at the February Alzheimer's Disease Research Summit 2015: Path to Treatment and Prevention, these recommendations were designed to provide the wider AD research community with a strategy for speeding development of effective interventions for AD and related dementias. The recommendations call for a general change in the ways in which academic, biopharmaceutical, and government sectors participating in AD research and therapy generate, share, and use knowledge to propel development of critically needed therapies. "Alzheimer's research is entering a new era in which creative approaches for detecting, measuring and analyzing a wide range of biomedical data sets are leading to new insights about the causes and course of the disease," said NIH Director Francis S. Collins, MD, PhD. "In these times of significant fiscal constraints, we need to work smarter, faster, and more collaboratively. These recommendations underscore the importance of data sharing and multidisciplinary partnerships to a research community that looks to the NIH for guidance on the way forward."

More than 60 AD and chronic disease experts from academia, industry, nonprofit organizations, and advocacy groups joined to develop the research recommendations. These outline new scientific approaches to address critical knowledge gaps and propose ways to harness emerging technologies to accelerate treatments for individuals at all stages of the disease. They also identify infrastructure and partnerships necessary to successfully implement the new research agenda.

Among the overarching and priority AD research themes identified in the recommendations were goals to: understand all aspects of healthy brain aging and cognitive resilience to inform strategies for AD prevention; expand integrative, data-driven research approaches, such as systems biology and systems pharmacology; develop computational tools and infrastructure to enable storage, integration, and analysis of large-scale biologic and other patient-relevant data; leverage use of wearable sensors and other mobile health technologies to inform discovery science as well as research on AD care; support and enable Open Science in basic, translational, and clinical research; change academic, publishing, and funding incentives to promote collaborative, transparent, and reproducible research; invest in development of a new translational and data science workforce; and engage citizens, caregivers, and patients as equal partners in AD research. The recommendations were considered by the National Advisory Council on Aging at its meeting on May 12 and 13 and will be used to update and expand specific milestones for achieving the goals of the National Plan to Address Alzheimer's Disease (http://aspe.hhs.gov/daltcp/napa/NatlPlan2014.shtml).

National Institutes of Health

FROM THE LITERATURE

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 section on noteworthy reviews of the literature.

PET and Dementia

In an article in the May 19 issue of the *Journal of the American Medical Association* (2015;313:1939–1949), Ossenkoppele and colleagues from the VU Medical Center (Amsterdam, The Netherlands) brought together the work of researchers from more than a dozen countries to provide a meta-analysis of published studies on the prevalence of PET positivity in a wide range of dementia syndromes. Articles published between 2004 and 2015 were reviewed, and authors of studies that met criteria for meta-analysis were included as authors on the review. The final study included data on 1,359 individuals with clinically diagnosed Alzheimer disease (AD) and 538 with non-AD dementia, as well as a reference group of 1,849 healthy participants and an independent sample of 1,369 individuals with AD assessed at autopsy. Associations were identified between amyloid-β positivity on PET and age, apolipoprotein ε4 (APOE-ε4) status, and type of dementia. Data indicated that in the group of individuals with AD dementia, the prevalence of amyloid positivity decreased from age 50 to 90 y in APOE-ε4 noncarriers (86% at 50 y, 68% at 90 y) as well as (less markedly) in APOE ε4 carriers (97% at 50 y, 90% at 90 y). Similar associations between age and APOE-ε4 status with amyloid positivity were seen in the group with AD assessed at autopsy. Results indicated that in individuals with non-AD dementias, amyloid positivity increased with age from 60 to 80 y and APOE-ε4 status. For the group with dementia with Lewy bodies, APOE-ε4 carriers showed a PET positivity prevalence of 63% at 60 y and 83% at 80 y, with respective figures for noncarriers at 29% and 54%. For the group with frontotemporal

dementia, APOE-ε4 carriers showed a PET positivity prevalence of 19% at 60 y and 43% at 80 y, with respective figures for noncarriers at 5% and 14%. For the group with vascular dementia, APOE-ε4 carriers showed a PET positivity prevalence of 25% at 60 y and 64% at 80 y, with respective figures for noncarriers at 7% and 29%. The authors concluded that "these findings indicate the potential clinical utility of amyloid imaging for differential diagnosis in early-onset dementia and to support the clinical diagnosis of participants with AD dementia and noncarrier APOE-ε4 status who are older than 70 years."

Journal of the American Medical Association

PET in Individuals Without Dementia

In a second widely reported article in the May 19 issue of the *Journal of the American Medical Association* (2015;313:1924–1938), Jansen and colleagues from the VU Medical Center (Amsterdam, The Netherlands) brought together the work of more than 100 international researchers to provide a meta-analysis of published studies on the prevalence of amyloid-β pathology in individuals without dementia, including data on participants with normal cognition (n = 2,914), subjective cognitive impairment (SCI; n = 697), and mild cognitive impairment (MCI; n = 3,972). The analysis included 55 studies published before April 2014 that met inclusion criteria. The researchers looked at the prevalence of amyloid pathology on PET or in cerebrospinal fluid and Alzheimer disease (AD) risk factors (age, apolipoprotein E [APOE] genotype, sex, and education). For all 3 groups analyzed, the prevalence of amyloid pathology increased between 50 and 90 y: for normal cognition, 10%–44%; for SCI, 12%–43%, and for MCI, 27%–71%. Over all groups, APOE-ε4 carriers showed 2 to 3 times higher prevalence estimates than noncarriers. The age at which 15% of those with normal cognition were amyloid positive was ~40 y for APOE ε4ε4 carriers, ~50 y for APOE-ε2ε4 carriers, ~55 y for APOE-ε3ε4 carriers, ~65 y for APOE-ε3ε3 carriers, and 95 y for APOE-ε2ε3 carriers. The authors concluded that these and other findings "suggest a 20- to 30-y interval between first development of amyloid positivity and onset of dementia," a finding with direct implications for earlier identification of disease and expansion of studies to identify effective early treatments.

Journal of the American Medical Association

Pre-HCT PET in NHL

Bachanova, from the University of Minnesota Medical Center (Minneapolis) and colleagues from more than 30 U.S. and international institutions reported on May 13 ahead of print in *Biology of Blood and Marrow Transplantation* on the utility of pretransplantation ^{18}F-FDG PET imaging in predicting outcomes after allogeneic hematopoietic cell transplantation (HCT) for non-Hodgkin lymphoma (NHL). The study included 336 patients (202 male, 134 female; median age, 55 y) with chemotherapy-sensitive NHL scheduled for allogeneic HCT between 2007 and 2012 who underwent ^{18}F-FDG PET imaging at a median of 1 mo before transplantation. Diagnoses included follicular (n = 104), large cell (n = 85), mantle cell (n = 69), and mature NK or T cell (n = 78) lymphoma. PET findings were positive in 159 and negative in 177 patients. At 3-y follow-up, relapse/progression was seen in 40% of patients in the PET-positive group and 26% in the PET-negative group. These respective figures were 43% and 47% for progression-free survival and 58% and 60% for overall survival. Additional analysis indicated that a positive pretransplant PET finding was associated with increased risk of relapse/progression but not with worse overall or progression-free survival and did not predict graft-vs-host disease. The authors concluded that a positive PET scan prior to HCT "should not be interpreted as a barrier to a successful allograft" and that "PET status does not appear to predict survival after allogeneic HCT for NHL."

Biology of Blood and Marrow Transplantation

^{123}I-MIBG Scintigraphy and Lewy Body Disease

In an article e-published on May 15 ahead of print in *BMC Neurology*, Lamotte et al. from University Hospital of Caen (France) reported on a study investigating delayed heart–to–mediastinum ratios from ^{123}I-MIBG cardiac scintigraphy in diagnosis of parkinsonian syndromes and differentiation of Parkinson disease (PD) and Lewy body dementia (LBD) from other disease. The study included records and imaging data from 62 patients with parkinsonian syndrome, each of whom had undergone ^{123}I-MIBG scintigraphy and ^{123}I-ioflupane SPECT dopaminergic imaging between 2009 and 2013. Optimal delayed heart–to–mediastinum ratios were calculated and sensitivity, specificity, and likelihood ratios were determined for the 20 patients ultimately diagnosed with PD, 22 with LBD, and 20 with other diseases. ^{123}I-MIBG scintigraphy, but not ^{123}I-ioflupane SPECT, was able to distinguish PD and LBD from other disease, using an optimal delayed heart–to–mediastinum ratio cutoff of 1.48. Using this cutoff, sensitivity and specificity in making this distinction were 83.3% and 85%, respectively, with positive and negative likelihoods of 5.5 and 0.2, respectively. Although a cutoff of 1.2 showed a trend toward differentiating between PD and LBD, this trend did not reach the level of significance. The authors added that "further prospective studies in a large number of subjects with parkinsonian syndromes are needed to confirm our findings and to help to understand the pathophysiology of LB-related disorders."

BMC Neurology

PET/MR and Carotid Endarterectomy

Folke Pedersen et al. from the Rigshospitalet and University of Copenhagen (Denmark) reported on May 14 ahead of print in *Arteriosclerosis, Thrombosis, and Vascular Biology* on a study of PET/MR detection of activated macrophages in carotid atherosclerotic plaque before endarterectomy. The study included 10 patients

scheduled for endarterectomy who underwent simultaneous PET/MR imaging to measure ^{64}Cu-DOTATATE uptake in carotid artery plaques. The researchers found that tracer uptake was significantly higher in symptomatic plaque than in contralateral arteries. Real-time quantitative polymerase chain reaction analysis of 62 plaque segments from the 10 patients assessed gene expression of markers associated with plaque vulnerability, and these results were correlated with mean standardized uptake values on imaging. CD163 (but not CD68) was found to independently correlate with ^{64}Cu-DOTATATE uptake, suggesting that PET with this tracer "is detecting alternatively activated macrophages," an association that potentially could "improve noninvasive identification and characterization of vulnerable plaques."

Arteriosclerosis, Thrombosis, and Vascular Biology

PET and RCT in Nasopharyngeal Cancer

In a study e-published on May 17 ahead of print in *Strahlentherapue und Onkologie*, Su et al. from the First Affiliated Hospital of Wenzou Medical University (China) reported on a study assessing the ability of ^{18}F-FDG PET to predict tumor response to radiochemotherapy in nasopharyngeal carcinoma. The study included 46 patients who had undergone PET imaging before receiving intensity-modulated radiation therapy either after or in tandem with chemotherapy. After treatment, 32 patients (69.6%) experienced clinical complete responses. Maximum standardized uptake value (SUV_{max}) of ^{18}F-FDG on pretreatment imaging had a positive predictive value of 90.6%. In general, patients with $SUV_{max} \leq 10$ had higher clinical complete response rates than those with $SUV_{max} > 10$, leading the authors to conclude that the "SUV_{max} of the primary tumor before treatment is an independent predictor of tumor response in nasopharyngeal carcinoma."

Strahlentherapue und Onkologie

4D V/Q PET/CT and Lung IMRT

Siva and colleagues from the Peter MacCallum Cancer Center (Melbourne, Australia) reported on April 29 ahead of print in *Radiotherapy and Oncology* on a study designed to assess the utility of functional lung avoidance using intensity-modulated radiation therapy (IMRT) guided by 4D ventilation/perfusion (V/Q) PET/CT. Twenty patients with non–small cell lung cancer underwent 4D V/Q PET/CT before 60 Gy of definitive radiation (as part of chemotherapeutic regimens). Using a 70th-centile standardized uptake value (SUV) threshold, "highly perfused" and "highly ventilated" lung volumes were delineated. A "ventilated" lung volume was created using a 50th-centile SUV threshold. Four IMRT plans were devised for each patient: 1 for each of the thresholded volumes and 1 for the anatomic lung. Mean lung dose and V5, V10, V20, V30, V40, V50, and V60 for each of the plans were calculated from dosimetric data. Plans using the "highly perfused" lung volumes results in 13.0% reductions in mean lung dose (1.7 Gy), and functional V5, V10, and V20 were improved by 13.2%, 7.3%, and 3.8%, respectively, with this plan. The other 2 plans resulted in no significant sparing of dose to functional lung. The authors concluded that "IMRT plans adapted to perfused but not ventilated lung on 4D V/Q PET/CT allowed for reduced dose to functional lung whilst maintaining consistent plan quality."

Radiotherapy and Oncology

PSMA Radioguided Surgery in Prostate Cancer

In an article e-published on May 6 ahead of print in *European Urology*, Maurer et al from the Technische Universität München (Germany) reported on the use of ^{68}Ga-labeled prostate-specific membrane antigen (PSMA)–radioguided surgery for metastatic lymph nodes in prostate cancer. The study included 1 patient with primary prostate cancer and evidence of lymph node metastasis and 4 patients with evidence of recurrent disease to regional lymph nodes on ^{68}Ga-PSMA-N,N'-bis [2-hydroxy-5-(carboxyethyl)benzyl]ethylenediamine-N,N'-diacetic acid (^{68}Ga-PSMA-HBED-CC) PET hybrid imaging. Each patient received an intravenous injection of a ^{111}In-PSMA investigation and therapy agent 24 h before surgery. A gamma probe with acoustic and visual feedback was used to intraoperatively track metastatic lymph nodes. Ex vivo analysis confirmed that all lymph nodes identified as positive in vivo corresponded to PSMA-avid metastatic disease. The intraoperative gamma probe also detected all PSMA-positive lesions seen on preoperative ^{68}Ga-PSMA-HBED-CC PET, including small subcentimeter metastatic lymph nodes. In 2 patients, PSMA-radioguided surgery identified additional lesions that were close to known tumor deposits and not detected by preoperative PET.

European Urology

PET/CT and Dose Painting in Bone Mets

Berwouts et al. from Ghent University and Ghent University Hospital (Belgium) reported on May 14 ahead of print in *Radiotherapy and Oncology* on a study integrating biologic information from ^{18}F-FDG PET/CT into dose painting by numbers (DPBN) for radiotherapy planning in patients with bone metastases. In this phase II trial, 45 patients were randomized in groups of 15 to 8 Gy in a single fraction with conventionally planned radiotherapy (arm A), 8 Gy in a single fraction with PET-guided DPBN (arm B), or 16 Gy in a single fraction with DPBN (arm C). In arms A, B, and C, respective overall responses of 8 (53%), 12 (80%), and 9 (60%) patients were seen. The estimated odds ratio for overall response for arm B versus arm A was 3.5 and for arm C versus arm A was 1.31. The researchers will use the arm B approach (single fraction of 8 Gy with PET-guided DPBN) in a phase III trial.

Radiotherapy and Oncology

PET Insert for PET/MR Brain Imaging

In an article in the May issue of *Medical Physics* (2015;42:2354) Jung,

from Sogang University (Seoul, Korea) and colleagues from the Korea Advanced Institute of Science and Technology (Daejeon) and the Korea Institute of Radiological and Medical Sciences (Seoul) reported on the development of a hybrid imaging device with insertable PET for simultaneous PET and MR imaging of the human brain. The authors described the specifications of the apparatus as well as validation and stability testing, with sample images acquired in a brain phantom. The PET detector block used a 4×4 matrix of detector modules, each consisting of a 4×4 array LYSO scintillators coupled to a 4×4 Geiger-mode avalanche photodiode array. The researchers found no significant degradation of PET by MR across numerous MR imaging sequences. The authors concluded that this "compact and lightweight PET insert for hybrid PET/MRI" is feasible and can be developed using the Geiger-mode avalanche photodiode arrays and charge signal transmission method for routine use in brain imaging without significant interference.

Medical Physics

Reviews

Review articles provide an important way to stay up to date on the latest topics and approaches by offering valuable summaries of pertinent literature. The Newsline editor recommends several reviews accessioned into the PubMed database in April, May, and June 2015. In an article e-published on May 15 ahead of print in *Current Opinion in Pulmonary Medicine*, Usmanji et al. from Radboud University Medical Center (Nijmegen, The Netherlands) provided an "Update on F-18-fluoro-deoxy-glucose-PET/computed tomography in nonsmall cell lung cancer." Kjaer and Knigge, from the University of Copenhagen (Denmark) reviewed the "Use of radioactive substances in diagnosis and treatment of neuroendocrine tumors" in the June issue of the *Scandinavian Journal of Gastroenterology* (2015;50:740–747). In an article e-published on April 30 ahead of print in *Clinical Cancer Research*, van Dijk et al. from Radboud University Medical Center (Nijmegen, The Netherlands) published "PET imaging in head and neck cancer patients to monitor treatment response: a future role for EGFR-targeted imaging." Salvatori et al. from the Università Cattolica del Sacro Cuore (Rome, Italy) and the University of Naples (Italy) provided an overview of "Imaging in endocrinology: ^{18}F-FDG PET/CT in differentiated thyroid carcinoma: clinical indications and controversies in the diagnosis and follow-up of differentiated thyroid cancer," e-published on May 6 ahead of print in the *European Journal of Endocrinology*. In an article e-published on April 28 ahead of print in *Insights into Imaging*, Keraliya et al. from the Harvard Medical School/Brigham and Women's Hospital (Boston, MA) published "Beyond PET/CT in Hodgkin lymphoma: a comprehensive review of the role of imaging at initial presentation, during follow-up, and for assessment of treatment-related complications." Stamatis, from University Duisburg Essen (Germany), reviewed "Staging of lung cancer: the role of noninvasive, minimally invasive, and invasive techniques" on May 14 ahead of print in the *European Respiratory Journal*. In an article e-published on April 28 ahead of print in *Nature Review. Clinical Oncology*, Grootjans and colleagues from Radboud University Medical Center, Leiden University Medical Center, and Maastricht University Medical Center (all in The Netherlands) provided an overview of "PET in the management of locally advanced and metastatic NSCLC." Finnema et al. from the Karolinska Institutet (Stockholm, Sweden) described the "Application of cross-species PET imaging to assess neurotransmitter release in brain" on April 30 ahead of print in *Psychopharmacology (Berl)*. "Current and future trends in multimodality imaging of coronary artery disease" were reviewed on April 25 ahead of print in *Expert Review of Cardiovascular Therapy* by Alexanderson-Rosas et al. from the Instituto Nacional de Cardiología Ignacio Chávez (Mexico City, Mexico). Reagan and Friedberg from the University of Rochester Medical Center (NY) looked at "Advancing radioimmunotherapy and its future role in non-Hodgkin lymphoma" in the May issue of *Future Oncology* (2015;11:1543–1553). In an article e-published on May 15 ahead of print in the *European Archives of Oto-Rhino-Laryngology*, Cammaroto and colleagues from the University of Messina (Italy) published "The role of PET/CT in the management of patients affected by head and neck tumors: a review of the literature."