Health Care Innovation Awards Announced

Health and Human Services Secretary Kathleen Sebelius announced on May 15 a nearly $1 billion initiative intended to fund awards and evaluation to build on current work to transform the health care system by delivering better care and lowering costs. The second-round Health Care Innovation Awards will fund applicants with a high likelihood of driving health care system transformation and delivering better outcomes. Last year, the Centers for Medicare & Medicaid Services (CMS) awarded 107 round-one Health Care Innovation Awards selected from almost 3,000 applications to organizations that are currently testing innovative solutions to improve outcomes and reduce costs. Projects are located in urban and rural areas, all 50 states, the District of Columbia, and Puerto Rico.

The second round of awards differs from the first in that CMS is specifically seeking innovations in 4 areas: rapidly reducing costs for patients with Medicare and Medicaid in outpatient hospital and other settings; improving care for populations with specialized needs; testing improved financial and clinical models for specific types of providers, including specialists; and linking clinical care delivery to preventive and population health. Like the first round, these awards will emphasize results and ensure program integrity. For more information, including a fact sheet and Funding Opportunity Announcement, see: http://innovation.cms.gov/initiatives/Health-Care-Innovation-Awards/Round-2. Applications will be accepted until August 15.

U.S. Department of Health and Human Services

Alzheimer PET AUC Infographic Available

In January 2013, SNMMI and the Alzheimer's Association published the first appropriate use criteria (AUC) for brain amyloid imaging in Alzheimer disease (*J Nucl Med.* 2013;54:476–490). To share this information more widely, in particular with physicians who order studies, SNMMI has created an infographic that provides a visual triage reminder of the recommended AUC for PET β-amyloid imaging.

Although elevated β-amyloid levels are one of the defining pathologic features of Alzheimer disease, many elderly people with normal cognition also have elevated levels, as do individuals with conditions other than Alzheimer dementia. Therefore, clinical use of amyloid PET requires careful consideration. The infographic starts with the recommendation for assessment by a dementia expert and takes the viewer through a brief decision tree. The user is reminded that appropriate criteria include: persistent or progressive unexplained memory problems and impairments demonstrated by standard medical exams, unusual clinical presentations, and/or atypically early age of onset. Inappropriate criteria include: 65 y or older and meeting standard definitions and tests for Alzheimer disease, no clinical confirmation of impairment, need for test to determine dementia severity, test requested solely on the basis of family history of dementia, test requested as a substitute for genotyping, or test requested for nonmedical reasons. The graphic also includes reminders on potential impacts on patient care, as well as other pertinent factors. The infographic is available for download at: http://interactive.snm.org/index.cfm?PageID=12610.

SNMMI

New Erlotinib Use Approved

The U.S. Food and Drug Administration (FDA) on May 14 approved the EGFR Mutation Test, a companion diagnostic for the cancer drug Tarceva (erlotinib; Roche Molecular Systems, Pleasanton, CA). This is the first FDA-approved companion diagnostic that detects epidermal growth factor receptor (EGFR) gene mutations, which are present in ~10% of non–small cell lung cancers (NSCLC). The test was approved with an expanded use for Tarceva as a first-line treatment for patients with NSCLC metastases and who have certain mutations in the EGFR gene. "The approval of the EGFR Mutation Test will allow physicians to identify NSCLC patients who are candidates for receiving Tarceva as first-line therapy," said Alberto Gutierrez, PhD, director of the Office of In Vitro Diagnostics and Radiological Health in the FDA Center for Devices and Radiological Health. "Companion diagnostics play an important role in determining which therapies are the safest and most effective for a particular patient."

The safety and effectiveness of the cobas EGFR Mutation Test was established with clinical data showing that, on average, NSCLC patients with specific types of EGFR mutations (exon 19 deletions or exon 21 L858R substitution mutations) lived without their disease progressing for 10.4 mo after Tarceva treatment, compared with 5.4 mo for those who received a standard 2-drug chemotherapy regimen. The approval is Tarceva's fourth indication and the third use for lung cancer. The FDA approved Tarceva in 2010 for maintenance treatment of patients with locally advanced or metastatic NSCLC whose disease had not progressed after 4 cycles of platinum-based first-line chemotherapy. Tarceva was originally approved in November 2004 for treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen.

U.S. Food and Drug Administration

Amyvid and CMS Coverage

Eli Lilly and Company and Avid Pharmaceuticals, makers of Amyvid, the FDA-approved PET agent for

β-amyloid imaging, held a conference call on May 16 to discuss with media representatives and others the anticipated Centers for Medicare & Medicaid Service's (CMS) draft decision on coverage for Amyvid and similar diagnostic agents. Kathy Fay Mahdoubi covered the call for *Molecular Imaging* in its May 20 issue.

Wei-Li Shao, senior director of the Alzheimer business division at Eli Lilly and Company, noted during the call that a draft decision is expected in late June or July. Of special concern for the company and its affiliated scientists was the noncoverage decision issued earlier this year by the CMS Medicare Evidence Development and Coverage Advisory Committee, which cited low-to-intermediate confidence that PET amyloid imaging would lead to enhanced outcomes. "Treatments exist to improve health outcomes," Shao said. "Lilly believes that requiring a diagnostic tool to serve the same role as a treatment in improving health outcomes is inappropriate. We along with the experts in the field believe the true value of these diagnostic imaging agents is that for the very first time in clinical practice, physicians can determine whether patients with signs and symptoms of cognitive impairment have underlying amyloid pathology."

Shao and Daniel Skovronsky, MD, PhD, president and CEO of Avid Radiopharmaceuticals, subsidiary of Eli Lilly and Company, summarized for the conference call participants efforts by community members and organizations, including SNMMI, in support of reimbursement, with detailed research and compilation of appropriate use criteria for amyloid imaging. "These groups outlined concerns that we at Lilly fully echo, including that failing to provide coverage for this new technology will suppress innovation and research in the field of dementia in addition to preventing patients with potential Alzheimer disease and related dementias from having access to tools that could aid in early and accurate diagnosis that could lead to appropriate treatment and care management," said Skovronsky.

Shao described the 3 coverage possibilities that might be included in the anticipated draft decision: noncoverage, coverage in full, or coverage with evidence development (CED). "We believe that CED should not be applied in cases where the FDA approval process has expressly evaluated and endorsed the use of a drug or biologic in a specific patient population," said Shao. "We feel this is an unnecessary step that is hindering patients from gaining access to important treatment or scans that could have an impact on their diagnosis or treatment. While we do not believe CED is appropriate, CMS may still choose to issue a CED as its draft decision in July. If the draft decision is CED, CMS could ask Lilly or any other interested stakeholders to conduct a registry trial and/or a randomized controlled trial to collect data the agency has identified as the evidence gap needed to gain coverage of the diagnostic tool. This decision would limit β-amyloid imaging agents only to those within the trials deemed necessary to conduct."

Skovronsky was asked by a conference call participant about the utility of diagnostic tests for conditions that currently have no viable treatment options. "It's true that we don't yet have today antiamyloid therapies or other therapies that represent a true cure for Alzheimer disease," he responded, "But we do have a myriad of interventions; we have drugs that are approved; we have management strategies that do offer real benefits for Alzheimer's patients. In addition, once we have accurate diagnoses we can manage the comorbidities of Alzheimer disease patients better, so it really is quite important even today, even with the therapeutics we have today, to diagnose Alzheimer's early and accurately."

Molecular Imaging

"Unclogging" Amyloid Pathology

In an article e-published on April 23 ahead of print in *Neuron,* Gricuic et al. from the Massachusetts General Hospital and Harvard Medical School (Boston, MA) reported on results of a study suggesting a potential strategy for developing treatments to stem the Alzheimer disease process. Such a strategy would be based on the group's finding that inhibition of the transmembrane protein CD33 mitigates β-amyloid pathology. "Too much CD33 appears to promote late-onset Alzheimer's by preventing support cells from clearing out toxic plaques, key risk factors for the disease," said Rudolph Tanzi, PhD, one of the authors, in a press release issued by the National Institutes of Health (NIH), which funded the study. "Future medications that impede CD33 activity in the brain might help prevent or treat the disorder."

Tanzi and colleagues reported in 2008 that variation in the CD33 gene was identified as significant in the largest genome-wide study of Alzheimer-affected families. The gene was known to make a protein that regulates the immune system, but its function in the brain remained unclear. To discover how it might contribute to Alzheimer disease, the researchers initiated genetic, biochemistry, in vitro, and mouse experiments.

They found over-expression of CD33 in microglia in postmortem brains from patients who had late-onset Alzheimer disease. The more CD33 protein on the cell surface of microglia, the more β-amyloid proteins and plaques had accumulated in their brains. The researchers found that brains in individuals who had inherited a version of the CD33 gene that protected them from Alzheimer disease showed conspicuously reduced amounts of CD33 on the surface of microglia and less β-amyloid. Brain levels of β-amyloid and plaques were also markedly reduced in mice engineered to underexpress or lack CD33. Microglia cells in these animals were more efficient at clearing out the debris, which the researchers traced to levels of CD33 on the cell surface. Evidence also suggested that CD33 works with another Alzheimer risk gene in microglia to regulate inflammation in the brain.

Neuron

National Institutes of Health

LEU ^{99}Mo Production at LANL

Los Alamos National Laboratory (LANL) announced on May 13 that irradiated uranium fuel had been recycled and reused for ^{99}Mo production, with "virtually no losses" in ^{99}Mo yields or uranium recovery. In a press release, LANL indicated that "this demonstrates the viability of the separation process, as well as the potential for environmentally and cost-friendly fuel recycling."

The National Nuclear Security Administration's Global Threat Reduction Initiative (GTRI) implements the U.S. policy to minimize and eliminate the use of highly enriched uranium (HEU) in civilian applications. In support of this objective, GTRI is working with U.S. commercial entities and the U.S. national laboratories to develop a diverse set of non-HEU-based technologies to produce ^{99}Mo in the United States. The U.S. national laboratories conduct research and development, engineering and design support, and proof of concept demonstrations. GTRI has been working with LANL to ensure its technical expertise is available to support GTRI's commercial partners, including Morgridge Institute for Research-SHINE Medical Technologies (MIR-SHINE), which proposes to use a particle accelerator to produce ^{99}Mo from a mildly acidic low-enriched uranium (LEU) solution.

Researchers at Los Alamos described their activities in successfully proving the technical viability of the initial stage of ^{99}Mo recovery from LEU solution through a direct scaled-down demonstration of the proposed industrial process. The researchers developed methodologies for preparing and analyzing uranium sulfate fuel, safely containing the fuel during irradiation at a the Los Alamos Neutron Accelerator Science facility, and performing chemical flow-sheet testing using a separation apparatus applicable to both low and high levels of radiation. Unlike traditional HEU-based processes, the challenge is to recover the ^{99}Mo from a large excess of LEU and leave the uranium in the same chemical form to allow for recycling. The team found that nearly all of the uranium could be recovered after ^{99}Mo separations were performed. The LEU fuel that passed through the column separation process was irradiated again, and once more the fission-generated ^{99}Mo was separated in high yield. When the same fuel was irradiated a third time, no observable loss was noted in the subsequent ^{99}Mo recovery. The results confirm the viability of both the ^{99}Mo separation process and uranium fuel recycling, which can lower operating costs and minimize waste generation.

Los Alamos National Laboratory

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 small section on noteworthy reviews of the literature.

Predicting Brain Amyloidosis in MCI

Tosun et al. from the University of California, San Francisco, and the VA Medical Center (San Francisco, CA) reported on May 18 ahead of print in *Annals of Neurology* on a study designed to identify an imaging signature predictive of brain amyloidosis with potential for routine use as a screening tool to identify those individuals with mild cognitive impairment (MCI) who are most likely to have high levels of brain amyloidosis. The study included 62 participants with MCI who underwent structural MR and ^{11}C-labeled Pittsburgh compound PET imaging. The researchers identified an anatomic shape variation–based neuroimaging predictor of brain amyloidosis and defined a structural MR–based brain amyloidosis score (sMRI-BAS). They validated the positive predictive abilities of the sMRI-BAS for β-amyloid in a separate group of 153 MCI patients with cerebrospinal fluid biomarker data positive for β-amyloid but without amyloid on PET imaging. The predictive powers of the sMRI-BAS were compared with those of the apolipoprotein E (ApoE) genotype and hippocampal volumes. The anatomic shape variations found to be predictive of brain amyloidosis included, as expected, the medial temporal lobe, temporal–parietal association cortices, posterior cingulate, precuneus, hippocampus, amygdala, caudate, and fornix/stria terminals. The ability of the sMRI-BAS combined with ApoE genotype status to predict β-amyloid positivity was significantly better than that of either predictor separately. Hippocampal volume was not found to be an independent predictor of brain amyloidosis in MCI. The authors pointed to these efforts as among "the first attempts to use an imaging technique that does not require amyloid-specific radioligands for identification of individuals with brain amyloidosis" and suggested that these findings "could lead to development of multidisciplinary/multimodality brain amyloidosis biomarkers that are reliable, minimally invasive, and widely available."

Annals of Neurology