NACCIH Members Present

Dr. Martin Blaser, New York, NY
Dr. David Borsook, Waltham, MA
Dr. Donald Brater, Indianapolis, IN
Dr. Alice Clark, University, MS
Dr. Stephen Ezeji-Okoye, Palo Alto, CA
Dr. Steven George, Durham, NC
Dr. Christine Goertz, Davenport, IA
Dr. Bin He, Minneapolis, MN
Dr. Patricia Herman, Santa Monica, CA
Dr. Steven Hersch, Charlestown, MA
Dr. Susmita Kashikar-Zuck, Cincinnati, OH
Dr. Janice Kiecolt-Glaser, Columbus, OH
Dr. Helene Langevin, Boston, MA
Dr. Cynthia Price, Seattle, WA
Dr. Eric Schoomaker, Bethesda, MD
Dr. Reed Tuckson, Sandy Springs, GA
Dr. ChenChen Wang, Boston, MA

Speaker

Dr. George Santangelo, Bethesda, MD

NACCIH Members Not Present

Dr. Tracy Gaudet, Washington, DC
Dr. Richard Niemtzow, Alexandria, VA

Members of the Public

Iris Aharonovich
Judy Horman
Wei Liu
Michelle Turner
I.  Closed Session

The first portion of the sixtieth meeting of the National Advisory Council for Complementary and Integrative Health (NACCIH) was closed to the public, in accordance with the provisions set forth in Sections 552b(c)(4) and 552b(c)(6), Title 5, U.S.C., and Section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2).

A total of 88 applications were assigned to NCCIH. Of these, 30 were reviewed by NCCIH, 58 by Center for Scientific Review. Applications that were noncompetitive, not discussed, or were not recommended for further consideration by the scientific review groups were not considered by Council. Council agreed with staff recommendations on 41 applications, requesting $10,972,259 in total costs.

II. Open Session—Call to Order

The open session convened at 10:00 a.m. Dr. Martin Goldrosen, NACCIH Executive Secretary, called the meeting to order. The minutes of the NACCIH June 2016 meeting were approved unanimously.

III. NCCIH Director’s Welcome and Report to Council

NCCIH Director Dr. Josephine Briggs opened her report with staffing news. New appointments across the National Institutes of Health (NIH) include Dr. Diana Bianchi as Director of the Eunice Kennedy Shriver National Institute of Child Health and Human Development, Dr. Patricia Flatley Brennan as Director of the National Library of Medicine (NLM), and Dr. Eric Dishman as Director of the Precision Medicine Initiative (PMI) Cohort Program. Among new NCCIH staff are Dr. Viatcheslav Soldatenkov, Senior Review Officer in the Office of Extramural Activities, and four trainees in the Division of Intramural Research. Recent departures include Dr. John Williamson, Chief of the Basic and Mechanistic Research Branch, Division of Extramural Research, who accepted an academic position at the University of Dayton.

In legislative news, Congress enacted a continuing resolution to fund the Government from October 1 to December 9, 2016, and both the Senate and the House have advanced funding bills out of appropriations committees. NCCIH’s budget through December 9 is 0.5 percent lower than last year. It is difficult to make budgetary predictions prior to the November elections. There may be another continuing resolution. Dr. Briggs discussed the budget mechanism table, including data on several major types of NCCIH grant awards by type from Fiscal Years (FY) 2006 through 2016.

NIH has launched the second Trial to Assess Chelation Therapy (TACT2) to study whether the highly significant benefit of chelation therapy seen in one subgroup—participants with diabetes—in the first TACT clinical trial can be replicated. The awardees are Mount Sinai Medical Center in Miami and the Duke Clinical Research Institute. The primary funder is NCCIH, with co-funding by the National Heart, Lung, and Blood Institute; the National Institute of Diabetes and Digestive and Kidney Diseases; and the National Institute of Environmental Health Sciences. The study’s assessment of heavy metals will be performed by the Centers for Disease Control and Prevention. Dr. Briggs then moved to news coverage of NCCIH, noting a positive trend and providing examples. The Center is looking forward to a lecture on October 17 by Dr. Roger Chou of Oregon Health & Science University as part of NCCIH’s

**Discussion.** In response to a question from Dr. Blaser, Dr. Briggs said that compared with the period from 2006 to her NCCIH arrival in 2008, the Center now has fewer smaller awards and more R01 awards and has seen a slight uptick in career awards and a fall in training grants. At present, NCCIH’s distribution of large and small grants is reasonably typical of NIH. The Center’s success rate for applications is quite low. The budget will be discussed further at the February 2017 Council meeting.

Dr. Tuckson praised NCCIH’s communication efforts, inquired about support of NCCIH by the NIH media office, asked whether Dr. Briggs anticipates a stronger connection with the new NLM director, and suggested outreach to health journalists. Dr. Briggs said that the Center is doing a lot in all these areas but could always do more. She added that NCCIH has an excellent relationship with the NIH Director of Communications and his staff, and explained the NIH-NCCIH process for press releases. She invited Ms. Catherine Law of the NCCIH Communications Office to comment further. Ms. Law described Ms. Kat Danielson’s work with the NIH Communications Director’s Office, Ms. Irene Liu’s and the Web team’s work with NLM through the MedlinePlus site, an upcoming NCCIH feature on chronic pain in *MedlinePlus* magazine, and the Center’s effort to syndicate its Web pages. Ms. Law will talk further with Dr. Tuckson.

Dr. Briggs said that the Center is beginning to talk to organizations involved in public outreach on problems related to the opioid epidemic about a potential outreach role in this area for the Center. She is also discussing with Dr. Brennan the capture of information about health practices in electronic health records (EHRs), including to assist the research enterprise. Dr. Schoomaker asked about integration of interagency efforts (as with the Departments of Defense and Veterans Affairs) on information products, including their linkage and presentation. Dr. Briggs replied that this effort is not as integrated as it should be and offers an important opportunity. Dr. Brater commented about the typical lack of fields for complementary modalities in EHRs—if they will be necessary for research, should NIH Institutes and Centers invest in techniques like natural language processing? Dr. Briggs said that there is a lot of discussion and concern about these questions at NIH although less expertise. The NIH Health Care Systems Research Collaboratory works with EHR data and has been gaining some experience. She has found in her work on the PMI Cohort Program that certain EHR fields lend themselves to capturing this kind of information for research, while many others do not. But she sees the potential as enormous and something that the country needs to care about. Dr. Tuckson termed the present moment “a perfect storm” and a major opportunity, including because of the opioid epidemic, and suggested that NCCIH connect with the National Academy of Medicine’s (Institute of Medicine’s) work on the learning health care system. Dr. Briggs noted that NIH can control some “levers,” but there are other, major levers controlled by other parties. She has seen widespread interest in more coordination.

Dr. Herman commented that EHR systems are designed for purposes other than research and asked whether a calculation could be attempted, and then shared with major EHR providers, of how much more research could be accomplished if needed changes were made. Dr. Briggs talked about the Sync for Science pilot program, which is a collaboration between the White House and NIH to allow people to access their health data and send it to researchers in support of the goals of PMI. Other collaborators include some major EHR developers. Dr. Goertz commented on the Spine Institute for Quality (Spine IQ), a nonprofit organization whose mission includes use of clinical data registries.
IV. Insurance Coverage and Out-of-Pocket Expenditures for Complementary Health Approaches


While use can be seen as a marker of the value of complementary approaches, it is an insensitive measure, and the researchers sought to find out more about these approaches’ monetary value, including out-of-pocket spending on them. The primary data source was the 2012 National Health Interview Survey (NHIS). The NHIS is America’s preeminent health survey, in which tens of thousands of civilian, noninstitutionalized U.S. adults are interviewed by the Centers for Disease Control and Prevention about their health- and illness-related experiences. When applicable, adults also report as proxies on a sample child in their household. Every 5 years starting in 2002, the NHIS has included a special supplement containing questions on the use of complementary health approaches.

Major topics within his team’s analyses have included spending on complementary approaches overall and for treatment of specific health conditions; primary reasons for use of various approaches; possible causes of spending differences, e.g., between adults and children; and spending on three broad categories of complementary approaches (practitioner-based, self-care, and natural product supplements). Comparisons to spending on conventional medical care were also drawn. Findings on family income and health insurance coverage as push-pull factors that might impact a person’s ability to pay for complementary approaches were discussed.

Discussion. Dr. Blaser commented on a finding that people at lower incomes pay much higher percentages of their income for complementary approaches than people at higher incomes. Dr. Nahin said that this reflects a value issue and should be explored further. Age should also be explored. Responding to questions from Dr. Borsook, Dr. Nahin said he has started an analysis that will link NHIS data to Medical Expenditures Panel Survey (MEPS) data, and spoke briefly about the feasibility of researching in the NHIS whether children and young adults prefer complementary approaches as a primary component of their health care.

Dr. Schoomaker supported surveys like the NHIS being done in military populations, commented on a possible effect of TRICARE’s “hybrid coverage,” and suggested studying whether insurance coverage issues drive people toward drug treatments, especially for pain. Dr. Nahin was receptive to this idea and noted that he will be studying people in different pain categories over the next 2 years using MEPS data; this will include looking at drug use. Dr. Herman added as another consideration people’s ability to take time off from work to see a complementary practitioner. There was a brief discussion of several regional factors (where complementary health professional schools are located, cost of living, etc.) that could affect the use and costs of complementary practices. Dr. Goertz mentioned her study on per capita supply of doctors of chiropractic in relation to opioid use by Medicare beneficiaries. Dr. Tuckson...
suggested a need for consumers to have a way to know whether complementary care is high quality, predictable, and cost effective, and to consider whether the research community could contribute to this.


Part I. In the first of two presentations in this session, Dr. Partap Khalsa, Deputy Director of the Division of Extramural Research, presented on “Manual Therapies Portfolio: Focusing on Mechanistic Outcomes.” Dr. Khalsa summarized findings by a staff working group that analyzed the impact of published papers on mechanistic research in NCCIH’s manual therapies portfolio.

Manual therapies are widely used by the U.S. population, mostly for treatment of neuromusculoskeletal conditions but also for various nonmusculoskeletal conditions. NCCIH has funded most of NIH’s studies on these therapies and almost all the mechanistic grants (the number is relatively small). These mechanistic studies have focused on the areas of joint/spine biomechanics, soft-tissue biomechanics, neuromuscular responses, the peripheral and central nervous system, and biochemical neurotransmitter responses (local and systemic). At NCCIH, manual therapies are a subset of a large domain: mind and body approaches. Dr. Khalsa explained the definition his team used and its search strategy for studies that focused on or included mechanisms. The process ultimately yielded 59 unique, competing awards focused on or including mechanisms, leading to 184 associated publications of significant relevance to the topic. To investigate how influential those publications have been, the team used a new tool, the iCite Relative Citation Ratio (RCR).

The group’s major finding was that the influence of the NIH portfolio in manual therapies research in mechanistic areas was similar to, if not slightly greater than, the median for all publications on which NIH has provided support. NCCIH’s studies have positively influenced the scientific field. Dr. Khalsa provided several examples of publications by NCCIH grantees with high RCR values.

Part II. Council Member Dr. Helene Langevin, an NCCIH grant recipient, presented on “Mechanotherapeutics and Connective Tissue” (CT). She discussed selected work by her laboratories at the University of Vermont and Brigham and Women’s Hospital. She opened by asking what massage, acupuncture, and yoga have in common. The answer is that all apply mechanical forces (whether active or passive) to CT—such as a stroke in massage, a stretch in yoga, or the characteristic winding response by CT to an acupuncture needle. Mechanical forces are gaining prominence again in physiology after dominance by biochemistry for many decades. These forces are extremely important in biology and influence biological processes in organisms at all levels of function.

The term “mechanotherapeutics” has been coined for treatments that leverage physical forces or target mechanical signaling, as a pathway or core part of the treatment. In a larger context, such treatments exist both in conventional medicine (e.g., as stents, orthodontics, and certain drugs), and in complementary and integrative health. CT is an important part of the whole body and the musculoskeletal system but has not yet been studied much. In this field, the biomechanics of limbs are being reexamined. In addition, Dr. Langevin and her team are looking again at the immune system. Many responses and reactions occur in CT, as does cellular transport, and one question is whether immune responses are affected by mechanical forces in CT.
The speaker discussed some of her team’s study results on the effects of stretch and mechanical forces on CT and outcomes such as pain and the inflammatory response (e.g., whether that response moves in the direction of resolution versus the direction of chronicity). In one study, the team showed that in rats with a subcutaneous inflammatory lesion on the back induced by carrageenan, stretching for 10 minutes twice per day reduced inflammation and improved pain 2 weeks after the carrageenan. In a later (controlled) study also done in rats, periods of stretching over 49 hours had several benefits: they reduced thickness of the inflammatory lesion \textit{in vivo} and migration of neutrophils \textit{ex vivo}, and increased the concentration of resolvin in the lesions \textit{in vivo} and \textit{ex vivo}. Effects were similar for active and passive stretching, which suggested that there is a direct mechanical impact of stretching on pro-resolution mechanisms within local CT.

Chronic inflammation that does not resolve includes fibrosis, which in turn affects how people can move and how they feel about moving; this has application in chronic pain. Evidence exists that pathology of CT may be associated with back pain, but more needs to be learned, including whether there are implications for treating it in people. Dr. Langevin closed by encouraging listeners to seek better understanding of connections between systems. There is an opportunity for integrative medicine, she added, because conventional medicine has a tradition of dividing the mind and body and dividing people into systems (as seen, for example, in the array of medical specializations). Integrative medicine and manual therapies can challenge us to think about people more holistically.

**Discussion.** Dr. Kashikar-Zuck asked whether something could be happening in the CT of people with joint laxity/hypermobility such that they do not obtain a therapeutic effect from stretching. Dr. Khalsa commented that Dr. Langevin and a number of other NCCIH-funded investigators are interested in looking at the genetic basis for these conditions and to what extent epigenetics are modified by environmental exposures. In addition, there are commercial interests trying to combine genetic, epigenetic, and/or phenotyping data; one question will be how to use these data to better identify people who may have hypermobility or hypomobility and to study how this affects CT. Dr. Langevin agreed and noted that many people who get injured in yoga do so because they are already too loose, which raises the question of how much different people should stretch. This “dosing” question is extremely important and not a one-size-fits-all situation, and her team is studying doses of stretch in animals, including for force, strain, and frequency.

Dr. Kiecolt-Glaser said that this lecture may have provided a potential mechanism in stretching that could apply to her yoga trials. Dr. Langevin commented that her team is focusing on the inflammatory processes in tissues, a neglected area in research, and this could spill over systemically. Dr. Schoomaker thought that these modalities might represent a form of “disruptive technology,” and if so, perhaps NCCIH could look into technology transfer and technology research to expand its funding. In response to a question from Dr. Khalsa, Dr. George commented briefly on work by his group that has involved looking not just at the effects of selected manual therapies in the body but at the roles of various psychosocial processes by which people respond to them. Context can override some of the biological effects. For example, manual therapies seemed to dampen pain sensitivity more than a placebo or control. However, clinical outcomes have not always followed this pattern exactly, which suggests that there are other ways people get relief, e.g., from positive or negative expectations. Dr. Langevin commented that the biomechanical piece may still be there along with the psychosocial piece, and the latter does affect behavior, as seen, e.g., in fear of movement.
Dr. Goertz mentioned a couple of studies that her group has done on high-velocity and low-amplitude (HVLA) thrusts and asked whether Dr. Langevin has done anything in this area or would be interested in it. Dr. Langevin responded that she has not done anything yet, is interested in it, and considers both HV and LA important areas to explore, as is the duration of stimulus. Dr. Price thought that Dr. Langevin’s work showed much potential to “go places in mental health” that have begun to be explored but need more work. Dr. Khalsa agreed and said that NCCIH has a number of active grants in this topic area. Dr. Borsook asked whether there is a dose-response process, and Dr. Langevin answered that this is an intriguing area; it is a reason her team measures leukotrienes and resolvins, and they are working to map further apparent shifts with stretching (including of macrophages and inflammation resolution). Dr. Khalsa said that the clinical data on this are interesting and there does appear to be a dose-response relationship, including optimal numbers of sessions of manual therapies to treat pain conditions. Dr. Borsook differentiated targeting force to a localized area from a generalized practice of, for example, yoga. Dr. Langevin agreed, noting that her team’s current model is a focal area of inflammation, and the findings could best apply to something like a fascial tear, as people could acquire from shoveling snow. Magnetic resonance imaging (MRI) studies are beginning to detect inflammation in fasciae. There would be a difference between applying the correct approach of manual stimulation to such an injury in contrast to a whole-body approach for diffuse pain. The use of anti-inflammatory agents was briefly discussed.

In response to a query from Dr. Briggs, Dr. Langevin explained the technique of ultrasound elastography (UE), which can be described as an ultrasound movie over time when a person is performing a specific movement or a controlled displacement. She gave details on what UE can and cannot do and an example of its use in oncology (to measure tumor stiffness). Dr. Khalsa commented that UE has begun to be used in a variety of different settings, including in the NIH Intramural Research Program. Dr. Langevin said that her team is working with the Brigham and Women’s Hospital Department of Radiology to develop a combination of ultrasound and MRI. Dr. Borsook asked whether the speaker had looked at the effects of local anesthetic on her two biomarkers, since it is a treatment for trigger points. Dr. Langevin said that the topic of muscle would have to be a separate talk, but she knew of some techniques involving dry needling to help a muscle relax; this could be occurring in the CT as well, but that is not yet known. Dr. Wang commented that the concepts in the lecture mirrored the teachings in the fundamental textbook on traditional Chinese medicine.

Dr. Borsook saw this session as illustrating an area of great opportunity and potential impact. The domain could be called something like “biomechanical domains,” and investment in it would lift up some other domains as well. Dr. Briggs expressed enthusiasm for the value that this direction could add to the Center’s portfolio, adding that one of the large challenges with these approaches is the power of the placebo and factors like expectations, context, and reassurance—sometimes these become the signal. Figuring out more sensitive methods as Dr. Langevin is doing should allow researchers to get to fundamental biological mechanisms.

VI. Development of New Metrics To Evaluate the Impact of NIH-funded Research

Dr. George Santangelo, director of the Office of Portfolio Analysis (OPA) in NIH’s Division of Program Coordination, Planning, and Strategic Initiatives, discussed his team’s work on developing novel metrics to increase the rigor of evaluation of the impact of NIH-funded research. Two areas of the OPA mission are to coordinate portfolio analysis activities at NIH and develop a science of portfolio analysis. For the
latter, he outlined his Office’s practice of using existing data-driven approaches to characterize research investments and their resulting impact, and developing and delivering new tools and approaches as well as augmenting existing ones. Dr. Santangelo described and gave examples of some of the major tools that his team has developed or is developing: for content analysis, IN-SPIRE and Word2vec; for automated disambiguation, iClean; for effective bibliometrics, iCite; for mapping translational science, iTrans, which is in beta testing; and for tracking patents, licensing, and startup activity, iTech (now in development).

Dr. Santangelo noted discussions and publications by researchers on limitations of the Impact Factor (IF), a citation metric long used to augment expert opinion. As an alternative to IF that would address its limitations, his team developed the Relative Citation Ratio (RCR). It is available in iCITE, a free, easy-to-use Web tool with which users can calculate the RCR of the articles they choose in the NLM’s PubMed system. Ultimately, the aim for both iCite and RCR is assessment of scientific impact through a multifaceted, article-level, open-access approach. RCR values are normalized, benchmarked citation rates that measure the influence of an article—relative to what is expected given the scope of the scientific topic—rather than the quality, importance, or impact of the work. The scientific topic is defined by the article’s cocitation network, a highly resolved, dynamic determination of the target audience.

Dr. Santangelo also discussed the iTrans tool, which is in beta testing. The need for diversified metrics for research assessment has included metrics for mapping translation of research from bench to bedside. The speaker gave an example of how iTrans can track translational development of cancer immunotherapeutic agents by calculating and providing content visualizations for patterns of citations in human, animal, and cell and molecular studies and in basic, translational, and clinical research, within a given timeframe.

Dr. Santangelo offered several closing points. Quantitative data-driven approaches can inform scientific portfolio management. Effective data cleaning is critical. The RCR is a validated, article-level replacement for widely used but inaccurate and/or imprecise measures of scholarly influence. Tracking the outcomes and measuring the impact of investments in biomedical research requires methods to monitor translation of basic and/or patented discoveries into improvements in human health. The grand challenge in portfolio analysis of biomedical research is to meet the needs of decisionmakers by enabling successful predictions about gaps, overlap, emerging areas, translation, and impact on human health.

Discussion. Dr. Blaser asked how Dr. Santangelo factors into the RCR how long it takes a paper to “take off” in terms of its influence. Dr. Santangelo explained publication patterns and parameters that the RCR takes into account, and added that one area his team is looking at is kinetics. Dr. Borsook asked whether NIH, through this tool, could contribute to the relative impact that coauthors have, mentioning a problem in academia where “teams are talked about, but not lauded.” Dr. Santangelo said that team “conciliance” (bringing methods together) applies and pulling together network analyses of coauthors and the influence of those papers might help identify impact—but, analytically, this would be a very complex question to answer. Dr. Tuckson asked whether the speaker is presenting to the advocacy community. He thought doing this would show progress and movement, give a sense of excitement and enthusiasm about what NIH is doing, and help people break out of siloes and cross preconceived lines of distinction. Dr. Santangelo said he thought this made sense, and he has done a little public speaking, but
he would have to consult Dr. James Anderson of his team about this. He has begun receiving requests to do analyses for the public, but OPA does analyses only for NIH. He is interested in looking for and finding ways things are connected (this can be done computationally), such as connecting two fields not previously known to be connected. These kinds of findings would have to be “flagged for inspection”—i.e., reviewed and interpreted by subject matter experts. Dr. Briggs commented that an interesting aspect of NCCIH’s mission is that the Center takes things that are often outside the boundaries of conventional disciplines, and there is much that these tools can teach us.

VII. Applying iCite: Bibliographic Analysis of the NCCIH Portfolio

NCCIH Deputy Director Dr. David Shurtleff presented on an NCCIH staff project to use the iCite and RCR tools that Dr. Santangelo had just described to examine publications resulting from NCCIH grants from 2002 to 2014. NCCIH’s RCR factor is quite strong relative to the average. The group looked at three key areas of the Center’s portfolio: meditation, placebo, and chronic pain. The findings included the numbers of grants, subprojects, search scope, number of resulting publications found in iCite, and various aspects of their RCR values, as an indicator of their influence. Dr. Shurtleff also showed examples of publications in each of the three areas.

With respect to the meditation portfolio, articles based on NCCIH-funded research on two subtopics, fundamental neuroscience and clinical research, appeared to be having the most influence (as indicated by RCR ratings). In the placebo portfolio, the most influential subtopics were basic neuroscience, symptom management, and clinical research. In analyzing for chronic pain, the team was able to compare NCCIH research grants with grants across NIH as a whole because of coding factors. Both were very similar in median RCR, range of RCR, and other factors on overall influence. NCCIH does have differences from NIH as a whole in terms of focus in this research area. Most of NCCIH’s influence was in fundamental neuroscience and in treatment; most of the research NIH supported was in fundamental basic cellular and molecular biology.

Dr. Shurtleff’s explained that iCite is one of several tools that NCCIH can and will use to assess the output of its funded research. NCCIH clearly seems to be influencing the field in a positive and above-average way. RCR is just one measure of “output,” and there will be a need to capture other outcomes such as innovation, clinical uptake, patents, economic activity at large, and public health.

Discussion. Dr. Briggs commented that she was very happy about these tools and the findings about NCCIH’s portfolio. The Center’s topics are outside the mainstream, but the work it funds is impactful. She added that tools are going to be imperfect. While NCCIH has an interest in influencing people making health care decisions, she cautioned against “turning things solely into numbers” and believing that “numbers are the only thing that matter.” A member asked Dr. Santangelo whether his team has any interest in learning more about “convergences,” such as events, that cause some publications to suddenly become impactful well after publication. He replied that such events are rare and computationally difficult to detect but are one reason that his team would like to drill down the time points in the database even further to months, not just years. But this question would be different from identifying why an “outlier” suddenly was recognized. While interesting and probably doable, that ability appears to be a long way off.
X. Public Comment and Adjournment

No public comments were offered.

The meeting was adjourned at 2:50 p.m.

We hereby certify that, to the best of our knowledge, the foregoing minutes are accurate and complete.

Martin Goldrosen, Ph.D.  
Executive Secretary  
National Advisory Council for Complementary and Integrative Health

Josephine Briggs, M.D.  
Chairperson  
National Advisory Council for Complementary and Integrative Health