HHS and 2013 AD Update

The U.S. Department of Health and Human Services (HHS) on June 14 released the *National Plan to Address Alzheimer's Disease: 2013 Update*, a follow-up to the initial plan released in May 2012. The update reflects progress over the last year, as well as new and revised action steps. The original plan, ordered under the 2011 National Alzheimer's Project Act, includes efforts to: identify ways to prevent and effectively treat Alzheimer disease (AD) by 2025; enhance care for AD patients; expand support for people with dementia and their families; improve public awareness; and track data to support these efforts. The plan was developed collaboratively by experts in aging and AD from federal, state, private, and nonprofit organizations.

The update included highlights of achievements over the past year. Among these were: (1) The AD Research Summit 2012: Path to Treatment and Prevention, a meeting at which the National Institutes of Health brought together international experts to develop recommendations on how best to advance research; (2) Grants provided by the Health Resources and Services Administration issued to train >10,000 health care providers on topics from dementia diagnosis to effective behavior management for people with dementia and their caregivers; and (3) Launch of www.alzheimers.gov, an HHS Web site designed to increase public awareness and connect individuals with diagnoses to additional information and support resources.

The updated plan also identifies additional steps that HHS and its partners will take. These include: (1) Development of a unified AD training curriculum for primary care providers to help deliver high-quality dementia care, including strategies for best interventions to reduce hospitalization and emergency department use among those with AD; (2) Enhanced detection of elder abuse and neglect through aging networks and program providers who work with the Alzheimer population, including demonstration grants to legal services groups who assist families and communities affected by AD; and (3) Development of an expanded Dementia Capability Toolkit for state and local health networks who provide dementia services in their communities.

The *National Plan to Address Alzheimer's Disease: 2013 Update*, is available at http://aspe.hhs.gov/daltcp/napa/NatlPlan2013.shtml.

U.S. Department of Health and Human Services

PET in Depression Therapy Selection

On June 12, the National Institutes of Health (NIH) issued a press release reviewing the results of an NIH-funded study in which baseline PET imaging in depressed patients indicated whether antidepressant medication or psychotherapy would provide the most effective treatment. The study, "Toward a neuroimaging treatment selection biomarker for major depressive disorder," by McGrath from Emory University (Atlanta, GA) and a consortium of psychiatric and neurologic investigators, was published in *JAMA Psychiatry* online on the same day as the NIH release.

"Our goal is to develop reliable biomarkers that match an individual patient to the treatment option most likely to be successful, while also avoiding those that will be ineffective," explained Helen Mayberg, MD, a professor at Emory and senior author of the study. Determining whether a specific patient with depression would best respond to psychotherapy or medication is currently based on informed trial and error. In the absence of objective guidance that could predict improvement, clinicians typically try a treatment that they (or the patient) prefer for a short period to determine whether it works. As a result, only about 40% of patients achieve remission from depression following initial treatment.

The study included men and women (18–60 y old) with currently untreated major depressive disorder. All patients underwent both ^{18}F-FDG PET imaging to assess glucose metabolism and high-resolution T1-weighted MR imaging. Imaging results were coregistered. Patients were then randomly assigned to 12 wk of treatment with either escitalopram oxalate or 16 sessions of cognitive behavior therapy (CBT). The goal was to find an imaging biomarker for these 2 potential first-line treatments. The ideal imaging biomarker in this instance would be a brain activity pattern that distinguishes escitalopram remitters from both escitalopram nonresponders and CBT remitters while also distinguishing CBT remitters from both CBT nonresponders and escitalopram remitters.

Of 65 patients who completed the protocol, 38 patients with clear outcomes and usable PET data were included in the primary analysis: 12 remitters to CBT, 11 remitters to escitalopram, 9 nonresponders to CBT, and 6 nonresponders to escitalopram. Activity in one specific brain area emerged as a pivotal predictor of outcomes from the 2 treatments. Right anterior insula hypometabolism (relative to whole-brain mean) was associated with remission to CBT and poor response to escitalopram, whereas insula hypermetabolism was associated with remission to escitalopram and poor response to CBT. "If these findings are confirmed in follow-up replication studies, scans of anterior insula activity could become clinically useful to guide more effective initial treatment decisions, offering a first step towards personalized medicine measures in the treatment of major depression" said Mayberg.

National Institutes of Health
JAMA

SNMMI on Reimbursement for Radiopharmaceuticals

On June 10, at its 2013 Annual Meeting in Vancouver, British Columbia, SNMMI released a position statement on adequate and appropriate reimbursement for nuclear medicine and molecular imaging procedures. The statement included common questions, general background, and the society's consensus position on both current problems and coming challenges in reimbursement for radiopharmaceuticals.

Among the key questions that SNMMI indicated as deserving close consideration were: (1) How are nuclear medicine and molecular imaging radiopharmaceuticals currently reimbursed in the hospital outpatient setting? (2) Why is the nuclear medicine and molecular imaging industry hesitant to invest in new technologies for the creation of domestic supply of ^{99}Mo, the parent isotope of ^{99m}Tc? and (3) How does the conversion of ^{99}Mo produced with highly-enriched uranium (HEU) to ^{99}Mo produced with non-HEU impact reimbursement rates for nuclear medicine and molecular imaging procedures? In addition to reviewing current difficulties faced in adequate reimbursement, the statement looked to a near future in which the United States will need to secure new, reliable supplies of ^{99}Mo produced with non-HEU. The SNMMI position statement is available at http://interactive.snm.org/index.cfm?PageID=12723.

SNMMI

CASNM Annual Meeting

The Chinese American Society of Nuclear Medicine (CASNM) held its annual meeting on June 11 in Vancouver, Canada, during the SNMMI Annual Meeting. More than 100 participants, including delegates from the Chinese Society of Nuclear Medicine (CSNM), attended the dinner event. CASNM was established in 1977 as a nonprofit, nonpolitical organization. The membership of CASNM is not restricted to practitioners living in North America and has additional participants from Europe, Australia, Asia, and elsewhere. The current president of CASNM is Xiao-Feng Li, MD, PhD, from the University of Louisville (KY), and the secretary/treasurer is Hancheng Cai, PhD, from Wayne State University (Detroit, MI).

At the Vancouver event, the 2013 CASNM Lifetime Achievement award was presented to Hank F. Kung, PhD, from the University of Pennsylvania (Philadelphia). Among his many scientific achievements is development of the U.S. Food and Drug Administration–approved amyloid imaging agent florbetapir (^{18}F AV-45).

CASNM Koon Yan (Chris) Pak Young Scientist awards went to Zhibo Liu from the University of British Columbia (Vancouver), for "Kit ^{18}F-radiolabeling based on B–F bond formation"; Min Zhou, PhD, from the MD Anderson Cancer Center (Houston, TX), for "Radioactive ^{64}Cu-CuS nanoparticles and near-infrared laser irradiation for combined radiotherapy and phothothermal therapy: in-vivo feasibility study in animal models", and Zhenhua Hu, PhD, from the Chinese Academy of Sciences, for "Endoscopic Cerenkov luminescence imaging of nude mice with gastric tumors." Zhen Cheng, PhD, from Stanford University (CA) also highlighted the achievements of physicians and scientists of Chinese origin in the last year.

During the past year, CASNM has taken several steps toward strengthening the organization and expanding its activities. The relationship between CASNM and CSNM is also growing. Yongxue Zhang, MD, reviewed the development of CSNM and introduced its attendees. Rui An, MD, on behalf of CSNM, introduced the First Global Conference of Chinese Professionals in Nuclear Medicine and Molecular Imaging, to be held November 1–3, 2013, in Xiamen, China, sponsored by CSNM, CASNM, and other nuclear medicine and molecular imaging associations. This conference is expected to be one of the largest nuclear medicine and molecular imaging meetings for Chinese professionals.

The 2014 CASNM annual meeting will be held in conjunction with the 61st SNMMI Annual Meeting in St. Louis, MO. For more information about CASNM, see www.casnmmi.org.

Xiaoyuan Chen, PhD
Bethesda, MD
Xiao-Feng Li, MD, PhD
Louisville KY

Each month the editor of Newsline selects articles on diagnostic, therapeutic, research, and practice issues from a range of international publications. Most selections come from outside the standard canon of nuclear medicine and radiology journals. These briefs are offered as a monthly window on the broad arena of medical and scientific endeavor in which nuclear medicine now plays an essential role. The lines between diagnosis and therapy are sometimes blurred, as radiolabels are increasingly used as adjuncts to therapy and/or as active agents in therapeutic regimens, and these shifting lines are reflected in the briefs presented here. We have also added a small section on noteworthy reviews of the literature.

PET and Optical Imaging in Ovarian Cancer

Liu et al. from Princess Margaret Cancer Centre (Toronto, Canada) reported in the May 25 issue of *Theranostics* (2013;3:420–427) on a clinical strategy for ovarian cancer imaging using a novel probe including 3 parts: (1) a multimodal porphyrin, pyropheophorbide-α; (2) a folate-receptor targeting molecule; and (3) a pharmacomodulation peptide linker conjugating pyro to folate. When labeled with ^{64}Cu, the result is a probe that allows sensitive PET and optical imaging of primary and micrometastatic ovarian cancer at all stages of diagnosis and treatment. The authors described the development of the probe, as well as in vitro studies in human ovarian cancer cells and in vivo in serous ovarian cancer xenografts. With both PET and fluorescence imaging, the probe identified folate receptor–positive xenografts as well as experimental micrometastases in peritoneum. The ability to pinpoint metastatic deposits has promise for more complete debulking. The probe demonstrated both optical imaging and optical "tuning" capabilities, allowing tumor detection at multiple wavelengths. The authors concluded that the probe is a "novel clinical imaging strategy that could substantially improve the prognosis of patients with ovarian cancer by allowing pre-, post-, and intraoperative tumor monitoring, detection, and possibly treatment throughout all stages of therapy and tumor progression." They added that the probe "has the capacity to act as a 'one size fits all' probe for detecting and monitoring serous ovarian cancer."

Theranostics

PET/MR in Adult Gliomas

In an article e-published on June 16 ahead of print in the *Journal of Neuro-Oncology*, Berntsson et al. from Uppsala University (Sweden) reported on correlations between perfusion/diffusion MR imaging and ^{11}C-methionine (^{11}C-MET) PET in preoperative evaluation of suspected adult low-grade gliomas. The study included 24 such adults who underwent ^{11}C-MET PET as well as perfusion and diffusion MR imaging. After surgery, histology confirmed diagnoses in 23 patients (18 grade II and 5 grade III gliomas). Automated coregistration of MR and PET images allowed measurement of maximum relative cerebral blood volume ($rCBV_{max}$) and minimum mean diffusivity in tumor areas with highest ^{11}C-MET uptake on PET. In all 23 tumors, a well-defined area of highest tracer uptake was visible. Regions with $rCBV_{max}$ corresponded with these regions in all tumors, and regions with minimum mean diffusivity corresponded with hotspot regions in 20 tumors. The authors concluded that "Taken into account the difficulties of measuring perfusion abnormalities in nonenhancing gliomas, this study demonstrates that coregistered MET PET and perfusion MR imaging facilitates the identification of regions with $rCBV_{max}$." They added that the "lack of a clear positive correlation between tumor metabolism in terms of MET uptake and tumor vascularity measured as $rCBV_{max}$ suggests that combined perfusion MR/PET provides complementary baseline imaging data in these tumors."

Journal of Neuro-Oncology

PET/CT and Statin Therapy

Tawakol et al. from the Massachusetts General Hospital and Harvard Medical School (Boston, MA) reported on May 30 ahead of print in the *Journal of the American College of Cardiology* on a multicenter feasibility study using ^{18}F-FDG PET/CT to determine whether high-dose statin treatment results in greater and more rapid reduction in atherosclerotic inflammation than low-dose therapy. The study included 83 adults with risk factors for or established atherosclerosis not currently taking high-dose statins. Participants were randomized to either 10 or 80 mg atorvastatin/d and underwent ^{18}F-FDG PET/CT imaging of the ascending thoracic aorta and carotid arteries at baseline and 4 and 12 wk after initiation of therapy. Target-to-background ratios (TBRs) of tracer uptake within the artery wall were assessed. A total of 67 participants completed all of the imaging components of the study. The authors found that at 12 wk TBRs in the index vessel were significantly reduced from baseline with the higher statin dose but not with the lower dose. This difference was seen as early as 4 wk after initiation of therapy, at which point the higher dose had resulted in a 12.5% reduction in TBRs compared with a 6.4% reduction with the lower dose. These reductions are likely to represent changes in atherosclerotic plaque inflammation. The authors concluded that ^{18}F-FDG PET imaging "may be useful in detecting early treatment effects in patients at risk or with established atherosclerosis."

Journal of the American College of Cardiology

^{213}Bi-RIT and Hypoxic Tumors

In an article e-published on May 28 in *PLoS One*, Wulbrand et al. from the Technische Universität München

(Germany) reported on an in vitro study of the characteristic effects of a ^{213}Bi-anti-epidermal growth factor receptor (EGFR) immunoconjugate on hypoxic and normoxic tumor cells. The study focused on CAL33 cells (derived from squamous cell carcinoma) that were either incubated with a ^{213}Bi-anti-EGFR monoclonal antibody (MAb) or irradiated with photons with an energy of 6 MeV under both hypoxic and normoxic conditions. Cell oxygenation and cell survival were analyzed. CAL33 cell survival and viability decreased after increasing concentrations of ^{213}Bi-anti-EGFR MAb as well as after increasing photon radiation. However, survival and viability of normoxic cells were significantly lower than hypoxic cells after photon radiation. Cell death was independent of hypoxic status with ^{213}Bi-anti-EGFR MAb. The authors concluded that α-particle emitting ^{213}Bi-immunoconjugates eradicate hypoxic tumor cells as effectively as normoxic cells and that "^{213}Bi-radioimmunotherapy seems to be an appropriate strategy for treatment of hypoxic tumors."

PLoS One

Brown Fat and Cold-Induced Thermogenesis

Chen et al. from the National Institutes of Health (Bethesda, MD) reported on June 18 ahead of print in the *Journal of Clinical Endocrinology and Metabolism* on a study designed to illuminate the role of brown adipose tissue (BAT) activation in cold-induced thermogenesis (CIT). The study included 24 healthy volunteers (14 men, 10 women) who first underwent ^{18}F-FDG PET imaging after an overnight stay in a room maintained at either 24°C (n = 12) or 19°C (n = 12). After 36 h, participants crossed over to the alternative temperature setting and otherwise identical conditions, followed by a second PET scan. Tracer uptake at the 2 ambient temperatures was used to assess BAT activity in a 3D region of interest in the upper torso by comparing the uptake at the 2 temperatures, and energy expenditures were assessed. Exposure at 19°C resulted in increased energy expenditures. Additional analyses indicated that a difference in BAT activity, age, and sex were independent contributors to individual variability in CIT. The authors noted that this study is the first to show a spectrum of BAT activation among healthy adults during mild cold exposure, a spectrum not previously recognized by conventional PET or PET/CT assessment. Their data suggest that a small reduction in ambient temperature—within the range of climate-controlled buildings—is sufficient to increase human BAT activity, so that the "enhancement of cold-induced BAT stimulation may represent a novel environmental strategy in obesity treatment."

Journal of Clinical Endocrinology and Metabolism

^{99m}Tc-GSA SPECT/CT and Liver Lobe Function

In an article published in the June 7 issue of the *World Journal of Gastroenterology* (2013;19:3217–3225) Sumiyoshi et al. from the Kochi Health Sciences Center (Japan) reported on a study using ^{99m}Tc-galactosyl human serum albumin (^{99m}Tc-GSA) SPECT/CT fusion images to evaluate functional differences in the 2 liver lobes of noncirrhotic patients. The study included the records of 30 noncirrhotic patients who had undergone ^{99m}Tc-GSA SPECT/CT and who had either an extrahepatic tumor or a small intrahepatic tumor. Percentage volume and percentage function of each liver lobe were calculated, along with other functional and volume parameters. The median percentage volume and percentage function were 62.6% and 67.1%, respectively, in the right lobe, and 31.0% and 28.7% in the left lobe. The median function-to-volume ratios of the right lobe were significantly higher than those of the left lobe. These function-to-volume ratios showed significant correlations with the left-to-right portal vein diameter ratio in both lobes. The authors concluded that ^{99m}Tc-GSA SPECT/CT fusion imaging "demonstrated that the function of the left lobe was significantly decreased compared with that of the right lobe in noncirrhotic livers." They added that these results suggest that postsurgical remnant liver function and the tolerable extent of hepatectomy might be dependent on the region of the hepatectomy; i.e., that residual liver function might be lower after right-sided hepatectomy than left-sided hepatectomy, even if the resected volumes were equivalent.

World Journal of Gastroenterology

PET, MR, and Early Aβ Assessment

Doré and a consortium of Australian researchers reported in the May 27 issue of *JAMA Neurology* (2013;27:1–9) on a longitudinal analysis of the relationships among β-amyloid (Aβ) deposition, gray matter atrophy, and memory impairment in cognitively healthy individuals and in individuals with Alzheimer disease (AD). The study included 93 healthy elderly controls and 40 patients with AD from the Australian Imaging, Biomarkers, and Lifestyle Study of Aging. All participants underwent ^{11}C-Pittsburgh compound B (^{11}C-PiB) PET and MR imaging and neuropsychologic evaluation. At 18- and 36-mo follow-up, 54 of the controls underwent repeat scans as well as repeat neuropsychologic evaluation. The researchers saw a significant reduction in cortical thickness in the precuneus and hippocampus associated with episodic memory impairment in the PET-positive controls compared with the PET-negative group. Cortical thickness was also negatively correlated with neocortical tracer uptake in the PET-positive group. Analysis over time showed a faster rate of gray matter atrophy in the temporal lobe and the hippocampi in the PET-positive group. The authors concluded that "in asymptomatic individuals, Aβ deposition is associated with gray matter atrophy and memory impairment," with earliest signs of atrophy detected in the hippocampus, posterior cingulate, and precuneus regions. As disease progressed, even over the relatively short period of this study, this atrophy became more extensive in the temporal lobes. The authors suggested that these findings "support the notion that Aβ deposition is not a benign process and that interventions with

anti-Aβ therapy at these early stages have a higher chance to be effective."

JAMA Neurology

^{18}F-FDG PET/CT and Merkel Cell Carcinoma

In an article e-published on June 18 ahead of print in *Dermatologic Surgery*, Ibrahim et al. from the University of Rochester Medical Center (NY) reported on ^{18}F-FDG PET/CT imaging in the management of Merkel cell carcinoma, in which clinical decision making is currently challenged by a lack of consensus on evaluation and treatment guidelines. The retrospective study included the records of 20 patients diagnosed with Merkel cell carcinoma who underwent a total of 39 PET/CT scans. In addition to imaging data, clinical and histologic findings were reviewed. The authors looked at the value of PET/CT in initial staging and ongoing management and investigated whether specific patient or tumor characteristics can predict when PET/CT is more effective in guiding management strategies. In 4 patients (20%), PET/CT provided previously unknown information, leading to changes in management in 3 of these cases. These and other results led the authors to conclude that ^{18}F-FDG PET/CT ^{18}F-FDG PET/CT "is a valuable tool for initial staging and to assess response to therapy of patients diagnosed with Merkel cell carcinoma" and that larger prospective studies are needed to establish optimal timing for imaging in this setting.

Dermatologic Surgery

PET/CT in Triple-Negative Breast Cancer

Ohara et al. from Hiroshima University (Japan) reported on June 8 ahead of print in *Breast* on a study evaluating the ability of ^{18}F-FDG PET/CT to correctly identify stage and predict outcomes in operable breast cancers. The study included the records of 311 patients with primary invasive breast cancer who underwent PET/CT before initial curative surgery. The maximum standardized uptake value (SUV_{max}) cutoff for predicting cancer recurrence was 3.8 in all patients but was 8.6 in patients with triple-negative subtype breast cancer. Three-year disease-free survival rates were 98.8% in patients with tumor $SUV_{max} \leq 3.8$ and 91.6% for those with tumor $SUV_{max} > 3.8$. High SUV_{max} was significantly associated with large tumor size, lymph node metastases, high nuclear grade, lymphovascular invasion, negative hormone receptor status, and positive HER2 status. Additional analyses showed that high SUV_{max} and negative hormone receptor status were significantly associated with poor prognosis. In patients with the triple-negative subtype, 3-y disease-free survival rates were 90.9% for patients with tumor $SUV_{max} \leq 8.6$ and 42.9% for those with tumor $SUV_{max} > 8.6$. In these individuals, high SUV_{max} was the only significant independent prognostic factor. The authors concluded that ^{18}F-FDGPET/CT is "useful for predicting malignant behavior and prognosis in patients with operable breast cancer, especially the triple-negative subtype."

Breast

^{11}C-MET PET and Carbon Ion RT

Toubaru et al from the National Institute of Radiological Sciences (Chiba, Japan) reported on June 13 ahead of print in *Radiation Oncology* on a study assessing the accuracy of ^{11}C-methionine (^{11}C-MET) PET in predicting the results of heavy-particle therapy in primary adenoid cystic carcinomas of the head and neck. The retrospective study included 67 patients who underwent PET or PET/CT with ^{11}C-MET before and 1 mo after completion of carbon ion radiotherapy. Patients were followed for a minimum of 12 mo after treatment.

Tracer accumulation in tumor was evaluated using the semiquantitative tumor to normal tissue ratio (TNR). Average TNRs before and after treatment were 4.8 (±1.5) and 3.0 (±1.3), respectively. A high TNR before treatment was a significant predictor of metastasis and disease-specific survival. A high TNR after treatment was a significant predictor of local recurrence. Along with the pre- and posttreatment TNRs, tumor size and age were also found to be related to outcomes. The authors concluded that ^{11}C-MET PET or PET/CT can be useful for predicting or determining the therapeutic efficacy of carbon ion radiotherapy."

Radiation Oncology

REVIEWS

Review articles provide an important way to stay up to date on the latest topics and approaches by providing valuable summaries of pertinent literature. The Newsline editor recommends several reviews accessioned into the PubMed database in June. In an article e-published on June 14 ahead of print in *Leukemia & Lymphoma,* Meignan et al. from the Hôpital Henri Mondor (Créteil, France) and colleagues published a "Report on the 4th International Workshop on Positron Emission Tomography in Lymphoma held in Menton, France, 3–5 October 2012." Laube et al. from the Institute of Radiopharmaceutical Cancer Research (Dresden, Germany) provided "Radiolabeled COX-2 inhibitors for noninvasive visualization of COX-2 expression and activity: a critical update" in *Molecules* (2013;18:6311–6355). In the June 13 online issue of *Oral Oncology*, Lai and Khong offered "Updates on MR imaging and ^{18}F-FDG PET/CT imaging in nasopharyngeal carcinoma." Tifilieff and Martinez from Columbia University (New York, NY) and the University of Bordeaux (France) described "Kappa-opioid receptor signaling in the striatum as a potential modulator of dopamine transmission in cocaine dependence" on June 3 ahead of print in *Frontiers in Psychiatry.* In an article in the July issue of *Gastrointestinal Endoscopy Clinics of North America* (2013;23:707–723), Carns et al. from Rice University (Houston, TX) reviewed "Optical molecular imaging in the gastrointestinal tract." On June 19 in *Clinical Cancer Research*, Keereweer et al. from Erasmus Medical Center (Rotterdam, The Netherlands) and Leiden University Medical Center (The Netherlands) reported on "Optical image-guided cancer surgery: challenges and limitations."