

The Twentieth Meeting of
 THE CHRONIC FATIGUE SYNDROME ADVISORY COMMITTEE
 US DEPARTMENT OF HEALTH AND HUMAN SERVICES



Holiday Inn, Columbia Room, 550 C Street, SW
 Washington, DC 20024
 Tuesday, November 8, 2011 – 9:00 am to 5:00 pm

Voting Membership

Name		Term
Chairman Christopher R. Snell, PhD	Stockton, CA	04/01/07 to 04/01/12
Dane B. Cook, PhD	Madison, WI	05/10/10 to 05/10/14
Jordan D. Dimitrakoff, MD, PhD	Boston, MA	05/10/10 to 05/10/14
Eileen Holderman	Galveston, TX	05/10/10 to 05/10/14
Michael Houghton, PhD	Danville, CA	05/10/10 to 05/10/14
Leonard Jason, PhD	Chicago, IL	04/01/07 to 04/01/12
Steven P. Krafchick, MPH, JD	Seattle, WA	07/01/10 to 07/01/14
Nancy Klimas, MD	Miami, FL	04/01/07 to 04/01/12
Susan M. Levine, MD	New York, NY	05/10/10 to 05/10/14
Gailen D. Marshall Jr., MD, PhD	Jackson, MS	05/10/10 to 05/10/14
Ann Vincent, MD	Rochester, MN	04/10/11 to 04/10/15

Ex Officio Membership

Agency for Health Research and Quality
Beth A. Collins Sharp, PhD, RN
 Senior Advisor for Women’s Health
 and Gender Research

Food and Drug Administration
Theresa Michele, MD
 Medical Officer Team Leader
 Center for Drug Evaluation and Research

Centers for Disease Control and Prevention
Ermias Belay, MD
 Associate Director for Epidemiologic Science
 Division of High-Consequence Pathogens

Health Resources and Services Administration
Deborah Willis-Fillinger, MD
 Senior Medical Advisor
 HIV/AIDS Bureau

Center for Medicare and Medicaid Services
Alaine Perry, MPH
 Senior Advisor for Disability
 and Special Need Population
 CMS Center for Strategic Planning

National Institutes of Health

Primary

Charles Wells, PhD

Senior Advisor

Office of Research on Women's Health

Office of the Director

Alternate

Janine Austin Clayton, MD

Deputy Director

Office of Research on Women's Health

Office of the Director

Social Security Administration

Primary

Cheryl A. Williams

Director

Office of Medical Listings Improvement

Alternate

Michele Schaefer

Acting Deputy Director

Office of Medical Listings Improvement

Designated Federal Officer

Nancy C. Lee, MD

Deputy Assistant Secretary for Women's Health

Alternate Designated Federal Officer

Martha D. Bond

Senior Public Health Advisor

Office on Women's Health

Agenda

9:00 a.m.	Call to Order	pg	Dr. Christopher R. Snell, PhD
	Opening Remarks		<i>Chair, CFSAC</i>
	Roll Call, Housekeeping	pg	Dr. Nancy C. Lee, MD
			<i>Designated Federal Officer</i>
9:10 a.m.	International Classification of Diseases - Clinical Modification (ICD-CM)	pg	Donna Pickett, RHIA, MPH National Center for Health Statistics
10:00 a.m.	Public Comment	pg	Public
11:15 a.m.	Break		
11:30 a.m.	Welcome Statement from the Assistant Secretary for Health	pg	Howard K. Koh, MD, PhD
Noon	Agency Updates: AHRQ, CMS, FDA, HRSA	pg	Ex Officio Members
1 p.m.	Subcommittee Lunch	pg	Subcommittee Members
2 p.m.	Public Comment	pg	Public
2:45 p.m.	Break	Pg	

3 p.m.	Future Interdisciplinary Research for CFS Utilizing a Variety of Scientific Disciplines	Pg	Gailen Marshall, MD, PhD Committee Discussion
4 p.m.	Committee Discussion Past CFSAC Recommendations	Pg	Committee Members
5 p.m.	Adjourn	Pg	

Opening Remarks

Dr. Lee introduced herself as the new Designated Federal Officer (DFO) for the Chronic Fatigue Syndrome Advisory Committee (CFSAC). Dr. Lee is also the Deputy Assistant Secretary for Women’s Health at the Department of Health and Human Services (DHHS).

Dr. Lee reminded meeting participants that the proceedings were being audio streamed to allow people to call in and listen remotely. She urged participants to speak into their microphones and make sure they are turned on (as indicated by a red light).

Dr. Lee asked the voting and *ex-officio* members to introduce themselves. A formal call to order, roll call, and housekeeping remarks were delayed until after Donna Pickett’s presentation on international disease classification.

Voting Members:

Dr. Dane B. Cook, Assistant Professor of Kinesiology, University of Wisconsin-Madison, researching exercise and functional brain imaging in chronic fatigue syndrome (CFS).

Mr. Steven P. Krafchick, attorney representing CFS patients, specializing in helping them receive long-term disability benefits from private policies.

Dr. Ann Vincent, general internist at the Mayo Clinic with a research interest in CFS and fibromyalgia.

Dr. Leonard Jason, psychologist at DePaul University, with an interest in CFS diagnostic issues, epidemiology, and case definition.

Dr. Susan M. Levine, physician treating CFS and fibromyalgia patients in New York City.

Dr. Christopher Snell, CFSAC Chair and Professor, University of the Pacific, Stockton, California, with an interest in functional aspects of CFS.

Dr. Nancy Klimas, University of Miami, investigator and clinician who cares for patients with CFS.

Dr. Gailen Marshall, University of Mississippi, a clinical immunologist interested in biomarkers for CFS.

Dr. Jordan Dimitrakoff, Harvard Medical School, studying chronic pelvic pain syndrome, interstitial cystitis, and their relationship with CFS.

Eileen Holderman, CFS patient advocate.

Ex Officio Members:

Dr. Theresa Michele, Division of Pulmonary, Allergy, and Rheumatology Products in the Center for New Drugs at the Food and Drug Administration (FDA)

Dr. Beth Collins Sharp, Senior Advisor for Women’s Health and Gender Research, Agency for Healthcare and Research Quality (AHRQ)

Dr. Ermias Belay, the Centers for Disease Control and Prevention (CDC)

Dr. Deborah Willis-Fillinger, Health Resources and Services Administration (HRSA)

Alaine Perry, Center for Medicare and Medicaid Services (CMS)

Dr. Charles Wells, National Institutes of Health (NIH)

CFSAC Staff:

Ms. Martha Bond, Senior Public Health Advisor for the Office on Women’s Health and Alternate DFO

International Classification of Diseases—Clinical Modification (ICD-CM)

Donna Pickett, National Center for Health Statistics (NCHS/Centers for Disease Control and Prevention)

The International Classification of Diseases (ICD) has been in existence for about 100 years. The current version used in the United States is ICD-9-CM, which is a clinical modification of the World Health Organization (WHO) classification.

The ICD is used for a variety of purposes. Its original purpose was to classify the causes of mortality (the death registration). More recently, many countries use ICD for the capture of morbidity statistics in a variety of settings, including inpatient hospital settings, physicians’ offices, and outpatient clinics. The ICD is also used for insurance reimbursement, particularly by providers who must send in ICD numbers with their claims.

ICD-9 was published in 1974. The United States, in agreement with the WHO, created a clinical modification of the ICD that has more detail than the WHO classification. ICD-9-CM has been updated annually since 1985. Prior to ICD-10, the WHO had no update process. The ICD-9-CM Coordination and Maintenance Committee meet twice a year in March and September. Proposals to modify a classification can come from a variety of stakeholders, including hospitals, specialty groups, and individual providers.

The first request to include information about CFS in ICD-9-CM was in 1990. An alphabetical index was created to guide users to the appropriate code (780.7- Malaise and fatigue) in Chapter 16, Signs, Symptoms, & Other Ill-defined Conditions. In 1997, a second request occurred for a new code for CFS. A new code was approved and implemented in October 1998. The code is titled “Chronic fatigue syndrome” and is numbered 780.71, a subcategory of Malaise and fatigue.

ICD-10 is being used for morbidity purposes everywhere in the world except the United States. ICD-10 was approved by the International Conference for the 10th Revision of the ICD in 1989. ICD-10 was

adopted by the World Health Assembly in 1990. The Tabular List was published in 1992; the Alphabetic Index in 1995.

The NCHS/CDC began evaluating the use of ICD-10 specifically for morbidity purposes. On the mortality side, which is the coding of death certificates, the United States has used ICD-10 since 1999. The NCHS/CDC examined whether ICD-10 actually addressed all of the concepts that had been added to ICD-9-CM.

This review was done in consultation with physician groups, clinical coders from the in- and outpatient settings, researchers, epidemiologists, and others. There were three phases of development:

Phase 1 – 1994-1995

Phase 2 – 1995-1996 – Included a comment period during which users could address issues with ICD-10 and where it was lacking.

Phase 3 – 1997-the present – Included a public comment period (12/97-2/27/98) during which the entire ICD-10-CM was posted online. The comments resulted in changes to ICD-10-CM. The American Hospital Association conducted a pilot test in conjunction with the American Health Information Management Association in June/July 2003. The pilot test resulted in program modifications to ICD-10-CM. From then on, NCHS/CDC has been simultaneously updating ICD-10-CM and ICD-9-CM every year. Bird flu and severe acute respiratory syndrome (SARS), for example, have been added to ICD-9-CM.

The time came when the United States realized that it could no longer update ICD-9-CM because it was running out of room to add more codes. For this reason, ICD-10-CM became an important focus. The same process used to update ICD-9-CM will be used to update ICD-10-CM. Only minimal updates will be done to ICD-9-CM leading up to October 1, 2013 when ICD-10-CM and ICD-10-PCS (the procedure coding system that will be used in the inpatient setting) will be implemented. ICD-10-CM and ICD-9-CM have been maintained side-by-side through NCHS/CDC's public process:

- Proposals to add new information must be sent two months in advance of NCHS/CDC's March or September meeting.
- Meetings are open to the public.
- A tentative agenda is published in the *Federal Register* and on the NCHS/CDC website approximately one month in advance of the meeting.
- Comments are encouraged during the meeting, but NCHS/CDC also asks that people submit their comments in writing to facilitate a public record of those comments.

Implementation of ICD-10-CM on October 1, 2013 is tied to the standards adoption process specified in HIPAA [the Health Insurance Portability and Accountability Act]. There have been multiple hearings about migrating to the ICD-10-CM code sets:

- More than 8 hearings were held between 1997 and 2003 by the National Committee on Vital Health Statistics (NCVHS—a Federal advisory committee). NCVHS also wrote a letter in November 2003 to the DHHS Secretary recommending migration to the ICD-10-CM code sets.
- A Notice of Proposed Rulemaking was published in August 2008 and a Final Rule was published in January 2009.

ICD-10 Coding:

Chapter VI – Diseases of Nervous System

G93 Other disorders of the brain
G93.3 Postviral fatigue syndrome
Benign myalgic encephalomyelitis

ICD-10-CM Coding:

Chapter VI – Diseases of Nervous System
G93 other disorders of brain
G93.3 Postviral fatigue syndrome
Benign myalgic encephalomyelitis

And also:

R53.82 Chronic fatigue, NOS
Chronic fatigue syndrome, NOS

NCHS/CDC discussed two options at its September 14, 2011 Coordination and Maintenance Committee Meeting:

Option 1 – Proposal received in July 2011 from the Coalition 4 ME/CFS that CFS be moved from R53.82 to G93.3.

Option 2 – NCHS/CDC proposal to expand G93.3 to create a unique code for CFS to ensure that data captured for the last 13 years with the current CFS code in ICD-9-CM will not disappear.

The public comment period on these options closes on November 18, 2011.

Coordination and Maintenance Committee website to view the proposals and a discussion of the options: http://www.cdc.gov/nchs/icd/icd9cm_maintenance.htm

Website to view ICD-10-CM: <http://www.cdc.gov/nchs/icd/icd10cm.htm>

Call to Order

Dr. Snell formally called the CFSAC meeting to order and opened the floor to questions for Ms. Pickett.

Committee Discussion

Dr. Klimas: What is the decision process for choosing an option after the comment period closes?

Ms. Pickett: NCHS/CDC will evaluate the comments. There are two issues open for comment:

Issue 1 - the options themselves

- There may be overwhelming support for one or the other proposal.
- There could be divided opinion, including partial support for a proposal that is then revised and considered during another meeting.
- Commenters could submit alternative proposals (possibly requiring another meeting).

- Issues may be submitted for clarification (possibly requiring another meeting).

Issue 2 - the current freeze

ICD-9-CM and ICD-10-CM are in a partial freeze. We will not be implementing any new codes for 9-CM and 10-CM to keep the codes stable while the industry prepares its systems to use ICD-10-CM. The industry requested that we do this. The only new codes that will be created at this point will be related to new diseases and new technologies. Commenters can discuss whether any modification meets the qualifications for making a change during the freeze.

Dr. Klimas: How can CFSAC best provide its input?

Ms. Pickett: Advisory committees do not often weigh in as a committee. They generally weigh in as individuals. But NCHS is open to all comments. CFSAC can weigh in whatever way is appropriate under FACA [the Federal Advisory Committee Act].

Dr. Jason: If CFSAC makes a recommendation on these options to the DHHS Secretary and she in turn submits a comment to you, would that have more weight? PANDORA, the ME/CFS coalition, and others made a presentation to you expressing a strong preference for Option 1. Would you be willing for this committee to articulate why they thought Option 1 is superior to Option 2?

Ms. Pickett: Taking the second question first: Option 2 attempts to recognize that there has been a unique code for CFS in ICD-9-CM for the last 13 years. There are a number of researchers and others who use that code. Option 1 would move CFS back under G93.3 with no further specification. Some researchers and others found that to be extremely problematic. They did not want to see the data disappear for that code. That was the reason NCHS/CDC put forth Option 2, in recognition that there has been a unique code for 13 years.

In regard to making a recommendation to the Secretary, I cannot speak to that. We have not had a circumstance like that in the past where we receive a comment letter related to a coding issue from a Federal advisory committee.

Dr. Jason (to Dr. Lee): Is it appropriate to make such a recommendation to the Secretary even though it has not been done before?

Dr. Lee: Last May we did have this recommendation and it went to the Secretary. Individual CFSAC members were encouraged to make comments through normal NCHS channels. If CFSAC makes a recommendation, it must be gotten to NCHS by Nov 18. I would have to research a more sustainable response to your question.

Dr. Jason: Is it possible to find out what the Secretary's response was to our unanimous recommendation six months ago?

Dr. Lee: We can look into that.

Dr. Levine: If we disagree with NCHS's final decision, is there a way to appeal?

Ms. Pickett: The next step depends on the comments filed by all users of the classification codes, not just CFSAC. Many times when an option is not supported, we work with groups to create a consensus option. That would then be presented at a public meeting.

Dr. Klimas: Who weighs the different comments? Are physicians, researchers, and other professionals weighted the same as the general public?

Ms. Pickett: We do not weight particular groups in one way or the other. One of the key things we are looking at is whether the comments really relate to the classification and placement of conditions within the classification and the appropriateness of the comments in relation to the need for instructional notes. One of the things we do not do as part of the public process when updating a classification is look at reimbursement issues. That is a whole different track. We are looking to ensure that what is being added to or modified within the classification is clinically accurate and is consistent with the structure and conventions of the ICD. The final decision makers are the director for the NCHS and the center administrators for CMS. Those two organizations have responsibility for classifications as a whole.

Dr. Jason: Does the DHHS Secretary oversee NCHS? Did CFSAC's recommendation from six months ago get to your office? Have you considered it and do you have any comment on it? You eloquently described some arguments in favor of Option 2. Could you discuss the arguments you were given in September in support of Option 1?

Ms. Pickett: The rationale for Option 1 is in the background that was presented with the proposal. The concern with moving CFS into G93.3 with no further expansion of that category is that data from 13 years disappears. In terms of what the coalition was requesting, they were hoping to have CFS align itself the way it is in ICD-10. The issue there is that ICD-10 does not have a breakout for CFS and CFS did not exist in the WHO ICD-9.

Dr. Jason: Does your agency fall within the mandate of the DHHS Secretary and what implications might that have? Have you seen CFSAC's recommendation, reflected on it, and made any decisions on whether or not it is worthwhile?

Ms. Pickett: I have been made aware of the recommendation. What the recommendation did not do is fully specify what modifications you wanted in the classification. You have to show what a proposal looks like according to the tabular list and how you are modifying it according to the structure and conventions of the classification. There is a difference between having a recommendation that says, "Move something," and actually having a proposal that can be brought to the public for full discussion, which is what the coalition did.

Mr. Krafchick: The ICD-9 often weighs heavily in reimbursement and disability questions. I did not know that was not considered when you modify the classifications. If a patient is classified under something that weighed more toward a mental health condition than a physical condition, that would have great implications in whether a person can get disability benefits beyond 24 months. This is something very, very critical to a lot of people in the country. It also has great implications for providers getting reimbursement for care given. The most common use for ICD-9 now is healthcare reimbursement.

Ms. Pickett: Reimbursement issues are outside of how and why we update the classification. Business decisions are made by the insurers relative to the codes but we do not interact with them at all on those business decisions. The placement of diseases in chapters is based on where the WHO has placed them. We just build on what the WHO has done in many instances.

Dr. Vincent: Is Chronic Fatigue (CF) going to be separated from CFS?

Ms. Pickett: The only thing that would be removed from the R53.82 in Option 1 would be the term “chronic fatigue syndrome.” The code for CF would remain in the Signs and Symptoms chapter. There would still be a unique code for CF.

Dr. Levine: It concerns me that reimbursement issues are not being taken into account. I do not see the point of changing the code if we are not going to take reimbursement issues into account. Who are you changing it for?

Ms. Pickett: All users of data. The ICD-9-CM was used long before it was used for reimbursement purposes. Medicare did not start using the codes for reimbursement until 1983. Trying to incorporate reimbursement use cases which vary by payer is next to impossible. What we are doing is modifying the classification to be consistent more or less with the WHO classification. There are multiple use cases. Reimbursement is not the only one. Reimbursement is not discussed as part of the meeting and that announcement is made at all meetings.

Ms. Holderman: How much of a role does consulting other agencies such as the CDC have? How does looking at agencies’ medical literature play a role?

Ms. Pickett: Literature is submitted to us many times with proposals. Many of the medical groups will also supply a literature review with their comments. If we are having trouble sorting out the variations that are being presented, we will reach out to medical groups. We do not consult just the CDC. We have established links with other external groups that we work with frequently to help us sort out the issues. We can also look to the CDC, AHRQ, and others.

Ms. Holderman: Does NCHS give more weight to one agency over another?

Ms. Pickett: No.

Dr. Jason: This issue has generated a tremendous amount of controversy over the last few months in terms of CFSAC members getting emails and phone calls from the larger patient and physician community. Has your office also gotten a lot of communications from outside individuals concerning this issue? Do you have a sense of why this is such a pressing issue for the patient community? Do you have a sense of what the difference is between CF and CFS?

Ms. Pickett: Currently all email is going into a general committee inbox. The inbox is filling up rapidly. Staff and I are not looking at it, however, until the comment period closes on November 18. This is normal practice to wait until the end of a comment period to sort through comments. That way, we do not get an early view that leans one way or the other.

As far as definitions, they are not in the classifications. We look to the provider community to help us with definitions. At end of the day, if providers diagnose a patient with any disease, they are using their clinical judgment to make that diagnosis determination. We are not looking at case definitions. We are aware that there are conflicting or differing definitions out there, but definitions are not in the classification.

Dr. Jason: In the past, have organizations that are as multi-disciplinary as CFSAC been sought out for advice when controversial and difficult decisions have to be made in classifications?

Ms. Pickett: In trying to sort out issues, we would go to subject matter experts. It depends on the issue. I’m not talking about CFS specifically. It could be the American Medical Association, the Academy of

Urology, orthopedic surgeons...we reach back to external groups. We do have established links for that. Normally we would not have reached back to an entire advisory committee. We would be focusing on specific subject matter experts.

Dr. Lee: About how many conditions are covered under ICD-10?

Ms. Pickett: We haven't had a count of how many conditions. There are approximately 160,000 codes in ICD-10-CM.

Dr. Levine: Do you ever have people from SSA disability or private disability companies weigh in on your choice of whether or not to update the coding process?

Ms. Pickett: It has been rare that an insurance company would weigh in. Insurance company representatives have attended meetings, but as far as actual comment letters on a clinical entity, no. Generally they defer to the clinical subject matter experts for that clinical expertise. How they handle codes is their business decision.

Dr. Jason: In the area of CFS, there is an international scientific organization that represents the science of this particular field. Are you aware of that organization? Would it be appropriate to reach out to the officers for consultation and would it be instructive given the controversy that you're dealing with?

Ms. Pickett: We reach out to external bodies on all issues whether or not they are controversial. You never know when something is controversial. We want to make sure that we are talking to everybody. We have not often reached out to international groups because the clinical modification is used in the United States. We look to US experts. We have had international experts reach out to us on other issues. They have not necessarily done that with CFS. They have that option. ICD-10-CM, as with ICD-9-CM, was developed for use in the United States. We are looking to make sure that the US perspective is handled correctly.

Dr. Klimas: There actually is only one organization and it represents the United States. The IACFS/ME [International Association of CFS/ME] is really the only group of experts to go to.

Roll Call

At the conclusion of the committee discussion session, **Dr. Snell** conducted a roll call of CFSAC members who were not present during earlier introductions:

Absent from Roll Call: voting member **Dr. Michael Houghton** and *ex officio* member Cheryl Williams, Social Security Administration (SSA).

Housekeeping

Dr. Lee noted:

- The location of a CFSAC meeting message board at the back of the meeting room.
- The location of public restrooms.
- Staff would be taking CFSAC members' lunch orders after the meeting break.
- The timing of normal procedures to open the meeting was changed in order to ensure that Donna Pickett could make her presentation on ICD-CM, an important CFS issue. Dr. Lee said that May 2011 CFSAC meeting minutes would be approved at a later time.

Public Comment

Christine Williams

- Former CFSAC *ex officio* member who worked for AHRQ.
- Retired from Federal service in June 2011 after 30 years due to CFS/myalgic encephalomyelitis (ME).
- Spent her career in health policy and health services research, half the time as a senior health policy advisor for Senate Majority Leader George Mitchell (D-ME) and the balance of her career at AHRQ.
- Experienced sudden onset of flu-like symptoms in August 2008 that never resolved.
- Took seven months of persistent online searching to locate a physician with expertise in CFS/ME.
- Struggled to complete her remaining 2 ½ years of Federal service so she could retire. Had to forgo after-work activities, spending her limited energy working.

Ms. Williams outlined five suggestions for DHHS to maximize its opportunity to make an enormous difference in the lives of people with CFS/ME:

- 1) Leadership: The department must provide public and active leadership. The DHHS Secretary, Assistant Secretary for Health, and other leaders have exhibited their commitment to CFS issues, but the commitment must extend to all levels in the department and agencies and it must be backed up with action.
- 2) Research: NIH, AHRQ, and other DHHS research agencies must lead in CFS/ME research, make it a priority, build on new studies, partner with other research institutions, and include reverse translational research from clinical experience.
- 3) International Consensus Criteria: DHHS needs to be more involved in the development of a more refined case definition of CFS/ME, including the recently developed International Consensus Criteria (ICC). The existing broadness of case definitions is a barrier to meaningful research.
- 4) Convener: DHHS can build on the 2011 NIH State of the Knowledge Conference to facilitate an ongoing “Learning Network” to help researchers and clinicians collaborate across disciplines.
- 5) Coordination across DHHS: Agencies should not duplicate efforts but instead partner to maximize resources and initiatives and serve as a source of current scientific information on websites.

DHHS can rise to the challenge as it did with the AIDS epidemic and be a leader in the search for effective treatments.

Mary Dimmock

- Mother of a 24 year old man who came down with ME/CFS in 2010.
- Son is sick with a disease that patients have suffered from tremendously for 30 years while the government has seriously under-funded research, focused studies on psychiatric issues, and set

forth confusing definitions that classify a devastating neurological disease with generalized fatigue and depression.

Asked CFSAC to address two critical issues:

- **Reclassification of CFS in ICD-10-CM** – Until CFS is renamed ME, it is especially critical that the disease be properly classified. Option 2 is not acceptable because it would create one sub-code for ME/CFS cases that are virally triggered and another sub-code for cases that are not virally triggered. ME/CFS must be reclassified as a neurological disease before ICD-10-CM is implemented in 2013.
- **Replacement of the Fukuda case definition** with one that reflects the specific and unique nature of ME/CFS as a disease with significant neurological pathologies. Fukuda does not describe a neurological disease and does not adequately describe other facets of ME/CFS, including the hallmark post-exertional malaise.

Until these issues are addressed, a million sons and daughters will continue to suffer and die in the “parallel universe” in which CFS forces them to live.

Anonymous Commenter (via phone)

- Many patients with ME are dying from microvascular cardiac disease.
- The NIH Women’s Ischemia Syndrome Evaluation (WISE) presents a huge opportunity for research synergy and funding on heart disease in ME.
- Persistent undiagnosed chest pain is rampant among ME patients. But patients presenting with atypical angina receive rote cardiac tests focused on blocked coronary arteries. These tests routinely miss a microvascular diagnosis.
- WISE researchers do not fully understand the mechanism of cardiac ischemia but they know that patients with clear-as-a-bell coronary arteries can have deadly cardiac ischemia. They know that microvascular and endothelial dysfunctions can and do kill.
- The WISE initiative is one with which CFS researchers could dovetail. The profile of WISE patients is uncannily similar to that in ME.
- WISE research arose because women die far more often than men from cardiovascular causes.
- WISE research to identify “novel risk markers” for women’s cardiovascular risk found a familiar pattern. Given the many parallels between WISE and ME patients, research into microvascular/endothelial pathology could prove pivotal for both groups.
- NIH is pouring money and attention into atypical angina. Collaboration with the WISE teams could supercharge funding and foster recognition of the seriousness of ME.
- Robust ME criteria must be used, including the requirement of post-exertional malaise.
- Shame on CFSAC for not making its meeting more accessible by providing live video streaming.

Andrew Bokelman (via phone)

- Came down with CFS in 2005. Was diagnosed with prostate cancer in January 2008 and three months later, with a squamous cell carcinoma on his tongue. Having CFS has been much worse than dealing with two cancers. CFS keeps him housebound and so sick that he needs help with basic personal care.
- People did not dismiss his cancer as they do his CFS. They dismiss CFS because he does not look sick and can articulate with the same strength and focus as healthy people.

- With most illnesses, people are seen as heroic for all they accomplish despite being sick. With CFS, accomplishments are used to dismiss patients. This dismissive attitude is caused by:
- The fatigue-centric model, with a misleading name and description that leads doctors to look for energizing solutions and ignore inflammation, immunity, and neurocognitive issues. Part of the solution is changing the disease's name and description according to the ICC.
- Misrepresentation and selective omission of CFS information, particularly on the CDC website. For example, the website treatment information is based on Oxford criteria studies that define CFS with only physical and mental fatigue. Tender lymph nodes, sore throat, and post-exertional malaise are not included. DHHS should stop condoning this and explain how this corrupts the understanding of CFS. The CDC website is also missing important information about medications.

New leadership in key positions at DHHS and the CDC has made some positive changes. Hopefully this is a sign of more to come, not just a brief flurry of activity.

Mary Schweitzer

- Has been sick with CFS for 16 years. Was a rising professor of history when struck down by CFS. Is able to testify only because she is on Ampligen, which she has taken on and off since 1999. When not taking Ampligen, she relapses and becomes too sick to be coherent, does not understand much of what is said to her, has severe pain behind the eyes and in the neck, has severe headaches, is light sensitive, and has difficulty walking. She has been diagnosed with viral encephalitis and exhibits the symptoms of ME. She has tested positive for a toxic stew of viruses, some in her spinal fluid. For example, she has been diagnosed seven times in the last 20 year with Epstein-Barr virus (EBV).
- It is disingenuous to think that there is no relationship between the viruses in her spinal fluid and her encephalitic symptoms. The CDC website, however, would not reveal a link because it does not mention them.
- Although the CDC website has dropped the paragraph discouraging testing for viruses in connection with CFS, it still maintains that testing positive for EBV does not indicate CFS.
- The CDC website has no information about the link between cancer and repeatedly testing positive for EBV, as does Dr. Daniel Peterson.
- Ampligen costs \$20,000 a year for medicine and testing alone.
- Both new physicians' toolkits on the CDC website emphasize cognitive behavior therapy and graded exercise as the treatment of choice for CFS. The page links to St. Bartholomew's Hospital in London, which offers graded exercise and cognitive behavior therapies. Peter White, a CFSAC advisor in the past, has his psychiatric practice at St. Bartholomew's.
- It is silly to think that one can cure ME and EBV with cognitive behavior.
- A study by Dr. Snell and his colleagues show that ME patients cannot do aerobic exercise due to their inability to use oxygen and dispense carbon dioxide properly.
- Cognitive therapy for someone who is very sick is cruel. No one would try to treat a lung cancer patient by discussing his faulty illness beliefs. Empire Blue Cross/Blue Shield will not reimburse Dr. Schweitzer for treatments until she attends two weeks of cognitive therapy.
- It is dangerous to direct people to do graded exercise if you do not know what is going on with their systems. One does not know the symptoms involved.

Pat Fero

- Stated that no one in the room is responsible for the misuse of CFS grant funds.
- Took a tutorial in July 2011 about the misuse of funds on the grants.gov website.

- Recruited Charlotte Von Sails to assist in the grants investigation project.
- Used Freedom of Information Act requests to examine NIH grant awards from 2000-2010. Worked to eliminate researchers from the long list of those who apparently misspent grants for CFS research.
- Looked for any information indicating that the researcher had an interest in CFS. Used sources including the NIH Reporter, PubMed, the grantees' affiliated institutions, and Google. The process took about two to three hours per person.
- Started out with 47 researchers of concern. The goal was to eliminate as many as possible.
- Definition of misuse of funds: 1) The research materially deviates from the intent of the grant or 2) the research has nothing to do with CFS. One example is a grant of \$1.3 million to set up a bio bank. Could find no evidence that the bank was set up.
- Will file information with the Office of the Inspector General showing \$18.56 million in misused NIH grant funding for CFS research.

Kim McCleary

- President and CEO of the CFIDS Association of America.
- Noted that results of a small phase II study of Rituxan was released in Norway in October 2011 showing tremendous promise for 67 percent of CFS patients who received two doses. The hunt is on for better clues as to why this therapy worked.
- Called for a mobilization in the US that equals the effort launched to follow up on promising laboratory results linking the XMRV virus to CFS. There is tremendous opportunity to leverage many of the resources assembled to address XMRV:
 - The NIH Clinical Center has already identified a well-characterized CFS cohort.
 - The Center has experience with the use of monoclonal antibody therapies.
 - The NIH Undiagnosed Diseases Program has reported that in its first two years of operation, one of the most common diagnoses was CFS. These people represent another source of patients for study.
 - The National Institute of Allergy and Infectious Diseases (NIAID) has invested in a multi-center network to collect samples for the Lipkin study.
 - CDC has let a contract to a collaborative of CFS expert physicians who will meet in November 2011.

These could be the beginning infrastructure to support a long-needed clinical trials group that could be activated to pursue findings such as the one from Norway. DHHS should not allow the emergency alert system that responded so effectively to XMRV to go dormant. CFS is still here and a mobilization effort is needed as urgently as it was two years ago to disarm the disease.

Tina Tidmore for Toby Vokal (via phone)

- Observed that in our society, being a man is associated with emotional strength, physical strength, and a strong character. Toby's physical strength was taken from him at 18 with the onset of CFS. He has ended up living with his mother at age 34 with no vitality, career, or normal recreation.
- Said that Toby has retained his strength of character and will apply it to hold CFSAC and related government agencies accountable to the American public.
- Noted that at the May 2011 meeting, the CDC *ex officio* agreed to have CFSAC members advise the agency on correcting the misleading and outdated information on its website. This has not happened. Called for the information to be changed or taken down within the next month.

- Called on CFSAC to provide a live video stream of its meetings in recognition of CFSAC patients' cognitive difficulties.
- Stated that CFSAC must create a more fair system for public comment, such as first-come, first served.
- Questioned why CFS is in a different code in the US than in every other country. There may be subgroups and different triggers, but all CFS patients have the same disease.
- Contended that NCHS Option 2 contradicts the WHO ICD-10 coding, contradicts research that shows CFS often has a viral trigger, and confuses physicians as to what research to apply to their patients. It classifies ME and post viral fatigue syndrome (PVFS) with a different code than CFS and makes CFS the lead term for the disease.
- Said that Option 1 corrects these problems by putting ME, PVFS, and CFS in the same code in the chapter for neurological diseases. It also brings the field closer to doing away with the "CFS" term. Called on CFSAC to recommend Option 1.

Nancy McGrory Richardson

- Education and Outreach Director for Hemispherx Biopharma
- Hemispherx paired with Chronix Biomedical to file a provisional US patent application in March 2011 on a blood test for CFS. The test analyses fragments of DNA often released into the bloodstream during apoptosis (cell death). The test focuses on measuring "signature" alterations in specific regions of the chromosomes, allowing detection of disease-damaged cells without the need to biopsy cells or tissue. These patient-unique signatures have the potential to be useful for diagnosing CFS.
- FDA has suggested that a reliable diagnostic test would be valuable in identifying potential participants in new CFS trials. Once Hemispherx is confident that the Chronix diagnostic test is predictive, it will be appropriate to meet with FDA to discuss protocol for the phase III clinical trial.
- The Chronix test may help predict how different individuals respond to Ampligen.
- Hemispherx reported initial findings in September 2011 of its studies of potential CFS markers. DNA extracted from serum samples of CFS subjects and health controls was sequenced and compared to the human genome. Four genes were identified that separated CFS subjects from the control group. Hemispherx will accelerate this line of investigation.
- Hemispherx will stop its research on markers for XMRV.
- Hemispherx is submitting to FDA a request for an additional extension to the company's new drug application (NDA) and expects FDA to grant the request.
- Ampligen has been transferred to the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) within FDA. Hemispherx is taking steps to ensure that progress is not stalled by this change.

Dr. Lee noted that FACA rules require that anyone testifying before CFSAC must submit his or her written statement before oral testimony. The CFSAC public comment schedule was rearranged at the last minute because several commenters did not submit written testimony. In addition, CFSAC support staff is doing extensive photocopying on the spot to be able to distribute testimony, creating some delays.

Dr. Snell emphasized the importance of public testimony in CFSAC's mission and encouraged future submission of written comments as early as possible to allow as many people to testify as possible.

Beth Schipper (testimony read by Lorie Kroger)

- Words cannot convey how desperate CFS patients are for basic compassionate care, let alone educated, knowledgeable, and proactive treatment protocols. It is hard to believe that this level of barbaric treatment continues to be practiced by some in the medical profession towards ME/CFS patients unless you witness this in person and first hand.

Bob Miller and **Ms. Kroger** presented a brief skit depicting how CFS patients (represented by Mr. Miller) are often mistreated by emergency room doctors (represented by Ms Kroger). The skit was based on real stories. Mr. Miller presented with some typical CFS symptoms including a pain running from the base of his skull down his spine, nausea, lack of appetite, sensitivity to noise and light, dizziness, weakness, and fatigue. He said that he had been seeking a diagnosis for six months. Ms. Kroger consulted the physician's toolkit from the CDC website. She followed the recommended psychiatric evaluation and sent Mr. Kroger, over his protests, to the hospital psychiatric ward for a 48-hour observation period.

Ms. Kroger said that she knows of four CFS patients who have been referred to the hospital psychiatric ward in the last year. She said that CFS patients are afraid to go to the emergency room for fear of being treated as recommended on the CDC website. She called on CFSAC to change the CDC website and recommend that CFS be reclassified under the same code as ME.

Approval of May 2011 Meeting Minutes

Dr. Jason noted a correction distributed via email to the minutes of CFSAC's May 2011. **Dr. Marshall** moved that the minutes be approved with that correction. **Mr. Krafchick** seconded the motion. **Dr. Snell** announced that the minutes were approved unanimously.

Conflict of Interest Statement

Dr. Lee read the conflict of interest disclosure statement governing CFSAC proceedings. The statement declares that members are subject to Federal conflict of interest laws and regulations. All members of CFSAC are in compliance with Federal ethics and conflict of interest laws. CFSAC members have been screened for potential financial conflicts of interest of their own as well as those of their spouses, minor children, and employers.

Dr. Lee asked CFSAC members if they have any concerns about the agenda. **Dr. Klimas** noted that a member of the Rituxan research team would be attending the meeting and suggested that there be an opportunity to discuss the Norwegian study in the context of CFS research issues. **Mr. Krafchick** seconded an interest in speaking with the researcher.

Break

Dr. Snell announced a 15 minute break.

Welcome Statement from the Assistant Secretary for Health

Howard K. Koh, MD, PhD, Assistant Secretary for Health

- Thanked Dr. Snell for his dedication and five years of service on CFSAC, including serving as chair.
- Thanked CFSAC on behalf of DHHS for addressing the many critical and challenging areas of CFS. Too many patients are suffering with CFS and the expertise of committee members is needed.
- Requested that CFSAC members introduce themselves and give their affiliation. Committee members did so.
- Noted that CFSAC is addressing all aspects of CFS—research, education, patient care/quality of life. Many more answers are needed in these critical areas.
- Reviewed the progress DHHS has made in the field of CFS, especially since the last CFSAC meeting:
 - 1) NIH held its first-ever State of the Knowledge meeting on CFS in April 2011. The key issue for that meeting was lack of standards for research in the field, including differences in study design, sampling methods, patient characteristics and assessments, and even a basic definition. There was a robust discussion at the meeting of what should be the minimal data elements moving forward. Noted that Dr. Jason will present an outline later in the meeting of a manuscript for developing these minimal data elements. This will allow for greater consistency in comparing studies in the literature. As a physician and former professor, Dr. Koh said that he was involved in many research trials and understands the importance of starting with some very basic research elements.
 - 2) The CFSAC Patient Care/Quality of Life Subcommittee is working with CDC on updating its website to address the concerns of CFS advocates and patients. Dr. Koh thanked Dr. Klimas and Ms. Holderman in advance for addressing the website issue later in the meeting.
 - 3) Noted that better answers in the field of CFS are needed and researchers must take the broadest approach to getting those answers. Thanked Dr. Marshall in advance for addressing interdisciplinary approaches to research later in the meeting. Emphasized the importance of the integrative research approach.
 - 4) Noted that a meeting of DHHS leaders was convened in spring 2011. The status of work on CFS and the activities being engaged in by CFSAC were presented. Also discussed at great length was how patients are suffering. DHHS Secretary Kathleen Sebelius asked Dr. Koh to convey her thanks to CFSAC for its work. She has asked those working on CFS throughout the department to coordinate their efforts more strongly. Dr. Koh's office and that of Dr. Lee, the new Director of the Office on Women's Health, are creating a working group on CFS. The group will report back to the Secretary an inventory of efforts in the field of CFS going on throughout the department. The group will do its best to coordinate strategies across the department in a more coherent fashion. The group will make its work available on the CFSAC website.
 - 5) Described Dr. Lee as an outstanding scientist and thanked her for taking on her new role as Director of the Office for Women's Health. He noted that Dr. Lee attended the IACFS/ME Biannual Conference in September 2011 on Ottawa, Canada, to hear about scientific developments in the areas dealt with by CFSAC and to network with researchers. Dr. Koh also thanked Ms. Bond for her work as senior public health advisor to Dr. Lee and CFSAC.

- 6) Expressed a desire to continue to make communications with CFS patients and advocates as positive and constructive as possible. Noted that Dr. Lee is reviewing the CFSAC web page and developing a list serve to increase communication with the CFS community. Her office is working more closely with the SSA on data exchanges. She is also looking into updating the CFSAC charter and bylaws, which expire next year.
- 7) Said that DHHS wants to improve communication with non-governmental organizations (NGOs) related to CFS and noted that Dr. Lee is exploring the legal, logistical, charter, and bylaw issues connected with adding more NGO voices to CFSAC.
- 8) Expressed enthusiasm for Dr. Lee's hiring of Christine Williams as special advisor. He noted Ms. Williams' outstanding reputation in public health, her service as an *ex officio* CFSAC member, and the open and constructive way she shares information about having come down with CFS. He described Ms. Williams as the "ideal link for all of us" because she has multiple perspectives on CFS issues.

Dr. Koh concluded that these areas of progress are just the beginning. He acknowledged the many unanswered questions in the field. He said that the working group will be coordinating closely with CFSAC *ex officio* members to report back to Secretary Sebelius on the inventory that the working group is collecting right now.

Dr. Koh thanked the CFSAC members who are rotating off the committee in spring 2012: Drs. Snell, Klimas (Patient Care/Quality of Life Subcommittee chair), and Jason (Research Subcommittee chair), adding that CFSAC may well find avenues to tap their expertise again. Dr. Koh also welcomed Dr. Vincent as a new CFSAC member.

Committee Discussion

Dr. Jason thanked Koh for regularly attending CFSAC meetings and discussing issues with CFSAC members between meetings. Dr. Jason noted that neither of these actions occurred consistently in the past. Dr. Jason also thanked Dr. Koh for hiring excellent staff to replace those who have stepped down. Dr. Jason observed that all but one *ex officio* member has turned over in the four years that he has served on CFSAC. He said that it takes a year or two to learn the turf and work cooperatively in the networks that are critical. He asked Dr. Koh how to deal with the fact that the support staff and *ex officio* CFSAC members have a certain amount of turnover that makes consistency and progress potentially more difficult.

Dr. Koh: Dr. Wanda Jones, previous DFO and current Deputy Assistant Secretary for Health, is providing a lot of guidance to me and Dr. Lee despite Dr. Jones's huge portfolio. Ms. Williams will provide a point of continuity for Dr. Lee and Ms. Bond. All four of the Secretary's counselors are now familiar with CFS issues. The Secretary wants agencies dealing with CFS to be more integrative across DHHS. I would like to think that with all those forces together, we can take a coordinated departmental approach to CFS issues.

Dr. Klimas: Dr. Jones has always brought to the committee a real sense of what could be done within the structure of DHHS. For those of us who are not familiar with government, it can take literally years to understand what and how to work together. Kim McCleary earlier today pointed out how aggressive, correct, and fast the government's response to XMRV was. That was an example of how things can happen. What I would like to see is that kind of motivation going forward without the

banner of XMRV to rally under. A skit during public testimony depicted what happens when a doctor looks up CFS online and sends the patient to the psych ward to be put on so many psychotropic drugs that the patient would not have any energy left in his or her body. The ignorance of my profession is appalling. If there's one thing we could do with motivation and speed it would be an all out effort to educate the clinicians on just the first and second thing to do when they see a patient in crisis with this illness. If you could just put the force of you office behind that—let's just do it.

Dr. Koh: We are trying to put more emphasis into that precise area. I understand that HRSA is working on professional education. You are absolutely right. The lack of awareness and understanding in this area is too great.

Dr. Willis-Fillinger: Specific activities to train physicians about CFS are a very focused area. Instead we have talked about generic training. Generically we have mechanisms in place to share information with communities and providers. Sharing information specifically about CFS is not something that I can say at this point we are committed to, but with your direction I can definitely take that suggestion back.

Mr. Krafchick: One of the most important sources of information for everybody now is the internet. The websites that are talking about CFS—whether it is NIH or CDC or whoever—have a profound effect on the reimbursers for insurance and disability. It is important that websites get some priority so that the science and what is known about the condition is considered. Also critical is a case definition that is accepted by IACFS/ME. There needs to be some consistency in the information that comes out to help all of the people who are suffering with CFS as well as the researchers.

Dr. Koh: That consistency theme is going to be part of Dr. Jason's presentation, particularly the CDC and CFSAC websites. Thank you for raising that.

Dr. Snell: Thank you for attending the meeting. I would urge you to go back and push forward this idea of a concerted effort within HHS where people are talking to each other about the illness and looking at mechanisms currently in place so that we can really leverage funding that is available in these difficult times. If CFS—or whatever we choose to call it—occurred overnight and this many people came down with this unexplained illness, I cannot imagine what the push would be to find a cure.

Dr. Koh: Thank you for your passion. This is a very important public health issue. There are too many people suffering and we need some answers. We have a group that is so dedicated, and I'd like to think that with the new team and the advances that I have reported, that progress will continue. Keep the communications coming.

Agency Updates

Agency for Healthcare Research and Quality

Beth A. Collins Sharp, *Senior Advisor for Women's Health and Gender Research*

- Noted that this is her first meeting. Thanked Ms. Williams for her orientation to the CFSAC committee and expressed relief that Ms. Williams will continue to advise the committee.
- Likes to say the full name of her agency so people think about what the Agency for Healthcare Research and Quality actually does and how it differs from other agency missions. Each of those words is important. AHRQ is a research agency that focuses on health *care*, meaning health

services and quality of care, not particular health conditions. AHRQ is interested in the care surrounding CFS and other diseases. The agency portfolios are about health care, not particular diseases. For example, the agency is interested in patient safety, patient-centered care, and health information technology.

- AHRQ's mission does not include setting policy, making coverage decisions, generating regulations, or making clinical recommendations. What the agency does focus on is research data and evidence that can then directly inform all those other things. AHRQ produces and supports the generation of evidence that can inform other decisions. Part of the mission is also dissemination and translation of the evidence. For AHRQ, translation is not from the bench to the bedside, but from the research bedside to the actual patient bedside. AHRQ is interested in what is going to happen in real life.
- A lot of AHRQ's work is user driven. There are many areas where the public can recommend research topics. In the grants program, the topics that are of interest to the researchers are the topics that are then reviewed.
- One grant for which the findings have come out is Project Echo. Healthcare for individuals with hepatitis C was delivered via health information technology from academic microcenters in New Mexico to individuals in extremely rural areas in New Mexico. It was very successful. The patient outcomes were much improved. This was a good example of a project where healthcare was delivered in a new way, evaluated, and researched systematically. The disease could have been CFS or any other. This is an example of a very successful research program that was funded through the AHRQ grant program and published since the May 2011 CFSAC meeting.

The following are two more resources where the work comes from the outside in:

- **National Guideline Clearinghouse (NGC).** Professional societies and groups, practitioners, and provider groups can submit clinical guidelines that they have developed. The guidelines must meet certain criteria for quality. The evidence behind them needs to be sound. There is an editorial board. When the guidelines are placed in the clearinghouse, they are searchable. There are communities to discuss the clinical guidelines. It helps a great deal with the dissemination of the guidelines.
- A search of NGC for ME/CFS revealed only five guidelines posted for clinical care. Of those, only one had CFS for the topic area. The others were food allergy, irritable bowel syndrome, celiac disease, and hepatitis B. Somewhere in these guidelines, CFS was referenced. The one CFS guideline comes from the U.K. National Health Service. There has been work lately on clinical guidance for CFS. There were findings presented at the meeting in Ottawa. Those who are working on them are encouraged to submit guidelines to the NGC so that they will be available publicly.
- **Innovations Exchange.** This is a clearinghouse for innovations. Examples include things that have worked well in a local setting, may not be ready as a full clinical guideline, but may be a quality tool. The innovation can be shared to gather feedback and be available to be implemented in another place. A search revealed three quality tools listed for CFS. Two come from the Office on Women's Health and the other is a 2008 Veteran's Administration clinical guideline for unexplained fatigue and pain.

- Ms. Sharp encouraged those involved in CFS to contribute to these two sites because there is a lot of traffic. It is a wonderful way to promote the sharing of information. Ms. Sharp distributed to CFSAC members and the public distribution table some paper bookmarks with an imprint of the clearinghouse's electronic bookmark. This information is also available on www.guideline.gov. That site will lead to all clearinghouses and exchanges.

Committee Discussion

Dr. Jason: Is it possible for a Project Echo-type demonstration activity to occur for CFS giving that there are thousands of people in rural areas who could probably benefit? What would be the mechanism for getting that to occur? Several CFSAC members have been developing a healthcare primer for the last year and a half. Does AHRQ reach out to groups to provide them funding to help finalize these types of projects or do groups external to your agency come to you with finished products?

Dr. Sharp: Project Echo was a grant mechanism. Given that it was so successful, there are a number of individuals who are interested in Project Echo for a variety of conditions. I cannot guarantee that there would be a Project Echo for CFS, but the agency would be interested in possibly providing a grant to fund a successful project like Echo that is implemented in another area. Because a method has been funded before for a different health condition does not dissuade the agency from considering the replication of that method in another area. I would also refer you to the Project Echo researchers themselves because they also have thoughts about spreading this to other areas.

As far as funding the healthcare primer, traditionally individuals come to us first rather than us having a direct solicitation. That does not mean that the primer might not fit under one of our requests for proposals.

Dr. Levine: In general, if someone submits a grant proposal to you, would you have to research the epidemiology of that condition? Would you want to know the approximate prevalence of illness? Would it make a more compelling request for funding if there was a higher population affected?

Dr. Sharp: One of the priority decision-making considerations for all grants is burden of disease. This does not necessarily mean prevalence. The burden of disease for CFS is obvious, but it would need to be described in the grant to those who may not find it obvious. Although burden of disease does not mean prevalence, it is helpful to have prevalence data when you can find them.

Dr. Snell: Is there a format for unsolicited proposals?

Dr. Sharp: AHRQ follows the NIH formats and uses the electronic submission program. The format is exactly the same as an NIH grant. It is available on the agency website.

Dr. Snell: Being realistic in this day and age is funding available or would we be wasting our time writing a proposal?

Dr. Sharp: I do not want to discourage you at all. Strong proposals are important to us. It is hard to predict from one funding cycle to the next how it is going to be. When I talk to potential grantees, I tell them not to try to play a timing game with the funding stream. Strength of the proposal comes first. It is a financially constrained time but AHRQ wants to continue to move the strong science projects forward.

Dr. Jason: Sometimes agencies have priorities as to the things that they are interested in. Where does CFS fit in with the list of potential issues and is there any way that CFSAC could make a recommendation to your agency that could bring CFS to a higher priority to be considered for funding?

Dr. Sharp: Realistically, our mission is so completely entrenched in healthcare and health services that having a particular condition called out is not going to happen. It is not going to happen for heart disease or cancer, either. There are priority areas that include some disease conditions, but it all goes back to patient care burden.

Dr. Jason: How did it happen with hepatitis C, which is a very specific illness?

Dr. Sharp: That was chosen by the researcher as the test case for this health service delivery process.

Dr. Lee: I know that 10 years ago, AHRQ did an evidence review for CFS. What is that process? Is it something that is needed? Is it something that the DHHS working group should be pushing for?

Dr. Sharp: I brought the executive summary of that review. That was published in December 2002 and it was a systematic review related to disability and CFS. The Evidence-Based Practice Center (EPC) does systematic reviews of evidence on a particular topic. The topics are nominated by individuals; patient, professional, or clinician groups; or government agencies that have a decision that needs to be informed by evidence. The 2002 CFS report was requested by SSA to inform its decision-making in a particular area related to the disability associated with CFS. If a Federal agency requests the report, it also must fund it. If you are not a government agency—the most common request is from a professional society developing a clinical guidelines—the individual or group will nominate the topic and explain why it is important, why there is sufficient burden of disease and need, and how it will be used. The agency is not interested in producing reports just for the sake of producing reports. AHRQ actually wants the report to be used. Those interested in nominating topics from a non-government perspective may do so online at www.effectivehealthcare.ahrq.gov. The nomination goes through a prioritization process and if it is selected, there is an evidence review generated. AHRQ pays about \$500,000 (give or take) for a systematic review.

Dr. Jason: The 2002 report is outdated. Is there any possibility of that being updated? How could that get started? Could CFSAC be the group to get that process started? What is the next step?

Dr. Sharp: Updates are handled exactly the same way. If an update request comes from a Federal agency, that agency must fund the update. A request can also come from outside the Federal government. The request for an update does not have to come from the same agency (in this case SSA) that requested the original report. I am not aware that CFSAC has the funding.

Dr. Snell: We can wait until SSA does its report tomorrow and mention that they ask for an update.

Center for Medicare and Medicaid Services

Alaine Perry, Senior Advisor for Disability and Special Need Population, CMS Center for Strategic Planning

- CMS has participated with CFSAC for about a year.

- Ms. Perry said that she appreciates the opportunity to participate on the committee and learn, particularly from public comments.

Brief Overview of CMS

- CMS runs the Medicare program and the Federal portion of the Medicaid and Children's Health Insurance programs, both of which are joint Federal/state programs. Ms. Perry brought wallet cards and booklets containing CMS data, such as number of beneficiaries.
- The new function that CMS gained at the beginning of 2011 is administration and implementation of the Affordable Care Act's new rules for the private insurance market. CMS tasks include enforcing the ban on insurance limits; helping states review premium increases, and overseeing the new medical loss ratio rules.
- Along with the states, CMS is also administering the early retirement insurance program and the preexisting condition insurance plan (PCIP). PCIP is a newly available insurance option.
- Another important provision of the Affordable Care Act implemented by CMS is the continuing development and oversight of www.healthcare.gov. The website's goal is to provide clear and understandable information to the American public about new and existing health insurance options that may be available to them.
- CMS is also involved in the Federal portion of the state-based Health Insurance Exchanges that will be up and running in 2013.

Progress on CFSAC requests from May 2011 Meeting

- **Virtual learning network focused on CFS that links researchers, expert clinicians, and clinicians who want to learn more about patients with this condition.** CFSAC had requested information on how the CMS Innovation Center might be one of the supporters of such a network. The Innovation Center is a new center within CMS charged with testing innovations in healthcare service delivery in Medicare and Medicaid, including innovations that potentially could spread more broadly. The Center is funded to test innovations over the next 10 years. CFSAC members should have received via email the link to the Center's website, which describes in detail the organization's processes and criteria for choosing the innovations it wants to fund. At this stage the Center is soliciting general ideas for types of projects that it might want to develop further by sending requests for proposals (RFPs) or solicitations for proposals. The current stage is not a formal solicitation, but an attempt to get input from different groups, providers, patient groups, and any members of the public.
- **Data Sheets on CMS Spending on CFS.** The data is still partial because some information is challenging to get or not readily available at this time. The sheets distributed at the CFSAC meeting represent Medicare spending only on Parts A and B, which are the traditional fee for service Medicare for hospitals, physician care, and outpatient care. The data do not include prescription drugs or Medicare Advantage Plans, which are not under the fee for service system. Under Advantage Plans, participants join a plan through which their healthcare is provided. The data sheets provide total spending under Part A and Part B and the total count for the number of individuals.

- The sheet labeled “for Principal Diagnosis Code 78071, Chronic Fatigue Syndrome” represents everyone in Medicare Part A and B in 2010 who had any claim under Part A or B with CFS coded as the principal diagnosis.
- The second sheet represents a run of the same data for people with a CFS diagnosis in 2010 in any position on the claim. Using this method, the number of people jumps to about 300,000 as opposed to about 100,000 when CFS was the principal diagnosis.
- The data is for all claims, not just those for CFS and not just from people determined to be disabled by CFS and on Medicare for that reason. The data covers, for example, someone on Medicare because he or she is 67 years old. The data represents anyone who had a visit to a provider and was coded with a CFS diagnosis. The numbers are broken into the categories of Aged, Disabled, End Stage Renal Disease (a small percentage of the total) and Disabled with End Stage Renal Disease.

Committee Discussion

Dr. Jason: You have come back with incredible information. We have been making a request for this information for about 10 years. The Innovation Center sounds like a wonderful opportunity. Thank you for sending the link to us. As you set your agenda, is it better to give you input as individual members or would it carry more weight if it came from an advisory committee? If there was a solicitation or RFAs for funding for a particular area in the future, would it be better for CFSAC members to make individual requests to your agency or could CFSAC as a group make a recommendation that CFS is so underfunded that it could be a priority area for your agency?

Ms. Perry: At this stage of submitting ideas, I think either. I am not sure how the Center would assess who the input comes from. Its mission is to both improve healthcare quality and lower costs at the same time, or reduce costs without reducing quality. The Center is looking for innovations that would do those things. The innovations would make healthcare more efficient and effective and apply broadly. There is a more detailed explanation on the website.

Ms. Perry (in response to several clarification questions from Ms. Holderman):

- This is all national data.
- By far the most people in the age category are over 65. The most common case is that a person is initially entitled to Medicare because of a disability. When that person turns 65, he or she is converted. The person may have the same disability but is now eligible for Medicare because of age.
- A person could have CFS and even have been determined eligible for Medicare because of CFS. If, however, no provider in 2010 put down that diagnosis, the person would not appear in this data.
- Cannot answer on the spot how the data handles people who receive CFS diagnoses from multiple providers.

Ms. Holderman discussed several more concerns:

- The fact that PCIP covers preexisting conditions for adults is not really being promoted. A lot of Americans do not know about it and there are a low number of applicants for it. Who is responsible for getting the message out about that?
- Although PCIP is under the Affordable Care Act, it is pretty pricey. What can be done about that?
- PCIP requires that someone be uninsured for six months. For someone who is disabled, that can be catastrophic. It does not sound like the Affordable Care Act has gone far enough.
- There is a problem for CFS patients who relinquish their entitlement to Medicare because they have other means to pay for health insurance. If at some point down the line, they need to get back on Medicare, SSA and Medicare make that person wait for six months. One would think that patients would not be penalized for deciding not to use a government entitlement. Those patients also must pay penalties for premiums that make insurance two or three times more costly.

Ms. Perry: I can take to CMS the concerns you mentioned about outreach. Some of the issues you mentioned about enrollment periods may be statutory. I am not sure how much is law and how much is at CMS's discretion. I think that some of the things you mentioned are probably in the statute and cannot be changed except by Congress. I can try to get you some more information.

Dr. Klimas: It is important to realize that less than 20% of CFS patients are diagnosed. When you look at these data, these are the 20% that are diagnosed of the 20% that go on to have Medicare access by age or disability, and the government is spending more than \$100 million a year in Medicare reimbursements in that very small subgroup. We need to put that all in perspective when we are spending only \$6 million a year in research. The math just boggles the mind. It is very important to see these numbers—they are just staggering. I really appreciate your hard work.

Food and Drug Administration

Dr. Theresa Michele, *Medical Officer Team Leader, Center for Drug Evaluation and Research*

- On January 16, 2011, the Office of New Drugs announced that all of the new applications for ME/CFS treatment—regardless of the proposed mechanism of action or the primary endpoint—will be assigned to the Division of Pulmonary, Allergy, and Rheumatology products. This includes new drug applications (NDAs), which are marketing applications for small molecule products; biologics licensing applications (BLAs), which are marketing applications for biologic products; and investigational new drug applications (INDs), which are the applications that allow investigational products to be studied in humans. This also includes products that are already on the market for other indications but there is a desire to study them in CFS.
- The transfer of applications is now complete and as part of this transfer, I have transitioned as the CFSAC *ex officio* member, replacing my colleague, Dr. Marc Cavaille-Coll, whom I would like to recognize for his many years of service to CFSAC. We are in the process of determining an alternate CFSAC FDA member.

- One of the goals of this transfer is to allow development of expertise on ME/CFS within the division. We have begun a process to educate our cross-disciplinary reviewers on ME/CFS.
- Another goal of the transfer is to give sponsors and investigators one-stop shopping for ME/CFS applications—in other words, a medical home for these applications. The division very much welcomes dialog in the form of pre-IND meetings if anyone is considering human trials. That applies to both individual investigators as well as drug company sponsors. If you would like to request such a meeting, there is a formal process for doing so. You can send a request to Ms. Sandra Barnes in our division.
- This consolidation allows the division to work toward facilitating development end points for trials in ME/CFS in collaboration with the Study Endpoints and Labeling Development team. There are new development pathways available at the FDA for qualification of clinical trial outcomes assessments. These are entirely new processes that did not exist a few years ago that allow qualification outside the traditional drug development pathway. Access additional information about these processes at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf>.

Committee Discussion

Dr. Jason: Is it possible to get information about how many ME/CFS drugs are currently being reviewed? Could that be something you could be updating us about at our regular meetings?

Dr. Michele: Under law, I am not permitted to discuss anything about a particular application or even give you general information about applications, be they drugs that are under investigation or even drugs that are approved. Once a drug does get approved, the entire review process is available on the website. You do not have to go under the Freedom of Information Act. The information just appears there for all new approvals. If a product is not approved, we are not allowed to say a thing about it. There is a lot of desire to change that under the auspices of trying to be more transparent in government, but under current law I am not allowed to do that. Whether or not I could provide aggregate information, I suspect I cannot, but I will look into that and report back to the committee.

Dr. Levine: Concerning the new drug from Norway—if an investigator wants to try it on one ill CFS patient, is there a mechanism in place for getting compassionate drug approval for a CFS patient, and how realistic is that?

Dr. Michele: A physician can prescribe for an individual patient any drug that is on the market for any patient for any reason. If you wish to do a clinical trial of said product, then that would fall under the IND regulation. You would submit an IND application that contains chemistry information about the drug (where are you getting it, how is it manufactured), whatever toxicology information is known, and what your protocol is. That is the most important part—to make sure that whatever you are doing has enough belts and suspenders on it to make sure that the safety of the patients is taken into account in your clinical trial. That is really the purpose of the IND process—to ensure the safety of patients in clinical trials. For an IND to be approved, you do not really need to show that your drug works. All you have to do is show that your drug would be safe for investigation.

Dr. Snell: There is a lot of information on your website about acceptable outcome measures for trials. What is the process for determining acceptable outcome measures for CFS?

Dr. Michele: Right now we don't really know what an acceptable outcome measure would be because we do not have any drugs approved. As such, the regulatory pathway for approval has yet to be determined. What I would encourage sponsors to do if they are near approval would be to talk to us about it. There are processes for sponsors to request meetings. I would also encourage you if you are interested in developing a new outcome measurement to put it through the qualification process that I was mentioning. I think that this is quite exciting because prior to this point in time, the only way that a new clinical outcomes assessment could be put into play is through a drug development process. You had to have a drug in order to get an outcome measure approved. Now we have a process by which non-drug companies can come forward with outcome measures and walk them through the qualification process. I think it will help push the innovation, which is why it is part of our critical pathway.

Mr. Krafchick: What outcome measures were used for the approval of Lyrica and Cymbalta [fibromyalgia drugs that Dr. Michele confirmed would have come under the rheumatology group if they were going through approval today]?

Dr. Michele: In general, in order to get approval, you have to show in clinical trials that your product is better than either a placebo or better than what is on the market. The regulatory language that is approved under law is very specific about the evidence base that is required for approval. It is generally two Phase III reproducible trials. Lyrica and Cymbalta were approved for pain. Prior to two years ago, the rheumatology group was under the pain area. Those drugs, since they are still approved for pain, fall under the Division of Anesthesia and Pain Products rather than our division.

Lunch

Dr. Snell postponed **Dr. Willis-Fillinger's** HRSA report until after lunch.

Dr. Snell declared a recess for lunch.

Public Comments

Joan Militello (via phone)

- Mother of a bright and beautiful 17 year old daughter whose life has been greatly affected by the lack of knowledge in both the medical and education field regarding ME/CFS/fibromyalgia.
- Janine became ill in 2007 after a bout with shingles. The doctor in an urgent care center immediately diagnosed and started treatment. Her pediatrician sent her to specialists after not accepting the diagnosis.
- Janine was not able to return to school until February 2008 and it was short lived. Her doctors and school officials insisted she had school phobia. They pushed her to the point that all she could do was cry. The family decided that she will not return to school until she is well.
- Mother surf the internet seeking help. Janine's doctors refused to talk to the Center for Infectious Diseases. One remarked that "Janine has her own agenda."

- Mother has more than 10 pages documenting each doctor we have seen and treatments we have tried.
- There is a great need to educate medical professionals about ME/CFS/fibromyalgia, especially in young people. Most doctors who deal with young children and adolescents have no idea what is going on.
- Janine has so many different symptoms that we continue to seek out specialists who can help improve her quality of life. A few have helped. For the most part the family gets the look of being completely insane.
- Implored CFSAC to create a center of excellence or at least make funding available to teach doctors and educators about this cruel and debilitating disease.
- Janine's goal is to go away to college because she did not have the high school social experience. Her family does not discourage her. She knows her limitations but will not let them keep her from being the best that she can be.
- Gave special thanks to Dr. Levine and the parent and teen members of "Speak Up About Me" for their support and encouragement.

Dr. Janet Smith (via phone)

- CFS patient, a practicing physician, and a participant in the Ampligen clinical trial for CFS.
- Started urological practice in 1987. Became ill with ME/CFS in February 1994 after a viral infection turned to pneumonia. Is fortunate because she can still function in a modified manner but only with aggressive treatment and with the experimental drug Ampligen, which she has been on for almost 10 years.
- In the last 72 hours, she went from feeling very well to having muscle aches so painful that she could not get out of bed to go to the bathroom, sit up, or make a phone call for help. She realized that this is what most people with ME/CFS experience every day without hope for the future. Suicides are occurring routinely within the ME/CFS group. People need hope and help now, not in five or 10 years.
- CFS patients need diagnostic markers and treatments. Physicians who have treated both AIDS patients and ME/CFS patients concur that ME/CFS patients are much sicker than their HIV patients.
- There is new research for diagnosis or treatments that are occurring in the world. Norway physicians are using a chemotherapy drug with good results. Researchers at Bond University in Australia are looking at natural killer cells in spinal fluid as possible biomarkers for immune abnormalities. This is an international disease that needs to be recognized and researched. There needs to be an ICD-10 classification for ME.
- There needs to be a better way to keep track of biospecimens from people with ME/CFS. A grant to IACFS/ME or the CFIDS Association could be made to set up an informational exchange of biospecimens with contact information, specimen type, etc.

- New nonprofit organizations are aggressively asking for private contributions to fund research. But the lack of funding in this country is painful. As a result the advances are being made in Norway and Australia.
- There is also concern that there seems to be no interest among young physicians to take over the role of the original pioneers such as Dr. Peterson and Dr. Klimas. Regional centers of excellence, which have been requested by CFSAC and continue to be ignored, could diagnose patients and return them to their local physicians with treatment plans. Fellowships need to be funded so pioneers can pass their unwritten knowledge to the next generation.
- Her hope is that medical text books will have a whole section on ME/CFS with etiology, diagnosis, and treatments and that all physicians will know what ME/CFS is and how to treat it.

Dr. Kenneth J. Friedman (via phone)

- Informed CFSAC and other stakeholders in the ME/CFS community about an opportunity to restore ME/CFS research and education and related scholarly activities to one of this country's most populated states—New Jersey. The governor of New Jersey has formed a University of Medicine and Dentistry of New Jersey (UMDNJ) Advisory Committee to advise him as to the future of UMDNJ. UMDNJ, the largest free-standing academic healthcare university in the United States, could remain intact or could be dismantled with its components given to other state institutions.
- The impetus for a UMDNJ Advisory Committee may be the corroded image of UMDNJ caused by its purposeful \$35 million double billing of Medicare.
- Of concern to the ME/CFS community is the February 2010 university decision to ban ME/CFS research education and related scholarly activities. According to that policy:
 - 1) Scholarly activity related to ME/CFS can only be performed outside of regular normal business hours.
 - 2) The university's portals to the internet cannot be used for any ME/CFS research.
 - 3) The university email client server cannot be used to correspond with anyone about anything related to ME/CFS.
- UMDNJ controls all three of the state's medical schools as well as the state's only dental school, school of nursing, school of health related professions, school of public health, and graduate school of biomedical sciences. Its ban impacts patient care in the greater New York metropolitan area as well as research and healthcare provider education and training throughout the United States.
- If the ban persists, other institutions may institute similar policies.
- UMDNJ's actions are clearly an attack on academic freedom, which is the right of college and university faculty to pursue their academic interests wherever they may be, and should be opposed on that basis.

- However, of particular concern to the ME/CFS community is the refusal of UMDNJ to honor the CDC's ME/CFS policy as articulated by its director, Julie Gerberding, in 2006: "We are committed to improving the awareness that this [ME/CFS] is a real illness and that people need real medical care and they deserve the best possible help that we can provide."
- Why does DHHS continue to provide funding to UMDNJ when UMDNJ has decided that ME/CFS activity is not a professional activity permitted of its faculty? Why does DHHS continue to give money to a university that knowingly and deliberately violates this CDC mandate?
- The UMDNJ Advisory Committee has received employee testimony expressing the belief that the university should be retained in its current configuration. Stakeholders of the ME/CFS community may have a different opinion, since dismantling UMDNJ would remove the ban and restore ME/CFS activities to New Jersey healthcare centers. CFSAC may wish to make a recommendation.
- Public comments may be submitted to publiccomment@gov.state.nj.us.

Gabby Klein (via phone)

- Is a 56 year old wife, mother, and grandmother. Has been suffering from severe symptoms of ME/CFS for the past 9 years. Used to be an active member of society who worked full time, raised children, took care of the household, and did charity work. This all came to a halt in February 2002 when she contracted a stomach virus that lasted for weeks. Her condition kept deteriorating until she had to quit her job.
- Doctors did not know how to test and the results kept coming back negative. Because they could not see her pain, they thought she was exaggerating. She found a specialist who finally diagnosed her with ME/CFS, but by that time her condition was so bad that the physician has not been able to reverse the damage. She is mostly housebound and feels like she has the flu all the time. She suffers from insomnia and severe headaches. She cannot stand or walk for more than a few minutes. She suffers from cognitive problems that are very disturbing, including memory loss, word retrieval problems and sensory overload from being around her grandchildren. When she tells people she has ME/CFS, they roll their eyes and tell her to get out more and exercise.
- Asked for the following CFSAC actions to reconcile these problems:
 - Education for the medical profession, particularly the general practitioners and internists who are the first line of defense in the medical system.
 - Removal of the antiquated information on the CDC website that has been there for 20 years. Replacing it with the International Consensus Criteria that came out a few months ago would be a good start.
 - Funding for studies to come up with real biomarkers. Although ME/CFS affects 1.7 million people, CFS is allotted \$6 million in research funding.
 - Minimal insurance coverage for CFS. Patients often become penniless. It is time for US health agencies to increase public awareness and allocate public funding for public care.

- Proper coding in ICD-10-CM under “diseases of the nervous system” at G93.3 so that patients can get the medical care and disability coverage that they need and deserve.

Robert Miller

- Here today due to the drug Ampligen. Without it, he is homebound. It is not a cure, but at least he is not at stuck at home in bed.
- There have been a lot of changes for CFSAC since the last meeting. Dr. Mangan has retired, Dr. Wanda Jones is gone, and half the committee members are new or about to shift. There is no live webcast for patients, which should be a must. But we have to keep from being distracted because more has happened in ME/CFS since the last meeting:
- Thankfully the blood working group and other scientists pursued the truth about XMRV. The story may not be over yet. Early on, there was hope that XMRV represented a real breakthrough. He advocated for scientists to pursue their research until they had the truth. Lots of American science says it was not XMRV, so once again we know what ME/CFS is not.
- Last week scientists in Norway published data showing that Rituxin, a B-cell depleting drug used for lymphoma, had dramatic results on a small group of ME/CFS patients. It has blown the lid off of science again because if these results hold out, the primary conclusion is that ME/CFS is an autoimmune disease.
- Years ago, an American CFS patient who developed lymphoma had the same experience with Rituxin. Why did American scientists not pursue the Rituxin experience years ago? When will American scientists be funded properly to prove what ME/CFS *is*, not just to prove what it is not? The answer is that NIH and CDC are neglecting ME/CFS patients. NIH’s and CDC’s tiny budget for ME/CFS is going toward disproving XMRV. Ten percent of NIH’s measly \$6 million per year budget is now going to researchers at Stonybrook to test self treatment models. Really? Conserve my energy and feel better?
- We need real science to solve ME/CFS. We need clinical trials to learn what works and what does not. We do not need GET [graded exercise therapy] or CBT [cognitive behavioral therapy]. We have done that for 25 years and it does not work. If making us well is not reason enough for serious research, then do it so you can save the \$20 billion a year that it costs this economy.
- Mr. Miller closed his testimony with what ME/CFS advocates call The Obama Promise—a statement by President Barack Obama: “It’s up to you and me to use our brains to figure things out and I believe that we can figure this out.”

Jennifer Spotila (via phone)

Do you think CFSAC is effective? All of you serve with the best interests of patients in mind. But let us review the track record or lack thereof for the recommendations that you send to the Secretary:

- Regional centers for research and clinical care? No.
- Healthcare provider education and training? No.

- Use of the name ME/CFS across all agencies? No.
- Research funding commensurate with the burden of this illness? No.
- National effort to arrive at a new consensus case definition? No.
- No meaningful action; no meaningful funding. All your work, and what is there to show for it? You should be angry, or at least frustrated. Five years ago you recommended that NIH issue a new RFA on CFS. It did not happen. Many patients expected new funds to be made available after the State of the Knowledge meeting. It has not happened. You know that there is an urgent need for research funding and we need you to hold DHHS accountable.
- Recommend that NIH issue an RFA for CFS research backed by \$10 million in funding and that this RFA be issued in the next six months. This money must be spent on CFS, not related conditions. No more money should go to CDC for other psychological approaches.
- We have begged NIH to spend money to research the pathophysiology, objective diagnostics, and treatment. We have begged you to help us. For NIH to spend \$600,000 on a study of illness self-management is an insult to every CFS patient.
- At the State of the Knowledge meeting, Dr. Collins said that Secretary Sebelius had directed NIH to give CFS “special attention.” Today we learned about a new HHS Working Group on CFS. But talking is not doing. Test this alleged commitment to CFS. Make a recommendation that NIH issue a \$10 million RFA for CFS research in the next six months. At the next CFSAC meeting we could see if special attention translates into meaningful action.
- Do not accept “woe is me” budget talk from Federal officials. We know that money can be found for high priorities. Dr. Fauci’s appropriation of \$2 million for the Lipkin XMRV study proves that. Money is available but the agency leaders are making conscious choices to spend the money on illnesses that are a higher priority. NIH’s FY 2012 budget request is for \$32 billion. The current level of NIH funding for CFS research is the equivalent of pocket lint. The money is there. It is just that NIH does not think that we are worth it.
- As long as we have to deal with CFS, you have to deal with us. We are still here. Deal with it.

Denise Lopez-Majano on behalf of Alexander Lopez-Majano

- I am often asked about the biggest obstacles I face because of ME/CFS. There is the paucity of successful ME/CFS treatments and the endless problems finding knowledgeable medical professionals. Beyond those is the daily struggle for acceptance of the severity of ME/CFS that stems from the erroneous perception that this is a psychological condition.
- I want more education. I want a profession. Since I can only leave the house two times a week, since I can only study for 20 minutes at a time, perhaps three times a week, it will probably take me a long time to obtain my college education and find a job. This should not be the case. There needs to be:
 - successful treatments for ME/CFS

- many more medical professionals who know about CFS and treat and respect patients
 - a uniform definition
 - wide and accurate information dissemination
- Work hard. I want my life back and so does my brother.

Melanie Pruitt (via phone)

- December at Christmas time marks 10 years since I caught the virus that led to ME/CFS. My youngest child is 18, which means he has lived more of his life with a sick mother than not. I have never added my voice to public testimony before but I would like to share two things that have become incredibly important to me:
- **Continue to pursue ways to educate primary care physicians about ME/CFS.**
I live in the Pacific Northwest, very far away from ME/CFS specialists. I had to fly across the country to even get an official diagnosis. I have heard it said that if my doctor is not familiar with or does not acknowledge the existence of ME/CFS, I should find another doctor. That is not as easy as it sounds. No doctor's offices will tell me if they treat ME/CFS patients due to confidentiality rules. I rarely have the energy to meet the doctor by going for an initial appointment. It takes time for a doctor and patient to get to know each other and develop a relationship of trust. Changing doctors over and over gives me a bad reputation. I have yet to come across a PCP [primary care physician] willing to invest time to fully understand ME/CFS. It would be so much better if there was one reliable, authoritative resource with treatment information to which I could direct my doctor. There are no ME/CFS specialists in my area, but I have come across caring PCPs who would make use of such a resource. The current CDC website is inadequate; in fact, it does harm.
- **Continue to address the issue of insurance, coding, and ME/CFS.** I am a middle class American who is lucky enough to have good health care coverage. Yet I have spent eight months working with one representative to get a visit with my ME/CFS specialist covered. I was told by the company that they would cover the visit as long as I had billing codes. I was told by the provider that appropriate codes would be provided so that I could get reimbursed. And yet I am still waiting on codes to be coordinated. ME/CFS issues and treatments are difficult to fit into regular billing codes. Clearly, if this very large insurance company is struggling to coordinate codes with this wonderful provider, something is wrong.
- I find that I now can no longer afford medical treatment from my ME/CFS specialist even with one of the best insurance policies around. You can hardly imagine what a hopeless feeling that is.

Future Interdisciplinary Research for CFS Utilizing a Variety of Scientific Disciplines

Gailen Marshall, MD, PhD

Challenges to Interdisciplinary Translational Research

- **The same scientific terms can have different meanings to different stakeholders depending on interpretations.** For example, there is a broad variety of uses of the term "psychosomatic." The

colloquial use of the term in our society is that it is all in your head and it is not real. CFS patients and those who take care of them are well aware that the disease is not all in people's heads. Yet no one can argue that there is a single category of illness that does not affect one's mind when one has a physical illness. The mind and the body are inseparable. Unfortunately in our society, anything that can be determined below the ears is worth treating. Anything above the ears is not really important. That's a tragedy in our allopathic medical system. On behalf of my profession, I apologize. There are those of us who believe that will change. Not fast enough, but it will ultimately change.

- **Cultural/social influences** (see paragraph above)
- **Clinical vs. basic influences** – In an academic medical center, the basic science faculty and the clinical faculties are at each other's throats with some degree of regularity. They approach the same research problem from very different perspectives.
- **Personal/professional bias perspective** – This is illustrated by the proverb of the 10 blind men and the elephant. Each man could feel one part of the animal and all had very different perspectives on trying to describe the elephant. What they could have benefited from is an eleventh person who could take the data from the other 10 and synthesize an overall description which probably would have been an accurate description of what an elephant is like.
- **A natural conflict exists in the approach for information between a scientist and a clinician.** I was a basic scientist who went to medical school with the intent of gaining a degree so I could go back to the lab and make a difference. What I did not realize is that I would fall in love with taking care of patients as well. I am well aware of this dichotomy between how one is trained as a scientist and how one is trained as a clinician.
- **Scientists** look for generalizable knowledge that will ultimately be applicable to people.
- **Clinicians**, in contrast, care for the individual patient by balancing the components of the illness that are generalizable (what we now call "evidence-based" medicine) with the responsibility to acknowledge and deal with the individual variability that makes each one of us unique human beings.
- **Truly translational research** has to account for both perspectives while remaining objective to the results derived from the study—the idea of following the data with the *a priori* understanding that no single intervention works for everyone, even with the same cause. If you do not believe that, remember that there are 67 different antibiotics that are marketed to treat bacterial pneumonia. The difference is that if a patient has bacterial pneumonia, the physician is likely to treat them with antibiotics, not get them to do cognitive behavioral therapy.
- **Many research efforts are discipline egocentric.**
 - There is the old idea that if it does not have a $p < .05$ it is not real.
 - The other extreme is that if it has a $p < .05$, then it is real. Neither of these statements is true.
 - There is also the view that "using my methodology is the (only) correct way to look at this problem." It is how we are trained. There are many methodologies used to address the same question. That is a fundamental problem of science, particularly at the clinical level, that many of us are dealing with inside and outside of ME/CFS research.
- **The "Reverse" Translational Research Approach**

- **The classic translational research model** is bench to bedside and back again. You formulate a mechanism, you see if it might work, and then you come back and see how to modify it from there.
- **The “reverse” approach** starts with the patient and collects the information from the patient. It starts with the problems that the researcher is seeing. It is almost by definition an epidemiology approach, and from that you formulate ideas that might have common mechanisms and common rationales for similar interventions. Or at the very least, by seeing the variability among the population that you would assess, you can then try to account for the variability in response.

Requires a relatively “pure” population or at least a “common clinical” population.

- **Approaches using “biomarkers” need strong clinical correlates**
 - Some are relatively clear. There are good biomarkers for tumors. There are good biomarkers for renal function. When you go on a dialysis machine, you know your kidneys are not working anymore. There are good biomarkers associated with mortality.
 - Unfortunately, many of the challenges with CFS research are due to a lack of clear clinical correlates:
- **Etiology(ies)**
- **Variable symptom complexes**
- **Overlap syndromes** – Very few CFS patients say they have seven of the eight disease criteria and no other physical problems that are labeled as other conditions, including chemical sensitivity, CFS/fibromyalgia, and other autoimmune etiologies. Are these truly overlap syndromes or are they modifiers or co-factors? Addressing that and understanding it is critically important as we address what we are trying to do, which is find biomarkers that have clinical correlates that can be measured in a large population of patients.

Recommending Translational Research Priorities

- **Basic science approach to a research question:**
 - Identify the question
 - Identify the population
 - Identify the system that will be used to study the population
 - Design the study with adequate controls. The goal is to have only a single variable.

An example would be studying the ME/CFS overlap through studying the pain of ME/CFS along with the pain of fibromyalgia. Ideally, the study would compare patients with overlap versus those who have “pure” fibromyalgia versus those who have “pure” ME/CFS.

- **Data analysis plans and ultimate conclusions/applications are highly dependent upon how the above steps are implemented.**
- **Interdisciplinary Research for ME/CFS**

The 10 blind men with the elephant are the multi-disciplinary approach. The eleventh person who could see and integrate what he had been told by the others is the true interdisciplinary researcher. In interdisciplinary research it is important to:

- **Decide on a definition of the illness.** What are the essential criteria? This would be independent of trying to come up with new consensus criteria. That is something that should be done, but it is not something that we have to wait on to do effective interdisciplinary research with ME/CFS patients. Researchers must define, however, the characteristics of the population for whom the researchers are intervening.
- **Determine the minimal data that are necessary for comparative study.** Dr. Jason has led a team that has done an elegant job in writing a paper that discusses this.
- **Execute careful construction designed to optimize the answer to the research question.**
- **Incorporate strong consideration of confounders/modifiers** (psychological, physical, pharmacological, etc.)

Components for Optimal interdisciplinary Research in ME/CFS

Members of both the lists below (basic science disciplines on the left, clinical disciplines on the right) are important because they see the variations of ME/CFS on a regular basis. Getting input from these experts is extremely important to interdisciplinary research:

Epidemiology	Internal Medicine
Genetics	- Generalists
Physiology	- Sub-specialists
Psychology	Physical Medicine and Rehabilitation
Endocrinology	Pediatrics
Immunology	Psychology/Psychiatry
Sociology	

A provocative statement for further discussion:

Approaches to ME/CFS Research Should be Focused on a Reverse Translational Model

Rituxin serves as an example. Patients who had been treated by Rituxin for a clinical indication had improved ME/CFS symptoms. Why would you expect Rituxin to work in certain patients—maybe all—patients with ME/CFS? The very testable hypothesis with reverse translational research: If B cells are a reservoir for certain types of latent viruses and you get rid of the reservoir, the viral titer is going to diminish, the individual will not have to respond to the virus, and the individual will get better.

Committee Discussion

Dr. Jason: You can have an intervention that affects multiple illnesses. But should there not be basic criteria? Shouldn't the research be able to start out by saying "this ME/CFS"? It is not that criteria cannot change over time. But there needs to be something that brings all those different fields together to say "this is it" or "this is not it." Researchers need to be able to say, "We think that these people have a particular illness or disease." Is that not the starting point for anything we do in basic research?

Dr. Marshall: No question about it. Your model is not an unrealistic model to start with. Cancer is an example. Decades ago researchers understood what cancer did, but they thought it was one disease. The treatment was basically the same: a surgical component, a chemotherapy component, and a radiation component. Cancer was thought of as the same disease in different manifestations. We have come to understand that while there is a commonality of biological and clinical characteristics of cancer, there now are departments of every organ system cancer at every major cancer center. Even general oncologists tend to specialize in one kind of cancer or another.

When researchers do clinical cancer trials, they come up with a regimen that they think will work on the organ system that they are interested in and select patients accordingly. They would not bring a prostate cancer patient into a brain cancer protocol. On the other hand, we need to avoid systematically excluding a patient who may benefit. In early cancer trials, researchers put colon, brain, and lung cancer into the same group until they learned what was beginning to work and what was not. Research is a balance between these two.

Some caution is called for with Rituxan because:

- It is an extraordinarily expensive drug.
- It is not without side effects. Knocking out somebody's B cells with a drug that was designed to get rid of malignant B cells is not trivial from an immunological standpoint.
- Some assumptions may not be true. For example, the fact that a B cell is a reservoir for a virus does not mean that the patient has an autoimmune disease. There are B cell diseases that do not make auto antibodies that attack a virus.

A reverse approach to translational research creates categories in which patients must fall for an initial study. In the case of the Norwegian Rituxan study, the two categories were patients who did and did not have auto antibodies. These categories were used as predictors of how patients might respond to Rituxan. This is an example of reverse translational research using principles that are not new in a rational way to methodically evaluate a treatment as quickly and as rationally as possible to provide clinicians an idea of what group of patients is more likely to respond to Rituxan.

Dr. Jason: There is specialization that has occurred with cancer over the last 50 years. But still they can say, "We're dealing with cancer." There will also probably be subtypes of ME/CFS. We know that there are clinical differentiations. If we learn from the history of other diseases, have not most of those illnesses and diseases started with a paradigm involving people coming together saying, "We are going to classify people this way. It might not be completely right, but at least we are going to have an agreement so that we can compare samples across laboratories"? Without that, are we always going to be at a disadvantage for ever being able to find uniform biomarkers?

Dr. Marshall: I think you are making the case for starting with the clinical complex and then moving to the biomarkers that help explain the clinical complex. That is a more cost-effective way to do it and it has the potential to begin to address the value of the interventions that we propose because it forces us to think about what kind of outcome marker we want. I suspect that if I asked ME/CFS patients if they would rather have me do a therapy to improve the biomarker or to make them function better, they would not care about the biomarker except as it helps them function.

The clinical research world is littered with a graveyard of biomarkers on which millions of dollars were spent trying to show relevance because early studies showed a statistical association. I suggest that rather than starting from some consensus diagnosis with criteria for people with ME/CFS, we go out and

take clinicians who see these patients all the time, get them in same room, discuss how to categorize these people clinically, then go back in lab and say, "Are markers there or not there? Are there interventions that may be useful?" That is an old school approach that I think is more likely to give us some answers and get others outside of our community to take these patients and this line of research more seriously.

Mr. Krafchick: That is exactly what happened with fibromyalgia. In the late 1980s, a group dealing with the disease got together and discussed the core of what they had to accept to do research on this condition. They did a study on the tender points. Since then there has been an explosion of research on that. For CFS, it has always been a mushy diagnosis with a lot of disagreement. I am certain that even if you use a clinical approach to defining CFS, you need to define what we are talking about at some root level so that you can begin to define populations to study to get to your biomarkers or whatever else you want to study.

Dr. Marshall: I am on same bandwagon. I am saying we simply start with the clinical criteria not with some consensus diagnosis condition no matter whose it is, because not everyone with CFS would be included. Categorize the individuals in terms of what they are dealing with in their everyday lives. My guess is that if you ask clinicians who care for patients with the illness, they can do some groupings of the kind of patients they see. Start there and work backwards. That is the reverse translational model that I have.

Mr. Krafchick: Why couldn't you just start with the Canadian Consensus and decide for better or for worse that you are going to use that definition and then study the patients and see how it falls out? The problem is that there has not been any agreement on what criteria to use to do the research and really push it forward.

Mr. Marshall: The more specific you can get, the better off you are going to be as you begin to ask questions backwards about which subpopulation of patients will respond to what treatment. The fibromyalgia group did not define their criteria in a vacuum. They used clinical information to do it.

Mr. Krafchick: They all sat around and talked about what they were seeing in their practices. They then did a study of the tender points because that seemed to be the one area that everybody was talking about. Which one of the 30 or 40 CFS symptoms are we going to use to give us a specificity and reliability to diagnose a significant number of people? The fibromyalgia clinicians were able to identify a group. What we need is a commonality of proof. I mentioned the Canadian Consensus criteria because they exist and they are accepted by a lot of people. We could start there and move forward with our research. As the research develops, maybe we refine the criteria. I have been listening to this kind of discussion for years and years and years. The difference between the fibromyalgia community and the CFS community is simply the agreement on a case definition and classification criteria. I think had that happened in CFS, at least the studying would be further along.

Dr. Klimas: It is really important in all this conversation that we do not lose sight that researchers frequently attempt to narrow things down at the expense of as much as 80% of the rest of the population. We have to be careful in case definitions that we acknowledge that it is merely for research purposes because when we accept more narrow definitions, including the ICC, we are throwing out vast numbers of patients. It will have a very real impact on their ability to get disability, etc., because they do not meet the case definition. A research case definition and a clinical case definition are two different animals. Be careful. The first HIV case definition was men 18-65 who were dying of a small series of infections. We did that to get at the virus that caused that illness. Twenty-five percent of people dying

of AIDS in the first year did not meet the case definition. We must be careful that we do not tie ourselves into a brand new knot.

I get so confused by the changing language of science. “N of one” [studies] means that you saw something interesting in somebody that makes you reframe and rethink. It is very important that we do not lose sight of those observations. Dr. John Chia is one of the best “n of one” people I know. He makes some of the most astute observations in his clinical practice that he acts on, and in a year or two, it is changing the standard of care. The man has got some tremendous belief in what he sees.

Every clinician in this area needs to pay attention to that because we learn so much from a patient who got better or a patient who got worse from a therapy in a way that was completely unexpected. This is tremendously important. There are very few ways to categorize this. There are few journals that would accept these kinds of observations. The *IACFS Bulletin* certainly would. We should be doing more and more case reports of interesting things.

Dr. Levine: I do agree with Dr. Klimas, that good clinical observations are very much needed in this field. I also agree with Dr. Marshall that CFS, unlike other illnesses such as HIV and lung cancer, involves so many of the body’s systems. How do we reign in all of the specialists you were talking about in this so-called interdisciplinary study? How do we get the geneticists and endocrinologists?

Dr. Marshall: I can tell you as a clinical researcher that what always gets them interested are biomarkers. When some family members are getting sick and some are not, that begs the question of a genetic link. Endocrinologists may be drawn in by a discussion of the postural hypotension subcomponent that is talked about as the potential adrenal component. Endocrinologists may be interested in a study of how Florinef may benefit CFS patients. As you design these research ideas, you engage the various groups. You do not pull 20 of them into the same room to talk about it. You would start with those who would do the primary care of a particular set of CFS patients. If you were going to study an intervention, you would bring in a person with expertise in that intervention.

Dr. Levine: I have had to become a Jack-of-all trades in the last 20 years of my practice. The complexity of the disease warrants almost a new discipline. There should be a CFS fellowship to train students in all aspects of the disease. You cannot just be an infectious disease doctor or rheumatologist and understand CFS. Medical education has to make room for this as a whole new area.

Dr. Marshall: ME/CFS is a primary care disease right now. It is not a specialty disease yet. I think that there may come a time when some types of ME/CFS patients will be cared for by sub-specialists of the primary clinical problem. I still think that whatever the common mechanism is that explains the symptom complex and the physical manifestations of CFS, there is not a single pathway. There are different pathways. We are only beginning to get an idea of the central mechanism and we do not have a clue about what the underlying pathways are in individual patients. That is why, in my mind, CFS is very much a primary care illness. In terms of primary care, internal medicine, pediatrics, and family medicine, there should be a rotation to ME/CFS clinics. With centers of excellence, there would be a more natural way for that to occur.

Dr. Willis-Fillinger: I do not see any dissonance between your approaches to the case definition. Dr. Klimas, I love your warning to avoid forcing ourselves into little boxes. I think that over time, these things will play themselves out. If you start with Dr. Marshall’s approach, eventually the two will meet someplace in the middle. I keep thinking about Bayesian theory where you are looking for groupings. You are looking for a larger percentage of folks who have a particular expression so that you can determine what explains that particular expression and try out therapies. As this same process occurs

with other groups and other expressions, you focus very quickly on what groups will be most responsive to different therapies. The Bayesian approach to research fits with this model.

Dr. Marshall: The Fukuda criteria were not clinical criteria; they were research criteria that ended up being clinical criteria. We have an unfortunate, very real example of what can happen in that context.

Whenever clinicians hear ME/CFS there is total confusion: “What is it? What can I do about it?” It is not that they are not interested. They feel helpless like everyone else. If you can put something in their hands that says, “These people are going to tend to respond this way and these people are going to respond this way”—the Bayesian theory, just like you said—there is value in that.

When we come to the FDA and say that we want to do an IND to look at an agent to treat ME/CFS, they are going to want to know what the endpoint is. Researchers used three different measures for fibromyalgia, but the three different measures were for the clinical assessment of one clinical outcome, which was pain. Researchers showed that one intervention was sufficiently better according to the criteria that the FDA has set. That is the process in our society that is going to be necessary to get these things paid for. We can talk until the cows come home about how it should not be that way, but we need to work within the system to get our patients some relief in a timeframe that would be of value to them.

Ms. Holderman: I think that we are already there. We have the biomarkers. So what is the obstacle? No offense here, but it has been political. Our government agencies in their websites and printed materials keep saying that we do not have biomarkers, but we do, including low natural killers cells and RNAs. We just need the health agencies to acknowledge that we have them and to move forward. The science is here.

Mr. Marshall: As researchers we have the biomarkers; as clinicians we do not. There is the dichotomy. Natural killer cells are an example. We still are not sure about the role of natural killer cells:

- There are very few patients who have been born with a natural killer cell deficiency.
- We know that there are a lot of things that will affect natural killer cells that have nothing to do with ME/CFS.
- There are ME/CFS patients who do not have abnormal natural killer cells.

For a super specialist like Dr. Klimas, following natural killer cells in terms of patient treatments has a certain value. She has an expertise and a lab. It is true on a research basis that killer cells are a good biomarker for disease activity in ME/CFS. On an individual basis, it is not true yet. We need to take those biomarkers that are candidates—just like the therapies that are candidates—pull them into the clinic, and show their variabilities and values for an individual patient. We are not there yet for regular generalist care. It takes people who are highly skilled to do that. There are so few specialists like that, and not all ME/CFS patients can get to them. We need internists, pediatricians, family doctors, and emergency room staff to be able to look at biomarkers and use them as a guide for patient care. That is why we need to take a reverse translational approach.

Dr. Michele: You said a number of things that our group within FDA would resonate with. Biomarkers must be tied to “feels, functions, and survives,” which is how products are approved. We could say that biomarker X is not normal and the patient could reply, “Congratulations. I still feel awful.” The biomarkers are wonderful to explore, but eventually we need to get to the point where those biomarkers mean something in a clinical trial. This field is so new that we have to look at a lot of things in a clinical trial because we have no idea what the right endpoints are. Eventually we will get there.

Just a reminder that whatever endpoint we do get to has to be tied back to something that is clinically meaningful to the patient.

Dr. Klimas: I think what you say about biomarkers is very good. Where we are now is that we know our patients are sick and have poor function. We can measure function. It is not very hard. We have been using biomarkers to mediate therapy. A biomarker is also a test of concept. You can measure all of the parameters that affect the mediator over the course of an intervention and see if the intervention is actually effective on the system that you were trying to intervene upon. There is nothing preventing us from doing clinical trials using functional markers. We should not be sitting on our hands waiting for that magic biomarker while we have very reasonable interventions to put into play.

I was not going to attack the NK cells, which by the way reflect the Cytotoxic T cell, which by the way is one of Gailen's favorite things, and by the way is very measurable in a reproducible fashion using a flow cytometer with a POR for and granzyme assay, but OK, I did not say that.

Dr. Marshall: What she said is absolutely true, but they don't do those in hospital labs. They do those in research labs. What they could do and what they *do* are two different things.

Dr. Jason: I want to thank Dr. Marshall for opening things up and giving us some time to think and play around with ideas. We have not had enough of that. We need some time at each of our CFSAC meetings to think out of the box. I would like to discuss some ideas that are out of the box:

- During this meeting, I have been tabulating how many times people have said "CFS" and "CSF." I would like to suggest that because we cannot seem to pronounce the acronym right, why don't we get rid of the acronym?
- Researchers can use certain case definitions for their purposes, and we can have clinical case definitions that can also be used. There is no reason that one obviates the use of the other.
- There needs to be an outcome for these types of discussions because I think they are so critically important. I disagree with some of the clinical observations that people are making. I think it is really statistical methods and neural networks that are hopefully going to drive this conversation. There are methods that are being used in the sciences that we can bring into our field that can help solve some of our problems. Artificial intelligence is an example of a way to help us think through this. We can have computer models help us.
- Right now we have Oxford criteria, London criteria, Fukuda criteria, and Canadian 2003 criteria. Our science is not going to be given legitimacy as long as we are always using different criteria. No one is going to take us seriously. We have to deal with that issue at some point.

Mr. Krafchick: One thing that we could do is recommend that DHHS convene a group of technical experts in this area to come up with an agreed set of criteria for research and publish it.

Dr. Marshall: That is the segue for Dr. Jason's discussion tomorrow. My personal belief is that it is not going to happen inside the government, it is going to happen outside if it. It is going to come from the scientists and clinicians who will exert the pressure in the literature. I am with Dr. Klimas—let's come up with a set of criteria that are evidence-based.

This discussion was purposely provocative. This is not going to be an either/or, it is going to be a both/and. We need to have a clear component of reverse translational research as we ask the questions because that is going to help us formulate the questions. But I think we have to have an orderly scientific way that involves all the things that Dr. Jason and others mentioned to allow us to do it. This is

the whole idea of interventional research. You have got to be able to ask the right questions before you will ever get the right answers.

You get a group of people together and say, "This is how we are going to define ME/CFS." We go to the FDA and ask to do a clinical trial or we go to NIH and get a grant to examine something within the context of that. We publish those data in the scholarly literature. We follow the data. We do that in a timely fashion that has got an application to it to help our patients as quickly and as rationally as we as can. The first dictum of medicine is "Do no harm." We do not want to hurt people, but we can use that idea to sit around and do nothing for years. We can go forward. We do not have to wait on agreement on criteria. The list of different criteria that we have has left us scratching our heads and wondering which one to use.

Mr. Krafchick: That is exactly what happened with fibromyalgia on the 1980s before the pain study.

Dr. Marshall: Your point of bringing fibromyalgia to the forefront as a model for us to understand is a very important thing to do because there is no reason to reinvent the wheel if we do not have to do that.

Dr. Willis-Fillinger: There is another benefit of reverse translational research: the rapidity with which you are able to refine your hypothesis. As you draw that model, including those loops would be very powerful.

Ms. Perry: One thing we have not talked a lot about is DHHS's initiative around electronic health records and how transformative that could potentially be in advancing research to a whole new level. All of a sudden there will be a vast repository of data that we have never had before. That can really feed into all types of research.

Dr. Dimitrakoff: I do not know how easy it is to get a group of experts to agree on a single definition. You can start with a list of things that people agree on, construct a set of criteria, agree on a number of symptoms or signs, and see how they actually cluster data and see the patterns for subgroups. I remember in the field of lung cancer when a mechanism was found. When the drug was actually tried, it only worked on only 10% of people with lung cancer. Then you can go back and test all the people with lung cancer for that mutation and only use the drug to treat those who have that mutation. When you treat that group, you get 90%-100% effectiveness. In CFS, we need to start off with a clinical definition, then look for biomarkers that can be found in patients, and target the treatments based on those biomarkers.

Dr. Marshall: You do not have to look for 60%-80% response. A 30% response compared to a placebo response of 5% should be enough of a signal to think that this could be a good therapy for the subgroup. The natural tendency, because the CFS community has been so disenfranchised, is to play homerun derby and try to hit it over the fence. The skeptics say that if a therapy only works for 30% of the people, it is not useful. I think that we have to stand up and say that is crazy. If it works in 30% of the people, that is a signal and we need to pursue it. That is something that this committee can have some impact on.

Break

Dr. Snell announced a 10 minute break.

Committee Discussion – Past CFSAC Recommendations

Dr. Snell: One of the concerns is that not only are our recommendations not being adopted, but we are getting very little feedback on what has happened to them once we have sent them on. While these recommendations are made to the Secretary, many of them mention agencies within HHS. We might ask the relevant *ex officios* to report back what has happened with the recommendations, including whether they have had any communication with the Secretary's office.

Dr. Jason: It is my recollection that during the last two CFSAC meetings, Dr. Jones [former DFO] said that she would meet with Dr. Koh and report back to us the status of where recommendations stand.

Dr. Lee: With this transition, I was unaware that Dr. Jones had talked about that. We should use the *ex officios* as well. There are multiple ways that we can get information from the agencies. That is what the *ex officios* are here for, among other things. Knowing how this department works, that may be the most efficient way of dealing with it. Also, as Dr. Koh mentioned, we have this new effort looking at CFS strategy. The counselor to the Secretary, who is an immediate advisor, has drafted a memo that will go to all the agency heads. The memo asks each agency to send a representative to the strategic group who is a high level person who can make decisions for the agency. Since I am chairing that group, I will present the recommendations that come out of these two days and make them a point of discussion.

Dr. Jason: There are so many recommendations in the back of our meeting binder that I am afraid if we tried to go through them all, we would only get through the first page. Is there a priority of which ones we should focus on? Some of them have been acted upon; some of them have not. Why is it we have no communication on recommendations that are at the top of our priority list?

Dr. Snell: We need to push to get some feedback. The problem is, we asked fairly forcibly last time to get some feedback and it has fallen into a black hole again. As we were discussing earlier, there is a lack of continuity that compromises the functioning of this committee sometimes. It is unfortunate that we only meet twice a year. Although we have numerous telephone conversations, things fall into the gaps.

Dr. Jason: My understanding is that we were going to have regular meetings between the chairs of the subcommittees, you (Dr. Snell), Dr. Koh, and other DHHS leadership and that some of these issues were going to be resolved during the six months since the last CFSAC meeting. Can you tell us whether any of that has happened over the last six months?

Dr. Snell: That has not happened. We also have not gotten Dr. Koh's participation in any of the subcommittee meetings between this and the last CFSAC meeting. That is a little disappointing.

Dr. Marshall: By my quick count, there are 58 recommendations, 27 of which are as yet unresolved. What about CFSAC parsing those into rough categories and make them the object of subcommittee meetings tomorrow where we cut some of them down and come up with two or three strong recommendations? The trees are getting lost because of the forest. So cut most of the forest down.

Dr. Snell: Many of them are recreations of the same issue rewritten to make the language stronger.

Dr. Marshall: We can consolidate and get rid of or withdraw the ones that are no longer relevant or that we think at the moment are unattainable. We can start getting things done that can get done and that the Secretary can act on. We must be rational about what we are going to be able to affect. We have had a recommendation to change the name of CFS to ME for five years, but we are not going to be able

to affect that change immediately. There are more immediate things that we can begin to do, and advocate for the name change in other ways.

Dr. Jason: Dr. Jones said a year ago at the CFSAC meeting that the recommendations we have been making have not made their way up to the Secretary. Dr. Jones said that she was going to do everything possible to have a better system set up. It seems that somehow the mechanism of the Secretary actually taking action on our recommendations has sometimes been problematic. Has that problem been fixed? Until we get that dealt with, we could come up with the best recommendations in the world and nothing will be done with them.

Dr. Marshall: We are an advisory committee to the Secretary. It would be incredibly naïve to think that she is going to take all our advice. But if you have advisors, seek their advice, then decide to do something different, you should provide those advisors some feedback out of courtesy and respect for their efforts. You may say, "You had some good ideas. I took this part but decided not to take that part." We are missing this process. You can take this information back to Dr. Koh. If we never hear anything, we do not know if our recommendations are falling on deaf ears, if they are good ideas but they are not quite what they need to be, or if they are actually being implemented and we do not know anything about it. Feedback helps us do our job better.

Dr. Snell: I have made that point a number of times. It frustrates me because it is not the way I work. If you make a recommendation to somebody, you expect them to come back and say what they did or did not like or explain that there is no funding for implementation. You expect a dialog. It is frustrating when you never go beyond making the recommendation. It almost feels like *déjà vu* when we go through the same routines and everything is exactly the same as the last time. I appreciate everybody else's frustration. I cannot believe how long we have been here and we are still asking these questions.

Dr. Levine: When a recommendation is checked off as having been implemented by DHHS, such as developing a public awareness campaign, does that imply that we are not going to continue to work on it? What I would like to do is clean up this list and clarify whether or not anything has really been done. Should we have the subcommittees decide which two or three recommendations are priorities and follow through in between meetings?

Dr. Lee: Some of these recommendations go back to 2004. It would take some time to consider updating the chart.

Dr. Jason: I cycled off this committee in 2007 and was one of the members who came up with the 2004-2007 set of recommendations. When I asked what had happened with 10 different recommendations made during that time, I was told that nothing had happened.

Dr. Snell: When we have been most productive is when agencies have responded to what we have said at our meetings and offered to work with us independent of the recommendations. But those instances have been few and far between because of the way things operate. It would be nice to understand the level of autonomy that organizations within DHHS have to see whether we can suggest direct working relationships with those entities or whether that is outside the mandate of CFSAC. When we make recommendations that somebody does not like, we are reminded that we are here to make recommendations to the Secretary, which seems one way of avoiding difficult issues.

Dr. Marshall: Let me say this without sounding seditious. All the things we talk about and all the testimony we hear is a matter of public record. Dr. Jason's presentation on CFS research reports creates a forum for discussion that is not a formal part of our role as advisors. This could be extended to the

literature on other CFS issues, including disability and coding. By getting the dialog started in a scholarly fashion, I do not think that we are end running anyone. We are not being disingenuous to our role as advisors to the Secretary. That does not stop us from gathering information and using it in a conscionable way to advance the field and get the word out. Politicians respond to letters and public pressure. These discussions help us advance the field, and at the same time do not deny the reality how things get done inside our governmental system, of which we are a part.

Dr. Snell: The things that we have achieved outside of making recommendations to the Secretary are the things that I am most proud of. They moderate the level of frustration I have about the recommendations. Otherwise I would be leaving CFSAC with a really heavy heart. We have achieved some very positive gains but they have had very little to do with any recommendations that we made.

Dr. Jason: The good thing is that we have mobilized a tremendous amount of public interest. There are hundreds if not thousands of people who look to us for leadership. We have some remarkably well-connected, bright, caring DHHS employees here who really want to work and help. We hear what they are saying and they are really making contributions. Yes, we have done a lot. The question now is how we as a committee can do more and how we can figure out how to get through some of these snags. One of the things that Mike Miller said so well multiple times with Dr. Jones's encouragement is that we sometimes have too many wishes. We get weighted down because we have so many things that are needed. To the extent that we can have a couple of targeted, focused objectives and make consistent progress with them, we have a better chance of ultimately being effective.

Ms. Perry: Some of the recommendations are cut and dry—such as increasing funding—and it is clear what they mean. Some—such as developing a national research and clinical network—need to be fleshed out considerably. What would that network look like? There is planning and design work that would need to be done before you get to funding. You do not have time during your discussion sessions to design an entire complex structure. Is there role for CFSAC or parts of the committee to work on fleshing out recommendations further than they appear in a three-sentence summary? Or is that the DHHS's role?

Dr. Snell: If you look at the last recommendation on the list, it offers to make our expertise available to the department in consultation for any projects. As an example of that, several CFSAC members were tapped by NIH to sit on the State of the Knowledge planning committee. Also, some of the recommendations are kept broad because we were told that we could not have very specific ones. We keep trying for a national network of centers of excellence while leaving some room for negotiation about what that looks like. We are not adamant that it has to adopt a particular model. We just want to at least get it off the ground.

Dr. Michele: Lest the departing members of the committee feel that they have not contributed, I just want to be very clear. Although your recommendations were not specifically addressed to the agency, the report that I just gave you is the direct result of your efforts, including putting our energies into trying to focus our resources to provide a better interface for drug development. Please know your efforts are respected and appreciated. We are actively acting on them whether or not they are written down in a check box.

Ms. Holderman: The biggest concern is not the *ex officios*, but the Secretary of DHHS. We are hearing feedback from the *ex officios*. We need some kind of protocol or strategy—maybe discussed with Dr. Koh in the next leadership meeting—for exactly what he would like from us in the way of developing a system where we give the recommendations and get a specific response. What we do not want to do is

spend a lot of time developing a recommendation if we know it is not going to be heard. If we get even confirmation that there is interest, then CFSAC would develop its recommendations to the fullest.

Mr. Krafchick: I have only been on the committee for a year. There is a level of frustration. When I look at the recommendations, they are clearly able to be categorized. You could probably crunch a couple of them into one. But I was struck by the point that was just made. With that kind of feedback—telling us that a recommendation is not specific enough, or asking us what we really mean—we could have grappled with any one of these and made it more useful. Maybe the DHHS working group is a vehicle for getting things accomplished more so than we have in the past with a collaborative relationship.

Dr. Snell: Dr. Koh said this morning that they are looking to change the charter and expand CFSAC. That would make it a perfect vehicle for smaller working groups within CFSAC to operate outside of the twice yearly meetings and do things that would be particularly productive.

Dr. Lee: What I can do next is have Dr. Koh be on one of our leadership calls. We can ask him how he suggests that we set up a system to get feedback on our recommendations. I think that through discussion, we are going to come up with a solution. I do not think that he knows the answer and I do not think that we do. Having the discussion would be a start. What is going to happen after we have the discussion with him is unknown. I think that that is a good agenda item for the leadership call.

Dr. Snell: If we had known ahead of time that he was considering changing the structure of this committee in the charter that would have been a major discussion for this meeting. We could have come prepared to think about what sort of things we recommend for changing CFSAC.

Dr. Lee: We can do that over next six months. That was the plan all along.

Dr. Klimas: One of the themes in our recommendations has been centers of excellence. Sometimes we hear some nuggets from the *ex officios* that make one think that we could almost pull it off through such things as demonstration projects for education, demonstration projects for clinical care, or NIH clinical trials networks. When you put this spider web of possibilities together, you can almost create a center of excellence that incorporates different components. I would like to challenge the *ex officios* to come up with that precious concept: How can this be done? Even if it is a virtual platform, it is possible to think creatively and help us struggle with this concept. What we keep hearing over and over again from our patients is that they cannot access knowledgeable care. The obstacle to that has been the lack of clinical trials due to the lack of centers that do research with an adequate patient base. It is like a vicious little thread that you pull on, and the whole garment comes apart. Think through your centers' capacities. What can we do in a very real way—not just conceptually—to create the network that is needed. I think it is feasible. From what I hear, there are resources that have not been tapped.

Dr. Jason: That could be a recommendation involving not only the *ex officios*, but getting Dr. Koh and the Secretary working on it with us. We could bring all of these pieces together and make it work and keep our focus on that and not give up. It is doable if we do not get distracted by everything else.

Mr. Krafchick: We have heard about things like the Echo Project and efforts working toward affordable care. It would take somebody at the Secretary's level to pay for centers of excellence through a joint funding effort taken from various agencies. I share Dr. Klimas's view that there are tantalizing pieces that come out, but not any concerted effort to see whether it really would be doable.

Dr. Snell: It seems doable if everybody looks at their resources to see what pieces they could contribute. It should be cost effective if it is done over a number of agencies. It may ultimately save money, which would be a huge selling point.

Mr. Krafchick: It would help the patients and their quality of life and quality of care if it were done.

Adjournment

Dr. Klimas motioned that the meeting be adjourned. **Dr. Marshall** seconded the motion. **Dr. Snell** adjourned the meeting.