MESSAGE FROM THE CHIEF

GREETINGS FROM THE MGH! I hope you’re enjoying the lovely Spring season.

In this issue of our newsletter, we shift our attention to the concept of ‘secondary prevention’ of Alzheimer’s disease and related dementias. It is a term that is used to identify and detect diseases in its earliest stages, before it is symptomatic. While we may still have some ways to go before we find the keys to the ‘primary prevention’ (stopping the development of the disease before it occurs) of Alzheimer’s disease, researchers are already embarking on clinical trials for individuals who may be at risk for the disease (see Shift Towards Prevention by Dr. Reisa Sperling on page 3). Check out our interview with Dr. Olivia Okereke (on page 4) for tips on healthy aging, and read more about our Center’s collaboration on the decades-long Nurses’ Health Study – one of the largest studies of women’s health that has generated important data on lifestyle factors and health. Our popular Guest Column returns with a fascinating insight by Jerry Flaherty (Vice-President of Medical & Scientific Affairs, MA/NH Chapter) on the Alzheimer’s Association’s advocacy on your behalf.

“Præventioni melius quam remedium” (‘prevention is better than cure’) is the famous quote attributed to the great 15th century Dutch humanist, Desiderius Erasmus. It is just as relevant to citizens of our fast-paced, globalized world as it was in the Renaissance Ages.
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Shift Towards Prevention
by Reisa A. Sperling, MD, MMSc

As 10,000 Baby-Boomers are now turning age 65 every day in the United States, there is a renewed sense of urgency to move towards prevention of Alzheimer’s disease dementia. President Obama signed the National Alzheimer’s Project Act (NAPA) into law last year, and the first goal announced by the medical working group this winter is to “Prevent and Effectively Treat Alzheimer’s Disease by 2025”. Currently, most Alzheimer’s clinical trials are conducted at the stage of mild to moderate dementia, when there is already significant loss of brain tissue. Although we all hope that the Phase III trials for bapineuzumab and solaneuzumab due to be reported early this fall are successful, there is a growing sense that we may need to treat this disease much earlier to have the best chance of slowing the clinical course. It may not be practical yet to begin “primary prevention” trials that will require many thousands of participants and take 10 or 20 years to complete. However, we do now have the tools to begin “secondary prevention” trials in individuals with Alzheimer’s disease beginning in their brain but who do not yet have any symptoms. These trials will be conducted in participants at-risk by virtue of their genetic predisposition or individuals who have evidence of early brain changes of Alzheimer’s disease on imaging or biomarker tests.

Several secondary prevention trial initiatives are already in the planning stages, including the Dominantly Inherited Alzheimer Network (DIAN) and the Alzheimer Prevention Initiative (API) clinical trials in participants with a known genetic risk factor for early onset familial Alzheimer’s disease, and the Anti-Amyloid Treatment in Asymptomatic Alzheimer’s disease (A4 trial). The A4 trial will identify clinically normal older individuals who have evidence of amyloid plaques on PET amyloid imaging and randomize them to receive an anti-amyloid treatment or placebo for three years to determine if we can prevent memory decline. We hope all of these trials will be funded to begin in 2013, and if so, the Massachusetts ADRC will be participating in both the DIAN and the A4 trials.

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News Flash

PET Amyloid Imaging Approved by FDA
by Keith A. Johnson, MD

The Food and Drug Administration (FDA) approved on April 10th a brain imaging method for individuals who are being evaluated for Alzheimer’s Disease (AD) or other causes of progressive cognitive impairment. The new method uses a drug called Amyvid (also known as Florbetapir or AV-45) along with Positron Emission Tomography (PET). MGH ADRC researchers were co-investigators for the clinical trial in which Amyvid was developed and have used this and other, similar PET methods for research purposes since 2005.

Amyvid PET can detect the brain β-amyloid plaques that are a major component of the damage occurring in patients with cognitive impairment due to AD and are always seen in AD patients at autopsy. β-amyloid is a type of protein that forms plaques in patients with AD and some other cognitive disorders. A negative Amyvid scan indicates few to no plaques and reduces the likelihood that any cognitive impairment is due to AD. A positive scan indicates that moderately to severely elevated numbers of β-amyloid plaques are present.

It is important to note that a positive Amyvid PET scan does not establish a diagnosis of AD, because the test may be positive in other disorders as well as in normal older individuals. While the FDA’s action is seen as a positive development for the fight against AD, particularly as this technology is increasingly useful in clinical trials of new drugs, the diagnosis of AD dementia should still occur in a clinician’s office where multiple factors require evaluation.

Dr. Janet Woodcock, director of FDA’s Center for Drug Evaluation and Research, said on the FDA website: “Many Americans undergo evaluations to try to determine the cause for a decline in cognitive functioning. Until now, the brain content of β-amyloid neuritic plaques could only be determined with a brain biopsy or examination of the brain at autopsy. This imaging agent is one tool to help physicians in the assessment of their patients by serving as an adjunct to other diagnostic evaluations.”

The value of PET scans and other AD diagnostic tests for predicting the future development of AD dementia is the subject of active investigation at the MADRC. It may someday be possible to use these methods not only to assist in diagnosis, but also to assess and tailor response to therapy.
A Conversation with Olivia I. Okereke, MD, MS

Dr. Okereke, you are a geriatric psychiatrist with diverse interests in a variety of mental health and public health issues. Tell us something about your background, and how you came to develop your passion in these fields.

**Dr. Okereke:** I was born and raised in Buffalo, New York, but have lived here in the New England area ever since college. I received an undergraduate degree in biology from Harvard University and then medical school degree from Yale. My college experiences as a research assistant in a cognitive neuroscience group during college, and later in an Alzheimer disease research unit through most of medical school, prompted an interest in the brain, behavior and cognition. Before then, I had not thought specifically about a career in these fields. Early on during my education, I had the great fortune of interacting with wonderful mentors, including a geriatric psychiatrist. These were people who inspired me as role models on how to provide excellent care to older people while conducting high-quality research. After medical school, I went on to train in psychiatry at Massachusetts General and McLean Hospitals and then to become a board-certified geriatric psychiatrist. Also, I have had a family member with Alzheimer disease. So, I can relate to the experiences of patients and families on a ‘ground-floor’ level, and I understand the sense of urgency about tackling this disease. Over the years, my interests have expanded to thinking more broadly about mental health in older people – cognitive functioning and emotional well-being and, of course, how to optimize these.

You have received a number of grants to pursue research in the roles of dietary/lifestyle factors and well-being in older men and women. Did you work with a specific clinical or community population group?

**Dr. Okereke:** Fortunately, even in the very challenging current funding environment, I have received several grants from the federal government and foundations, such as the Alzheimer’s Association. You mentioned dietary and lifestyle factors, and these are strong interests of mine. The reason is simple – diet and lifestyle habits, such as physical activity, are “modifiable”: They are things that people can actually change and can largely control on their own. They also appear to have substantial impacts on a variety of health aspects, such as cardiovascular disease. So, this suggests they could be essential – and empowering – tools for prevention of things like dementia or depression in older people. For example, last month at a scientific meeting, I presented our recent findings that diets high in omega-3s, mono-unsaturated fats (olive oil is a major source) or omega-3-rich fish were related to less decline in memory in a group of 6,000 older women whose cognition was tested over a 4-5 year time span.

The work I do involves data collected from very large groups of people – often tens or even hundreds of thousands of people – in what is known as a cohort study. This is typical of such epidemiologic research because you need to observe a lot of people, with a large number of characteristics and behaviors over a very broad range, in order to understand how these health and lifestyle factors relate to their long-term trajectories in things like cognitive function or mood. The particular cohort studies I’ve focused on include the Nurses’ Health Study and Women’s Health Study – which are both comprised entirely of women – and the Physicians’ Health Study, which is an all-male cohort study. The men and women in these cohort studies have participated for 20 years, 30 years or more – so, the vast majority of them are now in their senior years. I can only...
begin to describe how extraordinary their dedication is and how important their contributions to knowledge of human health have been! I feel lucky to be a part of this work.

Have you found the keys to longevity, vitality and happiness?

Dr. Okereke: Well, certainly, I would have told people by now, if so! All kidding aside, I think it is important to think first about what these things really mean, and where these ideas come from. There was a time when people were mostly concerned with number of years lived, or “lifespan.” Until recently, men and women did not live very long anyway, so there weren’t too many people around to inform us on the subject. Then, everyone increasingly realized it isn’t just a matter of how long we live, but how vital and robust those older years are – something that we now term “healthspan.” But what about happiness? It would seem that, without this, even a physically robust 90-year-old would not feel he has a good quality of life. So, with regard to “the keys to longevity, vitality and happiness”: while achieving any one of these may be within reach, what we really need to think about is how to help people to achieve all three at the same time. There is an emerging field devoted to this concept – sometimes called “successful aging” – and I have a lot of interest in this. My Nurses’ Health Study colleagues and I have recently reported on this: for example, maintaining regular physical activity and healthy weight during mid-life years may increase the likelihood of being a “successful ager.”

You are also an active ‘citizen’ on a number of committees. What are they? Tell us about your engagement with these groups.

Dr. Okereke: That’s right. I’m a member of the Medical and Scientific Advisory Committee and Board of Directors of the Alzheimer’s Association Massachusetts and New Hampshire Chapter. In 2008, I chaired the Chapter’s Annual Meeting and awards celebration. As part of my involvement with this wonderful organization, I regularly participate in Association events and community-based senior health education events, including outreach and education for minority elders. It’s really a great way to ensure that the knowledge and skills I have been privileged to attain are translated back to the community. Since 2004, I’ve done four presentations at the annual Alzheimer’s professionals’ conference, sponsored by the Alzheimer’s Association Chapter, and will be back again this year. This is a great way to disseminate the latest science to care professionals across our region. I’ve also participated in the Walk to end Alzheimer’s as a member of the MADRC Greater Boston team. 2011 was my second consecutive year as a member of the “Elite Feet” – an individual raising $1,000–$3,000. Hopefully, this year will be a three-peat!

What advice would you give to a student, particularly someone from a minority community, who aspires to achieve similar scholastic and professional success in your field?

Dr. Okereke: It’s so important to stay focused on one’s goals. Students today are dealing with so many distractions – especially the digital ones: Social media, texting and so on – that my peers and I never had to contend with! I think some of the most important things are to make studying and scholastic success a priority and to keep strong connections with the people who will help you stay on that path - parents, good friends, teachers and other positive influences. While, it’s also important to maintain broad interests as much as possible - sports, music, clubs - it’s really key to know when and how to focus. Teachers and parents can help with that. Role models are important for all children, but sometimes even more so for minority children, as it can be incredibly important for them to see successful people who look like them. Finally, my advice is get advice! As a student and to this very day, whenever I have professional challenges, I find it extremely helpful to talk with someone I admire and to get input: whether that person had dealt with similar problems and, if so, how he or she handled them. That would be a great lifelong habit for a student to cultivate.

Lastly, tell us something about your personal interests that most of us do not know, and that you’re willing to share!

Dr. Okereke: Sure! One thing that many of my colleagues here at the MADRC know is that I perform every year in concerts with the Harvard-Radcliffe Chorus. I started choral singing as a college student – really, on a lark. It seemed like a fun thing to do because my roommate and other friends sang in various groups. But it’s really become a big part of my life over the years. In addition to singing alto, I play the piano. I just really love music. Hmmm … maybe being active in music might turn out to be one of those “keys” to successful aging? ♦
Perspectives from the Alzheimer’s Association

By Gerald Flaherty

I can think of no more exciting time than the present to be engaged in the work of the Alzheimer’s Association and partners such as the Mass. ADRC. My view is shaped largely by 23 years at the Association. But it’s also influenced by my prior work on Alzheimer’s issues as an analyst and legislative aide in our state Senate and my role as an Alzheimer’s family caregiver, two experiences that led in a very sequential way to my work at the Association. At no other time have there been so many opportunities, both for dementia care coordination (in particular as a consequence of the Affordable Care Act) and for early disease recognition, intervention and prevention. Nor has there been such an extraordinary level of collaboration among scientists in the local, national and international research communities.

“I think the motivating spirit of collaboration among all of us engaged in this work is reflected in an excerpt from a letter written by neurologist A.R. Luria to Oliver Sacks, quoted in Dr. Sacks’ The Man Who Mistook His Wife for a Hat and Other Clinical Tales: “Man does not consist of memory alone. He has feeling, will, sensibility, moral being. It is there you may touch him, and see a profound change.”

Conversely, there has never been more need for support of our collective efforts. Alzheimer’s disease is the only cause of death in the top 10 in the U.S. that cannot be prevented, effectively slowed, or cured. The Alzheimer’s Association estimates the cost of dealing with Alzheimer’s disease during the next 40 years at a staggering $20 trillion. By 2050, as many as 16 million Americans will have the disease, creating an enormous strain on families, the health care system and the federal budget.

National Alzheimer’s Project Act (NAPA)

To address these challenges, Congress unanimously passed the National Alzheimer’s Project Act, with the strong support of the Alzheimer’s Association and its advocates. NAPA was signed into law by President Barack Obama in January, 2011.

This new law created an Alzheimer’s Advisory Council, composed of leaders in research, care, services, local government and nonprofit associations, and required the development of a National Alzheimer’s Plan. In April this year, the Advisory Council agreed on a set of recommendations for inclusion in the National Alzheimer’s Plan, described by Alzheimer’s Association President and CEO Harry Johns as “a blueprint to address the Alzheimer’s crisis now and in the longer term.”

In support of the National Alzheimer’s Plan, more than 700 advocates from across the country gathered in Washington late in April to meet with members of Congress during the 2012 Alzheimer’s Association Advocacy
Forum and press for the $100 million commitment to Alzheimer’s research and caregiver support services included the President’s FY2013 budget request to Congress.

The Alzheimer’s Association is working with the Obama Administration to ensure the full recommendations of the Advisory Council are included in the final draft of the National Alzheimer’s Plan. The federal government expects to have a finalized plan incorporating much of this feedback by late spring.

**Exploring Alzheimer’s prevention**

The Alzheimer’s Association Research Roundtable is made up of more than 130 scientists from the pharmaceutical industry, academia, the NIH, the FDA, and the European Medicines Agency. At their October 2011 meeting in Washington, these scientists shared their perspectives on conducting prevention trials in Alzheimer’s disease.

Chaired by Drs. Reisa Sperling of Brigham and Women’s Hospital and the Mass. ADRC and Robert Brashear of Janssen Alzheimer Immunotherapy, the group looked to other fields where prevention trials have succeeded, such as in cardiovascular disease, to learn how clinical trial design and other factors contributed to that success. Since brain changes in Alzheimer’s begin years before symptoms such as memory loss occur, researchers have a substantial window of opportunity to intervene to slow or stop the physiological processes causing brain change, and to prevent the development of Alzheimer’s symptoms that are eventually life altering (see Alzheimer’s Association Update, Volume 8/Issue 1/January 2012; a complete report on this meeting will appear in a future issue of *Alzheimer’s & Dementia*).

In March, the Alzheimer’s Association also awarded its largest ever research grant - $4.2 million - to the Dominantly Inherited Alzheimer’s Network, established by NIA in 2008 and conducted by an international network of 11 leading research centers, including the Mass. ADRC. The goal is to move forward more quickly with innovative drug and biomarker trials in people with genetically based, young-onset Alzheimer’s disease. The Association believes this project has the potential to dramatically accelerate the pace of discovery of treatment and prevention strategies for Alzheimer’s.

At the 2011 Alzheimer’s Association International Conference, DIAN researchers presented the clinical, cognitive, MRI, PET, cerebrospinal fluid, and blood biomarkers from the first group of DIAN participants. They reported data from the initial 150 enrollees (the registry will eventually total 400 individuals). The results suggest that brain chemistry and imaging changes can be detected at least 10 years and perhaps up to 20 years before the expected age of onset of Alzheimer’s. According to the researchers, the results demonstrate the feasibility and promise of performing Alzheimer’s prevention studies in this special population. And by studying Alzheimer’s in rare individuals destined to get the disease because of their genes, we can learn more about the vast majority of people with Alzheimer’s.

Other initiatives aimed at stopping Alzheimer’s before its damage cascades through the brain include the recent study of cell-to-cell transmission involving tau protein that starts in the entorhinal cortex. This exciting work is being done in mice at two sites, including the Mass. ADRC under the direction of its chief, Dr. Bradley Hyman.

But even if drugs based on current theories work, we will need more options. Experts don’t expect a “magic bullet,” but something more like an AIDS or chemo “cocktail,” and any specific drug’s effectiveness may vary by individual biology and tolerance. While prevention strategies are not yet proven, researchers are also optimistic about the potential effect of modifiable risk factors. The best evidence points to keeping physically active, controlling heart disease risk factors such as high blood pressure and cholesterol, excess weight, Type 2 diabetes and smoking, and being intellectually and socially active.

**Gerald Flaherty is Vice President for Medical & Scientific Programs at the Alzheimer’s Association, Massachusetts/New Hampshire Chapter.**

The Alzheimer’s Association is the leading voluntary health organization in Alzheimer research, care and support, having granted over $292 million to more than 2,000 research projects, including many conducted at the Mass. ADRC.

You can get updates on the National Alzheimer’s Project Act at [alz.org/napa](http://alz.org/napa) and follow the NAPA conversation on Twitter through hash tag #AlzForum or through our national FaceBook page at [facebook.com/actionalz](http://facebook.com/actionalz).
Some Thoughts from Our Participants

Since 1998 my wife Florence and I have been volunteers for a longitudinal program at Massachusetts General Hospital which is investigating how the brain changes as people grow older. And as volunteers, we consider it to be a privilege and a rewarding experience to be part of a team that includes so many dedicated and knowledgeable doctors, nurses, technicians, coordinators, and students who are making such important contributions to medical science and mental health.

Florence and I also believe that we have benefited greatly from this study. First of all, we have been made very conscious of how imperative it is to keep active both mentally and physically as we grow older. The many cognitive and memory tests that were part of the program each year gave us the incentive to engage in activities that would slow down or prevent mental decline as the years passed by. Secondly, we learned a great deal about the techniques of brain research used by the researchers. These techniques included MRIs, fMRIs, PET Scans and a painless spinal tap.

Lastly, when we were asked to donate our brains to the Massachusetts General Hospital for continued research, we both consented because our long experience as volunteers helped us to understand how important this donation would be.

Fred and Florence Perkins
March 26, 2012
Watertown, MA

As children growing up we learned that the word research was a synonym for travesty. Because of the Tuskegee Project no self-respecting African-American would voluntarily enter a research program. Because of the stigma attached to the word ‘research’, decades passed without accurate input of African-American data. That also meant that the conclusions of the research were flawed because it did not truly portray the population. Without that African-American participation, minorities did not always receive the benefits of the study that they might have.

It is humbling to know that these studies that we are participating in – help the elderly population prolong their life expectations. What we find out in these studies are the reasons humans evolve as they do. The health care disparity between whites and other minorities is now a great problem. We continue to sign up for these research projects now, because we feel that research, if done properly, can and should benefit all people.

Helen Young and Barbara Gumes
March 25, 2012
Boston, MA
Greetings from the Clinical Coordinator

To our Memory Study participants:

Although it was a mild winter, it’s nice to have spring here … with summer right behind. The longer days and warmer weather seem to bring along a sense of wanting to do things, to be more active, to start anew.

All of us here are constantly amazed by all the varied things you do. We love to hear stories of events you’ve had with family and friends, of trips you’ve taken, of activities you’re involved in. And we’re inspired by your day-in and day-out commitments that fill up your daily life. You take care of grandchildren … go to the gym … work … volunteer … walk … go to church … cook … garden … belong to organizations … the list goes on and on. Often when I go into the waiting area, I see you reading, knitting, doing crossword puzzles, talking with Kelly or other study participants. You so generously give us hours of your time and the personal touch makes it even more enjoyable for us.

Research suggests that having social ties and being physically active may contribute to “successful aging.” It sounds so simple but takes time and perseverance. I commend you all for finding ways to make your life richer and more fulfilling. It brings to mind some words from Henry Wadsworth Longfellow:

“For age is opportunity no less
Than youth itself, though in another dress.
And as the evening twilight fades away
The sky is filled with stars, invisible by day.”

Enjoy the days of spring and summer! And thank you for spending some of those days with us in the Memory Study!

Jeanette Gunther
Clinical Coordinator

Announcing A New Centralized Telephone Number For Inquiries About Our Studies!

Interested in learning more about research studies and how you can get involved? Patients, caregivers, family members, and healthy volunteers can call Caroline Sullivan at 617-643-5200 to learn about all of the exciting research opportunities we have going on at the MADRC! ♦
The Nurses’ Health Study
by Francine D. Grodstein, ScD

The Nurses’ Health Study (NHS), which is based at Brigham and Women’s Hospital, is one of the largest studies of women’s health. The ongoing NHS began in 1976, with 120,000 female nurses, most of whom still participate in the study. Every two years, the participants receive a mailed questionnaire regarding their lifestyle and health, enabling researchers to evaluate how lifestyle can influence health. For example, researchers from the Nurses’ Health Study were among the first to identify an increase in cardiovascular disease among those with high intake of trans-fatty acids; this led to the current requirement in the US to label the trans-fatty acid content of all foods, and to many efforts to reduce the levels of trans-fat in our food supply.

In 1995, Nurses’ Health Study researchers, led by Dr. Francine Grodstein (a member of the MADRC advisory board), began to track cognitive function in the oldest participants of the Nurses’ Health Study – a total of 20,000 women age 70 years and older. The women receive regular cognitive tests by telephone. Some of the major findings from this research include a report that regular physical activity, including just walking for exercise, can reduce the likelihood of cognitive decline with aging. Many of the nurses in the cohort have provided blood samples too (they just had a colleague draw their blood, and then mailed their tubes of blood to Brigham and Women’s Hospital!). Nurses’ Health Study and MADRC researchers have collaborated on research trying to find biomarkers in early life that predict risk of memory impairment later in life, and have already shown that measuring levels of amyloid beta in plasma – even at relatively young ages – might eventually help identify people who are at risk of developing memory disorders. We hope that by finding high-risk patients at younger ages, we can intervene to maintain memory at earlier stages, before irreversible degeneration has occurred in the brain.

Dr. Grodstein’s team has worked closely with many MADRC staff and faculty in developing this research, including inviting local NHS participants to come to the MADRC for evaluations. Currently, the NHS and MADRC are working together on a new project to try to collect brains from NHS participants after they die. By linking together all the health and lifestyle information the nurses have provided for the past 35 years with detailed information directly from their brains, we will try to discover why some people age without any memory problems while others have more trouble.

Francine D. Grodstein, ScD

Some of the major findings from this research include a report that regular physical activity, including just walking for exercise, can reduce the likelihood of cognitive decline with aging.
25th Year of a Time-Honored Center Tradition

by Liang Yap, PhD

The Massachusetts Alzheimer’s Disease Research Center and the Boston University Alzheimer’s Disease Center have traditionally organized an annual research poster session that is held on the Massachusetts General Hospital campus, and this year was no exception. In fact, 2012 marks the Silver Anniversary of what has become our Center’s ‘the Rites of Spring’ tradition. This year, we invited the Harvard NeuroDiscovery Center to co-sponsor the event. In anticipation of a larger-than-usual turnout, the Joseph B. Martin Conference Center at Harvard Medical School was selected as the new venue of what is now a highly-anticipated and fun networking event.

55 teams of local-area investigators showcased their cutting-edge research in the basic and translational sciences in the beautiful Rotunda space of the Martin Conference Center on February 8, 2012. While the majority of the researchers were from the Harvard and Boston University communities, posters were also submitted by teams from MIT, Brandeis University, University of Massachusetts and Pfizer, Inc.

Piping-hot coffee and a delicious array of breakfast items kept the stimulating conversations flowing. Bliss! What a wonderful way to build bridges across the research community.

This way to the poster session! ... Here’s what we found!

Posters in the rotunda space

Even the atrium walkway was filled!
Teas & Strengthening Ties with the Asian Community…
by Liang Yap, PhD

WE PRODUCED a successful 6-week educational program on Alzheimer’s Disease, Parkinson’s Disease and Stroke for health care providers who work with the local Asian communities in the Fall of 2011. Building on the decade-long partnership that our Center has established with the Greater Boston Chinese Golden Age Center, we collaborated with Dr. Albert Y. Hung of the MGH Movement Disorders Unit to create a culturally-sensitive program that included guest lecturers from the MGH Stroke Service, MGH Physical Therapy/Occupational Therapy Services, MGH Social Services and the Spaulding Rehabilitation Hospital.

Close to 50 staff personnel from 13 provider organizations attended the training series, and the importance of engaging under-represented minorities in research resonated with the audience’s keen awareness of the debilitating impact of these diseases in their own communities. We were thrilled to learn that post-training ‘tests’ and surveys indicated significant gains in overall knowledge, and attendees had requested for more programs that will enhance their care delivery skills with the elderly.

Stay tuned for similar community events! ✶