

BRI RESEARCH CENTER EVALUATION:

Connors-BRI Center for Research on Women's Health & Gender Biology

Chair: Jill Goldstein, PhD; **Co-chair:** Julie Buring, ScD.

Research Advisory Committee: Philip DeJager, MD, Ph.D.; Francine Grodstein, ScD; Paula Johnson, MD, MPH; Ursula B. Kaiser, MD; Elizabeth Karlson, MD; Samia J. Khoury, MD; Stella Kourembanas, MD; Meryl S. LeBoff, MD; JoAnn E. Manson, MD, Dr.PH, MPH; Karin Michels, Sc.D.; Cynthia Casson Morton, PhD; Page Pennel, M.D.; Janet Rich-Edwards, ScD, MPH; Ellen Seely, MD; Emily Stern, MD; Louise Wilkins-Haug, MD, PhD (Barbara Bierer, MD, Advisor)

I. Mission

Women and men have different risks for the onset, expression, course and treatment response in a number of diseases that occur at different stages of development and throughout the aging process. The mechanisms that explain many of these sex differences are still unclear. We believe that BWH is at the leading edge of sex and gender-based science, given the vast array of expertise of the BWH faculty in women's health/sex differences and our shared desire to develop the research infrastructure necessary to promote discovery in this emerging field. Thus, the mission of the Connors-BRI Center of Research on Women's Health and Gender Biology is to lead in the discovery of mechanisms that will explain sex differences in morbidity and mortality and diseases specific to women. The Center takes a lifespan perspective to identify etiologic mechanisms during fetal development, puberty, adulthood, and aging, with some focus on periods specific to women such as child-bearing years, perimenopause, and menopause. We are particularly interested in fostering translational models of investigating sex-specific vulnerabilities to illnesses and promoting the undertaking of outcomes and operational research that addresses issues important to women's health, sex differences, and health care. We are also committed to creating and educating the next generation of leaders in women's health/gender biology research, given that this is a new field and BWH has the ability to help define this field. We were particularly aware of developing goals that were "added value" to the goals of individual members of our Center.

II. History

The Mary Horrigan Connors Center for Women's Health & Gender Biology was established in 2002 through the generosity of Jack and Eileen Connors. Dr. Jill Goldstein was recruited in 2004 to become its first Director of Research and established the Connors Center Research Advisory Committee (RAC), whose purpose was to guide the development and implementation of the research infrastructure using shared knowledge of cross discipline senior investigators at BWH. At its inception, the Connors Center RAC had the following goals:

1. Build on the strengths of women's health and gender biology research across the hospital by integrating population-level studies with preclinical and other clinical studies to advance our knowledge of sex-specific disease biomarkers. *We believe that there are some shared mechanisms* for understanding gender biology and pathology across organs and tissues (e.g., heart and brain). These shared mechanisms, in part, involve hormones, genes, and inflammatory pathways.
2. Build the case for recognition that puberty, pregnancy/delivery, perimenopause, menopause and post-menopause are significant opportunities to influence the trajectory of women's health with regard to clinical outcomes (e.g. CVD, diabetes, osteoporosis, cognitive decline, depression) and factors affecting outcomes (e.g. endocrine states, inflammatory factors).

3. Create a new model for investigation of sex differences in clinical medicine as part of our research efforts. This helped to redefine the field expanding the notion of women's health from a sole focus on reproductive medicine to a broader vision of understanding sex effects across all domains of medicine.

The BWH Biomedical Research Institute (BRI) was established in October 2005 and, given the similarity of purpose with the Connors Center Research infrastructure, was a seamless fit to merge with the Connors RAC, becoming the Connors-BRI Center for Research on Women's Health and Gender Biology. In 2006, Dr. Goldstein and the RAC, with Dr. Julie Buring as BRI co-chair, became the core faculty group to develop a research agenda in women's health and gender biology for BWH-BRI. Over the course of approximately 8 years, the committee has changed membership only slightly, with core members remaining primarily constant. A few members were added (Janet Rich-Edwards, ScD, Emily Stern, MD, Page Pennell, MD, Ellen Seely, MD, Karin Michels, ScD) and few members from the original RAC left the committee due to other responsibilities (Christopher Crum, MD; Julie Glowacki, Ph.D; George Mutter, MD; Ellice Lieberman, MD).

The Connors-BRI Center held its first retreat in April 2007. The major goals of the retreat were to: identify the "big science" questions that informed the biology of sex effects in medicine that would be addressed less efficiently in single labs; bring together the larger community at BWH to conduct women's health/sex differences research; and develop a strategic plan for cross-disciplinary translational work for the future. Approximately 30 scientists were invited from the BWH women's health research community to attend this retreat. The retreat began with a review of the broad scientific and institutional goals of our Connors-BRI Center, namely: to take a lifespan perspective on sex differences in morbidity and mortality spanning fetal development through aging; investigate shared mechanisms involving hormones, genes, inflammation; initiate and promote research across a continuum from biology to physiology and clinical trials/behavior and policy; strategically recruit and develop investigators and develop shared resources; and relate knowledge to sex-specific treatment and prevention. Databases available for this type of research were reviewed. "Big science questions" involved:

- genetic/epigenetic determinants of sex-specific disease outcomes;
- causes of increased incidence of autoimmune diseases in women compared with men;
- sex-specific inflammatory impact on health and disease;
- differential expression of diabetes by sex;
- fetal antecedents of sex differences in chronic diseases;
- sex differences in aging, osteoporosis, and depression and the brain.

This first retreat served to launch subsequent retreats and workshops, RAC discussions about initiating the development of a new prenatal family cohort, funding of pilot studies, and the development of an interdisciplinary and interdepartmental program project grant.

III. Current Strategic Priorities (2008-2013)

The mission and goals above reflect a broader vision for the life of the Center and, within this framework, the Connors-BRI RAC developed four strategic priorities in 2008.

1. Innovative and Cross-Disciplinary Science: Our work has focused on a few substantive domains that reflect key strengths of BWH in the arena of women's health and sex differences in medicine.

1a) *Sex differences in CVD, Diabetes, Obesity and other Metabolic Syndrome Disorders:*

1a1) In order to advance this area of work, in 2008 we were awarded sponsorship by the Radcliffe Institute for Advanced Study for a two-day workshop on "Unexplored Sex Differences in Cardiovascular Disease".

Participants included 23 scientists from Harvard, Yale, Columbia, University of Pennsylvania, and Albert Einstein Schools of Medicine who lead basic and clinical research in endothelial dysfunction, inflammation, endocrine predictors of CVD risk, and the links between sex differences in psychiatric outcomes with cardiovascular function. Novel connections were made between disciplines, and a sense of urgency arose regarding the importance of both gender and early life development in determining cardiovascular risk. A consensus emerged from the workshop that novel and practical research findings would emerge from a research program focused on the intersection of pregnancy complications, including preeclampsia, gestational diabetes, preterm delivery, and fetal growth restriction, with increased risk of CVD in mothers as they aged as well as the impact of these pregnancy complications on the subsequent health of the offspring (i.e., models of fetal programming of chronic disease).

A subgroup of us, led by Dr. Rich-Edwards, designed an integrated, cross-disciplinary program to investigate the association of preeclampsia with CVD. The aim of the program project was to characterize vascular dysfunction emerging after preeclampsia and test whether a history of preeclampsia predicted future CVD. The PPG, submitted in 2011, consisted of a population-level study, experimental clinical research, and analogous animal studies. Although it was enthusiastically received and scored well, it fell short of being funded. We continue to pursue funding for components of this PPG. In addition, the work led to a publication with our RAC members taking the lead (Rich-Edwards JW, McElrath TF, Karumanchi A, Seely EW. Breathing life into the lifecourse approach: pregnancy history and cardiovascular disease in women. *Hypertension* 2010 56(3):331-4.) Related to this PPG, a group of us are designing an internet-based intervention program to motivate lifestyle change for CVD risk reduction in women with a history of preeclampsia; this will be submitted as a Patient-Centered Outcomes Research project.

We also used the model of convening “exploratory seminar workshops of experts to cross-fertilize ideas” to initiate new proposals in our other strategic domains of interest (e.g. recent workshop on sex differences in autoimmune disorders, discussed below).

1a2) Under the CVD/Metabolic domain, we are also taking a leadership role in forming new collaborations with Psychiatry, Women’s Health, and Bariatric Surgery (under Scott Shikora, MD, FACS, who is planning the development of the Metabolic Center at BWH). Studies with Psychiatry and Women’s Health are focusing on central nervous system control of food intake and the behavioral components to food motivation (reward) circuitry, mood and other substance use, and the impact of other associated behaviors with regard to the success of weight reduction after surgery and pre-surgery selection for success. Junior faculty in Psychiatry and the Connors Center have devised a pilot study with Dr. Shikora to begin this new collaboration.

1a3) Finally, the Connors-BRI Center for Women’s Health & Gender Biology is planning a workshop in Spring 2013 that will focus on sex differences in the etiology and consequences of obesity. The workshop will address sex differences in the pathogenesis and consequences of obesity and will cover many facets of obesity over the life course as it relates to women, including: childhood obesity, obesity during puberty/adolescence, pregnancy and its effects on the mother (e.g., preeclampsia and gestational diabetes), the fetus, and the future health of the unborn child, obesity during the postpartum period, obesity consequences (such as risks of cancer, effects on cognition, etc.), and obesity during menopause. The workshop will also address the interactions between obesity, ethnicity and culture, sleep disorders, and disorders related to mood (e.g. depression) and anxiety. Additionally, there will be discussion on interventional strategies for obesity in women ranging from prevention to treatment and from the individual to populations (e.g., lifestyle, drugs, surgery and public health).

The workshop will begin with a general overview of obesity and its clinical and public health consequences, followed by two sessions addressing these various topics, and ending with a panel discussion, lunch, and a competitive poster session. There is also a tentative plan to invite participation from the makers of the 2012 HBO 'Weight of the Nation' documentary on obesity in the United States, which was jointly sponsored by the Institute of Medicine, the National Institutes of Health and the Centers for Disease Control & Prevention.

1b) *Sex Differences in Neuropsychiatric Disorders and their Comorbidity with General Medical Disorders:*

Psychiatric disorders, such as depression, anxiety and substance use disorders, have demonstrated substantial sex differences in incidence and have a high comorbidity with numerous chronic diseases, such as CVD, autoimmune disorders and Alzheimer's. BWH is in a unique position with regard to the study of gender neurobiology and defining the field with regard to its impact in clinical medicine given the quorum of investigators across disciplines studying these issues. We have begun collaborative efforts to create a BWH Gender Neurobiology focus bringing together women's health, psychiatry, neurology, endocrinology, radiology and genetics. We have shared this vision with the BRI Center for Neuroscience and are working closely developing new proposals for submission next year. BWH also has the capacity and expertise to develop sex-specific treatments of these disorders and thus impact chronic disease comorbidity in general. We are working to build the infrastructure in order to operationalize this.

1b1) Interactions with Neurosciences Research Center: The Connors-BRI Center has actively fostered interdisciplinary interactions with the Neurosciences. Three members of the Connors/BRI Research Advisory Committee sit on the BRI Neurosciences Research Center (NRC) Committee (Drs. Goldstein, Stern and DeJager), allowing for direct communication of ideas and initiatives between these Centers. This has substantively enhanced the brain-related research goals of the Connors-BRI Center, as well as the gender biology research goals of the NRC. An example is the upcoming NRC Workshop on December 13, 2012, a forum to discuss current research innovations and initiatives in three major areas of Neuroscience. One of these will be devoted to sex differences in the brain. Dr. Goldstein will be the primary featured speaker for this, followed by three investigators presenting current work in this area. The directors of the NRC felt it was critical to further expose the Neuroscience community to this important field and to promote discussion of possible new areas of intersection, innovation, and collaboration. There is time dedicated to dialogue about this after the presentations, during lunch and the poster session.

1b2) Interactions with National Network of Depression Centers: Another important brain-related area of intersection exists between the Connors-BRI Center and the National Network of Depression Centers (NNDC). The NNDC, founded in 2007, is an organization dedicated to transforming depression and bipolar treatment, maintenance of wellness, and the eventual prevention of mood disorders. It brings together 21 of the nation's top Centers of Excellence in this area, with initiatives ranging from basic and clinical science to clinical implementation and issues regarding innovative care and delivery approaches. BWH is a founding member of this organization, and one of the initial focused task groups to be implemented was in Women & Mood Disorders, which is chaired nationally by Dr. Laura Miller at BWH. This area is of critical importance given the high prevalence of mood disorders in the female population. Dr. Goldstein, a member of the BWH NNDC team and the Women's Mental Health task force, gave a presentation on the underlying neural circuit dysfunction and how it differs between the sexes in depression, at one of the national NNDC meetings, and Dr. Stern, who also performs work in this area, is a member of the new NNDC Biomarkers task group. These interactions/initiatives provide an important mechanism for the work being done on sex differences in the brain

associated with the Connors-BRI Center to be brought to bear on the problem of mood disorders nationally through the NNDC.

Ic) Sex Differences in Autoimmune Disorders: Autoimmune disorders, such as multiple sclerosis, lupus, and rheumatoid arthritis, have almost exclusively a higher incidence in women than men. However, the reasons for this are unclear. BWH is one of the leading institutions in the world studying autoimmune disorders, and we have the potential to become a leading institution in understanding this substantial sex difference in medicine and have the capacity to develop sex-specific treatments in this arena given the infrastructure already in place at BWH. In the pursuit of this vision, we convened an exploratory workshop in this domain in order to bring together expertise across BWH departments and outside experts to begin to investigate this issue at BWH. The “Sex Influences in Autoimmune Diseases” workshop was held on June 4-5, 2012 in the Royal Sonesta Hotel in Cambridge, MA. The workshop, co-chaired by Tanuja Chitnis, MD, and Samia Khoury, MD in BWH Neurology, was sponsored by funds from the Connors-BRI, the Connors Center itself, and the Partners Multiple Sclerosis Center at the Brigham. The goal of the workshop was to bring together high level international researchers working on sex influences in autoimmune disease with Brigham researchers to 1) review the current knowledge in the field, 2) identify major knowledge gaps, 3) stimulate new ideas and cross-fertilization and 4) stimulate collaborative and interdisciplinary projects. There were 14 speakers, including 6 from BWH Departments of Rheumatology and Neurology, and 40 attendees including 5 BWH postdoctoral fellows who had demonstrated a specific research interest in sex influences.

The workshop identified several important knowledge gaps, including the need to understand sexually differential immunological changes through the lifespan and during life events, such as pregnancy, and their effects on autoimmune disease course. The differential effects of risk factors for autoimmune disease including genetic and environmental influences such as the gut microbiome were raised as important future avenues of research. Furthermore, the need for pregnancy registries of women utilizing immunotherapies in all autoimmune diseases was discussed. Several collaborative projects were discussed, and a proposal for a clinical trial using hormone therapy was developed. A review of the topics discussed by speakers will be disseminated through a special focused journal issue of “Clinical Immunology”.

Id) Menopause and General Medical Disorders and Disorders of Aging: Women and men age differently related to the body and brain. In fact, men and women are at different risks for disorders of aging, including a 2-fold increase in Alzheimers in women (not only due to the fact that they live longer). One component of sex differences in aging of the brain and body is the hormonal shifts in ages late 40’s to 50’s in perimenopause and menopause. We are one of the leading institutions in the world with expertise in menopause and women’s health and disorders of aging. We have initiated and participated in a number of events to create an awareness that sex differences in aging is a critical arena of work and one for which BWH should be a leading institution. In 2011, we participated in the BRI Workshop on Aging by Goldstein giving a presentation on sex differences in aging of the memory circuitry in order to underscore the importance of this arena.

Id1) Healthy Aging Cohort Development: Headed by Connors-BRI Women’s Health and BRI Neuroscience, we are working on establishing a BWH Healthy Aging Cohort following healthy men and women from ages 40-60 and beyond in order to understand the effects of the aging process at the organismal level. This will enable: (1) the development of predictive algorithms and selection of new technologies to enhance patient management; and (2) provide insights into future therapies for aging-related decline of interconnected biological systems that support human health function. We will recruit a cohort of 5,000 BWH patients with primary care physicians at

BWH and follow them prospectively via routine tests and evaluations performed as part of primary care, as well as periodic clinical and research evaluations selected by investigators affiliated with the cohort. The BWH Healthy Aging Cohort leverages several existing resources at BWH that enable integration with current, cutting edge projects and many of other large epidemiologic studies being conducted at BWH. These include: the *BWH PhenoGenetic Project*, which will supply their sample processing, archiving and distribution pipeline; the *OurGenes project*, with which we will integrate our recruitment efforts and exchange data and samples; *New England Family Studies of the Fetal Programming of Disease*, a 50-year NIMH follow up study of a prenatal cohort (in part initiated in 1959-1966 at BWH) that includes brain imaging, neuropsychology of cognitive decline, hormones, inflammatory markers, and genotyping data from the adult offspring (now 45-52 years of age), which will be used to inform and integrate with the proposed healthy aging cohort; and *BWH/RUSH University Collaborative Program* exploring the genetic and epigenetic architecture of aging-related cognitive decline, which has designed predictive algorithms integrating genetic and environmental risk factors that can be deployed in the BWH Healthy Aging Cohort to test their relevance in a younger population.

We envision the development of a “next generation” clinic in which physicians from different pertinent specialties interface with patients as requested by their primary care provider, to facilitate integration of care across specialists and testing of novel operational methods and technological platforms with which to enhance patient care to prevent and treat disorders of aging early. Further, the Health Aging Cohort’s investigative team will be open to members of any specialty promoting interdisciplinary research collaboration. Through its development, we will establish a new hospital-wide resource for the BWH community, particularly junior investigators, one that will fuel many grant proposals and clinically meaningful investigations in coming decades as participants age. To date, we wrote a white paper and a protocol and will be obtaining funding in the fall of 2012. This is a key endeavor reflecting our role in the development of shared resources at BWH.

1d2) One related domain of aging is musculoskeletal, given that there is high rate of musculoskeletal disorders (e.g. osteoporosis, osteoarthritis) in women after menopause. The Connors-BRI Center is working with the Center for Musculoskeletal Disorders to develop new collaborative proposals focused in this arena integrating BWH’s Women’s Health services (at the Gretchen and Edward Fish Center for Women’s Health) with basic and clinical investigators at BWH.

1e) Other Substantive Domains of Interest from a Women’s Health/Sex differences Perspective:

The Connors-BRI was actively involved in the organization and development of a BRI interdisciplinary research workshop on vitamin D in 2010 and a clinical seminar/workshop on this topic in 2011. The first workshop, organized by Drs. Julie Glowacki, JoAnn Manson, and Scott Weiss, took place on April 29, 2010. The goal of the workshop was to bring together the diverse cadre of BWH investigators who have an interest in vitamin D to foster innovative and collaborative research. Speakers and attendees included BWH basic and clinical investigators with expertise, interest, and/or research programs in vitamin D, providing a forum for faculty and trainees to learn about ongoing research on this topic, network with other investigators with similar interests, and learn about the scientific resources available at BWH to facilitate this research. Specific topics discussed included: mechanisms of vitamin D actions, vitamin D and musculoskeletal health and fracture prevention, research on cancer, cardiometabolic and renal disease, women’s health, maternal/neonatal outcomes, neurosciences/cognition, infection, respiratory diseases, and autoimmune disorders, as well as the rationale/design of the VITamin D and OmegA-3 Trial (VITAL). In addition, a panel discussion addressed the BWH resources available for vitamin D research, 25(OH)D assay issues, and clinical topics such as when to screen, which assay to use, for which level to aim, and what dose of vitamin D to recommend to patients.

Connors-BRI speakers included Julie Glowacki (former RAC member), JoAnn Manson, Meryl Leboff, and Janet Rich-Edwards. Other speakers represented a diverse array of disciplines throughout BWH. Many collaborations were fostered by this workshop, including research on vitamin D and reproductive health and several interdisciplinary ancillary studies that leverage the VITAL trial resource.

A second workshop/seminar on vitamin D, organized by Drs. Julie Glowacki, Meryl Leboff, JoAnn Manson, and Scott Weiss, took place on May 9, 2011. The program, which focused on Vitamin D Recommendations in 2011, was intended primarily for a clinical audience to help clinicians understand and interpret the recently-released Institute of Medicine (IOM) guidelines on vitamin D intake. The main speaker was Bess Dawson-Hughes, MD, Senior Scientist and Director, Bone Metabolism Laboratory, Jean Mayer USDA HNRCA, Tufts University, followed by a panel discussion with Drs. Leboff, Manson, and Weiss. The seminar and panel discussion provided an overview of the current state of knowledge on vitamin D intake, serum 25(OH)D levels, and clinical health outcomes.

2. Development of Shared Resources:

In order to support innovative science, cross-disciplinary collaboration, and the development of young investigators and trainees, the Connors-BRI has built a research infrastructure that includes: space and processes for a generative “think tank” to identify and encourage research in women’s health and sex differences in medicine; support for pilot funding for research efforts; and some administrative support. We are working on developing several avenues of shared data resources for collaborators, young investigators and trainees (such as access to population data, tissue, etc.) and establishing seed funding programs for innovative pilot work leading to proposals.

2a) Healthy Aging Cohort (see above)

2b) OurGenes, OurHealth, OurCommunity in Collaboration with the Gretchen and Edward Fish Center for Women’s Health: The OurGenes, OurHealth, OurCommunity project, a hospital-wide study to create a biobank of samples linked to health information provided by Brigham patients, initiated recruitment at the Fish Center for Women’s Health in January of 2011. OurGenes, a flagship project funded by the BRI, strives to provide researchers with the samples linked with data on lifestyle, environment, family history, and the electronic medical record for innovative science to understand the causes of and cures for disease. The collaborative relationship between the Fish Center for Women’s Health and the OurGenes, OurHealth, OurCommunity study has contributed to OurGenes’ success by recruiting primary care patients who are seen at the Fish Center. Dr. Elizabeth Karlson, who has been instrumental in directing OurGenes has also been on the Connors-BRI RAC, and thus relationships between our Center and this project have been close. Approximately 50% of eligible Fish patients who were approached participated in OurGenes. The successful consent rate was attributable to the Fish Centers’ motivated clinical team and phlebotomy staff. Eight physicians from the Fish Center are collaborating with OurGenes research assistants to recruit eligible patients, and the clinical staff and phlebotomy team have assisted research assistants to identify, track, and draw blood on participants. To date, OurGenes consented 2,700 patients and collected blood samples on 2,500, including 403 from the Fish Center.

2c) Family Cohort Development: We have been actively working on launching a new BWH Family Cohort, a pluripotent longitudinal cohort starting in early pregnancy, and following mother, father, and child through pregnancy, the postpartum years and the offspring’s life. Based on our tradition of and expertise in longitudinal cohort research, and the 8,000 pregnancies delivered at the hospital yearly, BWH is an ideal setting for this

endeavor. What we envision is a research database registry, a “family cohort” (including clinical and sociodemographic information, family history, and clinical specimen storage—i.e. blood and placental tissue), and where mothers, fathers and their offspring would be followed over time. The “family cohort” would allow us to collect targeted blood and urine samples, and perform general medical and psychiatric assessments, and provide subjects who would undergo imaging modality potentials for mothers during pregnancy and for the young family in the years postpartum. The results of these assessments would enable us to address important unanswered questions about the impact of pregnancy complications on future chronic disease in the mother, and the fetal programming of sex differences in chronic disease in the offspring including disorders such as CVD, depression, and autoimmune diseases. In establishing a longitudinal family cohort, we would create a resource that could be used by many researchers to study a broad range of topics in medicine. To date, we designed and budgeted the framework of the cohort over its first decade, identified a core of investigators committed to creating the Family Cohort as a platform for innovative research, and have begun fundraising activities to secure support at the NIH and philanthropy levels.

2d) Women’s Integrated Learning Laboratory (WILL): Developing Clinical Research Opportunities-Patient Registry at the Fish Center for Women’s Health: The Fish Center for Women’s Health is recognized as a leader in women’s health care for creating an interdisciplinary model of care within an academic medical center. The Fish Center encompasses twelve specialties (internal medicine, gynecology, cardiology, endocrinology including diabetes, gastroenterology, rheumatology, orthopedics, physical medicine and rehabilitation, neurology, dermatology, psychiatry, and nutrition). To support this model, we are developing a learning laboratory of collaborations with physicians, investigators and patients to generate sex and gender-specific knowledge. In 2007, the Connors Center began to develop a research infrastructure at the Fish Center to include a women’s health patient registry designed as a research and quality improvement tool to advance women’s health through practice-based clinical investigation. Core functions of the registry will include serving as a source of pilot data for clinical research and providing data for on-going improvement of clinical and educational programs. Efforts to date include a pilot study of use of an interactive electronic patient history form to gather more consistent and in-depth medical and lifestyle information across specialties; participating as a pilot site in the OurGenes study; and working with the Department of Medicine, BWPO, and the Center for Clinical Excellence to collect, stratify, and review outcomes data by sex and by sex and race to better understand and address disparities.

3. Training the Next Generation of Leaders in Women’s Health

3a) Building Interdisciplinary Research Careers in Women’s Health: From Bench to Bedside (BIRCWH): One of the first successes of our Center’s activity was a 2005 institutional K12 training grant to support junior faculty, from the NIH Office for Research on Women’s Health program called, Building Interdisciplinary Research Careers in Women’s Health (BIRCWH – Goldstein, PI; Kaiser, Program Director). This integrative BWH-based, Harvard-wide training program has engaged mentors and trainees from BWH as well as other Harvard-affiliated institutions, including BIDMC, MGH, DFCI, McLean Hospital and HSPH, among others – demonstrating leadership of BWH across Harvard in Women’s Health. Our program is entitled “Hormones and Genes in Women’s Health: From Bench to Bedside” (ORWH- NICHD K12 HD051959, 2005-2015), with an emphasis on translational research across the lifespan. We developed a model of mentorship and training to educate the next generation of “translational” investigators and create an identity for the field of “women’s health and gender biology” research. As a testament to our program’s effectiveness, many of our ‘graduating’ Scholars have successfully transitioned to other funding sources, including individual K and R01 awards. Many Scholars have continued to participate in our program’s activities because of the mentorship and networking

benefits they derive from the program. This program has also been successful in bringing together basic and clinical junior faculty from a broad range of disciplines, many of whom have subsequently forged new interdisciplinary collaborative research projects. As a further testament to the success of this training endeavor, it was selected for renewal for a second cycle and we are now in the seventh year of this K award program.

3b) Integrating Women's Health and Gender Biology into Studies of Health and Disease: Networking for Early and Senior Investigators: In Fall 2010, the Connors-BRI Center conducted a Workshop entitled "Integrating Women's Health and Gender Biology into Studies of Health and Disease: Networking for Early and Senior Investigators". The purpose of the Workshop was to bring together BWH trainees (postdoctoral fellows, junior researchers, residents), young faculty and senior faculty working in the areas of women's health and gender biology to showcase their respective accomplishments through formal presentations and a competitive poster session. The formal portion of the workshop began with a keynote address given by Dr. Betsy Nabel, BWH President on "Gender Biology in the Age of Personalized Medicine: Role the BWH Should Play". This was followed by the BIRCWH Scholars summarizing their current research projects and the impact of the BIRCWH program on their career development and their integration of women's health and gender biology into their research. In addition, a series of three senior faculty spoke on "Lessons from my journey: How we developed our careers in women's health and utilized resources in the BWH community", with the chosen speakers representing the areas of population sciences research, clinical research, and basic research. A total of 55 participants presented posters during the competitive poster session, and three were selected for awards.

3c) Global Women's Health Fellowship: As of July 1, 2012, the Global Women's Health Fellowship, initiated by RAC member Paula Johnson, MD (executive director of the Connors Center), is entering its sixth year and has graduated six Global Women's Health Fellows. This Brigham-based Fellowship is a Partners GME/PEC approved two-year training program in global women's health research. It offers fellows the time, space and seed funding to develop and apply their research skills and experience to significantly impact the health of women around the world. The Fellowship is a fully interdisciplinary endeavor that requires engagement of mentors with clinical, research and career development expertise to provide a solid mentoring team. Its curricular activities include educational seminar series, journal clubs, and research retreats. These resources are made open to a broader global health trainee community within Harvard. This past spring, the Fellowship hosted its second bi-annual research retreat, a work-in-progress workshop, where 10 trainees presented their research grants/manuscripts for review with senior faculty from BWH, MGH, HSPH, and HMS. Examples of research include: evaluating HPV vaccine roll-out strategies in South Africa; assessing barriers to health care for women and children displaced by hurricane Katrina; assessing preventing mother-to-child transmission of HIV (PMTCT) effectiveness in Botswana; understanding gender-based violence and reproductive health in displaced populations and conflict settings; examining epidemiological and economic impacts of CVD on women in India; and evaluating the integration of family planning and cancer screening into a comprehensive women's health primary care model in Rwanda. Five graduated fellows have gone on to pursue research in global women's health within BWH and HMS. Two Fellows received NIH early career grants within the first two years of joining the HMS faculty. Three of the six graduated fellows have established Global Women's Health programs with research components at leading academic medical centers (UCSF, BIDMC, and BMC). Our RAC has initiated discussions of how to better integrate the global women's health initiatives with the work of our BWH Connors-BRI Center, which is one of our goals in the coming academic year.

3d) Revamping Women's Neurology (Research and Clinical): Dr. Mary Angela O'Neal initiated The Women's Neurology Conference Series in September 2011, with the goal of bringing together clinicians and researchers

from several disciplines at the intersection of mutual interests, to foster education, improved patient outcomes, and clinical research. The conferences are held every one to two months; two-thirds are clinical-based conferences with presentations of interesting and instructive cases from our rich patient environment at BWH and one third research. Attendees are from the departments of neurology, psychiatry, obstetrics, anesthesiology, medicine/endocrinology, and radiology and are video-taped and available on-line. The series has increased awareness and interest in interdisciplinary care and research in women's neuroscience health, ultimately fostering interest of faculty and trainees to develop careers in these areas. Attendees also learn to think in terms of critical gender-based differences in phenotypic expression of neuropsychiatric disorders serving a key training and education mission. The current conferences are being evaluated for CME credit, and a request was submitted to start a new HMS course on Women's Neurology for Spring, 2013. Dr. Pennell, RAC member, is directing the research component in women's epilepsy research. New research collaborations with a focus on sex-specific issues in neuropsychiatric disorders include collaborations with Drs. Jill Goldstein (Women's Health (Medicine) and Psychiatry), Laura Miller (Psychiatry), and Page Pennell (Neurology and Women's Health), Emily Stern (Radiology) and Drs. Tom McElrath (OB/Fetal) and Linda VanMarter (Neonatology).

4. Year of Visibility 2011-2012: Over the last year our RAC initiated specific events to increase the visibility of the importance of a women's health and sex differences in medicine perspective at BWH. Although we initiated our Center by bringing together senior faculty in these arenas, we increased our visibility and engagement of junior faculty and trainees over the last year. This is represented by the events we held (described in above text) and our continued training foci. In addition, early on we developed the *Connors-BRI Center for Research on Women's Health and Gender Biology Website*. In order to accomplish our goal of fostering collaborative work encompassing women's health and gender biology, as well as developing shared resources, the Connors-BRI developed a website located on the BWH BRI home page: <http://www.brighamandwomens.org/research>. The website includes a summary of the Center's mission, departmental affiliations, and investigators and individual profiles of the leadership and RAC members, with information regarding affiliation, training, contact information, research keywords, and selected publications.

5. Alignment with the Mission of the BRI:

Following this is a schemata of the Connors-BRI activities over the past five years. It illustrates in a summary fashion how we have fostered innovative substantive work across BRI Centers and have had success in promoting career development and visibility. While we have described our various activities above each under one domain, all of our center activities are planned strategically by our RAC to be cross-cutting across multiple domains and multiple BRI centers. This is in part due to the fact that "women's health" and "sex differences research" is by its very nature interdisciplinary, but also due to the commitment of senior faculty at BWH across departments and fields of study. Measures of our success include: initiation of new collaborations across multiple substantive domains, new grants awarded, success of our trainees, establishing visibility and the importance of women's health and sex differences in medicine as fields of study at BWH and nationally, and the fact that the membership of our RAC has remained for the most part stable, given the interest and success of our Center in establishing "added value" to the work of our individual RAC members.

Connors/BRI Center for Women's Health and Gender Biology Response to BRI Research Center Evaluation

Connors BRI Center Activities (Categories 1,2 and 3 Below Reflect BRI Evaluation)

<i>BRI/Connors Center Activities</i>	1. Fostering Innovative Interdisciplinary Research Across BRI Centers						2. Enabling/ Promoting Career Development and Education	3. Outreach - Communicating and Fundraising
	Cancer Research Center	Cardiovascular, Diabetes, and Metabolic Disorders Research Center	Center for Human Genetics at the BRI	Infectious and Immunologic Diseases Research Center	Musculoskeletal Research Center	Neurosciences Research Center		
<i>Innovative and Cross-Disciplinary Science</i>								
Women's Health Research Retreat (Spring 2007)	x	x	x		x	x	x	x
Radcliffe Institute for Advanced Study Exploratory Seminar on Unexplored Sex Differences in Cardiovascular Disease (Dec. 2008)		x	x			x	x	x
Autoimmune & Sex Differences Exploratory Seminar (June, 2012)			x			x	x	x
Obesity & Sex Differences Event (Spring, 2013)		x	x		x	x	x	x
Neurosciences & Sex Differences (Fall, 2012)			x			x	x	x
Program Project Grant (CVD)		x	x				x	x
Bariatric Surgery, Brain & Sex Differences		x				x	x	
National Network of Depression Charter Member		x	x			x	x	x
Growing Research Advisory Committee		x	x	x	x	x	x	x
Connors-BRI Center for Research on Women's Health & Gender Biology Website with Researcher Profiles	x	x	x	x	x	x	x	x
Vitamin D workshop		x	x	x	x	x	x	
<i>Development of Shared Resources</i>								
Healthy Aging Cohort Development		x	x	x	x	x	x	x
Family Cohort Development		x	x	x	x	x	x	x
OurGenes Pilot at Fish Center for Women's Health	x	x	x		x			
Women's Learning Laboratory (WILL) at Fish Center		x	x	x	x	x	x	x
<i>Training and Education</i>								
Building Inter-Disciplinary Research Careers in Women's Health	x	x	x	x	x	x	x	
Integrating Women's Health and Gender Biology into Studies of Health and Disease: Networking for early and senior investigators (Nov. 2010)	x	x	x	x	x	x	x	
Global Women's Health		x	x	x	x	x	x	x
Revamping Women's Neurology/Research, Clinical	x	x				x	x	