more in IEM diagnosis and management
• Specialty-focused and relevant
## GMCE: SPECIALTY OUTREACH

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<td>Pediatric Pathology</td>
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<td>Adult Outreach Begins...</td>
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</table>
• Specialty-focused and relevant
• Symptom-based
Examples...

**Metabolic Approach to Hyperammonemia**

**Metabolic Approach to Abdominal Pain**

**Failure to Thrive: A Metabolic Approach**
Mark S. Korson, MD
Tufts Medical Center
Boston, MA

**Liver Disease in the Neonate: A Metabolic Approach**

**When to Think Metabolic When You're Doing GI**

**Liver Disease in Children: A Metabolic Approach**
Mark S. Korson, MD
Tufts Medical Center
Boston, MA

**Metabolic Approach to Hypoglycemia**

**Metabolic Approach to Vomiting**

**Using a Dietary History to Make a Metabolic Diagnosis**
Mark S. Korson, MD
Tufts Medical Center
Boston, MA
• Specialty-focused and -relevant
• Symptom-based
• Case-oriented
• Clinical and practical
• Specialty-focused and -relevant
• Symptom-based
• Case-oriented
• Clinical and practical
• Treatable disorders are prioritized
• Specialty-focused and relevant
• Symptom-based
• Case-oriented
• Clinical and practical
• Treatable disorders are prioritized
• Interactive
For practicing physicians -

• Conferences
For practicing physicians -

• Conferences
## Metabolic Approach to Symptoms in the Newborn

<table>
<thead>
<tr>
<th>Topics</th>
<th>Pre-evaluation % Correct</th>
<th>Post-Evaluation % Correct</th>
<th>Percent Improvement</th>
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<tbody>
<tr>
<td>Blood gas interpretation</td>
<td>29%</td>
<td>77%</td>
<td>48%</td>
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<tr>
<td>Metabolic testing</td>
<td>52%</td>
<td>67%</td>
<td>15%</td>
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<tr>
<td>Management of a metabolic crisis</td>
<td>48%</td>
<td>60%</td>
<td>13%</td>
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<tr>
<td>Hypoglycemia and fasting intolerance</td>
<td>36%</td>
<td>63%</td>
<td>27%</td>
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<tr>
<td>ACMG ACT sheets for newborn screening</td>
<td>26%</td>
<td>67%</td>
<td>41%</td>
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<td>Disorders with metabolic ketoacidosis and high ammonia</td>
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<td>91%</td>
<td>57%</td>
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<td>Testing for causes of hypoglycemia</td>
<td>60%</td>
<td>65%</td>
<td>6%</td>
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<tr>
<td>Hyperbilirubinemia and metabolic liver disease</td>
<td>67%</td>
<td>91%</td>
<td>24%</td>
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<tr>
<td>Hypotonia in disorders of intoxicication</td>
<td>14%</td>
<td>53%</td>
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<td>93%</td>
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<tr>
<td>Fatty acid oxidation defects</td>
<td>62%</td>
<td>84%</td>
<td>22%</td>
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Metabolic Approach to Symptoms in the Newborn

Are you considering any changes to your practice as a result of participating in this symposium?

- Yes: 81%
- No: 12%
- NA: 7%
Metabolic Approach to Symptoms in the Newborn

Would you recommend this symposium to a colleague?

- Yes: 98%
- No: 2%
For trainees -

• Online training modules
Non-metabolic clinicians

- Knowledge about metabolic disease is included in the training curriculum of:
  - Pediatric neurology
  - Pediatric gastroenterology
  - Neonatology
  - Developmental pediatrics
  - Pediatric ER/critical medicine
  - General pediatrics

<table>
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<td>General pediatrics</td>
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*Excludes US osteopathic programs*
For trainees -

• Online training modules:
  – Symptom-based workshops (“Lecture Hall”)
  – Patient presentations (“Clinic”)
  – Relevant references (“Library”)
  – Self-assessment (“Examination Hall”)
For trainees and students -

• Online metabolic electives
For trainees and students -

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For trainees and students -

• Online metabolic electives
Goal –
Endorsement by specialty societies so that all trainees are encouraged to learn about metabolic disease
Introducing Jean-Marie Saudubray
World-renowned metabolic geneticist in Europe

Co-director of NAMA

A “metabolic treasure”

Has developed dozens of clinically-based algorithms and diagnostic approaches, patient-tested during his career

Permits these to be used by GMCE
Neonatal hyperammonemia

Hyperammonemia

Glutamine
Low-normal

Glutamine
Elevated

Preterm

THAN
Normal AA profile

Organic acid
Acylcarnitines

Organic acidurias
MMA – PA Acidosis

FAO defects
MCAD – VLCAD - TPD Hypoglycemia

Hypoglycemia
HI-HA
HMG

Citrulline
↑↑

U Orotic acid
↑
normal

NAGS D
CPS D
CAVA

P5CS D
↓ Orn – pro – arg
starved hyper-NH3

HHH s
↑ Homocit

CIT 2
↑ Met – Tyr
A-FP- galactose

PC deficiency
Lactic acidosis

Full Term

Citrulline
↓

Citrulline
↑

Citrulline
↑↑

Citrulline
↑↑↑

Ornithine
Elevated

Ornithine
Normal

↓ Arg – Lys – Orn
↑ U Arg – Lys – Orn
↑ U Orotic acid
LPI

↑ ASA
↑ U Orotic acid
ASL D

↑ U Orotic acid
ASS D

Ornithine
Only transiently normal
OAT D

Arg
↑ Ala
OTC D

↑↑ Arg
ARGININEMIA
“Never miss a treatable disease!”
The Metabolic Community

- The Patients and Families
- Pharma
- Formula/food companies
- Insurance companies

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Focus on Industry

• ... and GMCE share a common mission
• Patient identification through physician education
• Need in Industry for education to understand better the disease and its impact on patients and families
GMC Approach

• “Never-Miss-A-Treatable-Disease” brochure line
  – Symptom-based information vs disease-based information
“Never-Miss-A-Treatable-Disease” brochure line

Training seminars for officers and employees of Industry
• “Never-Miss-A-Treatable-Disease” brochure line
• Training seminars for officers and employees of Industry
• Access to experts for Research and Development
The Metabolic Community

The Patients and Families

Disease Foundations

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Focus on Disease Foundations

• ....and GMCE share a common mission
• Seek increased awareness about their disease(s) which supports diagnosis, advocacy, research and treatment development
• Unprecedented promotion of awareness:
  – Practicing MDs, trainees, students
  – Key specialist targets
Approach

• Collaboration to develop a library of Patient Presentations, and a corresponding Speakers Bureau

• The “Damian Project”

Damian
pyruvate dehydrogenase def’y
• “Damian Project” to be included in:
  – Live conferences
  – eLearning modules
  – Online electives
  – Resource for medical schools
The Metabolic Community

The Patients and Families

Patient Advocacy
Focus on Patient Advocacy Organizations

• ....and GMCE share a common mission
• Need for increased collaboration with disease foundations, government, and Industry
• NORD, Genetic Alliance, Global Genes, CORD
Approach

- Opportunities to strengthen collaboration between disease foundations, patient communities, government, and Industry
The Metabolic Community

Global Initiatives

The Patients and Families
Focus on Global Initiatives

- Increasing recognition of metabolic medicine
- Newborn screening initiation and expansion
• Establishment of a “Developing World Tier” of metabolic medicine
Establishment of a “Developing World Tier” of metabolic medicine

- Develop easy-to-understand, unambiguous protocols for diagnosis and management
• Establishment of a “Developing World Tier” of metabolic medicine
  – Develop easy-to-understand, unambiguous protocols for diagnosis and management
  – Utilize cheaper laboratory technologies
HYPERAMMONEMIA

PRIMARY METABOLIC ACIDOSIS with INCREASED ANION GAP?

PRESENT:
Check ketones

ABSENT:
Check LFTs

HIGH
Organic acidemias

LOW
Fatty acid oxidation defects

ABNORMAL
Liver failure

NORMAL/NEAR NL
Urea cycle defect
The Metabolic Community

Who else?

The Patients and Families

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A New Metabolism Era!

- Metabolic medicine:
  - cannot remain just within the realm of the “centers of excellence”
A New Metabolism Era!

- Metabolic medicine:
  - cannot remain just within the realm of the “centers of excellence”
  - must be more “accessible” to community stakeholders
A New Metabolism Era!

- Metabolic medicine:
  - cannot remain just within the realm of the “centers of excellence”
  - must be more “accessible” to community stakeholders
  - must be relevant globally
A New Metabolism Era!

- Metabolic medicine:
  - cannot remain just within the realm of the “centers of excellence”
  - must be more “accessible” to community stakeholders
  - must be relevant globally
  - must look attractive and actively recruit
CARE