Adherence and Self-Management in Cystic Fibrosis: A Critical Part of Precision Medicine

Gregory Sawicki, MD, MPH

Director, Cystic Fibrosis Center
Division of Respiratory Diseases
Boston Children’s Hospital

Assistant Professor of Pediatrics
Harvard Medical School
Faculty Disclosures

• Consultant / Grant Support
  – Genentech
  – Gilead
  – Novartis
  – Vertex
Cystic Fibrosis

- Inherited, multi-system disorder affecting the respiratory tract, GI tract, sweat glands, reproductive tract, liver and other organ systems

- Pulmonary disease is major cause of morbidity and mortality

- Chronic infection/inflammation and progressive lung disease predominates
CF Pathophysiology

1. Abnormal Gene
2. Abnormal Protein
3. Altered Ion Transport & Abnormal Mucus Secretion
4. Infection & Inflammation
5. Organ Destruction & Respiratory Failure
A Story of Progress

Figure 7. A. Patient with Cystic Fibrosis of the Pancreas at two years, six months. B. Lungs at one year, two months. C. Lungs at two years, six months. When infection becomes established in the viscid secretion of the bronchioles at an early age, and persists, the lungs show progressive development of peribronchial infiltration and emphysema. The atrial state deteriorates with advance of the infection. (Reproduced from Plate V, May, C. D. and Lowe, C. U., Fibrosis of the ancreas in Infants and Children. J. Pediat., 34:663 (1949) with permission of C. V. Mosby, St. Louis.)

1950 1989 2015
Median Predicted Survival Age, 1989-2013 (in 5 year bands)

The median predicted age of survival has increased from 33.4 years in 2003 to 40.7 years in 2013.

CFF 2013 Registry Report
CF: A Changing Epidemiology
Center-Level Improvement in Outcomes 2003 - 2013

GLI reference equations were used to calculate FEV₁ percent predicted.

Goals:
- FEV₁ 100% predicted
- BMI 50th percentile

CFF 2013 Registry Report
Lung Function Outcomes Have Improved

CFF 2013 Registry Report
Why Have Outcomes in CF Improved?

• Earlier Diagnosis
  – Spread of newborn screening
  – Ability to initiate early intervention / therapies

• New Therapeutics
  – CF-specific medications approved starting in the mid 1990’s
  – Robust therapeutic pipeline

• Improved Care Delivery Systems
  – Success of quality improvement
New Therapies for CF: A Timeline

- Pulmozyme Approval
- Inhaled Tobramycin Approval
- Chronic Azithromycin for +PsA
- Hypertonic Saline
- Inhaled Aztreonam Approval
New Therapies for CF: A Timeline

- Pulmozyme Approval
- Chronic Azithromycin for +PsA
- Inhaled Aztreonam Approval
- Hypertonic Saline
- Inhaled Tobramycin Approval
- Ivacaftor Approval
- Orkambi Approval

CF Care: At the Dawn of Precision Medicine?
Precision Medicine

NIH Precision Medicine Initiative (2015)

• To enable a new era of medicine through research, technology, and policies that empower patients, researchers, and providers to work together toward development of individualized treatments.

• Tailors treatment and prevention strategies to people’s unique characteristics, including their genome, microbiome, health history, lifestyle, environment, and diet.

• Incorporates many different types of data, including data about the patient collected by health care providers and the patients themselves.

https://www.whitehouse.gov/precision-medicine
The Promise of Precision Medicine

- Individual
- Genetics
- Health System

Personalized Health and Outcomes
### CFTR Mutation Classes: Targets for Precision Medicine

#### Chart

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>CFTR is created, reaches cell surface and functions properly, allowing transfer of chloride and water.</td>
<td>G542X, W1282X, R553X</td>
</tr>
<tr>
<td>Class I</td>
<td>No functional CFTR created.</td>
<td>F508del, N1303K, I507del</td>
</tr>
<tr>
<td>Class II</td>
<td>CFTR protein is created, but misfolded, keeping it from reaching the cell surface.</td>
<td>G551D, S549N, V520F</td>
</tr>
<tr>
<td>Class III</td>
<td>CFTR protein is created and reaches cell surface, but does not function properly.</td>
<td>R117H, D1152H, R553X</td>
</tr>
<tr>
<td>Class IV</td>
<td>The opening in the CFTR protein ion channel is faulty.</td>
<td>3849+10kbC-&gt;T, 2789+5G-&gt;A, A455E</td>
</tr>
<tr>
<td>Class V</td>
<td>CFTR is created in insufficient quantities.</td>
<td></td>
</tr>
</tbody>
</table>

#### Adapted from:


CFF 2013 Registry Report
FDA Approval of Orkambi: July 2, 2015

“The FDA encourages manufacturers to develop new and innovative treatments for serious rare diseases like cystic fibrosis,” said John Jenkins, M.D., director of the Office of New Drugs, Center for Drug Evaluation and Research. “Today’s approval significantly broadens the availability of targeted treatments for the specific defects that cause cystic fibrosis.”
Precision Medicine for Some with CF?

- 47% delF508 Homozygous
- 30% delF508 Heterozygous
- 10% at least one Class III CFTR mutation
- 5% at least one Class I CFTR mutation
# The Pipeline for CFTR Modulators

<table>
<thead>
<tr>
<th>CFTR Modulation</th>
<th>Pre-clinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>To Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kalydeco™ (also known as ivacaftor)</td>
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<td></td>
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<tr>
<td>Orkambi™ (lumacaftor + ivacaftor)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ataluren (formerly known as PTC124)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VX-661 + ivacaftor</td>
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<tr>
<td>Riociguat</td>
<td></td>
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<tr>
<td>QBW251</td>
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<td></td>
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<tr>
<td>N91115</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>QR-010</td>
<td></td>
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</tbody>
</table>
Are Novel CFTR Modulator Therapies Sufficient?

What are the threats to “personalized genetic therapy”?
Precision Medicine Framework

- Environment
- Microbiome
- Adherence
- Disease knowledge
- Social Support
- SES Determinants
- Lifestyle

• Transition to Adult Care
• Training/Medical Education
• Cost of care
• Access

Personalized Health and Outcomes
CF clinical scenario #1

- A 16-year-old starting secondary school with a busy social life; training to secure a spot on swim and soccer teams
- Baseline FEV$_1$ is 89% predicted
  - Daily medications include dornase alfa, hypertonic saline, pancreatic enzymes, vitamins, antacid
- Since her last clinic visit, she has noticed some increased cough during high exertion at soccer practice
- FEV$_1$ is down 6% from last visit
- She states she is consistently taking her medications; however, her parents tell you that she feels she doesn’t need to take all her meds because she feels well and is active with sports
- Her parents are busy with two younger children and rely on her to responsibly take her meds
CF clinical scenario #2

• A 28-year-old, successful young professional with mild disease
• Baseline FEV$_1$ 60% predicted
• Medications include: hypertonic saline, dornase alfa, alternate month inhaled antibiotics, pancreatic enzymes, vitamins, nutritional supplements, azithromycin, ursodiol
• Recently began new job requiring significant travel
• After 3 years without an exacerbation, he experienced 2 exacerbations in the last year, with FEV$_1$ decline of 5% at last visit, treated with oral antibiotics
• FEV$_1$ at current visit is 50% predicted
Challenges to CF care through the life span
Diagnosis

Adulthood

Adolescence

Childhood

Infancy

Newborn Screening

Infant Care Practices

Diagnosis
Nutritional Assessment
Pulmonary Function Assessment
Monitoring for Complications
Prevention of Disease Progression
Education About CF
Assessment of Family Functioning and Social Supports
Nutritional Assessment
Pulmonary Function Assessment
Monitoring for Complications
Prevention of Disease Progression
Education About CF
Assessment of Family Functioning and Social Supports

Infancy

Newborn Screening
Diagnosis
Infant Care Practices

Transition
Self-Management
Shared Decision-Making

Adolescence

Adulthood

ADHERENCE
Some Terminology

• “Compliance”
  – The accuracy with which a person follows the regimen prescribed by a health professional

• “Adherence”
  – Extent to which a person’s behavior coincides with medical advice

• “Self-management”
  – Health behaviors of individuals and families use to care for a chronic condition

http://apps.who.int/iris/bitstream/10665/42682/1/9241545992.pdf
Adherence in CF: what do we know?
Adherence rates to CF respiratory medications are low

Mean MPRs for various long-term pulmonary medications used in cystic fibrosis. The bottom, midline, and top of each box represent the lower quartile, median, and upper quartile, respectively. The end points of the vertical lines represent the minimum and maximum values (♦ indicates the mean value). The composite MPR is the average of the individual drug MPRs.

Longitudinal Rates of Medication Fills over 5 years

Adherence to Ivacaftor (CFTR Modultator) Is Also Suboptimal!

Mean Adherence by EM: 61%

Saracusa CM et al, Journal of Cystic Fibrosis, 2015; 14:621-626
Impact of non-adherence on CF health outcomes

Courses of IVs

Lung function

- MPR = 80–100%  N=28  +0.53%
- MPR = 50–80%  N=31  -2.22%
- MPR <50%          N=36  -0.39%

Low adherence is associated with higher health care costs

Mean 12 month CF-related health care costs (US$)

- Low CMPR: $54,190
- Moderate CMPR: $45,239
- High CMPR: $34,432

CMPR, Composite Medication Possession Ratio

Challenges to Adherence and Self-Management

<table>
<thead>
<tr>
<th>Individual</th>
<th>Family</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age</td>
<td>• Family structure</td>
</tr>
<tr>
<td>• Gender</td>
<td></td>
</tr>
<tr>
<td>• Health literacy</td>
<td>• Disease knowledge</td>
</tr>
<tr>
<td>• Disease &amp; treatment knowledge</td>
<td>• Mental health / behavioral problems</td>
</tr>
<tr>
<td>• Mental health / behavioral problems</td>
<td></td>
</tr>
<tr>
<td>• Coping style</td>
<td></td>
</tr>
<tr>
<td>• Health beliefs &amp; perceptions</td>
<td>• Relationship quality</td>
</tr>
<tr>
<td></td>
<td>• Involvement in care</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Health Care System</th>
<th>Community</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Access to care</td>
<td>• Neighborhood</td>
</tr>
<tr>
<td>• Continuity of care</td>
<td></td>
</tr>
<tr>
<td>• Patient-provider communication</td>
<td>• School</td>
</tr>
<tr>
<td></td>
<td>• Peer support</td>
</tr>
<tr>
<td>• Shared decision making</td>
<td>• Illness stigma</td>
</tr>
<tr>
<td>• Frequency of clinic visits</td>
<td></td>
</tr>
<tr>
<td>• Provider biases</td>
<td></td>
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</tbody>
</table>

Adherence Typologies

**Unwitting**
- Patient and provider mistakenly believe that the patient is adherent

**Erratic**
- Patient understands and agrees with therapy but has difficulty consistently maintaining regimen

**“Rationalized”**
- Patient deliberately alters or discontinues therapy
Challenge to adherence #1: treatment burden and complexity
High treatment burden in CF

![Bar chart showing minutes per day for different therapies (oral: 9 minutes, exercise: 29 minutes, airway clearance: 29 minutes, nebulized: 41 minutes, total: 108 minutes).]

<table>
<thead>
<tr>
<th>Medications</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of oral medications</td>
<td>3 (0–7)</td>
</tr>
<tr>
<td>Number of nebulised medications</td>
<td>2 (0–5)</td>
</tr>
<tr>
<td>Number of inhaled medications (MDI)</td>
<td>1 (0–4)</td>
</tr>
<tr>
<td>Number of total medications</td>
<td>7 (0–20)</td>
</tr>
</tbody>
</table>
Challenge to adherence #2: measurement matters!

- **Self-report**
  - Daily diaries
  - Questionnaires
  - Interviews

- **Clinician-report**
  - Questionnaires

- **Pharmacy records**
  - Medication Possession Ratio (MPR)
  - Proportion of days covered (PDC)
  - Number of refills

- **Electronic monitors**
  - MEMS Caps
  - “Chipped” devices
  - MDI monitors
How Adherence is Measured Can Lead to Different Answers!

<table>
<thead>
<tr>
<th>Medications</th>
<th>Self-report</th>
<th>Prescription refill</th>
<th>Daily phone diary</th>
<th>Electronic monitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nebulised medications (antibiotics, dornase alpha)</td>
<td>65–93.6%&lt;sup&gt;1,2,3&lt;/sup&gt;</td>
<td>54–72%&lt;sup&gt;1,3&lt;/sup&gt;</td>
<td>33–57%&lt;sup&gt;1,4&lt;/sup&gt;</td>
<td>32–79%&lt;sup&gt;3,5,6&lt;/sup&gt;</td>
</tr>
<tr>
<td>Enzymes</td>
<td>89.5–90%&lt;sup&gt;4&lt;/sup&gt;</td>
<td>46.4%&lt;sup&gt;4&lt;/sup&gt;</td>
<td>---</td>
<td>42.5%&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Airway clearance (CPT, flutter)</td>
<td>40–74%&lt;sup&gt;4,7&lt;/sup&gt;</td>
<td>---</td>
<td>51–64%&lt;sup&gt;4&lt;/sup&gt;</td>
<td>---</td>
</tr>
</tbody>
</table>

An Example: Measuring Adherence to Pancreatic Enzymes

*Significantly different from other measurement methods (p < .05).

Modi AC et al. Journal of Cystic Fibrosis 2006 5, 177-185DOI: (10.1016/j.jcf.2006.03.002)
Electronic Monitoring

Advantages

- Continuous, long-term, real-time measure
- More objective than diaries or self-report
- Can identify a spectrum of issues
  - Underdosing
  - Delayed dosing
  - Drug “holidays”
  - “White-coat” adherence

Disadvantages / Challenges

- Device malfunction
  - Recording events that did not occur,
  - Fail to record events that did occur
  - Technology failure
- Cost
- Privacy concerns
Pharmacy Records

Advantages

• Identify what medications an individual has obtained
  – As opposed to what is prescribed
• Allows for evaluation of adherence over a longer time period without need for individual input/recall

Challenges

• Only measures dispensing of medication
• Not always clear exactly what has been prescribed
  – Dose / Frequency
  – “Overfilling” of Rx
  – Lack of written treatment plans
• May not account for changing treatments over time
  – Alternating antibiotics
  – Hospitalizations
Challenge to adherence #3: Identifying non-adherence

**Patient Report**

![Graph A](image1)

**Provider Report**

![Graph B](image2)

Challenge to adherence #4: Developmental issues in adolescence / young adulthood

- Greater desire for independence
- Less parental supervision
- More erratic life style (sleep, schedules)
- Social acceptance, disclosure, appearance
- Experimentation and risk-taking
- Invulnerability & long-term goals
Adherence rates vary by age

- CMPRs by age category. The bottom, midline, and top of each box represent the lower quartile, median, and upper quartile, respectively. The end points of the vertical lines represent the minimum and maximum values (♦ indicates the mean value). The CMPR is the average of the individual drug medication possession ratios.

Adherence in adolescents is best on weekdays during school term time

Fig. 1 Comparison of adherence to treatment for individual patients during a) weekdays and weekends and b) holidays and term-times. The horizontal thickened bars represent mean adherence for the group (*p<0.001).

Adherence in CF: Adolescent Perspectives

**Barriers**
- Immediate time pressures
  - Lack of time
  - Uncertain schedules
- Competing priorities
  - Balancing time trade-offs
- Privacy concerns
  - Wanting to be “normal”; not wanting to seem different or disabled
- Lack of perceived consequences
  - Not seeing an impact on one's health right away from skipping treatments or medications

**Facilitators**
- Improving understanding of the importance of therapies
- Fostering relationships with the CF care team
  - CF team should be creative in problem-solving with the adolescent and parent
- Empowering adolescents
  - Enabling parents to cede control and entrust responsibility to adolescents
- Establish a structure
  - Having a daily routine, “making it a ritual”

Addressing Non-Adherence: A Critical Part of Precision Medicine!

• Address treatment complexity
  – Explore ways to make therapies and interventions more practical

• Improve measurement
  – Refine methods to identify who is non-adherent
  – Development of technology, apps
  – Improve structured communication systems
  – Identify individual barriers to adherence

• Design interventions tailored to developmental trajectories
  – Facilitate youth-derived goals for adherence behaviors that incorporate parents, peers, and multi-disciplinary clinician input
  – Promote adult developmental milestones through early initiation and repeated practice of self-management skills
Consider “multi-component” interventions

- Education
- Reminders/cueing
- Self-monitoring
- Tailoring the regimen
- Health & behavioral feedback/coaching
- Problem-solving
- Mental health
- Social support
- Parent training
- Family therapy
- Cognitive behavioral therapy
- Motivational interviewing

Haynes RB et al. Cochrane Database of Systematic Reviews 2008.
Efforts at addressing adherence for individuals with CF in the US

The CFF Success with Therapies Research Consortium will identify and study interventions to improve adherence and related health outcomes among individuals with CF.
Precision Medicine in CF: The End of the Beginning?

• Health outcomes in CF have been improving for decades, in part due to advances in diagnosis, treatment, and care delivery

• Novel therapeutics targeting the genetic basis of CF hold great promise
  – How such therapies modify disease progression is yet unclear

• Precision medicine for CF needs to focus beyond genetic therapies
  – Individual and health system determinants of outcomes need to be evaluated
Addressing Adherence in CF: A Critical Part of Precision Medicine

- Non-adherence to chronic CF therapies is common and is linked to poor health outcomes
- Barriers to adherence are multi-factorial, involving the patient, family, clinician, and health system
- Key challenges include treatment burden, difficulties with measurement, and developmental concerns
- Interventions to improve adherence need to be developed, studied, and implemented on a larger scale
Thank you!